

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 <u>https://vtesurgical.questionpro.com</u>. 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 pharma	hould pharmacological prophylaxis vs. mechanical prophylaxis be used for patients undergoing surgery?								
POPULATION:	patients undergoing surgery								
INTERVENTION:	pharmacological prophylaxis								
COMPARISON:	mechanical prophylaxis 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;								
MAIN OUTCOMES:									
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		
NoIn the absence of prophylaxis, the risk of DVT and PE in patients undergoing major surgery can be considerable.Probably noWith VTE prevention strategies provided at physician discretion, a recent large registry study of several millionProbably yessurgical patients identified the rate of VTE during the index hospital admission for surgery of 0.2% (AssarehYes2014).VariesSymptomatic 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 EVI	DENCE					ADDITIONAL CONSIDERATIONS		
• Trivial o Small o Moderate	Outcomes	№ of participants	Certainty of the	Relative effect	Anticipated a (95% CI)	absolute effects*			
o Large o Varies o Don't know	(studies) Follow up		(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}	(15 RCTs) ^a		RR 0.92 (0.46 to	Study populat	ion			
				1.84)	9 per 1,000ª	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 populat	for former per			

Embolism - representing the moderate marker state assessed with:			2.96)	Low 0 per 1,000 ^f	1,000 (2 fewer to 7 more) 0 fewer per 1,000
Symptomatic PE follow up: range 5 days					(0 fewer to 1 more)
to 90 days				Moderate	
				0 per 1,000 ⁹	0 fewer per 1,000 (0 fewer to 0 fewer)
Symptomatic Proximal	2353 (6 RCTs)		RR 0.75	Study populat	ion
Deep Vein Thrombosis - representing the		MODERATE	(0.11 to 5.32)	2 per 1,000	1 fewer per 1,000 (2 fewer to 9 more)
moderate marker state				Low	·
assessed with: Symptomatic proximal DVT				1 per 1,000 ^f	0 fewer per 1,000 (0 fewer to 2 more)
follow up: range 5 days				Moderate	
to 90 days				0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 2 more)
Symptomatic	1934 (4. PCTc)	⊕⊕⊕⊖ MODERATE ^c	RR 0.16 (0.05 to 0.58)	Low	
Distal Deep Vein Thrombosis - representing the severe	(4 RCTs)			1 per 1,000 ^h	1 fewer per 1,000 (1 fewer to 0 fewer)
marker state assessed				Moderate	
with: Symptomatic distal DVT follow up: range 5 days				0 per 1,000 ^f	0 fewer per 1,000 (0 fewer to 0 fewer)
to 90 days				High	
				0 por 1 0009	A forwar nor

	1	1						
					1,000 (0 fewer to 0 fewer)			
Major	4844	⊕⊕⊕⊖ MODERATE ^{c,i}	RR 2.87	Study population				
Bleeding follow up: range 5 days to 90 days	(18 RCTs)		(1.68 to 4.92)	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	1342	⊕⊕⊖⊖ LOW ^{j,k}	RR 2.01 (0.29 to 14.05)	Study populat	Study population			
follow up: range 5 days to 90 days	(6 RCTs)			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'	26 more per 1,000 (18 fewer to 339 more)			
a Tha bi	acolina rick for	the study popu	lation conc	ists of the cont	rol group overt rate			
 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 distal 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.
- I. 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 anticipation	Undesirable Effects How substantial are the undesirable anticipated effects?									
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS								
o Large o Moderate • Small o Trivial o Varies o 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	Certainty of evidence What is the overall certainty of the evidence of effects?									
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS								
o Very low • Low o Moderate o High o 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 varia	ability 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:	
	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	
	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	
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	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 unc	ndesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention 		
Does the balance between desirable and unc JUDGEMENT o Favors the comparison o Probably favors the comparison • Does not favor either the intervention or the comparison o Probably favors the intervention	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).	ADDITIONAL CONSIDERATIONS

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Carge costs Moderate costs Negligible costs and savings Moderate savings Large savings Varies Don't know Certainty of evidence of re	 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 bood-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 \$15,503 for prophylaxis with diversoraban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as \$15,490 for prophylaxis with divaroaban, and \$15,708 for prophylaxis with other agents (enoxaparin, or enoxaparin plus warfarin). Resource use for mechanical proph	
What is the certainty of the evidence of reso		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

Very low O Low O Moderate O High O No included studies Cost effectiveness Does the cost-effectiveness of the intervent	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).	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 stakeh	olders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o No o Probably no • Probably yes o Yes o Varies o 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
o No o Probably no • Probably yes o Yes o Varies o 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 (7%). 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 (s3days) 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, isks and complicated monitoring procedures associated with antithrombotic use were reported as barriers to their use (Arepally 2010). A survey in Canadian ICUs showed that frug acquisition cost, fear of bleeding, lack of resident education, concern about renal failure, and habits were the top five barriers to LIMWH use (Cook 2014). Over 80% of 789 orthopedic surgeons were concerned or very concerned about fear, especially surgical-site bleeding. despecially surgical-site bleeding. Most responders favored 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 directl	

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).

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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
0	0	•	0	0

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

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 undergoin surgical procedures.

ASSESSMENT

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Is the problem a priority?

Is the problem a priority?									
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS		
o No o Probably no o Probably yes • Yes o Varies o Don't know	With VTE prevention surgical patients id 2014). Symptomati	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 a	anticipated effects?								
JUDGEMENT	RESEARCH EVI	DENCE		-			ADDITIONAL CONSIDERATIONS		
o Trivial ● Small									
o Moderate o Large o Varies	Outcomes	№ of participants	Certainty of the	effect	Anticipated (95% CI)	absolute effects*			
o Don't know		(studies) evidence Follow up (GRADE)			Risk with mechanical prophylaxis alone				
	Mortality follow up: range 4 days to 90 days 3717 ⊕⊕⊕⊖ (13 RCTs) ^a MODERA ⁻			RR 1.24	Study populat	tion			
					MODERATE	MODERATE		2.30) 1	16 per 1,000ª
					Low				
					9 per 1,000°	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	3909 (15 RCTs)		RR 0.34	Study populat	tion											
Pulmonary Embolism - representing the moderate]	MODERATE ^{b,e}	(0.12 to 0.94)	8 per 1,000	5 fewer per 1,000 (7 fewer to 0 fewer)											
marker state assessed				Low												
with: Symptomatic PE follow up: range 4 days				0 per 1,000 ^f	0 fewer per 1,000 (0 fewer to 0 fewer)											
to 90 days				Moderate												
				0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)											
Symptomatic Proximal		$\oplus \oplus \bigcirc \bigcirc$	RR 0.71 (0.07 to	Study populat	tion											
Deep Vein Thrombosis - representing the	(6 RCTs)	LOW ^h	6.75)		2 per 1,000	1 fewer per 1,000 (2 fewer to 13 more)										
moderate marker state				Low												
assessed with: Symptomatic proximal DVT						4		$\langle - \rangle$		$ \rightarrow $						1 per 1,000 ^f
follow up: range 7 days				Moderate												
to 90 days				0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 2 more)											
Symptomatic			RR 0.38	Low												
Distal Deep Vein Thrombosis - representing the severe		2.42)			(0.06 to 2.42)	1 per 1,000 ⁱ	0 fewer per 1,000 (1 fewer to 1 more)									
marker state assessed				Moderate												
with: Symptomatic distal DVT follow up:				0 per 1,000 ^f	0 fewer per 1,000 (0 fewer to 0 fewer)											

range 8 days				High	
to 90 days				0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)
Major	4174	⊕⊕⊕⊖	RR 1.64	Study populat	tion
bleeding follow up: range 7 days to 8 months		MODERATE ^{b,h}	(0.87 to 3.13)	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	2092 (3 RCTs) ⊕⊕⊖⊖ LOW ^{b,h}		RR 2.11	Study population	
follow up: range 7 days to 8 months		(0.42 to 10.70)	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)	
from s b. Very f c. The ba surgic	studies that incl ew studies des aseline risk con	luded surgical p cribed concealm sists of the con	atients with ent of alloo trol group e	h cancer or wit cation event rate from	rol group event rate hout cancer. htrials including han 50% of patient

d. e. f.	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%. Few or very few events, not enough to meet OIS criteria 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	
g. h. j.	outcome. 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 distal 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.	

Undesirable Effects How substantial are the undesirable anticipa	Undesirable Effects Now substantial are the undesirable anticipated effects?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
o Large o Moderate • Small o Trivial o Varies o Don't know						
Certainty of evidence What is the overall certainty of the evidence	of effects?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
o Very low • Low o Moderate o High o 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 varia	ability 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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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
 O Large costs Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies O 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 dateparin (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, FINSTEIN-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 \$15,690 for prophylaxis with rivaroxaban, and \$15,530 for prophylaxis (lindirect evidence): A health technology assess	

	2008. Up to 3 months after THR/TKR, mean incremental healthcare co associated with VTE, any bleeding, and major bleeding were \$2729, \$2 monthly costs versus matched THR/TKR controls without VTE or bleed \$9604; any bleeding: \$12,481 vs. \$9785; major bleeding: \$14,015 vs. \$ See Appendix 3 Table 1 for additional data on prophylaxis unit costs		
Certainty of evidence of re What is the certainty of the evidence of reso			
JUDGEMENT	RESEARCH EVIDENCE		ADDITIONAL CONSIDERATIONS
 Very low Low Moderate High No included studies 	The certainty of the evidence of resource requirements was judged as populations and study design (observational, retrospective data).	very low due to indirectness of the study	
Cost effectiveness Does the cost-effectiveness of the intervent	on favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE		ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention • Varies o No included studies 	We only identified two reports comparing mechanical combined with mechanical prophylaxis alone. One report compared the use of combin compression with and without the addition of low-molecular-weight h estimated to be cost-effective for high-risk gynecologic oncology patie compared six strategies including heparin plus stocking, and stocking o published in 1987, suggesting cost per additional life saved was \$82,33 compared with stocking only.	nation therapy external pneumatic eparin, the combination prophylaxis is nts undergoing surgery. One report only prophylaxis strategy. The study was	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 heal	Ith equity?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o 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 k	ey stakeholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o Don't know	No research evidence identified	
Feasibility Is the intervention feasible to impl	lement?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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
0	0	\bullet	0	0

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 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

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 ; Symptomati 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 EVID	ENCE					ADDITIONAL CONSIDERATIONS		
o No o Probably no o Probably yes • Yes o Varies o 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 anticip	ated effects?								
JUDGEMENT	RESEARCH EVID	ENCE					ADDITIONAL CONSIDERATIONS		
o Trivial o Small									
 Moderate O Large O Varies O Don't know 	participants the (studies) evi		Anticipated absolute effects* (95% CI)						
				Risk with mechanical prophylaxis alone	Risk difference with mechanical combined with pharmacological prophylaxis				
	Mortality 3717	⊕⊕⊕⊖	RR 1.24	Study population					
	follow up: range 4 days to 90 days	(13 RCTs)ª			MODERATE ^b (0.67 to 2.30)		16 per 1,000ª	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)				
		RR 0.34 (0.12 to	Study population						
	Embolism -		moderate"	0.94)	8 per 1,000	5 fewer per 1,000			

representing					fewer)	
the moderate marker state				Low	1	
assessed with: Symptomatic PE follow up:				0 per 1,000 ^f	0 fewer per 1,000 (0 fewer to 0 fewer)	
range 4 days to 90 days				Moderate		
				0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)	
Symptomatic	982	$\Theta \Theta \bigcirc \bigcirc$	RR 0.71	Study populati	on	
Thrombosis - representing	hrombosis -		2 per 1,000	1 fewer per 1,000 (2 fewer to 13 more)		
the moderate marker state				Low		
assessed with: Symptomatic proximal DVT				1 per 1,000 ^f	0 fewer per 1,000 (1 fewer to 3 more)	
follow up: range 7 days				Moderate		
to 90 days				0 per 1,000 ⁹	0 fewer per 1,000 (0 fewer to 2 more)	
Symptomatic	932 (5. DCTa)		RR 0.38 (0.06 to	Low		
Distal Deep Vein Thrombosis -	(5 RCTs)	LOW ^{b,h} (0.06 t 2.42)	•	1 per 1,000 ⁱ	0 fewer per 1,000 (1 fewer to 1 more)	
representing the severe				Moderate		
marker state assessed with: Symptomatic distal DVT		0 per 1,000 ^f	0 per 1,000 ^f	0 fewer per 1,000 (0 fewer to 0 fewer)		
follow up: range 8 days				High		
to 90 days			7	0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)	
Major bleeding	4174	⊕⊕⊕⊖	RR 1.64	Study populati	on	
follow up: range 7 days to 8 months	(14 RCTs)	4 RCTs) MODERATE ^{b,h} (0.87 to 3.13)	12 per 1,000	8 more per 1,000 (2 fewer to 25 more)		
				Low		
				12 por 1 0000	9 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	2092	@@ 00	RR 2.11	Study populat	ion
follow up: range 7 days to 8 months	(3 RCTs)	LOW ^{b,h}	(0.42 to 10.70)	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)
 c. The base non-call non-call surgica surgica with N= cancer anesthe of 0.8% e. Few or f. The base surgica 	ncer patients, i seline risk cons l patients with =591, and follo resection and esia until full a 6. very few even seline risk cons l patients with	sists of the con i.e. the trials the sists of event ri- cancer. Yamad w up time of 3 using mechanion mbulation a rise ts, not enough sists of event ri- pout cancer. In	trol group even at included le ates from obs oka 2015 (a p 0 days) repor cal IPC proph ok of mortality to meet OIS ates from obs	ent rate from tr ess than 50% of ervational study ropensity score ted in patients ylaxis from the of 0.7% and a criteria ervational study	risk of major bleeding y data including
estimat sympto	tes for sympton matic severe d	matic PE (0.03 listal DVT (0.0	d a risk of sy %), symptom 108%) have b	mptomatic VTE atic proximal D been calculated	of 0.3%. Baseline risk VT (0.054%) and

	assumptions that 10% of all symptomatic VTEs are PE episodes and 90% a episodes, of which 20% are symptomatic proximal DVTs and 80% symptom DVTs. Only 5% of the symptomatic distal DVTs are assumed to be severe I therefore, considered a critical outcome.	matic distal DVTs and,
	 h. Few events; confidence interval does not exclude a moderate or important combination therapy i. The baseline risk consists of the control group event rate (1.2%) from stud included surgical patients with cancer or without cancer. Baseline risk estin symptomatic distal DVT (0.06 %) has been calculated applying the assump only 5% of the symptomatic distal DVTs are severe DVTs j. The baseline risk consists of the control group event rate from trials includi cancer patients, i.e. the trials that included more than 50% of patients with 	dies that nates for ptions that ing surgical
Undesirable Effect How substantial are the under		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate		

Certainty of evidence What is the overall certainty of the evider	nce 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 v	ariability in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Important uncertainty or variability Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability o 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).	

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).	
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).	
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	
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).	
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	

or the comparison

○ Varies ○ Don't know

• Probably favors the intervention • Favors the intervention

Resources required How large are the resource requirer	ments (costs)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Large costs Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies O 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 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 regimes from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORDAI-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as \$15,669 for prophylaxis with rivaroxaban, and \$15,730 for prophylaxis with threat regiment (scoraparin, useriarin, or enoxaparin plus warfarin). Total inpatient hospital cost for knee replacement was reported as \$15,669 for prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxa	
	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 r	esource requirements (costs)?	
UDGEMENT	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).	
	ention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 equ	ity?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced • Probably no impact o Probably increased o Increased o Varies o 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	e to key stakeholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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	o implement?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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 (0bi 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 LIWH use (Cook 2014). Over 80% of 789 orthopedic surgeons were concerned or very concerned about 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 e	

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
0	0	0	•	0

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 pneum	atic 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 Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; Distal Deep Vein Thrombosis - representing the severe marker state ; 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						ADDITIONAL CONSIDERATIONS
O No In the absence of prophylaxis, the risk of DVT and PE in patients units on some considerable. With VTE prevention strategies provided at physician of several million surgical patients identified the rate of VTE during of 0.2% (Assareh 2014). O Varies O Don't know Symptomatic VTE post discharge in orthopedic and abdominal surg provided by physician discretion, has been reported in 4.7% and 3.3 2009).					ician discretion, a recent large registry study uring the index hospital admission for surgery surgery patients, with VTE prevention		
Desirable Effects How substantial are the desirable anticipated	effects?						
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial • Small o Moderate o Large	participants of (studies) evi	Certainty Relative		Anticipated absolute effects [*] (95% CI)		The panel discussed if the magnitude of the effect was moderate or small, and decided on a judgement of small.	
o Varies o Don't know		evidence (GRADE)		Risk with graduated compression stockings	Risk difference with pneumatic compression prophylaxis		
	Mortality	695 (5 RCTs)	⊕⊕⊖⊖ LOW ^{a,b}	RR 1.04 (0.16 to	Study population		
				6.63)	49 per 1,000	2 more per 1,000 (41 fewer to 274 more)	
					Low		
					55 per 1,000 ^c	2 more per 1,000 (46 fewer to 310 more)	
					Moderate		
					0 per 1,000 ^d	0 fewer per 1,000	

					fewer)														
Symptomatic		000	RR 0.56	Study populati	on														
Pulmonary Embolism - representing the moderate marker state	(8 RCTs)	LOW ^{a,e}	(0.17 to 1.86) ^f	17 per 1,000	7 fewer per 1,000 (14 fewer to 14 more)														
assessed with:				Low															
symptomatic PE				0 per 1,000 ⁹	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	100 (1. DCT)	000	not estimable	Study populati	Study population														
Proximal Deep Vein Thrombosis - representing the moderate	(1 RCT)	VERY LOW ^{a,e}		estimable	cstinubic	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)												
marker state assessed				Low															
with: symptomatic proximal DVT																			1 per 1,000 ⁹
				Moderate	Moderate														
				0 per 1,000 ^h	0 fewer per 1,000 (0 fewer to 0 fewer)														
Symptomatic		⊕000	RR 0.48	Low	Low														
Proximal Deep Vein Thrombosis - representing the moderate	Deep Vein hrombosis - epresenting	VERY LOW ^{a,e,i}	(0.25 to 0.92)	10 per 1,000 ^j	5 fewer per 1,000 (8 fewer to 1 fewer)														
marker state assessed				Moderate															
with: any proximal DVT				1 per 1,000 ^g	0 fewer per 1,000														

				High		
				0 per 1,000 ^h	0 fewer per 1,000 (0 fewer to 0 fewer)	
Symptomatic	100 (1. PCT)	000	not estimable	Low		
Distal Deep Vein Thrombosis - representing the severe	(1 RCT)	VERY LOW ^{a,e}		0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)	
marker state assessed				Moderate		
with: Symptomatic distal DVT follow up: mean 1 months				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	989 (5. DCT-)	S) ⊕OOO VERY LOW ^{a,b,i,1}	RR 0.55 (0.25 to 1.22)	Low		
Vein Thrombosis - representing the severe marker state				1 per 1,000 ^m	1 fewer per 1,000 (1 fewer to 0 fewer)	
assessed with: Any				Moderate		
distal DVT follow up: mean 1 months				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)	

 surgical non-cancer patients, i.e. the trials that included less than 50% of patients with cancer. Werk small number of events, not enough to meet OIS The estimate based on the measure of "any PE" from 4 trials with 2 events in 394 participants was R0.34 (95% CI [0.04, 3.24]). The baseline risk consists of event rates from observational study data including surgical patients with cancer. In patients undergoing all elective surgery Assarch et al. (2014) (a registry study) reported a risk of symptomatic VTE of 0.3%. Baseline risk settimates for symptomatic PE (0.03%), symptomatic proximal DVT (0.05%) and symptomatic Severe distal DVT (0.010%) have been calculated applying the assumptions that 10% of all symptomatic VTE of 0.3%. Baseline IDVTs and 80% are symptomatic distal DVTs. Only 5% of the symptomatic groximal DVTs of 0.30% are symptomatic distal DVTs. Only 5% of the symptomatic proximal DVT of concer patients and no observed bid end with an observed on the cancer polyation. The baseline risk estimates for symptomatic proximal DVT (1.9%) based on event rates from control group of included studies in the meta-analysis (5%) and the assumptions that 20% of any norximal DVT (1.9%) for any norximal DVT (0.15%) of any norximal DVT (1.9%) based on event rates from control group of included studies IDVTs are symptomatic grossimal DVT end symptomatic for symptomatic factors and the assumptions that 20% of any norximal DVT are symptomatic grossimal DVT end off. The baseline risk estimate for symptomatic factor DVTs and SUMS of SWS) and the assumptions that 20% of any norximal DVT are symptomatic factors and the assumptions that 20% of any norximal DVT are symptomatic factors and the assumptions that 20% of any norximal DVT are symptomatic symptomatic factors and the assumptions that 20% of any norximal DVT are symptomatic factors and the assumptions that 20% of any norximal DVT are symptomatic factors and the assumptions that 20% of any distal DVT (0.148%) based on

Undesirable Effects

How substantial are the undesirable anticipate	ed effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small • Trivial o Varies o 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	f effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Very low o Low o Moderate o High o 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 variab	ility in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O 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)	No bleeding trade off. However, the variability about how much people value PE and DVT alone was considered important.
	 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	

Г		I
	 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 thick locate the same restorement. 	
Balance of effects Does the balance between desirable and unde	thigh-length stockings (Wade 2017). sirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		
Resources required How large are the resource requirements (cost	ss)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Large costs Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies O 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. 	

Certainty of evidence o	See Appendix 3 Table 1 for additional data on prophylaxis unit costs	
What is the certainty of the evidence o		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 inte	rvention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o 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 stakehol	ders?	
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 im	plement?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No	Barriers to implementation of mechanical prophylaxis	
o Probably no	Patient compliance with sequential compression devices was higher when using battery-powered (85%)	
 Probably yes 	compared with conventional devices (47%). Of patients using battery-powered devices, 14% reported	
O Yes	major problems, which was 79% with conventional devices (Obi 2015). Twenty three percent of patients	
o Varies	receiving an automatic sequential leg compression system reported bothersome insomnia and in 3% the	
o Don't know	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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	O	•	

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 mechai	nical 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 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; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state; Symptomatic Distal D
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 EVI	DENCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	considerable. With study of several mi for surgery of 0.2% Symptomatic VTE	oost discharge in or ian discretion, has b	ategies provide ts identified th thopedic and al	ed at physician e rate of VTE odominal surg	discretion, a recend during the index ho gery patients, with	nt large registry ospital admission VTE prevention	
Desirable Effects How substantial are the desirable anticipated effects	ffects?						
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial • Small							
o Moderate O Large O Varies	Outcomes	Nº of participants	Certainty of the	Relative effect	Anticipated a effects* (959		
o Don't know		(studies) Follow up	evidence (GRADE)		Risk with no prophylaxis	Risk difference with mechanical prophylaxis	
	Mortality	1555 (10 RCTs)	⊕⊕⊖⊖ LOW ^{a,b}	RR 1.33 (0.71 to	Study populat	tion	
			2.51)	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	

					fewer)																								
Symptomatic	1469	⊕⊕⊖⊖	RR 0.61	Study population																									
Pulmonary Embolism - representing the moderate marker state	(9 RCTs)	LOW ^{b,e}	(0.27 to 1.40) ^f	22 per 1,000	9 fewer per 1,000 (16 fewer to 9 more)																								
assessed with:			-	Low																									
symptomatic PE				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)																								
	(8 RCTs)	⊕OOO VERY	RR 0.85 (0.41 to	Low																									
		LOW ^{b,h,i,j}	(0.41 to 1.75)	1.75)	19 per 1,000 ^k	3 fewer per 1,000 (11 fewer to 15 more)																							
				Moderate																									
																													1 per 1,000 ^g
				High																									
				2 per 1,000 ¹	0 fewer per 1,000 (1 fewer to 2 more)																								
Symptomatic	961 (7. PCTa)	0000	RR 0.66	Low																									
Distal Deep (7 RCTs) Vein Thrombosis - representing the severe	(7 KUIS)	VERY	(0.50 to 0.86)	2 per 1,000 ^p	1 fewer per 1,000 (1 fewer to 0 fewer)																								
marker state assessed				Moderate																									
with: any distal DVT				0 per 1,000 ⁹	0 fewer per 1,000																								

					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	-	-			-
blinded was no b. Small a appred c. The ba includi 50% o d. There observ e. None o blinded reporte f. The es events g. The ba includi	of the studies us d. In six studies t (adequately) number of even ciable benefit or seline risk cons ng surgical non- f patients with o are no studies i ed BLR data wa of the studies us d. In six studies ed. timate based or in 451 particip- seline risk cons ng surgical pati- e surgery Assar	the random reported. its. Confiden an apprecia ists of the co- cancer patie cancer. ncluding mo as identified se placebo, as the allocation the measu ants was RR ists of event ents without	ization and ce interval ble harm w ontrol grou ents, i.e. th re than 50° for the can although in on concealr re of "any I 1.01 (95% crates from cancer. In	Vor allocation of does not exclu- vith mechanical p event rate fro- e trials that inco- % of cancer par- cer population. four the assess nent was not (a PE" from 5 trial o CI [0.24, 4.26 observational patients under	concealment de an prophylaxis om trials cluded less tha tients and no sors were adequately) s with 12 5]) study data rgoing all

	· · · · ·
	 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 pisodes. 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 are symptomatic distal DVT (0.103%) consists of the control group of included studies in the meta-analysis (21.3%) and the assumptions that 20% of any distal DVT are symptomatic distal DVT are symptomatic distal DVT (0.103%) consists of the control group of included studies in the meta-analysis (21.3%) and the assumptions that 20% of any distal DVT are asymptomatic distal DVT rates that included more than 50% of patients with cancer (10.3%) and the assumptions that
Indesirable Effects	
Undesirable Effects	symptomatic distal DVTs are assumed to be severe DVTs and, therefore,

How substantial are the undesirable anticipated effects?

U

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small • Trivial o Varies o 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 The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the o Low critical outcomes. Moderate 0 High O No included studies Values Is there important uncertainty about or variability in how much people value the main outcomes? JUDGEMENT **RESEARCH EVIDENCE** ADDITIONAL CONSIDERATIONS The relative importance of the outcomes reported in the literature is indicated by utility values on a No bleeding trade off. However, the variability about how much Important uncertainty or variability • Possibly important uncertainty or variability scale of 0 to 1, where 0 = death and 1.0 = full health. The utility values reflect the relative value placed people value PE and DVT alone was considered important. on a given health state characterized by that condition, with higher values reflecting greater Probably no important uncertainty or variability importance: • No important uncertainty or variability No known undesirable outcomes 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).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 							
Resources required How large are the resource requirements (costs	?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
 o Large costs Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o 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 reque What is the certainty of the evidence of resource							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					

Very low Low O Low O Moderate O High O 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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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
 o Reduced o Probably reduced • Probably no impact o Probably increased o Increased o Varies o 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 stakeholde	ers?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o No o Probably no • Probably yes o Yes o Varies o 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
o No o Probably no • Probably yes o Yes o Varies o 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 of physicians shows that specific knowledge of guideline recommendations for the optimal use of antithrombotic agents use is low. (Arepaly 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 haspitalized surgical patients a hospital recommendation to continue thromboprophylaxis was given to 85% and wa	

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	
0	0	0	•	0	l

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 insertio	on 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 Distal Deep Vein Thrombosis - representing the severe 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

Duchlow							
Problem Is the problem a priority?							
> No > Probably no > Probably yes ● Yes > Varies > Don't know	be considerable. I	prophylaxis, the risk VC filters are commo y embolism in high r					
Desirable Effects Iow substantial are the desirable anticipated effects?							
Trivial Small							The panel was concerned about the
Moderate Large Varies Don't know	Outcomes	participants of (studies) ev	of the evidence (GRADE) CI	of the effect vidence (95%	Anticipated absolute effects [*] (95% CI)		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
o bon t know					Risk with no IVC filter	Risk difference with insertion of an inferior vena cava (IVC) filter	decision was to additionally consider observational studies in order to provide recommendation based on the best available evidence, for this prioritized question.
	Mortality	143680		RR 1.38	Study population		
	assessed with: all cause mortality	(12 observational studies) ^a	VERY LOW ^{b,c,d}	(0.81 to 2.37)	11 per 1,000	4 more per 1,000 (2 fewer to 15 more)	
	Symptomatic	869 (5	0000	RR 0.29	Study p	population	
	Pulmonary Embolism - representing the moderate marker state assessed	observational studies) ^a	VERY LOW ^{e,f,g}	(0.11 to 0.80) ^h	51 per 1,000	37 fewer per 1,000 (46 fewer to 10 fewer)	
	with: symptomatic				Low		
	PÉ				0 per 1,000 ⁱ	0 fewer per 1,000	

					0 fewer)	
Symptomatic Proximal	47 (1	0000	RR 0.32 (0.07 to	Low		
Deep Vein Thrombosis - representing the moderate marker state	observational study)	VERY LOW ^{j,k,I}	1.42)	52 per 1,000 ^m	35 fewer per 1,000 (49 fewer to 22 more)	
assessed with: any				Moderat	-	
proximal DVT				1 per 1,000 ⁱ	0 fewer per 1,000 (1 fewer to 0 fewer)	
Symptomatic	142127	€000	RR 2.19	Low		
Proximal Deep Vein Thrombosis - representing the moderate	ng		(1.07 to 4.50)	1 per 1,000 ⁱ		
marker state assessed				Moderat	te	
with: any DVT				0 per 1,000 ^p	0 fewer per 1,000 (0 fewer to 1 more)	
Symptomatic	142080	0000	RR 2.72	Low		
Distal Deep Vein Thrombosis - representing the severe	(9 observational studies) ^a	VERY LOW ^{b,q,r}	(1.41 to 5.21)	0 per 1,000 ^s	0 fewer per 1,000 (0 fewer to 0 fewer)	
marker state assessed				Moderat	e	
with: any DVT				0 per 1,000 ⁱ	0 fewer per 1,000 (0 fewer to 0 fewer)	
(Rajas b. Seriou c. The w impor d. Differ statist e. Two s f. Patier	ody of evidence sekhar 2011), fro is risk of bias. ide confidence in tant harm of the ences in point es ical heterogenei tudies considere ts included are s its. They may no	om which th nterval does interventio stimate. Une ty p= 0.01. d a historica surgically tre	e estimates not exclude n explained in al control. eated cance	of effect e a benef consisten r patients	: were poolec iit or an cy I2=57%, s and trauma	

	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.	
k.	Insertion of the filter based on attending surgeon preference. Patients surgically treated for pathologic lower extremity fractures	
κ.	from metastatic malignancies: they may be not representative of	
	the population of interest.	
١.	Small number of patients considered and events identified. Wide	
	confidence interval not excluding important benefits or harms. The baseline risk estimate for symptomatic proximal DVT (5.2%)	
m.	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.	
о.	Differences in point estimate. Unexplained inconsistency I2=77%,	
-	statistical heterogeneity p< 0.01.	
р.	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?		
o Large • Moderate o Small o Trivial o Varies o Don't know		
Certainty of evidence What is the overall certainty of the evidence of effects?		
• Very low o Low o Moderate o High o 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 interve	ention or the comparison?	
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 OLow OModerate OHigh ONo included studies		
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the	comparison?	
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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?		
o No • Probably no o Probably yes o Yes o Varies o Don't know	No research evidence identified	Probably not acceptable to all groups (patients, providers, administrators).

Feasibility Is the intervention feasible to implement?		
O NO • Probably no O Probably yes O Yes O Varies O 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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	•	0	0	0

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

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 ; 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 EV	IDENCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o 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 EV	IDENCE					ADDITIONAL CONSIDERATIONS
o Trivial o Small • Moderate o Large	Outcomes№ of participantsCertainty of theRelative effectAnticipated absolute effects* (95% CI)						
o Varies o Don't know	(studies) Follow up			ADE) ČI)	Risk with standard course antithrombotic prophylaxis	Risk difference with extended course prophylaxis	
	Mortality 4574	4574 (11 RCTs)		RR 0.98 (0.64 to	Study population		
				1.49)	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			Study populatio	n																	
Embolism - representing the moderate		NODERATE	0.98)			5 per 1,000	4 fewer per 1,000 (5 fewer to 0 fewer)														
marker state (assessed				Moderate	Moderate																
with: symptomatic PE)					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	(12 RCTs) MODERATE ⁹	RR 0.25 (0.17 to	Low																		
Deep Vein Thrombosis - representing the				0.37)						11 per 1,000 ^h	9 fewer per 1,000 (9 fewer to 7 fewer)										
moderate marker state					Moderate																
assessed with: any proximal DVT			X																	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		⊕⊕⊕⊖	RR 0.62	Low																	
Distal Deep Vein Thrombosis - representing the severe			s) MODERATE' (0.41 0.94)				1 per 1,000 ^j	0 fewer per 1,000 (0 fewer to 0 fewer)													
marker state assessed				Moderate																	
with: any distal DVT				0 per 1,000 ^f	0 fewer per 1,000																

				High		
				0 per 1,000 ^f	0 fewer per 1,000 (0 fewer to 0 fewer)	
	RR 0.88	Study populatio	n			
bleeding	eeding (11 RCTs) LOW ^a (0.38 to 2.00)	6 per 1,000	1 fewer per 1,000 (4 fewer to 6 more)			
		3	Low			
				3 per 1,000 ^b	0 fewer per 1,000 (2 fewer to 3 more)	
					Moderate	
			10 per 1,000°	1 fewer per 1,000 (6 fewer to 10 more)		
Reoperation	576 (3 RCTs)	⊕CCC VERY	RR 1.54	Study population		
		LOW ^{a,k}	(0.20 to 12.10)	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°	10 more per 1,000 (14 fewer to 200 more)	

Undesirable Effects How substantial are the undesirable anticipated effects?								
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
o Large o Moderate • Small o Trivial o Varies o Don't know								
Certainty of evidence What is the overall certainty of the evidence of	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 variab	bility in how much people value the main outcomes?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability O 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 under	esirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		
Resources required How large are the resource requirements (cos	sts)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Large costs Moderate costs O Negligible costs and savings O Moderate savings o Large savings o Varies o 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 hip replacement was reported as \$15,669 for prophylaxis with rivaroxaban, and \$15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Resource use for disease (indirect evidence): Vekeman	

Certainty of evidence of rec What is the certainty of the evidence of resou		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Very low o Low o Moderate o High o 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	on favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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
ReducedProbably 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

o Probably no impact o Probably increased o Increased o Varies o 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 stakeh	olders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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
o No o Probably no • Probably yes o Yes o Varies o 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 LIMWH 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	

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)	

 $\langle \cdot \rangle$

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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	0	•	0

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	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	There is uncertainty about the opti administration may increase antith operative bleeding.					
Desirable Effects How substantial are the desirab	le anticipated effects?					
JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS
• Trivial o Small o Moderate o Large o Varies o Don't know	Outcomes Nº of partici (studies) Follow-up	ipants Of the evidence (GRADE)	Relative effect (95% CI)	Anticipated abso effects Risk with delayed (post- operative- after 12 hours) antithrombotic administration	Risk difference with early (post- operative-	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.
	Mortality assessed with: Mortality follow up: range 9 days to 6 months	9972 ⊕○○ (6 VERY RCTs) 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 -	9744 ⊕○○○ (6 VERY	RR 0.63 (0.23 to	Based on study BLR	population	
	moderate marker state assessed with: any PE follow up: range 9 days to 6 months	assessed with: any PE follow up: range 9 days		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 –	5732 (5	⊕OOO VERY	RR 0.88 (0.40 to	Based on study BLR	population
representing the moderate marker state assessed with: any proximal DVT follow up: range 9 days	RCTs)	LOW ^{a,c,g,h}	1.96)	4 per 1,000 ⁱ	0 fewer per 1,000 (2 fewer to 4 more)
to 6 months				Low	
				1 per 1,000 f	0 fewer per 1,000 (0 fewer to 1 more)
Symptomatic Distal Deep Vein Thrombosis –	5680 (5	⊕OOO VERY	RR 0.68 (0.41 to 1.12) ^c	Based on study BLR	population
representing the severe marker state assessed with: any distal DVT follow up: range 9 days to 6 months	RCTs)	LOW ^{a,c,j,k}		1 per 1,000 ¹	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	,000 /er to
 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: 1² = 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 (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 of PE and therefore, considered important curcome. g. Heterogeneity between studies: 1² = 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 1² = 63%, OR=0.92 (0.491, 1.69) i. The baseline risk consists of the control group event rate (1.3.1%) from studies included in th meta-analysis. Baseline risk estimates for symptomatic proximal DVT sa resymptomatic 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	most ne th d nt l in the 08%) t 10% re v/Ts ent , cify in the oximal erent lting on of d in DVTs,

Undesirable Effects How substantial are the undesirable a	nticipated effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate • Small o Trivial o Varies o Don't know		
Certainty of evidence What is the overall certainty of the ev	idence of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Very low o Low o Moderate o High o 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 of	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 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:
Studies additionally described the following regarding patients experiences and preferences for VTE propriyiaxis.
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					
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 							
Resources required How large are the resource requirements (c	osts)?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
 o Large costs o Moderate costs Negligible costs and savings o Moderate savings o Large savings o Varies o 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 hip 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 w	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							
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 intervent	tion favor the intervention or the comparison?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies No included studies 	No research evidence identified							
Equity What would be the impact on health equity	?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
o Reduced o 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 Acceptability Is the intervention acceptable to key stake	eholders?	equity, assuming that prophylaxis would typically be short-term for this population.
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
o No o Probably no • Probably yes o Yes o Varies o 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 specialits 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 when 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)	

 $\langle \cdot \rangle$

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	Conditional recommendation against the	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	the intervention or the comparison	intervention	intervention
0	0	•	0	0

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

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVII	DENCE		ADDITIONAL CONSIDERATIONS			
● Trivial ○ Small							
o Moderate o Large o Varies	Outcomes	№ of participants	Certainty of the	Relative effect	Anticipated ab effects [*] (95%		
o Don't know		(studies) Follow up		i) CI)	Risk with other anticoagulant	Risk difference with Aspirin	
	Mortality		RR 2.32	Study populatio	n		
		(8 RCTs)		(0.15 to 36.90)	1 per 1,000	1 more per 1,000 (1 fewer to 33 more)	
	Symptomatic	Symptomatic Pulmonary Embolism - representing the moderate marker state assessed with:		RR 1.49	Study population		
	Embolism - representing the moderate marker state		(0.37 to 6.09)	3 per 1,000	1 more per 1,000 (2 fewer to 14 more)		
					High		
	symptomatic PE				7 per 1,000 ^e	3 more	

					1
follow up: range 7 days to 6 months					(4 fewer to 36 more)
Symptomatic	(7 RCTs) VERY (0.51 to LOW ^{a,d,f} 4.34)		-	Study population	n
Proximal Deep Vein Thrombosis - representing the moderate			6 per 1,000	3 more per 1,000 (3 fewer to 19 more)	
marker state assessed				Low	
with: proximal symptomatic or any symptomatic DVT follow up: range 7 days to 6 months				0 per 1,000 ^{g,h}	0 fewer per 1,000 (0 fewer to 1 more)
Symptomatic	1746	⊕000	RR 1.45	Study population	
Distal Deep Vein Thrombosis - representing the moderate	j e		VERY (0.86 to LOW ^{a,f,i} 2.46) 2	24 per 1,000	11 more per 1,000 (3 fewer to 35 more)
marker state assessed		Low			
with: distal or any symptomatic DVT follow up: range 6 weeks to 6 months				0 per 1,000 ^{g,h}	0 fewer per 1,000 (0 fewer to 0 fewer)
Major	1072	⊕⊕⊖⊖	RR 2.63	Study population	n
bleeding follow up: range 7 days to 6 months	(6 RCTs) ⁱ	LOW ^{a,i}	(0.64 to 10.79)	4 per 1,000 ^j	6 more per 1,000 (1 fewer to 35 more)
Reoperation - not reported	-	-	-	-	-
study after r	was blinded, an andomization	d 2 studies of	excluded 89	ocation concealm % and 20%. of pa come but we assu	articipants

 events if not reported. Most studies did not properly report whether or not PEs were symptomatic and their severity. 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. 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 Most studies did not report whether or not DVT events were symptomatic, proximal or distal, and their severity. 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 VTE on patients without prophylaxis, Huang (2011) DVT rates of 0.99% on aspirin and 0.84% on LIMWH 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. 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. 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
o Large o Moderate • Small o Trivial o Varies o 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	
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability O 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: 0.15 (standard gamble) (Hogg 2013) Major intracranial 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:		

 Pavors the comparison Probably favors the comparison Does not favor either the intervention or 		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Balance of effects Does the balance between desirable and unde	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 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).	
	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:	

○ Varies ○ Don't know

Resources required

How large are the resource requirements (costs)?									
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS							
 O Large costs O Moderate costs Negligible costs and savings O Moderate savings O Large savings O Varies O 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 regimes 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 (2015/10 mg QD), and \$22.00 for generic enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as \$15,669 for prophylaxis with rivaroxaban, and \$15,530 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)								

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?								
JUDGEMENT	JUDGEMENT RESEARCH EVIDENCE							
o Very low • Low o Moderate o High o 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	n favor the intervention or the comparison?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention • Varies o 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						
o Reduced o Probably reduced o Probably no impact • Probably increased o Increased o Varies o 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 	Panel considered that aspirin might be accepted by patients i general, but there might be a variability in stakeholders acceptability, including some clinicians who belief that aspirin not effective.					
Feasibility Is the intervention feasible to implement?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
o No o Probably no o Probably yes • Yes o Varies o 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 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 (Sarrt 2013) In hospitalized surgical patients a hospital					

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)	

 $\langle \cdot \rangle$

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	Conditional recommendation against the	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	the intervention or the comparison	intervention	intervention
0	0	•	0	0

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	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?

is the problem a priority:							
JUDGEMENT	RESEARCH EVI	DENCE			ADDITIONAL CONSIDERATIONS		
o No o Probably no o Probably yes • Yes o Varies o Don't know	of PE is 3% (Nation: identifiable risk fac patients undergoin	rophylaxis, for patier al Clinical Guideline C tors for VTE. Other, t g different types of s and Assareh 2014).					
Desirable Effe							
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial ● Small							
o Moderate o Large o Varies	Outcomes	№ of participants		Relative	effects [*] (95% CI)		
o Don't know		(studies) evidence Follow up (GRADE)	(95% CI)	Risk with LMWH prophylaxis	Risk difference with DOACs prophylaxis		
	Mortality	41846	കക	RR 0 94	Study populat	ion	

				prophylaxis	with DOACs prophylaxis
Mortality	41846		RR 0.94	Study populat	ion
follow up: range 10 days to 35 days	(38 RCTs) ^a	MODERATE⁵	(0.53 to 1.66)	1 per 1,000	0 fewer per 1,000 (1 fewer to 1 more)
Symptomatic	41634	000	RR 0.74	Study populat	ion
Pulmonary Embolism - representing the moderate marker state	(38 RCTs)	MODERATE ^{b,c}	(0.50 to 1.10)	3 per 1,000	1 fewer per 1,000 (1 fewer to 0 fewer)
assessed with: Non Fatal				High	
Symptomatic Pulmonary				7 per 1,000 ^d	2 fewer per

embolism follow up: range 10 days to 35 days					(3 fewer to 1 more)
Symptomatic	39924	0000	RR 0.56	Low	
roximal Deep /ein hrombosis - epresenting he moderate	bosis - senting oderate	1 per 1,000 ^e	1 fewer per 1,000 (1 fewer to 0 fewer)		
arker state ssessed with:		Ма	Moderate		
ymptomatic VT bllow up: ange 10 days o 35 days				0 per 1,000 ^{f,g}	0 fewer per 1,000 (0 fewer to 0 fewer)
Symptomatic	39924	0000	RR 0.56	Low	
Distal Deep Vein Thrombosis - representing the severe	(38 RCTs)	HIGH	IGH ^c (0.39 to 0.79)	0 per 1,000 ^h	0 fewer per 1,000 (0 fewer to 0 fewer)
narker state ssessed with:		м	Moderate		
ymptomatic VT bllow up: ange 10 days o 35 days		0	25	0 per 1,000 ^{f,g}	0 fewer per 1,000 (0 fewer to 0 fewer)
lajor bleeding	46382	•••	RR 1.03	Study populat	ion
ollow up: ange 10 days o 35 days	(38 RCTs)	MODERATE ^{b,i}	(0.79 to 1.35)	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	33560	000	RR 1.43	Study populat	ion
eading to eoperation assessed with: Bleeding eading to eoperation	(38 RCTs)	MODERATE⁵	(0.75 to 2.71)	1 per 1,000	0 fewer per 1,000 (0 fewer to 2 more)

range	aw up: ge 10 days 5 days
b. c. d. e. f. g.	 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. n. 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. . Some heterogeneity detected (I2=21%)

Undesirable Effects How substantial are the undesirable an	ticipated effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small • Trivial o Varies o 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 evid	lence of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low • Moderate o High o 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 of	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 variabili No known undesirable outcomes 	Pulmonary embolism: range 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)	
	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 unc	Does the balance between desirable and undesirable effects favor the intervention or the comparison?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 							
Resources required How large are the resource requirements (co	osts)?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
o Large costs o Moderate costs o Negligible costs and savings o Large savings • Varies o 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 studyevaluating the financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in388 patients with injuries of the lower limb requiring immobilization, the total pay (cost of healthcarepractitioner) and non-pay (consumables, drugs and blood-test investigations) costs for prophylaxis withdalteparin (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) perpatient.Merli et al. 2010, compared the total direct medical costs associated with VTE prophylaxis withenoxaparin and unfractionated heparin (UFH) in patients with a diverse range of medical and surgicalconditions conferring VTE risk using hospital discharge and billing records between January 2002 andDecember 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 groupwere \$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 kneereplacement and hip replacement based on an economic model from a hospital perspective developedusing treatment regimens from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomizedclinical trials. Anticoagulant treatment unit cost was reported as \$8.46 re rivaroxaban (20/15/10 mg QD),and \$22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost	Varies depending on the country or jurisdiction.					

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	vs. \$9710.	
	See Appendix 3 Table 1 for additional data on prophylaxis unit costs	
Certainty of evidence of rec What is the certainty of the evidence of resource		1
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Very low Low O Moderate O High O 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 interventio	n favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 stakehol	ders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o 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 O Yes O Varies O 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
o No o Probably no • Probably yes o Yes o Varies o 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 to continue, thromboprophylaxis was continued in 65%. (Schellong 2015) An assessment of 22 Spani	

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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	Ο	•	

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	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

Is the problem a priority?							
JUDGEMENT	RESEARCH EVIDE	INCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	In the absence of pro the risk of PE is 3% (N patients with identifi estimate the risk of D lower (rates of VTE o	lational Clinical Gu able risk factors for N/T in patients und	ideline Centre, 201 r VTE. Other, big re ergoing different ty	0). Pharmacol gistry studies of pes of surger	ogical agents a of several million	re used in on patients,	
Desirable Effe							
JUDGEMENT	RESEARCH EVIDE	INCE					ADDITIONAL CONSIDERATIONS
o Trivial o Small ● Moderate o Large o Varies o Don't know	Outcomes	Outcomes № of Certainty of			Relative Anticipated absolute		
		participants (studies)	the evidence	effect (95%	effects* (-	
		Follow up	(GRADE)	CI)	Risk with Warfarin	Risk difference with LMWH	
	Mortality	4227 (5. DCT-)					
	follow up: range 14 days to 6 months	(5 RCTs)	LOW ^a	(0.14 to 1.88)	3 per 1,000	2 fewer per 1,000 (3 fewer to 3 more)	
	Symptomatic Pulmonary	5431 (F. DCTa)		RR 0.83	Low		
	Pulmonary	(5 RCTs)	VERY LOW ^{a,b}	(0.27 to 2.56)	1 per	0 fewer	

marker state				High	
assessed with: any PE follow up: range 10 days to 3 months				7 per 1,000 ^d	1 fewer per 1,000 (5 fewer to 11 more)
Symptomatic	3620	0 000	RR 0.61	Low	
Proximal Deep Vein Thrombosis - representing the moderate	(6 RCTs)	VERY LOW ^{b,e,f}	(0.36 to 1.02)	15 per 1,000 ^g	6 fewer per 1,000 (9 fewer to 0 fewer)
marker state assessed with:				Moderate	
any Proximal DVT follow up: range 6 days to 14 days				0 per 1,000 ^{h,i}	0 fewer per 1,000 (0 fewer to 0 fewer)
Symptomatic	731	000	RR 0.61	Low	<u>'</u>
Distal Deep Vein Thrombosis - representing the severe	(2 RCTs)	LOW ^{b,e}	(0.42 to 0.88)	3 per 1,000 ^j	1 fewer per 1,000 (2 fewer to 0 fewer)
marker state assessed with:				Moderate	
any Distal DVT follow up: range 6 days to 14 days				0 per 1,000 ^{h,i}	0 fewer per 1,000 (0 fewer to 0 fewer)
Major bleeding	7467		RR 1.81	Study pop	ulation
follow up: range 14 days to 6 months	(7 RCTs)	MODERATE ^{k,I}	(1.31 to 2.50)	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. PCTo)		RR 3.09	Study population	
	(2 RCTs)	MODERATE ⁿ	(0.13 to 75.48)	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 DVT. We rated down for indirectness. f. Although the C1 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 f. 14%) 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 0.48% on UMM i. The baseline risk consists of the control group event rate (2.4%) from studies included in the meta-analysis. Baseline risk estimates for symptomatic proximal DVT (1.4%) has been calculated applying the assumptions that 20% of any proximately 90% of the VTEs are DVTs, 20% of DVTs are proximal, 80% 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 unblind			
 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 blas 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 blas. 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 were 0.68%. Parvizi (2015) reports a rate of symptomatic PE were 0.68%. Parvizi (2015) reports a rate of 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 from symptomatic DVTs. h. Mauck (2013) reports a rate of 0.4% for symptomatic TE. Jameson (2011) DVT rates of 0.84% of any proximal DVTs are symptomatic proximal DVTs. h. Mauck (2013) reports a rate of 0.4% for symptomatic TE. Jameson (2011) DVT rates of 0.84% of the latter severe was applied. j. The baseline risk consists of the control group event rate (27.9%) from studies included in the mata-analysis. Baseline risk estimates for symptomatic DVTs. h. Mauck (2013) reports a rate of 0.4% for symptomatic TE. Jameson (2011) DVT rates of 0.84% of the latter severe was applied. j. The baseline risk consists of the control group event rate (27.9%) from studies included in the mata-analysis. Baseline risk estimates for symptomatic distal DVTs are symptomatic distal DVTs are symptomatic the pay of a symptomatic distal DVTs are proximal DVTs. k. Desplite the lack of blinding, we			
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Undesirable Effects How substantial are the undesirable anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
o Large o Moderate • Small o Trivial o Varies o 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 variabi	lity 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				
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 						
Resources required How large are the resource requirements (cost	s)?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
 O Large costs Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies O 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 regimes from the ROCKET-AF, EINSTEIN-DVT and PE, and RECORD1-3 randomized (clinical trials. Anticoagulant treatment unit cost was reported as \$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, r					

Certainty of evidence of req What is the certainty of the evidence of resour		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low • Low o Moderate o High o No included studies Cost effectiveness	The certainty of the evidence of resource requirements was judged as low due to considerations about study design (observational, retrospective data).	
Does the cost-effectiveness of the intervention	favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 stake	holders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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
o No o Probably no o Probably yes • Yes o Varies o 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	Conditional recommendation against the	Conditional recommendation for either the		Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	0	•	0

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

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVID	ENCE		ADDITIONAL CONSIDERATIONS			
o Trivial o Small • Moderate o Large o Varies o Don't know							
	participants the evidence effect	participants (studies)	the evidence	Relative effect (95%	Anticipated absolute effects [*] (95% CI)		
			Risk with UFH	with difference			
		1549 (5. DCT-)		RR 0.26	Study population		
	assessed with: all-cause mortality follow up: range 7 days to 2 months	(5 RCTs)	HIGHª	(0.03 to 2.36)	4 per 1,000	3 fewer per 1,000 (4 fewer to 5 more)	
	Symptomatic 2534	⊕⊕⊕⊖	RR 0.37	Low			
	Pulmonary Emolism - representing the moderate marker state	(10 RCTs)	MODERATE⁵	(0.19 to 0.71)	5 per 1,000 ^c	3 fewer per 1,000 (4 fewer to 1 fewer)	
	assessed with:				Moderat	e	

any PE				7 per 1,000 ^d	4 fewer per 1,000 (6 fewer to 2 fewer)		
Symptomatic	2336	⊕⊕⊕⊖	RR 0.48	Low	Low		
Proximal Deep Vein Thrombosis - representing the moderate	(8 RCTs)	MODERATE®	(0.34 to 0.69)	12 per 1,000 ^f	6 fewer per 1,000 (8 fewer to 4 fewer)		
marker state assessed with:				Moderate	2		
proximal DVT				0 per 1,000 ^{g,h}	0 fewer per 1,000 (0 fewer to 0 fewer)		
Symptomatic	1504		RR 1.18	Low			
Distal Deep Vein Thrombosis - representing the severe	(6 RCTs)	MODERATE ^{e,i}	(0.81 to 1.72)	0 per 1,000 ^j	0 fewer per 1,000 (0 fewer to 0 fewer)		
marker state assessed with:				Moderate			
distal DVT				0 per 1,000 ^{g,h}	0 fewer per 1,000 (0 fewer to 0 fewer)		
Major bleeding	2278	•••	RR 0.55	Study population			
•	(6 RCTs)	MODERATE ^{k,I,m}	(0.27 to 1.13)	41 per 1,000	19 fewer per 1,000 (30 fewer to 5 more)		
Reoperation	321 (2. PCTc)		not	Study population			
	(2 RCTs)	MODERATE ^a	estimable	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)		
narrow o downgra b. Seven o investiga c. The bas studies	confidence inter aded for imprec If 10 included st ators. eline risk consis included in the	s, wide confidenc val around absol ision. cudies did not blin sts of the control meta-analysis. B 6) has been calcu	lute effects nd participa group even aseline risk	and we dio nts and/or t rate (2.3 estimates	d not study 8%) from for		

	 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 assumed to be severe DVTs. k. Estimate of effect includes both appreciable benefit and appreciable harm. 1. 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 impreciable 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 anticipate	ed effects? RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Large O Moderate O Small Trivial O Varies O Don't know 		

Certainty of evidence

What is the overall certainty of the evidence	of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low • Moderate o High o 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 varia	bility in how much people value the main outcomes?	-
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O 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: 0.15 (standard gamble) (Hogg 2013) Major intracranial 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 unde	sirable effects favor the intervention or the comparison? RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Large costs Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies O 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 RECORDI-3 randomized clinical trials. Anticoagulant treatment unit cost was reported as \$15,490 for prophylaxis with nivaroxaban, 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 \$15,570 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Resource use for	

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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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
 o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o 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
JODGEIMENT		
○ No	Barriers to implementation of pharmacological prophylaxis	
o Probably no	A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear	
o Probably yes	against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that	
• Yes	concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use	
o Varies	were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug	
o Don't know	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)	
	Tatiler than a decrease in VTL and similar breeding risk. (dirizburg 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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	0	0	\bullet

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 DO	AC 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;
ETTING:	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	Pro	b	em
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JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o 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	le anticipated effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small o Trivial o 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.

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low • Low o Moderate o High o 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 variabil	ity in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Important uncertainty or variability Possibly important uncertainty or variability Orobably 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: 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 t	

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 	A potential difference in the effect with specific drugs and especially between DOAC classes (Anti-Ila 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
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings • Varies o 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 prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement twas reported as \$15,696 for prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus war	Varies depending on the country or jurisdiction.

Certainty of evidence of req What is the certainty of the evidence of resour		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low • Low o Moderate o High o 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	n favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o Don't know 	No research evidence identified	
Acceptability Is the intervention acceptable to key stakehold	lers?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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?

s the intervention feasible to implement?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
o No	Barriers to implementation of pharmacological prophylaxis						
○ Probably no	A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear						
Probably yes	against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that						
o Yes	concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic						
Varies	use were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug						
Don't know	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	Conditional recommendation against the	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	the intervention or the comparison	intervention	intervention
0	0	•	0	0

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 pharma	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 EVIE	DENCE					ADDITIONAL CONSIDERATIONS	
o No o Probably no o Probably yes • Yes o Varies o Don't know	instance, patients u	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 Effe ow substantial are the desiral					X			
JUDGEMENT	RESEARCH EVIE	DENCE					ADDITIONAL CONSIDERATIONS	
o Trivial o Small • Moderate o Large	Outcomes	Outcomes № of C participants c		Relative effect	Anticipated absolute effects [*] (95% CI)			
o Varies o Don't know			evidence (GRADE)	ĊI)	Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis		
	Mortality	14213	€000	RR 0.95	Study population			
	(follow-up 10 days to 3 months)	(9 RCTs)	VERY LOW ^{a,b}	(0.84 to 1.07)	71 per 1,000	4 fewer per 1,000 (11 fewer to 5 more)		
	Symptomatic		0000	RR 0.49	Study population	1		
	Pulmonary Embolism - representing the moderate marker state	(9 RCTs)		(0.33 to 0.72)	11 per 1,000	6 fewer per 1,000 (7 fewer to 3 fewer)		
	assessed				Low			

with: symptomatic PE				3 per 1,000 ^c	2 fewer per 1,000 (2 fewer to 1 fewer)	
Symptomatic	13813	⊕000	RR 0.51	Low	1	
Proximal Deep Vein Thrombosis - representing the moderate	(5 observational studies)	VERY LOW ^{d,e}	(0.38 to 0.69) ^f	3 per 1,000 ⁹	1 fewer per 1,000 (2 fewer to 1 fewer)	
marker state (follow-up 10				Moderate		
days to 3 months) assessed with: any Proximal DVT				25 per 1,000 ^c	12 fewer per 1,000 (16 fewer to 8 fewer)	
Distal Deep	13813	⊕000	RR 0.85	Low		
Vein Thrombosis - representing the severe marker state	(5 RCTs)				OW ^{b,d,e} 1.29) ^h 0 per 1,000 ⁱ	0 fewer per 1,000 (0 fewer to 0 fewer)
(follow-up 10 days to 3				Moderate		
months) assessed with: any Distal DVT				4 per 1,000 ^c	1 fewer per 1,000 (2 fewer to 1 more)	
Major	14415	@@ OO	RR 1.24	Study population		
bleeding follow up: range 10 days to 3 months	(11 RCTs)	LOW ^a	(1.12 to 1.37)	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	13645	0000	RR 1.05	Study population		
(follow-up 14 days to 35 days)	(3 RCTs)	VERY LOW ^{b,j,k}	(0.82 to 1.35)	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, Sazaki 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 DVT are symptomatic proximal DVT. 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 asymptomatic	
Undesirable Effects How substantial are the undesirable antici JUDGEMENT	pated effects? RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

O Large O Moderate • Small O Trivial O Varies O 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 eviden	ce of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Very low o Low o Moderate o High o 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 va	riability in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O 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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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.

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings • Varies o 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 peritent 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 rivaroaban (20/15/10 mg QD), and \$22.00 for generic enoxaparin, domg DQ). Total inpatient hospital cost for knee replacement was reported as \$15,699 for prophylaxis with rivaroaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as \$15,699 for prophylaxis with	DOACs are not "labelled" for use in HFR in the USA Aspirin data are not included here but drug cost fo aspirin is very low.

Certainty of evidence of n What is the certainty of the evidence of re		
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 interve	ention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o 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 equi	ity?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced • Probably no impact o Probably increased o Increased o Varies o 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 stake	eholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no	No research evidence identified	Long term administration of LMWH was considered lacceptable by patients.

Aspirin was seen as more acceptable.

• Probably yes o Yes

o Varies ○ Don't know

Feasibility

s the intervention feasible to implement?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
o No o Probably no • Probably yes o Yes o Varies o 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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	0	•	0

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 p considerable. For ir for post-operative ^v overall symptomati thromboprophylaxi was 7.1%.	nstance, patients ur VTE. Gao et al (2010 ic VTE rate was 7.99	ndergoing surge 6) studied 1177 % (73/1177) and	dered at high risk 008 and 2012. The ose not on										
Desirable Effects How substantial are the desirable anticipated end	ffects?													
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS							
• Trivial o Small o Moderate	Outcomes participants of (studies) evi	comes participants	Certainty of the	Relative effect	Anticipated absolute effects* (95% CI)									
o Large o Varies o Don't know		evidence (95% (GRADE) CI)	Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis										
	(follow-up 10 to 14 days) (2 RCTs) VER LOW Pulmonary 251 ⊕○ Embolism - (3 RCTs) VER			RR 0.47	Study population									
			(0.10 to 2.12)	74 per 1,000	39 fewer per 1,000 (66 fewer to 82 more)									
		0 000		Study population										
			LOW ^{c,d,e} 81.3	LOW ^{c,d,e} 81.32)			e 81.32)	Y ^{c,d,e} (0.06 to)W ^{c,d,e} 81.32)	.OW ^{c,d,e} 81.32)	OW ^{c,d,e} 81.32)	(0.06 to 81.32)	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 populat	ion								

1								
Thrombosis - representing the moderate			5.43) ^h		per 1,000 (7 fewer to 391 more)			
marker state (follow-up 10				Moderate				
to 14 days)				25 per 1,000 ^f	31 more per 1,000 (2 fewer to 111 more)			
Distal Deep	139	⊕000	RR 0.66	Study populat	tion			
Vein Thrombosis - representing the severe distal DVT	(2 RCTs)	VERY LOW ^{a,i}	(0.21 to 2.07) ^j	103 per 1,000	35 fewer per 1,000 (81 fewer to 110 more)			
marker state (follow-up 10				Moderate				
to 14 days)							4 per 1,000 ^f	1 fewer per 1,000 (3 fewer to 4 more)
Major	251 (3 RCTs)	⊕000	RR 0.85 (0.19 to	Study population				
bleeding (follow-up 10 to 14 days)			(3 Kers)	(5 (C13)		(3 RCTs) VERY LOW ^{k,l,m}	3.79)	62 per 1,000
				Low				
				5 per 1,000 ^f	1 fewer per 1,000 (4 fewer to 14 more)			
Reoperation	0 (0 studios)	-	not estimable	Study population				
	(0 studies)	studies)		0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)			
b. Only 7 benefi downg c. For tw availal randor level.	e study (Pini 19 events among t with either int raded two level o of the studies ole. One of the nization. For the	139 people; ervention. Fo (Pini 1989, studies had ese reasons	95% CI do or these rea Hoffmann 1 over 20% lo we rated do	es not exclude sons, the score 996) only the a oss to follow-up own for risk of b	e was abstracts were post bias by one			
availal randor level.	ole. One of the	studies had ese reasons	over 20% lo we rated do	oss to follow-up own for risk of t	post bias by o			

Trivial
Varies
Don't know

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 variabil	ity in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O 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: 0.15 (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 undes	irable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		

Resources required

How large are the resource requirements (costs)?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o Large costs • Moderate costs o Negligible costs and savings o Large savings o 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 (inical trials. Anticoagulant treatment unit cost was reported as \$8.84 for rivaroxaban (20/15/10 mg QD), and \$22.00 for generic enoxaparin (PUM gDQ). Total inpatient hospital cost for knee replacement was reported as \$15,669 for prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total impatient hospital cost for hagents (in USD per patient per month associated with VTE,				

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 	One report compared enoxaparin with unfractionated heparin, and concluded Enoxaparin dominated unfractionated heparin in the thromboprophylaxis for hip fracture patients (Drummond 1994).	
the comparison Probably favors the intervention 	Indirect evidence from total hip or knee arthroplasty, and gynecological surgery patients was used to	
 Favors the intervention 	inform the cost-effectiveness. The results from indirect evidence suggested LMWH cost-effective	
o Varies	compared with UFH. (Fowler 2014, Lazo-Langner 2012, Maxwell 2000, Wade 2008).	
○ No included studies		

Equity

What would be the impact on health equity?

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

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No	Barriers to implementation of pharmacological prophylaxis	
o Probably no	A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear	
 Probably yes 	against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that	
• Yes	concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use	
o Varies	were reported as barriers to their use. (Arepally 2010) A survey in Canadian ICUs showed that drug	
○ Don't know	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)	
	Constal barriers for implementation	
	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
0	0	•	Ο	0

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 pharma	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 s the problem a priority?							
IUDGEMENT	RESEARCH EVI	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes ● Yes o Varies o Don't know	In the absence of p	In the absence of prophylaxis, the risk of DVT and PE in patients undergoing major general surgical procedures is high.					
Desirable Effects low substantial are the desirable and	nticipated effects?						
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial o Small							
 Moderate Large Varies 	Outcomes	№ of participants	rticipants of the effectudies) evidence (950	Relative effect	Anticipated absol (95% CI)	ute effects*	
o Don't know		Follow up		(95% CI)	Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis	
	Mortality	22592	⊕⊕⊕⊖	RR 0.75	Study population		
	follow up: range 6 days to 10 weeks	(18 RCTs)	MODERATE ^a	(0.61 to 0.93)	17 per 1,000	4 fewer per 1,000 (7 fewer to 1 fewer)	
	Symptomatic			RR 0.48 Study p	Study population		
	embolism - representing the moderate	embolism - 0.88) representing the moderate marker state	(0.26 to 0.88)	11 per 1,000	6 fewer per 1,000 (8 fewer to 1 fewer)		
	-			Low			
	Symptomatic PE				0 per 1,000°	0 fewer per 1,000 (0 fewer to 0 fewer)	
	Symptomatic	11806	0000	RR 0.38	Low		

					l.	
Proximal DVT- representing the moderate	resenting		(0.14 to 1.00)	2 per 1,000 ⁹	1 fewer per 1,000 (2 fewer to 0 fewer)	
marker state				Moderate		
assessed with: any Proximal DVT follow up: range 6 days to 10 weeks				1 per 1,000 ^c	0 fewer per 1,000 (0 fewer to 0 fewer)	
Symptomatic	11924	⊕⊕⊖⊖	RR 0.52	Low		
Distal DVT- representing the severe marker state	(7 RCTs)	LOW ^{h,i}	(0.31 to 0.87)	0 per 1,000 ^j	0 fewer per 1,000 (0 fewer to 0 fewer)	
assessed with: any				Moderate		
Distal DVT follow up: range 6 days to 10 weeks				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	Study population		
biccuirig	(15 ((15)	HODERATE	1.77)	26 per 1,000	6 more per 1,000 (3 fewer to 20 more)	
Reoperation	1520	⊕⊕00	RR 0.93	Study population		
	(6 RCTs)	LOW ^{1,m}	(0.35 to 2.50)	12 per 1,000	1 fewer per 1,000 (8 fewer to 18 more)	
rated blindir b. Seriou estima c. Spyro hospit sympt d. Seriou rated descri	as high risk of l ng in 5 out of 19 is risk of bias. S ate rated as hig poulos 2009 rep alization. The a comatic DVTs (2 is risk of bias. S as high risk of l ption of the allo	bias due to lac studies. Studies that ca h risk of bias ported a rate of ssumption tha 0% distal and Studies that ca bias due to lac ocation concea	ck of concea arried a con due to lack of 0.3% syr at 10% wer l 80% prox arried large ck of blindir ilment in 6	siderable weight for of blinding in 5 out nptomatic VTE ever e symptomatic PEs imal) was applied. weight for the over ig in 3 out of 6 stud out of 6 studies.	9 studies and lack of • the overall effect of 16 studies. hts during index and 90% were all effect estimate	

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.
 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.
 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.
 Mean 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
O Large O Moderate Small O Trivial O Varies O Don't know		

Certainty of evidence What is the overall certainty of the evidence of effects?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o Very low ● Low o Moderate o High o 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 s there important uncertainty about or va	riability in how much people value the main outcomes?				
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o Important uncertainty or variability • Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability o 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		
	undesirable effects favor the intervention or the comparison?	
	undesirable effects favor the intervention or the comparison? RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large costs	Resource use for pharmacological prophylaxis (indirect evidence):	
 Moderate costs 	Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the	
Negligible costs and savings	financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of	
o Moderate savings	the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables,	
o Large savings o Varies	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	
o Don't know	f 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 r What is the certainty of the evidence of re		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o 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 interve	ntion favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 equi	ty?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced • Probably no impact o Probably increased o Increased o Varies o 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 stake	eholders?	
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	ESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Probably no Ass o Probably yes ph • Yes an o Varies (Au o Don't know ed 78 res cu Ge Cli An for sys as an Lau An (nr (nr (nr (nr (nr (nr (nr (nr (nr) (nr)	arriers to implementation of pharmacological prophylaxis survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear against the use of harmacological 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. trepally 2010) A survey in Canadian ICUs showed that drug acquisition cost, fear of bleeding, lack of resident ducation, concern about renal failure, and habits were the top five barriers to LMWH use. (Cook 2014) Over 80% of 89 orthopedic surgeons were concerned or very concerned about bleeding, especially surgical-site bleeding. Most seponders favored anticoagulants that could offer a reduced bleeding risk and similar VTE prevention compared to urrent anticoagulants rather than a decrease in VTE and similar bleeding risk. (Ginzburg 2011) eneral barriers for implementation: linicians low knowledge and organization of care mong 17 VTE specialists working in acute trusts in the UK, interviews revealed that no one feels directly responsible or VTE risk scoring and prophylaxis. Concern was expressed regarding the low level of VTE knowledge throughout the sterm. (McFarland 2014) survey of physicians shows that specific knowledge of guideline recommendations for the optimal use of thithrombotic agents use is low. (Arepally 2010) ack of local guidelines mong surgeons in Australia and New Zealand lack of awareness, lack of local hospital guidelines and logistical issues to to specified) were most commonly cited as barriers to implementation of VTE prophylaxis was given to 85% and as implemented in 97%. In 15% of patients without a hospital recommendation to continue, thromboprophylaxis as continued in 65%. (Schellong 2015) n 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) enera	

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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	0	•	0

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	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 EVI	DENCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know							
Desirable Effects How substantial are the desirable anticipated	effects?						
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS
• Trivial							
o Small o Moderate o Large o Varies o Don't know	Outcomes № of participants (studies) Follow up	participants	Certainty of the	Relative effect (95% CI)	Anticipated absolute effects [*] (95% CI)		
		(studies) Follow up	evidence (GRADE)		Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis	
	Mortality	41896	@@@ ()	RR 1.03	Study populat	tion	
	follow up: range 7 days to 8 weeks		(0.89 to 1.18)	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	41228 (20 PCTa)		RR 0.91	Study populat	tion	
	Pulmonary Embolism -	(39 RCTs)	MODERATE ^{e,f}	(0.63 to 1.30)	3 per 1,000	0 fewer per	

representing the					(1 fewer to 1 more)
moderate marker state				Low	
assessed with: Symptomatic PE follow up:				0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)
range 7 days to 8 weeks				Moderate	
to 8 weeks				1 per 1,000 ^h	0 fewer per 1,000 (0 fewer to 0 fewer)
Symptomatic	4249	@ 000	RR 1.01	Study populat	ion
Proximal DVT - representing the moderate marker state assessed with: Symptomatic Proximal DVT follow up:	(6 RCTs)	VERY LOW ^{i,j}	(0.20 to 5.00)	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)
range 8 days to 8 weeks				Moderate	
to 8 weeks				5 per 1,000 ^h	0 fewer per 1,000 (4 fewer to 20 more)
Symptomatic	4587	⊕⊖⊖⊖ VERY LOW ^{j,k}	RR 1.01 (0.30 to 3.44)	Low	
Distal Deep Vein Thrombosis - representing the severe	(8 RCTs)			0 per 1,000 ⁱ	0 fewer per 1,000 (0 fewer to 0 fewer)
marker state assessed				Moderate	
with: Symptomatic Distal DVT follow up: range 8 days			0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)	
to 8 weeks				High	
				1 per 1,000 ^h	0 fewer per

Bleeding follow up: range 7 days to 8 weeks (43 RCTs) MODERATE ^e (0.78 to 1.20) 16 per 1,000 0 fewer r 1,000 (4 fewer t more) Low 15 per 1,000 ^c 0 fewer r 1,000 (3 fewer t more) Moderate 56 per 1,000 ^h 2 fewer 11 more) Reoperation follow up: range 7 days to 8 weeks 12040 (21 RCTs) $\oplus \oplus \oplus \bigcirc$ ReoDERATE ^m RR 0.79 MODERATE ^m RS 0.79 (0.57 to 1.08) 18 per 1,000 4 fewer r 1,000 (12 fewer r 1,000 (12 fewer r 1,000 (12 fewer r 1,000 (13 fewer r 1,000 (14 fewer r 1,000 (12 fewer r 1,000 (14 fewer r 1,000 (14 fewer r 1,000 (12 fewer r 1,000 (14 fewer r 1,000 (12 fewer r 1,000 (14 fewer r 1,000 (12 fewer r 1,000 (14 fewer r 1,000 (12 fewer r 1,000 (10 fewer r		12.100				more)
Follow up: range 7 days to 8 weeks1.2016 per 1,000 (4 fewer t more)0 fewer r 1,000 (4 fewer t more)1.20)16 per 1,000 (4 fewer t more)0 fewer r 1,000 (3 fewer t more)Reoperation follow up: range 7 days to 8 weeks12040 (21 RCTs) $\oplus \oplus \oplus \bigcirc$ MODERATE**RR 0.79 (0.57 to 1.08)Study population 18 per 1,000 (8 fewer t more)Reoperation follow up: range 7 days to 8 weeks12040 (21 RCTs) $\oplus \oplus \oplus \bigcirc$ MODERATE**RR 0.79 (0.57 to 1.08)Study population 18 per 1,000 (8 fewer t more)	Major Bleeding	42409 (43 RCTs)	⊕⊕⊕⊖ MODERATE ^e	RR 0.97 (0.78 to	Study popula	tion
Reoperation follow up: range 7 days to 8 weeks 12040	follow up: range 7 days to 8 weeks	(HODERATE	· ·	16 per 1,000	(4 fewer to 3
Reoperation follow up: range 7 days to 8 weeks12040 (21 RCTs) $\oplus \oplus \oplus \bigcirc$ MODERATE** RR 0.79 (0.57 to 1.08)Study population12040 (21 RCTs) $\oplus \oplus \oplus \bigcirc$ MODERATE** RR 0.79 (0.57 to 1.08)Study population18 per 1,000 (8 fewer t more)4 fewer p 1,000 (8 fewer t more)14 per 1,000c (6 fewer t3 fewer p 1,000 (6 fewer t					Low	
Reoperation follow up: range 7 days to 8 weeks 12040 (21 RCTs) $\oplus \oplus \oplus \bigcirc$ MODERATE ^m RR 0.79 (0.57 to 1.08) Study population 18 per 1,000 (8 fewer t more) 4 fewer p 1,000 (8 fewer t more) Low						(3 fewer to 3
Reoperation follow up: range 7 days to 8 weeks 12040 (21 RCTs) • • • • • • • • • • • • • • •					Moderate	
follow up: range 7 days to 8 weeks (21 RCTs) MODERATE ^m (0.57 to 1.08) 18 per 1,000 (8 fewer t more) Low 14 per 1,000 (6 fewer t						(12 fewer to
range 7 days to 8 weeks	follow up: range 7 days			(0.57 to	Study population	
14 per 1,000 ^c 3 fewer p 1,000 (6 fewer t					18 per 1,000	(8 fewer to 1
1,000 ^c 1,000 (6 fewer t					Low	
more)						3 fewer per 1,000 (6 fewer to 1 more)
Moderate					Moderate	
1,000 ^d per 1,000						11 fewer per 1,000 (22 fewer to 4 more)

	 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 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 (0.024%) 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 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 a	
Undesirable Effects		

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
0 Large		
 Moderate 		
o Small		
• Trivial		
o Varies		
o Don't know		

Certainty of evidence

Certainty of evidence What is the overall certainty of the evidence	of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Very low o Low o Moderate o High o 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 varia	bility in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O 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

Balance of effects Does the balance between desirable and under JUDGEMENT • 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	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	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).	

Resources required How large are the resource requirements (costs)?

How large are the resource requirements (cos		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Large savings o Varies o 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 (ABM gQD). Total inpatient hospital cost for hip replacement was reported as \$15,699 for prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpa	
Certainty of evidence of rec What is the certainty of the evidence of resou		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

 o Very low o Low o Moderate o High o No included studies Cost effectiveness Does the cost-effectiveness of the intervention	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.	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 and SEK 665 for 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
o Reduced o Probably reduced	No research evidence was identified.	ADDITIONAL CONSIDERATIONS 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 stakehol	ders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no ● Probably yes o Yes o Varies o Don't know	No research evidence was identified.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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:	Post discharge the feasibility may be different for UFH vs. LMWH
	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	Conditional recommendation against the	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	the intervention or the comparison	intervention	intervention
0	0	•	0	0

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. No 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 EVII	DENCE					ADDITIONAL CONSIDERATIONS
 No Probably no Probably yes Yes Varies Don't know 	NSQIP) database, 3	RESEARCH EVIDENCE 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 ow substantial are the desira	able anticipated effects?	DENCE				Ţ.	ADDITIONAL CONSIDERATIONS
		JENCE					ADDITIONAL CONSIDERATIONS
o Small o Moderate o Large o Varies o Don't know	Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absol (95% CI) Risk with no pharmacological prophylaxis	Risk difference	
	Mortality	22592	⊕⊕⊕⊙	RR 0.75	Study population		
	follow up: range 6 days to 10 weeks	(18 RCTs)	MODERATE®	(0.61 to 0.93)	17 per 1,000	4 fewer per 1,000 (7 fewer to 1 fewer)	
	Symptomatic	18467	⊕⊕⊕⊙	RR 0.48	Study population		
	Pulmonary embolism - representing the moderate	(16 RCTs)	MODERATE ^b	(0.26 to 0.88)	11 per 1,000	6 fewer per 1,000 (8 fewer to 1 fewer)	
	marker state -				Low		
	Symptomatic PE			0 per 1,000 ^c	0 fewer per 1,000		

					fewer)
Symptomatic	11806	⊕000	RR 0.38	Low	
Proximal DVT- representing the moderate	(6 RCTs)	VERY LOW ^{d,e,f}		2 per 1,000 ^g	1 fewer per 1,000 (2 fewer to 0 fewer)
marker state assessed				Moderate	
with: Any Proximal DVT follow up: range 6 days to 10 weeks				0 per 1,000 ^c	0 fewer per 1,000 (0 fewer to 0 fewer)
Symptomatic	11924	$\oplus \oplus \infty$	RR 0.52	Low	
Distal DVT- representing the severe marker state assessed	(7 RCTs)	LOW ^{h,i}	(0.31 to 0.87)	0 per 1,000 ^j	0 fewer per 1,000 (0 fewer to 0 fewer)
with: Any Distal DVT				Moderate	
				0 per 1,000 ^c	0 fewer per 1,000 (0 fewer to 0 fewer)
Major		⊕⊕⊕⊙	RR 1.24	Study population	
bleeding		MODERATE ^k	(0.87 to 1.77)	26 per 1,000	6 more per 1,000 (3 fewer to 20 more)
Reoperation	1520	$\oplus \oplus \infty$	RR 0.93	Study population	1
	(6 RCTs)	LOW ^{I,m}	(0.35 to 2.50)	12 per 1,000	1 fewer per 1,000 (8 fewer to 18 more)
rated blindir b. Seriou	as high risk of l ng in 5 out of 19 Is risk of bias. S	pias due to lac 9 studies. Studies that ca	k of concea	alment in 3 out of siderable weight f	erall effect estimate 19 studies and lack o for the overall effect
c. Popula (GallR under	ation-based stud isk and Nationa going laparosco	dy report inclu Il Patients Reg pic cholecyste	iding data f ister, Swed ctomies wh	len). From a samp no did not receive	European registries ple of 34,884 patients

 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; 12=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 DVT by screening, and differ importantly from the diagnostic of symptomatic distal DVT by screening, and differ importantly from the diagnostic for symptomatic distal DVT. i. Serious indirectness. Patients included in the studies have diagnostic of visual 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 for assumptions that 20% of any concell effect estimate to symptomatic distal DVTs are assumed to be severe DVTs. k. Serious indirection. 95% of the symptomatic distal DVTs are assumed to be severe DVTs. k. Serious indirection. 95% of the symptomatic distal DVTs are assumed to be sufficient. k. Serious indirection. 95% of the symptomatic distal DVTs are assumed to be sufficient. k. Serious indirection. 95% of the symptomatic distal DVT		
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	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	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT **RESEARCH EVIDENCE** ADDITIONAL CONSIDERATIONS 0 Large No surgery specific baseline risk data for major bleeding was available. Only the bleeding risk from trials on major o Moderate Small general surgery was available as indirect evidence. o Trivial o Varies The panel considered that undesirable effects were small for major general surgery. The panel discussed that with O Don't know 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 over an certainty of the evide		
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		
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 				
Resources required How large are the resource requirements	(rosts)?			
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS		
 O Large costs Moderate costs Negligible costs and savings O Moderate savings O Large savings O Varies O 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 predefined 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) 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 \$15,669 for prophylaxis with rivaroxaban, and \$15,530 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient costial cost for knee replacement evidence): Veekeman et al. 2011, reported the cost burden of VTE in total hip replacement (THR) and total knee replacement (TKR) surgical populations bas			

JUDGEMENT	RESEARCH EVIDENCE ADDITIONAL CO	NSIDERATIONS
o Very low o Low o Moderate o 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 interve	ntion favor the intervention or the comparison?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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				
o Reduced o Probably reduced • Probably no impact o Probably increased o Increased o Varies o 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 stak	eholders?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
⊙ No ⊙ Probably no ● Probably yes	No research evidence identified					

o Yes o Varies o Don't know

Feasibility

s the intervention feasible to implement?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o No o Probably no o Probably yes • Yes o Varies o 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 Co	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	•	0	0	0

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 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 EVI	DENCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	Patients undergoin symptomatic DVT i lumbar laminecton (46/2956) for DVTs associated with sig neurosurgical patie	n patients receiving ny, lumbar spinal fu and 0.2% (34/1520 nificant morbidity.					
Desirable Effects How substantial are the desirable a	nticipated effects?						
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial ● Small o Moderate	Outcomes	participants of the (studies) eviden	of the	effect nce (95%	Anticipated absol (95% CI)	lute effects*	
o Large o Varies o Don't know			evidence (GRADE)		Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis	
	Mortality -		⊕⊕⊖⊖ LOW ^{a,b}	RR 1.27 (0.57 to 2.86)	Study population		
	RCTs				35 per 1,000	9 more per 1,000 (15 fewer to 65 more)	
	Mortality -	674	●000		Study population		
	NRS	S (2 VERY observational studies)	(0.46 to 1.13)	115 per 1,000	32 fewer per 1,000 (62 fewer to 15 more)		
	Symptomatic		0 000	RR 0.84	Study population		
	Embolism - representing the moderate	Embolism - LC representing the	VERY LOW ^{f,g,h}		14 per 1,000	2 fewer per 1,000 (13 fewer to 359 more)	
	marker state				Low		
	assessed with: Symptomatic				2 per 1,000 ⁱ	0 fewer per 1,000	

PE					more)	
Symptomatic Pulmonary	776 (2	⊕OOO VERY	RR 0.18 (0.01 to	Study population		
Embolism - representing the moderate	m - observational nting studies) te	LOW ^{c,f,j}	3.76)	5 per 1,000	4 fewer per 1,000 (5 fewer to 13 more)	
marker state - NRS				Low		
assessed with: Symptomatic PE	tic			2 per 1,000 ⁱ	2 fewer per 1,000 (2 fewer to 6 more)	
Symptomatic		000	RR 0.50	Low		
Proximal (2 RCTs) DVT - representing the moderate marker state	LOW ^{k,I}	(0.30 to 0.84) ^m	23 per 1,000 ⁿ	11 fewer per 1,000 (16 fewer to 4 fewer)		
assessed				Moderate		
with: Any Proximal DVT				3 per 1,000 ^{°,p}	2 fewer per 1,000 (2 fewer to 1 fewer)	
Symptomatic		0000	RR 0.54	Low		
Distal DVT - epresenting he severe narker state assessed	(1 RCT)	VERY LOW ^{i,q,r}	(0.27 to 1.08) ^m	2 per 1,000 ^s	1 fewer per 1,000 (1 fewer to 0 fewer)	
with: Any Distal DVT				Moderate	Moderate	
				1 per 1,000 ^{o,p}	0 fewer per 1,000 (0 fewer to 0 fewer)	
Major	1156		RR 1.57	Study population		
Bleeding - RCTs	(7 RCTs)	LOW ^{t,u}	(0.70 to 3.50)	17 per 1,000	10 more per 1,000 (5 fewer to 43 more)	
Major	930	⊕000	RR 1.45	Study population		
Bleeding - NRS	(3 observational studies)	VERY LOW ^{v,w}	(0.30 to 7.12)	7 per 1,000	3 more per 1,000	

						more)
eoperation 192		0000	RR 0.43	Study population		
RCTs	s (2 RCTs) VERY LOW ^{x,y}		(0.06 to 2.84)	31 per 1,000	18 fewer per 1,000 (29 fewer to 57 more)	
a. b. c. d.	of bia 5 stud Very s Seriou factor Seriou	s due to lack o dies and lack o serious impreo us risk of bias. 's us imprecision	of information of concealmer cision. Wide c . Studies did . 95% CI is c	about the nt in [2 out onfidence ir not analyze onsistent wi	sequence genera of 5 studies. Iterval with only findings adjustir th the possibility	ate rated as unclear risk ation process in 3 out of 45 events in total ng for confounding y for important benefit
e.	in tota Seriou	al. us inconsisten	cy. Unexplain	ed inconsist	ency, with point	t estimates widely
	43%)					hi square= 0.12; I2=
f.						5 events in total
g. h.	Studie	es that carried	l Íarge weight	for the ove		dies: $I^2 = 64\%$ (P=0.10) ate rated as unclear risk ut of 4 studies.
i.	surge	ries (cervical s	spine, lumbar	laminecton	ny, lumbar spina	09 on elective spinal al fusion, spinal trauma, 0.2% (34/15204)
j.	Seriou	us inconsisten	cy. Moderate	inconsisten	cy, with point es	stimates widely different $e = 0.18$; $I2 = 41\%$).
k.	Studie	es that carried	l large weight	for the ove		ate rated as high risk of
١.	Seriou	us indirectness	s. Patients we	re identified	through screer	ning ultrasound. None of sm before venography.
m.	If any contro were amon no pro be 0.6 1,000 fewer the N would event	DVT detected bled trials (RC a total of 137 g 927 patients ophylaxis grou 55 (95% CI: 0 (from 21 few per 1000 (fro RS, the RR wo be 96 fewer	d by screening (T) and two n events (53 ir s for the RCTs (p) among 41 0.47 to 0.89), er to 96 fewer (m 1 fewer to build be 0.48 (per 1,000 (fro 6, or 2 fewer	g was consid on-randomi prophylaxi s, and 72 ev 5 patients f and the risk er) using the 2 fewer) ba 95% CI: 0. om 35 fewer	dered a surrogat zed studies (NR s group and 84 i rents (32 in prop or the NRS. For difference wou control group e used on the base 29 to 0.81), and to 131 fewer) (te, then six randomized S) measured it; there in no prophylaxis group) ohylaxis group and 40 in the RCTs, the RR would and be 64 fewer per event rate of 17.7%, or 1 eline risk of 0.32%. For the risk difference using the control group 2 fewer) based on the
n.	includ (2.26	ed in the met	a-analysis. Ba calculated app	aseline risk plying the a	estimates for sy	1.3%) from studies mptomatic proximal DVT 20% of any proximal
0.	Rates and u	of proximal a ndergoing ele	nd distal sym ctive spinal s	ptomatic D urgeries (ce	rvical spine, lum	ceiving no prophylaxis Ibar laminectomy, ported in Glotzbecker

	 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 anticip		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large • Moderate o Small o Trivial o Varies o Don't know		

Certainty of evidence What is the overall certainty of the evidence	Certainty of evidence /hat 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 var	riability 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 	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)					
 No important uncertainty or variability No known undesirable outcomes 	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:					

	 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). 	
	ndesirable effects favor the intervention or the comparison?	
JUDGEMENT • 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	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

JUDGEMENT
-
 Moderate costs Negligible costs and savings Moderate savings Large savings Varies Don't know

Cost effectiveness Does the cost-effectiveness of the interver	ition 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 equit	y?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o 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 stake	holders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no ● Probably yes o Yes o Varies o Don't know	No research evidence identified	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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)	
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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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	•	0	0	0

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	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 EVIDEN	ICE				
o No o Probably no o Probably yes • Yes o Varies o Don't know	and distal symptomatic surgeries (cervical spin reported in Glotzbecke complications in this po	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 ant	icipated effects?					
JUDGEMENT	RESEARCH EVIDEN	ICE				
o Trivial • Small o Moderate o Large o Varies	Outcomes	№ of participants (studies)	participants of the		Relative Anticipateffect	
o Don't know		Follow up	evidence (GRADE)	(95% CI)	Risk with UFH	Risk difference with LMWH prophylaxis
	Mortality	795 (5 RCTs)	⊕⊕⊖⊖ LOW ^{a,b}	RR 0.34 (0.04 to	Study population	
				3.21)	5 per 1,000	3 fewer per 1,000 (5 fewer to 11 more)
	Symptomatic Pulmonary	Symptomatic Pulmonary Embolism - representing the moderate marker state			Low	
	Embolism - representing the moderate marker state				3 per 1,000 ^e	2 fewer per 1,000 (3 fewer to 8 more)
	assessed with: Any PE				Modera	te
					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	150	0000	RR 1.00	Low		
Proximal Deep Vein Thrombosis - representing the moderate marker state	(1 RCT)	VERY LOW ^{h,i,j}	(0.14 to 6.91) ^{k,I}	5 per 1,000 ^m	0 fewer per 1,000 (5 fewer to 32 more)	
assessed with: Any Proximal				Moderat	e	
OVT				3 per 1,000 ⁿ	0 fewer per 1,000 (2 fewer to 17 more)	
				High		
				7 per 1,000°	0 fewer per 1,000 (6 fewer to 41 more)	
Symptomatic	200 (1 RCT)	€ VERY LOW ^{c,j,p}	RR 0.33 (0.01 to 7.93) ^{k,i}	Low		
Distal Deep Vein Thrombosis - representing the severe marker state				0 per 1,000 ^q	0 fewer per 1,000 (0 fewer to 1 more)	
assessed with: Any Distal DVT				Moderat	e	
,				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	⊕⊕⊖⊖	RR 0.76	Study p	opulation	
(4 RCTs) LOW ^{t,u}	(0.20 to 2.95)	22 per 1,000	5 fewer per 1,000 (18 fewer to 43 more)			

 assumptions that 20% of any proximal DVTs are symptomatic proximal DVTs. 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. A retrospective analysis of 581 patients undergoing surgery for intracranial meningioma (Hoefnagel 2014) reported a rate of symptomatic proximal DVT of 0.7%. 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 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 assumed to be severe DVTs. 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. A retrospective analysis of 581 patients undergoing surgery for intracranial meningioma (Hoefnagel 2014) reported a rate of symptomatic distal DVT of 0.14%. 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. 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. 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	
o Large o Moderate o Small • Trivial o Varies o 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 lor critical outcomes.	west certainty of evidence for the		
Values Is there important uncertainty about or variabili	ty 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 scale of 0 to 1, where 0 = death and 1.0 = full health. The utility value on a given health state characterized by that condition, with higher vimportance: Pulmonary embolism: range 0.63-0.93 (different methods) (Hogg 20 Deep vein thrombosis: range 0.64-0.99 (different methods) (Hogg 20 Marvig 2015, Utne 2016) 	es reflect the relative value placed values reflecting greater 013, Hogg 2014, Locadia 2004)		
	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 20	13)		
	Major intracranial bleeding event: 0.15 (standard gamble) (Hogg 20	13)		
	Central nervous system bleeding: range 0.29-0.60 (standard gamble	e) (Lenert 1997, O'Meara 1994)		

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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 undes	irable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		
Resources required How large are the resource requirements (costs	?(
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Large costs Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o 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 (201.15/10 mg QD), and \$22.00 for generic enoxaparin (40mg DQ). Total inpatient hospital cost for hip replacement was reported as \$15,696 for prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for hip replacement was reported as \$15,696 for prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin, or	

Certainty of evidence of requ	 \$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 	
What is the certainty of the evidence of resource		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low O Low O Moderate O 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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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
o Reduced	No research evidence identified	The panel judged that there would be no impact on equity,

 o Probably reduced Probably no impact o Probably increased o Increased o Varies o Don't know 		assuming that prophylaxis would typically be short-term for this population.
Acceptability Is the intervention acceptable to key stakeholde	rs?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o Don't know	No research evidence identified	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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)	

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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	0	•	0

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

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.

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ASSESSMENT

Problem

Is the problem a priority?							
JUDGEMENT	RESEARCH EVID	DENCE		ADDITIONAL CONSIDERATIONS			
o No o Probably no o Probably yes • Yes o Varies o Don't know	There is substantial baseline risk for VTI TURP, one survey o respondents routin- methods; 50 used fo This question is a hi consequences of ex risk of VTE and risk	and bleeding in th f British urologists ely used VTE proph ow dose heparin, e gh priority because cessive bleeding w					
Desirable Effects How substantial are the desirable	anticipated effects?						
JUDGEMENT	RESEARCH EVID	DENCE					ADDITIONAL CONSIDERATIONS
• Trivial o Small o Moderate				7			The panel considered the desirable effects to be comparable to the one of laparoscopic cholecystectomy
o Large O Varies	Outcomes	Nº of participants	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects [*] (95% CI)		surgery.
○ Don't know					Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis	
	Mortality	22592		RR 0.75	Study population		
	follow up: range 6 days to 10 weeks	(18 RCTs)	MODERATE ^a	(0.61 to 0.93)	17 per 1,000	4 fewer per 1,000 (7 fewer to 1 fewer)	
	Symptomatic	Pulmonary (16 RCTs) MODERA Embolism - representing the moderate marker state		RR 0.48 (0.26 to	Study population		
	Embolism - representing the moderate marker state		MODERATE	0.88)	11 per 1,000	6 fewer per 1,000 (8 fewer to 1 fewer)	
	assessed with:				Low		
	Symptomatic PE				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	11806 (C. DCT-)	⊕○○○ VERY LOW ^{d,e,f}	RR 0.38 (0.14 to 1.00)	Low		
Proximal Deep Vein Thrombosis - representing the moderate	(6 RCTs)			2 per 1,000 ^g	1 fewer per 1,000 (2 fewer to 0 fewer)	
marker state assessed				Moderate		
with: Any Proximal DVT follow up: range 6 days to 10 weeks				0 per 1,000°	0 fewer per 1,000 (0 fewer to 0 fewer)	
			C	High		
				1 per 1,000 ^c	1 fewer per 1,000 (1 fewer to 0 fewer)	
Symptomatic Distal Deep	11924 (7 RCTs)	⊕⊕⊖⊖ LOW ^{h,i}	RR 0.52 (0.31 to	Low		
Vein Thrombosis - representing the severe	(7 KCIS)		0.87)	0 per 1,000 ^j	0 fewer per 1,000 (0 fewer to 0 fewer)	
marker state assessed				Moderate		
with: Any Distal DVT follow up: range 6 days to 10 weeks				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 bleeding22045 (15 RCTs) $\oplus \oplus \oplus \bigcirc$ MODERATEk RR 1. (0.87 1.77)			RR 1.24	Study population		
		26 per 1,000	6 more per 1,000 (3 fewer to 20 more)			

Reoper	ation	1520	$\Theta \Theta \bigcirc \bigcirc$	RR 0.93	Study population	ı
		(6 RCTs)	LOW ^{I,m}	(0.35 to 2.50)	12 per 1,000	1 fewer per 1,000 (8 fewer to 18 more)
					Low	I
					2 per 1,000 ⁿ	0 fewer per 1,000 (1 fewer to 3 more)
a. b.	rated a blindin Seriou	as high risk of g in 5 out of 1 s risk of bias.	bias due to la 9 studies. Studies that c	ick of concea	Iment in 3 out of siderable weight for	erall effect estimate 19 studies and lack of or the overall effect
c.	Tikkine sympto estima have b are PE	en et al. (2018 omatic VTE of tes for sympto een calculateo s and 90% are) reported, in 0.2% (low-ris omatic PE, syr l applying the symptomatic	patients und k group) and mptomatic pr assumptions c DVTs; 20%	oximal DVT and s s that 10% of all t of all the sympto	oaseline-risk of group). Baseline-risk ymptomatic distal DVT he symptomatic VTEs
d.	Seriou rated a	as high risk of	bias due to la	ck of blindin		rall effect estimate dies. There was not
e.						ostic of proximal DVT tomatic proximal DVT.
f.	Seriou		y. Unexplaine	d inconsister		mates different (P-
g.	The ba sin the has be	seline risk cor meta-analysi	sists of the cost. Baseline ris applying the a	ontrol group k estimates	for symptomatic p	from studies included roximal DVT (0.22%) proximal DVTs are
h.	Seriou	s indirectness.	Patients inclu		tudies have diagn Inostic of symptor	ostic of distal DVT by
i.	Seriou: estima	s risk of bias. te rated as hig	Studies that c gh risk of bias	arried a cons due to lack	siderable weight fo	or the overall effect 1 out of 7 studies and
j.	lack of blinding in 3 out of 7 studies. 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					
k.		omatic distal D s imprecision.				benefit and harm.
Ι.	Seriou estima lack of	s risk of bias. te rated as hig blinding in 2	Studies that c oh risk of bias out of 6 studie	arried a cons due to lack es.	siderable weight for of concealment in	or the overall effect 1 out of 6 studies and
m.						important benefit and 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 Effect How substantial are the undes		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Large O Moderate Small O Trivial O Varies O Don't know Certainty of evider	nce	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.
What is the overall certainty or		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low • Low o Moderate o High o No included studies	The overall certainty of the estimates of effects was based on the lowest certainty of evidence for the critical outcomes.	

Values

UDGEMENT	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	
o No known undesirable outcomes	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
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		Baseline VTE rates and bleeding were considered as making this judgment.

Resources required How large are the resource requirements (costs)? **RESEARCH EVIDENCE** ADDITIONAL CONSIDERATIONS JUDGEMENT Large costs Resource use for pharmacological prophylaxis (indirect evidence): Moderate costs Negligible costs and savings Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the Moderate savings 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 O Large savings o Varies and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient was 46 O Don't know 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 predefined 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

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

bleeding: \$14,015 vs. \$9710.

Certainty of evidence of What is the certainty of the evidence of it		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o 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 interv	ention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 equ	iity?	
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 stal	reholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no ● Probably yes o Yes o Varies	No research evidence identified	

o Don't know

Feasibility

Is the intervention feasible to implement?								
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
o No o Probably no o Probably yes • Yes o Varies o 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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	•	0	0	0

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	hould 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 prior	ity?						
JUDGEMENT	RESEARCH EVIDENCE		ADDITIONAL CONSIDERATIONS				
o No o Probably no o Probably yes • Yes o Varies o Don't know	There is substantial practice varia VTE and bleeding in the different revealed that despite a lack of cle 230 of the 280 urologists who too (Golash et al. 2002). This question is a high priority be excessive bleeding with pharmace pharmacological prophylaxis in Th						
Desirable Effe	ects he desirable anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
• Trivial							
o Small o Moderate o Large	Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects [*] (95% CI)		
o Varies o Don't know					Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis	
	Mortality	tality 41896	41896 (35 RCTs) ⊕⊕⊙ LOW ^{a,b,c}	RR 1.03 (0.89 to 1.18)	Study population		
	follow up: range 7 days to 8 weeks	(35 RCTs)			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	41228	⊕⊕⊖⊖	RR 0.91	Study population	า	
	Embolism - representing moderate marker state	(39 RCTs)	LOW ^{c,f,g}	(0.63 to 1.30)	3 per 1,000	0 fewer per	

assessed with: Symptomatic PE Image: Symptomatic PE Image: Symptomatic PE Image: Symptomatic Proximal DVT - representing moderate marker state assessed with: Symptomatic proximal DVT 4249 (6 RCTs) Image: Symptomatic Proximal PCT 4249 (6 RCTs) Image: Symptomatic Proximal PCT 1 per 1,000 ¹ Image: Symptomatic Proximal PCT 1 per 1,000 ¹ Image: Symptomatic Proximal PCT DVT - representing moderate marker state assessed with: Symptomatic proximal DVT 4249 (6 RCTs) Image: Symptomatic Symptomatic Proximal PCT Image: Symptomatic Proximal PCT 1 per 1,000 ¹ Image: Symptomatic Proximal PCT DVT - representing moderate marker state assessed with: Symptomatic proximal DVT 4249 (1 fewer to 0 femer) Image: Symptomatic Proximal PCT 1 per 1,000 ¹ Image: Symptomatic Proximal PCT DVT Symptomatic Proximal PCT 4249 (1 fewer to 0 femer) Image: Symptomatic Proximal PCT Image: Symptomatic Proximal PCT Image: Symptomatic Proximal PCT Image: Symptomatic Proximal PCT Image: Symptomatic PC	T					
Symptomatic Proximal DVT 4249						
Symptomatic Proximal DVT4249 (6 RCTs) $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW*JA*RR 1.01 (0.20 to 0.00 fewer to 0 fewer)Study population 0 fewer to 0 fewer)DVT1 per 1,000' (0.6 fewer to 0 fewer)0 fewer to 0 fewer)DVT0 fewer to 0 fewer)1 per 1,000' (0.6 fewer to 0 fewer)DVT0 per 1,000' (0.6 fewer to 0 fewer)DVT1 per 1,000' (0.6 fewer to 0 fewer)DVT1 per 1,000'' (0.6 fewer to 0 fewer)DVT1 per 1,000'' (0.6 fewer to 0 fewer)DVT1 per 1,000''' (0.6 fewer to 0 fewer)High1 per 1,000'' (1 fewer to 6 more)High5 per 1,000'' (4 fewer to 20 more)					Low	
Symptomatic Proximal DVT - representing moderate marker state assessed with: Symptomatic proximal DVT 4249					0 per 1,000 ^h	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) $\oplus \bigcirc \bigcirc$ VERY LOW ^{-,j,k} RR 1.01 (0.20 to 5.00) Study population DVT - representing moderate marker state assessed with: Symptomatic proximal DVT 4249 (6 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOW ^{-,j,k} RR 1.01 (0.20 to 5.00) Study population DVT - representing moderate marker state assessed with: Symptomatic proximal DVT 4249 (6 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOW ^{-,j,k} RR 1.01 (0.20 to 5.00) Study population DVT 0 per 1,000 ⁱⁿ 0 fewer per 1,000 (0 fewer to 0 fewer) 0 fewer per 1,000 (0 fewer to 0 fewer) Moderate 1 per 1,000 ⁱⁿ 0 fewer per 1,000 (1 fewer to 6 more) High High Sper 1,000 ⁱⁿ 0 fewer per 1,000 (1 fewer to 20 more)					Moderate	
Symptomatic Proximal DVT - representing moderate marker state assessed with: 4249 (6 RCTs) $\Psi \bigcirc \bigcirc \bigcirc$ VERY LOW^{-1,1,k} RR 1.01 (0.20 to 5,00) Study population 1 per 1,000 O fewer per 1,000 (1 fewer to 6 more) DVT DVT O fewer per 1,000 O fewer per 1,000 (1 fewer to 6 more) DVT O per 1,000 ^h O fewer per 1,000 (0 fewer to 0 fewer) DVT O per 1,000 ^h O fewer per 1,000 (0 fewer to 0 fewer) Moderate 1 per 1,000 ^h O fewer per 1,000 (0 fewer to 0 fewer) High Fewer to 20 more) High S per 1,000ⁱ O fewer per 1,000 (4 fewer to 20 more) 					1 per 1,000 ^h	1,000 (0 fewer to 0
Symptomatic Proximal DVT - representing moderate marker state assessed with: 4249 (6 RCTs)					High	
DVT - representing moderate marker state assessed with: Symptomatic proximal DVT (6 RCTs) VERY LOW ^{c,j,k} (0.20 to 5.00) 1 per 1,000 0 fewer per 1,000 (1 fewer to 6 more) DVT 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	1,000 (0 fewer to 0
moderate marker state assessed with: Symptomatic proximal DVT 5.00) 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 High Fight 5 per 1,000 ⁱ 0 fewer per 1,000 (4 fewer to 20 more)				(0.20 to	Study population	on
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)	moderate marker state assessed with: Symptomatic proximal	(6 RCTs)	VERY LOW ^{c,j,k}		1 per 1,000	1,000 (1 fewer to 6
Image: state of the state					Low	
1 per 1,000h0 fewer per 1,000 (1 fewer to 6 more)High5 per 1,000h0 fewer per 1,000 (4 fewer to 20 more)					0 per 1,000 ^h	0 fewer per 1,000 (0 fewer to 0 fewer)
1,000 (1 fewer to 6 more) High 5 per 1,000 ⁱ 0 fewer per 1,000 (4 fewer to 20 more)					Moderate	
5 per 1,000 ⁱ 0 fewer per 1,000 (4 fewer to 20 more)					1 per 1,000 ^h	1,000 (1 fewer to 6
1,000 (4 fewer to 20 more)					High	
					5 per 1,000 ⁱ	1,000 (4 fewer to 20
Symptomatic Distal DVT 4587 \oplus OOO RR 1.01 Based on Study population	Symptomatic Distal DVT	4587	⊕000	RR 1.01	Based on Study	population
- representing severe marker state assessed with: Symptomatic Distal DVT(8 RCTs)VERY LOW ^{c,j,k} (0.30 to 3.44)2 per 1,000 ¹ 0 fewer per 1,000 (2 fewer to 5 more)	marker state assessed with:	(O KUIS)	VEKY LOW ^{C,J,K}	3.44)	2 per 1,000 ¹	1,000 (2 fewer to 5
Low					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	$\Theta \Theta \bigcirc \bigcirc$	RR 0.97	Study populatio	n
	(43 RCTs)	LOW ^{c,f}	(0.78 to 1.20)	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	⊕⊕⊖⊖ LOW ^{c,n}	RR 0.79	Study populatio	n
	(21 RCTs)		(0.57 to 1.08)	18 per 1,000	4 fewer per 1,000 (8 fewer to 1 more)
				Low	-
				2 per 1,000°	0 fewer per 1,000 (1 fewer to 0 fewer)
				Moderate	
				51 per 1,000 ^e	11 fewer per

 o Large o Moderate o Small Trivial o Varies o Don't know 		
Certainty of ev What is the overall certa	idence inty of the evidence of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Very low o Low o Moderate o High o 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 uncer	tainty about or variability in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability o 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: 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)	
variability	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 effe	cts							
Does the balance betwee	en desirable and undesirable effects favor the intervention or the comparison?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 								
Resources required How large are the resource requirements (costs)?								
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
 o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies 	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.							
⊙ Don't know	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							

comparison O Probably favors the	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	
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the 	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.	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.
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Cost effectiver	IESS ess of the intervention favor the intervention or the comparison?	
o Very low o Low o Moderate o 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.	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	idence of required resources the evidence of resource requirements (costs)?	
	See Appendix 3 Table 1 for additional data on prophylaxis unit costs	
	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.	
	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).	
	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.	

	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 impa	act 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 accept	ptable 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 feasil	ble to implement?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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	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	Conditional recommendation against the	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	the intervention or the comparison	intervention	intervention
0	0	•	0	0

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
o No o Probably no o Probably yes • Yes o Varies o Don't know	based observationa between 2000-201 and 20,438 (30.0 %	igh priority because ccessive bleeding w					
Desirable Effects How substantial are the desirable anticip	pated effects?						
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS
• Trivial o Small							
o Moderate o Large o Varies	par	Nº of Certainty participants of the	of the	effect	Anticipated absolute effects [*] (95% CI)		
o Don't know		(studies) Follow up	pharmacological w prophylaxis p	Risk difference with pharmacological prophylaxis			
	Mortality	22592		RR 0.75	Study population		
	follow up: range 6 days to 10 weeks	(18 RCTs)	MODERATE ^a	(0.61 to 0.93)	17 per 1,000	4 fewer per 1,000 (7 fewer to 1 fewer)	
	Symptomatic Pulmonary			RR 0.48 (0.26 to	Study population		
		0.88)	11 per 1,000	6 fewer per 1,000 (8 fewer to 1 fewer)			
					Low		
	Symptomatic PE				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		●○○○	RR 0.38	Low	8
Proximal Deep Vein Thrombosis- representing the moderate	(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)
marker state assessed				Moderate	
with: Any Proximal DVT follow up: range 6 days to 10 weeks				1 per 1,000°	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	11924 (7 PCTc)	⊕⊕⊖⊖ LOW ^{h,i}	RR 0.52 (0.31 to	Low	
Vein Thrombosis - representing the severe	(7 RCTs)		0.87)	0 per 1,000 ^j	0 fewer per 1,000 (0 fewer to 0 fewer)
marker state assessed				Moderate	
assessed with: Any Distal DVT follow up: range 6 days to 10 weeks				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	22045	•••	RR 1.24	Study population	
bleeding	(15 RCTs)	MODERATE ^k	(0.87 to 1.77)	26 per 1,000	6 more per 1,000 (3 fewer to 20 more)

Reoperation	1520		RR 0.93	Study population	l
	(6 RCTs)	LOW ^{I,m}	(0.35 to 2.50)	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)
b. Serio estim c. Tikkir with	ate rated as hig ien et al. (2018 standard pelvic	Studies that ca h risk of bias) reported, in lymph node di	arried a cons due to lack patients und issection, a l	of blinding in 5 ou lergoing robotic ra baseline-risk of sy	adical prostatectomy mptomatic VTE of 0.5%
 b. Serio estim c. Tikkir with s (low- PE, sy apply symp and 5 d. Serio rated descr e. Serio by sc f. Serio value g. The b incluc symp 20% h. Serio scree i. Serio estim lack o 	us risk of bias. ate rated as higher ate rated as higher standard pelvic risk group) and ymptomatic pro- ing the assump tomatic DVTs; 2 % of the remai- us risk of bias. as high risk of iption of the all- us indirectness. reening, and differ sus inconsistence chi square = 0. aseline risk con- led surgical pat tomatic proxima- of any proxima- of any proxima- us indirectness. ning, and differ us risk of bias. ate rated as high f blinding in 3	Studies that ca ah risk of bias) reported, in lymph node di 1.9% (high-ri ximal DVT and tions that 10% 20% of all the nder part are Studies that ca bias due to lac ocation concea Patients inclu ffer importantly v. Unexplained 06; I2=54% % sists of the co- ients with can al DVT (0.22% I DVTs are syn Patients inclu importantly fr Studies that ca gh risk of bias out of 7 studies	arried a cons due to lack patients und issection, a l sk group). E d symptomati of all the s symptomatic arried large ck of blinding alment in 6 c ded in the s y from the c d inconsisten %) introl group cer or withou b) has been inptomatic pr ded in the s rom the diag arried a cons due to lack is.	of blinding in 5 ou lergoing robotic ra- paseline-risk of sy paseline-risk estim- cic distal DVT have ymptomatic VTEs c DVTs are sympt c distal DVTs. weight for the ove g in 3 out of 6 studies. tudies have diagne liagnostic of symp cy, with point esti event rate (1.1%) ut cancer. Baseline calculated applyin oximal DVTs. tudies have diagne nostic of symptom siderable weight for for concealment in	or the overall effect t of 16 studies. adical prostatectomy mptomatic VTE of 0.5% ates for symptomatic e been calculated are PEs and 90% are omatic proximal DVTs erall effect estimate dies. There was not ostic of proximal DVT tomatic proximal DVT. imates different (P-) from studies that e risk estimates for g the assumptions that ostic of distal DVT by

	 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 antic	cipated effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate • Small o Trivial o Varies o Don't know		
Certainty of evidence What is the overall certainty of the evide	nce of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low • Low o Moderate o High o No included studies		
Values Is there important uncertainty about or v	ariability 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 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) 	

		I
	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 		

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O 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) 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 \$15,669 for rivorxobalan (20/15/101 mg QD), and \$2:200 for generic enoxaparin (40mg QD). Total inpatient hospital cost for knee replacement was reported as \$15,6490 for prophylaxis with rivaroxaban, and \$15,730 for prophylaxis with other agents (enoxaparin, varfarin, or enoxaparin plus warfarin). Total inpatient hospital cost for knee replacement was reported as \$15,640 for prophylaxis with rivaroxaban, and \$15,730 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin).<td></td>	

Certainty of evidence of What is the certainty of the evidence of		
IUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o 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 interv	rention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 equ	uity?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o 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 sta	keholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no ● Probably yes o Yes o Varies	No research evidence identified	

o Don't know

Feasibility

Is the intervention feasible to implement	nt?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o 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	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	•	0	0	0

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	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 EVIL	RESEARCH EVIDENCE ADDITIONAL CONSIDERATIONS							
o No o Probably no o Probably yes • Yes o Varies o 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 e	ffects?								
JUDGEMENT	RESEARCH EVI	DENCE					ADDITIONAL CONSIDERATIONS		
• Trivial o Small									
o Moderate o Large o Varies	p. (s	participants of (studies) ev	Certainty of the evidence	Relative effect (95%	Anticipated absolute effects* (95% CI)				
o Don't know			(GRADE)	(93% CI)	Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis			
	Mortality	41896 (35 RCTs) ⊕⊕⊖ LOW ^{a,b,c}	@@ 00	RR 1.03 (0.89 to 1.18)	Study population				
	follow up: range 7 days to 8 weeks		LOW ^{a,b,c}		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 fower to 0					

					more)
Symptomatic Pulmonary	41228 (39 RCTs)	⊕⊕⊖⊖ LOW ^{c,f,g}	RR 0.91 (0.63 to	Study population	
Embolism - representing the moderate marker state	(39 KCTS)	LOW	1.30)	3 per 1,000	0 fewer per 1,000 (1 fewer to 1 more)
assessed with:				Low	
Symptomatic PE follow up: range 7 days to 8 weeks				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		0000	RR 1.01 (0.20 to	Study popula	tion
Proximal Deep Vein Thrombosis - representing the moderate	(6 RCTs)	VERY LOW ^{c,j,k}	5.00)	1 per 1,000	0 fewer per 1,000 (1 fewer to 6 more)
marker state assessed				Low	
with: symptomatic Proximal DVT follow up: range 8 days				1 per 1,000 ^h	0 fewer per 1,000 (1 fewer to 4 more)
to 8 weeks				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

					20 more)
Symptomatic Distal Deep	4587 (8 RCTs)	⊕⊖⊖⊖ VERY LOW ^{c,j,k}	RR 1.01 (0.30 to	Based on stud BLR	ly population
Vein Thrombosis - representing the severe marker state			3.44)	2 per 1,000 ¹	0 fewer per 1,000 (2 fewer to 5 more)
assessed with:				Low	
symptomatic distal DVT follow up: range 8 days to 8 weeks				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	42409 (43 RCTs)	⊕⊕⊖⊖ LOW ^{c,f}	RR 0.97 (0.78 to	Study population	
follow up: range 7 days to 8 weeks			1.20)	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		RR 0.79	Low	
follow up: range 7 days		LOW ^{c,n}	(0.57 to 1.08)	18 per	4 fewer per

 a. Only seven studies reported appropriate allocation concealment 51 per 1,000 (22 fewer to fewer) High 51 per 1,000 (22 fewer to 4 more) a. Statistical heterogeneity for subgroup analysis (p=0.05) and 12=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 with cancer , than in studies with less than 50% of patients with cancer. d. Control group risk in studies with less than 50% of patients with cancer. f. Only ten studies reported appropriate allocation concealment g. 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 Ro8. h. In patients undergoing robotic radical prostatectomy with standard pelvid lymph node dissection Tikkinen et al. (2017) reported, a baseline-risk of symptomatic UTE 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 (s) and 0.5%) have been calculated applying the assumptions that 10% of all the symptomatic DVTs 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 proximal DVTs and S% of the remainder part are symptomatic distal DVTs. i. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophyl	to 8 w	eeks					(8 fewer to 1 fewer)
 a. Only seven studies reported appropriate allocation concealment b. Statistical heterogeneity for subgroup analysis (p=0.05) and 12=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 majo general surgical procedures. d. Control group risk in studies with less than 50% of patients with cancer. f. Only the 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 pelvit 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 DVTs are symptomatic DVTs. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis Changolkar et al. (2014) reported, a risk of symptomatic DVTs. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as thromboprophylaxis Changolkar et al. (2024%) has been calculated applying the assumptions that 10% of all the symptomatic DVTs are symptomatic DVTs. In patients undergoing cancer related surgery (retrospective cohort, N=1017) and using UFH as stromboprophylaxis 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 PTE (0.068%), symptomatic proximal DVT (0.12%) and 80% distal DVT. Only a 5% of the symptomatic distal DVTs are symptomatic froximal DVTs are symptomatic proximal DVT (0.12%) and						Moderate	
 a. Only seven studies reported appropriate allocation concealment b. Statistical heterogeneity for subgroup analysis (p=0.05) and 12=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 with cancer , than in studies with less than 50% of patients with cancer . d. Control group risk in studies with less than 50% of patients with cancer. e. Control group risk in studies with less than 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 pelvin 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 DVTs are symptomatic DVTs. i. In patients undergoing cancer related surgery (retrospective cohort, N=017) 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 proximal DVT (0.12%) and symptomatic PE (0.068%), symptomatic VTE of 3.4%, 2.6% of DVT and 2.6% of PE. Baseline-risk estimates for symptomatic PE episodes and 90% are DVT episodes, where a 20% are symptomatic proximal DVT s and 80% distal DVT. Only a 5% of the symptomatic proximal DVT (0.12%) and symptomatic Severe DVTs and therefore, considered important outcome. 						14 per 1,000 °	(0 fewer to 0
 a. Only seven studies reported appropriate allocation concealment b. Statistical heterogeneity for subgroup analysis (p=0.05) and 12=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 majo general surgical procedures. d. Control group risk in studies with less than 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 pelvil 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 DPE (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 CVTEs are PEs and 90% are symptomatic VTE of 3.4%, 2.6% of DVT and 2.6% of PE. Baseline-risk estimates for symptomatic proximal DVT (0.12%) and symptomatic PTE (0.068%), symptomatic proximal DVT (0.12%) and symptomatic PTE (0.068%), symptomatic proximal DVT (0.12%) and symptomatic Schangolkar 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 PTE (0.068%), symptomatic proximal DVT (0.12%) and symptomatic Svere distal DVT (0.024%) hav been calculated applying the assumptions that 10% of all the symptomatic proximal DVT (0.12%) and symptomatic Svere distal DVT (0.024%) hav been calculated applying the assumptions that 10% of all the symptomatic						High	
 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 majo 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 pelvid 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 DVTs 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 severe distal DVT (0.024%) have been calculated applying the assumptions that 10% of all the symptomatic proximal DVT (0.12%) and symptomatic severe distal DVT (0.024%) have been calculated applying the assumptions that 10% of all the symptomatic proximal DVT (0.12%) and S0% of the symptomatic distal DVTs are 80% distal DVT. Only a 5% of the symptomatic distal DVTs are 80% distal DVT. Only a 5% of the symptomatic distal DVTs are assumed to be severe DV							per 1,000 (22 fewer to
been calculated applying the assumptions that 10% of all the symptomal 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.	c. e. f. g. h.	further sugges than in Only of radical genera Contro Contro Only te Probab conside In patie lymph sympto (N=63 PE (0.0 and sy applyin and 90 sympto Sympto In patie N=101 reporte PE. Bas	decrease on m ted in studies i studies with le ne study (Bonci prostatectomy I surgical proce I group risk in s I group	nortality with ncluding mo ass than 50% inelli 2001) v ; Most of the dures. studies with studies with studies with rted appropri- events to me vith RoB. grobotic rad Tikkinen et 5% (low-ris 5% (low-ris 5% (low-ris 5% (low-ris 5%), symptom al DVT (0.12 ions that 100 natic DVTs; 1 DVTs and 5 /Ts. g cancer rela FH as throm mptomatic V nates for syr	a LMWH (co re than 50% of cancer was conduct e evidence less than 5 >=50% of iate allocat eet optimal lical prostat cal. (2017) sk group) a aseline-risk atic proxim % of all the 20% of all the 20% of all the 20% of the re ated surger boprophyla /TE of 3.4% mptomatic	mpared with UI % of patients w population ted in patients was extrapolate 0% of patients patients with ca ion concealmen information siz tectomy with st reported, a bas nd 1.9% (high- estimates for s ial DVT (0.09% %) have been ca symptomatic V the symptomate temainder part a y (retrospective xis Changolkar o, 2.6% of DVT PE (0.068%), s	FH) is ith cancer , undergoing ed from major with cancer. ancer. it e, limitation andard pelvic seline-risk of risk group) symptomatic and 0.342%) calculated /TEs are PEs ic DVTs are are e cohort, et al. (2014) and 2.6% of ymptomatic
participants and health care providers.	j.	VTEs a sympto sympto conside Kakkar	re PE episodes omatic proxima omatic distal DV ered important (1993) was cla	and 90% ar I DVTs and 8 /Ts are assu outcome. assified as hi	e DVT episo 30% distal I med to be igh risk of t	odes, where a 2 DVT. Only a 5% severe DVTs an	20% are of the od therefore,

k. Very small number of events to meet optimal information size. The

	 confidence interval does not exclude an important benefit or harm. I. 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
o Large o Moderate o Small • Trivial o Varies o Don't know		
Certainty of evidence What is the overall certainty of the evidence of	effects?	•
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low Low O Moderate O High O No included studies		

Values

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

Is there important uncertainty about or variability in how much people value the main outcomes?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O 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:						
o no important uncertainty of 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 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 undesi	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)	2	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o 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. Anticoaguiant treatment unit cost was reported as \$15,500 for prophylaxis with ther agents (enoxaparin, or enoxaparin (40mg DQ). Total inpatient hospital cost for hip replacement was reported as \$15,690 for prophylaxis with rivaroxaban, and \$15,500 for prophylaxis with other agents (enoxaparin, warfarin, or enoxaparin plus warfarin). Resource use for disease (indirect evidence): Vekeman et al. 2011, repo	

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

,		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o 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
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 stakeholde	rs?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
o No o Probably no • Probably yes o Yes o Varies o Don't know	No research evidence identified							
Feasibility Is the intervention feasible to implement?								
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
o No o Probably no • Probably yes o Yes o Varies o 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 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 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
0	0	•	0	0

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

•	acological 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 EVID	DENCE					ADDITIONAL CONSIDERATIONS
 No Probably no Probably yes Yes Yes Varies Don't know 	prophylaxis the inci	dence of symptom	atic VTE in pati	ents undergoi	ake this a high priority qu ng cardiac surgery is 0.5 tr ophylaxis in these patients	o 3.0% (Di Nisio, 2015). It	
Desirable Effects How substantial are the desirable an	iticipated effects?						
JUDGEMENT	RESEARCH EVIL	DENCE					ADDITIONAL CONSIDERATIONS
• Trivial o Small o Moderate							The panel discussed use of indirect evidence. Question is about post-op low dose prophylactic anticoagulant.
o Large o Varies o Don't know	Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect (95%	Anticipated absol (95% CI)	lute effects*	The panel discussed that during surgery most patients will get therapeutic dose of heparin for prevention of graft thrombosis.
		Follow up	(GRADE)	ĊI)	CI) Risk with no Risk dir pharmacological with pharma	Risk difference with pharmacological prophylaxis	
	Mortality	76 (1 RCT)	⊕⊕⊖⊖ LOWª	not estimable	Study population	1	
		(2.1.2.)			0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)	
	Symptomatic Pulmonary	119 (2 RCTs)	⊕⊕⊖⊖ LOW ^{b,c}	RR 2.40 (0.10 to	Low		
	Embolism - representing the moderate marker state assessed			55.79)	4 per 1,000 ^d	5 more per 1,000 (3 fewer to 198 more)	

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

Reoperation - not	0 (studies)	-	not estimable	Study population	1
reported				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
 b. Unclead outcom risk of c. No or scena d. The basin the has be sympt e. Baseli 53/14 applie likely f. Althou effect surrog g. The basin the been of sympt h. Seriou assign detect i. The basin cludd sympt j. Lowes (from 	ar risk of bias in me evaluation w f bias. very few events rio where PEs, D aseline risk cons e meta-analysis een calculated a tomatic proxima ne risk for symp 63 = 3.62 %. T is. All proximal D varied between ugh the outcome was considered gates for proxim aseline risk cons meta-analysis. calculated apply tomatic proxima us indirectness. ned to the placel ted by DUS at th aseline risk cons ed surgical patie tomatic distal DV tomatic distal DV tomatic distal DV tomatic distal DV	several dor vas blinded. s and a sma DVTs and ma sists of the o . Baseline ri pplying the I DVTs. btomatic VTI he assumpt DVTs are ass the includer in the stud to be direct al DVT repro- sists of the o Baseline ris ring the assu I DVTs. Patients well bo group de sists of the o ents with ca VT (0.024 % Ts are assum VTs are assu n the low ris assuming t	mains, but w Most inform II number of ajor bleeding control group sk estimates assumptions E calculated ion that 10% sumed to be d RCTs lies was sym t, because si esenting the control group k estimates umptions that re identified veloped an a ischarge froi control group ncer or with b) has been tomatic dist umed to be sisk group froi hat 80% of the solution of the sist of the sist of the solution of the sist of the sist of the solution of the sist of the sist of the sist of the solution of the sist of the sist of the sist of the sist of the solution of the sist of the sist of the sist of the solution of the sist of the sist of the sist of the sist of the solution of the sist of the sist of the sist of the sist of the solution of the sist of the sist of the sist of the sist of the solution of the sist of the sis	patients in the st gs are likely to occ o event rate (0%) s for symptomatic s that 20% of any from control arm o of symptomatic moderate. The d uptomatic and pro ymptomatic and pro through duplex u asymptomatic righ n the hospital o event rate (2.4% out cancer. Baselic calculated applyin al DVTs and that of severe DVTs. m Ho 2015 and the the DVTs (represent	ade because the ies at low or unclear udies, in a clinical cur from studies included proximal DVT (0%) proximal DVTs are of trials in Ho 2015: VTE events are PE uration of follow-up ximal DVT, the relative proximal DVT are good r state. from studies included proximal DVT (0%) has ximal DVTs are ltrasound. One patient the peroneal DVT, %) from studies that ne risk estimates for g the assumptions that

Undesirable Effects How substantial are the undesirable antic	ipated effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small • Trivial o Varies o 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 eviden	ce 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 va	ariability 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: 0.15 (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).

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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	Resource use for pharmacological prophylaxis (indirect evidence):	The indirect evidence was considered too indirect to be
Moderate costs	Depending on the types of prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating the	considered. The judgement is based on panel discussion
Negligible costs and savings Moderate savings	financial implication of VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with injuries of	The panel discussed cost of prophylaxis compared to
D Large savings	the lower limb requiring immobilization, the total pay (cost of healthcare practitioner) and non-pay (consumables,	overall cost of procedures (as small percentage), as well
o Varies	drugs and blood-test investigations) costs for prophylaxis with dalteparin (mean duration of prophylaxis per patient	as volume cost considering number of procedures, whic
o Don't know	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.	was considered moderate.
	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 What is the certainty of the evidence		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Very low o Low o Moderate o High o No included studies Cost effectiveness	The indirect evidence that was identified was deemed to not provide enough information for decision making in th context of this research question and, therefore, a judgment of no included studies was made.	ne
	ervention favor the intervention or the comparison? RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Favors the comparisonProbably favors the comparison	No evidence directly addresses the cost-effectiveness of pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing cardiac or major vascular surgery.	The panel considered there is uncertainty about the effectiveness, however additional cost for using the

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).

intervention is required.

	•••
LO	uitv

o Varies

or the comparison

O Favors the intervention

O No included studies

What would be the impact on health equity?

• Probably favors the intervention

• Does not favor either the intervention

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o 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 sta	Acceptability the intervention acceptable to key stakeholders?				
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o No o Probably no • Probably yes o Yes o Varies o Don't know	No research evidence identified				
Feasibility Is the intervention feasible to implemen	nt?				
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o No O Probably no O Yes O Varies O 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				

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)	

 $\langle \cdot \rangle$

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
0	0	•	0	0

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

	-	em
-		

Is the problem a priority?							
JUDGEMENT	RESEARCH EVII	DENCE			ADDITIONAL CONSIDERATIONS		
o No o Probably no o Probably yes • Yes o Varies o Don't know	Both the frequency the absence of pro 0.5 to 3.0% (Di Nisi prophylaxis in thes	phylaxis the incider o, 2015). It is critica	nce of symptom I to define bot	ardiac surgery is			
Desirable Effects How substantial are the desirable anticipated	effects?						
JUDGEMENT	RESEARCH EVII	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial • Small • Moderate							
o Large o Varies o 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 ⊕⊕○○ RR 4.55 (1 RCT) LOW ^{a,b} (0.22 to				Study population		
	93.4		93.81)	0 per 1,000 0 fewer per 1,000 (0 fewer to 0 fewer)			
	Symptomatic Pulmonary	233 (1 RCT)	⊕⊕⊖⊖ LOW ^{a,b}	not estimable	Low		
	Embolism - representing				0 per 1,000 ^c	0 fewer per 1 000	

the moderate marker state assessed with: any PE364 (3 RCTs) $\bigoplus \bigcirc \bigcirc \bigcirc$ VERY LOW ^{a,b,e} RR 1.33 (0.30 to 6.01)Low $4 \text{ fewer per 1,000^d}$ $4 \text{ fewer per 1,000^d}$ 4 fewer to 0 fewer)Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any DVT, one study proximal DVT 364 (3 RCTs) $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW ^{a,b,e} RR 1.33 (0.30 to 6.01)LowModerate 0.00^{f} $2 \text{ more per 1,000^{f}}$ $2 \text{ more per 1,000^{f}}$ $2 \text{ more per 1,000^{f}}$ (4 fewer to 28 more)Symptomatic Distal Deep Vein Thrombosis - representing 364 (3 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOW ^{a,b,e} RR 1.20 (0.45 to 3.22) $11 \text{ more per 1,000^{g}}$ Symptomatic Distal Deep Vein Thrombosis - representing 364 (3 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOW ^{a,b,e} 2 Low						
Symptomatic Proximal Deep Vein Thrombosis - representing proximal DVT 364 (3 RCTs) $\oplus \bigcirc \bigcirc \bigcirc$ 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 marker state assessed with: any DVT, one study reporting proximal DVT 364 (3 RCTs) $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW ^{a,b,e} RR 1.33 (0.30 to 6.01) Low Moderate 4 fewer to 28 more) 2 more per 1,000 (4 fewer to 28 more) Symptomatic Distal Deep Vein Thrombosis - representing 364 (3 RCTs) $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW ^{a,b,e} RR 1.20 (0.45 to 3.22) Low O per 1,000 ^g 0 fewer per 1,000 ^g 0 fewer per 1,000 ^g 0 fewer per 1,000 ^g	marker state assessed					
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any DVT, one study reporting proximal DVT364 (3 RCTs) $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOWa,b,e RR 1.33 (0.30 to 6.01)LowModerate marker state assessed with: any DVT, one study reporting proximal DVT364 (3 RCTs) $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOWa,b,e RR 1.33 (0.30 to 6.01)LowModerate 33 per 1,000d 1 more per 1,000 (2 fewer to 28 more)Symptomatic Distal Deep Vein Thrombosis - representing364 (3 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOWa,b,e RR 1.20 (0.45 to 3.22)LowDistal Deep Vein Thrombosis - representing364 (3 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOWa,b,eLow0 per 1,000g (0 fewer per 1,000g0 fewer per 1,000g	with: any PE				Moderate	
Proximal Deep Vein Thrombosis - representing the moderate marker state assessed with: any DVT, one study reporting proximal DVT(3 RCTs)VERY LOWa,b,e(0.30 to 6.01)6 per 1,000f2 more per 1,000 (4 fewer to 28 more)Moderate study reporting proximal DVTModerate33 per 1,000d11 more per 1,000 (23 fewer to 165 more)Symptomatic Distal Deep Vein Thrombosis - representing364 (3 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOWa,b,eRR 1.20 (0.45 to 3.22)LowO per 1,000g (0 fewer per 1,000 (0 fewer to 1)0 fewer per 1,000 (0 fewer to 1)					4 per 1,000 ^d	1,000 (4 fewer to 4
Thrombosis - representing the moderate marker state 				(0.30 to	Low	
with: any DVT, one study reporting proximal DVTModerateModerate33 per 1,000d11 more per 1,000 (23 fewer to 165 more)Symptomatic Distal Deep Vein Thrombosis - representing364 (3 RCTs) $\oplus \bigcirc \bigcirc$ VERY LOWa,b,eRR 1.20 (0.45 to 3.22)LowO per 1,000gO fewer per 1,000g0 fewer per 1,000g	Deep Vein Thrombosis - representing the moderate marker state assessed with: any DVT, one		LOW ^{a,b,e}		6 per 1,000 ^f	1,000 (4 fewer to
reporting proximal DVT364 (3 RCTs) \oplus CO VERY LOWa,b,eRR 1.20 (0.45 to 3.22)LowLow0 per 1,000g0 fewer per 1,000g0 fewer per 1,000g0 fewer per 1,000g					Moderate	
Distal Deep (3 RCTs) VERY (0.45 to Vein Thrombosis - representing 0 per 1,000 ^g 0 fewer per 1,000 (0 fower to 1	reporting		0			per 1,000 (23 fewer to
Thrombosis - representing 0 per 1,000 ⁹ 0 fewer per 1,000 (0 fewer to 1)	Distal Deep		VERY	(0.45 to	Low	1
the severe distal DVT marker state	Thrombosis - representing the severe distal DVT				0 per 1,000 ⁹	1,000 (0 fewer to 1
assessed Moderate	with: any				Moderate	1
DVT, one study reporting distal DVT1 per 1,000h0 fewer per 1,000 (1 fewer to 2 more)	study reporting				1 per 1,000 ^h	1,000 (1 fewer to 2

Major bleeding]	233 (1 RCT)	⊕⊕⊖⊖ LOW ^{a,b}	RR 0.91 (0.19 to	Study popula	tion
				4.42)	27 per 1,000	2 fewer per 1,000 (22 fewer to 92 more)
Reopera not repo		-	-	-	-	-
b. c. d. е. f. g. h.	in prac No or v bleedir The ba studies sympto 20% o Baselir Ho 201 VTE ev The du Seriou: scannii The ba studies sympto assum DVTs. The ba studies Baselir calcula sympto are ass Lowest estima	tice very few even ags are likely seline risk co included in omatic PE (0° f any PE are ne risk for syn 5: 53/1463 rents are PE a ration of follo s included in omatic proxim pomatic proxim ptions that 2° seline risk co is that include he risk estimated applying omatic distal sumed to be baseline risk	hts, in a clinic to occur onsists of the the meta-ana %) has been symptomatic mptomatic VT = 3.62 %. The applies. All pro- box-up likely vo s. Patients we onsists of the the meta-ana nal DVT (0.56 0% of any pro- onsists of the d surgical para tes for symp the assumpti DVTs and thas severe DVTs. < in the low ri s) provided a	control grou lysis. Baselir calculated ap PE. E calculated ap PE. E calculated e assumptio oximal DVTs varied betwee re identified control grou lysis. Baselir 5%) has been oximal DVTs control grou tients with ca tomatic dista ons that 20% at only 5% of sk group fro ssuming tha	12 hours) was where PEs, DVT p event rate (0 he risk estimate oplying the assu- from control a n that 10% of s are assumed t en the included through screen p event rate (2 he risk estimate n calculated ap are symptoma p event rate (4 ancer or withou al DVT (0.04 % % of any distal f the symptoma m Ho 2015 and t 80% of the D i 5% of those s	s and major %) from es for umptions that rm of trials in symptomatic o be moderate. RCTs. ning Duplex- .8%) from es for plying the tic proximal .0%) from t cancer.) has been DVTs are atic distal DVTs the highest VTs

Undesirable Effects

How substantial are the undesirable anticipated effects?

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

effects?	
RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
ity in how much people value the main outcomes?	
RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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 reflect the relative value placed on a given health state characterized by that condition, with higher 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).	
	RESEARCH EVIDENCE tty in how much people value the main outcomes? RESEARCH EVIDENCE 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 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: 0.15 (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) patientswo

	 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 under	sirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention 		

Resources	•	
PACALIFCAC	rodurod	
NENUUUEN		

How large are the resource requirements (costs)?

How large are the resource requirements (cost		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Large costs Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o 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.	The evidence was considered too indirect to be considered. The judgement is based on panel discussion.
	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	

o Very low o Low o Moderate	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.	
Certainty of evidence What is the certainty of the evidence JUDGEMENT		ADDITIONAL CONSIDERATIONS
	 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 	

Cost effectiveness

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

Equity What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Reduced o Probably reduced Probably no impact o Probably increased 	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.
o Increased o Varies o Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

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

Feasibility Is the intervention feasible to implement?

Is the intervention feasible to imp		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No	Barriers to implementation of pharmacological prophylaxis	
o Probably no		
 Probably yes 	A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear	
o Yes	against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that	
o Varies	concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic use	
o Don't know	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)	

 $\langle \cdot \rangle$

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 for either the intervention or the comparison

Conditional recommendation for the intervention

0

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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 pharma (indirect evider	cological prophylaxis vs. no pharmacological prophylaxis be used for patients undergoing surgery following major trauma nce)?
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 EVI	DENCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	with use of thromb	oprophylaxis. Major in the event of he	or bleeding is a ad injury. The b	lso a commor palance of the		g VTE complications even ing complication of major rmacological prophylaxis	
Desirable Effects How substantial are the desira	ble anticipated effects?						
JUDGEMENT	RESEARCH EVII	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial o Small • Moderate o Large	Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absol (95% CI)		The judgement of moderate desirable effects was based on reduction in VTE and mortality.
o Varies o Don't know					Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis	
	Mortality (follow-up	14213 (9 RCTs)	⊕OOO VERY	RR 0.95 (0.84 to	Study population		
	10 days to 3 months)		LOW ^{a,b,c}	1.07)	71 per 1,000	4 fewer per 1,000 (11 fewer to 5 more)	
					Low		

				20 per 1,000 ^d	1 fewer per 1,000 (3 fewer to 1 more)	
				Moderate 5 per 1,000 ^e	0 fewer per	
				5 pci 1,000	1,000 (1 fewer to 0 fewer)	
Symptomatic Pulmonary	14134 (9 RCTs)	⊕⊖⊖⊖ VERY	RR 0.49 (0.33 to	Low		
Embolism - representing moderate marker state assessed with:		LOW ^{a,c}	0.72)	15 per 1,000 ^d	8 fewer per 1,000 (10 fewer to 4 fewer)	
Symptomatic PE				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	0000	RR 0.51	Low		

Proximal Deep Vein Thrombosis - representing the	(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 marker state (follow-up 10 days to 3 months)				Moderate 70 per 1,000 ^e	34 fewer per
assessed with: any proximal DVT				liek	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	13813 (5 RCTs)	⊕OOO VERY	RR 0.85 (0.56 to	Low	
Vein Thrombosis - representing the severe marker state	(5 RCTs)	LOW ^{b,c,g,h}	1.29) ^k	54 per 1,000 ^d	8 fewer per 1,000 (24 fewer to 16 more)
(follow-up 10 days to 3 months)				Moderate	
assessed with: any distal DVT				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 -	14415 (11 RCTs)	⊕⊖⊖⊖ VERY	RR 1.24 (1.12 to	Low	
representing moderate marker states		LOW ^{a,c}	1.37)	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 ⁱ	14 more per 1,000 (7 more to 21 more)
Reoperation (follow-up	13645 (3 RCTs) ^m	⊕ VERY	RR 1.05 (0.82 to	Study population	
14 days to 35 days)	LOW ^{b,c,n,o}	1.35)	17 per 1,000 ^m	1 more per 1,000 (3 fewer to 6 more)	

	 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. 	
	 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 	
Undesirable Effects	 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 	
How substantial are the undesirable antic	pated effects? RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o Large o Moderate o Small o Trivial • Varies o 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 evider	ce 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 va	ariability 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	Pulmonary embolism: range 0.63-0.93 (different methods) (Hogg 2013, Hogg 2014, Locadia 2004)	
 No important uncertainty or variability 	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).	

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

	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
	ADDITIONAL CONSIDERATIONS
rophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating TE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with juiring immobilization, the total pay (cost of healthcare practitioner) and non-pay od-test investigations) costs for prophylaxis with dalteparin (mean duration of 46 days, with a range of 6 to 168 days) was £107.54 (\$143.18 in 2011 USD) per patient, (\$191.71 in 2011 USD) per patient. the total direct medical costs associated with VTE prophylaxis with enoxaparin and) in patients with a diverse range of medical and surgical conditions conferring VTE risk billing records between January 2002 and December 2006. After adjustment for pre- length of stay and patients' diagnosis severity level, the mean adjusted total direct for the UFH group were \$6443 (2010 USD) and \$5363 (2010 USD) for the enoxaparin	
	blogical prophylaxis (indirect evidence): prophylaxis used, the costs are shown to vary. Menakaya et al. 2013, a study evaluating VTE prophylaxis in a United Kingdom trauma clinic, showed that in 388 patients with equiring immobilization, the total pay (cost of healthcare practitioner) and non-pay lood-test investigations) costs for prophylaxis with dalteparin (mean duration of s 46 days, with a range of 6 to 168 days) was £107.54 (\$143.18 in 2011 USD) per patient, 19 (\$191.71 in 2011 USD) per patient. d the total direct medical costs associated with VTE prophylaxis with enoxaparin and H) in patients with a diverse range of medical and surgical conditions conferring VTE risk d billing records between January 2002 and December 2006. After adjustment for pre-ig length of stay and patients' diagnosis severity level, the mean adjusted total direct e for the UFH group were \$6443 (2010 USD) and \$5363 (2010 USD) for the enoxaparin 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
o Very low o Low	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	
o Moderate	made.	
HighNo included studies		

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 	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	The panel noted that there is indirect evidence of cost- effectiveness of prophylaxis in other settings when prophylaxis is
o Does not favor either the intervention or the	incurred for each thromboembolic event avoided if enoxaparin 30 mg every 12h were routinely used as	effective.
o Probably favors the intervention	prophylaxis in trauma patients, compared with no prophylaxis. (Wade 2000)	Given considerations about effectiveness, the panel noted that in
O Favors the intervention	Indirect evidence on other population suggested pharmacological prophylaxis is cost-effective compared	
Varies No included studies		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		
 o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o 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 stakeholde	ers?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o Don't know	No research evidence identified	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
0 No	Barriers to implementation of pharmacological prophylaxis	
 Probably no 		
Probably yes	A survey among Malaysian orthopedic surgeons showed that risk of bleeding was the greatest fear	
o Yes	against the use of pharmacological prophylaxis. (Zairul-Nizam 2003). A survey of physicians showed that	
o Varies	concerns over bleeding risks and complicated monitoring procedures associated with antithrombotic	
o Don't know	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)	

	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

Strong recommendation against the	Conditional recommendation against the	Conditional recommendation for either the		Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	•	0	•	0

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	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 EVID	DENCE					ADDITIONAL CONSIDERATIONS				
o No o Probably no o Probably yes • Yes o Varies o Don't know	complications even devastating complic	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 EVID	DENCE					ADDITIONAL CONSIDERATIONS				
 ○ Trivial ● Small ○ Moderate 							Panel noted no difference in mortality and PE (low event rates), most benefit for asymptomatic DVT.				
o Large o Varies	Outcomes	participants (studies)	Certainty of the evidence (GRADE)	Relative effect	Anticipated absolute effects [*] (95% CI)						
o Don't know				(95% CI)	Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis					
	Mortality	Mortality 846 ⊕⊕⊖⊖ (3 RCTs) LOW ^a			Study populat	tion					
			LOW		5 per 1,000	2 more per 1,000 (4 fewer to 54 more)					
	Symptomatic Pulmonary	767 (3 RCTs)	LOW ^a (0.1)	RR 1.04 (0.11 to	Based on Study population						
	Embolism - representing the moderate marker state	Embolism - representing the moderate		9.92)	1 per 1,000 ^b	0 fewer per 1,000 (1 fewer to 5 more)					
	assessed with: any PE				Low						
	follow up: range 10 days to 8 weeks	days to 8								2 per 1,000 ^c	0 fewer per 1,000 (2 fewer to 16 more)
					Moderate						

				2 per 1,000 ^c	0 fewer per 1,000 (2 fewer to 16 more)		
Symptomatic	701	⊕⊕⊕⊖	RR 0.57	Low			
Proximal Deep Vein Thrombosis - representing the moderate	(2 RCTs)	MODERATE	10DERATE ^d (0.25 to 1.31)		6 fewer per 1,000 (10 fewer to 4 more)		
marker state assessed				Moderate			
with: any proximal DVT follow up: range 10 days to 30 days				3 per 1,000°	1 fewer per 1,000 (2 fewer to 1 more)		
Symptomatic	701	⊕⊕⊕⊖	RR 0.74	Based on stud	y population		
Distal Deep Vein Thrombosis - representing the severe	(2 RCTS)	MODERATE	(2 RCTs) MODERATE ^d	^a (0.46 to 1.20)	(0.46 to 1.20)	1 per 1,000 ^f	0 fewer per 1,000 (1 fewer to 0 fewer)
marker state assessed				Low			
with: any distal DVT follow up: range 10 days to 30 days		2		1 per 1,000 ^c	0 fewer per 1,000 (0 fewer to 0 more)		
Major	846 ⊕⊕○○		RR 2.40	Study population			
Bleeding follow up: range 10 days to 8 weeks	(3 RCTs)	LOW ^a	(0.53 to 10.78)	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 anticipate	d effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate • Small o Trivial o Varies o 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			
o 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 variab	ility in how much people value the main outcomes?				
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or variability O 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: 0.15 (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 pharmac				

	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 under	sirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		
Resources required How large are the resource requirements (cos	ts)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Large costs Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies O 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	

Certainty of evidence of reco What is the certainty of the evidence of reco		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Very low o Low o Moderate o 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 interventio		
JUDGEMENT o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison • Probably favors the intervention o Favors the intervention o Varies o No included studies	RESEARCH EVIDENCE 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)	ADDITIONAL CONSIDERATIONS
Equity What would be the impact on health equity?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o 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 stakehold	lers?	
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
o No o Probably no • Probably yes o Yes o Varies o 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) 	
	 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 guidelinesAmong 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 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)	

	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

Strong recommendation against the	Conditional recommendation against the	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	the intervention or the comparison	intervention	intervention
0	0	•	0	0

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 pharma	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 EVIE	DENCE					ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	This question is a hi consequences of ex			•	dure, the post-operative r	risk of VTE, the serious	
Desirable Effects How substantial are the desirable	anticipated effects?						
JUDGEMENT	RESEARCH EVIE	DENCE					ADDITIONAL CONSIDERATIONS
o Trivial o Small							
 Moderate Large Varies 	Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect (95%	Anticipated absolute effects [*] (95% CI)		
o Don't know		(studies) evidence Follow up (GRADE)		(95%) CI)	Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis	
	Mortality	Mortality follow up: range 6 days to 10 weeks22592 (18 RCTs) $\oplus \oplus \oplus \bigcirc$ MODERATEa RR 0.75 (0.61 to 0.93)Study population 4 fewer per 17 per 1,000 (7 fewer to 1 fewer)		Study population			
	range 6 days						
	Symptomatic	18467 (16 PCTc)		RR 0.48 Study population			
	Embolism - representing the moderate marker state	representing the moderate	0.88)	11 per 1,000	6 fewer per 1,000 (8 fewer to 1 fewer)		
	with:			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	11806	⊕000	RR 0.38	Low	1
Proximal Deep Vein Thrombosis- 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 1,0009	1 fewer per 1,000 (2 fewer to 0 fewer)
Symptomatic	11924 (7 PCTc)		RR 0.52	Low	
Distal Deep Vein Thrombosis- representing the severe marker state assessed with: any distal DVT follow up: range 6 days to 10 weeks	(7 RCTs)	LOW ^{h,i}	(0.31 to 0.87)	0 per 1,000 ⁱ	0 fewer per 1,000 (0 fewer to 0 fewer)
Major	22045		RR 1.24	Study population	
bleeding	(15 RCTs)	MODERATE ^k	(0.87 to 1.77)	26 per 1,000	6 more per 1,000 (3 fewer to 20 more)
Reoperation	1520 (6 RCTs)	⊕⊕⊖⊖ LOW ^{I,m}	RR 0.93 (0.35 to	Study population	
			2.50)	12 per 1,000	1 fewer per 1,000 (8 fewer to 18 more)
rated a blindin b. Serious estimat c. The ba	ns high risk of b g in 5 out of 19 s risk of bias. S te rated as high seline risk in ob	ias due to lack studies. tudies that car risk of bias d pservational st	c of conceal rried a cons ue to lack c udies for V	weight for the overal ment in 3 out of 19 iderable weight for t of blinding in 5 out o TE ranges from 0% i of high risk women (studies and lack of he overall effect f 16 studies. n low risk

ГТ	1	
	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.	
1.	Serious inconsistency. Unexplained inconsistency, with point estimates different (P-value chi square= 0.06; I2=54% %)	
a	The baseline risk consists of the control group event rate (1.1%) from studies included	
9.	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.	
	Serious imprecision. 95% CI is consistent with the possibility for benefit and harm. Serious risk of bias. Studies that carried a considerable weight for the overall effect	
1.	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	
	$\mathbf{\nabla}$	

Undesirable Effects How substantial are the undesirable a	ticipated effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate • Small o Trivial o Varies o 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 evi	dence of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low • Low o Moderate o High o 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 o	r variability in how much people value the main outcomes?	-
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 O Important uncertainty or variability Possibly important uncertainty or variability O Probably no important uncertainty or 		
variability o No important uncertainty or variability o No known undesirable outcomes	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		
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison or Probably favors the intervention o Favors the intervention o Varies o Don't know 				
Resources required How large are the resource requirements	s (costs)?			
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS		
 O 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 dateparin (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 \$15,69 for prophylaxis with rivaroxaban, and \$15,708 for prophylaxis with other agents (enoxaparin, warfarin), or enoxaparin plus warfarin). Total inpa			

Certainty of evidence of What is the certainty of the evidence of r		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o 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 interve	ention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 equ	ity?	
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 stak	eholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no ● Probably yes	No research evidence identified	

o Yes o Varies o Don't know		
Feasibility Is the intervention feasible to impleme	nt?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o 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. (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 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 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 55%. (Schellong 2015)	

				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

Strong recommendation against the	Conditional recommendation against the	Conditional recommendation for either the	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	intervention or the comparison	intervention	intervention
0	0	0	•	0

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 EVIE	DENCE				
o No o Probably no o Probably yes • Yes o Varies o Don't know	This question is a hi VTE, the serious co					
Desirable Effects How substantial are the desirable and	ticipated effects?					
JUDGEMENT	RESEARCH EVIE	DENCE				
● Trivial ○ Small						
o Moderate o Large o Varies	Outcomes	№ of participants	Certainty of the	Relative effect	Anticipated a effects [*] (95 ^o	
○ Don't know		(studies) Follow up	evidence (GRADE)	(95% CI)	Risk with UFH prophylaxis	Risk difference with LMWH prophylaxis
	Mortality	41896	⊕⊕◯◯ LOW ^{a,b,c} RR 1.0 (0.89 to 1.18)	⊕⊕◯◯ RR 1.03	Study populat	ion
	follow up: range 7 days to 8 weeks	(35 RCTs)				18 per 1,000
					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 Moderate 40 per 1,000 ^h High 1 per 1,000 ⁱ	0 fewer per 1,000 (0 fewer to 0 fewer) 4 fewer per 1,000 (15 fewer to 12 more) 0 fewer per 1,000	
	4249 (6 RCTs)	-	RR 1.01 (0.20 to	Study populat	(0 fewer to 0 fewer) ion	
- representing the moderate marker state assessed with:			5.00)	1 per 1,000 Low	0 fewer per 1,000 (1 fewer to 6 more)	
Symptomatic Proximal DVT follow up: range 8 days to 8 weeks		0		2 per 1,000 ^d	0 fewer per 1,000 (2 fewer to 8 more)	
	$\left(\right)$			Moderate 5 per 1,000 ⁱ	0 fewer per 1,000 (4 fewer to 20 more)	
Symptomatic Distal DVT -	4587 (8 RCTs)	⊕OOO VERY	RR 1.01 (0.30 to	Low		
representing the severe marker state assessed	(3.10.5)	LOW ^{b,j,k}	3.44)	0 per 1,000 ⁱ	0 fewer per 1,000 (0 fewer to 0 fewer)	
with: Symptomatic				Moderate		
Distal DVT follow up: range 8 days to 8 weeks				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	42409	⊕⊕⊖⊖	RR 0.97	Study populat	ion	
Bleeding follow up: range 7 days to 8 weeks	(43 RCTs)	LOW ^{b,r}	LOW ^{b,f}	(0.78 to 1.20)	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	@@ OO	RR 0.79	Study populat	ion	
follow up: range 7 days to 8 weeks	(21 RCTs)	LOW ^{b,n} (0.57 to 1.08)	18 per 1,000	4 fewer per 1,000 (8 fewer to 1 more)		
				Low	1	
			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)	

- 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 (0.11%) has been calculated applying the assumptions that only 5% of the symptomatic distal DVTs are severe DVTs e. Control group risk in studies with >=6 SW of patients with cancer. f. 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 oursinal 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 bita a doubling of dds for bleeding with pharmacological thromborpophylaxis in women undergoing hysterectoring for being disease. Murray 2016n reported a indence of 4% symptomatic PE following radial systectomy i. Changolkar et al. (2014) reporting for patient patient provided is systectomy g. Changolkar et al. (2014) reporting in patients that as doubling of were schoord, in patients provident DV (10.2%) and sand 90% distal DVT. DN ex of the symptomatic TVEs are PE episodes and 90% was charsflead but? For 61 A 4%. Semiatic provident DV (10.2%) and base and 90% was classified as the risk of the symptomatic treat in patients with a essumptions that 10% of the risk or binding of bruing of schoord provides. k. Very small number of events to meet optimal DVT (D0.1%) from studies that information size. The confident interval does not exclude an important benefit to rarm. j. Kakkar 1939 was classified as high risk of bias for binding of study participants and health care providers. k. Very small number of events to cornol group event rate (0.2%) from studies that include

Undesirable Effects How substantial are the undesirable anticipated	effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small • Trivial o Varies o Don't know		
Certainty of evidence What is the overall certainty of the evidence of e	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 variabili	ty 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 undes	irable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		
Resources required How large are the resource requirements (costs	5)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o 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 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 plus warfarin). Total inpatient hospital cost for knee replacement was reported as \$15,699 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 \$15,699 for prophyla	

	vs. \$9710.	
	See Appendix 3 Table 1 for additional data on prophylaxis unit costs	
Certainty of evidence of requ What is the certainty of the evidence of resource		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o 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 fa	avor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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	The panel considered differences observed between LMWH and UFH were not meaningful.

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 stakeholde	rs?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o Don't know	No research evidence identified	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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) 	

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)	

	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

Strong recommendation against the	Conditional recommendation against the	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	intervention	the intervention or the comparison	intervention	intervention
0	0	•	0	0

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.