ASH Draft Recommendations for VTE Prevention in Surgical Hospitalized Patients

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please visit **https://vtesurgical.questionpro.com**. Only comments submitted via the online survey will be reviewed by the guideline panel.

The public comment period for these draft recommendations ends **July 18, 2018**.

RECOMMENDATIONS

Question 1: Should pharmacological prophylaxis vs. mechanical prophylaxis be used for patients undergoing surgery?

> The ASH guideline panel suggests using either pharmacological prophylaxis or mechanical prophylaxis in patients undergoing surgery (conditional recommendation based on low certainty in the evidence about effects.)

Question 2: Should mechanical combined with pharmacological prophylaxis vs. mechanical prophylaxis alone be used for patients undergoing surgery?

> The ASH guideline panel suggests using either combined prophylaxis with mechanical and pharmacological methods or prophylaxis with mechanical methods alone in surgical patients (conditional recommendation based on low certainty of the evidence about effects).

Question 3: Should pharmacological combined with mechanical prophylaxis vs. pharmacological prophylaxis alone be used for patients undergoing surgery?

> The ASH guideline panel suggests using combined prophylaxis with mechanical and pharmacological methods over prophylaxis with pharmacological agents alone in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Question 4: Should pneumatic compression prophylaxis vs. graduated compression stockings be used for prophylaxis in surgical patients?

> The ASH guideline panel suggests using Intermittent Compression Devices over Graduated Compression Stockings in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Question 5: Should mechanical prophylaxis vs. no prophylaxis be used for patients undergoing surgery?

The ASH guideline panel suggests using mechanical prophylaxis over no mechanical prophylaxis in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Question 6: Should insertion of an inferior vena cava (IVC) filter vs. no IVC filter be used for patients undergoing surgery?

The ASH guideline panel suggests not using Inferior Vena Cava Filter in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Question 7: Should extended vs. standard course antithrombotic prophylaxis be used for patients undergoing surgery?

The ASH guideline panel suggests using extended course antithrombotic prophylaxis in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Question 8: Should early vs. delayed antithrombotic administration be used in patients undergoing surgery?

The ASH guideline panel suggests either early administration (post-operative, within 12 hours) or late administration (post-operative- after 12 hours) of antithrombotic prophylaxis in surgical patients. (conditional recommendation based on very low certainty of the evidence about effects).

Question 10: Should ASA vs. other anticoagulant be used for patients undergoing total hip or knee arthroplasty?

The ASH guideline panel suggests using either aspirin or other pharmacological agents in patients undergoing total hip arthroplasty or total knee arthroplasty (conditional recommendation based on very low certainty of the evidence about effects).

Question 11: Should Direct Oral anticoagulants (DOAC) vs. Low Molecular Weight heparin (LMWH) prophylaxis be used for patients undergoing total hip or knee arthroplasty?

The ASH guideline panel suggests using DOACs rather than LMWH in patients undergoing total hip or knee arthroplasty (conditional recommendation based on moderate certainty of the evidence about effects).

Question 12: Should LMWH vs. Warfarin be used for patients undergoing total hip or knee arthroplasty?

The ASH guideline panel suggests using LMWH over warfarin in patients undergoing total hip or knee arthroplasty (conditional recommendation based on very low certainty of the evidence about effects).

Question 13: Should LMWH vs. UFH be used for patients undergoing total hip or knee arthroplasty?

The ASH guideline panel recommends LMWH over UFH in patients undergoing total hip or knee arthroplasty (strong recommendation based on moderate certainty of the evidence about effects).

Question 14: Should one DOAC vs. another DOAC be used for patients undergoing total hip or knee arthroplasty?

The ASH guideline panel suggests using any of the DOACs in patients undergoing total hip or knee arthroplasty (conditional recommendation based on low certainty of the evidence about effects).

Question 15: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing hip fracture repair?

The ASH guideline panel suggests using pharmacological prophylaxis over no pharmacological prophylaxis in surgical patients undergoing surgery for hip fracture repair (conditional recommendation based on very low certainty of the evidence about effects).

Question 16: Should LMWH vs. UFH be used for patients undergoing hip fracture repair?

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing surgery for hip fracture repair (conditional recommendation based on very low certainty of the evidence about effects).

Question 17: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing major general surgery?

The ASH guideline panel suggests using pharmacological prophylaxis in patients undergoing major general surgery (conditional recommendation based on low certainty of the evidence about effects).

Question 18: Should LMWH vs. UFH prophylaxis be used for patients undergoing major general surgery?

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing major general surgery procedures (conditional recommendation based on very low certainty of the evidence about effects).

Question 19: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing laparoscopic cholecystectomy?

The ASH guideline panel suggests against pharmacological prophylaxis over no prophylaxis in patients undergoing laparoscopic cholecystectomy (conditional recommendation based on low certainty of the evidence about effects)

Question 20: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing major neurosurgical procedures?

The ASH guideline panel suggests not using pharmacological prophylaxis in patients undergoing major neurosurgical procedures (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
Mechanical prophylaxis would be routinely used in this population when possible.

Question 21: Should LMWH vs. UFH prophylaxis be used for patients undergoing major neurosurgical procedures?

The ASH guideline panel suggests using LMWH over UFH in patients undergoing major neurosurgical procedures (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
This recommendation is applicable to the subset of patients deemed at high risk of VTE in whom pharmacological prophylaxis appears indicated (see Q20).

Question 22: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing transurethral resection of the prostate?

The ASH guideline suggests against pharmacological prophylaxis in undergoing transurethral resection of the prostate (conditional recommendation based on low certainty of the evidence about effects).

Question 23: Should LMWH vs. UFH prophylaxis be used for patients undergoing transurethral resection of the prostate?

The ASH guideline suggests using either LMWH or UFH in patients undergoing transurethral resection of the prostate (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
This recommendation is applicable to the subset of patients deemed at high risk of VTE in whom pharmacological prophylaxis appears indicated (see Q22).

Question 24: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing radical prostatectomy?

The ASH guideline panel suggests against pharmacological prophylaxis in patients undergoing radical prostatectomy (conditional recommendation based on low certainty of the evidence about effects).

Question 25: Should LMWH vs. UFH prophylaxis be used for patients undergoing radical prostatectomy?

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing radical prostatectomy (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
This recommendation is applicable to the subset of patients deemed at high risk of VTE in whom pharmacological prophylaxis appears indicated (see Q24).

Question 26: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing cardiac or major vascular surgery?

The ASH guideline panel suggests using either pharmacological prophylaxis or no prophylaxis in patients undergoing cardiac and major vascular surgical procedures (conditional recommendation based on very low certainty of the evidence about effects).

Question 27: Should LMWH vs. UFH prophylaxis be used for patients undergoing cardiac or major vascular surgery?

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing cardiac or major vascular surgical procedures (conditional recommendation based on very low certainty of the evidence about effects)

Question 28: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing surgery following major trauma?

The ASH guideline panel suggests prophylaxis rather than no prophylaxis in patients undergoing surgery following major trauma who are at low to moderate risk of bleeding (Conditional recommendation based on very low certainty of the evidence about effects).

The ASH guideline panel suggests no prophylaxis rather than prophylaxis in patients undergoing surgery following major trauma who are at high risk of bleeding (Conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
Mechanical prophylaxis would be routinely used in this population when possible (e.g. no lower limb injuries).

Question 29: Should LMWH vs. UFH prophylaxis be used for patients undergoing surgery following major trauma?

The ASH guideline panel suggests either using LMWH or UFH in patients undergoing surgery following major trauma. (Conditional recommendation based on low certainty of the evidence about effects).

Question 30: Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing major gynecological procedures?

The ASH guideline panel suggests pharmacological prophylaxis over no prophylaxis in patients undergoing major gynecological procedures (conditional recommendation based on low certainty of the evidence about effects).

Question 31: Should LMWH vs. UFH prophylaxis be used for patients undergoing major gynecological procedures?

The ASH guideline panel suggests either LMWH or UFH in patients undergoing major gynecological surgery procedures (conditional recommendation based on very low certainty of the evidence about effects).

QUESTION-1

Should pharmacological prophylaxis vs. mechanical prophylaxis be used for patients undergoing surgery?	
POPULATION:	patients undergoing surgery
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	mechanical prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major Bleeding ; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. Mechanical methods are another form of thromboprophylaxis for such patients undergoing surgical procedures. Such devices act to prevent venous stagnation in the lower limbs by promoting venous outflow. Mechanical methods include: graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD) and sequential compression devices (SCD). Unlike pharmacological agents, mechanical methods are not associated with an increased risk of bleeding. This EtD compares the effectiveness and safety of pharmacological thromboprophylaxis with mechanical thromboprophylaxis in hospitalized patients undergoing surgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable. With VTE prevention strategies provided at physician discretion, a recent large registry study of several million surgical patients identified the rate of VTE during the index hospital admission for surgery of 0.2% (Assareh 2014). Symptomatic VTE post discharge in orthopedic and abdominal surgery patients, with VTE prevention provided by physician discretion, has been reported in 4.7% and 3.1% of patients respectively (Spyropoulos 2009).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	(see table below)	

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with mechanical prophylaxis	Risk difference with pharmacological prophylaxis
Mortality follow up: range 5 days to 90 days	4235 (15 RCTs)[a]	⨁⨁◯◯ LOW[b,c]	**RR 0.92** (0.46 to 1.84)	Study population	
				9 per 1,000[a]	**1 fewer per 1,000** (5 fewer to 7 more)
				Low	
				8 per 1,000[d]	**1 fewer per 1,000** (4 fewer to 7 more)
				Moderate	
				7 per 1,000[e]	**1 fewer per 1,000** (4 fewer to 6 more)
Symptomatic Pulmonary	3654 (13 RCTs)	⨁⨁◯◯ LOW[c]	**RR 1.04** (0.36 to	Study population	
				4 per 1,000	**0 fewer per**

Embolism - representing the moderate marker state assessed with: Symptomatic PE follow up: range 5 days to 90 days			2.96)		**1,000** (2 fewer to 7 more)
				Low	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 1 more)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: Symptomatic proximal DVT follow up: range 5 days to 90 days	2353 (6 RCTs)	⊕⊕⊕◯ MODERATE[c]	**RR 0.75** (0.11 to 5.32)	Study population	
				2 per 1,000	**1 fewer per 1,000** (2 fewer to 9 more)
				Low	
				1 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 2 more)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 2 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Symptomatic distal DVT follow up: range 5 days to 90 days	1934 (4 RCTs)	⊕⊕⊕◯ MODERATE[c]	**RR 0.16** (0.05 to 0.58)	Low	
				1 per 1,000[h]	**1 fewer per 1,000** (1 fewer to 0 fewer)
				Moderate	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				0 per 1,000[g]	**0 fewer per**

					1,000 (0 fewer to 0 fewer)
Major Bleeding follow up: range 5 days to 90 days	4844 (18 RCTs)	⊕⊕⊕◯ MODERATE[c,i]	**RR 2.87** (1.68 to 4.92)	Study population	
				6 per 1,000	**12 more per 1,000** (4 more to 25 more)
				Low	
				6 per 1,000[d]	**11 more per 1,000** (4 more to 24 more)
				Moderate	
				8 per 1,000[e]	**15 more per 1,000** (5 more to 31 more)
Reoperation follow up: range 5 days to 90 days	1342 (6 RCTs)	⊕⊕◯◯ LOW[j,k]	**RR 2.01** (0.29 to 14.05)	Study population	
				1 per 1,000	**1 more per 1,000** (1 fewer to 19 more)
				Low	
				0 per 1,000[d]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				26 per 1,000[l]	**26 more per 1,000** (18 fewer to 339 more)

a. The baseline risk for the study population consists of the control group event rate from studies that included surgical patients with cancer or without cancer.
b. There was serious concern about risk of bias in the studies because they were not blinded with unclear information about allocation concealment, or because they provided insufficient information to make a judgment about risk of bias domains.
c. Small number of events, with wide confidence interval for the relative effect, including both appreciable benefit and harm. However, based on low baseline risk, the CI for the absolute effect is narrow and, therefore, we downgraded for

	imprecision only by one level. d. The baseline risk consists of the control group event rate from trials including surgical non-cancer patients, i.e. the trials that included less than 50% of patients with cancer. e. The baseline risk consists of event rates from observational study data including surgical patients with cancer. Yamaoka 2015 (a propensity score matched analysis, with N=591, and follow up time of 30 days) reported in patients undergoing colorectal cancer resection and using mechanical IPC prophylaxis from the beginning of anesthesia until full ambulation a risk of mortality of 0.7% and a risk of major bleeding of 0.8%. f. The baseline risk consists of event rates from observational study data including surgical patients without cancer. In patients undergoing all elective surgery Assareh et al. (2014) (a registry study) reported a risk of symptomatic VTE of 0.3%. Baseline risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% are symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. g. The baseline risk consists of event rates from observational study data including surgical patients with cancer. Yamaoka 2015 (a propensity score matched analysis, with N=591, and follow up time of 30 days) reported in patients undergoing colorectal cancer resection and using mechanical IPC prophylaxis from the beginning of anesthesia until full ambulation, a risk of symptomatic VTE of 0.2%. Baseline risk estimates for symptomatic PE (0.02%), symptomatic proximal DVT (0.036%) and symptomatic severe distal DVT (0.0072%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. h. The baseline risk consists of the control group event rate (1.5%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.075%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs i. Not downgraded for RoB, although majority of the studies had some risk of bias concern because they were not blinded or had insufficient information to make a judgment about risk of bias domains, a sensitivity analysis excluding studies with high RoB showed a similar effect with RR 3.80 (1.11 to 12.97), from 7 studies with 23 events in 2727 participants. j. Not downgraded for RoB, although majority of the studies had some risk of bias concern because they were not blinded or had insufficient information to make a judgment about risk of bias domains, a sensitivity analysis excluding studies with high RoB showed a similar effect with a RR 1.11 (0.01 to 86.80), from 2 studies with 3 events in 477 participants. k. Downgraded by two levels for very serious concerns about imprecision due to the very small number of events, with very wide confidence interval for the relative effect, including appreciable benefit and harm. l. The baseline risk consists of the control group event rate from trials including surgical cancer patients, i.e. the trials that included more than 50% of patients with cancer.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		Re-operation due to bleeding was also considered as a separate outcome. While the panel was interested in the outcome of reoperation due to bleeding or adverse events, based on the reporting in most studies we were unable to distinguish the cause of reoperation and were not aware of how many of these related to bleeding.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004)	

	Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological and mechanical prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015). For patients using mechanical methods to prevent VTE, in general patients would like to continue with the same method (Maxwell 2002). However, discomfort with the mechanical methods is a major complaint with this intervention (Brady 2007, Wade 2017). Most patients prefer knee-length stockings rather than thigh-length stockings (Wade 2017).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for mechanical prophylaxis (indirect evidence):** A health technology assessment (Dennis 2015) based on the CLOTS 3 trial, a multi-centre trial in the United Kingdom assessing use of intermittent pneumatic compression (IPC) for VTE prophylaxis in hospitalized immobile stroke patients, estimated an average cost of £64.10 ($99.36 in 2013 USD) per patient for the cost of sleeves, fitting and monitoring. The mean total hospital costs including IPC were estimated at £12,567 ($19,478 in 2013 USD). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as very low due to indirectness of the study populations and study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Six reports compared mechanical prophylaxis with pharmacological prophylaxis in surgical patients (Mamdani 1996, Maxwell 2000, Oster 1987, Vermahos 2000, Wade 2015, CE Writing 2012). Mechanical prophylaxis included external pneumatic compression, compression stocking, and sequential compression devices. Pharmacological prophylaxis compared included enoxaparin, low-dose heparin, dalteparin, UFH, LMWH. In general, the mechanical methods were cost-saving compared with pharmacological prophylaxis. Several reports suggested mechanical methods were cost-effective compared with pharmacological prophylaxis, except one report suggested low-dose heparin is more cost-effective than sequential compression devices (Velmahos 2000).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A study aiming to assess current thromboprophylaxis practice amongst neurosurgeons working in the United Kingdom found that over 90% of 62 respondents would initiate mechanical prophylaxis at admission, in each of the four cases addressed in the survey, which cover the major sub-types of traumatic brain injury with a range of VTE risk factors. There was greater variation on the decision to commence pharmacological prophylaxis (PTP) and consultants showed a higher willing to commence PTP across all cases, being low molecular weight heparin (LMWH) the favoured PTP agent in over 90% of respondents. There was significant variability in the timing of initiation of PTP within and between cases. The median times to commence PTP across all four cases ranged from 1 to 7 days (Jamjoom 2016).	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional devices (47%). Of patients using battery-powered devices, 14% reported major problems, which was 79% with conventional devices (Obi 2015). Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early (Cindolo 2009). A systematic review of observational studies (7 for compression devices, 1 for compression stockings) assessing patient adherence to mechanical thromboprophylaxis after surgery reported similar average adherence rates of 75% (range 40%-89%) in patients with shorter follow-up (≤3days) and in patients with longer follow-up (>3days) (Craigie 2015). **Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use (Arepally 2010). A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use (Cook 2014). Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk (Ginzburg 2011). **General barriers to implementation:** **Clinicians' low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system (McFarland 2014). A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries (Zairul-Nizam 2003). A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low (Arepally 2010). Lack of local guidelines Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013). In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65% (Schellong 2015). An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines (Saturno 2011).	

	General facilitators for implementation A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19% (Kahn 2013). A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives (Cook 2014).	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either pharmacological prophylaxis or mechanical prophylaxis in patients undergoing surgery (conditional recommendation based on low certainty in the evidence about effects.)

Justification

The trivial effect of the pharmacological on desirable outcomes does not outweigh the small effect on bleeding rates. However, the panel considered a balance not favouring either approaches due to the low certainty of the evidence together with the lack of information on the effectiveness, and feasibility of extended prophylaxis use of mechanical interventions, where compliance might be an issue.

In patients with a high risk of bleeding, the balance of effects may favour mechanical methods over pharmacological methods.

Subgroup considerations

The panel perceived it important to make distinction between different patient groups based on their baseline risk of bleeding depending on the type of surgical procedure.
In patients at high risk of bleeding, mechanical prophylaxis (alone) is preferred.
The panel further recognizes that due to the nature of the surgical procedure (for example: some lower extremity surgeries), mechanical prophylaxis may not be feasible in some settings.

Implementation considerations

Appropriate timing of the intervention administration should be ensured, following recommended starting and dosing algorithms for medication as per approved indications.
When mechanical devices interventions are selected, special considerations need to consider to ensure an appropriate compliance.
Some methods of mechanical prophylaxis may be not feasible following discharge from hospital.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies using appropriate clinical outcomes would be of value to add more certainty to this recommendation. One issue is the optimal duration of compression (hours per day) needed for VTE prevention with IPCD; further device standardization is encouraged.

QUESTION-2

Should mechanical combined with pharmacological prophylaxis vs. mechanical prophylaxis alone be used for surgical patients?	
POPULATION:	surgical patients
INTERVENTION:	mechanical combined with pharmacological prophylaxis
COMPARISON:	mechanical prophylaxis alone
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism -representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state ; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. Mechanical methods are another form of thromboprophylaxis for such patients undergoing surgical procedures. Such devices act to prevent venous stagnation in the lower limbs by promoting venous outflow. Mechanical methods include: graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD) and sequential compression devices (SCD). Unlike pharmacological agents, mechanical methods are not associated with an increased risk of bleeding. This EtD compares the effectiveness and safety of combined pharmacological and mechanical thromboprophylaxis with mechanical thromboprophylaxis alone in hospitalized patients undergoing surgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable. With VTE prevention strategies provided at physician discretion, a recent large registry study of several million surgical patients identified the rate of VTE during the index hospital admission for surgery of 0.2% (Assareh 2014). Symptomatic VTE post discharge in orthopedic and abdominal surgery patients, with VTE prevention provided by physician discretion, has been reported in 4.7% and 3.1% of patients respectively (Spyropoulos 2009).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with mechanical prophylaxis alone	Risk difference with mechanical combined with pharmacological prophylaxis
Mortality follow up: range 4 days to 90 days	3717 (13 RCTs)[a]	⨁⨁⨁◯ MODERATE[b]	**RR 1.24** (0.67 to 2.30)	Study population	
				16 per 1,000[a]	**4 more per 1,000** (5 fewer to 21 more)
				Low	
				9 per 1,000[c]	**2 more per 1,000** (3 fewer to 12 more)
				Moderate	
				7 per 1,000[d]	**2 more per 1,000** (2 fewer to 9 more)

ADDITIONAL CONSIDERATIONS

Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: Symptomatic PE follow up: range 4 days to 90 days	3909 (15 RCTs)	⊕⊕⊕◯ MODERATE[b,e]	**RR 0.34** (0.12 to 0.94)	Study population	
				8 per 1,000	**5 fewer per 1,000** (7 fewer to 0 fewer)
				Low	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: Symptomatic proximal DVT follow up: range 7 days to 90 days	982 (6 RCTs)	⊕⊕◯◯ LOW[h]	**RR 0.71** (0.07 to 6.75)	Study population	
				2 per 1,000	**1 fewer per 1,000** (2 fewer to 13 more)
				Low	
				1 per 1,000[f]	**0 fewer per 1,000** (1 fewer to 3 more)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 2 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Symptomatic distal DVT follow up:	932 (5 RCTs)	⊕⊕◯◯ LOW[b,h]	**RR 0.38** (0.06 to 2.42)	Low	
				1 per 1,000[i]	**0 fewer per 1,000** (1 fewer to 1 more)
				Moderate	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 0 fewer)

range 8 days to 90 days				High	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding follow up: range 7 days to 8 months	4174 (14 RCTs)	⊕⊕⊕◯ MODERATE[b,h]	**RR 1.64** (0.87 to 3.13)	Study population	
				12 per 1,000	**8 more per 1,000** (2 fewer to 25 more)
				Low	
				12 per 1,000[c]	**8 more per 1,000** (2 fewer to 26 more)
				Moderate	
				8 per 1,000[d]	**5 more per 1,000** (1 fewer to 17 more)
Reoperation follow up: range 7 days to 8 months	2092 (3 RCTs)	⊕⊕◯◯ LOW[b,h]	**RR 2.11** (0.42 to 10.70)	Study population	
				2 per 1,000	**2 more per 1,000** (1 fewer to 18 more)
				Low	
				2 per 1,000[c]	**2 more per 1,000** (1 fewer to 19 more)
				Moderate	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. The baseline risk for the study population consists of the control group event rate from studies that included surgical patients with cancer or without cancer.
b. Very few studies described concealment of allocation
c. The baseline risk consists of the control group event rate from trials including surgical non-cancer patients, i.e. the trials that included less than 50% of patients with cancer.

	d. The baseline risk consists of event rates from observational study data including surgical patients with cancer. Yamaoka 2015 (a propensity score matched analysis, with N=591, and follow up time of 30 days) reported in patients undergoing colorectal cancer resection and using mechanical IPC prophylaxis from the beginning of anesthesia until full ambulation a risk of mortality of 0.7% and a risk of major bleeding of 0.8%. e. Few or very few events, not enough to meet OIS criteria f. The baseline risk consists of event rates from observational study data including surgical patients without cancer. In patients undergoing all elective surgery Assareh et al. (2014) (a registry study) reported a risk of symptomatic VTE of 0.3%. Baseline risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% are symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. g. The baseline risk consists of event rates from observational study data including surgical patients with cancer. Yamaoka 2015 (a propensity score matched analysis, with N=591, and follow up time of 30 days) reported in patients undergoing colorectal cancer resection and using mechanical IPC prophylaxis from the beginning of anesthesia until full ambulation, a risk of symptomatic VTE of 0.2%. Baseline risk estimates for symptomatic PE (0.02%), symptomatic proximal DVT (0.036%) and symptomatic severe distal DVT (0.0072%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. h. Few events; confidence interval does not exclude a moderate or important harm from combination therapy i. The baseline risk consists of the control group event rate (1.2%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.06 %) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs j. The baseline risk consists of the control group event rate from trials including surgical cancer patients, i.e. the trials that included more than 50% of patients with cancer.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004)	

	Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological and mechanical prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015). For patients using mechanical methods to prevent VTE, in general patients would like to continue with the same method (Maxwell 2002). However, discomfort with the mechanical methods is a major complaint with this intervention (Brady 2007, Wade 2017). Most patients prefer knee-length stockings rather than thigh-length stockings (Wade 2017).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No research evidence was identified.	The panel considered the balance may favour one option over the other, when risk is stratified, for instance in patients with low risk of VTE and/or high risk of bleeding, the balance of effects may favour mechanical methods.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran£143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for mechanical prophylaxis (indirect evidence):** A health technology assessment (Dennis 2015) based on the CLOTS 3 trial, a multi-centre trial in the United Kingdom assessing use of intermittent pneumatic compression (IPC) for VTE prophylaxis in hospitalized immobile stroke patients, estimated an average cost of £64.10 ($99.36 in 2013 USD) per patient for the cost of sleeves, fitting and monitoring. The mean total hospital costs including IPC were estimated at £12,567 ($19,478 in 2013 USD). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December	

	2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as very low due to indirectness of the study populations and study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	We only identified two reports comparing mechanical combined with pharmacological prophylaxis vs. mechanical prophylaxis alone. One report compared the use of combination therapy external pneumatic compression with and without the addition of low-molecular-weight heparin, the combination prophylaxis is estimated to be cost-effective for high-risk gynecologic oncology patients undergoing surgery. One report compared six strategies including heparin plus stocking, and stocking only prophylaxis strategy. The study was published in 1987, suggesting cost per additional life saved was $82,333 for heparin combined stocking, compared with stocking only.	The panel considered the cost effectiveness may be achieved in patients with high-risk for VTE. While, for low VTE risk patients the comparison is favoured.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		The panel judged that there would probably be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional devices (47%). Of patients using battery-powered devices, 14% reported major problems, which was 79% with conventional devices (Obi 2015). Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early (Cindolo 2009). A systematic review of observational studies (7 for compression devices, 1 for compression stockings) assessing patient adherence to mechanical thromboprophylaxis after surgery reported similar average adherence rates of 75% (range 40%-89%) in patients with shorter follow-up (≤3days) and in patients with longer follow-up (>3days) (Craigie 2015). **Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use (Arepally 2010). A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use (Cook 2014). Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk	

	and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk (Ginzburg 2011). **General barriers to implementation:** **Clinicians' low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system (McFarland 2014). A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries (Zairul-Nizam 2003). A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low (Arepally 2010). Lack of local guidelines Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013). In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65% (Schellong 2015). An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines (Saturno 2011). **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19% (Kahn 2013). A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives (Cook 2014).	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either combined prophylaxis with mechanical and pharmacological methods or prophylaxis with mechanical methods alone in surgical patients (conditional recommendation based on low certainty of the evidence about effects).

Justification

The panel considered the balance of the small effect of the combined prophylaxis on both desirable and undesirable outcomes may favour one option over the other, when risk is stratified, for instance in patients with high VTE risk and/or low risk of bleeding the balance may favour combined approach while in patient with low risk of VTE and/or high risk of bleeding, the balance of effects may favour mechanical methods.

In patients at high risk of VTE, the balance of effects may favour combined prophylaxis over pharmacological methods, while in patients with high risk of bleeding, the balance of effects may favour mechanical methods over combined prophylaxis with pharmacological and mechanical methods

Subgroup considerations

The baseline risk of VTE and bleeding are important considerations and would depend on clinical characteristic as well as on surgery type.

Implementation considerations

Appropriate timing of the intervention administration should be ensured, following recommended starting and dosing algorithms for medication as per approved indications.
When mechanical devices interventions are selected, special considerations need to ensure appropriate compliance.

Monitoring and evaluation

None

Research priorities

The duration of compression (hours per day) needed for VTE prevention with IPCD; device standardization.
Studies enabling identification of baseline risk would be valuable to identify patients particularly likely to benefit from combined prophylaxis strategies.
Further high-quality studies using appropriate clinical endpoints would be of value to increase certainty of recommendation.

QUESTION-3

Should pharmacological combined with mechanical prophylaxis vs. pharmacological prophylaxis alone be used for surgical patients?	
POPULATION:	surgical patients
INTERVENTION:	pharmacological combined with mechanical prophylaxis
COMPARISON:	pharmacological prophylaxis alone
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state ; Major bleeding ; Reoperation ;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. Mechanical methods are another form of thromboprophylaxis for such patients undergoing surgical procedures. Such devices act to prevent venous stagnation in the lower limbs by promoting venous outflow. Mechanical methods include: graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD) and sequential compression devices (SCD). Unlike pharmacological agents, mechanical methods are not associated with an increased risk of bleeding. This EtD compares the effectiveness and safety of combined pharmacological and mechanical thromboprophylaxis with pharmacological thromboprophylaxis alone in hospitalized patients undergoing surgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable. With VTE prevention strategies provided at physician discretion, a recent large registry study of several million surgical patients identified the rate of VTE during the index hospital admission for surgery of 0.2% (Assareh 2014). Symptomatic VTE post discharge in orthopedic and abdominal surgery patients, with VTE prevention provided by physician discretion, has been reported in 4.7% and 3.1% of patients respectively (Spyropoulos 2009).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with mechanical prophylaxis alone	Risk difference with mechanical combined with pharmacological prophylaxis
Mortality follow up: range 4 days to 90 days	3717 (13 RCTs)[a]	⊕⊕⊕◯ MODERATE[b]	**RR 1.24** (0.67 to 2.30)	Study population	
				16 per 1,000[a]	**4 more per 1,000** (5 fewer to 21 more)
				Low	
				9 per 1,000[c]	**2 more per 1,000** (3 fewer to 12 more)
				Moderate	
				7 per 1,000[d]	**2 more per 1,000** (2 fewer to 9 more)
Symptomatic Pulmonary Embolism -	3909 (15 RCTs)	⊕⊕⊕◯ MODERATE[b,e]	**RR 0.34** (0.12 to 0.94)	Study population	
				8 per 1,000	**5 fewer per 1,000** (7 fewer to 0

representing the moderate marker state assessed with: Symptomatic PE follow up: range 4 days to 90 days					fewer)
				Low	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: Symptomatic proximal DVT follow up: range 7 days to 90 days	982 (6 RCTs)	⊕⊕◯◯ LOW[h]	**RR 0.71** (0.07 to 6.75)	Study population	
				2 per 1,000	**1 fewer per 1,000** (2 fewer to 13 more)
				Low	
				1 per 1,000[f]	**0 fewer per 1,000** (1 fewer to 3 more)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 2 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Symptomatic distal DVT follow up: range 8 days to 90 days	932 (5 RCTs)	⊕⊕◯◯ LOW[b,h]	**RR 0.38** (0.06 to 2.42)	Low	
				1 per 1,000[i]	**0 fewer per 1,000** (1 fewer to 1 more)
				Moderate	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding follow up: range 7 days to 8 months	4174 (14 RCTs)	⊕⊕⊕◯ MODERATE[b,h]	**RR 1.64** (0.87 to 3.13)	Study population	
				12 per 1,000	**8 more per 1,000** (2 fewer to 25 more)
				Low	
				12 per 1,000[c]	**8 more per 1,000**

					(2 fewer to 26 more)
				Moderate	
				8 per 1,000[d]	**5 more per 1,000** (1 fewer to 17 more)
Reoperation follow up: range 7 days to 8 months	2092 (3 RCTs)	⊕⊕◯◯ LOW[b,h]	**RR 2.11** (0.42 to 10.70)	Study population	
				2 per 1,000	**2 more per 1,000** (1 fewer to 18 more)
				Low	
				2 per 1,000[c]	**2 more per 1,000** (1 fewer to 19 more)
				Moderate	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. The baseline risk for the study population consists of the control group event rate from studies that included surgical patients with cancer or without cancer.
b. Very few studies described concealment of allocation
c. The baseline risk consists of the control group event rate from trials including surgical non-cancer patients, i.e. the trials that included less than 50% of patients with cancer.
d. The baseline risk consists of event rates from observational study data including surgical patients with cancer. Yamaoka 2015 (a propensity score matched analysis, with N=591, and follow up time of 30 days) reported in patients undergoing colorectal cancer resection and using mechanical IPC prophylaxis from the beginning of anesthesia until full ambulation a risk of mortality of 0.7% and a risk of major bleeding of 0.8%.
e. Few or very few events, not enough to meet OIS criteria
f. The baseline risk consists of event rates from observational study data including surgical patients without cancer. In patients undergoing all elective surgery Assareh et al. (2014) (a registry study) reported a risk of symptomatic VTE of 0.3%. Baseline risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% are symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome.
g. The baseline risk consists of event rates from observational study data including surgical patients with cancer. Yamaoka 2015 (a propensity score matched analysis, with N=591, and follow up time of 30 days) reported in patients undergoing colorectal cancer resection and using mechanical IPC prophylaxis from the beginning of anesthesia until full ambulation, a risk of symptomatic VTE of 0.2%. Baseline risk estimates for symptomatic PE (0.02%), symptomatic proximal DVT (0.036%) and

	symptomatic severe distal DVT (0.0072%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. h. Few events; confidence interval does not exclude a moderate or important harm from combination therapy i. The baseline risk consists of the control group event rate (1.2%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.06 %) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs j. The baseline risk consists of the control group event rate from trials including surgical cancer patients, i.e. the trials that included more than 50% of patients with cancer.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015).	

	Studies additionally described the following regarding patients' experiences and preferences for pharmacological and mechanical prophylaxis: For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015). For patients using mechanical methods to prevent VTE, in general patients would like to continue with the same method (Maxwell 2002). However, discomfort with the mechanical methods is a major complaint with this intervention (Brady 2007, Wade 2017). Most patients prefer knee-length stockings rather than thigh-length stockings (Wade 2017).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for mechanical prophylaxis (indirect evidence):** A health technology assessment (Dennis 2015) based on the CLOTS 3 trial, a multi-centre trial in the United Kingdom assessing use of intermittent pneumatic compression (IPC) for VTE prophylaxis in hospitalized immobile stroke patients, estimated an average cost of £64.10 ($99.36 in 2013 USD) per patient for the cost of sleeves, fitting and monitoring. The mean total hospital costs including IPC were estimated at £12,567 ($19,478 in 2013 USD). **Costs of disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as very low due to indirectness of the study populations and study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Two reports compared the cost-effectiveness of pharmacological combined with mechanical prophylaxis vs. pharmacological prophylaxis. One report suggested stocking plus heparin cost $15,000 additionally to save a life. A recent health technology report concluded the adjunctive use of GCSs appears to represent good value for money to the NHS across the different populations considered (Oster 1987, Wade 2015).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A SR, which includes nine randomised controlled trials and seven observational studies, exploring patient preference and adherence to thigh and knee length graduated compression stockings for the prevention of deep vein thrombosis in surgical patients, showed that patients preferred knee length stockings over thigh length stockings. Many of included studies in the SR were poorly reported with an unclear risk of bias (Wade 2016). A CCT study including 105 gynecology patients undergoing exploratory laparotomy, assessed patient's knowledge of risk and prevention of postoperative venous thromboembolism (VTE). It shows that providing patients with a simple educational pamphlet significantly increased patient's self-perceived knowledge of SCDs ((73.1% reported their knowledge as 'very good' compared with a 30.2% in the group without education), actual knowledge of VTE (92.3% vs. 73.6% with correct answer on when to wear SCD), and compliance with SCDs on postoperative day one (53.9% in the education group vs. 30.2% in the control group (Nahar 2016). A study aiming to assess current thromboprophylaxis practice amongst neurosurgeons working in the United Kingdom found that over 90% of 62 respondents would initiate mechanical prophylaxis (MTP) at admission, in each of the four cases addressed in the survey, which cover the major sub-types of traumatic brain injury with a range of VTE risk factors. There was greater variation on the decision to commence pharmacological prophylaxis (PTP) and consultants showed a higher willing to commence PTP across all cases, being low molecular weight heparin (LMWH) the favoured PTP agent in over 90% of respondents. There was significant variability in the timing of initiation of PTP within and between cases. The median times to commence PTP across all four cases ranged from 1 to 7 days (Jamjoom 2016).	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional devices (47%). Of patients using battery-powered devices, 14% reported major problems, which was 79% with conventional devices (Obi 2015). Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early (Cindolo 2009). A systematic review of observational studies (7 for compression devices, 1 for compression stockings) assessing patient adherence to mechanical thromboprophylaxis after surgery reported similar average adherence rates of 75% (range 40%-89%) in patients with shorter follow-up (≤3days) and in patients with longer follow-up (>3days) (Craigie 2015). **Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use (Arepally 2010). A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use (Cook 2014). Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk (Ginzburg 2011). **General barriers to implementation:** **Clinicians' low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system (McFarland 2014). A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as	

	common a problem in Malaysia as in western countries (Zairul-Nizam 2003). A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low (Arepally 2010). Lack of local guidelines Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013). In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65% (Schellong 2015). An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines (Saturno 2011). **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19% (Kahn 2013). A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives (Cook 2014).	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using combined prophylaxis with mechanical and pharmacological methods over prophylaxis with pharmacological agents alone in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The moderate effects of the combined interventions prophylaxis on desirable effect probably outweigh the trivial effect on harms. However, there is a very low certainty of the evidence and possibly important variability on patients' values and preferences. Although the cost of the intervention was considered to be moderate, it was nevertheless considered to probably be cost-effective. There are no equity, acceptability or feasibility concerns for the implementation of the combined pharmacological and mechanical intervention.

The panel found a likely net benefit in favor of combined prophylaxis. Given the underlying uncertainty in the setting of low quality evidence, this is conditional recommendation. Contributing factors were further uncertainty about patients' values and preferences and their variability, the costs associated with IPCD and resulting issues of equity.

Subgroup considerations

The panel considered the balance of the moderate effect of the combined prophylaxis on desirable outcomes. In patients with high VTE risk would particularly favour the combined approach.

Implementation considerations

Appropriate timing of the intervention administration should be ensured, following recommended starting and dosing algorithms for medication as per approved indications.
When mechanical devices interventions are selected, special considerations need to consider to ensure an appropriate compliance.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies using appropriate clinical outcomes would be of value to add more certainty to this recommendation.
Studies enabling identification of baseline risk would be valuable to identify patients particularly likely to benefit from combined prophylaxis strategies.
The duration of compression (hours per day) needed for VTE prevention with IPCD; device standardization.

QUESTION-4

Should pneumatic compression prophylaxis vs. graduated compression stockings be used for surgical patients?	
POPULATION:	surgical patients
INTERVENTION:	pneumatic compression prophylaxis
COMPARISON:	graduated compression stockings
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). Mechanical methods are another form of thromboprophylaxis for such patients undergoing surgical procedures. Such devices act to prevent venous stagnation in the lower limbs by promoting venous outflow. Mechanical methods include: graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD) and sequential compression devices (SCD). Unlike pharmacological agents, mechanical methods are not associated with an increased risk of bleeding. This EtD compares the effectiveness and safety of mechanical prophylaxis using IPCD and SCD devices with GCS in hospitalized patients undergoing surgical procedures.

ASSESSMENT

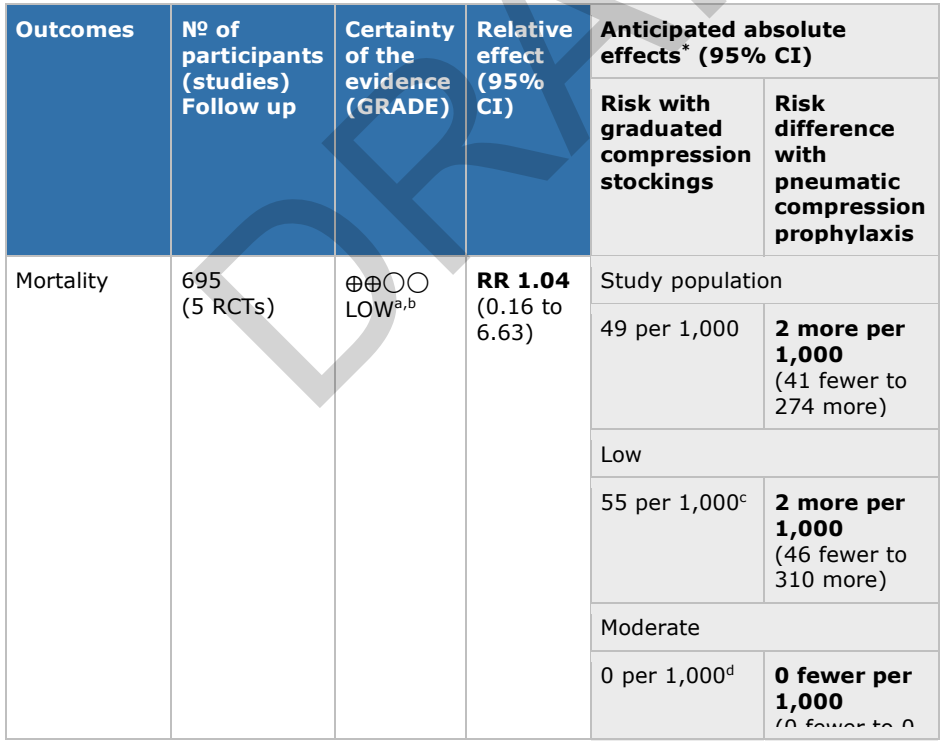
Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable. With VTE prevention strategies provided at physician discretion, a recent large registry study of several million surgical patients identified the rate of VTE during the index hospital admission for surgery of 0.2% (Assareh 2014). Symptomatic VTE post discharge in orthopedic and abdominal surgery patients, with VTE prevention provided by physician discretion, has been reported in 4.7% and 3.1% of patients respectively (Spyropoulos 2009).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		The panel discussed if the magnitude of the effect was moderate or small, and decided on a judgement of small.

					fewer)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: symptomatic PE	1077 (8 RCTs)	⊕⊕◯◯ LOW[a,e]	**RR 0.56** (0.17 to 1.86)[f]	Study population	
				17 per 1,000	**7 fewer per 1,000** (14 fewer to 14 more)
				Low	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				16 per 1,000[d]	**7 fewer per 1,000** (13 fewer to 14 more)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: symptomatic proximal DVT	100 (1 RCT)	⊕◯◯◯ VERY LOW[a,e]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Low	
				1 per 1,000[g]	**1 fewer per 1,000** (1 fewer to 1 fewer)
				Moderate	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any proximal DVT	1089 (6 RCTs)	⊕◯◯◯ VERY LOW[a,e,i]	**RR 0.48** (0.25 to 0.92)	Low	
				10 per 1,000[j]	**5 fewer per 1,000** (8 fewer to 1 fewer)
				Moderate	
				1 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0

					fewer)
				High	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Symptomatic distal DVT follow up: mean 1 months	100 (1 RCT)	⨁◯◯◯ VERY LOW[a,e]	not estimable	Low	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[k]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Any distal DVT follow up: mean 1 months	989 (5 RCTs)	⨁◯◯◯ VERY LOW[a,b,i,l]	**RR 0.55** (0.25 to 1.22)	Low	
				1 per 1,000[m]	**1 fewer per 1,000** (1 fewer to 0 fewer)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. No study described allocation concealment and they were not blinded.
b. Small number of events and/or sample size. The confidence interval does not exclude an important harm.
c. The baseline risk consists of the control group event rate from trials including

	surgical non-cancer patients, i.e. the trials that included less than 50% of patients with cancer. d. The baseline risk consists of the control group event rate from trials including surgical cancer patients, i.e. the trials that included more than 50% of patients with cancer. e. Very small number of events, not enough to meet OIS f. The estimate based on the measure of "any PE" from 4 trials with 2 events in 394 participants was RR 0.34 (95% CI [0.04, 3.24]). g. The baseline risk consists of event rates from observational study data including surgical patients without cancer. In patients undergoing all elective surgery Assareh et al. (2014) (a registry study) reported a risk of symptomatic VTE of 0.3%. Baseline risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% are symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. h. There are no studies including more than 50% of cancer patients and no observed BLR data was identified for the cancer population. i. Screening detected events. j. The baseline risk estimate for symptomatic proximal DVT (1%) based on event rates from control group of included studies in the meta-analysis (5%) and the assumptions that 20% of any proximal DVT are symptomatic proximal DVT episodes. k. The baseline risk consists of the control group event rate (0%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs l. Unexplained inconsistency, I-square= 63% m. The baseline risk estimate for symptomatic distal DVT (0.148%) based on event rates from control group of included studies in the meta-analysis (14.8%) and the assumptions that 20% of any distal DVT are symptomatic distal DVT episodes and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome.	
Undesirable Effects		

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		There were no adverse effects considered critical. There are possible adverse effects that were not judged as critical such as decreasing mobility. Also, the devices can be uncomfortable. Harms can result in some patients such as those with fractures of the leg.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Studies additionally described the following regarding patients' experiences and preferences for VTE**	No bleeding trade off. However, the variability about how much people value PE and DVT alone was considered important.

	prophylaxis: Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological and mechanical prophylaxis:** For patients using mechanical methods to prevent VTE, in general patients would like to continue with the same method (Maxwell 2002). However, discomfort with the mechanical methods is a major complaint with this intervention (Brady 2007, Wade 2017). Most patients prefer knee-length stockings rather than thigh-length stockings (Wade 2017).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for mechanical prophylaxis (indirect evidence):** A health technology assessment (Dennis 2015) based on the CLOTS 3 trial, a multi-centre trial in the United Kingdom assessing use of intermittent pneumatic compression (IPC) for VTE prophylaxis in hospitalized immobile stroke patients, estimated an average cost of £64.10 ($99.36 in 2013 USD) per patient for the cost of sleeves, fitting and monitoring. The mean total hospital costs including IPC were estimated at £12,567 ($19,478 in 2013 USD). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710.	

	See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as very low due to indirectness of the study populations and study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No direct research evidence identified comparing the cost-effectiveness of pneumatic compression prophylaxis vs. graduated compression stockings in surgical patients. Indirect evidence from two reports comparing mechanical prophylaxis with no prophylaxis in surgical patients, showed that prophylaxis reduces the risk of VTE, but also increases the cost; in general, the mechanical prophylaxis is cost-effective (The ICER for IPC in the US healthcare system perspective study was $39,545 per QALY gained and the cost-effectiveness ratio less than $40,000/mortality avoided IPC according to other study), although the cost-effectiveness of mechanical prophylaxis strategies depends on the types of prophylaxis. (Casele 2006, Mamdani 1996)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would probably be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	Patient's view (panel member) was that mechanical interventions are acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional devices (47%). Of patients using battery-powered devices, 14% reported major problems, which was 79% with conventional devices (Obi 2015). Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early (Cindolo 2009). A systematic review of observational studies (7 for compression devices, 1 for compression stockings) assessing patient adherence to mechanical thromboprophylaxis after surgery reported similar average adherence rates of 75% (range 40%-89%) in patients with shorter follow-up (≤3days) and in patients with longer follow-up (>3days) (Craigie 2015). **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using Intermittent Compression Devices over Graduated Compression Stockings in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The panel considered the balance probably favours the IPC devices, although acknowledged the very low certainty of the evidence, and concerns about the impact on health equity in settings where IPC is not available. Overall, IPC is considered acceptable and feasible.

Subgroup considerations

A limitation of this data is most of the evidence comes from orthopaedics (elective hip and knee arthroplasty).

Implementation considerations

When mechanical devices interventions are selected, special considerations need to consider to ensure an appropriate compliance.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies using appropriate clinical outcomes would be of value to add more certainty to this recommendation.
The duration of compression (hours per day) needed for VTE prevention with IPCD; device standardization.
Studies in settings other than orthopedic would warranted.

QUESTION-5

Should mechanical prophylaxis vs. no prophylaxis be used for surgical patients?	
POPULATION:	surgical patients
INTERVENTION:	mechanical prophylaxis
COMPARISON:	no prophylaxis
MAIN OUTCOMES:	Mortality ; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). Mechanical methods are another form of thromboprophylaxis for such patients undergoing surgical procedures. Such devices act to prevent venous stagnation in the lower limbs by promoting venous outflow. Mechanical methods include: graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD) and sequential compression devices (SCD). Unlike pharmacological agents, mechanical methods are not associated with an increased risk of bleeding. This EtD compares the effectiveness and safety of any mechanical thromboprophylaxis with no thromboprophylaxis in hospitalized patients undergoing surgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable. With VTE prevention strategies provided at physician discretion, a recent large registry study of several million surgical patients identified the rate of VTE during the index hospital admission for surgery of 0.2% (Assareh 2014). Symptomatic VTE post discharge in orthopedic and abdominal surgery patients, with VTE prevention provided by physician discretion, has been reported in 4.7% and 3.1% of patients respectively (Spyropoulos 2009).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no prophylaxis	Risk difference with mechanical prophylaxis
Mortality	1555 (10 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.33** (0.71 to 2.51)	Study population	
				19 per 1,000	**6 more per 1,000** (5 fewer to 28 more)
				Low	
				19 per 1,000[c]	**6 more per 1,000** (6 fewer to 29 more)
				Moderate	
				0 per 1,000[d]	**0 fewer per 1,000** (0 fewer to 0

					fewer)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: symptomatic PE	1469 (9 RCTs)	⊕⊕◯◯ LOW[b,e]	**RR 0.61** (0.27 to 1.40)[f]	Study population	
				22 per 1,000	**9 fewer per 1,000** (16 fewer to 9 more)
				Low	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[d]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any proximal DVT	1575 (8 RCTs)	⊕◯◯◯ VERY LOW[b,h,i,j]	**RR 0.85** (0.41 to 1.75)	Low	
				19 per 1,000[k]	**3 fewer per 1,000** (11 fewer to 15 more)
				Moderate	
				1 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				2 per 1,000[l]	**0 fewer per 1,000** (1 fewer to 2 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: any distal DVT	961 (7 RCTs)	⊕◯◯◯ VERY LOW[m,n,o]	**RR 0.66** (0.50 to 0.86)	Low	
				2 per 1,000[p]	**1 fewer per 1,000** (1 fewer to 0 fewer)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0

					fewer)
				High	
				1 per 1,000[q]	**0 fewer per 1,000** (1 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state - not reported	-	-	-	**-**	**-**
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state - not reported	-	-	-	**-**	**-**

a. None of the studies use placebo, although in five the assessors were blinded. In six studies the randomization and/or allocation concealment was not (adequately) reported.
b. Small number of events. Confidence interval does not exclude an appreciable benefit or an appreciable harm with mechanical prophylaxis
c. The baseline risk consists of the control group event rate from trials including surgical non-cancer patients, i.e. the trials that included less than 50% of patients with cancer.
d. There are no studies including more than 50% of cancer patients and no observed BLR data was identified for the cancer population.
e. None of the studies use placebo, although in four the assessors were blinded. In six studies the allocation concealment was not (adequately) reported.
f. The estimate based on the measure of "any PE" from 5 trials with 12 events in 451 participants was RR 1.01 (95% CI [0.24, 4.26])
g. The baseline risk consists of event rates from observational study data including surgical patients without cancer. In patients undergoing all elective surgery Assareh et al. (2014) (a registry study) reported a risk of symptomatic VTE of 0.3%. Baseline risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% are symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be

	severe DVTs and, therefore, considered a critical outcome. h. There is inconsistency supported by differences in estimation points, high I2 value (57%), and statistically significant heterogeneity of effect estimate (p=0.02). i. Studies reporting any proximal DVT, rather than symptomatic. j. None of the studies use placebo, although in three the assessors were blinded. In four studies the randomization and/or allocation concealment was not (adequately) reported. k. The baseline risk estimate for symptomatic proximal DVT (1.94%) based on event rates from control group of included studies in the meta-analysis (9.7%) and the assumptions that 20% of any proximal DVT are symptomatic proximal DVT episodes. l. The baseline risk for symptomatic proximal DVT (0.2%) consists of the control group event rate from trials that included more than 50% of patients with cancer (1%) and the assumptions that 20% of any proximal DVT are symptomatic proximal DVT episodes. m. None of the studies use placebo, and only in one, the assessors were blinded. In three studies the allocation concealment was not (adequately) reported. n. Studies reporting any distal DVT, rather than symptomatic. o. Sample size or number of events does not meet the optimal information size p. The baseline risk estimates for distal proximal DVT (0.213%) based on event rates from control group of included studies in the meta-analysis (21.3%) and the assumptions that 20% of any distal DVT are symptomatic distal DVT episodes and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. q. The baseline risk for symptomatic distal DVT (0.103%) consists of the control group event rate from trials that included more than 50% of patients with cancer (10.3%) and the assumptions that 20% of any distal DVT are symptomatic distal DVT episodes and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		No adverse effects considered critical. The panel discussed the possible adverse effects that were not judged as critical (causing immobility). Some patients find mechanical devices uncomfortable. Harms can result from inappropriate effects (such as patients with fractures)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological and mechanical prophylaxis:** For patients using mechanical methods to prevent VTE, in general patients would like to continue with the same method (Maxwell 2002). However, discomfort with the mechanical methods is a major complaint with this intervention (Brady 2007, Wade 2017). Most patients prefer knee-length stockings rather than thigh-length stockings (Wade 2017).	No bleeding trade off. However, the variability about how much people value PE and DVT alone was considered important.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for mechanical prophylaxis (indirect evidence):** A health technology assessment (Dennis 2015) based on the CLOTS 3 trial, a multi-centre trial in the United Kingdom assessing use of intermittent pneumatic compression (IPC) for VTE prophylaxis in hospitalized immobile stroke patients, estimated an average cost of £64.10 ($99.36 in 2013 USD) per patient for the cost of sleeves, fitting and monitoring. The mean total hospital costs including IPC were estimated at £12,567 ($19,478 in 2013 USD). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleedingwere $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as very low due to indirectness of the study populations and study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Two reports were identified comparing mechanical prophylaxis with no prophylaxis in surgical patients. Prophylaxis reduces the risk of VTE, but also increases the cost; in general, the mechanical prophylaxis is cost-effective, but the cost-effectiveness of mechanical prophylaxis strategies depends on the types of prophylaxis (Casele 2006, Mamdani 1996).	The panel considered the higher cost of IPC devices compared to stockings.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	Patient's view (panel member) was that mechanical interventions are acceptable to most stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional devices (47%). Of patients using battery-powered devices, 14% reported major problems, which was 79% with conventional devices (Obi 2015). Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early (Cindolo 2009). A systematic review of observational studies (7 for compression devices, 1 for compression stockings) assessing patient adherence to mechanical thromboprophylaxis after surgery reported similar average adherence rates of 75% (range 40%-89%) in patients with shorter follow-up (≤3days) and in patients with longer follow-up (>3days) (Craigie 2015). **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using mechanical prophylaxis over no mechanical prophylaxis in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The panel considered the balance probably favors the mechanical interventions, although acknowledged the very low certainty of the evidence, the possibly important variability on patient's values and preferences and concerns about the impact on health equity in settings where IPC is not available. Overall, IPC is considered acceptable and feasible. The panel recognizes the variety of different IPCD available (uniform, sequential, battery operated).

This recommendation applies to patients that are considered at risk of VTE.

Subgroup considerations

A limitation of this data is most of the evidence comes from orthopaedics (elective hip and knee arthroplasty).

Implementation considerations

When mechanical devices interventions are selected, special considerations need to consider to ensure appropriate compliance.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies using appropriate clinical outcomes would be of value to add more certainty to this recommendation.
The duration of compression (hours per day) needed for VTE prevention with IPCD; device standardization.
High quality comparative studies outside the orthopedics setting would particularly be warranted.

QUESTION-6

Should insertion of an inferior vena cava (IVC) filter vs. no IVC filter be used for surgical patients?	
POPULATION:	surgical patients
INTERVENTION:	insertion of an inferior vena cava (IVC) filter
COMPARISON:	no IVC filter
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state ;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). One method used to prevent PE is an IVC filter, which is a device placed in the inferior vena cava designed to capture an embolism from a DVT and prevents of its passage to the pulmonary arteries. This EtD compares the effectiveness and safety of the use of an IVC filter as a thromboprophylaxis measure with no IVC filter in hospitalized patients undergoing major surgical procedures or experiencing major trauma.

ASSESSMENT

Problem

Is the problem a priority?

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable. IVC filters are commonly used in clinical practice as a prophylactic measure to prevent pulmonary embolism in high risk surgical settings.	

Desirable Effects

How substantial are the desirable anticipated effects?

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no IVC filter	Risk difference with insertion of an inferior vena cava (IVC) filter
Mortality assessed with: all cause mortality	143680 (12 observational studies)[a]	⊕◯◯◯ VERY LOW[b,c,d]	**RR 1.38** (0.81 to 2.37)	Study population	
				11 per 1,000	**4 more per 1,000** (2 fewer to 15 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: symptomatic PE	869 (5 observational studies)[a]	⊕◯◯◯ VERY LOW[e,f,g]	**RR 0.29** (0.11 to 0.80)[h]	Study population	
				51 per 1,000	**37 fewer per 1,000** (46 fewer to 10 fewer)
				Low	
				0 per 1,000[i]	**0 fewer per 1,000** (0 fewer to

The panel was concerned about the feasibility of addressing this question, as only a very small RCT was identified. The panel had reservation about considering evidence from observational studies, However, after a discussion and voting the decision was to additionally consider observational studies in order to provide a recommendation based on the best available evidence, for this prioritized question.

					0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any proximal DVT	47 (1 observational study)	⊕◯◯◯ VERY LOW[j,k,l]	**RR 0.32** (0.07 to 1.42)	Low	
				52 per 1,000[m]	**35 fewer per 1,000** (49 fewer to 22 more)
				Moderate	
				1 per 1,000[i]	**0 fewer per 1,000** (1 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any DVT	142127 (10 observational studies)[a]	⊕◯◯◯ VERY LOW[b,n,o]	**RR 2.19** (1.07 to 4.50)	Low	
				1 per 1,000[i]	**1 more per 1,000** (0 fewer to 2 more)
				Moderate	
				0 per 1,000[p]	**0 fewer per 1,000** (0 fewer to 1 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: any DVT	142080 (9 observational studies)[a]	⊕◯◯◯ VERY LOW[b,q,r]	**RR 2.72** (1.41 to 5.21)	Low	
				0 per 1,000[s]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[i]	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. The body of evidence consists of observational studies and one RCT (Rajasekhar 2011), from which the estimates of effect were pooled.
b. Serious risk of bias.
c. The wide confidence interval does not exclude a benefit or an important harm of the intervention
d. Differences in point estimate. Unexplained inconsistency I2=57%, statistical heterogeneity p= 0.01.
e. Two studies considered a historical control.
f. Patients included are surgically treated cancer patients and trauma patients. They may not entirely represent the population of

	interest. g. Small number of events. h. There were altogether 15 studies providing very low certainty evidence that reported any PE; there were 421 events among 172448 patients; RR would be 0.63 (0.30 to 1.34) with an absolute risk difference of 1 fewer per 1000 (from 2 fewer to 1 more) at studies' control group risk; and with an absolute risk differences of 0 fewer (from 0 fewer to 0 more) at the estimated risk of 0.03% i. The baseline risk consists of event rates from observational study data including surgical patients without cancer. In patients undergoing all elective surgery Assareh et al. (2014) (a registry study) reported a risk of symptomatic VTE of 0.3%. Baseline risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) have been calculated applying the assumptions that 10% of all symptomatic VTEs are PE episodes and 90% are DVT episodes, of which 20% are symptomatic proximal DVTs and 80% are symptomatic distal DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. j. Review of the charts of patients from a musculoskeletal oncology database. There was no control of the possible confounding. Insertion of the filter based on attending surgeon preference. k. Patients surgically treated for pathologic lower extremity fractures from metastatic malignancies: they may be not representative of the population of interest. l. Small number of patients considered and events identified. Wide confidence interval not excluding important benefits or harms. m. The baseline risk estimate for symptomatic proximal DVT (5.2%) based on event rates from control group of included studies in the meta-analysis (26.1%) and the assumptions that 20% of any Proximal DVT are symptomatic proximal DVT events. n. Eight studies reporting any DVT which is used as a surrogate for symptomatic proximal DVT. One study reporting on symptomatic DVT (any proximal or distal) and another one on any proximal DVT. o. Differences in point estimate. Unexplained inconsistency I2=77%, statistical heterogeneity p< 0.01. p. The baseline risk estimate for symptomatic proximal DVT (0.02%) based on event rates from control group of included studies in the meta-analysis (0.5%) and the assumptions that 20% of any DVT are any symptomatic DVT and that 20% of those are symptomatic proximal DVT events. q. Differences in point estimate. Unexplained inconsistency I2=70%, statistical heterogeneity p<0.01. r. Eight studies reporting any DVT and used as a surrogate for symptomatic distal DVT, one study reporting as symptomatic DVT (any proximal or distal). s. The baseline risk estimate for symptomatic distal DVT (0.004%) based on event rates from control group of included studies in the meta-analysis (0.5%) and the assumptions that 20% of any DVT are symptomatic DVT episodes, being the 80% of those symptomatic distal DVT and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93**(different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99**(different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:**	

	Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **No research evidence was identified regarding patients' experiences and preferences specifically for use of IVC filters for thromboprophylaxis.**	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Cost of interventions:** Indirect Evidence from IVC utilization for treatment: Conners et al. 2002 reported the cost of different IVC placements: The average hospital charges related to filter placement were $4558 for patients who underwent IVC filter placement in the angiography suite and $2170 for patients who underwent duplex scan–directed bedside placement, which yielded a mean difference of $2388. Ebaugh et al. 2011 reported the cost of different IVC placements: Hospital charges for eight patients undergoing IVUS VCF placement were compared with those of eleven controls (5 men, 6 women; age range, 37-84 years; mean, 61 years) undergoing conventional VCF placement during the same time period. The estimated total difference in dollars saved was $14,092, if this savings is extended to all 26 patients. Cost analysis (excluding physician services) showed an even greater potential for savings, because the cost for an individual IVUS procedure was $880 less than conventional placement. **Cost of interventions: (additional sources):** According to the Medicare CPT (Current Procedural Terminology), the reimbursement amount for IVC Filter Placement is $3,795.28. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	The panel considered there would also be an additional cost related to the removal of the devices, compared with the no use of IVC.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Two studies compared the cost-effectiveness of IVC vs no IVC in surgical patients. Compared with no prophylaxis, the cost of prevent a PE was $93,700; while another study concluded the expected QALYs were similar for pneumatic compression device (PDC), PDC plus weekly serial Doppler ultrasound (SDU) and prophylactic vena cava filter (VCF), but the prophylaxis VCF was the most costly strategy. The site of placing VCF is a key factor to influence the cost of IVC. (Brasel 1997, Tola 1999) Another cost comparison study demonstrated the cost-saving when it is placed in the ICU compared with radiology suites and operation room. (Chiasson 2009)	

Equity

What would be the impact on health equity?

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	

Acceptability

Is the intervention acceptable to key stakeholders?

○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	Probably not acceptable to all groups (patients, providers, administrators).

Feasibility Is the intervention feasible to implement?		
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	The panel considered the intervention might not be available in many settings.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests not using Inferior Vena Cava Filter in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The evidence from observational studies with a very low certainty showed a possible increased harm and a cost cost-effectiveness that was considered as probably favouring not using IVC filters. Moreover, there were concerns about its acceptability by stakeholders and its feasibility as a prophylaxis intervention, as it is not available in many of the settings.

Subgroup considerations

None

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

Well-designed randomized controlled trials evaluating IVC filters in the prophylactic setting are needed to determine if use of these agents should be considered in any setting for the reduction of life-threatening symptomatic pulmonary embolism.

QUESTION-7

Should extended course prophylaxis vs. standard course antithrombotic prophylaxis be used for surgical patients?	
POPULATION:	surgical patients
INTERVENTION:	extended course prophylaxis
COMPARISON:	standard course antithrombotic prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state (assessed with: symptomatic PE); Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state ; Major bleeding ; Reoperation ;
SETTING:	inpatient and outpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. Patients often continue to have limited mobility after surgery even when they are discharged from the hospital. Many patients will require inpatient rehabilitation or rehab at home. Therefore, the role for extended antithrombotic prophylaxis has been investigated. Trends towards outpatient surgeries and shorter recovery times may translate to more postoperative VTE occurring after hospital discharge. This may provide a rationale for extended VTE prophylaxis after hospital discharge. This EtD compares the effectiveness and safety of the use of extended course of pharmacological thromboprophylaxis with a standard course of pharmacological thromboprophylaxis in hospitalized patients undergoing surgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The risk of VTE in surgical patients extends beyond the acute hospitalization period due to being a pro-thrombotic state and reduced mobility. Therefore, extending the period of time for antithrombotic prophylaxis is being investigated. Extension of the prophylaxis period may be associated with increased bleeding risks as well as cost and inconvenience for patients. In one study longitudinal cohort study post-discharge VTE accounted for 64.8% of all recorded VTE and was independently predictive od 90-day mortality (Bouras et al. 2015). Another study in hip and knee arthroplasty patients showed that by including post-discharge VTE events in addition to pre-discharge VTE events, the quality rankings of hospitals based on postoperative VTE changed significantly (Kester et al. 2014).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard course antithrombotic prophylaxis	Risk difference with extended course prophylaxis
Mortality	4574 (11 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.98** (0.64 to 1.49)	Study population	
				20 per 1,000	**0 fewer per 1,000** (7 fewer to 10 more)
				Low	
				10 per 1,000[b]	**0 fewer per 1,000** (4 fewer to 5 more)
				Moderate	
				42 per 1,000[c]	**1 fewer per 1,000** (15 fewer to

					21 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state (assessed with: symptomatic PE)	4603 (11 RCTs)	⊕⊕⊕◯ MODERATE[d]	**RR 0.31** (0.10 to 0.98)	Study population	
				5 per 1,000	**4 fewer per 1,000** (5 fewer to 0 fewer)
				Moderate	
				0 per 1,000[e]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				1 per 1,000[f]	**1 fewer per 1,000** (1 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any proximal DVT	4546 (12 RCTs)	⊕⊕⊕◯ MODERATE[g]	**RR 0.25** (0.17 to 0.37)	Low	
				11 per 1,000[h]	**9 fewer per 1,000** (9 fewer to 7 fewer)
				Moderate	
				1 per 1,000[e]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				1 per 1,000[f]	**1 fewer per 1,000** (1 fewer to 1 fewer)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: any distal DVT	3732 (10 RCTs)	⊕⊕⊕◯ MODERATE[i]	**RR 0.62** (0.41 to 0.94)	Low	
				1 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 0

					fewer)
				High	
				0 per 1,000[f]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding	4708 (11 RCTs)	⊕⊕◯◯ LOW[a]	**RR 0.88** (0.38 to 2.00)	Study population	
				6 per 1,000	**1 fewer per 1,000** (4 fewer to 6 more)
				Low	
				3 per 1,000[b]	**0 fewer per 1,000** (2 fewer to 3 more)
				Moderate	
				10 per 1,000[c]	**1 fewer per 1,000** (6 fewer to 10 more)
Reoperation	576 (3 RCTs)	⊕◯◯◯ VERY LOW[a,k]	**RR 1.54** (0.20 to 12.10)	Study population	
				10 per 1,000	**6 more per 1,000** (8 fewer to 115 more)
				Low	
				6 per 1,000[b]	**3 more per 1,000** (5 fewer to 67 more)
				Moderate	
				18 per 1,000[c]	**10 more per 1,000** (14 fewer to 200 more)

a. Small number of events. The confidence interval doesn't exclude an important benefit or harm
b. Risk in control groups of studies with =<50% of participants with cancer
c. Risk in control groups of studies with >50% of participants with cancer

	d. Very small number of events not meeting the optimal information size. e. In patients undergoing all elective surgery (registry type study), Assareh et al. (2014) reported, a risk of symptomatic VTE of 0.3%. Baseline-risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) in the population undergoing surgery have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVTs and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DVTs and therefore, considered important outcome. f. In patients undergoing Radical Cystectomy for Malignancy, VanDlac 2014 (A retrospective observational, N=1307) reported a 6% incidence of any VTE and 3.3% of any DVT. Baseline-risk estimates for symptomatic PE (0.12%) symptomatic proximal DVT (0.132%) and symptomatic severe distal DVT (0.0232%) in the population undergoing surgery and using pharmacological thromboprophylaxis have been calculated applying the assumptions that 20% of any VTE and any DVT are symptomatic events, 10% of symptomatic VTE are PE, 20% of the symptomatic DVT are symptomatic proximal DVT and the 80% symptomatic distal DVT. Furthermore, only 5% of the symptomatic distal DVTs are assumed to be severe DVTs and, therefore, considered a critical outcome. g. Any proximal DVT, screening detected, used as a surrogate for Symptomatic proximal DVT h. The baseline risk consists of the control group event rate (5.7%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic proximal DVT (1.14%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. i. Any distal DVT, screening detected, used as a surrogate for Symptomatic distal DVT j. The baseline risk consists of the control group event rate (5.9%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.059%) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. k. None of the studies (appropriately) report the allocation concealment	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004)	

	Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran£143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304,	

	respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as very low due to indirectness of the study populations and study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Thirteen studies reported the use of extended with short course for the same medication as prophylaxis strategies (Bergqvist 1999, Bergqvist 2000, Bischof 2006, Cain 2012, Dahl 2003, Davies 2000, Detournay 1998, Dranitsaris 2009, Haentjens 2004, Sarasin 1996, Sarasin 2002, Skedgel 2007, Uppal 2012), while four other studies compared extended treatment with another medication (the comparisons included extended fondaparinux with enoxaparin, extended enoxaparin compared with warfarin, and extended rivaroxaban compared with enoxaparin in another) (Capri 2010, Duran 2011, Dahl 2003, Friedman 2000). In general, the extended prophylaxis is cost effective compared with short-course prophylaxis Across different settings, except one study suggested ten days of dalteparin was cost-effective compared to the extended prophylaxis, and another suggested the marginal cost of extended prophylaxis with LMWH was too expensive.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced	Evidence from a study including 3,484 high-risk orthopaedic surgery patients, showed 79% of patients received guideline-recommended treatment with LMWH, UFH, fondaparinux and or VKA at discharge, and	The panel judged that there are patient subgroups (economically disadvantaged) who would not be likely to

○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	88% of these patients were compliant with therapy after discharge. The most common reason for non-compliance (33.4%) was “drug was not bought”. (Bergqvist 2012)	receive the same treatments. Self-administration (especially with injectable pharmacologic prophylaxis) may also preclude implementation of extended prophylaxis.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Not all patients would accept extended prophylaxis (especially for self-injection prophylaxis). Similarly, payers may not be willing to provide coverage for extended prophylaxis without clear cost-effective advantages.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue,	

	thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using extended course antithrombotic prophylaxis in surgical patients (conditional recommendation based on very low certainty of the evidence about effects).

Justification

This recommendation is based upon evidence from two high risk surgical settings only (joint arthroplasty and major cancer surgery).

Subgroup considerations

None

Implementation considerations

Education of patients provides, and payers of the benefits of extended prophylaxis will be needed to help maximize implementation.
Risks of thrombosis and bleeding risks in individual patients' consideration for extended prophylaxis.
Limited evidence addressing extended prophylaxis in lower risk surgical settings.

Monitoring and evaluation

If patients are discharged on extended pharmacologic prophylaxis then appropriate labs (e.g. creatinine and platelet count) as well as clinical monitoring for postoperative bleeding need to be considered depending on prophylaxis agent used.

Research priorities

More research is needed to determine which subgroups would benefit most from extended VTE prophylaxis after surgery.
Further high-quality research using clinically important outcomes in a variety of settings would be warranted.

QUESTION-8

Should early (post-operative- within 12 hours) vs. delayed (post-operative- after 12 hours) antithrombotic administration be used for patients undergoing surgery?	
POPULATION:	patients undergoing surgery
INTERVENTION:	early (post-operative- within 12 hours)
COMPARISON:	delayed (post-operative- after 12 hours) antithrombotic administration
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - Non-Fatal - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis – representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis – representing the severe marker state; Major bleeding; Reoperation
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of early pharmacological antithrombotic prophylaxis use with delayed prophylaxis in hospitalized patients undergoing surgical procedures

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is uncertainty about the optimal timing of pharmacological prophylaxis in perioperative setting. Early administration may increase antithrombotic efficacy. However early administration may also increase the risk of post-operative bleeding.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See table below	Based on a panel discussion, both studies that compared different drugs and their timing as well the same drug with different timing were included in the meta-analysis. The certainty of the evidence of effects was subsequently downgraded for indirectness.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with delayed (post-operative- after 12 hours) antithrombotic administration	Risk difference with early (post-operative- within 12 hours)
Mortality assessed with: Mortality follow up: range 9 days to 6 months	9972 (6 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 1.57** (0.77 to 3.19) [c]	3 per 1,000	**1 more per 1,000** (1 fewer to 6 more) [c]
Symptomatic Pulmonary Embolism - Non Fatal - representing the moderate marker state assessed with: any PE follow up: range 9 days to 6 months	9744 (6 RCTs)	⊕◯◯◯ VERY LOW [a,b,c,d]	**RR 0.63** (0.23 to 1.72) [c]	**Based on study population BLR**	
				1 per 1,000 [e]	**0 fewer per 1,000** (1 fewer to 1 more)
				Low	

					0 per 1,000 [f]	**0 fewer per 1,000** (0 fewer to 0 fewer)
	Symptomatic Proximal Deep Vein Thrombosis – representing the moderate marker state assessed with: any proximal DVT follow up: range 9 days to 6 months	5732 (5 RCTs)	⨁◯◯◯ VERY LOW [a,c,g,h]	**RR 0.88** (0.40 to 1.96)	**Based on study population BLR**	
					4 per 1,000 [i]	**0 fewer per 1,000** (2 fewer to 4 more)
					Low	
					1 per 1,000 [f]	**0 fewer per 1,000** (0 fewer to 1 more)
	Symptomatic Distal Deep Vein Thrombosis – representing the severe marker state assessed with: any distal DVT follow up: range 9 days to 6 months	5680 (5 RCTs)	⨁◯◯◯ VERY LOW [a,c,j,k]	**RR 0.68** (0.41 to 1.12) [c]	**Based on study population BLR**	
					1 per 1,000 [l]	**0 fewer per 1,000** (1 fewer to 0 fewer)
					low	
					0 per 1,000 [f]	**0 fewer per 1,000** (0 fewer to 0 fewer)
	Major bleeding assessed with: Major Bleeding follow up: range 9 days to 6 months	10271 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,m]	**RR 1.63** (0.81 to 3.29)	7 per 1,000	**5 more per 1,000** (1 fewer to 17 more)
	Reoperation assessed with: major bleeding requiring reoperation follow up: range 9 days to 6 months	10271 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 1.84** (0.89 to 3.80)	2 per 1,000	**2 more per 1,000** (0 fewer to 6 more)

Pulmonary Embolism - (assumed to be representing moderate marker state) assessed with: fatal PE and non fatal PE follow up: range 9 days to 6 months	9744 (6 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 0.71** (0.29 to 1.72) [c]	6 per 1,000	**2 fewer per 1,000** (4 fewer to 4 more) [c]

a. In all studies, patients were only evaluated if they had a valid venogram. In several studies there were over 20% missing patient data for that reason. Moreover, Colwell (2007) the most direct evidence, was an open-label trial resulting in no participant, personnel, and outcome blinding. We rated down for risk of bias by one level.
b. Turpie (2009), Turpie (2005) and Ginsberg (2007) compared DOACs with heparins (with different times of administration)
c. Given the width of the confidence interval, it is likely to cross the decision threshold and there is potential for appreciable benefits and harms.
d. Heterogeneity between studies: I^2 = 42% (P=0.14), but removing studies with different interventions did not remove heterogeneity
e. The baseline risk consists of the control group event rate (0.6%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic PE (0.12%) has been calculated applying the assumptions that 20% of any PE are symptomatic PE
f. In patients undergoing all elective surgery (registry type study), Assareh et al. (2014) reported, a risk of symptomatic VTE of 0.3%. Baseline-risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) in the population undergoing surgery have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVTs and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DVTs and therefore, considered important outcome.
g. Heterogeneity between studies: I^2 = 71% (P=0.009), but removing studies with different interventions did not remove heterogeneity
h. For all 5 studies, Proximal DVT was used as a surrogate for DVT Upper Leg - Moderate, resulting in indirectness being downgraded. Addition of Colwell (2007), which did not specify location of DVT resulted in I^2 = 63%, OR=0.92 [0.49,1.69]
i. The baseline risk consists of the control group event rate (1.9%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.38%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs.
j. Heterogeneity between studies: I^2 = 90% (P<0.00001), but removing studies with different interventions did not remove heterogeneity
k. For all 5 studies, Distal DVT was used as a surrogate for DVT Lower Leg - Severe, resulting in indirectness being downgraded. Addition of Colwell (2007), which did not specify location of DVT resulted in I^2 = 88%, OR=0.72 [0.46,1.12]
l. The baseline risk consists of the control group event rate (13.1%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (xx %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs, and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs.
m. Heterogeneity between studies: I^2 = 55% (P=0.05), but removing studies with different interventions did not remove heterogeneity

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99**(different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004)	

	Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological and mechanical prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304,	Considering both groups will use the intervention, and more reoperations and blood transfused in the early, versus few extra PEs that occur. VTEs prevented could save costs

	respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as very low due to indirectness of the study populations and study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced	No research evidence identified	The panel judged that there probably would be no impact on

● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue,	

	thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests either early administration (post-operative, within 12 hours) or late administration (post-operative- after 12 hours) of antithrombotic prophylaxis in surgical patients. (conditional recommendation based on very low certainty of the evidence about effects).

Justification

None

Subgroup considerations

None

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

Further high quality studies using clinically important outcomes would be helpful to provide greater certainty about the benefits and risks of early pharmacological prophylaxis.

QUESTION-10

Should Aspirin prophylaxis vs. other anticoagulant prophylaxis be used for patients undergoing total hip or knee arthroplasty?	
POPULATION:	patients undergoing total hip or knee arthroplasty
INTERVENTION:	Aspirin prophylaxis
COMPARISON:	other anticoagulant prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - severe the moderate marker state; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. Research suggests that for patients undergoing total knee or hip arthroplasty, antithrombotic prophylaxis with both anticoagulants and aspirin are effective for the prevention of VTE. However, evidence for the comparative effectiveness of aspirin prophylaxis is limited due to a lack of high quality randomized control trials (Balk, 2017). This EtD compares the effectiveness and safety of aspirin prophylaxis compared with other anticoagulant prophylaxis for prevention of VTE in hospitalized patients undergoing total hip or knee arthroplasty.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, for patients undergoing total hip replacement, the risk of DVT is 45% and the risk of PE is 3% (National Clinical Guideline Centre, 2010). Pharmacological agents are used in patients with identifiable risk factors for VTE. Other, big registry studies of several million patients, estimate the risk of DVT in patients undergoing different types of surgery to be orders of magnitudes lower (rates of VTE of 0.2%) (Spyropoulos 2009 and Assareh 2014).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with other anticoagulant	Risk difference with Aspirin
Mortality	1884 (8 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 2.32** (0.15 to 36.90)	Study population	
				1 per 1,000	**1 more per 1,000** (1 fewer to 33 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: symptomatic PE	1836 (8 RCTs)	⨁◯◯◯ VERY LOW[a,c,d]	**RR 1.49** (0.37 to 6.09)	Study population	
				3 per 1,000	**1 more per 1,000** (2 fewer to 14 more)
				High	
				7 per 1,000[e]	**3 more**

follow up: range 7 days to 6 months					(4 fewer to 36 more)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: proximal symptomatic or any symptomatic DVT follow up: range 7 days to 6 months	1746 (7 RCTs)	⊕◯◯◯ VERY LOW[a,d,f]	**RR 1.49** (0.51 to 4.34)	Study population	
				6 per 1,000	**3 more per 1,000** (3 fewer to 19 more)
				Low	
				0 per 1,000[g,h]	**0 fewer per 1,000** (0 fewer to 1 more)
Symptomatic Distal Deep Vein Thrombosis - representing the moderate marker state assessed with: distal or any symptomatic DVT follow up: range 6 weeks to 6 months	1746 (7 RCTs)	⊕◯◯◯ VERY LOW[a,f,i]	**RR 1.45** (0.86 to 2.46)	Study population	
				24 per 1,000	**11 more per 1,000** (3 fewer to 35 more)
				Low	
				0 per 1,000[g,h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding follow up: range 7 days to 6 months	1072 (6 RCTs)[j]	⊕⊕◯◯ LOW[a,i]	**RR 2.63** (0.64 to 10.79)	Study population	
				4 per 1,000[j]	**6 more per 1,000** (1 fewer to 35 more)
Reoperation - not reported	-	-	-	**-**	**-**

a. Most studies did not report or reported no allocation concealment, only one study was blinded, and 2 studies excluded 8% and 20%. of participants after randomization
b. Most studies did not explicitly report this outcome but we assumed no

	events if not reported. c. Most studies did not properly report whether or not PEs were symptomatic and their severity. d. Very few events and results are very fragile despite relatively narrow CI around the risk difference; sensitivity analyses (assuming best and worst case scenarios based on the incomplete reporting) showed large variation of the estimate of a relative effect. e. Jameson (2011) reports that rates symptomatic PE were 0.68% in 108,000 patients from a National Joint Registry England and Wales. Parvizi (2015) reports a rate of symptomatic PE of 1.07% over 26,415 cases of TJA f. Most studies did not report whether or not DVT events were symptomatic, proximal or distal, and their severity. g. Mauck (2013) reports a rate of 0.4% for symptomatic VTE. Other studies have shown: Lee (2012) 0.46% for symptomatic VTE on patients without prophylaxis, Huang (2016) rates of symptomatic DVT: 0.8 to 1.7% on aspirin, Jameson (2011) DVT rates of 0.99% on aspirin and 0.84% on LMWH h. The assumption that approximately 90% of the VTEs are DVTs, 20% of DVTs are proximal, 80% distal and 5% of the latter severe was applied. i. Few events; CI around the risk difference does not exclude an appreciable harm with ASA or no difference; sensitivity analyses (assuming best and worst case scenarios based on the incomplete reporting) showed large variation of the estimate of a relative effect. j. Studies report risk major bleeding rates of 0.5% for aspirin, 2% for warfarin (Parvizi). 1% for LMWH (Gerkens 2010)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them	

	are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological and mechanical prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	Six reports compared the cost-effectiveness of aspirin vs anticoagulants prophylaxis for total hip or knee arthroplasty patients. Two studies suggested aspirin may be cost effective compared with warfarin, while other reports favored low-molecular weight heparin over aspirin. However, all reports suggested aspirin saved costs and resources. (Abdool-Carrim 1997, Alho 1984, Gutowski 2015, Mostafavi 2015, Sarasin 2002, Schousboe 2013)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified	Panel considered that aspirin might be accepted by patients in general, but there might be a variability in stakeholders acceptability, including some clinicians who belief that aspirin is not effective.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in	

	hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either aspirin or other pharmacological agents in patients undergoing total hip arthroplasty or total knee arthroplasty (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The trivial impact of aspirin prophylaxis on desirable effects does not outweigh its small impact on undesirable effects. The supporting evidence was judged to be of very low certainty.
While the cost is considered to be negligible and probably cost-effective, there is possibly an important variability in patients' values and preferences as well as some acceptability concerns among different stakeholders.
There are no equity or feasibility concerns for the use of the aspirin as thromboprophylactic agent.

Subgroup considerations

None

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

There is great need for large randomized controlled trials using clinically important endpoints as the primary outcome measure.

QUESTION-11

Should DOACs prophylaxis vs. LMWH prophylaxis be used for patients undergoing total hip or knee arthroplasty?	
POPULATION:	patients undergoing total hip or knee arthroplasty
INTERVENTION:	DOACs prophylaxis
COMPARISON:	LMWH prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major bleeding; Bleeding leading to reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of DOAC prophylaxis with LMWH prophylaxis for prevention of VTE in hospitalized patients undergoing total hip or knee arthroplasty.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, for patients undergoing total hip replacement, the risk of DVT is 45% and the risk of PE is 3% (National Clinical Guideline Centre, 2010). Pharmacological agents are used in patients with identifiable risk factors for VTE. Other, big registry studies of several million patients, estimate the risk of DVT in patients undergoing different types of surgery to be orders of magnitudes lower (rates of VTE of 0.2%) (Spyropoulos 2009 and Assareh 2014).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with LMWH prophylaxis	Risk difference with DOACs prophylaxis
Mortality follow up: range 10 days to 35 days	41846 (38 RCTs)[a]	⨁⨁⨁◯ MODERATE[b]	**RR 0.94** (0.53 to 1.66)	Study population	
				1 per 1,000	**0 fewer per 1,000** (1 fewer to 1 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: Non Fatal Symptomatic Pulmonary	41634 (38 RCTs)	⨁⨁⨁◯ MODERATE[b,c]	**RR 0.74** (0.50 to 1.10)	Study population	
				3 per 1,000	**1 fewer per 1,000** (1 fewer to 0 fewer)
				High	
				7 per 1,000[d]	**2 fewer per 1,000**

embolism follow up: range 10 days to 35 days					(3 fewer to 1 more)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: Symptomatic DVT follow up: range 10 days to 35 days	39924 (38 RCTs)	⊕⊕⊕⊕ HIGH[c]	**RR 0.56** (0.39 to 0.79)	Low	
				1 per 1,000[e]	**1 fewer per 1,000** (1 fewer to 0 fewer)
				Moderate	
				0 per 1,000[f,g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Symptomatic DVT follow up: range 10 days to 35 days	39924 (38 RCTs)	⊕⊕⊕⊕ HIGH[c]	**RR 0.56** (0.39 to 0.79)	Low	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[f,g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding follow up: range 10 days to 35 days	46382 (38 RCTs)	⊕⊕⊕◯ MODERATE[b,i]	**RR 1.03** (0.79 to 1.35)	Study population	
				8 per 1,000	**0 fewer per 1,000** (2 fewer to 3 more)
				Moderate	
				10 per 1,000[j]	**0 fewer per 1,000** (2 fewer to 4 more)
Bleeding leading to reoperation assessed with: Bleeding leading to reoperation	33560 (38 RCTs)	⊕⊕⊕◯ MODERATE[b]	**RR 1.43** (0.75 to 2.71)	Study population	
				1 per 1,000	**0 fewer per 1,000** (0 fewer to 2 more)

follow up: range 10 days to 35 days					

a. A sensitivity analysis excluding dose-finding studies was conducted and did not significantly change results in terms of point estimates or confidence intervals. Mortality: 0.94 [0.53, 1.66] I2=0% vs 0.79 [0.40, 1.57] I2=0%; Non-Fatal Pulmonary embolism: 0.74 [0.50, 1.10] I2=0% vs 0.91 [0.43, 1.94] I2=35%; Symptomatic DVT: 0.56 [0.39, 0.79] I2 7% vs 0.50 [0.31, 0.81] I2=0%; Major bleeding: 1.03 [0.79, 1.35] I2 21% vs 1.11 [0.80, 1.52] I2=5%.
b. For decision making the certainty range around the effect estimates was felt to cross decision thresholds.
c. There was a considerable proportion of missing outcome data. We conducted a sensitivity analysis assuming that the risk of participants randomized but not counted in the intervention group was 3 times the risk of participants randomized and counted on the analysis. Also we assumed that the risk of participants randomized but not counted in the control group was the same that the risk of participants randomized and counted. Such analysis did not appreciably change the results.
d. In 108,000 patients from a National Joint Registry England and Wales, Jameson (2011) reports that rates symptomatic PE were 0.68%. Parvizi (2015) reports a rate of symptomatic PE of 1.07% over 26,415 cases of TJA
e. The baseline risk consists of the control group event rate (0.6%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.12%) has been calculated applying the assumptions that 20% of any symptomatic DVTs are symptomatic proximal DVTs.
f. Mauck (2013) reports a rate of 0.4% for symptomatic VTE. Other studies have shown: Lee (2012) 0.46% for symptomatic VTE on patients without prophylaxis, Jameson (2011) DVT rates of 0.84% on LMWH
g. The assumption that approximately 90% of the VTEs are DVTs, 20% of DVTs are proximal, 80% distal and 5% of the latter severe was applied.
h. The baseline risk consists of the control group event rate (0.6%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.024%) has been calculated applying the assumptions that 80% of any symptomatic DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs.
i. Some heterogeneity detected (I2=21%)
j. Gerken (2010) reports major bleeding rates of 1% for LMWH

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		Concerns were raised around the directness of the population, primarily with regards to the baseline risk of bleeding and reoperation.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	Level of certainty downgraded from high to moderate as there is an overlap of the thresholds for desirable and undesirable effects (when considering the worst-case scenarios] and because of indirectness concerns, as included patients in FDA trials may differ from patients in clinical practice. As the body of evidence included dose-finding studies, the panel also considered a a sensitivity analysis excluding these studies, which did not significantly change results in terms of point estimates or confidence intervals.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004)	

	Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015	Varies depending on the country or jurisdiction.

	vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	15 reports compared the cost-effectiveness of DOACs with LMWH. Most of them concluded DOACs cost-effective compared with LMWH, some of the results even suggested the dominance of DOACs over LMWH. (Diamantopoulos 2010, Duran 2011, Duran 2012, Hamidi 2013, Holmes 2012, Lazo-Langner 2012, Mahmoudi 2013, McCullagh 2009, McDonald 2012, Monreal 2013, Postma 2012, Revankar 2013, Ryttberg 2011, Wolowacz 2009, Zindel 2012)	Panelists pointed out that cost-effectiveness might vary on different jurisdictions. Specifically, differences in LMWH pricing may affect the cost-effectiveness of DOAC over LMWH.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	Panelist considered that DOAC are generally less expensive, may increase patients' independence and are easier to administer.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	No research evidence identified	The lack of reversibility of the anticoagulant effect was not felt to be a major barrier to accepting DOACs.

● Probably yes ○ Yes ○ Varies ○ Don't know		In general, injections are less preferred thank oral administration, hence DOAC may increase compliance. Acceptability felt to be important because compliance may differ between the interventions.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using DOACs rather than LMWH in patients undergoing total hip or knee arthroplasty (conditional recommendation based on moderate certainty of the evidence about effects).

Justification

An anonymous voting took place for the decision about DOAC vs LMWH: **Conditional recommendation for DOAC:** 5 votes, **Conditional recommendation for either DOAC or LMWH:** 4 votes

Subgroup considerations

None

Implementation considerations

Insurance coverage may influence the decision; thus, clinicians should take this into consideration.
Clinicians should also ensure there is adequate patient education about the medication, including the limited reversibility of DOACs and other outcomes.

Monitoring and evaluation

Post marketing evaluations are necessary to establish the long-term safety of DOACs on a broader population.

Research priorities

High quality head to head studies comparing different DOACS would be warranted.
Further studies regarding the optimal timing of post-operative administration of DOACs are warranted.

QUESTION-12

Should LMWH prophylaxis vs. Warfarin prophylaxis be used for patients undergoing total hip or knee arthroplasty?	
POPULATION:	patients undergoing total hip or knee arthroplasty
INTERVENTION:	LMWH prophylaxis
COMPARISON:	Warfarin prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH prophylaxis compared with warfarin prophylaxis for prevention of VTE in hospitalized patients undergoing total hip or knee arthroplasty.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, for patients undergoing total hip replacement, the risk of DVT is 45% and the risk of PE is 3% (National Clinical Guideline Centre, 2010). Pharmacological agents are used in patients with identifiable risk factors for VTE. Other, big registry studies of several million patients, estimate the risk of DVT in patients undergoing different types of surgery to be orders of magnitudes lower (rates of VTE of 0.2%) (Spyropoulos 2009 and Assareh 2014).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Warfarin	Risk difference with LMWH
Mortality follow up: range 14 days to 6 months	4227 (5 RCTs)	⊕⊕◯◯ LOW[a]	**RR 0.51** (0.14 to 1.88)	Study population	
				3 per 1,000	**2 fewer per 1,000** (3 fewer to 3 more)
Symptomatic Pulmonary Embolism - representing the moderate	5431 (5 RCTs)	⊕◯◯◯ VERY LOW[a,b]	**RR 0.83** (0.27 to 2.56)	Low	
				1 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 1 more)

marker state assessed with: any PE follow up: range 10 days to 3 months				High	
				7 per 1,000[d]	**1 fewer per 1,000** (5 fewer to 11 more)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any Proximal DVT follow up: range 6 days to 14 days	3620 (6 RCTs)	⊕◯◯◯ VERY LOW[b,e,f]	**RR 0.61** (0.36 to 1.02)	Low	
				15 per 1,000[g]	**6 fewer per 1,000** (9 fewer to 0 fewer)
				Moderate	
				0 per 1,000[h,i]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: any Distal DVT follow up: range 6 days to 14 days	731 (2 RCTs)	⊕⊕◯◯ LOW[b,e]	**RR 0.61** (0.42 to 0.88)	Low	
				3 per 1,000[j]	**1 fewer per 1,000** (2 fewer to 0 fewer)
				Moderate	
				0 per 1,000[h,i]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding follow up: range 14 days to 6 months	7467 (7 RCTs)	⊕⊕⊕◯ MODERATE[k,l]	**RR 1.81** (1.31 to 2.50)	Study population	
				15 per 1,000	**12 more per 1,000** (5 more to 22 more)
				High	
				20 per 1,000[m]	**16 more per 1,000** (6 more to 30 more)
Reoperation	899 (2 RCTs)	⊕⊕⊕◯ MODERATE[n]	**RR 3.09** (0.13 to 75.48)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

	a. Very few events. The 95% confidence interval includes both no effect and appreciable harm exceeding a minimal important difference. b. In all studies, patients were only evaluated if they either had a valid venogram or a PE. In several studies there were over 20% missing patient data for that reason. We rated down for risk of bias by one level. Two trials were open label trials but they were small and did not importantly influence the results. We did not further downgrade for risk of bias. c. The baseline risk consists of the control group event rate (0.3%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic PE (0.06%) has been calculated applying the assumptions that 20% of any PE are symptomatic PE. d. In 108,000 patients from a National Joint Registry England and Wales, Jameson (2011) reports that rates symptomatic PE were 0.68%. Parvizi (2015) reports a rate of symptomatic PE of 1.07% over 26,415 cases of TJA e. Venography is a surrogate for symptomatic DVT. We rated down for indirectness. f. Although the CI of the studies are overlapping, the I square is 67% indicating high heterogeneity g. The baseline risk consists of the control group event rate (7.4%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (1.48%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. h. Mauck (2013) reports a rate of 0.4% for symptomatic VTE. Jameson (2011) DVT rates of 0.84% on LMWH i. The assumption that approximately 90% of the VTEs are DVTs, 20% of DVTs are proximal, 80% distal and 5% of the latter severe was applied. j. The baseline risk consists of the control group event rate (27.9%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.279 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. k. Despite the lack of blinding, we did not lower the certainty for risk of bias because the unblinded studies did not importantly influence the results and the outcome was objective. l. Probably no enough events to reach optimal information size. m. Parvizi (2015) reports a rate of major bleeding of 2% on warfarin n. Few events. The 95% confidence interval includes both benefits and appreciable harm	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994)	

	Treatment with LMWH: 0.993 (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)	

	per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We included twenty reports for cost-effectiveness of warfarin vs LMWH. The results were inconclusive regarding to which strategy is cost-effective. Warfarin is less costly compared with LMWH. However, there is conflict in economic evaluation results, with some of the analyses suggested warfarin leads to better outcome thus dominates LMWH. While others suggested although LMWH incurs additional cost, it also lead to additional gain in effectiveness, and depending on the cost of LMWH, LMWH may be cost-effective compared with warfarin. (Anderson 1998, Bell 2001, Botteman 2002, Caprini 2002, Dahl 2003, Dranitsaris 2009, Francis 1999, Friedman 2000, Garcia-Zozaya 1998, Hawkins 1998, Hull 1997, Lazo-Langner 2012, Menzin 1995, Nerurkar 2002, O'Brien 1994, Sarasin 2002, Saunders 1998, Skedgel 2007, Wade 2000b, Wade 199)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Among 3,484 high-risk orthopedic surgery patients 79% received guideline-recommended treatment with LMWH, UFH, fondaparinux and or VKA at discharge at discharge. 88% of these patients were compliant with therapy after discharge. The most common reason for non-compliance (33.4%) was “drug was not bought”. (Bergqvist 2012)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified	Patient views on INR testing and the impact on diet of warfarin use indicate that warfarin is less acceptable. Injections are also coming with burden. Moreover, the panel considered that lack of insurance and high copays and resources will influence acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines**	

	Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using LMWH over warfarin in patients undergoing total hip or knee arthroplasty (conditional recommendation based on very low certainty of the evidence about effects).

Justification

This recommendation is based on an overall very low certainty of effects due to a lack of high quality studies to inform mainly the potentially desirable effects of LMWH versus warfarin.

Subgroup considerations

None

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

None

Research priorities

Further high-quality studies using clinically important outcomes would be of value to improve the certainty of the recommendation.

Question-13

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing total hip or knee arthroplasty?	
POPULATION:	patients undergoing total hip or knee arthroplasty
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH prophylaxis with UFH prophylaxis for prevention of VTE in hospitalized patients undergoing total hip or knee arthroplasty.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, for patients undergoing total hip replacement, the risk of DVT is 45% and the risk of PE is 3% (National Clinical Guideline Centre, 2010). Pharmacological agents are used in patients with identifiable risk factors for VTE. Other registry studies of several million patients estimate the risk of DVT in patients undergoing different types of surgery at rates of VTE of 0.2%) (Spyropoulos 2009 and Assareh 2014).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH	Risk difference with LMWH
Mortality assessed with: all-cause mortality follow up: range 7 days to 2 months	1549 (5 RCTs)	⊕⊕⊕⊕ HIGH[a]	**RR 0.26** (0.03 to 2.36)	Study population	
				4 per 1,000	**3 fewer per 1,000** (4 fewer to 5 more)
Symptomatic Pulmonary Emolism - representing the moderate marker state assessed with:	2534 (10 RCTs)	⊕⊕⊕◯ MODERATE[b]	**RR 0.37** (0.19 to 0.71)	Low	
				5 per 1,000[c]	**3 fewer per 1,000** (4 fewer to 1 fewer)
				Moderate	

any PE				7 per 1,000[d]	**4 fewer per 1,000** (6 fewer to 2 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: proximal DVT	2336 (8 RCTs)	⊕⊕⊕◯ MODERATE[e]	**RR 0.48** (0.34 to 0.69)	Low	
				12 per 1,000[f]	**6 fewer per 1,000** (8 fewer to 4 fewer)
				Moderate	
				0 per 1,000[g,h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: distal DVT	1504 (6 RCTs)	⊕⊕⊕◯ MODERATE[e,i]	**RR 1.18** (0.81 to 1.72)	Low	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[g,h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding	2278 (6 RCTs)	⊕⊕⊕◯ MODERATE[k,l,m]	**RR 0.55** (0.27 to 1.13)	Study population	
				41 per 1,000	**19 fewer per 1,000** (30 fewer to 5 more)
Reoperation	321 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Small number of events, wide confidence interval for the relative effect,but narrow confidence interval around absolute effects and we did not downgraded for imprecision.
b. Seven of 10 included studies did not blind participants and/or study investigators.
c. The baseline risk consists of the control group event rate (2.3%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic PE (0.46%) has been calculated applying the assumptions

	that 20% of any PE are symptomatic PE. d. In 108,000 patients from a National Joint Registry England and Wales, Jameson (2011) reports that rates symptomatic PE were 0.68%. Parvizi (2015) reports a rate of symptomatic PE of 1.07% over 26,415 cases of TJA e. DVT assessed with venography. Venography is a surrogate for symptomatic DVT. We rated down for indirectness. f. The baseline risk consists of the control group event rate (8.5%) from studies included in the meta-analysis Baseline risk estimates for symptomatic proximal DVT (1.7%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. g. Mauck (2013) reports a rate of 0.4% for symptomatic VTE. Jameson (2011) DVT rates of 0.84% on LMWH. h. The assumption that approximately 90% of the VTEs are DVTs, 20% of DVTs are proximal, 80% distal and 5% of the latter severe was applied. i. Estimate of effect includes both appreciable benefit and appreciable harm. The imprecision is considered together with the indirectness and the overall certainty downgraded for one level. j. The baseline risk consists of the control group event rate (13%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.13 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. k. Estimate of effect includes both appreciable benefit and appreciable harm. l. I-squared = 34% for overall estimate of effect. Planes 1988 and Senaran 2006 both showed 2 major bleeds in LMWH group versus 0 major bleeds in UFH group. Downgraded for imprecision, did not downgrade another level for inconsistency. m. Four of six included trials did not blind participants and/or study investigators (open label trial).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65**(standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76**(time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of	

	them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran£143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Sixteen reports compared UFH with LMWH for prophylaxis of VTE in total hip or knee arthroplasty patients. The results suggested LMWH cost-effective compared with UFH, and some of them suggested the dominance of LMWH. (Bergqvist 1993, Bergqvist 1996, Borris 1994, Borris 1996, Brosa Riestra 2003, Caprini 2002, Deitelzweig 2008, Drummond 1994, Fowler 2014a, Hawkins 1997, Heerey 2005, Lazo-Langner 2012, Lloyd 1997, Marchetti 1999, McGarry 2004, Wade 2008)	Panel members mentioned that the cost-effectiveness may differ between countries but probably favored LMWH in the US.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Among 3,484 high-risk orthopedic surgery patients 79% received guideline-recommended treatment at discharge. 88% of these patients were compliant with therapy after discharge. The most common reason for non-compliance (33.4%) was “drug was not bought”. (Bergqvist 2012)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

The ASH guideline panel recommends LMWH over UFH in patients undergoing total hip or knee arthroplasty (strong recommendation based on moderate certainty of the evidence about effects).

Justification

This recommendation is based on the panel's judgment that the balance of effects clearly favored the intervention.

Subgroup considerations

None

Implementation considerations

The panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

None

Research priorities

None

QUESTION-14

Should one DOAC vs. another DOAC be used for patients undergoing total hip or knee arthroplasty?	
POPULATION:	patients undergoing total hip or knee arthroplasty
INTERVENTION:	one DOAC
COMPARISON:	another DOAC
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major bleeding; Bleeding leading to reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. Research suggests that for patients undergoing total knee or hip arthroplasty, antithrombotic prophylaxis with both anticoagulants and aspirin are effective for the prevention of VTE. However, evidence for the comparative effectiveness of aspirin prophylaxis is limited due to a lack of high quality randomized control trials (Balk, 2017). This EtD compares the effectiveness and safety of aspirin prophylaxis compared with other anticoagulant prophylaxis for prevention of VTE in hospitalized patients undergoing total hip or knee arthroplasty.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Pharmacological agents are frequently used for the prevention of VTE in patients undergoing higher risk surgical procedures such as total hip or knee replacement. Large registry studies showed that in patients receiving ASA or LMWH prophylaxis after total knee or hip arthroplasty had PE rates from 0.45% to 0.68% (Jameson 2011 and Jameson 2011).	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	We tested for potential differences in the relative effects between specific drugs and especially between drug classes (Anti-IIa vs Anti-Xa). We found no interaction for any of the outcomes. **Mortality:** test for interaction all the drugs p=0.75; Anti-IIa vs Anti-Xa p=0.45 **Pulmonary embolism:** test for interaction all the drugs p=0.95; Anti-IIa vs Anti-Xa p=0.82 **DVT**: test for interaction all the drugs p=0.48; Anti-IIa vs Anti-Xa p=0.46 **Major bleeding**: test for interaction all the drugs p=0.06; Anti-IIa vs Anti-Xa p=0.71	Given the lack of evidence for a subgroup effect between different DOACs, the panel judged desirable and undesirable effects to be likely similar.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	We tested potential differences in the effect with specific drugs and especially between classes (Anti-IIa vs Anti-Xa). We found no interaction for any of the outcomes. **Mortality:** test for interaction all the drugs p=0.75; Anti-IIa vs Anti-Xa p=0.45 **Pulmonary embolism:** test for interaction all the drugs p=0.95; Anti-IIa vs Anti-Xa p=0.82 **DVT**: test for interaction all the drugs p=0.48; Anti-IIa vs Anti-Xa p=0.46 **Major bleeding**: test for interaction all the drugs p=0.06; Anti-IIa vs Anti-Xa p=0.71	Given the lack of evidence for a subgroup effect between different DOACs, the panel judged desirable and undesirable effects to be likely similar.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	A potential difference in the effect with specific drugs and especially between DOAC classes (Anti-IIa vs Anti-Xa) was tested and no interaction was found for any of the outcomes	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran£143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleedingwere $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	Varies depending on the country or jurisdiction.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Four reports compared the cost-effectiveness of different DOACs. They concluded Apixaban and Rivaroxaban would generate lower costs than dabigatran. (Dequen 2014, Gómez-Cerezo 2012, McCullagh 2009, Monreal 2013)	The panel judged that any differences would likely not be meaningful.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	The lack of reversibility of most DOACs was not felt as a major barrier.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using any of the DOACs in patients undergoing total hip or knee arthroplasty (conditional recommendation based on low certainty of the evidence about effects).

Justification

Given the absence of trials of direct comparisons of specific DOACs and no demonstrable subgroup effect, the ASH panel did not suggest any specific DOAC as drug of choice.

Subgroup considerations

None

Implementation considerations

Insurance coverage may influence the decision; thus, clinicians should take this into consideration.
Clinicians should also ensure there is adequate patient education about the medication, including the limited reversibility of DOACs and other outcomes.

Monitoring and evaluation

Post marketing evaluations are necessary to establish the long-term safety of DOACs on a broader population.

Research priorities

High quality head to head studies comparing different DOACS would be warranted.
Further studies regarding the optimal timing of post-operative administration of DOACs are warranted.

QUESTION-15

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing hip fracture repair?	
POPULATION:	patients undergoing hip fracture repair
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality (follow-up 10 days to 3 months); Pulmonary Embolism - representing the moderate marker state; Proximal Deep Vein Thrombosis - representing the moderate marker state (follow-up 10 days to 3 months); Distal Deep Vein Thrombosis - representing the severe distal DVT marker state (follow-up 10 days to 3 months); Major bleeding; Reoperation (follow-up 14 days to 35 days);
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of antithrombotic prophylaxis with no antithrombotic prophylaxis in hospitalized patients undergoing hip fracture repair.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing surgery is very considerable. For instance, patients undergoing surgery for hip fracture are in the highest category for post-operative VTE. In the absence of prophylaxis, fatal PE occurs in 3.6 to 12.9% of patients (Eriksson, Bauer, Lassen, & Turpie, 2001).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	Nº of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Mortality (follow-up 10 days to 3 months)	14213 (9 RCTs)	⊕◯◯◯ VERY LOW[a,b]	**RR 0.95** (0.84 to 1.07)	Study population	
				71 per 1,000	**4 fewer per 1,000** (11 fewer to 5 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed	14134 (9 RCTs)	⊕◯◯◯ VERY LOW[a]	**RR 0.49** (0.33 to 0.72)	Study population	
				11 per 1,000	**6 fewer per 1,000** (7 fewer to 3 fewer)
				Low	

with: symptomatic PE				3 per 1,000[c]	**2 fewer per 1,000** (2 fewer to 1 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state (follow-up 10 days to 3 months) assessed with: any Proximal DVT	13813 (5 observational studies)	⊕◯◯◯ VERY LOW[d,e]	**RR 0.51** (0.38 to 0.69)[f]	Low	
				3 per 1,000[g]	**1 fewer per 1,000** (2 fewer to 1 fewer)
				Moderate	
				25 per 1,000[c]	**12 fewer per 1,000** (16 fewer to 8 fewer)
Distal Deep Vein Thrombosis - representing the severe marker state (follow-up 10 days to 3 months) assessed with: any Distal DVT	13813 (5 RCTs)	⊕◯◯◯ VERY LOW[b,d,e]	**RR 0.85** (0.56 to 1.29)[h]	Low	
				0 per 1,000[i]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				4 per 1,000[c]	**1 fewer per 1,000** (2 fewer to 1 more)
Major bleeding follow up: range 10 days to 3 months	14415 (11 RCTs)	⊕⊕◯◯ LOW[a]	**RR 1.24** (1.12 to 1.37)	Study population	
				83 per 1,000	**20 more per 1,000** (10 more to 31 more)
				Low	
				5 per 1,000[c]	**1 more per 1,000** (1 more to 2 more)
Reoperation (follow-up 14 days to 35 days)	13645 (3 RCTs)	⊕◯◯◯ VERY LOW[b,j,k]	**RR 1.05** (0.82 to 1.35)	Study population	
				17 per 1,000	**1 more per 1,000** (3 fewer to 6 more)

	a. Only abstracts, or otherwise limited information were available for 6 studies (Agnelli 1992, Galasko 1978, Jorgensen 1992, Kew 1999, Li 2008); randomization not reported or not properly done in 2 studies (Barrie 1974, Sasaki 2008); loss of follow-up >20%, or unexplained drop-out in 5 studies (Agnelli 1992, Galasko 1976, Jorgensen 1992, Kew 1999, Lassen 1989) b. The confidence interval does not exclude an appreciable benefit or no difference c. Gao et al (2016) studied 1177 patients who had HFS between 2008 and 2012. The overall symptomatic VTE rate was 7.9% (73/1177), PE rate was 0.3% (4/1177). The VTE rate in the group non-compliant with thromboprophylaxis group was highest: PE 0.3%; proximal symptomatic DVT: 2.5%; distal symptomatic DVT: 7.1%; major bleeding 0.5% without thromboprophylaxis. Prior history of VTE, hormone replacement therapy and existing cancer increased the odds 2 (cancer) to 15 (hormone replacement) fold. d. Only abstracts, or otherwise limited information available and loss of follow-up >20% or unexplained drop-out in 2 studies (Agnelli 1992, Kew 1999) e. One study used 1,25 Fibrinogen levels as an indicator of VTE (Powers 1989) f. Additional 7 studies measured and reported any DVT, if they were included the RR would be 0.52 [0.39, 0.71] g. The baseline risk consists of the control group event rate (1.4%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic proximal DVT (0.28%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. h. Additional 7 studies measured and reported any DVT, if they were included the RR would be 0.65 [047, 0.91] i. The baseline risk consists of the control group event rate (1.5%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.015 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. j. One study (Lassen 1989) excluded patients post randomization, for multiple reasons, including "reoperation" k. One study (Rodgers 2000) did not explicitly report on "reoperation", however did report on hematoma requiring evacuation, wound infection with frank pus	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		It was pointed out by the panel that the bleeding risk is driven by the study by Rogers et al (aspirin). The estimates may be higher if heparin was used as an antithrombotic agent.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health.The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013)	

	Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		There was moderate benefit and small harm. This judgement is influenced by the certainty of the evidence (very low) and the variability of the values.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	DOACs are not "labelled" for use in HFR in the USA. Aspirin data are not included here but drug cost for aspirin is very low.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis. Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis. However, the cost-effectiveness also depends on the types of pharmacological prophylaxis.	It was felt that the evidence is not sufficiently direct.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Among 3,484 high-risk orthopedic surgery patients, 79% received guideline-recommended treatment with LMWH, UFH, fondaparinux and or VKA at discharge at discharge. Of these, 88% were compliant with therapy after discharge. The most common reason for non-compliance (33.4%) was “drug was not bought”. (Bergqvist 2012)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	Long term administration of LMWH was considered less acceptable by patients. Aspirin was seen as more acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using pharmacological prophylaxis over no pharmacological prophylaxis in surgical patients undergoing surgery for hip fracture repair (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The moderate impact of pharmacological prophylaxis on desirable effect probably outweighs its trivial impact on undesirable effects, although the supporting evidence was judged as very low certainty. There is possibly an important variability in patients' values and preferences and the cost will varies depending on the types of prophylaxis. However, it is considered there are no equity, acceptability or feasibility concerns for the implementation of the intervention.

Subgroup considerations

Patients treated with aspirin were considered in a subgroup analysis. The evidence indicated no subgroup effect with regards to desirable and undesirable effects.

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

None

QUESTION-16

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing hip fracture repair?	
POPULATION:	patients undergoing hip fracture repair
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality (follow-up 10 to 14 days); Pulmonary Embolism - representing the moderate marker state (follow-up 10 to 14 days); Proximal Deep Vein Thrombosis - representing the moderate marker state (follow-up 10 to 14 days); Distal Deep Vein Thrombosis - representing the severe distal DVT marker state (follow-up 10 to 14 days); Major bleeding (follow-up 10 to 14 days); Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH prophylaxis with UFH prophylaxis for prevention of VTE in patients undergoing hip fracture repair.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable. For instance, patients undergoing surgery for hip fracture (HFS) are considered at high risk for post-operative VTE. Gao et al (2016) studied 1177 patients who had HFS between 2008 and 2012. The overall symptomatic VTE rate was 7.9% (73/1177) and PE rate was 0.3% (4/1177). In those not on thromboprophylaxis, the proximal symptomatic DVT rate was 2.5% and the distal symptomatic DVT rate was 7.1%.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
Mortality (follow-up 10 to 14 days)	139 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b]	**RR 0.47** (0.10 to 2.12)	Study population	
				74 per 1,000	**39 fewer per 1,000** (66 fewer to 82 more)
Pulmonary Embolism - representing the moderate marker state (follow-up 10 to 14 days)	251 (3 RCTs)	⨁◯◯◯ VERY LOW[c,d,e]	**RR 2.13** (0.06 to 81.32)	Study population	
				9 per 1,000	**10 more per 1,000** (8 fewer to 711 more)
				Low	
				3 per 1,000[f]	**3 more per 1,000** (3 fewer to 241 more)
Proximal Deep Vein	139 (2 RCTs)	⨁⨁◯◯ LOW[a,g]	**RR 2.24** (0.92 to	Study population	
				88 per 1,000	**100 more**

Thrombosis - representing the moderate marker state (follow-up 10 to 14 days)			5.43)[h]		**per 1,000** (7 fewer to 391 more)
				Moderate	
				25 per 1,000[f]	**31 more per 1,000** (2 fewer to 111 more)
Distal Deep Vein Thrombosis - representing the severe distal DVT marker state (follow-up 10 to 14 days)	139 (2 RCTs)	⊕◯◯◯ VERY LOW[a,i]	**RR 0.66** (0.21 to 2.07)[j]	Study population	
				103 per 1,000	**35 fewer per 1,000** (81 fewer to 110 more)
				Moderate	
				4 per 1,000[f]	**1 fewer per 1,000** (3 fewer to 4 more)
Major bleeding (follow-up 10 to 14 days)	251 (3 RCTs)	⊕◯◯◯ VERY LOW[k,l,m]	**RR 0.85** (0.19 to 3.79)	Study population	
				62 per 1,000	**9 fewer per 1,000** (50 fewer to 173 more)
				Low	
				5 per 1,000[f]	**1 fewer per 1,000** (4 fewer to 14 more)
Reoperation	0 (0 studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. For one study (Pini 1989) only an abstract was available
b. Only 7 events among 139 people; 95% CI does not exclude an appreciable benefit with either intervention. For these reasons, the score was downgraded two level.
c. For two of the studies (Pini 1989, Hoffmann 1996) only the abstracts were available. One of the studies had over 20% loss to follow-up post randomization. For these reasons we rated down for risk of bias by one level.
d. For all studies, reported only as any PE. One study (Monreal 1989) reported

	as high probability VQ scan. e. Only 7 events among 251 patients; 95% CI does not exclude an appreciable benefit with either intervention f. Gao et al (2016) studied 1177 patients who had HFS between 2008 and 2012. The overall symptomatic VTE rate was 7.9% (73/1177), PE rate was 0.3% (4/1177). The VTE rate in the group non-compliant with thromboprophylaxis group was highest: PE 0.3%; proximal symptomatic DVT: 2.5%; distal symptomatic DVT: 7.1%; major bleeding 0.5% without thromboprophylaxis. Prior hi... g. Only 20 events; CI does not exclude an appreciable benefit with LMWH or no difference. h. One additional study (Hoffman 1996) reported only any DVT; if this study was included then RR would be 1.16 [0.35 to 3.79] i. Only 12 events among 139 patients; CI does not exclude an appreciable benefit with either intervention. j. One additional study (Hoffman 1996) reported only any DVT; if this study was included then RR would be 0.55 (0.29 to 1.04) k. For one of the studies (Pini 1989) only the abstract was available, and limited information was available with respect to methodology. Blinding with respect to bleeding outcomes was not specified. For these reasons we rated down for risk of bias by one level. l. There were 13 events among 139 patients; CI does not exclude an appreciable benefit with either intervention. m. Two of the studies only reported data on wound hematoma (Pini, Hoffman) and one study reported on Hematoma and GIB)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65**(standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993**(time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:**	

	For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran£143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	One report compared enoxaparin with unfractionated heparin, and concluded Enoxaparin dominated unfractionated heparin in the thromboprophylaxis for hip fracture patients (Drummond 1994). **Indirect evidence** from total hip or knee arthroplasty, and gynecological surgery patients was used to inform the cost-effectiveness. The results from indirect evidence suggested LMWH cost-effective compared with UFH. (Fowler 2014, Lazo-Langner 2012, Maxwell 2000, Wade 2008).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Among 3,484 high-risk orthopedic surgery patients 79% received guideline-recommended treatment with LMWH, UFH, fondaparinux and or VKA at discharge at discharge. 88% of these patients were compliant with therapy after discharge. The most common reason for non-compliance (33.4%) was “drug was not bought”. (Bergqvist 2012)	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing surgery for hip fracture repair (conditional recommendation based on very low certainty of the evidence about effects).

Justification

This recommendation is based on the panels judgment that the balance of effects favored neither the intervention nor the comparison.

Subgroup considerations

None

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

None

Research priorities

Higher quality studies would be of interest but may not be priority in the field at present.

QUESTION-17

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing major general surgery?	
POPULATION:	Patients undergoing major general surgery
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis- representing the severe marker state; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of pharmacological antithrombotic prophylaxis compared with no antithrombotic prophylaxis in hospitalized patients undergoing major general surgery.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major general surgical procedures is high.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Mortality follow up: range 6 days to 10 weeks	22592 (18 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.75** (0.61 to 0.93)	Study population	
				17 per 1,000	**4 fewer per 1,000** (7 fewer to 1 fewer)
Symptomatic Pulmonary embolism - representing the moderate marker state - Symptomatic PE	18467 (16 RCTs)	⊕⊕⊕◯ MODERATE[b]	**RR 0.48** (0.26 to 0.88)	Study population	
				11 per 1,000	**6 fewer per 1,000** (8 fewer to 1 fewer)
				Low	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic	11806	⊕◯◯◯	**RR 0.38**	Low	

ADDITIONAL CONSIDERATIONS

Proximal DVT- representing the moderate marker state assessed with: any Proximal DVT follow up: range 6 days to 10 weeks	(6 RCTs)	VERY LOW[d,e,f]	(0.14 to 1.00)	2 per 1,000[g]	**1 fewer per 1,000** (2 fewer to 0 fewer)
				Moderate	
				1 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Distal DVT- representing the severe marker state - assessed with: any Distal DVT follow up: range 6 days to 10 weeks	11924 (7 RCTs)	⊕⊕◯◯ LOW[h,i]	**RR 0.52** (0.31 to 0.87)	Low	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				2 per 1,000[c]	**1 fewer per 1,000** (1 fewer to 0 fewer)
Major bleeding	22045 (15 RCTs)	⊕⊕⊕◯ MODERATE[k]	**RR 1.24** (0.87 to 1.77)	Study population	
				26 per 1,000	**6 more per 1,000** (3 fewer to 20 more)
Reoperation	1520 (6 RCTs)	⊕⊕◯◯ LOW[l,m]	**RR 0.93** (0.35 to 2.50)	Study population	
				12 per 1,000	**1 fewer per 1,000** (8 fewer to 18 more)

a. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 3 out of 19 studies and lack of blinding in 5 out of 19 studies.
b. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 5 out of 16 studies.
c. Spyropoulos 2009 reported a rate of 0.3% symptomatic VTE events during index hospitalization. The assumption that 10% were symptomatic PEs and 90% were symptomatic DVTs (20% distal and 80% proximal) was applied.
d. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 3 out of 6 studies. There was not description of the allocation concealment in 6 out of 6 studies.
e. Serious indirectness. Patients included in the studies have diagnostic of proximal DVT

	by screening, and differ importantly from the diagnostic of symptomatic proximal DVT. f. Serious inconsistency. Unexplained inconsistency, with point estimates different (P-value chi square= 0.06; I2=54% %) g. The baseline risk consists of the control group event rate (1.1%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.22%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. h. Serious indirectness. Patients included in the studies have diagnostic of distal DVT by screening, and differ importantly from the diagnostic of symptomatic distal DVT. i. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 7 studies and lack of blinding in 3 out of 7 studies. j. The baseline risk consists of the control group event rate (1.3%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.013 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. k. Serious imprecision. 95% CI is consistent with the possibility of benefit and harm. l. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 6 studies and lack of blinding in 2 out of 6 studies. m. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 17 events in total.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	In this case, the recommendation was sufficiently supported by the favorable impact on desirable effects for which there was higher quality evidence.	Different kinds of procedures are mixed, leading to less confidence in the major bleeding outcome. Panel discussed that the conservative approach would be to judge certainty as low and consider indirectness of the major bleeding/baseline bleeding. The panel also discussed a judgement of moderate based if not downgrading major bleeding for imprecision, but there is the consideration of different bleeding risks in the different major surgeries. Hetereogenious procedures are pooled (not statistical heterogeneity).

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993**(time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015).	

	Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis: For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Three reports compared pharmacological prophylaxis with no pharmacological prophylaxis in patients undergoing major general surgery. In general, pharmacological prophylaxis is cost-effective. However, the cost-effectiveness also depends on the types of pharmacological prophylaxis. (Bergqvist 1996, Hull 1982, Mamdani 1996) Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis (Blondon 2012, Bradley 2010, Hull 1982, Mamdani 1996, Teoh 2011, Wade 2000).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using pharmacological prophylaxis in patients undergoing major general surgery (conditional recommendation based on low certainty of the evidence about effects).

Justification

This recommendation was based on the panel's judgment that the desirable effects probably favor the intervention. The overall certainty of evidence was low.

Subgroup considerations

None

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.

QUESTION-18

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing major general surgery?	
POPULATION:	patients undergoing major general surgery
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal DVT - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major Bleeding ; Reoperation ;
SETTING:	inpatients
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH prophylaxis with UFH prophylaxis for prevention of VTE in patients undergoing major general surgery.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
Mortality follow up: range 7 days to 8 weeks	41896 (35 RCTs)	⨁⨁⨁◯ MODERATE[a,b]	**RR 1.03** (0.89 to 1.18)	Study population	
				18 per 1,000	**1 more per 1,000** (2 fewer to 3 more)
				Low	
				14 per 1,000[c]	**0 fewer per 1,000** (2 fewer to 3 more)
				Moderate	
				52 per 1,000[d]	**2 more per 1,000** (6 fewer to 9 more)
Symptomatic Pulmonary Embolism -	41228 (39 RCTs)	⨁⨁⨁◯ MODERATE[e,f]	**RR 0.91** (0.63 to 1.30)	Study population	
				3 per 1,000	**0 fewer per 1,000**

representing the moderate marker state assessed with: Symptomatic PE follow up: range 7 days to 8 weeks					(1 fewer to 1 more)
				Low	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				1 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal DVT - representing the moderate marker state assessed with: Symptomatic Proximal DVT follow up: range 8 days to 8 weeks	4249 (6 RCTs)	⨁◯◯◯ VERY LOW[i,j]	**RR 1.01** (0.20 to 5.00)	Study population	
				1 per 1,000	**0 fewer per 1,000** (1 fewer to 6 more)
				Low	
				1 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 2 more)
				Moderate	
				5 per 1,000[h]	**0 fewer per 1,000** (4 fewer to 20 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Symptomatic Distal DVT follow up: range 8 days to 8 weeks	4587 (8 RCTs)	⨁◯◯◯ VERY LOW[j,k]	**RR 1.01** (0.30 to 3.44)	Low	
				0 per 1,000[l]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				1 per 1,000[h]	**0 fewer per 1,000**

					(1 fewer to 2 more)
Major Bleeding follow up: range 7 days to 8 weeks	42409 (43 RCTs)	⊕⊕⊕◯ MODERATE[e]	**RR 0.97** (0.78 to 1.20)	Study population	
				16 per 1,000	**0 fewer per 1,000** (4 fewer to 3 more)
				Low	
				15 per 1,000[c]	**0 fewer per 1,000** (3 fewer to 3 more)
				Moderate	
				56 per 1,000[h]	**2 fewer per 1,000** (12 fewer to 11 more)
Reoperation follow up: range 7 days to 8 weeks	12040 (21 RCTs)	⊕⊕⊕◯ MODERATE[m]	**RR 0.79** (0.57 to 1.08)	Study population	
				18 per 1,000	**4 fewer per 1,000** (8 fewer to 1 more)
				Low	
				14 per 1,000[c]	**3 fewer per 1,000** (6 fewer to 1 more)
				Moderate	
				51 per 1,000[d]	**11 fewer per 1,000** (22 fewer to 4 more)

a. Only seven studies reported appropriate allocation concealment
b. Statistical heterogeneity for subgroup analysis (p=0.05) and I2=74% suggested a further decrease on mortality with LMWH (compared with UFH) in studies including more than 50% of patients with cancer treated, than in studies with less than 50% of cancer population.
c. Control group risk in studies with less than 50% of patients with cancer.
d. Control group risk in studies with >=50% of patients with cancer.
e. Only ten studies reported appropriate allocation concealment
f. Probably not enough events to meet optimal information size, limitation downgraded together with RoB.

	g. Spyropoulos 2009 (retrospective cohort- registry type study, N=172,320) reported a rate of 0.3% symptomatic VTE events in patients undergoing abdominal surgery. Baseline-risk estimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.054%) and symptomatic severe distal DVT (0.0108%) in the population undergoing surgery have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVTs and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DVTs and therefore, considered important outcome. h. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis, Changolkar et al. (2014) reported a risk of symptomatic VTE of 3.4%, 2.6% of DVT and 2.6% of PE. Baseline-risk estimates for symptomatic PE (0.068%), symptomatic proximal DVT (0.12%) and symptomatic severe distal DVT (0.024%) have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVTs and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DVTs and therefore, considered important outcome. i. Kakkar 1993 was classified as high risk of bias due to lack of blinding of study participants and outcome assessors j. Very small number of events to meet optimal information size. The confidence interval does not exclude an important benefit or harm. k. The Kakkar (1993), study contributed a 58% to the overall estimation, and was classified as high risk of bias for blinding of study participants and health care providers l. The baseline risk consists of the control group event rate (0.2%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.01%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs m. Only three studies reported appropriate allocation concealment.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them	

	are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Two studies (Bergqvist 1996, Etchells 1999) reported the cost-effectiveness of LMWH compared with UFH in patients undergoing elective general abdominal surgery or elective hip surgery and another one low-dose heparin with heparin in patients after colorectal surgery. These two reports suggested general prophylaxis with LMWH would be more cost-effective than general prophylaxis with unfractionated heparin. Bergqvist (1996) analysed the relative costs were of (1) no prophylaxis against deep vein thrombosis (DVT), (2) selective treatment of DVT after confirmation of diagnosis, (3) general prophylaxis with standard low-dose unfractionated heparin and (4) general prophylaxis with low molecular weight heparin (LMWH) in patients undergoing elective general abdominal surgery or elective hip surgery. The mean calculated costs per patient undergoing general abdominal surgery were: Swedish crowns (SEK) 1950 for no prophylaxis, SEK 5710 for selective treatment of DVT, SEK 735 for prophylaxis with unfractionated heparin and SEK 665 for prophylaxis with LMWH. The corresponding costs for hip surgery were SEK 3930, SEK 10790, SEK 1730 and SEK 1390 respectively. General prophylaxis with LMWH would appear to be more cost-effective than general prophylaxis with unfractionated heparin. Etchells (1999) conducted a decision analysis with an economic perspective of a third-party payer. Although heparin and enoxaparin are equally effective, low-dose heparin is a more economically attractive choice for thromboembolism prophylaxis after colorectal surgery.	The panel considered differences observed between LMWH and UFH were not meaningful.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced	No research evidence was identified.	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for

● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		this population.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue,	Post discharge the feasibility may be different for UFH vs. LMWH

	thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing major general surgery procedures (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The panel judged both desirable and undesirable effects to be trivial and therefore balanced. The overall certainty of evidence was very low.

Subgroup considerations

If extended prophylaxis beyond hospital discharge is planned, LMWH may be given preference.

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

With both UFH and LMWH, patients' platelet count needs to be periodically monitored. With LMWH, renal function needs to be periodically monitored.

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.

QUESTION-19

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing laparoscopic cholecystectomy?	
POPULATION:	Patients undergoing laparoscopic cholecystectomy
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis- representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of pharmacologic prophylaxis with no pharmacologic prophylaxis for prevention of VTE in patients undergoing laparoscopic cholecystectomy.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Based on one study utilizing the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, 30-day postoperative VTE rate after laparoscopic cholecystectomy was 0.2%. Patients who developed VTE had higher mortality and worse outcomes (Alizadeh et al 2017).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Mortality follow up: range 6 days to 10 weeks	22592 (18 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 0.75** (0.61 to 0.93)	Study population	
				17 per 1,000	**4 fewer per 1,000** (7 fewer to 1 fewer)
Symptomatic Pulmonary embolism - representing the moderate marker state - Symptomatic PE	18467 (16 RCTs)	⨁⨁⨁◯ MODERATE[b]	**RR 0.48** (0.26 to 0.88)	Study population	
				11 per 1,000	**6 fewer per 1,000** (8 fewer to 1 fewer)
				Low	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0

					fewer)
Symptomatic Proximal DVT- representing the moderate marker state assessed with: Any Proximal DVT follow up: range 6 days to 10 weeks	11806 (6 RCTs)	⨁◯◯◯ VERY LOW[d,e,f]	**RR 0.38** (0.14 to 1.00)	Low	
				2 per 1,000[g]	**1 fewer per 1,000** (2 fewer to 0 fewer)
				Moderate	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Distal DVT- representing the severe marker state assessed with: Any Distal DVT	11924 (7 RCTs)	⨁⨁◯◯ LOW[h,i]	**RR 0.52** (0.31 to 0.87)	Low	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding	22045 (15 RCTs)	⨁⨁⨁◯ MODERATE[k]	**RR 1.24** (0.87 to 1.77)	Study population	
				26 per 1,000	**6 more per 1,000** (3 fewer to 20 more)
Reoperation	1520 (6 RCTs)	⨁⨁◯◯ LOW[l,m]	**RR 0.93** (0.35 to 2.50)	Study population	
				12 per 1,000	**1 fewer per 1,000** (8 fewer to 18 more)

a. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 3 out of 19 studies and lack of blinding in 5 out of 19 studies.
b. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 5 out of 16 studies.
c. Population-based study report including data from two majors European registries (GallRisk and National Patients Register, Sweden). From a sample of 34,884 patients undergoing laparoscopic cholecystectomies who did not receive any form of prophylaxis the incidence was of 0.186% for any VTE. The assumption that 20% of

	any VTE are symptomatic; 90% are DVTs and 10% are PEs was applied. d. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 3 out of 6 studies. There was not description of the allocation concealment in 6 out of 6 studies. e. Serious indirectness. Patients included in the studies have diagnostic of proximal DVT by screening, and differ importantly from the diagnostic of symptomatic proximal DVT. f. Serious inconsistency. Unexplained inconsistency, with point estimates different (P-value chi square= 0.06; I2=54% %) g. The baseline risk consists of the control group event rate (1.1%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.22%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. h. Serious indirectness. Patients included in the studies have diagnostic of distal DVT by screening, and differ importantly from the diagnostic of symptomatic distal DVT. i. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 7 studies and lack of blinding in 3 out of 7 studies. j. The baseline risk consists of the control group event rate (1.3%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.013 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. k. Serious imprecision. 95% CI is consistent with the possibility of benefit and harm. l. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 6 studies and lack of blinding in 2 out of 6 studies. m. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 17 events in total.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		No surgery specific baseline risk data for major bleeding was available. Only the bleeding risk from trials on major general surgery was available as indirect evidence. The panel considered that undesirable effects were small for major general surgery. The panel discussed that with no formal 'adjustement' factor, bleeding risk is likely lower in laparoscopic cholecystectomy. Based on the absolute effect, the panel decided on a final judgement of small. Assessing 2 available RCTs reporting on laparoscopic cholecystectomy, specifically, in one study there were 8 (2.3%) major bleeding events in the LMWH group and 11 events (3%) in the control group, and no bleeding events reported in either group in the other study.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65**(standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004)	

	Minor intracranial bleeding event: 0.75 (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing laparoscopic cholecystectomy. Indirect evidence based on two studies compared pharmacological prophylaxis with no pharmacological prophylaxis in patients undergoing major general surgery (Bergqvist 1996, Mamdani 1996). In general, pharmacological prophylaxis is cost-effective. However, the cost-effectiveness also depends on the types of pharmacological prophylaxis. Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis (Blondon 2012, Bradley 2010, Hull 1982, Mamdani 1996, Teoh 2011, Wade 2000)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional (47%). Of patients using battery-powered 14% reported major problems, which was 79% with conventional. (Obi 2015) Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early. (Cindolo 2009) **Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests against pharmacological prophylaxis over no prophylaxis in patients undergoing laparoscopic cholecystectomy (conditional recommendation based on low certainty of the evidence about effects).

Justification

This recommendation was based on the panel's judgement the potential desirable effects of pharmacological are outweighed by the undesirable effects. Underlying this judgement is the very low risk of VTE in this patient population.

Subgroup considerations

The above recommendation applies to average risk patients. Patients at increased risk of VTE (for example, due to prior history of VTE) may benefit from pharmacological prophylaxis. The same may apply to patients undergoing this procedure for a rare cancer indication.

Implementation considerations

None.

Monitoring and evaluation

None.

Research priorities

None.

QUESTION-20

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing major neurosurgical procedures?	
POPULATION:	Patients undergoing neurosurgical procedures
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality - RCTs; Mortality - NRS; Symptomatic Pulmonary Embolism - as described by the moderate marker state - RCTs; Symptomatic Pulmonary Embolism - as described by the moderate marker state - NRS ; Symptomatic Proximal Deep Vein Thrombosis - as described by the moderate marker state - RCTs ; Symptomatic Distal Deep Vein Thrombosis - as described by the severe marker state; Major Bleeding - RCTs; Major Bleeding - NRS; Reoperation - RCTs;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of antithrombotic prophylaxis with no antithrombotic prophylaxis in hospitalized patients undergoing neurosurgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients undergoing neurosurgery are at increased risk of venous thromboembolism. Rates of proximal and distal symptomatic DVT in patients receiving no prophylaxis and undergoing elective spinal surgeries (cervical spine, lumbar laminectomy, lumbar spinal fusion, spinal trauma, spinal tumors) were reported in Glotzbecker 2009 1.6% (46/2956) for DVTs and 0.2% (34/15204) for PEs. However, bleeding complications in this population can be associated with significant morbidity. Therefore, the decision for use of pharmacological prophylaxis in neurosurgical patients is particularly challenging.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Mortality - RCTs	1029 (5 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.27** (0.57 to 2.86)	Study population	
				35 per 1,000	**9 more per 1,000** (15 fewer to 65 more)
Mortality - NRS	674 (2 observational studies)	⨁◯◯◯ VERY LOW[c,d,e]	**RR 0.72** (0.46 to 1.13)	Study population	
				115 per 1,000	**32 fewer per 1,000** (62 fewer to 15 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state - RCTs assessed with: Symptomatic	434 (3 RCTs)	⨁◯◯◯ VERY LOW[f,g,h]	**RR 0.84** (0.03 to 27.42)	Study population	
				14 per 1,000	**2 fewer per 1,000** (13 fewer to 359 more)
				Low	
				2 per 1,000[i]	**0 fewer per 1,000** (2 fewer to 53

PE					more)
Symptomatic Pulmonary Embolism - representing the moderate marker state - NRS assessed with: Symptomatic PE	776 (2 observational studies)	⊕◯◯◯ VERY LOW[c,f,j]	**RR 0.18** (0.01 to 3.76)	Study population	
				5 per 1,000	**4 fewer per 1,000** (5 fewer to 13 more)
				Low	
				2 per 1,000[i]	**2 fewer per 1,000** (2 fewer to 6 more)
Symptomatic Proximal DVT - representing the moderate marker state assessed with: Any Proximal DVT	744 (2 RCTs)	⊕⊕◯◯ LOW[k,l]	**RR 0.50** (0.30 to 0.84)[m]	Low	
				23 per 1,000[n]	**11 fewer per 1,000** (16 fewer to 4 fewer)
				Moderate	
				3 per 1,000[o,p]	**2 fewer per 1,000** (2 fewer to 1 fewer)
Symptomatic Distal DVT - representing the severe marker state assessed with: Any Distal DVT	259 (1 RCT)	⊕◯◯◯ VERY LOW[l,q,r]	**RR 0.54** (0.27 to 1.08)[m]	Low	
				2 per 1,000[s]	**1 fewer per 1,000** (1 fewer to 0 fewer)
				Moderate	
				1 per 1,000[o,p]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major Bleeding - RCTs	1156 (7 RCTs)	⊕⊕◯◯ LOW[t,u]	**RR 1.57** (0.70 to 3.50)	Study population	
				17 per 1,000	**10 more per 1,000** (5 fewer to 43 more)
Major Bleeding - NRS	930 (3 observational studies)	⊕◯◯◯ VERY LOW[v,w]	**RR 1.45** (0.30 to 7.12)	Study population	
				7 per 1,000	**3 more per 1,000** (5 fewer to 40

					more)
Reoperation - RCTs	192 (2 RCTs)	⊕◯◯◯ VERY LOW[x,y]	**RR 0.43** (0.06 to 2.84)	Study population	
				31 per 1,000	**18 fewer per 1,000** (29 fewer to 57 more)

a. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of information about the sequence generation process in 3 out of 5 studies and lack of concealment in [2 out of 5 studies.
b. Very serious imprecision. Wide confidence interval with only 45 events in total
c. Serious risk of bias. Studies did not analyze findings adjusting for confounding factors
d. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 66 events in total.
e. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi square= 0.12; I2= 43%)
f. Very serious imprecision. Wide confidence interval with only 5 events in total
g. Serious inconsistency. Moderate heterogeneity between studies: I^2 = 64% (P=0.10)
h. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of blinding of outcome assessment in 2 out of 4 studies.
i. A systematic review of 25 NRS published by Glotzbecker 2009 on elective spinal surgeries (cervical spine, lumbar laminectomy, lumbar spinal fusion, spinal trauma, spinal tumors) reported an incidence of symptomatic PE of 0.2% (34/15204)
j. Serious inconsistency. Moderate inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square= 0.18; I2= 41%).
k. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of information about the incomplete outcome data
l. Serious indirectness. Patients were identified through screening ultrasound. None of the patients developed symptomatic venous thromboembolism before venography.
m. If any DVT detected by screening was considered a surrogate, then six randomized controlled trials (RCT) and two non-randomized studies (NRS) measured it; there were a total of 137 events (53 in prophylaxis group and 84 in no prophylaxis group) among 927 patients for the RCTs, and 72 events (32 in prophylaxis group and 40 in no prophylaxis group) among 415 patients for the NRS. For the RCTs, the RR would be 0.65 (95% CI: 0.47 to 0.89), and the risk difference would be 64 fewer per 1,000 (from 21 fewer to 96 fewer) using the control group event rate of 17.7%, or 1 fewer per 1000 (from 1 fewer to 2 fewer) based on the baseline risk of 0.32%. For the NRS, the RR would be 0.48 (95% CI: 0.29 to 0.81), and the risk difference would be 96 fewer per 1,000 (from 35 fewer to 131 fewer) using the control group event rate of 18.4%, or 2 fewer per 1000 (from 1 fewer to 2 fewer) based on the baseline risk of 0.32%.
n. The baseline risk consists of the control group event rate (11.3%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (2.26%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs.
o. Rates of proximal and distal symptomatic DVT in patients receiving no prophylaxis and undergoing elective spinal surgeries (cervical spine, lumbar laminectomy, lumbar spinal fusion, spinal trauma, spinal tumors) were reported in Glotzbecker

	2009 1.6% (46/2956) for DVTs and 0.2% (34/15204) for PEs p. We applied the assumption that approximately 20% of symptomatic DVTs are proximal, 80% distal and 5% of the latter severe q. One study that carried large weight for the overall effect estimate rated as high risk of bias due to lack of incomplete outcome data. r. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 40 events in total s. The baseline risk consists of the control group event rate (19.4%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.194 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. t. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of random sequence generation and lack of concealment in 4 out of 7 studies u. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 24 events in total. v. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 6 events in total. w. Serious risk of bias. Studies assessed comorbidities associate with high risk of DVT such obesity, heart failure, obesity, cancer, history of DVT, pregnancy, tobacco use, and history of hypercoagulable disorder. However, authors did not adjust for confounding factors. x. Very serious imprecision. Wide confidence interval with only 4 events in total y. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of random sequence generation and allocation concealment] in 1 out of 2 studies and lack of blinding of outcome assessment in 1 out of 2 studies.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015).	

	Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis: For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** **Costs of disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing major neurosurgical procedures. Indirect evidence on other populations suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis. However, the cost-effectiveness also depends on the types of pharmacological prophylaxis. (Blondon 2012, Bradley 2010, Hull 1982, Mamdani 1996, Teoh 2011, Wade 2000)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of	

	789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests not using pharmacological prophylaxis in patients undergoing major neurosurgical procedures (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
Mechanical prophylaxis would be routinely used in this population when possible.

Justification

This recommendation is based on the panel's assessment that the potential desirable effects in the average risk patient are outweighed by the potential undesirable effects.

Subgroup considerations

Pharmacological intervention might still be warranted in high-risk subgroups for example patients immobilized due to brain tumors, spinal cord injury, or with other reasons for prolonged immobility. In addition, based on the type of procedure undertaken, there may be low bleeding risk patients in whom pharmacologic prophylaxis is a consideration.

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.

QUESTION-21

Should LMWH prophylaxis vs. UFH be used for patients undergoing major neurosurgical procedures?	
POPULATION:	patients undergoing major neurosurgical procedures
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major Bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH prophylaxis with UFH prophylaxis in hospitalized patients undergoing neurosurgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients undergoing neurosurgery are at increased risk of venous thromboembolism. Rates of proximal and distal symptomatic DVT in patients receiving no prophylaxis and undergoing elective spinal surgeries (cervical spine, lumbar laminectomy, lumbar spinal fusion, spinal trauma, spinal tumors) were reported in Glotzbecker 2009 1.6% (46/2956) for DVTs and 0.2% (34/15204) for PEs. However, bleeding complications in this population can be associated with significant morbidity. Therefore, the decision for use of pharmacological prophylaxis in neurosurgical patients is particularly challenging.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH	Risk difference with LMWH prophylaxis
Mortality	795 (5 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 0.34** (0.04 to 3.21)	Study population	
				5 per 1,000	**3 fewer per 1,000** (5 fewer to 11 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: Any PE	300 (2 RCTs)	⨁⨁◯◯ LOW[b,c]	**RR 0.20** (0.01 to 4.03)[d]	Low	
				3 per 1,000[e]	**2 fewer per 1,000** (3 fewer to 8 more)
				Moderate	
				2 per 1,000[f]	**1 fewer per 1,000** (2 fewer to 5 more)
				High	

				46 per 1,000[g]	**37 fewer per 1,000** (46 fewer to 139 more)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: Any Proximal DVT	150 (1 RCT)	⊕◯◯◯ VERY LOW[h,i,j]	**RR 1.00** (0.14 to 6.91)[k,l]	Low	
				5 per 1,000[m]	**0 fewer per 1,000** (5 fewer to 32 more)
				Moderate	
				3 per 1,000[n]	**0 fewer per 1,000** (2 fewer to 17 more)
				High	
				7 per 1,000[o]	**0 fewer per 1,000** (6 fewer to 41 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Any Distal DVT	200 (1 RCT)	⊕◯◯◯ VERY LOW[c,j,p]	**RR 0.33** (0.01 to 7.93)[k,l]	Low	
				0 per 1,000[q]	**0 fewer per 1,000** (0 fewer to 1 more)
				Moderate	
				1 per 1,000[r]	**0 fewer per 1,000** (1 fewer to 4 more)
				High	
				1 per 1,000[s]	**1 fewer per 1,000** (1 fewer to 10 more)
Major Bleeding	629 (4 RCTs)	⊕⊕◯◯ LOW[t,u]	**RR 0.76** (0.20 to 2.95)	Study population	
				22 per 1,000	**5 fewer per 1,000** (18 fewer to 43 more)
Reoperation	200	⊕◯◯◯	not	Study population	

	(1 RCT)	VERY LOW[v,w]	estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of allocation concealment in 4 out of 5 studies, and high risk of bias due to lack of blinding in 1 out of 5 studies.
b. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 2 events in total.
c. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of allocation concealment and lack of blinding.
d. If PE assessed by clinical suspicion was considered a surrogate for PE representing the moderate marker state, then two randomized controlled trials (RCT) measured it; there were a total of 3 events among 345 patients (1 in LMWH group and 2 in UFH group). The RR would be 0.54 (0.05 to 5.81), and the risk difference would be 5 fewer per 1,000 (from 11 fewer to 54 more).
e. The baseline risk consists of the control group event rate (1.4%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic PE (0.28%) has been calculated applying the assumptions that 20% of any PE are symptomatic PE.
f. A retrospective analysis based on data from 244 US hospitals (Fang 2011) reported a rate of symptomatic PE of 0.16%. Patients in this report we undergoing spinal fusion procedures.
g. A retrospective analysis of 581 patients undergoing surgery for intracranial meningioma (Hoefnagel 2014) reported a rate of symptomatic PE of 4.6%.
h. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 4 events among 150 patients.
i. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of concealment.
j. Serious indirectness. Patients were identified through screening ultrasound. None of the patients developed symptomatic venous thromboembolism before venography.
k. If any DVT detected by screening was considered a surrogate, then two randomized controlled trials (RCT) measured it; there were a total of 8 events (5 in LMWH group and 3 in UFH group) among 279 patients. The RR would be 1.60 (95% CI: 0.42 to 6.06), and the risk difference would be 13 more per 1,000 (from 12 fewer to 108 more) using the control group risk of 2.1%.
l. If any symptomatic DVT was considered a surrogate, then three randomized controlled trials (RCT) measured it; there were a total of 29 events (14 in LMWH group and 15 in UFH group) among 416 patients. The RR would be 1.14 (0.35 to 3.69), and the risk difference would be 10 more per 1,000 (from 46 fewer to 192 more) using the control group risk of 7.1%.
m. The baseline risk consists of the control group event rate (2.7%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.54%) has been calculated applying the

	assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. n. A retrospective analysis based on data from 244 US hospitals (Fang 2011) reported a rate of symptomatic proximal DVT of 0.288%. Patients in this report we undergoing spinal fusion procedures. o. A retrospective analysis of 581 patients undergoing surgery for intracranial meningioma (Hoefnagel 2014) reported a rate of symptomatic proximal DVT of 0.7%. p. Very serious imprecision. Wide confidence interval with only 1 event among 200 patients and important harm or benefit is still likely or cannot be excluded q. The baseline risk consists of the control group event rate (1.0%) from studies included sin the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.01 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. r. A retrospective analysis based on data from 244 US hospitals (Fang 2011) reported a rate of symptomatic distal DVT of 0.0576%. Patients in this report we undergoing spinal fusion procedures. s. A retrospective analysis of 581 patients undergoing surgery for intracranial meningioma (Hoefnagel 2014) reported a rate of symptomatic distal DVT of 0.14%. t. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of concealment, and lack of blinding outcome assessment in 3 out of 4 studies. u. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 11 events in total. v. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as unclear risk of bias due to lack of concealment, and lack of blinding. w. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, with zero events in total.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994)	

	Treatment with LMWH: 0.993 (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** **Costs of disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and	

	$4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing major neurosurgical procedures. Indirect evidence from total hip or knee arthroplasty, and gynecological surgery patients was used to inform the cost-effectiveness. The results from indirect evidence suggested LMWH cost-effective compared with UFH (Bergqvist 1996, Drummond 1994, Etchells 1999, Fowler 2014a, Lazo-Langner 2012, Maxwell 2000, Wade 2008).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced	No research evidence identified	The panel judged that there would be no impact on equity,

○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and	

	logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using LMWH over UFH in patients undergoing major neurosurgical procedures (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
This recommendation is applicable to the subset of patients deemed at high risk of VTE in whom pharmacological prophylaxis appears indicated (see Q 20).

Justification

UFH may be favored over LMWH in cranial surgery patients due to higher risk of bleeding events.
The finding that UH may be favored over LMWH comes from observational studies suggesting UH may have lower bleeding rates. However, this data was not seen in RCT.
Mechanical prophylaxis (pneumatic compression) is routinely used in this population.

Subgroup considerations

Both agents should be used with caution in patients at high risk of bleeding.

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.
Further high quality observational studies may be helpful to identify higher risk patients for VTE and major bleeding with use of anticoagulant prophylaxis.

QUESTION-22

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing transurethral resection of the prostate?	
POPULATION:	Patients undergoing transurethral resection of the prostate
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major Bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of pharmacological antithrombotic prophylaxis with no pharmacologic prophylaxis in hospitalized patients undergoing transurethral resection of the prostate.

ASSESSMENT

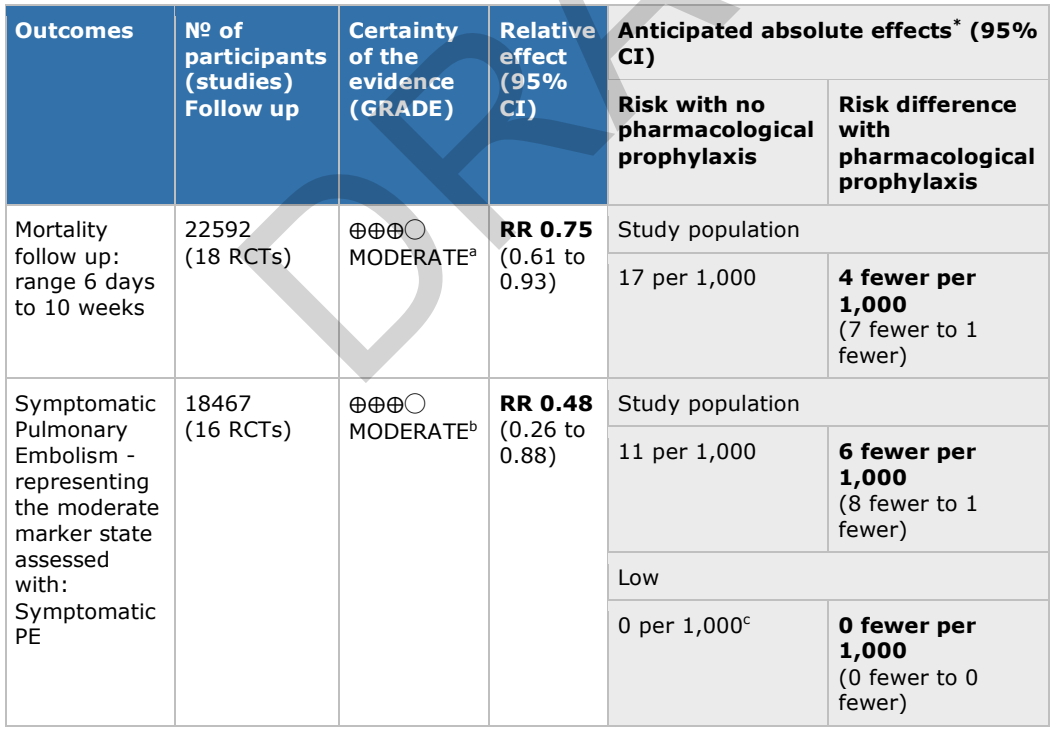
Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is substantial practice variation in utilization of VTE prophylaxis in urologic surgeries likely due to the variability in baseline risk for VTE and bleeding in the different urologic surgeries (Tikkinen et al. 2018). Specifically with regard to TURP, one survey of British urologists revealed that despite a lack of clear evidence or guidelines 280 of 362 (77%) of respondents routinely used VTE prophylaxis with TURP; 230 of the 280 urologists who took precautions used mechanical methods; 50 used low dose heparin, either with stockings or alone (Golash et al. 2002). This question is a high priority because of the frequency of this procedure, the post-operative risk of VTE, the serious consequences of excessive bleeding with pharmacologic prophylaxis. However, the specific trade-off between baseline risk of VTE and risk of bleeding with pharmacological prophylaxis in TURP patients is unknown.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		The panel considered the desirable effects to be comparable to the one of laparoscopic cholecystectomy surgery.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Mortality follow up: range 6 days to 10 weeks	22592 (18 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.75** (0.61 to 0.93)	Study population	
				17 per 1,000	**4 fewer per 1,000** (7 fewer to 1 fewer)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: Symptomatic PE	18467 (16 RCTs)	⊕⊕⊕◯ MODERATE[b]	**RR 0.48** (0.26 to 0.88)	Study population	
				11 per 1,000	**6 fewer per 1,000** (8 fewer to 1 fewer)
				Low	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)

				High	
				1 per 1,000[c]	**0 fewer per 1,000** (1 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: Any Proximal DVT follow up: range 6 days to 10 weeks	11806 (6 RCTs)	⊕◯◯◯ VERY LOW[d,e,f]	**RR 0.38** (0.14 to 1.00)	Low	
				2 per 1,000[g]	**1 fewer per 1,000** (2 fewer to 0 fewer)
				Moderate	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				1 per 1,000[c]	**1 fewer per 1,000** (1 fewer to 0 fewer)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Any Distal DVT follow up: range 6 days to 10 weeks	11924 (7 RCTs)	⊕⊕◯◯ LOW[h,i]	**RR 0.52** (0.31 to 0.87)	Low	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding	22045 (15 RCTs)	⊕⊕⊕◯ MODERATE[k]	**RR 1.24** (0.87 to 1.77)	Study population	
				26 per 1,000	**6 more per 1,000** (3 fewer to 20 more)

Reoperation	1520 (6 RCTs)	⊕⊕◯◯ LOW[l,m]	**RR 0.93** (0.35 to 2.50)	Study population	
				12 per 1,000	**1 fewer per 1,000** (8 fewer to 18 more)
				Low	
				2 per 1,000[n]	**0 fewer per 1,000** (1 fewer to 3 more)

a. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 3 out of 19 studies and lack of blinding in 5 out of 19 studies.
b. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 5 out of 16 studies.
c. Tikkinen et al. (2018) reported, in patients undergoing TURP, a baseline-risk of symptomatic VTE of 0.2% (low-risk group) and 0.8% (high-risk group). Baseline-risk estimates for symptomatic PE, symptomatic proximal DVT and symptomatic distal DVT have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PEs and 90% are symptomatic DVTs; 20% of all the symptomatic DVTs are symptomatic proximal DVTs and 5% of the remainder part are symptomatic distal DVTs.
d. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 3 out of 6 studies. There was not description of the allocation concealment in 6 out of 6 studies.
e. Serious indirectness. Patients included in the studies have diagnostic of proximal DVT by screening, and differ importantly from the diagnostic of symptomatic proximal DVT.
f. Serious inconsistency. Unexplained inconsistency, with point estimates different (P-value chi square= 0.06; I2=54% %)
g. The baseline risk consists of the control group event rate (1.1%) from studies included sin the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.22%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs.
h. Serious indirectness. Patients included in the studies have diagnostic of distal DVT by screening, and differ importantly from the diagnostic of symptomatic distal DVT.
i. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 7 studies and lack of blinding in 3 out of 7 studies.
j. The baseline risk consists of the control group event rate (1.3%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.013 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs
k. Serious imprecision. 95% CI is consistent with the possibility of benefit and harm.
l. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 6 studies and lack of blinding in 2 out of 6 studies.
m. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 17 events in total.

	n. The review by Tikkinen et al. (2017) indicates a baseline risk of 0.2% reoperation due to bleeding in patients not prophylaxed undergoing TURP.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		The panel discussed whether the control group event rate for major bleeding from trials including major general surgery patients was reflective of the event rate that would be seen in patients undergoing TURP. The panel deemed that the event rates for these surgery types would be similar. Furthermore, the panel discussed the reported event rates from the ROTBUS systematic review (Tikkinen et al. 2017) for re-operation due to major bleeding in TURP patients were thought to be an underestimate due to the method of reporting and possible publication bias.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95** (time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Baseline VTE rates and bleeding were considered as making this judgment.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgment of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing transurethral resection of the prostate. Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis (Bergqvist 1996, Hull 1982, Mamdani 1996)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional (47%). Of patients using battery-powered 14% reported major problems, which was 79% with conventional. (Obi 2015) Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early. (Cindolo 2009) **Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The ASH guideline suggests against pharmacological prophylaxis in undergoing transurethral resection of the prostate (conditional recommendation based on low certainty of the evidence about effects).

Justification

This recommendation is largely driven by low quality evidence indicating risk of bleeding with pharmacologic prophylaxis outweighing the benefit in regards to VTE prevention in addition to the moderate costs required for universal implementation of pharmacologic prophylaxis in this commonly performed procedure.

Subgroup considerations

None

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.
Further studies patient values regarding prevention of VTE and bleeding would allow for optimal shared decision-making regarding thromboprophylaxis for TURP.

QUESTION-23

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing transurethral resection of the prostate?	
POPULATION:	patients undergoing transurethral resection of the prostate
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing moderate marker state; Symptomatic Proximal DVT - representing moderate marker state; Symptomatic Distal DVT - representing severe marker state; Major Bleeding ; Reoperation ;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH prophylaxis with UFH prophylaxis for prevention of VTE in patients undergoing transurethral resection of the prostate.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is substantial practice variation in utilization of VTE prophylaxis in urologic surgeries likely due to the variability in baseline risk for VTE and bleeding in the different urologic surgeries (Tikkinen et al. 2018). Specifically with regard to TURP, one survey of British urologists revealed that despite a lack of clear evidence or guidelines 280 of 362 (77%) of respondents routinely used VTE prophylaxis with TURP; 230 of the 280 urologists who took precautions used mechanical methods; 50 used low dose heparin, either with stockings or alone (Golash et al. 2002). This question is a high priority because of the frequency of this procedure, the post-operative risk of VTE, the serious consequences of excessive bleeding with pharmacologic prophylaxis. However, the specific trade-off between baseline risk of VTE and risk of bleeding with pharmacological prophylaxis in TURP patients is unknown.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
Mortality follow up: range 7 days to 8 weeks	41896 (35 RCTs)	⨁⨁◯◯ LOW[a,b,c]	**RR 1.03** (0.89 to 1.18)	Study population	
				18 per 1,000	**1 more per 1,000** (2 fewer to 3 more)
				Low	
				14 per 1,000[d]	**0 fewer per 1,000** (2 fewer to 3 more)
				Moderate	
				52 per 1,000[e]	**2 more per 1,000** (6 fewer to 9 more)
Symptomatic Pulmonary Embolism - representing moderate marker state	41228 (39 RCTs)	⨁⨁◯◯ LOW[c,f,g]	**RR 0.91** (0.63 to 1.30)	Study population	
				3 per 1,000	**0 fewer per 1,000**

assessed with: Symptomatic PE					(1 fewer to 1 more)
				Low	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				1 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				1 per 1,000[i]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal DVT - representing moderate marker state assessed with: Symptomatic proximal DVT	4249 (6 RCTs)	⨁◯◯◯ VERY LOW[c,j,k]	**RR 1.01** (0.20 to 5.00)	Study population	
				1 per 1,000	**0 fewer per 1,000** (1 fewer to 6 more)
				Low	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				1 per 1,000[h]	**0 fewer per 1,000** (1 fewer to 6 more)
				High	
				5 per 1,000[i]	**0 fewer per 1,000** (4 fewer to 20 more)
Symptomatic Distal DVT - representing severe marker state assessed with: Symptomatic Distal DVT	4587 (8 RCTs)	⨁◯◯◯ VERY LOW[c,j,k]	**RR 1.01** (0.30 to 3.44)	Based on Study population	
				2 per 1,000[l]	**0 fewer per 1,000** (2 fewer to 5 more)
				Low	

				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 1 more)
				Moderate	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 1 more)
				High	
				1 per 1,000[i]	**0 fewer per 1,000** (1 fewer to 2 more)
Major Bleeding	42409 (43 RCTs)	⊕⊕◯◯ LOW[c,f]	**RR 0.97** (0.78 to 1.20)	Study population	
				16 per 1,000	**0 fewer per 1,000** (4 fewer to 3 more)
				Low	
				15 per 1,000[d]	**0 fewer per 1,000** (3 fewer to 3 more)
				Moderate	
				56 per 1,000[m]	**2 fewer per 1,000** (12 fewer to 11 more)
Reoperation	12040 (21 RCTs)	⊕⊕◯◯ LOW[c,n]	**RR 0.79** (0.57 to 1.08)	Study population	
				18 per 1,000	**4 fewer per 1,000** (8 fewer to 1 more)
				Low	
				2 per 1,000[o]	**0 fewer per 1,000** (1 fewer to 0 fewer)
				Moderate	
				51 per 1,000[e]	**11 fewer per 1,000**

					(22 fewer to 4 more)

a. Only seven studies reported appropriate allocation concealment
b. Statistical heterogeneity for subgroup analysis (p=0.05) and I2=74%. Suggesting a further decrease on mortality with LMWH (compared with UFH) in studies including more than 50% of patients with cancer treated , than in studies with less than 50% of cancer population
c. There were no studies of TURP; we extrapolated from major general surgical procedures.
d. Control group risk in studies with less than 50% of patients with cancer.
e. Control group risk in studies with >=50% of patients with cancer.
f. Only ten studies reported appropriate allocation concealment
g. Probably not enough number of events to meet optimal information size, limitation considered together with RoB.
h. Tikkinen et al. (2017) (SR including 38 studies) reported that patients undergoing TURP or equivalent had a baseline-risk of symptomatic VTE of 0.2% (in low-risk group) and 0.8% (in high risk) (N=13320 patients in 4 studies). Baseline-risk estimates for symptomatic PE (0.02% in low-risk patients, 0.08% in high risk), symptomatic proximal DVT (0.036% in low-risk patients, 0.144% in high risk), and symptomatic distal DVT (0.0072% in low-risk patients, 0.0288% in high risk), have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PEs and 90% are symptomatic DVTs; 20% of all the symptomatic DVTs are symptomatic proximal DVTs and 5% of the remainder part are symptomatic distal DVTs
i. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis, Changolkar et al. (2014) reported a risk of symptomatic VTE of 3.4%, 2.6% of DVT and 2.6% of PE. Baseline-risk estimates for symptomatic PE (0.068%), symptomatic proximal DVT (0.12%) and symptomatic severe distal DVT (0.024%) have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVTs and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DVTs and therefore, considered important outcome.
j. Kakkar 1993 was classified as high risk of bias due to lack of blinding of study participants and outcome assessors
k. Very small number of events to meet optimal information size. The confidence interval does not exclude an important benefit or harm.
l. The baseline risk consists of the control group event rate (0.2%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.01%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs
m. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis, Changolkar et al. (2014) reported a risk of 5.6% for major bleeding.
n. Only three studies reported appropriate allocation concealment
o. The review by Tikkinen 2017 indicates a baseline risk of 0.2% bleeding requiring intervention in patients not receiving prophylaxis and undergoing TURP. Anticoagulation will increase that baseline risk and evidence comparing pharmacological prophylaxis versus no pharmacological prophylaxis suggests an increase of 6.72 fold.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013)	

	Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records	

	between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgment of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**<u>Indirect Evidence:</u>** Two studies (Bergqvist 1996, Etchells 1999) reported the cost-effectiveness of LMWH compared with UFH in patients undergoing elective general abdominal surgery or elective hip surgery and another one low-dose heparin with heparin in patients after colorectal surgery. These two reports, considered indirect due to included population, suggested general prophylaxis with LMWH would be more cost-effective than general prophylaxis with unfractionated heparin. Bergqvist (1996) analysed the relative costs were of (1) no prophylaxis against deep vein thrombosis (DVT), (2) selective treatment of DVT after confirmation of diagnosis, (3) general prophylaxis with standard low-dose unfractionated heparin and (4) general prophylaxis with low molecular weight heparin (LMWH) in patients undergoing elective general abdominal surgery or elective hip surgery. The mean calculated costs per patient undergoing general abdominal surgery were: Swedish crowns (SEK) 1950 for no prophylaxis, SEK 5710 for selective treatment of DVT, SEK 735 for prophylaxis with unfractionated heparin and SEK 665 for prophylaxis with LMWH. The corresponding costs for hip surgery were SEK 3930, SEK 10790, SEK 1730 and SEK 1390 respectively. General prophylaxis with LMWH would appear to be more cost-effective than general prophylaxis with unfractionated heparin. Etchells (1999) conducted a decision	The panel considered differences observed between LMWH and UFH were not meaningful. Moreover, there is a lack of direct evidence on TURP population, where results might differ from major surgical populations.

	analysis with an economic perspective of a third-party payer. Although heparin and enoxaparin are equally effective, low-dose heparin is a more economically attractive choice for thromboembolism prophylaxis after colorectal surgery.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003)	Post discharge the feasibility may be different for UFH vs. LMWH.

	A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline suggests using either LMWH or UFH in patients undergoing transurethral resection of the prostate (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
This recommendation is applicable to the subset of patients deemed at high risk of VTE in whom pharmacological prophylaxis appears indicated (see Q 22).

Justification

The trivial difference in effects of the LMWH compared with UFH on both desirable and undesirable outcomes does not suggest a preference for on or the other treatment. Additionally, there was very low certainty of the evidence which was also indirect. On the other hand, there were no concerns regarding the equity, acceptability or feasibility of both intervention alternatives.

Subgroup considerations

None

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.

QUESTION-24

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing radical prostatectomy?	
POPULATION:	Patients undergoing radical prostatectomy
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis- representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of pharmacological antithrombotic prophylaxis with no pharmacologic prophylaxis in hospitalized patients undergoing radical prostatectomy.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients undergoing surgery for prostate cancer remain at increased risk for post-operative VTE. In one population-based observational study of 94,709 men with a diagnosis of prostate cancer who underwent radical prostatectomy between 2000-2010, 35,591 (52.2 %) received mechanical, 4,945 (7.2 %) pharmacologic, 7,720 (10.6 %) combination, and 20,438 (30.0 %) no VTE prophylaxis after radical prostatectomy. This question is a high priority because of the frequency of this procedure, the post-operative risk of VTE, the serious consequences of excessive bleeding with pharmacologic prophylaxis. However the specific trade-off between baseline risk of VTE and risk of bleeding with pharmacological prophylaxis in TURP patients is unknown.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Mortality follow up: range 6 days to 10 weeks	22592 (18 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.75** (0.61 to 0.93)	Study population	
				17 per 1,000	**4 fewer per 1,000** (7 fewer to 1 fewer)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: Symptomatic PE	18467 (16 RCTs)	⊕⊕⊕◯ MODERATE[b]	**RR 0.48** (0.26 to 0.88)	Study population	
				11 per 1,000	**6 fewer per 1,000** (8 fewer to 1 fewer)
				Low	
				1 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)

				High	
				2 per 1,000[c]	**1 fewer per 1,000** (1 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis- representing the moderate marker state assessed with: Any Proximal DVT follow up: range 6 days to 10 weeks	11806 (6 RCTs)	⊕◯◯◯ VERY LOW[d,e,f]	**RR 0.38** (0.14 to 1.00)	Low	
				2 per 1,000[g]	**1 fewer per 1,000** (2 fewer to 0 fewer)
				Moderate	
				1 per 1,000[c]	**1 fewer per 1,000** (1 fewer to 0 fewer)
				High	
				3 per 1,000[c]	**2 fewer per 1,000** (3 fewer to 0 fewer)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Any Distal DVT follow up: range 6 days to 10 weeks	11924 (7 RCTs)	⊕⊕◯◯ LOW[h,i]	**RR 0.52** (0.31 to 0.87)	Low	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				1 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding	22045 (15 RCTs)	⊕⊕⊕◯ MODERATE[k]	**RR 1.24** (0.87 to 1.77)	Study population	
				26 per 1,000	**6 more per 1,000** (3 fewer to 20 more)

Reoperation	1520 (6 RCTs)	⊕⊕◯◯ LOW[l,m]	**RR 0.93** (0.35 to 2.50)	Study population	
				12 per 1,000	**1 fewer per 1,000** (8 fewer to 18 more)
				Low	
				1 per 1,000[n]	**0 fewer per 1,000** (1 fewer to 2 more)
				High	
				14 per 1,000[n]	**1 fewer per 1,000** (9 fewer to 21 more)

a. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 3 out of 19 studies and lack of blinding in 5 out of 19 studies.
b. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 5 out of 16 studies.
c. Tikkinen et al. (2018) reported, in patients undergoing robotic radical prostatectomy with standard pelvic lymph node dissection, a baseline-risk of symptomatic VTE of 0.5% (low-risk group) and 1.9% (high-risk group). Baseline-risk estimates for symptomatic PE, symptomatic proximal DVT and symptomatic distal DVT have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PEs and 90% are symptomatic DVTs; 20% of all the symptomatic DVTs are symptomatic proximal DVTs and 5% of the remainder part are symptomatic distal DVTs.
d. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 3 out of 6 studies. There was not description of the allocation concealment in 6 out of 6 studies.
e. Serious indirectness. Patients included in the studies have diagnostic of proximal DVT by screening, and differ importantly from the diagnostic of symptomatic proximal DVT.
f. Serious inconsistency. Unexplained inconsistency, with point estimates different (P-value chi square= 0.06; I2=54% %)
g. The baseline risk consists of the control group event rate (1.1%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic proximal DVT (0.22%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs.
h. Serious indirectness. Patients included in the studies have diagnostic of distal DVT by screening, and differ importantly from the diagnostic of symptomatic distal DVT.
i. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 7 studies and lack of blinding in 3 out of 7 studies.
j. The baseline risk consists of the control group event rate (1.3%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.013 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs.

	k. Serious imprecision. 95% CI is consistent with the possibility of benefit and harm. l. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 6 studies and lack of blinding in 2 out of 6 studies. m. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 17 events in total. n. The estimates of non-fatal bleeding requiring reoperation range from 0.1% in patients undergoing open prostatectomy without pelvic lymph node dissection (PLND) to 1.4% for patients undergoing laparoscopic prostatectomy with extended PLND (Tikkinen 2017)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016)	

	Deep vein thrombosis patients' own current health: 0.95(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgment of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing radical prostatectomy. Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis (Bergqvist 1996, Hull 1982, Mamdani 1996).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Barriers to implementation of mechanical prophylaxis** Patient compliance with sequential compression devices was higher when using battery-powered (85%) compared with conventional (47%). Of patients using battery-powered 14% reported major problems, which was 79% with conventional. (Obi 2015) Twenty three percent of patients receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the system had to be removed early. (Cindolo 2009) **Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests against pharmacological prophylaxis in patients undergoing radical prostatectomy (conditional recommendation based on low certainty of the evidence about effects).

Justification

This recommendation is based on the panel's assessment that in the average patients undergoing radical prostatectomy (typically: robotic-assisted laparoscopic prostatectomy with no or limited lymph node dissection), the undesirable effects of pharmacological prophylaxis outweigh the benefits.

Subgroup considerations

None

Implementation considerations

Patients undergoing an extended node dissection and/or open radical prostatectomy may have a higher VTE risk and potentially benefit from pharmacological prophylaxis.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.
Further studies patient values regarding prevention of VTE and bleeding would allow for optimal shared decision-making regarding thromboprophylaxis for radical prostatectomy.

QUESTION-25

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing radical prostatectomy ?	
POPULATION:	patients undergoing radical prostatectomy
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality ; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state ; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state ; Major Bleeding ; Reoperation ;
SETTING:	inpatients
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH prophylaxis with UFH prophylaxis for prevention of VTE in patients undergoing radical prostatectomy.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients undergoing surgery for prostate cancer remain at increased risk for post-operative VGTE. In one population-based observational study of 94,709 men with a diagnosis of prostate cancer who underwent RP between 2000-2010, 35,591 (52.2 %) received mechanical, 4,945 (7.2 %) pharmacologic, 7,720 (10.6 %) combination, and 20,438 (30.0 %) no VTE prophylaxis after radical prostatectomy. This question is a high priority because of the frequency of this procedure, the post-operative risk of VTE, the serious consequences of excessive bleeding with pharmacologic prophylaxis. However, the specific trade-off between baseline risk of VTE and risk of bleeding with pharmacological prophylaxis in TURP patients is unknown.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
Mortality follow up: range 7 days to 8 weeks	41896 (35 RCTs)	⨁⨁◯◯ LOW[a,b,c]	**RR 1.03** (0.89 to 1.18)	Study population	
				18 per 1,000	**1 more per 1,000** (2 fewer to 3 more)
				Low	
				14 per 1,000[d]	**0 fewer per 1,000** (2 fewer to 3 more)
				Moderate	
				52 per 1,000[e]	**2 more per 1,000** (6 fewer to 9

					more)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: Symptomatic PE follow up: range 7 days to 8 weeks	41228 (39 RCTs)	⊕⊕◯◯ LOW[c,f,g]	**RR 0.91** (0.63 to 1.30)	Study population	
				3 per 1,000	**0 fewer per 1,000** (1 fewer to 1 more)
				Low	
				1 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				19 per 1,000[h]	**2 fewer per 1,000** (7 fewer to 6 more)
				High	
				1 per 1,000[i]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: symptomatic Proximal DVT follow up: range 8 days to 8 weeks	4249 (6 RCTs)	⊕◯◯◯ VERY LOW[c,j,k]	**RR 1.01** (0.20 to 5.00)	Study population	
				1 per 1,000	**0 fewer per 1,000** (1 fewer to 6 more)
				Low	
				1 per 1,000[h]	**0 fewer per 1,000** (1 fewer to 4 more)
				Moderate	
				3 per 1,000[h]	**0 fewer per 1,000** (3 fewer to 14 more)
				High	
				5 per 1,000[i]	**0 fewer per 1,000** (4 fewer to

					20 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: symptomatic distal DVT follow up: range 8 days to 8 weeks	4587 (8 RCTs)	⊕◯◯◯ VERY LOW[c,j,k]	**RR 1.01** (0.30 to 3.44)	Based on study population BLR	
				2 per 1,000[l]	**0 fewer per 1,000** (2 fewer to 5 more)
				Low	
				0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				1 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 2 more)
				High	
				1 per 1,000[i]	**0 fewer per 1,000** (1 fewer to 2 more)
Major Bleeding follow up: range 7 days to 8 weeks	42409 (43 RCTs)	⊕⊕◯◯ LOW[c,f]	**RR 0.97** (0.78 to 1.20)	Study population	
				16 per 1,000	**0 fewer per 1,000** (4 fewer to 3 more)
				Low	
				15 per 1,000[d]	**0 fewer per 1,000** (3 fewer to 3 more)
				Moderate	
				56 per 1,000[m]	**2 fewer per 1,000** (12 fewer to 11 more)
Reoperation follow up: range 7 days	12040 (21 RCTs)	⊕⊕◯◯ LOW[c,n]	**RR 0.79** (0.57 to 1.08)	Low	
				18 per 1,000[o]	**4 fewer per 1,000**

to 8 weeks					(8 fewer to 1 fewer)
				Moderate	
				14 per 1,000 [o]	**3 fewer per 1,000** (0 fewer to 0 fewer)
				High	
				51 per 1,000[e]	**11 fewer per 1,000** (22 fewer to 4 more)

a. Only seven studies reported appropriate allocation concealment
b. Statistical heterogeneity for subgroup analysis (p=0.05) and I2=74%. A further decrease on mortality with LMWH (compared with UFH) is suggested in studies including more than 50% of patients with cancer , than in studies with less than 50% of cancer population
c. Only one study (Boncinelli 2001) was conducted in patients undergoing radical prostatectomy; Most of the evidence was extrapolated from major general surgical procedures.
d. Control group risk in studies with less than 50% of patients with cancer.
e. Control group risk in studies with >=50% of patients with cancer.
f. Only ten studies reported appropriate allocation concealment
g. Probably not enough events to meet optimal information size, limitation considered together with RoB.
h. In patients undergoing robotic radical prostatectomy with standard pelvic lymph node dissection Tikkinen et al. (2017) reported, a baseline-risk of symptomatic VTE of 0.5% (low-risk group) and 1.9% (high-risk group) (N=6362 patients in 7 studies). Baseline-risk estimates for symptomatic PE (0.05% and 0.19%), symptomatic proximal DVT (0.09% and 0.342%) and symptomatic distal DVT (0.12% and 0.5%) have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PEs and 90% are symptomatic DVTs; 20% of all the symptomatic DVTs are symptomatic proximal DVTs and 5% of the remainder part are symptomatic distal DVTs.
i. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis Changolkar et al. (2014) reported,, a risk of symptomatic VTE of 3.4%, 2.6% of DVT and 2.6% of PE. Baseline-risk estimates for symptomatic PE (0.068%), symptomatic proximal DVT (0.12%) and symptomatic severe distal DVT (0.024%) have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVTs and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DVTs and therefore, considered important outcome.
j. Kakkar (1993) was classified as high risk of bias for blinding of study participants and health care providers.
k. Very small number of events to meet optimal information size. The

	confidence interval does not exclude an important benefit or harm. l. The baseline risk consists of the control group event rate (0.2%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.01%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs m. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis, Changolkar et al. (2014) reported, a risk of 5.6% for major bleeding. n. Only three studies reported appropriate allocation concealment o. The estimates of non-fatal bleeding requiring reoperation range from 0.1% in patients undergoing open prostatectomy without pelvic lymph node dissection (PLND) to 1.4% for patients undergoing laparoscopic prostatectomy with extended PLND (Tikkinen 2017).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	No direct evidence was identified for the specific population.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**Indirect Evidence:** Two studies (Bergqvist 1996, Etchells 1999) reported the cost-effectiveness of LMWH compared with UFH in patients undergoing elective general abdominal surgery or elective hip surgery and another one low-dose heparin with heparin in patients after colorectal surgery. These two reports, considered indirect due to included population, suggested general prophylaxis with LMWH would be more cost-effective than general prophylaxis with unfractionated heparin. Bergqvist (1996) analysed the relative costs were of (1) no prophylaxis against deep vein thrombosis (DVT), (2) selective treatment of DVT after confirmation of diagnosis, (3) general prophylaxis with standard low-dose unfractionated heparin and (4) general prophylaxis with low molecular weight heparin (LMWH) in patients undergoing elective general abdominal surgery or elective hip surgery. The mean calculated costs per patient undergoing general abdominal surgery were: Swedish crowns (SEK) 1950 for no prophylaxis, SEK 5710 for selective treatment of DVT, SEK 735 for prophylaxis with unfractionated heparin and SEK 665 for prophylaxis with LMWH. The corresponding costs for hip surgery were SEK 3930, SEK 10790, SEK 1730 and SEK 1390 respectively. General prophylaxis with LMWH would appear to be more cost-effective than general prophylaxis with unfractionated heparin. Etchells (1999) conducted a decision analysis with an economic perspective of a third-party payer. Although heparin and enoxaparin are equally effective, low-dose heparin is a more economically attractive choice for thromboembolism prophylaxis after colorectal surgery.	The panel considered differences observed between LMWH and UFH were not meaningful. Moreover, there is a lack of direct evidence on radical prostatectomy population, where results might differ from major surgical populations.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use	Post discharge the feasibility may be different for LMWH vs. UFH

	of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing radical prostatectomy (conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
This recommendation is applicable to the subset of patients deemed at high risk of VTE in whom pharmacological prophylaxis appears indicated (see Q 24).

Justification

The trivial effect of the LMWH compared with UFH on both desirable and undesirable outcomes does not favour a balance of the effect in any directions, moreover considering the very low certainty of the evidence and the indirectness of the evidence, with estimates from studies from major general surgical procedures. On the other hand, no concerns were considered regarding the equity, acceptability or feasibility of both intervention alternatives.

Subgroup considerations

None

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

None

Research priorities

Further high quality comparative studies, using appropriate clinical outcomes would be of value to add more certainty to these recommendations.
Further studies patient values regarding prevention of VTE and bleeding would allow for optimal shared decision-making regarding thromboprophylaxis for radical prostatectomy

QUESTION-26

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing cardiac or major vascular surgery?	
POPULATION:	patients undergoing cardiac or major vascular surgery
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Major bleeding; Reoperation - not reported; Venous thromboembolism (evidence from one non-randomised controlled study); Major bleeding (evidence from one non-randomised controlled study);
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of pharmacological thromboprophylaxis with no thromboprophylaxis in hospitalized patients undergoing cardiac or major vascular surgery.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both the frequency and relatively high post-operative risk of VTE make this a high priority question. In the absence of prophylaxis the incidence of symptomatic VTE in patients undergoing cardiac surgery is 0.5 to 3.0% (Di Nisio, 2015). It is critical to define both the benefits and risks of pharmacologic prophylaxis in these patients after surgery.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	<table><tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><th>Risk with no pharmacological prophylaxis</th><th>Risk difference with pharmacological prophylaxis</th></tr><tr><td>Mortality</td><td>76 (1 RCT)</td><td>⨁⨁◯◯ LOW[a]</td><td>not estimable</td><td>Study population</td><td></td></tr><tr><td></td><td></td><td></td><td></td><td>0 per 1,000</td><td>0 fewer per 1,000 (0 fewer to 0 fewer)</td></tr><tr><td>Symptomatic Pulmonary Embolism - representing the moderate marker state assessed</td><td>119 (2 RCTs)</td><td>⨁⨁◯◯ LOW[b,c]</td><td>RR 2.40 (0.10 to 55.79)</td><td>Low</td><td></td></tr><tr><td></td><td></td><td></td><td></td><td>4 per 1,000[d]</td><td>5 more per 1,000 (3 fewer to 198 more)</td></tr></table>	The panel discussed use of indirect evidence. Question is about post-op low dose prophylactic anticoagulant. The panel discussed that during surgery most patients will get therapeutic dose of heparin for prevention of graft thrombosis.

with: any PE				Moderate		
				4 per 1,000[e]	**5 more per 1,000** (3 fewer to 198 more)	
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: Any Proximal DVT	82 (2 RCTs)	⊕⊕◯◯ LOW[b,c,f]	**RR 2.85** (0.12 to 67.83)	Low		
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 0 fewer)	
				Moderate		
				7 per 1,000[e]	**12 more per 1,000** (6 fewer to 435 more)	
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: Any Distal DVT	82 (1 RCT)	⊕◯◯◯ VERY LOW[c,h]	**RR 0.32** (0.01 to 7.54)	Low		
				0 per 1,000[i]	**0 fewer per 1,000** (0 fewer to 2 more)	
				Moderate		
				1 per 1,000[j]	**1 fewer per 1,000** (1 fewer to 9 more)	
Major bleeding	76 (1 RCT)	⊕⊕◯◯ LOW[c]	**RR 2.85** (0.12 to 67.83)	Study population		
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)	

Reoperation - not reported	0 (studies)	-	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. No or very few events and a small number of patients in the studies
b. Unclear risk of bias in several domains, but we did not downgrade because the outcome evaluation was blinded. Most information is from studies at low or unclear risk of bias.
c. No or very few events and a small number of patients in the studies, in a clinical scenario where PEs, DVTs and major bleedings are likely to occur
d. The baseline risk consists of the control group event rate (0%) from studies included sin the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs.
e. Baseline risk for symptomatic VTE calculated from control arm of trials in Ho 2015: 53/1463 = 3.62 %. The assumption that 10% of symptomatic VTE events are PE applies. All proximal DVTs are assumed to be moderate. The duration of follow-up likely varied between the included RCTs
f. Although the outcome in the studies was symptomatic and proximal DVT, the relative effect was considered to be direct, because symptomatic and proximal DVT are good surrogates for proximal DVT representing the moderate marker state.
g. The baseline risk consists of the control group event rate (0%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs.
h. Serious indirectness. Patients were identified through duplex ultrasound. One patient assigned to the placebo group developed an asymptomatic right peroneal DVT, detected by DUS at the time of discharge from the hospital
i. The baseline risk consists of the control group event rate (2.4%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.024 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs.
j. Lowest baseline risk in the low risk group from Ho 2015 and the highest estimate (from trials) provided assuming that 80% of the DVTs (representing 90% of all VTEs) are distal and 5% of those severe distal DVTs

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		The risk of HIT development, although not prioritized as a critical outcome, was discussed using additional evidence from observational studies on UFH and LMHW, as there were no comparative RCT data in HIT for LMWH vs. UFH. The findings suggest a lower risk of developing HIT in patient treated with LMWH compared with those treated with UFH. (Kuitunen 2007, Martel 2005, Pouplard 1999, Smythe 2007).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013)	

	Central nervous system bleeding: range 0.29-0.60 (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel considered data for HIT in this population – which was not reported in the 3 included trials. Post-operative exposure may be a significant consideration given that these patients receive heparin during procedure.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	The indirect evidence was considered too indirect to be considered. The judgement is based on panel discussion. The panel discussed cost of prophylaxis compared to overall cost of procedures (as small percentage), as well as volume cost considering number of procedures, which was considered moderate.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgment of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing cardiac or major vascular surgery. Indirect evidence in other populations suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis. However, the cost-effectiveness also depends on the types of pharmacological prophylaxis (Bergqvist 1996, Borris 1994, Borris 1996, Brosa Riestra 2003, Nerurkar 2002).	The panel considered there is uncertainty about the effectiveness, however additional cost for using the intervention is required.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the concern limiting the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015)	

	An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either pharmacological prophylaxis or no prophylaxis in patients undergoing cardiac and major vascular surgical procedures (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The panel judged both desirable and undesirable effects to be trivial and therefore balanced. The certainty of evidence was very low. The risk of HIT (although not prioritized as a critical outcome) was discussed using additional evidence.

Subgroup considerations

In patient at a higher risk of VTE (previous history of VTE) prophylaxis might be considered over no prophylaxis.

Implementation considerations

None

Monitoring and evaluation

The panel suggests periodically monitoring patients' platelet counts.

Research priorities

Further research is needed to determine the role of pharmacologic prophylaxis in this population. Further research on the impact of postoperative heparin exposure on the development of HIT in cardiovascular surgery patients is needed.

QUESTION-27

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing cardiac or major vascular surgery?	
POPULATION:	patients undergoing cardiac or major vascular surgery
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe distal DVT marker state; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of LMWH thromboprophylaxis with UFH thromboprophylaxis in hospitalized patients undergoing cardiac or major vascular surgery

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both the frequency and relatively high post-operative risk of VTE make this a high priority question. In the absence of prophylaxis the incidence of symptomatic VTE in patients undergoing cardiac surgery is 0.5 to 3.0% (Di Nisio, 2015). It is critical to define both the benefits and risks of pharmacologic prophylaxis in these patients after surgery.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
Mortality	233 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 4.55** (0.22 to 93.81)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Pulmonary Embolism - representing	233 (1 RCT)	⨁⨁◯◯ LOW[a,b]	not estimable	Low	
				0 per 1,000[c]	**0 fewer per 1,000**

the moderate marker state assessed with: any PE					(0 fewer to 0 fewer)	
				Moderate		
				4 per 1,000[d]	**4 fewer per 1,000** (4 fewer to 4 fewer)	
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any DVT, one study reporting proximal DVT	364 (3 RCTs)	⊕◯◯◯ VERY LOW[a,b,e]	**RR 1.33** (0.30 to 6.01)	Low		
				6 per 1,000[f]	**2 more per 1,000** (4 fewer to 28 more)	
				Moderate		
				33 per 1,000[d]	**11 more per 1,000** (23 fewer to 165 more)	
Symptomatic Distal Deep Vein Thrombosis - representing the severe distal DVT marker state assessed with: any DVT, one study reporting distal DVT	364 (3 RCTs)	⊕◯◯◯ VERY LOW[a,b,e]	**RR 1.20** (0.45 to 3.22)	Low		
				0 per 1,000[g]	**0 fewer per 1,000** (0 fewer to 1 more)	
				Moderate		
				1 per 1,000[h]	**0 fewer per 1,000** (1 fewer to 2 more)	

Major bleeding	233 (1 RCT)	⊕⊕◯◯ LOW[a,b]	**RR 0.91** (0.19 to 4.42)	Study population	
				27 per 1,000	**2 fewer per 1,000** (22 fewer to 92 more)
Reoperation - not reported	-	-	-	**-**	**-**

a. The dose used in Farkas 1993 (7500 units q 12 hours) was higher than use in practice
b. No or very few events, in a clinical scenario where PEs, DVTs and major bleedings are likely to occur
c. The baseline risk consists of the control group event rate (0%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic PE (0%) has been calculated applying the assumptions that 20% of any PE are symptomatic PE.
d. Baseline risk for symptomatic VTE calculated from control arm of trials in Ho 2015: 53/1463 = 3.62 %. The assumption that 10% of symptomatic VTE events are PE applies. All proximal DVTs are assumed to be moderate. The duration of follow-up likely varied between the included RCTs.
e. Serious indirectness. Patients were identified through screening Duplex-scanning
f. The baseline risk consists of the control group event rate (2.8%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.56%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs.
g. The baseline risk consists of the control group event rate (4.0%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.04 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs.
h. Lowest baseline risk in the low risk group from Ho 2015 and the highest estimate (from trials) provided assuming that 80% of the DVTs (representing 90% of all VTEs) are distal and 5% of those severe distal DVTs.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	The risk of HIT development, although not prioritized as a critical outcome, has been discussed using additional evidence from observational studies on UFH and LMW, as there were no comparative RCT data in HIT for LMWH vs. UFH. The findings suggest a lower risk of developing HIT in patient treated with LMWH compared with those treated with UFH. (Kuitunen 2007, Martel 2005, Pouplard 1999, Smythe 2007) In a single-institution study, 328 patients exposed to UFH during cardiac catheterization for 1 to 3 months before surgery were postoperatively divided into 2 groups. Group 1 (n=157) received UFH and group 2 (n=171 received LMWH). HIT occurred in 6 patients in group 1, but no thrombocytopenia was observed in subjects receiving LMWH. Patients that were continuously treated with UFH showed higher levels of IgG1 antibodies in the plasma (IgG1 antibodies are associated with high risk of HIT). Levels of antibodies H-PF4 were not influenced by the different type of post-surgical antithrombotic treatment (Pouplard 1999). In a single-institution retrospective review (1-year period, patients exposed to UFH n=24,068) the incidence of HIT was of 0.2% 49/24,068 (0.76% in patients receiving therapeutic dose of IV UFH 41/5,415, and <0.1% in patients receiving antithrombotic prophylaxis with subcutaneous heparin 6/14,368). The author reported that approximately half of all new HIT cases were recognized in the cardiovascular surgery population (Smythe 2007). In a retrospective analysis of 2-years experience of a university hospital, the incidence of HIT in association with the administration of LMWH after cardiac surgery (CABG, OPCAB, VALVE) was 0.6% (20/3,465). A case-control study based on the data showed that patients with HIT had a higher risk of thromboembolic complications and death as compared to patients who did not develop HIT (Kuitunen 2007).	Discussed greater risk of bleeding with UFH, that the panel considered trivial.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for**	

	pharmacological prophylaxis: For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized	The evidence was considered too indirect to be considered. The judgement is based on panel discussion.

	clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing cardiac or major vascular surgery. Indirect evidence from total hip or knee arthroplasty, and gynaecological surgery patients was used to inform the cost-effectiveness. The results from indirect evidence suggested LMWH cost-effective compared with UFH. (Bergqvist 1996, Drummond 1994, Etchells 1999, Fowler 2014, Lazo-Langner 2012, Maxwell 2000, Wade 2008).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in	

	hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests using either LMWH or UFH in patients undergoing cardiac or major vascular surgical procedures (conditional recommendation based on very low certainty of the evidence about effects)

Justification

Evidence is either insufficient or of very low quality to recommend for or against any of the pharmacological prophylaxis. Benefits and risks are small and trivial. The risk of HIT, although not prioritized as a critical outcome, has been discussed using additional evidence. Given HIT is a significant risk following cardiac surgery, when the use of post-operative prophylaxis is considered, an anticoagulant with a lower risk of HIT(LMWH over UFH) should be considered.

Subgroup considerations

None

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

Panel suggest platelet count monitoring.

Research priorities

Further research is needed to determine the impact of thromboprophylaxis agent (LMWH versus UFH) on the development of HIT in cardiovascular surgery patients.

QUESTION-28

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing surgery following major trauma (indirect evidence)?	
POPULATION:	patients undergoing surgery following major trauma (indirect evidence)
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality (follow-up 10 days to 3 months); Symptomatic Pulmonary Embolism - representing moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state (follow-up 10 days to 3 months); Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state (follow-up 10 days to 3 months); Major bleeding - representing moderate marker states; Reoperation (follow-up 14 days to 35 days);
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of antithrombotic prophylaxis with no prophylaxis for prevention of VTE in patients undergoing surgery following major trauma.

ASSESSMENT

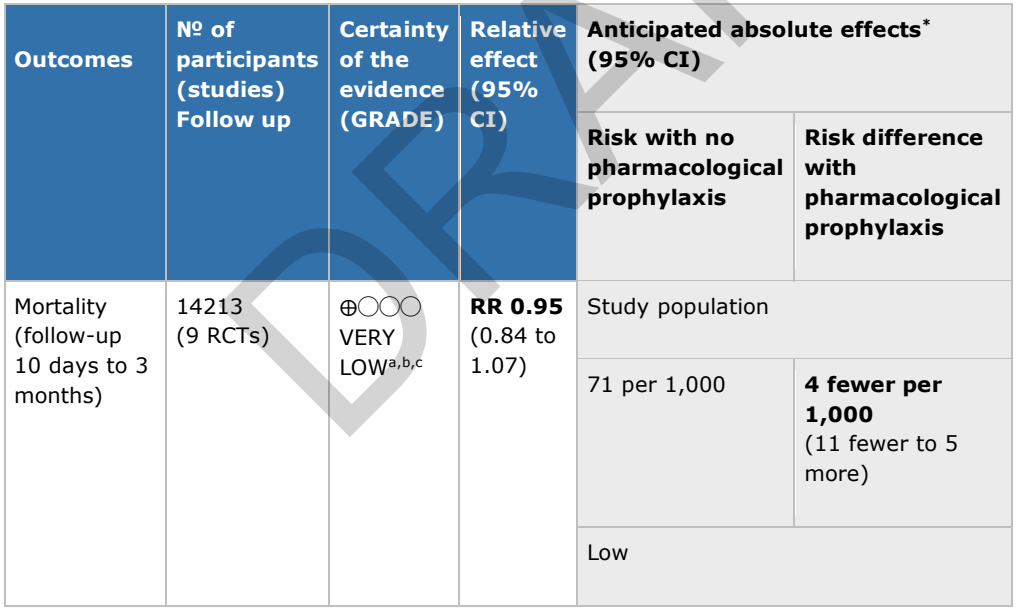
Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients experiencing major trauma are at increased risk of VTE with about 2% experiencing VTE complications even with use of thromboprophylaxis. Major bleeding is also a common and potentially devastating complication of major trauma particularly in the event of head injury. The balance of the benefits and risks of pharmacological prophylaxis must be carefully weighed in this patient population.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		The judgement of moderate desirable effects was based on reduction in VTE and mortality.

					20 per 1,000[d]	**1 fewer per 1,000** (3 fewer to 1 more)
					Moderate	
					5 per 1,000[e]	**0 fewer per 1,000** (1 fewer to 0 fewer)
Symptomatic Pulmonary Embolism - representing moderate marker state assessed with: Symptomatic PE	14134 (9 RCTs)	⊕◯◯◯ VERY LOW[a,c]	**RR 0.49** (0.33 to 0.72)		Low	
					15 per 1,000[d]	**8 fewer per 1,000** (10 fewer to 4 fewer)
					Moderate	
					3 per 1,000[e]	**2 fewer per 1,000** (2 fewer to 1 fewer)
					High	
					8 per 1,000[f]	**4 fewer per 1,000** (5 fewer to 2 fewer)
Symptomatic	13813	⊕◯◯◯	**RR 0.51**		Low	

	Proximal Deep Vein Thrombosis - representing the moderate marker state (follow-up 10 days to 3 months) assessed with: any proximal DVT	(5 RCTs)	VERY LOW[c,g,h]	(0.38 to 0.69)[i]	63 per 1,000[d]	**31 fewer per 1,000** (39 fewer to 20 fewer)
					Moderate	
					70 per 1,000[e]	**34 fewer per 1,000** (43 fewer to 22 fewer)
					High	
					6 per 1,000[j]	**3 fewer per 1,000** (4 fewer to 2 fewer)
	Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state (follow-up 10 days to 3 months) assessed with: any distal DVT	13813 (5 RCTs)	⊕◯◯◯ VERY LOW[b,c,g,h]	**RR 0.85** (0.56 to 1.29)[k]	Low	
					54 per 1,000[d]	**8 fewer per 1,000** (24 fewer to 16 more)
					Moderate	
					149 per 1,000[e]	**22 fewer per 1,000** (66 fewer to 43 more)
					High	

				1 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding - representing moderate marker states	14415 (11 RCTs)	⊕◯◯◯ VERY LOW[a,c]	**RR 1.24** (1.12 to 1.37)	Low	
				24 per 1,000[e]	**6 more per 1,000** (3 more to 9 more)
				Moderate	
				14 per 1,000[e]	**3 more per 1,000** (2 more to 5 more)
				High	
				57 per 1,000[l]	**14 more per 1,000** (7 more to 21 more)
Reoperation (follow-up 14 days to 35 days)	13645 (3 RCTs)[m]	⊕◯◯◯ VERY LOW[b,c,n,o]	**RR 1.05** (0.82 to 1.35)	Study population	
				17 per 1,000[m]	**1 more per 1,000** (3 fewer to 6 more)

a. Only abstracts, or otherwise limited information available for 6 studies (Agnelli 1992, Galasko 1978, Jorgensen 1992, Kew 1999, Li 2008); randomization not reported or not properly done in 2 studies (Barrie 1974, Sasaki 2008); loss of

	follow-up >20%, or unexplained drop-out in 5 studies (Agnelli 1992, Galasko 1976, Jorgensen 1992, Kew 1999, Lassen 1989) b. The Confidence interval does not exclude an appreciable benefit or no difference c. Serious indirectness. The estimates of effects are derived from studies that included hip fracture patients and not trauma patients. d. Control event rate from the meta-analysis comparing prophylaxis vs no prophylaxis in trauma patients e. Control event rate from the meta-analysis comparing LMWH to UFH in trauma patients f. Gudipati 2014 evaluated 7503 trauma patients in a cohort (single center in the UK) of whom 61 patients had CT-PA confirmed PE (after clinical suspicion) = 0.8%. 76% had thromboprophylaxis, over 90% of which with LMWH. This estimate is overall compatible with the baseline risk from the 4 trials reported here. g. Only abstracts, or otherwise limited information available and loss of follow-up >20% or unexplained drop-out in 2 studies (Agnelli 1992, Kew 1999) h. One study used 1,25 Fibrinogen levels as an indicator of VTE (Powers 1989) i. Additional 7 studies measured and reported any DVT, if they were included the RR would be 0.52 [0.39, 0.71] j. The baseline risk is higher than in the registry study by Paffrath et al which suggests a risk of clinically relevant VTE of 1.8% in a mixed trauma population of whom 80% underwent some form of thromboprophylaxis (PE risk is 10% of total = 0.18%; 10% are PEs = 0.18%; 90% are DVTs, of which 80% (1.296%) are distal (5% of which are symptomatic = 0.0648%) and 20% are proximal (=0.324%)). In that study the risk of PE among all VTEs was large (approximately 50%) - this study included 7937 patients in total. In a second study (Malinoski 2013) of mixed trauma patients (n = 411), the VTE incidence based on duplex screening was 7% in patients not receiving any form of prophylaxis. We adjusted the baseline risk based on the Paffrath study multiplying by 2 for the fact that most patients were prophylaxed. k. Additional 7 studies measured and reported any DVT, if they were included the RR would be 0.65 [047, 0.91] l. Baseline risk estimate from the CRASH-2 trial which was conducted on trauma patients with significant haemorrhage or at high risk of haemorrhage. Data are on the outcome of fatal bleeding. m. Baseline risk estimates for trauma patients is not available as no studies measured this outcome. n. One study (Lassen 1989) excluded patients post randomization, for multiple reasons, including "Reoperation" o. One study (Rodgers 2000) did not explicitly report on "reoperation", however did report on hematoma requiring evacuation, wound infection with frank pus	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know		The panel discussed separating the judgement into two groups, for 'high' risk bleeding group the judgement was large undesirable effects, and for 'low' risk bleeding group the judgement was small undesirable effects, and therefore the overall judgement was that undesirable effects will vary based on risk group.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance:	

variability ○ No important uncertainty or variability	**Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know		The panel judged that there would be moderate desirable effects, with large undesirable effects for a 'high' bleeding risk group, and small undesirable effects for a 'low' risk groups. Therefore, for the 'high' bleeding risk group the balance probably favours the comparison (no prophylaxis), and for the 'low' bleeding risk group the balance probably favours the intervention (prophylaxis). The panel also noted that for patients that are actively bleeding due to trauma, the balance favours the comparison (no prophylaxis). For patients that would be considered at average risk, physicians' judgement is required to assess a patient's bleeding risk and the balance of effects

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip	

	replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgment of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	A cost-effectiveness analysis compares enoxaparin 30mg/12 hrs with no prophylaxis in trauma patients in the USA. An institutional perspective was adopted. The results suggested a cost of $279.43 would be incurred for each thromboembolic event avoided if enoxaparin 30 mg every 12h were routinely used as prophylaxis in trauma patients, compared with no prophylaxis. (Wade 2000) Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis. However, the cost-effectiveness also depends on the types of pharmacological prophylaxis (Bergqvist 1996, Borris 1994, Borris 1996, Brosa Riestra 2003, Nerurkar 2002)	The panel noted that there is indirect evidence of cost-effectiveness of prophylaxis in other settings when prophylaxis is effective. Given considerations about effectiveness, the panel noted that in a 'high' bleeding risk group, cost-effectiveness probably favours the comparison (no prophylaxis), and in a 'low' bleeding risk group it probably favours the intervention (prophylaxis).

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation**: **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in	

	large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	●	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests prophylaxis rather than no prophylaxis in patients undergoing surgery following major trauma who are at low to moderate risk of bleeding (Conditional recommendation based on very low certainty of the evidence about effects).

The ASH guideline panel suggests no prophylaxis rather than prophylaxis in patients undergoing surgery following major trauma who are at high risk of bleeding (Conditional recommendation based on very low certainty of the evidence about effects).

Remarks:
Mechanical prophylaxis would be routinely used in this population when possible (e.g. no lower limb injuries).

Justification

The observed moderate benefits overweigh the small effect of the treatment on undesirable consequences in patients at low to moderate risk of bleeding, while in patients at high risk of bleeding the large undesirable consequences lead to a balance that probably favours the comparison. Furthermore, the very low certainty in evidence, which is indirect data from hip fracture repair studies, justifies a conditional recommendation.

Subgroup considerations

There were no additional subgroup considerations, other than the consideration of the patients' bleeding risk.

Implementation considerations

None

Monitoring and evaluation

- Patients that are actively bleeding would not receive prophylaxis
- Assessment of bleeding risk in patients (add the definition, patient characteristics for the two groups of 'high risk' and 'low to moderate risk')
- Re-addressing need for prophylaxis during hospital stay (e.g. when patient becomes stable)

Research priorities

Well-designed randomized controlled trials using clinically important VTE outcomes are required in patients at moderate risk of bleeding following trauma to determine the incremental benefit of pharmacological prophylaxis beyond mechanical methods alone.

Studies are also needed evaluating the timing pharmacological prophylaxis can be safely introduced in patients experiencing major bleeding including intracranial haemorrhage as a consequence of trauma when the bleeding risk is subsiding.

QUESTION-29

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing surgery following major trauma?	
POPULATION:	patients undergoing surgery following major trauma
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state; Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis -representing the severe marker state; Major Bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of pharmacological thromboprophylaxis with mechanical thromboprophylaxis in hospitalized patients undergoing surgical procedures.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients experiencing major trauma are at increased risk of VTE with about 2% experiencing VTE complications even with use of thromboprophylaxis. Major bleeding is also a common and potentially devastating complication of major trauma particularly in the event of head injury. The balance of the benefits and risks of pharmacological prophylaxis must be carefully weighed in this patient population.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
Mortality	846 (3 RCTs)	⨁⨁◯◯ LOW[a]	**RR 1.32** (0.14 to 12.39)	Study population	
				5 per 1,000	**2 more per 1,000** (4 fewer to 54 more)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: any PE follow up: range 10 days to 8 weeks	767 (3 RCTs)	⨁⨁◯◯ LOW[a]	**RR 1.04** (0.11 to 9.92)	Based on Study population	
				1 per 1,000[b]	**0 fewer per 1,000** (1 fewer to 5 more)
				Low	
				2 per 1,000[c]	**0 fewer per 1,000** (2 fewer to 16 more)
				Moderate	

ADDITIONAL CONSIDERATIONS

Panel noted no difference in mortality and PE (low event rates), most benefit for asymptomatic DVT.

				2 per 1,000[c]	**0 fewer per 1,000** (2 fewer to 16 more)
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any proximal DVT follow up: range 10 days to 30 days	701 (2 RCTs)	⊕⊕⊕◯ MODERATE[d]	**RR 0.57** (0.25 to 1.31)	Low	
				14 per 1,000[e]	**6 fewer per 1,000** (10 fewer to 4 more)
				Moderate	
				3 per 1,000[c]	**1 fewer per 1,000** (2 fewer to 1 more)
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state assessed with: any distal DVT follow up: range 10 days to 30 days	701 (2 RCTs)	⊕⊕⊕◯ MODERATE[d]	**RR 0.74** (0.46 to 1.20)	Based on study population	
				1 per 1,000[f]	**0 fewer per 1,000** (1 fewer to 0 fewer)
				Low	
				1 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 more)
Major Bleeding follow up: range 10 days to 8 weeks	846 (3 RCTs)	⊕⊕◯◯ LOW[a]	**RR 2.40** (0.53 to 10.78)	Study population	
				14 per 1,000	**20 more per 1,000** (7 fewer to 138 more)
Reoperation - not measured	-	-	-	**-**	**-**

a. The CI includes appreciable benefit with either intervention. The total number of events is small or very small.
b. The baseline risk consists of the control group event rate (0.3%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic PE (0.06%) has been calculated applying the assumptions that 20% of any PE are symptomatic PE.
c. The baseline risk is higher than in the registry study by Paffrath et al which suggests a risk of clinically relevant VTE of 1.8% in a mixed trauma

	population of whom 80% underwent some form of thromboprophylaxis (PE risk is 10% of total = 0.18%; 10% are PEs = 0.18% 90% are DVTs, of which 80% (1.296%) are distal (5% of which are symptomatic = 0.0648%) and 20% are proximal (=0.324%)). In that study the risk of PE among all VTEs was large (approximately 50%) - this study included 7937 patients in total. In a second study (Malinoski 2013) of mixed trauma patients (n = 411), the VTE incidence based on duplex screening was 7% in patients not receiving any form of prophylaxis. d. Although the number of events is considerable, the CI does not exclude an appreciable benefit with either intervention e. The baseline risk consists of the control group event rate (7.0%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic PE (1.4%) has been calculated applying the assumptions that 20% of any PE are symptomatic PE. f. The baseline risk consists of the control group event rate (14.9%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.149%) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		No data on reoperation. For major bleeding panel considered undesirable effect small.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004) **Gastrointestinal tract bleeding event: 0.65** (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are “not afraid of” the adverse events (Barcellona 2000, Haac 2016, O’Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:**	

	For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin).	

	Resource use for disease (indirect evidence): Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD) per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgement of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Four identified reports using decision-analytic models compared the cost-effectiveness of low-dose heparin and LMWH as for prevention of VTE in traumatic patients. Two studies concluded UFH strategy might be dominating the analysis in terms of life-years-saved, while another one estimated an acceptable cost additional life-years-saved ($2300 per life-year-saved) for LMWH. The fourth study concluded that LMWH represents a cost-effective alternative to UFH in terms of DVT prevented (Devlin 1998, Shorr 2001, Lynd 2007, Velmahos 2000). In addition, indirect evidence from total hip or knee arthroplasty, and gynecological surgery patients suggested LMWH cost-effective compared with UFH. (References)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests either using LMWH or UFH in patients undergoing surgery following major trauma. (Conditional recommendation based on low certainty of the evidence about effects).

Justification

The very minor differences of the effect of the intervention on benefit and undesirable outcomes leads to consider a balanced effect not favoring either options over the other. The benefits observed with LMWH were limited to the prevention of asymptomatic VTE which was not considered a clinically important endpoint by the panel. This potentially small therapeutic benefit of LMWH was negated by a small observed increase risk of major bleeding. It was recognized by the panel that the patients included in this study were selected to avoid those at high risk of bleeding.

Subgroup considerations

None

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

None

Research priorities

The priority research question in this patient population would be establishing the effectiveness and timing of pharmacological prophylaxis in patients receiving mechanical prophylaxis, rather than which agent should be used.

QUESTION-30

Should pharmacological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing major gynecological procedures?	
POPULATION:	Patients undergoing major gynecological procedures
INTERVENTION:	pharmacological prophylaxis
COMPARISON:	no pharmacological prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal Deep Vein Thrombosis- representing the moderate marker state; Symptomatic Distal Deep Vein Thrombosis- representing the severe marker state ; Major bleeding; Reoperation;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative setting. This EtD compares the effectiveness and safety of pharmacological thromboprophylaxis with no thromboprophylaxis in hospitalized patients undergoing major gynecological procedures.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	This question is a high priority because of the frequency of this procedure, the post-operative risk of VTE, the serious consequences of excessive bleeding with pharmacologic prophylaxis.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Mortality follow up: range 6 days to 10 weeks	22592 (18 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 0.75** (0.61 to 0.93)	Study population	
				17 per 1,000	**4 fewer per 1,000** (7 fewer to 1 fewer)
Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with: symptomatic PE	18467 (16 RCTs)	⨁⨁⨁◯ MODERATE[b]	**RR 0.48** (0.26 to 0.88)	Study population	
				11 per 1,000	**6 fewer per 1,000** (8 fewer to 1 fewer)
				Low	
				0 per 1,000[c]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	

				40 per 1,000	**21 fewer per 1,000** (30 fewer to 5 fewer)
Symptomatic Proximal Deep Vein Thrombosis-representing the moderate marker state assessed with: any proximal DVT follow up: range 6 days to 10 weeks	11806 (6 RCTs)	⊕◯◯◯ VERY LOW[d,e,f]	**RR 0.38** (0.14 to 1.00)	Low	
				2 per 1,000[g]	**1 fewer per 1,000** (2 fewer to 0 fewer)
Symptomatic Distal Deep Vein Thrombosis-representing the severe marker state assessed with: any distal DVT follow up: range 6 days to 10 weeks	11924 (7 RCTs)	⊕⊕◯◯ LOW[h,i]	**RR 0.52** (0.31 to 0.87)	Low	
				0 per 1,000[j]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major bleeding	22045 (15 RCTs)	⊕⊕⊕◯ MODERATE[k]	**RR 1.24** (0.87 to 1.77)	Study population	
				26 per 1,000	**6 more per 1,000** (3 fewer to 20 more)
Reoperation	1520 (6 RCTs)	⊕⊕◯◯ LOW[l,m]	**RR 0.93** (0.35 to 2.50)	Study population	
				12 per 1,000	**1 fewer per 1,000** (8 fewer to 18 more)

a. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 3 out of 19 studies and lack of blinding in 5 out of 19 studies.
b. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 5 out of 16 studies.
c. The baseline risk in observational studies for VTE ranges from 0% in low risk populations (Ageno 2007) to 11.6% in studies of high risk women (Zhang 2015).

	However, the latter study is likely at high risk of bias. Risk factors include malignancy (e.g. symptomatic VTE in 6.5% of women undergoing ovarian cancer surgery, Mokri 2013). One large registry found a risk of 1% VTE but it was unclear how many were symptomatic (Ritch 2011). A national cohort from Finland reported low VTE risks but a doubling of odds for bleeding with pharmacological thromboprophylaxis in women undergoing hysterectomy for benign disease. d. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 3 out of 6 studies. There was not description of the allocation concealment in 6 out of 6 studies. e. Serious indirectness. Patients included in the studies have diagnostic of proximal DVT by screening, and differ importantly from the diagnostic of symptomatic proximal DVT. f. Serious inconsistency. Unexplained inconsistency, with point estimates different (P-value chi square= 0.06; I2=54% %) g. The baseline risk consists of the control group event rate (1.1%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (0.22%) has been calculated applying the assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. h. Serious indirectness. Patients included in the studies have diagnostic of distal DVT by screening, and differ importantly from the diagnostic of symptomatic distal DVT. i. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 7 studies and lack of blinding in 3 out of 7 studies. j. The baseline risk consists of the control group event rate (1.3%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic distal DVT (0.013 %) has been calculated applying the assumptions that 20% of any distal DVTs are symptomatic distal DVTs and that only 5% of the symptomatic distal DVTs are assumed to be severe DVTs. k. Serious imprecision. 95% CI is consistent with the possibility for benefit and harm. l. Serious risk of bias. Studies that carried a considerable weight for the overall effect estimate rated as high risk of bias due to lack of concealment in 1 out of 6 studies and lack of blinding in 2 out of 6 studies. m. Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 17 events in total	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		Panel discussed increase in bleeding risk, based on various procedures pooled together. Considering disutility of spectrum of major bleeding.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	In this case, the recommendation was sufficiently supported by the favorable impact on desirable effects for which there was higher quality evidence.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004)	

	Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For anticoagulant therapy in general, most patients would prefer the oral doses compared with injections, mainly because of treatment burden due to injection (Barcellona 2000, Haac et al, 2016; Popoola 2016, Quante 2012, Sousou 2010, Wilke 2009, Wong 2015). For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Patients would like to switch to another anticoagulant if it is as effective as warfarin; this is mainly due to the treatment burden associated with monitoring, injection and dietary change due to warfarin use (Attaya 2012). Some patients would not switch if the cost of treatment increases. (Elewa 2004) Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002). Some patients using DOAC may switch to VKA due to fear of adverse effects and hair loss (Zolfaghari 2015).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditions conferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015 vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgment of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing major gynecological procedures. Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared with no prophylaxis (Blondon 2012, Bradley 2010, Hull 1982, Mamdani 1996, Teoh 2011, Wade 2000)	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	No research evidence identified	

○ Yes ○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests pharmacological prophylaxis over no prophylaxis in patients undergoing major gynecological procedures (conditional recommendation based on low certainty of the evidence about effects).

Justification

This recommendation is based on the panel's judgment that the desirable effects of pharmacological prophylaxis outweighed its undesirable effect resulting in a net patient benefit.

Subgroup considerations

This recommendation applies equally to patients undergoing surgery for benign and malignant conditions.

Implementation considerations

The panel considered that a majority of patients considered here, especially those at increased risk for VTE would also receive mechanical prophylaxis in addition.

Monitoring and evaluation

None

Research priorities

Given the low and very low quality of evidence informing this question in patients undergoing major gynaecological procedures, high quality studies are needed. Future studies should include a detailed characterization of the patient populations and follow-up times, documentation of prophylaxis use, and objective measurements of clinically important outcomes like symptomatic DVT, PE, and bleeding.
Further studies patient values regarding prevention of VTE and bleeding would allow for optimal shared decision-making regarding thromboprophylaxis for gynecological procedures.

QUESTION-31

Should LMWH prophylaxis vs. UFH prophylaxis be used for patients undergoing major gynecological procedures?	
POPULATION:	patients undergoing major gynecological procedures
INTERVENTION:	LMWH prophylaxis
COMPARISON:	UFH prophylaxis
MAIN OUTCOMES:	Mortality; Symptomatic Pulmonary Embolism - representing the moderate marker state ; Symptomatic Proximal DVT - representing the moderate marker state ; Symptomatic Distal DVT - representing the severe marker state; Major Bleeding ; Reoperation ;
SETTING:	inpatient
PERSPECTIVE:	clinical recommendation - population perspective
BACKGROUND:	Venous thromboembolism (VTE) is a common and potentially lethal disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE, a complication post-surgery, is associated with longer hospital stay, short-term morbidity, the potential for long-term disability, and even death (Kakkos et al., 2008). The use of pharmacological agents to prevent VTE (known as thromboprophylaxis) has become the standard of care in patients with identifiable risk factors for VTE, including surgery. Most commonly these pharmacological agents are a class of drugs known as anticoagulants that prevent and attenuate the formation of blood clots. Bleeding, most commonly occurring at the operative site, is the most common adverse event that can be associated with the use of pharmacological antithrombotic agents in the perioperative e setting. This EtD compares the effectiveness and safety of LMWH with UFH thromboprophylaxis in hospitalized patients undergoing major gynecological surgery.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	This question is a high priority because of the frequency of this procedure, the post-operative risk of VTE, the serious consequences of excessive bleeding with pharmacologic prophylaxis.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
Mortality follow up: range 7 days to 8 weeks	41896 (35 RCTs)	⊕⊕◯◯ LOW[a,b,c]	**RR 1.03** (0.89 to 1.18)	Study population	
				18 per 1,000	**1 more per 1,000** (2 fewer to 3 more)
				Low	
				14 per 1,000[d]	**0 fewer per 1,000** (2 fewer to 3 more)
				Moderate	
				52 per 1,000[e]	**2 more per 1,000** (6 fewer to 9 more)
Symptomatic	41228	⊕⊕◯◯	**RR 0.91**	Low	

Pulmonary Embolism - representing the moderate marker state assessed with: Symptomatic PE follow up: range 7 days to 8 weeks	(39 RCTs)	LOW[b,f,g]	(0.63 to 1.30)	0 per 1,000[h]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				40 per 1,000[h]	**4 fewer per 1,000** (15 fewer to 12 more)
				High	
				1 per 1,000[i]	**0 fewer per 1,000** (0 fewer to 0 fewer)
Symptomatic Proximal DVT - representing the moderate marker state assessed with: Symptomatic Proximal DVT follow up: range 8 days to 8 weeks	4249 (6 RCTs)	-	**RR 1.01** (0.20 to 5.00)	Study population	
				1 per 1,000	**0 fewer per 1,000** (1 fewer to 6 more)
				Low	
				2 per 1,000[d]	**0 fewer per 1,000** (2 fewer to 8 more)
				Moderate	
				5 per 1,000[i]	**0 fewer per 1,000** (4 fewer to 20 more)
Symptomatic Distal DVT - representing the severe marker state assessed with: Symptomatic Distal DVT follow up: range 8 days to 8 weeks	4587 (8 RCTs)	⨁◯◯◯ VERY LOW[b,j,k]	**RR 1.01** (0.30 to 3.44)	Low	
				0 per 1,000[l]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				Moderate	
				0 per 1,000[d]	**0 fewer per 1,000** (0 fewer to 0 fewer)
				High	

				0 per 1,000[i]	**0 fewer per 1,000** (0 fewer to 1 more)
Major Bleeding follow up: range 7 days to 8 weeks	42409 (43 RCTs)	⊕⊕◯◯ LOW[b,f]	**RR 0.97** (0.78 to 1.20)	Study population	
				16 per 1,000	**0 fewer per 1,000** (4 fewer to 3 more)
				Low	
				15 per 1,000[d]	**0 fewer per 1,000** (3 fewer to 3 more)
				Moderate	
				56 per 1,000[m]	**2 fewer per 1,000** (12 fewer to 11 more)
Reoperation follow up: range 7 days to 8 weeks	12040 (21 RCTs)	⊕⊕◯◯ LOW[b,n]	**RR 0.79** (0.57 to 1.08)	Study population	
				18 per 1,000	**4 fewer per 1,000** (8 fewer to 1 more)
				Low	
				14 per 1,000[d]	**3 fewer per 1,000** (6 fewer to 1 more)
				Moderate	
				51 per 1,000[e]	**11 fewer per 1,000** (22 fewer to 4 more)

a. Only seven studies reported appropriate allocation concealment
b. Large part of the evidence has been extrapolated from major general surgical procedures.
c. Statistical heterogeneity for subgroup analysis (p=0.05) and I2=74%. Suggesting a further decrease on mortality with LMWH (compared with UFH) in studies including more than 50% of patients with cancer treated, than in studies with less than 50% of cancer population
d. The baseline risk consists of the control group event rate (0.2%) in studies

	with less than 50% of patients with cancer. Baseline risk estimates for symptomatic distal DVT (0.01%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs e. Control group risk in studies with >=50% of patients with cancer. f. Only ten studies reported appropriate allocation concealment g. Probably not enough number of events to meet optimal information size, limitation considered together with RoB. h. The baseline risk in observational studies for VTE ranges from 0% in low risk populations (Ageno 2007) to 11.6% in studies of high risk women (Zhang 2015). However, the latter study is likely at high risk of bias. Risk factors include malignancy (e.g. symptomatic VTE in 6.5% of women undergoing ovarian cancer surgery, Mokri 2013). One large registry found a risk of 1% VTE but it was unclear how many were symptomatic (Rich 2011). A national cohort from Finland reported low VTE risks but a doubling of odds for bleeding with pharmacological thromboprophylaxis in women undergoing hysterectomy for benign disease. Murray 2016n reported a incidence of 4% symptomatic PE following radical cystectomy i. Changolkar et al. (2014) reported, in patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis, a risk of VTE of 3.4%. Baseline-risk estimates for symptomatic PE (0.068%), symptomatic proximal DVT (0.12%) and symptomatic severe distal DVT (0.024%) have been calculated applying the assumptions that 10% of all the symptomatic VTEs are PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVTs and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DVTs and therefore, considered important outcome j. Kakkar 1993 was classified as high risk of bias for blinding of study participants and health care providers. k. Very small number of events to meet optimal information size. The confident interval does not exclude an important benefit or harm. l. The baseline risk consists of the control group event rate (0.2%) from studies that included surgical patients with cancer or without cancer. Baseline risk estimates for symptomatic distal DVT (0.01%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs m. Changolkar et al. (2014) reported, in patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis, a risk of 5.6% for major bleeding. n. Only three studies reported appropriate allocation concealment	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**The relative importance of the outcomes** reported in the literature is indicated by utility values on a scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed on a given health state characterized by that condition, with higher values reflecting greater importance: **Pulmonary embolism: range 0.63-0.93** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004) **Deep vein thrombosis: range 0.64-0.99** (different methods) (Hogg 2013, Hogg 2014, Locadia 2004, Marvig 2015, Utne 2016) **Deep vein thrombosis patients' own current health: 0.95**(time trade off) (Locadia 2004)	

	Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) (Hogg 2013, Locadia 2004) **Muscular bleeding: 0.76** (time trade off) (Locadia 2004) **Minor intracranial bleeding event: 0.75** (standard gamble) (Hogg 2013) **Major intracranial bleeding event: 0.15** (standard gamble) (Hogg 2013) **Central nervous system bleeding: range 0.29-0.60** (standard gamble) (Lenert 1997, O'Meara 1994) **Treatment with LMWH: 0.993** (time trade off) (Marchetti 2001) **Studies additionally described the following regarding patients' experiences and preferences for VTE prophylaxis:** Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; (Haac 2016, Locadia 2004, Najafzadeh 2015, Quante 2012, Wong 2015) patients would like to avoid adverse events but most of them are "not afraid of" the adverse events (Barcellona 2000, Haac 2016, O'Meara 1994, Quante 2012, Wong 2015). **Studies additionally described the following regarding patients' experiences and preferences for pharmacological prophylaxis:** For patients who prefer injections over oral treatment, the reasons include belief that injections have a faster onset of effects and are safer (Quante 2012). Most patients (78%) receiving low molecular weight heparin would like to continue with the same methods (Maxwell 2002).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Resource use for pharmacological prophylaxis (indirect evidence):** Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 days, with a range of 6 to 168 days) was £107.54 ($143.18 in 2011 USD) per patient, and with dabigatran £143.99 ($191.71 in 2011 USD) per patient. Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis with enoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgical conditionsc onferring VTE risk using hospital discharge and billing records between January 2002 and December 2006. After adjustment for pre-defined covariates, including length of stay and patients' diagnosis severity level, the mean adjusted total direct medical costs per discharge for the UFH group were $6443 (2010 USD) and $5363 (2010 USD) for the enoxaparin group. Mody et al. 2014, reported on resource utilization (in 2012 USD) for VTE prophylaxis after knee replacement and hip replacement based on an economic model from a hospital perspective developed using treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as $8.84 for rivaroxaban (20/15/10 mg QD), and $22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for knee replacement was reported as $15,490 for prophylaxis with rivaroxaban, and $15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as $15,669 for prophylaxis with rivaroxaban, and $15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). **Resource use for disease (indirect evidence):** Vekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations based on health insurance claims in the U.S. between January 2004 and December 2008. Up to 3 months after THR/TKR, mean incremental healthcare costs (in USD)per patient per month associated with VTE, any bleeding, and major bleeding were $2729, $2696, and $4304, respectively. Total monthly costs versus matched THR/TKR controls without VTE or bleeding over 3 months were: VTE: $12,333 vs. $9604; any bleeding: $12,481 vs. $9785; major bleeding: $14,015	

	vs. $9710. See **Appendix 3 Table 1** for additional data on prophylaxis unit costs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	The indirect evidence that was identified was deemed to not provide enough information for decision making in the context of this research question and, therefore, a judgment of no included studies was made.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Two reports compared the cost-effectiveness of LMWH and UFH for patients undergoing surgical intervention for gynecologic malignancy . One report suggested no difference in effectiveness but UFH is less expensive. Another suggested LMWH is cost-effective (Maxwell 2000, Wade 2008). Maxwell 2000 A decision model was constructed to compare the external pneumatic compression, UFH and LMWH for women with cervical, endometrial, and ovarian cancer. The analysis was from a perspective of a USA Medical center. Cost-effectiveness estimates ranged from $27 per life-year saved for a 55-year-old endometrial cancer patient to $5132 per life-year saved for a 65-year-old with ovarian cancer. Although low molecular weight heparin and unfractionated heparin were cost-effective compared with no prophylaxis, each was less effective than external pneumatic compression in the base case. The results of the analysis were sensitive to assumptions about the relative risk of DVT, the life expectancy of the patient, the costs of future treatment, and the relative effectiveness of the different strategies. Wade 2008 A cost-effectiveness analysis was performed to compare LMWH, dalteparin, intermittent pneumatic calf compression (IPC) versus UFH in patients undergoing surgical intervention for gynecologic malignancy using published efficacy and safety data in the USA. The analysis was based on an institutional perspective. $6961.60 would be saved for each thromboembolic event averted, if dalteparin 5000 units daily was used over UFH 5000 units every 8 hours. Cost-effectiveness analyses comparing unfractionated heparin 3 times a day versus once daily dalteparin using published efficacy and safety data demonstrate cost savings if dalteparin were routinely utilized as VTE prophylaxis. Sensitivity analyses support this finding at the upper end of the range of reported proximal DVT, nonfatal pulmonary embolism, and major bleeding incidences. These findings should be viewed as preliminary, and institutions are encouraged to perform their own cost-effectiveness studies in this patient population.	The panel considered differences observed between LMWH and UFH were not meaningful.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		The panel judged that there would be no impact on equity, assuming that prophylaxis would typically be short-term for this population.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Barriers to implementation of pharmacological prophylaxis** A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 789 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) **General barriers for implementation:** **Clinicians low knowledge and organization of care** Among 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible for VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the system. (McFarland 2014) A survey among Malaysian orthopedic surgeons showed that 50% considered VTE as common a problem in Malaysia as in western countries. (Zairul-Nizam 2003) A survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepally 2010) **Lack of local guidelines** Among surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and	

	logistical issues (not specified) were most commonly cited as barriers to implementation of VTE prophylaxis (Smart 2013) In hospitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and was implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spanish acute care hospitals showed that VTE prophylaxis was relatively better in large hospitals and this was associated with the existence of VTE prophylaxis guidelines. (Saturno 2011) **General facilitators for implementation** A 2013 Cochrane systematic review showed that the use of alerts (computerized or paper-based), provider education or a multifaceted intervention increased appropriate thromboprophylaxis in hospitalized adult patients by 11-19%. (Kahn 2013) A survey in Canadian ICUs showed that top five reported facilitators for thromboprophylaxis were preprinted orders, education, daily reminders, audit and feedback, and local quality improvement initiatives. (Cook 2014)	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The ASH guideline panel suggests either LMWH or UFH in patients undergoing major gynecological surgery procedures (conditional recommendation based on very low certainty of the evidence about effects).

Justification

The panel judged that the trivial effect of LMWH compared with UFH on both desirable and undesirable outcomes did not favour a balance of the effect in any directions. This was based on very low certainty of the evidence that included issues of indirectness of the evidence, with effect size estimates taken from studies of major general surgical procedures. On the other hand, no concerns were expressed regarding the equity, acceptability or feasibility of both intervention alternatives.

Subgroup considerations

This recommendation applies equally to patients undergoing surgery for benign and malignant conditions.

Implementation considerations

Panel thought that both treatment options are already widely used and that therefore there should be little issues with regards to implementation.

Monitoring and evaluation

With both UFH and LMWH, patients' platelet counts needs to be periodically monitored. With LMWH, renal function needs to be periodically monitored.

Research priorities

Given the low and very low quality of evidence informing this question in patients undergoing major gynaecological procedures, high quality studies are needed. Future studies should include a detailed characterization of the patient populations and follow-up times, documentation of prophylaxis use, and objective measurements of clinically important outcomes like symptomatic DVT, PE, and bleeding.

Further studies patient values regarding prevention of VTE and bleeding would allow for optimal shared decision-making regarding thromboprophylaxis for gynaecological procedures.