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Antithrombotic therapy in arterial thrombosis and thromboembolism in COVID-19: An American College of Chest Physicians Expert Panel Report

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# Antithrombotic therapy in arterial thrombosis and thromboembolism in COVID-19:

# An American College of Chest Physicians Expert Panel Report

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**Key Words:** COVID-19; ACS/PCI; Stent thrombosis; Stroke; Atrial fibrillation; PAD; Limb ischemia.

**Authors' roles:** TP, BB, DC, GAD, JI, GN and GYHL drafted the manuscript, DA, OC, ACY, SH and LM reviewed the draft and provided additional input.

**Abbreviations:**

ABC: atrial fibrillation better care

ACE: angiotensin-converting enzyme

ACS: Acute coronary syndrome

AF: atrial fibrillation

AHA/ACC: American Heart Association/American College of Cardiology

ARDS: acute respiratory distress syndrome

ASA: acetylsalicylic acid

CHEST: the American College of Chest Physicians

CI: Confidence Interval

COVID-19: coronavirus disease 2019

DAPT: dual antiplatelet therapy

DES: drug-eluting stent

DOAC: direct oral anticoagulant

ECG: electrocardiography

EVT: endovascular treatment

HF: heart failure

ICU: intensive care unit

LMWH: low molecular weight heparin

LVO: large vessel occlusion

MACE: major adverse cardiovascular event

MALE: major adverse limb event

NAN-C: North American Neurovascular COVID-19 Consortium

OAC: oral anticoagulation

OR: Odds Ratio

PAD: peripheral artery disease

PCI: percutaneous coronary intervention

PICO: Population, Intervention, Comparator, Outcome

RCT: randomized clinical trial

rTPA: recombinant tissue plasminogen activator

SAPT: single antiplatelet therapy

sICH: symptomatic intracranial hemorrhage

ST: stent thrombosis

STEMI: ST segment elevation myocardial infarction

SVIN: Society of Vascular and Interventional Neurology

TIA: transient ischemic attack

UFH: unfractionated heparin

VKA: Vitamin K antagonist

VTE: venous thromboembolism

**Abstract**

BACKGROUND:

Increasing evidence shows that the risk of thrombotic complications in coronavirus disease 2019 (COVID-19) is associated with a hypercoagulable state. Several organizations have released guidelines for the management of COVID-19-related coagulopathy and prevention of venous thromboembolism. However, there is an urgent need for practical guidance on the management of arterial thrombosis and thromboembolism in this setting.

METHODS:

A group of approved panelists developed key clinical questions by using the PICO (Population, Intervention, Comparator, Outcome) format that addressed urgent clinical questions regarding prevention and management of arterial thrombosis and thromboembolism in patients with COVID-19. Using MEDLINE via Pubmed, a literature search was conducted and references were screened for inclusion. Data from included studies were summarized and reviewed by the panel. Consensus for the direction and strength of recommendations was achieved utilizing a modified Delphi survey.

RESULTS:

The review and analysis of the literature based on 11 PICO questions resulted in 11 recommendations. There was overall a low quality of evidence specific to the COVID-19 population. Consequently, many of the recommendations were based on indirect evidence and prior guidelines in similar populations without COVID-19.

CONCLUSIONS:

The existing evidence and panel consensus do not suggest a major departure from the management of arterial thrombosis as per pre-COVID-19 recommendations. Data on the optimal strategies for prevention and management of arterial thrombosis and thromboembolism in patients with COVID-19 is sparse. More high-quality evidence is needed to inform management strategies in these patients.

KEY WORDS:

COVID-19; ACS/PCI; Stent thrombosis; Stroke; Atrial fibrillation; PAD; Limb ischemia.

**Summary of Recommendations**

1. ***In hospitalized patients with Coronavirus disease 2019 (COVID-19) who have a baseline indication to antiplatelet therapy due to a prior acute coronary syndrome (ACS), we suggest continuing antiplatelet therapy unchanged. (conditional recommendation, ungraded consensus-based statement).***

   *Remark: Considerations on switching from ticagrelor or clopidogrel to prasugrel apply on a case-by-case basis if there are concerns for drug-drug interaction*

2. ***In hospitalized patients with COVID-19 and confirmed ACS, we recommend dual antiplatelet therapy (DAPT) to reduce the risk of recurrent ACS or death (strong recommendation, ungraded consensus-based statement).***

3. ***In hospitalized patients with COVID-19 and myocardial injury without an ACS, we suggest against the initiation of DAPT (conditional recommendation, ungraded consensus-based statement).***

4. ***In hospitalized patients with COVID-19 on DAPT for recent ACS who are receiving prophylactic-dose anticoagulant therapy for COVID-19, we suggest continuing DAPT (conditional recommendation, ungraded consensus-based statement).***

   ***In hospitalized patients with COVID-19 on DAPT for recent ACS who are on therapeutic-dose parenteral anticoagulant therapy for COVID-19, we suggest individualized decisions that consider the risk of bleeding regarding continuation of DAPT alongside anticoagulation (conditional recommendation, ungraded consensus-based statement).***

5. ***In outpatients with COVID-19 on antiplatelet therapy for a previous stroke, we suggest against the addition of or change to oral or subcutaneous anticoagulation (conditional recommendation, ungraded consensus-based statement).***

   ***In hospitalized non-intensive care unit (ICU) patients with COVID-19 on antiplatelet therapy for a previous stroke, we suggest continuation of the antiplatelet and addition of prophylactic-dose low molecular weight heparin (LMWH) (conditional recommendation, ungraded consensus-based statement).***

   *Remark: For carefully selected patients who have an indication for therapeutic-dose anticoagulation with LMWH for COVID-19 and have a favourable thrombotic/bleeding risk profile, continuation of the antiplatelet and addition of therapeutic-dose anticoagulation with LMWH may be considered.*

   ***In hospitalized ICU patients with COVID-19 on antiplatelet therapy for a previous stroke, we suggest continuation of the antiplatelet and addition of prophylactic-dose LMWH (conditional recommendation, ungraded consensus-based statement).***

6. ***In hospitalized patients with COVID-19 who present with acute ischemic stroke and have indication for recanalization therapy (intravenous administration of recombinant tissue plasminogen activator [rTPA] or endovascular treatment [EVT]), we suggest treatment with the indicated recanalization therapy (conditional recommendation, ungraded consensus-based statement).***

7. ***In hospitalized patients with COVID-19 and an acute stroke or transient ischemic attack (TIA) of no established etiology, we suggest treatment with antiplatelet therapy as per current recommendations for non-COVID-19 patients (conditional recommendation, ungraded consensus-based statement).***

8. ***In hospitalized non-ICU patients with COVID-19 on oral anticoagulation for atrial fibrillation (AF) in whom the discontinuation of oral anticoagulation is needed during hospitalization, we suggest switching over to therapeutic dose LMWH or unfractionated heparin (UFH) (conditional recommendation, ungraded consensus-based statement).***

   ***In hospitalized ICU patients with COVID-19 taking oral anticoagulation for AF, we suggest switching over to therapeutic-dose or prophylactic-dose LMWH or UFH, based on individualized decision making (conditional recommendation, ungraded consensus-based statement).***

9. ***In outpatients with COVID-19 and new-onset AF, we suggest starting a direct oral anticoagulant (DOAC) if their $CHA_2DS_2$-VASc score is $\geq$ 1 in males, and $\geq$ 2 in females; if DOACs cannot be used, we suggest a Vitamin K antagonist (VKA) with high time in therapeutic range (>70%) (conditional recommendation, ungraded consensus-based statement).***

   ***In hospitalized (either non-ICU or ICU) patients with COVID-19 and new-onset AF, we suggest starting therapeutic-dose parenteral anticoagulation irrespective of their $CHA_2DS_2$-VASc score. Long-term oral anticoagulation is suggested if the score is $\geq$ 1 in males or $\geq$ 2 in females (conditional recommendation, ungraded consensus-based statement).***

   *Remark:*

   *Antiplatelet therapy alone should not be used for the prevention of thromboembolism in patients with COVID-19 and new-onset AF.*

   *In accordance to previously published guidance, we recommend checking platelet count, coagulation parameters, and liver and renal function prior to starting antithrombotic medications.*

10. ***In hospitalized patients with COVID-19 and stable peripheral artery disease (PAD; i.e., no acute limb events or revascularization procedures within the past 30 days), we suggest continuation of antiplatelet therapy if concurrent prophylactic-dose anticoagulation for COVID-19 is being given (conditional recommendation, ungraded consensus-based statement).***

    ***In hospitalized patients with COVID-19 and stable PAD (i.e., no acute limb events or revascularization procedures within the past 30 days) who are receiving single antiplatelet***

***therapy and therapeutic-dose anticoagulation for COVID-19 is being given, we suggest individualizing the decision whether to continue or hold the antiplatelet agent (conditional recommendation, ungraded consensus-based statement).***

11. ***In hospitalized patients with COVID-19 and acute limb-threatening ischemia, we suggest early revascularization in consultation with vascular specialist, if conforming with clinical presentation, patient values, anatomy and resources (conditional recommendation, ungraded consensus-based statement).***

**Background**

Although COVID-19 primarily results in lung injury, it may also lead to cardiac[1,2], neurologic[3,4], renal[5,6], hepatic[7], hematologic[8], dermatologic[9] and other complications. The disease affects the cardiovascular system in multiple aspects, including disruption in established cardiovascular care pathways in clinical practice and increased risk of acute cardiovascular complications such as arterial or venous thrombosis/thromboembolism, myocardial injury, heart failure (HF) or cardiac arrhythmias[10-12], while it remains unclear whether COVID-19 infection results in specific long-term cardiovascular sequelae.

The increased risk of thrombotic complications in COVID-19 is associated with a prothrombotic or thrombophilic state resulting from multiple mechanisms[13-15] including excessive inflammation, endothelial cell activation and injury, platelet activation and hypercoagulability, with a complex interplay between multiple biochemical, proteolytic and cellular pathways[16,17]. Several organizations have released guidelines for the management of COVID-19-related coagulopathy[18-26] (e-Figure 1) that are periodically updated as new evidence becomes available (e-Figure 2 and e-Table 1). These guidelines consistently recommend that hospitalized patients with COVID-19 (excluding pregnant women) should receive at least a prophylactic-dose anticoagulation to prevent venous thromboembolism (VTE).

In a recent large cohort study, COVID-19 was associated with substantially increased incidence of both VTE and arterial thromboses (especially myocardial infarction and stroke), which declined with time from COVID-19 diagnosis, and the excess in incidence was higher and evident for a longer time after hospitalized than non-hospitalized COVID-19[27].

While patients with a preexisting indication for DAPT or oral anticoagulation (OAC) for a cardiovascular or cerebrovascular condition were excluded from the RCTs of antithrombotic treatment for COVID-19 (e-Table 1), published guidelines on antithrombotic therapy for COVID-19 generally recommend that patients hospitalized with COVID-19 who are taking anticoagulant or antiplatelet therapy for an underlying medical condition continue their treatment unless significant bleeding or other contraindications develop[18-26].

When considering continuation/intensification of antithrombotic treatment in patients with COVID-19 and an underlying medical condition, the benefit from reducing the risk of thromboembolic events needs to be balanced against the risk of bleeding, and there is an urgent need for a more specific practical guidance on the management of antithrombotic therapy for arterial thrombosis and thromboembolism in this setting.

The aim of this Expert Panel Report was to review the available evidence and provide practical recommendations addressing the management of antithrombotic therapy in patients with COVID-19 and the following medical conditions that have evidence-based international guidelines for the management in non-COVID-19 populations: I) recent or acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI), II) history of or acute stroke or transient ischemic attack (TIA), III) previously known or newly diagnosed atrial fibrillation (AF), or IV) peripheral artery disease (PAD)/acute limb ischemia.

**IMPORTANT EXPLANATORY NOTE:**

For consistency with other international documents and published randomized clinical trials (RCTs), in this document the following terms are used:

- **Prophylactic-dose anticoagulation** – refers to standard dosing regimen(s) of the respective anticoagulant agent used for the prevention of *venous* thromboembolism. These are akin to doses used in pre-COVID-19 trials of prophylactic anticoagulation.
- **Therapeutic-dose anticoagulation** – refers to full dosing regimen(s) of the respective anticoagulant agent used for the management of an acute thrombosis or prevention of *arterial* thrombosis/thromboembolism.
- **Intermediate dose anticoagulation** – refers to the escalated prophylactic dosing regimen(s), with drug doses higher than standard prophylactic doses but lower than therapeutic doses of the respective anticoagulant agent.



## Methods

The primary aim of this American College of Chest Physicians (CHEST) Expert Panel Report was to provide practical and immediate guidance in antithrombotic therapy for arterial thrombosis and thromboembolism in patients with COVID-19. We followed the standardized methodology for an Expert Panel Report developed by CHEST, utilizing various components of standard guideline and rapid guideline development, as appropriate[28].

*Expert Panel Composition*

The chair of the panel (T.P.) was appointed by CHEST and subsequently reviewed and approved by CHEST leadership. Panelists were nominated by the chair based on their expertise within the field of arterial thrombosis and thromboembolism. The final panel consisted of the guideline chair, ten panelists, methodologist (J.M.I.) and a member (J.L.) serving as a liaison to the CHEST Guidelines Oversight Committee.

*Conflicts of Interest*

All panelists were reviewed for potential conflicts of interest (COI) by the CHEST Professional Standards Committee. Nominees without any significant COIs were approved and those with potential intellectual and/or financial COIs that were manageable were “approved with management.” Panelists “approved with management” did not participate in discussions and did not vote on recommendations for which they had COIs. Panelists’ COIs are detailed in a COI grid in e-Appendix 1.

*Question Development*

The panel developed a total of 11 key clinical questions using the Population, Intervention, Comparator, and Outcome (PICO) format (Table 1).

**Table 1: PICO Questions.**

| | | |
|---|---|---|
| **SECTION I** | **ACUTE CORONARY SYNDROME (ACS)** | |
| **Question 1**<br><br>Should patients with pre-existing indication for antiplatelet therapy post an ACS discontinue or continue unchanged their antiplatelet regimen if they contract COVID-19? | **P** | Hospitalized COVID-19 patients with prior ACS |
| | **I** | Discontinuation of antiplatelet therapy |
| | **C** | Continuation of antiplatelet therapy with no changes |
| | **O** | Death, recurrent ACS, unplanned revascularization |
| **Question 2**<br><br>Should hospitalized patients with COVID-19 and objectively confirmed ACS receive DAPT or not? | **P** | Hospitalized COVID-19 patients presenting with typical ACS, with or without the need for a percutaneous coronary intervention (PCI) |
| | **I** | DAPT |
| | **C** | No DAPT |
| | **O** | Death, recurrent ACS, unplanned revascularization |
| **Question 3**<br><br>Should hospitalized patients with COVID-19 and myocardial injury without an ACS receive dual antiplatelet therapy or not? | **P** | Hospitalized COVID-19 patients presenting with raised cardiac troponins only |
| | **I** | DAPT |
| | **C** | No DAPT |
| | **O** | Death, myocardial infarction/ACS, unplanned revascularization |
| **Question 4**<br><br>Should hospitalized patients with COVID-19 who have had recent ACS/PCI and are receiving anticoagulant therapy be treated with DAPT or SAPT? | **P** | Hospitalized COVID-19 patients post recent ACS/PCI, receiving anticoagulant therapy |
| | **I** | DAPT |
| | **C** | SAPT |
| | **O** | Death, myocardial infarction/recurrent ACS, unplanned revascularization |
| **SECTION II** | **ISCHEMIC STROKE OR TRANSIENT ISCHEMIC ATTACK (TIA)** | |

| | | |
|---|---|---|
| **Question 5**<br><br>Should patients with COVID-19 on antithrombotic therapy for prior stroke or TIA have their antithrombotic treatment intensified? | **P** | Hospitalized and/or outpatients with COVID-19 who are treated with antiplatelet therapy because of previous stroke or TIA |
| | **I** | Intensification of antithrombotic treatment |
| | **C** | No intensification of antithrombotic treatment |
| | **O** | All-cause death, cardiovascular death, stroke or major adverse cardiovascular event, major or fatal bleeding, clinical deterioration of COVID-19 |
| **Question 6**<br><br>Should patients with COVID-19 who present with acute ischemic stroke and have indication for recanalization therapy (intravenous administration of rTPA or EVT), be treated with recanalization therapy? | **P** | Patients with COVID-19 who present with acute ischemic stroke and have indication for recanalization therapy |
| | **I** | Recanalization therapy |
| | **C** | No recanalization therapy |
| | **O** | Death, functional outcome, symptomatic haemorrhagic transformation, any haemorrhagic transformation, major or fatal bleeding |
| **Question 7**<br><br>Should patients with COVID-19 and acute ischemic stroke or TIA of no established etiology receive anticoagulant or antiplatelet therapy? | **P** | Hospitalized patients with COVID-19 and acute ischemic stroke or TIA of no established aetiology |
| | **I** | Anticoagulant therapy |
| | **C** | Antiplatelet therapy |
| | **O** | All-cause death, cardiovascular death, stroke or major adverse cardiovascular event, major or fatal bleeding, clinical deterioration of COVID-19 |
| **SECTION III** | **ATRIAL FIBRILLATION (AF)** | |
| **Question 8**<br><br>Should patients with pre-existing AF who are hospitalized with COVID-19 continue or discontinue their oral anticoagulant therapy? | **P** | Hospitalized patients with COVID-19 (ICU or non-ICU) and pre-existing AF |
| | **I** | Oral anticoagulation continued |
| | **C** | Oral anticoagulation discontinued |
| | **O** | All-cause death, cardiovascular death, stroke or major adverse cardiovascular event, major or fatal bleeding |

| | | |
|---|---|---|
| **Question 9**<br><br>Should patients with COVID-19 who develop incident AF receive anticoagulation if their $CHA_2DS_2$-VASc score is less than 2 (males) or less than 3 (females)? | **P** | Hospitalized and outpatients with COVID-19 and new-onset AF |
| | **I** | Anticoagulation |
| | **C** | No anticoagulation |
| | **O** | All-cause death, cardiovascular death, stroke or major adverse cardiovascular event, major or fatal bleeding |
| **SECTION IV** | **PERIPHERAL ARTERIAL DISEASE** | |
| **Question 10**<br><br>Should patients with stable PAD who are receiving antiplatelet therapy (with concomitant anticoagulant therapy) discontinue the antiplatelet treatment when hospitalized with COVID-19? | **P** | Hospitalized patients who are receiving antiplatelet therapy for stable PAD and anticoagulant therapy for COVID-19 |
| | **I** | Temporary discontinuation of antiplatelet therapy |
| | **C** | Continuation of antiplatelet therapy that existed prior to COVID-19 |
| | **O** | All-cause death, cardiovascular death, MACE, MALE, worsening COVID-19 severity |
| **Question 11**<br><br>Should patients hospitalized with COVID-19 complicated by acute limb threatening ischemia be treated with a surgical procedure or anticoagulation alone? | **P** | Hospitalized patients with COVID-19 complicated by acute limb threatening ischemia |
| | **I** | A revascularization strategy |
| | **C** | Anticoagulation alone |
| | **O** | All-cause death, cardiovascular death, MACE, MALE, worsening COVID-19 severity |

ACS, acute coronary syndrome; ICU, intensive care unit; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; TIA, transient ischemic attack; rTPA, recombinant tissue plasminogen activator; EVT, endovascular treatment; AF, atrial fibrillation; PAD, peripheral artery disease; MACE, major adverse cardiovascular event; MALE, major adverse limb event.

*Literature Search and Study Selection*

A comprehensive search using MEDLINE via PubMed was performed to identify evidence that could inform clinical decision-making. The search was conducted using a combination of the National Library of Medicine's Medical Subject Headings and key words (e-Appendix 2 with search strategy used).

Studies identified during the literature search were reviewed for relevance by a single panel member. Reviews, and expert opinions statements were excluded. Relevant studies were summarized to inform

recommendations for each PICO question. Given the limited evidence available, meta-analyses were not performed, and case series were included where deemed appropriate.

*Method for Achieving Consensus*

Results from the literature search and study summary were discussed among panel members. Each panel member had the opportunity to provide comments and suggestions for the direction and wording of recommendations for each question. All panelists participated in the development of suggestions to be incorporated in the initial round of a modified Delphi survey.

A modified Delphi survey was performed during which each panel member voted on the direction and strength of the recommendation. Consensus was achieved through up to three rounds of anonymous voting or until 80% agreement in directionality was reached for each recommendation with at least 75% of the panel participating. If no consensus was reached after the three survey rounds, a designation of "no recommendation" was given for that PICO question.

While this Expert Panel Report did not use the full approach of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group, recommendations determined to be "strong" used the wording "we recommend" and those determined to be "conditional" used the wording "we suggest" based on this approach.[29] Given the low quantity and quality of evidence in this area, it was determined *a priori* that a "strong recommendation" could only be considered if there was unanimous agreement amongst the panel for a strong recommendation AND if there was an acceptable paradigmatic situation to justify a strong recommendation[29]. Due to the need for rapid guidance and the limited data in this area, formal grading of the certainty of evidence was not performed and recommendations were primarily based on panel consensus with each recommendation described as an "ungraded consensus-based statement."

Target users of this document include physicians of different specialties involved in the management of patients with COVID-19 and a history of or an acute arterial thrombosis/thromboembolism.

**Results**

**SECTION I. ACUTE CORONARY SYNDROME**

From the search results, 92 citations were screened, and 6 addressing ACS in patients with COVID-19 were identified. Studies relevant for the specific research question are shown in e-Tables 2 and 3.

*<u>Question 1:</u> Should hospitalized patients with pre-existing indication for antiplatelet therapy post ACS discontinue or continue unchanged their antiplatelet regimen if they contract COVID-19?*

**CHEST Recommendation:**

***In hospitalized patients with Coronavirus disease 2019 (COVID-19) who have a baseline indication to antiplatelet therapy due to a prior acute coronary syndrome (ACS), we suggest continuing antiplatelet therapy unchanged. (conditional recommendation, ungraded consensus-based statement).***

*Remark: Considerations on switching from ticagrelor or clopidogrel to prasugrel apply on a case-by-case basis if there are concerns for drug-drug interaction*

Justification:

It is currently recommended that patients with an ACS receive DAPT with aspirin and a $P2Y_{12}$ inhibitor for 12 months after the index event. The inflammatory response and hemodynamic changes associated with COVID-19 may increase the risk of a prothrombotic state, and potentially a coronary thrombosis. Indeed, patients with COVID-19 and ST elevation myocardial infarction (STEMI) are more likely to present with features of high thrombus burden (e.g., multivessel thrombosis, stent thrombosis [ST], higher thrombus grade)[30].

Nevertheless, antiplatelet medications and PCI are underutilized in ACS patients with COVID-19, according to a multicentre study from England (e-Table 2)[31]. Even among patients undergoing PCI, the use of DAPT was significantly lower than in non-COVID-19 patients with PCI[31]. Patients with COVID-19 had higher in-hospital (24.2% vs 5.1%, p<0.001) and 30-day mortality (41.9% vs 7.2%, p<0.001) than patients without COVID-19. These risks remained significantly increased after adjusting for baseline characteristics. The use of antiplatelet therapy at discharge was not a significant risk factor of 30-day mortality in a COVID-19 ACS cohort[31].

These data might be indirectly extrapolated to patients who contract COVID-19 while already on antiplatelet medications following an ACS, suggesting no increase in mortality with ongoing antiplatelet therapy. Consistently, in a small observational study of consecutive patients hospitalized for COVID-19 (e-Table 2), there was no difference in the adjusted risk of acute respiratory distress syndrome (ARDS) or death during hospitalization between patients who received antecedent antiplatelet agents or anticoagulants compared with not receiving them, although the confidence intervals were wide[32].



*<u>Question 2:</u> Should hospitalized patients with COVID-19 and confirmed ACS receive DAPT or not?*

**CHEST Recommendation:**

***In hospitalized patients with COVID-19 and confirmed ACS, we recommend DAPT to reduce the risk of recurrent ACS or death (strong recommendation, ungraded consensus-based statement).***

Justification:

The diagnosis of myocardial infarction in COVID-19 patients may be challenging, as they may have non-specific rise in cardiac biomarkers, or even associated electrocardiographic (ECG) changes and wall motion abnormalities, in the absence of thrombotic ACS[33-36].

International guidelines strongly recommend (Class IA) that non-COVID-19 patients with an ACS receive DAPT with aspirin and a $P2Y_{12}$ inhibitor (prasugrel or ticagrelor preferentially, or clopidogrel in case of a high risk of bleeding or contraindications) for 12 months (or shorter, if concomitant anticoagulant therapy is indicated for other medical condition)[37,38]. High quality evidence is lacking to guide decisions for antithrombotic regimens in patients with ACS and COVID-19, as RCTs on anticoagulation for COVID-19 excluded patients taking DAPT and available evidence is limited mostly to case reports or observational studies (e-Table 2). In an observational study, for example, of 156 COVID-19 patients with ACS, 89.9% were discharged on DAPT[31].

Despite limited evidence, it is reasonable to extrapolate from pre-COVID-19 data and strongly recommend DAPT as the standard of care also in ACS patients with COVID-19, in line with the recommendation for non-COVID patients. Treatment duration should be 12 months, unless there is a compelling reason to administer coexisting anticoagulation, in which case aspirin could be discontinued early (during the index hospitalization or within the first month).

*Question 3: Should hospitalized patients with COVID-19 and myocardial injury receive DAPT or not?*

**CHEST Recommendation:**

***In hospitalized patients with COVID-19 and myocardial injury without an ACS, we suggest against the initiation of DAPT (conditional recommendation, ungraded consensus-based statement).***

Justification:

Elevation of cardiac troponins consistent with myocardial injury has been identified in patients hospitalized with COVID-19 with variable frequency (7-41%)[39-42]. While the cause(s) of this elevation have not been fully elucidated, the finding is more common in patients with more severe forms of COVID-19 and those with existing cardiovascular comorbidities and is associated with increased mortality[40,42-46]. A systematic review and meta-analysis found that an elevated level of cardiac troponins was associated with a ten-fold increased risk of adverse outcomes in COVID-19 patients[47]. This is consistent with studies in non-COVID-19 patients showing that cardiac injury is more common in the aging population and in those with cardiovascular comorbidities[48]. Elevated troponins were observed in 42.3% of ICU patients with non-COVID-19 acute respiratory disease[49].

While elevated troponin values reflect injury to the myocardial cells, they do not indicate the underlying pathophysiological mechanisms, and can arise from preload-induced mechanical stretch or physiological stresses in otherwise normal hearts, hence not necessarily related to acute plaque disruption[50]. Troponin elevation in COVID-19 could result from entities other than acute plaque disruption, including myocarditis, stress cardiomyopathy, acute HF, direct injury from SARS-CoV-2, etc.[51]. It is critical to note that the definition of MI includes the presence of myocardial cell necrosis (e.g., as suggested by an increase in cardiac biomarkers above the upper normal limit of the laboratory range) in a clinical setting consistent

with acute myocardial ischemia[52]. There is a documented increase in the risk of bleeding when DAPT is used that varies depending on the agent chosen and the individual patient bleeding risk factors.

To consider the use of DAPT, the net clinical benefit of reducing the risk of cardiovascular death or myocardial infarction must outweigh the risk of bleeding. In the setting of isolated cardiac troponins elevation, there is no supporting evidence that DAPT would decrease the risk of cardiac events. In fact, the pathophysiology of isolated troponin elevation in the absence of clinical signs of ischemia supports that these events in COVID-19 patients are not due to acute plaque disruption. Potential causes other than ACS should be considered.

*Question 4: Should hospitalized patients with COVID-19 who have had recent ACS/PCI and are receiving anticoagulant therapy be treated with DAPT or SAPT?*

**CHEST Recommendation:**

***In hospitalized patients with COVID-19 on DAPT for recent ACS who are receiving prophylactic-dose anticoagulant therapy for COVID-19, we suggest continuing DAPT (conditional recommendation, ungraded consensus-based statement).***

***In hospitalized patients with COVID-19 on DAPT for recent ACS who are on therapeutic-dose parenteral anticoagulant therapy for COVID-19, we suggest individualized decisions that consider the risk of bleeding regarding continuation of DAPT alongside anticoagulation (conditional recommendation, ungraded consensus-based statement).***

Justification:

Although stent thrombosis (ST) is a rare event, it is associated with high mortality rates. The risk of ST is higher among patients who underwent a PCI for ACS compared with elective PCI[53,54], and is the highest in the first 30 days after PCI[55], with an incidence of <2% in this period[56], decreasing to 0.7% per year due to DAPT and modern drug-eluting stents (DES)[57].

There have been an increasing number of reports of acute, subacute and delayed ST in COVID-19 patients[58-60], and the likely common factor in these events is the predominantly prothrombotic state induced by infection with SARS-CoV2[61,62], especially amongst patients with more severe COVID-19 disease. Extramedullary megakaryocytes in vascular beds of multiple organs, especially lungs and heart, appears to be a unique feature of COVID-19 that could play an important role in increased thrombotic risk[63,64]. The combination of increased platelet activation due to SARS-CoV2 binding to angiotensin-converting enzyme (ACE)-2[65], extramedullary megakaryocytes in the vasculature, formation of neutrophil extracellular traps accompanied by cellular death, tissue factor release, and complement-mediated prothrombotic state[66] may increase the risk of ST.

High quality evidence is lacking to guide antithrombotic regimens in patients on DAPT for recent ACS who contract COVID-19 and are anticoagulated as part of the COVID-19 management (e-Table 3) but there is

also no evidence that DAPT should be withheld in ACS patients on such regimens. Indeed, DAPT is the standard of care in ACS[37,38], and causal mechanisms of coronary thrombosis and thrombotic or ischemic recurrence require the administration of antiplatelet therapy.

The risk of bleeding with combination of DAPT and anticoagulant therapy likely depends, among other factors, on the intensity of anticoagulation (e.g., therapeutic anticoagulation carries a higher risk of bleeding than prophylactic anticoagulation). For patients with prophylactic anticoagulation, the task force agrees that the additional risk of bleeding with DAPT in COVID-19 patients with recent ACS is exceeded by the expected benefit. For patients with therapeutic anticoagulation, since the risks of bleeding with concomitant DAPT and anticoagulant therapy and ST/recurrent ischemia without DAPT vary depending on individual patient risk profile, in line with international non-COVID ACS guidelines[37,38], the task force suggests individualized treatment decision-making to minimize the bleeding and ischemic risks.

Research priorities:

Additional large studies are needed to understand the hemorrhagic and thrombotic event rates in patients with ACS who are diagnosed with COVID-19 and find effective thromboprophylactic strategies.

Studies of the therapeutic levels of clopidogrel, prasugrel and ticagrelor in patients with COVID-19 who are on therapy with protease inhibitors of the hepatic CYP3A4 may inform future recommendations on the preferential use of specific $P2Y_{12}$ inhibitor over the others.

There is a need to explore platelet reactivity in COVID-19 patients presenting with recent or acute thromboembolic events. Further adjustments to antiplatelet and anticoagulant therapy could be guided by bedside platelet function testing in COVID-19 patients on DAPT.

**SECTION II. STROKE/TIA**

From the search results, 571 citations were screened, and 43 addressing stroke/TIA in COVID-19 patients were identified. Studies relevant for the specific research question are shown in e-Tables 4 and 5.

*Question 5: Should hospitalized and/or outpatients with COVID-19 on antiplatelet therapy for prior stroke or TIA have their antithrombotic treatment intensified?*

**CHEST Recommendation:**

***In outpatients with COVID-19 on antiplatelet therapy for a previous stroke, we suggest against the addition of or change to oral or subcutaneous anticoagulation (conditional recommendation, ungraded consensus-based statement).***

***In hospitalized non-ICU patients with COVID-19 on antiplatelet therapy for a previous stroke, we suggest continuation of the antiplatelet and addition of prophylactic-dose LMWH. For carefully selected patients who have an indication for therapeutic-dose anticoagulation with LMWH for COVID-19 and have a favourable thrombotic/bleeding risk profile, continuation of the antiplatelet and addition of therapeutic-dose anticoagulation with LMWH may be considered (conditional recommendation, ungraded consensus-based statement).***

***In hospitalized ICU patients with COVID-19 on antiplatelet therapy for a previous stroke, we suggest continuation of the antiplatelet and addition of prophylactic-dose LMWH (conditional recommendation, ungraded consensus-based statement).***

Justification:

Approximately 0.9-2.7% of patients with COVID-19 may experience stroke, frequently with large vessel occlusion (LVO)[67-69]. COVID-19-related ischaemic strokes are associated with more cardiovascular risk factors and comorbidities, worse severity and functional outcomes, and higher mortality than non- COVID-19 strokes[70,71]. Observational data suggested that markers of coagulation and haemostatic activation (e.g., D-dimer elevation) significantly associate with thromboembolic events amongst COVID-19 patients[72]. An increased positivity of lupus anticoagulant was also observed in COVID-19 patients[73]. In the general population of patients with ischemic stroke or TIA, the AHA/ACC 2021 Guidelines recommend antiplatelet alone (Class 1) for those patients who have an isolated antiphospholipid antibody but do not fulfil the criteria for antiphospholipid syndrome, and warfarin (Class 2) in those who meet the criteria for the antiphospholipid syndrome[74].

If prophylactic-dose anticoagulation is chosen for COVID-19 patients with a recent stroke/TIA who are on DAPT, decision whether the patient will continue with dual or single antiplatelet treatment should be individualized. Further RCTs examining different antithrombotic treatment for COVID-19 patients are ongoing, but none is focusing on intensification of antithrombotic treatment for patients with previous stroke/TIA[75].

The current recommendations for antithrombotic treatment in patients with previous stroke/TIA are based on strong solid evidence[74]. Current evidence does not support deviation from these recommendations and, therefore, the panel recommends against intensification of antithrombotic therapy in COVID-19 patients with previous stroke/TIA. Further evidence from RCTs is needed.

*Question 6: Should patients with COVID-19 who present with acute ischemic stroke and have indication for recanalization therapy (intravenous administration of rTPA or EVT), be treated with recanalization therapy?*

**CHEST Recommendation:**

***In hospitalized patients with COVID-19 who present with acute ischemic stroke and have indication for recanalization therapy (intravenous administration of rTPA or EVT), we suggest treatment with the indicated recanalization therapy (conditional recommendation, ungraded consensus-based statement).***

Justification:

We found low quality and contradictory evidence across techniques and clinical outcomes, as summarized below per clinical outcome.

S*uccessful recanalization after EVT.* In a systematic case series review of EVT-treated COVID-19 patients for LVO, the successful recanalization rate was 83.1%[76], which is broadly comparable to the rate of 71% in non-COVID-19 patients[77]. In other reports, the rate of successful recanalization ranged from 100%[78] to 55.6% in a retrospective analysis reporting a lower rate of good/complete recanalization of the primary arterial occlusive lesion in COVID-19 compared with non-COVID-19 patients[79]. In the ET-COVID-19 study, the rates of successful and complete recanalization were 79.6% and 43%, respectively[80]. In the NAN-C/SVIN study, COVID-19 was associated with significantly lower odds of complete revascularization (e-Table 4)[81].

*Re-occlusion of the initially affected artery after successful recanalization with EVT.* In a systematic case series review of EVT-treated COVID-19 patients with LVO, the rate of early cerebral re-occlusion was 8.2%[76]. These rates seem to compare unfavorably to previous reports from the Bernese Stroke Registry (2.3%)[82], the REVASCAT trial (3.1%)[83] and the ASTRAL Registry (6.6%)[84].

*Intracranial hemorrhage after recanalization therapy.* Among 15128 patients in the Global COVID-19 Stroke Registry who were treated with rTPA or EVT, COVID-19 patients had higher rate of symptomatic hemorrhagic transformation (Odds Ratio [OR] 1.58; 95% Confidence Interval [CI] 1.18–2.12) and any symptomatic intracranial hemorrhage (sICH; OR 1.60; 95% CI 1.32–1.94) compared to contemporaneous non-COVID-19 patients[Marto JP, et al. European Stroke Journal 2022, Vol. 7(1S) 3–545, abstr]. In a systematic review of case series of EVT-treated COVID-19 patients for LVO, the rate of post-procedural hemorrhage was 4.1%[76] vs. 4.3% in non-COVID-19 patients[77]. In three other studies of EVT-treated COVID-19 patients, the rate of sICH was 5.4% in the ET-COVID-19 study[80], 11.1% (vs. 6.7% among non-COVID-19 patients) in the STROKOVID study[79], and 13.6% in a US study[78]. In the NAN-C/SVIN study, there was no significant difference in sICH between COVID-19 and non-COVID-19 patients treated with mechanical thrombectomy[81]. Among rTPA-treated COVID-19 patients, the reported rate of sICH was 4.3%[85]-12.5% (vs. 5.1% among non-COVID-19 patients, OR 2.0, 95%CI: 0.64-6.50)[79].

*Functional outcome and mortality after recanalization therapy.* In the Global COVID-19 Stroke Registry of patients treated with rTPA or EVT, COVID-19 patients had higher 24-hour mortality rate (OR 2.45; 95% CI 2.04–2.93) and 3-month mortality (OR 1.87; 95% 1.44–2.44), and worse 3-month modified Rankin score (OR 1.49; 95% 1.22–1.82) compared to contemporaneous non-COVID-19 patients[Marto JP, et al. European Stroke Journal 2022, Vol. 7(1S) 3–545, abstr]. This finding was also reported in smaller studies, reflecting the deleterious impact of COVID-19 on stroke outcomes[76,78-80,85-87]. However, EVT-treated

COVID-19 patients had higher rate of favorable discharge (47.1% vs. 32.4%) and similar rate of in-hospital death (29.8% vs. 30.6%) compared to COVID-19 patients who were not treated with EVT [86]. In the NAN-C/SVIN study, COVID-19 patients who were treated with mechanical thrombectomy had worse functional outcome at three months and higher in-hospital mortality compared with non-COVID-19 patients (42% vs. 19.1%)[81].

The available evidence suggests that among acute ischemic stroke patients treated with recanalization treatments, COVID-19 patients show higher rates of ICH and worse clinical outcomes compared to non-COVID-19 patients. Considering the relatively large beneficial effect of recanalization treatments, particularly of EVT, and the relatively low absolute risk of sICH in patients with acute ischemic stroke and COVID-19, recanalization treatments likely remain beneficial also in these patients.

*Question 7: Should hospitalized patients with COVID-19 and acute ischemic stroke or TIA of no established etiology receive anticoagulant or antiplatelet treatment?*

**CHEST Recommendation:**

***In hospitalized patients with COVID-19 and an acute stroke or TIA of no established etiology, we suggest treatment with antiplatelet therapy as per current recommendations for non-COVID-19 patients (conditional recommendation, ungraded consensus-based statement).***

Justification:

Strokes of undetermined source may be more frequent in COVID-19 patients, owing to the limited resources and time to complete a thorough investigation in such patients at high risk of dying in a health care system under high pressure[88-91]. In a multicenter registry, strokes of unestablished etiology were associated with higher odds of in-hospital mortality than strokes due to other etiology (OR 5.16, 95%CI 1.41-18.87)[89].

In the non-COVID-19 patients with stroke of undetermined etiology, antiplatelet treatment is recommended over anticoagulation to reduce the risk of recurrent stroke or other cardiovascular event, as the related trials of anticoagulation were not positive[92-94].

The COVID-19-associated coagulation abnormalities raised the hypothesis that perhaps anticoagulants may be beneficial over antiplatelets for COVID-19 patients with stroke of undetermined source. However, there is no data to support this strategy[95]. Indeed, anticoagulation can increase the risk of intracranial bleeding, and most hemorrhagic strokes in COVID-19 patients occurred in the setting of therapeutic anticoagulation and were associated with increased mortality[96].

To consider the use of anticoagulants instead of antiplatelets, the net clinical benefit of reducing stroke recurrence risk must outweigh bleeding risk. Current evidence does not support the hypothesis that

compared to antiplatelets, anticoagulation reduces the risk of recurrent stroke further, and on the contrary, indicates that the risk of intracranial bleeding might be higher. In this context, COVID-19 patients with stroke of undetermined etiology should be treated as the non-COVID-19 patients, i.e., with antiplatelet rather than anticoagulant.

Research priorities:

Further evidence is necessary about the safety and efficacy of stroke recanalization treatment in COVID-19 patients with acute ischemic stroke[97]. Additional studies are needed to identify the optimal antithrombotic treatment in specific groups of COVID-19 patients and stroke of undetermined etiology, e.g., those with cancer or elevated d-dimers. More data is needed to elucidate the value of adherence to an integrated post-stroke care pathway on long-term outcomes post-stroke, including patients with COVID-19 infection[98].

**SECTION III. ATRIAL FIBRILLATION**

From the search results, 84 citations were screened. Of these, three case-series[99-101] and three single-center or multicenter observational studies were identified as addressing the research question[102-104]. No RCTs were identified which addressed the research question. Studies relevant for the specific research question are shown in e-Table 6.

*Question 8: Should hospitalized patients with COVID-19 and pre-existing atrial fibrillation (AF) continue or discontinue their oral anticoagulant therapy?*

**CHEST Recommendation:**

***In hospitalized non-ICU patients with COVID-19 on oral anticoagulation for AF in whom the discontinuation of oral anticoagulation is needed during hospitalization, we suggest switching over to therapeutic dose LMWH or UFH (conditional recommendation, ungraded consensus-based statement).***

***In hospitalized ICU patients with COVID-19 taking oral anticoagulation for AF, we suggest switching over to therapeutic-dose or prophylactic-dose LMWH or UFH, based on individualized decision making (conditional recommendation, ungraded consensus-based statement).***

*Remarks:*

Justification:

Patients with COVID-19 and AF had a significantly lower survival probability and significantly higher risk of thromboembolic events compared with a propensity score-matched COVID-19 cohort without AF[105]. In general AF population, current international guidelines on the management of patients with AF recommend the use of OAC should be considered in patients with $CHA_2DS_2$-VASc score $\geq$1 in men and $\geq$2 in women[106-108]. However, this should be part of a holistic approach to the characterization and evaluation[109] and integrated care management of such patients given the improved outcomes with adherence to such an approach[110]. The principal general approach is likely to be similar, and should therefore be considered, for AF patients with COVID-19.

Anti-Xa levels should be used regularly to monitor heparin levels, as the presence of antiphospholipid antibodies has been described in COVID-19 patients and is associated with prolonged aPTT[111,112].

*Question 9: Should hospitalized and outpatients with COVID-19 who develop incident AF receive anticoagulation if their $CHA_2DS_2$-VASC score is less than 2 (males) or less than 3 (females)?*

**CHEST Recommendation:**

***In outpatients with COVID-19 and new-onset AF, we suggest starting a DOAC if their $CHA_2DS_2$-VASc score is $\geq$ 1 in males, and $\geq$ 2 in females; if DOACs cannot be used, we suggest VKAs with high time in therapeutic range (>70%) (conditional recommendation, ungraded consensus-based statement).***

***In hospitalized (either non-ICU or ICU) patients with COVID-19 and new-onset AF, we suggest starting therapeutic-dose parenteral anticoagulation irrespective of their $CHA_2DS_2$-VASc score. Long-term oral anticoagulation is suggested if the score is $\geq$ 1 in males or $\geq$ 2 in females (conditional recommendation, ungraded consensus-based statement).***

*Remark:*

*Antiplatelet therapy alone should not be used for the prevention of thromboembolism in patients with COVID-19 and new-onset AF.*

*In accordance to previously published guidance, we recommend checking platelet count, coagulation parameters, and liver and renal function prior to starting antithrombotic medications.*

Justification:

The associated comorbidities in patients with COVID-19 are mainly cardiovascular disorders, and are often risk factors for incident (and prevalent) AF[113]. There is evidence that new-onset AF in patients with COVID-19 is associated with decreased survival[114-116] and increased odds ratio for all-cause death and ischaemic stroke[117]. When COVID-19 patients develop AF, their survival probability is significantly lower in compared to matched adults without AF (82.7% vs. 88.3%, Log-Rank test p<0.0001; Risk Ratio 1.61, 95%CI 1.46, 1.78), with a greater risk of thromboembolic events (9.9% vs 7.0%, Log-Rank test *P* < .0001; Risk Ratio 1.41,

95%CI 1.26, 1.59)[105]. A retrospective Spanish cohort study of 160 patients showed a higher incidence of thromboembolic events (41.7% vs. 4.1%, p<0.001), thrombotic events followed by death (58.3% vs. 19.6%, p=0.006), and an increased length of stay in hospital (16.4 vs. 8.6 days, p<0.001) in patients with new-onset AF in COVID-19[118]. Of note, the $CHA_2DS_2$-VASc scores were not significantly different between new-onset AF and controls in this case series.

There is limited evidence published so far on managing anticoagulation for stroke prevention in new-onset AF patients with COVID-19. Current European and other international guidelines on the management of patients with AF recommend OACs for patients with a $CHA_2DS_2$-VASc score of $\geq$2 in males and $\geq$3 in females (Class I ), and OAC use should be considered in those with a $CHA_2DS_2$-VASc score of 1 in males and 2 in females (Class IIa recommendation); balancing the benefit of stroke prevention against the risk of bleeding with OAC use is an integral part of stroke risk management in all patients with AF considered for OAC use[106-108,119]. Our recommendations are based on the international guidelines pertaining to non-COVID-19 patients with AF and one small cohort study[118].

Research priorities:

The value of adherence to guideline-recommended ABC (Atrial fibrillation Better Care) pathway[110] in prevalent or incident AF patients with COVID-19, in hospital and outpatient settings, needs further assessment.

Whether addition of antiplatelet drugs to OAC improves large-vessel arterial thromboembolism outcomes in prevalent or incident AF patients with COVID-19, in hospital and outpatient settings, needs to be further investigated.

**SECTION IV. PERIPHERAL ARTERIAL DISEASE**

From the search results, 190 citations were screened, and 8 addressing peripheral arterial disease in patients with COVID-19 were identified. Studies relevant for the specific research question are shown in e-Table 7.

*Question 10: Should hospitalized patients with COVID-19 and stable PAD who are receiving antiplatelet therapy (with concomitant anticoagulant therapy) discontinue the antiplatelet treatment?*

**CHEST Recommendation:**

***In hospitalized patients with COVID-19 and stable PAD (i.e., no acute limb events or revascularization procedures within the past 30 days), we suggest continuation of antiplatelet therapy if concurrent prophylactic-dose anticoagulation for COVID-19 is being given (conditional recommendation, ungraded consensus-based statement).***

***In hospitalized patients with COVID-19 and stable PAD (i.e., no acute limb events or revascularization procedures within the past 30 days) who are receiving single antiplatelet therapy and therapeutic-dose anticoagulation for COVID-19 is being given, we suggest individualizing the decision whether to continue or hold the antiplatelet agent (conditional recommendation, ungraded consensus-based statement).***

Justification:

High-quality data to address this clinical question are still limited. In the INSPIRATION trial, among aspirin users, 3.2% of patients receiving intermediate-dose anticoagulation, compared with 1.2% of patient receiving prophylactic-dose anticoagulation developed major bleeding. Respective numbers for those not receiving aspirin at baseline were 2.1% vs. 1.4%[120]. The multiplatform RCT[121,122], the ACTION trial[123], or the RAPID trial[124] have not yet reported efficacy or safety outcomes based on use of aspirin or other antiplatelet agents at baseline.

Extrapolating from non-COVID-19 conditions, for stable patients with atherosclerotic vascular diseases who require full-intensity anticoagulation, it appears that anticoagulation monotherapy has at least similar efficacy and is associated with lower risk of bleeding[125]. However, if low-intensity anticoagulation is used in patients with COVID-19, single antiplatelet therapy should be continued in patients with stable PAD based on data from the pre-COVID-19 era[126].

*Question 11: Should patients hospitalized for COVID-19 complicated by limb-threatening ischemia be treated with a surgical procedure or anticoagulation alone?*

**CHEST Recommendation:**

***In hospitalized patients with COVID-19 and acute limb-threatening ischemia, we suggest early revascularization in consultation with vascular specialist, if conforming with clinical presentation, patient values, anatomy and resources (conditional recommendation, ungraded consensus-based statement).***

Justification:

Compared with non-COVID-19 patients with PAD, the degree of limb ischemia, rate of perioperative complications with revascularization and limb amputation all were significantly more common among patients with COVID-19[127-129], the latter irrespective of the time from presentation to imaging-confirmed diagnosis[127], and PAD was a multivariable predictor of increased mortality[130]. A greater thrombus burden with predilection for proximal arteries in patients with COVID-19 has been also reported[127]. A scoping review suggested that patients with COVID-19 suffering from acute limb-threatening limb ischemia tend to be younger and have a greater likelihood of arterial thrombosis in multiple distributions, compared with patients from the pre-COVID-19 era[131]. Another systematic review suggested that many patients with COVID-19 suffering from acute limb-threatening limb ischemia lacked the traditional risk factors, and were already on some form of antiplatelet or anticoagulant prophylaxis prior to the event[132]. Hence, the

symptoms suggesting lower-extremity ischemia in patients with COVID-19 should prompt diagnostic assessment and treatment of the vascular condition.

Insufficient data exist to inform the choice of treatment for patients with COVID-19 complicated by acute limb-threatening ischemia. The revascularization options include surgery, endovascular techniques, systemic and catheter-directed fibrinolysis. In a retrospective multicenter observational study of 26 patients with COVID-19 and acute arterial thrombosis, predominant presentation was a lower limb ischemia (23 patients), and limb salvage rate was lower than in non-COVID-19 patients, possibly owing to delayed diagnosis (most patients initially developed ischemia in the outpatient setting)[133]. In another retrospective series of 22 patients with acute limb-threatening ischemia in the setting of COVID-19, in addition to anticoagulation, 18 patients underwent surgical revascularization, and 4 patients underwent percutaneous revascularization. Three patients died from acute respiratory distress syndrome, and there were 2 major and 1 minor amputations during the hospitalization[134]. In contrast, in a systematic review of 194 cases, 123 underwent surgical revascularization, 37 had percutaneous angioplasty, and 32 were deemed too ill for procedural revascularization[132].

Considering the lack of high-quality data, it is reasonable to consider the treatment of COVID-19 associated acute limb-threatening ischemia similar to patients with the disease prior to the pandemic [131,135,136]. In this sense, anticoagulation should be started as early as possible. With respect to the choice of anticoagulant agents, if antiphospholipid antibody syndrome is suspected or present, based on the data from RCTs in non-COVID-19 patients, it may be prudent to avoid direct oral anticoagulants[137-139]. Approach for revascularization should be based on local expertise, technical procedural feasibility, and individual patient risks and values.

Research priorities:

More high-quality evidence is needed to inform optimal management of patients with COVID-19 infection and an acute peripheral arterial disease.

**Safety considerations in patients treated for COVID-19 and arterial thrombosis**

Surveillance of the potential drug-drug interactions between $P2Y_{12}$ inhibitors and protease inhibitors of the hepatic CYP3A4 is advised[140,141]. Several antiviral agents are known for multiple drug-drug interactions. Specifically, protease inhibitors such as lopinavir/ritonavir, atazanavir and darunavir/cobicistat are reported to inhibit the hepatic CYP3A4 and influence the activity of $P2Y_{12}$ platelet receptor inhibitors, especially clopidogrel (by impairing its bioactivations and reducing the active metabolite) and ticagrelor (by increasing its serum concentrations). To date, there is no specific evidence supporting the recommendation of prasugrel in preference to ticagrelor or clopidogrel in ACS patients with COVID-19.

However, switching from a pre-existing DAPT with ticagrelor or clopidogrel to DAPT with prasugrel might be an option to consider if concerns of drug-to-drug interaction and variable efficacy exist.

Recent literature highlighted the risk of diffuse alveolar hemorrhage in COVID-19 patients treated with DAPT after PCI[142]. Considering these findings, we suggest close monitoring of the patients on DAPT who also need anticoagulation due to COVID-19-related hospitalization. However, there are no clear guidelines or robust evidence to propose a threshold for the platelet count below which DAPT should be switched over to SAPT.

There have been reports of significant increases in plasma levels of DOACs measured in hospitalized patients with COVID-19 on antivirals[143]. There are several significant interactions between DOACs and proposed antiviral therapies for COVID-19 (especially lopinavir/ritonavir)[140]. Patients on VKA can also have instability of INR, despite previously adequate control in the community. This is due to fasting, diet changes, interaction with other drugs, or liver impairment. In hospitalized patients with COVID-19, switching OAC over to LMWH or UFH should be considered.

**Summary**

Since the onset of COVID-19 pandemic thromboprophylaxis has been considered as one of the cornerstones in the management of patients with COVID-19 patients. Optimal thromboprophylactic strategies have been initially informed by observational studies, with high quality RCTs providing important information later during the pandemic. Available RCT-based evidence supports therapeutic-dose anticoagulation in acutely ill non-ICU or ward patients using LMWH (the most well studied thromboprophylactic therapy in hospitalized COVID-19 patients) and suggests prophylactic-dose LMWH in critically ill (especially ICU) patients. While thromboprophylaxis should not be routinely used in outpatients, it may be considered in selected high-risk COVID-19 patients.

Although the anti-platelet, anti-inflammatory, anti-pyretic, and analgesic effects of aspirin could be beneficial in COVID-19 patients, currently available RCT-based evidence does not support aspirin use in this setting[144]. Similarly, studies investigating the use of a P2Y12 (mostly clopidogrel or ticagrelor) alone or in combination with aspirin yielded conflicting results[145,146].

Patients with a pre-existing indication for aspirin, DAPT or OAC were excluded from RCTs of thromboprophylaxis in COVID-19 patients, and there is no RCT-based high-quality data to inform optimal management of COVID-19 patients with pre-existing or acute cardiovascular or cerebrovascular thrombotic/thromboembolic event. Available (mostly observational) suggests that such patients should be generally managed as per the respective international guidelines for non-COVID-19 patients, but more high quality RCT-based data are needed to inform optimal management of these patients. General and specific research priorities are shown in Table 2.

**Table 2. Research priorities in patients with COVID-19 and recent or acute arterial thrombotic or thromboembolic event.**

| General research priorities | Comment |
|---|---|
| Better understanding of the rates of arterial thrombosis or thromboembolism in COVID-19 patients. | Available data suggests the incidence around 1%, varying from 0.1% to 3.1% depending on the COVID-19 disease severity[147]. |
| Better understanding of key mechanisms underlying arterial thrombosis or thromboembolism in COVID-19 patients. | Several platelet-coagulation pathways were shown to be activated in COVID-19 infection including coagulopathy, platelet activation and aggregation, vessel injury, alterations in fibrinolysis, endothelial dysfunction and altered neutrophil-platelet interaction resulting in increased formation of neutrophil extracellular traps (NETs) that facilitates arterial thrombosis and corelates well with COVID-19 disease severity[148].<br><br>It is currently unknown whether the formation of NETs can be reduced by antiplatelet or anticoagulant therapy. |
| Interactions between specific $P2Y_{12}$ inhibitors and COVID-19-directed therapies. | Studies of the therapeutic levels of clopidogrel, prasugrel and ticagrelor in patients with COVID-19 who are on therapy with protease inhibitors of the hepatic CYP3A4 may inform future recommendations on the preferential use of specific $P2Y_{12}$ inhibitor over the others. |
| The effects of changes in the dominant SARS-CoV-2 variants, increasing rates of vaccination, changes in natural immunity status and the availability of anti-COVID-19 therapies on individual patient thrombotic risk. | These changes might influence the choice of optimal thromboprophylactic therapy in individual patient with COVID-19. |
| **Condition** | **Specific research priorities** |
| **Acute coronary syndrome** | The role of bedside platelet function testing in COVID-19 patients on DAPT, which could be used to guide further adjustments in antiplatelet and anticoagulant therapy in patients with COVID-19 patients presenting with recent or ACS. |
| **Acute ischemic stroke** | The safety and efficacy of stroke recanalization treatment in COVID-19 patients with acute ischemic stroke[97]. |

| | |
|---|---|
| | Optimal antithrombotic treatment in specific groups of COVID-19 patients and stroke of undetermined etiology, e.g., those with cancer or elevated d-dimer.<br><br>The value of adherence to an integrated post-stroke care pathway on long-term outcomes post-stroke, including patients with COVID-19 infection[98]. |
| **Atrial fibrillation** | The value of adherence to guideline-recommended ABC (Atrial fibrillation Better Care) pathway[110] in prevalent or incident AF patients with COVID-19, in hospital and outpatient settings.<br><br>Whether addition of antiplatelet drugs to OAC improves large-vessel arterial thromboembolism outcomes in prevalent or incident AF patients with COVID-19, in hospital and outpatient settings. |
| **Peripheral arterial disease** | A greater incidence of peripheral arterial thrombosis compared to other arterial thrombotic events has been reported in patients with COVID-19[149]. More high-quality evidence is needed to inform optimal management of patients with COVID-19 infection and an acute peripheral arterial disease. |

DAPT, dual antiplatelet therapy; ACS, acute coronary syndrome; OAC, oral anticoagulant therapy; AF, atrial fibrillation.



**Conclusion**

Patients with COVID-19 and preexisting indication for DAPT or OAC for a cardiovascular or cerebrovascular condition were excluded from the RCTs of antithrombotic treatment for COVID-19. Data on the optimal strategies for prevention and management of ongoing arterial thrombosis and thromboembolism in patients with COVID-19 is also sparse. The existing evidence and panel consensus do not suggest a major departure from the management of arterial thrombosis as per evidence-based pre-COVID-19 recommendations. More high-quality evidence is needed to inform management strategies in patients with COVID-19 and arterial thrombosis.

**Figures**

**Figure 1. Summary of antithrombotic therapy in arterial thrombosis and thromboembolism in COVID-19.**

Figure legend:

Conditional recommendations are shown in yellow boxes, and strong recommendations in green.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; TIA, transient ischemic attack; ICU, intensive care unit; rTPA, recombinant tissue plasminogen activator; EVT, endovascular treatment; OAC, oral anticoagulant therapy; DOAC, direct oral anticoagulant; AF, atrial fibrillation.

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# I. COVID-19 and ACUTE CORONARY SYNDROME

## On antiplatelet therapy for *a prior* ACS

*All patients:*

**Antiplatelet therapy unchanged**

## Confirmed ACS

*All patients:*

**P2Y12 + ASA**

## Myocardial injury *without* ACS

*All patients:*

**DAPT *not* advised**

## Antiplatelet therapy for *recent* ACS

If on *prophylactic-dose anticoagulation* for COVID-19:

**DAPT continued**

If on *therapeutic-dose anticoagulation* for COVID-19:

**Individualized* decision on DAPT**

*Considering the risk of bleeding with DAPT continuation alongside anticoagulation.

# II. COVID-19 and STROKE/TIA

## On antiplatelet therapy for prior stroke/TIA

*Outpatients:*

**Antiplatelet continuation,**
no need to add or change to anticoagulant therapy

*Hospitalized non-ICU:*

**Antiplatelet continuation and addition of prophylactic-dose anticoagulation or Antiplatelet continuation and addition of therapeutic-dose anticoagulation in patients with favourable thrombotic/bleeding risk profile.**

*Hospitalized ICU:*

**Antiplatelet continuation and addition of prophylactic-dose anticoagulation.**

## Acute stroke with indication for reperfusion therapy

*All patients:*

**Reperfusion therapy (rTPA or EVT)**

## Acute stroke/TIA of no established etiology

*All patients:*

**Antiplatelet therapy**

# III. COVID-19 and ATRIAL FIBRILLATION

## On OAC for pre-existing AF

*ICU hospitalized:*

**Individualized decision on switching over to therapeutic-dose or prophylactic-dose heparin**

*Non-ICU hospitalized:*

**If discontinuation of OAC is needed, switch over to therapeutic-dose heparin**

## Incident AF

*Hospitalized (ICU or non-ICU):*

**Therapeutic-dose parenteral anticoagulation irrespective of the $CHA_2DS_2$-VASc score value, then long-term OAC, if $CHA_2DS_2$-VASc is ≥1 (male) or ≥2 (female)**

*Outpatients:*

**A DOAC, if $CHA_2DS_2$-VASc is ≥1 (males) or ≥2 (females)**

**If DOAC cannot be used, a VKA with high TTR (>70%)**

# IV. COVID-19 and PERIPHERAL ARTERIAL DISEASE

## On antiplatelet therapy for stable PAD

*If on prophylactic-dose anticoagulation for COVID-19:*

**Antiplatelet therapy continued**

*If on therapeutic-dose anticoagulation for COVID-19:*

**Individualized decision on continuation of antiplatelet therapy**

## Limb-threatening ischemia

*All patients:*

**Early revascularization in consultation with vascular specialist**
if conforming with clinical presentation, patient values, anatomy and resources

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

## e-Appendix 1 - COI Grid

| Panel Member | PICO Questions | Relationships and Management * |
|---|---|---|
| Davide Capodanno, MD, PhD | All PICO Questions 1-11 | Funds received for advisory boards with Bayer, AstraZeneca, and Daiichi Sankyo. Managed by disclosure and review of any writing assignments by Chair. |
| | | |
| Gheorghe-Andrei Dan, MD, PhD | All PICO Questions 1-11 | Funds received for consultancies with Boehringer Ingelheim, Pfizer, Bayer and Sanofi. Funds received for speaking engagements for Boehringer Ingelheim, Astra Zeneca, and Berlin-Chemie. Managed by disclosure and review of any writing assignments by Chair. |
| | | |
| George Ntaios, MD | All PICO Questions 1-11 | Funds received for speakers bureaus for AMGEN and Abbott. Managed by divestment from speakers bureaus. |

***No other panel members had conflicts related to the PICO questions.**

**Antithrombotic therapy in arterial thrombosis and thromboembolism in COVID-19:**

**CHEST Expert Panel Report**

**e-Appendix 2**

**Search strategy**

...



**SECTION I. ACUTE CORONARY SYNDROME**

**PICO Questions for Acute Coronary Syndrome**

**Antiplatelet/antithrombosis terms:**

"antithrombotic"[All Fields] OR "antithrombotics"[All Fields] OR "asa"[All Fields] OR ("cilostazol"[MeSH Terms] OR "cilostazol"[All Fields]) OR ("abciximab"[MeSH Terms] OR "abciximab"[All Fields] OR "reopro"[All Fields]) OR ("abciximab"[MeSH Terms] OR "abciximab"[All Fields]) OR ("tirofiban"[MeSH Terms] OR "tirofiban"[All Fields] OR "aggrastat"[All Fields]) OR ("tirofiban"[MeSH Terms] OR "tirofiban"[All Fields]) OR ("ticlopidin"[All Fields] OR "ticlopidine"[MeSH Terms] OR "ticlopidine"[All Fields] OR "ticlid"[All Fields]) OR ("ticlopidin"[All Fields] OR "ticlopidine"[MeSH Terms] OR "ticlopidine"[All Fields]) OR ("cangrelor"[Supplementary Concept] OR "cangrelor"[All Fields] OR "kengreal"[All Fields]) OR ("cangrelor"[Supplementary Concept] OR "cangrelor"[All Fields]) OR ("eptifibatide"[MeSH Terms] OR "eptifibatide"[All Fields]) OR ("eptifibatide"[MeSH Terms] OR "eptifibatide"[All Fields] OR "integrilin"[All Fields]) OR ("dipyridamol"[All Fields] OR "dipyridamole"[MeSH Terms] OR "dipyridamole"[All Fields] OR "persantin"[All Fields] OR "persantine"[All Fields]) OR ("dipyridamol"[All Fields] OR "dipyridamole"[MeSH Terms] OR "dipyridamole"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields] OR "brilinta"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields]) OR ("prasugrel hydrochloride"[MeSH Terms] OR

("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "effient"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel s"[All Fields]) OR ("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel s"[All Fields]) OR ("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "plavix"[All Fields] OR "clopidogrel s"[All Fields]) OR ("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "clopidogrel s"[All Fields]) OR ("aspirin"[MeSH Terms] OR "aspirin"[All Fields] OR "aspirins"[All Fields] OR "aspirin s"[All Fields] OR "aspirine"[All Fields]) OR "Platelet Aggregation Inhibitors"[Supplementary Concept] OR "platelet aggregation inhibitors/pharmacology"[MeSH Terms] OR "platelet aggregation inhibitors/administration and dosage"[MeSH Major Topic] OR ("antiplatelet"[All Fields] OR "antiplatelets"[All Fields])) AND

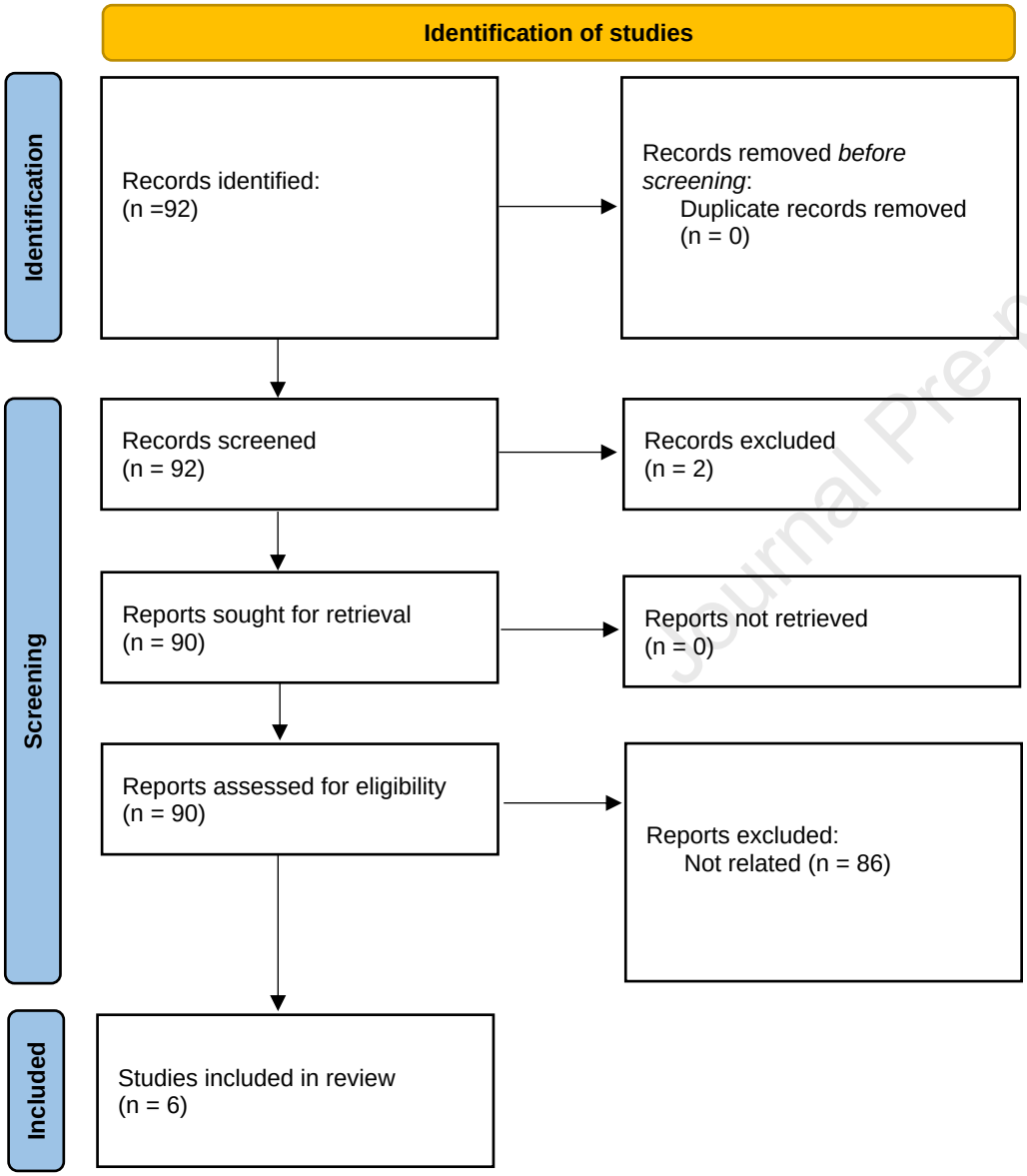
**Acute coronary syndrome terms:**

("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields] OR ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]) OR ("troponin"[MeSH Terms] OR "troponin"[All Fields] OR "troponins"[All Fields] OR "troponine"[All Fields]) OR "TnI"[All Fields] OR ("angina, unstable"[MeSH Terms] OR ("angina"[All Fields] AND "unstable"[All Fields]) OR "unstable angina"[All Fields] OR ("unstable"[All Fields] AND "angina"[All Fields])) OR ("non st elevated myocardial infarction"[MeSH Terms] OR ("non st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non st elevated myocardial infarction"[All Fields] OR ("non"[All Fields] AND "st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non st elevated myocardial infarction"[All Fields]) OR ("st elevation myocardial infarction"[MeSH Terms] OR ("st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "st elevation myocardial infarction"[All Fields] OR ("st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "st elevated myocardial infarction"[All Fields]) OR ("st elevation myocardial infarction"[MeSH Terms] OR ("st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "st elevation myocardial infarction"[All Fields]) OR ("non st elevated myocardial infarction"[MeSH Terms] OR ("non st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non st elevated myocardial infarction"[All Fields] OR ("non"[All Fields] AND "st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non st elevation myocardial infarction"[All Fields]) OR ("non st elevated myocardial infarction"[MeSH Terms] OR ("non st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non st elevated myocardial infarction"[All Fields] OR "nstemi"[All Fields] OR "nstemis"[All Fields]) OR ("st elevation myocardial infarction"[MeSH Terms] OR ("st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "st elevation myocardial infarction"[All Fields] OR "stemi"[All Fields] OR "stemis"[All Fields]) OR (("demand"[All Fields] OR "demanded"[All Fields] OR "demanding"[All Fields] OR "demands"[All Fields]) AND ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischaemias"[All Fields] OR "ischemias"[All Fields]))) AND

**COVID-19 terms:**

("coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "coronavirinae*"[All Fields] OR "coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "wuhan*"[All Fields] OR "hubei*"[All Fields] OR "Huanan"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "nCoV2019"[All Fields] OR "nCoV-2019"[All Fields] OR "COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "covid19"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "covid"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "corvid"[All Fields] OR "corvids"[All Fields] OR "HCoV-19"[All Fields] OR "HCoV19"[All Fields] OR "CoV"[All Fields] OR "2019 novel*"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "ncov"[All Fields] OR "n-cov"[All Fields] OR "SARS-CoV-2"[All Fields] OR "SARSCoV-2"[All Fields] OR "SARSCoV2"[All Fields] OR "SARS-CoV2"[All Fields] OR "SARSCov19"[All Fields] OR "SARS-Cov19"[All Fields] OR "SARS-Cov-19"[All Fields] OR "Ncovor"[All Fields] OR "ncorona*"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR ("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]))

**Appendix 2. The PRISMA diagram for ACUTE CORONARY SYNDROME.**



**SECTION II. STROKE/TIA**

**PICO Questions for Stroke/TIA**

**Stroke/TIA terms:**

("transient ischaemic attack"[All Fields] OR "ischemic attack, transient"[MeSH Terms] OR ("ischemic"[All Fields] AND "attack"[All Fields] AND "transient"[All Fields]) OR "transient ischemic attack"[All Fields] OR ("transient"[All Fields] AND "ischemic"[All Fields] AND "attack"[All Fields]) OR "tia"[All Fields] OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "cva"[All Fields]) OR ("brain ischaemia"[All Fields] OR "brain ischemia"[MeSH Terms] OR ("brain"[All Fields] AND "ischemia"[All Fields]) OR "brain ischemia"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR ("cerebral"[All Fields] AND "vascular"[All Fields] AND "accident"[All Fields]) OR "cerebral vascular accident"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR ("cerebrovascular"[All Fields] AND "accident"[All Fields]) OR "cerebrovascular accident"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields])) AND

**Antiplatelet/antithrombosis terms:**

(("antiplatelet"[All Fields] OR "antiplatelets"[All Fields] OR "platelet aggregation inhibitors/administration and dosage"[MeSH Major Topic] OR "platelet aggregation inhibitors/pharmacology"[MeSH Terms] OR "Platelet Aggregation Inhibitors"[Supplementary Concept] OR ("aspirin"[MeSH Terms] OR "aspirin"[All Fields] OR "aspirins"[All Fields] OR "aspirin s"[All Fields] OR "aspirine"[All Fields]) OR ("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "clopidogrel s"[All Fields]) OR ("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "plavix"[All Fields] OR "clopidogrel s"[All Fields]) OR ("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel s"[All Fields]) OR ("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "effient"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel s"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields] OR "brilinta"[All Fields]) OR ("dipyridamol"[All Fields] OR "dipyridamole"[MeSH Terms] OR "dipyridamole"[All Fields]) OR ("dipyridamol"[All Fields] OR "dipyridamole"[MeSH Terms] OR "dipyridamole"[All Fields] OR "persantin"[All Fields] OR "persantine"[All Fields]) OR ("eptifibatide"[MeSH Terms] OR "eptifibatide"[All Fields] OR "integrilin"[All Fields]) OR ("eptifibatide"[MeSH Terms] OR "eptifibatide"[All Fields]) OR ("cangrelor"[Supplementary Concept] OR "cangrelor"[All Fields]) OR ("cangrelor"[Supplementary Concept] OR "cangrelor"[All Fields] OR "kengreal"[All Fields]) OR ("ticlopidin"[All Fields] OR "ticlopidine"[MeSH Terms] OR "ticlopidine"[All Fields]) OR ("ticlopidin"[All Fields] OR

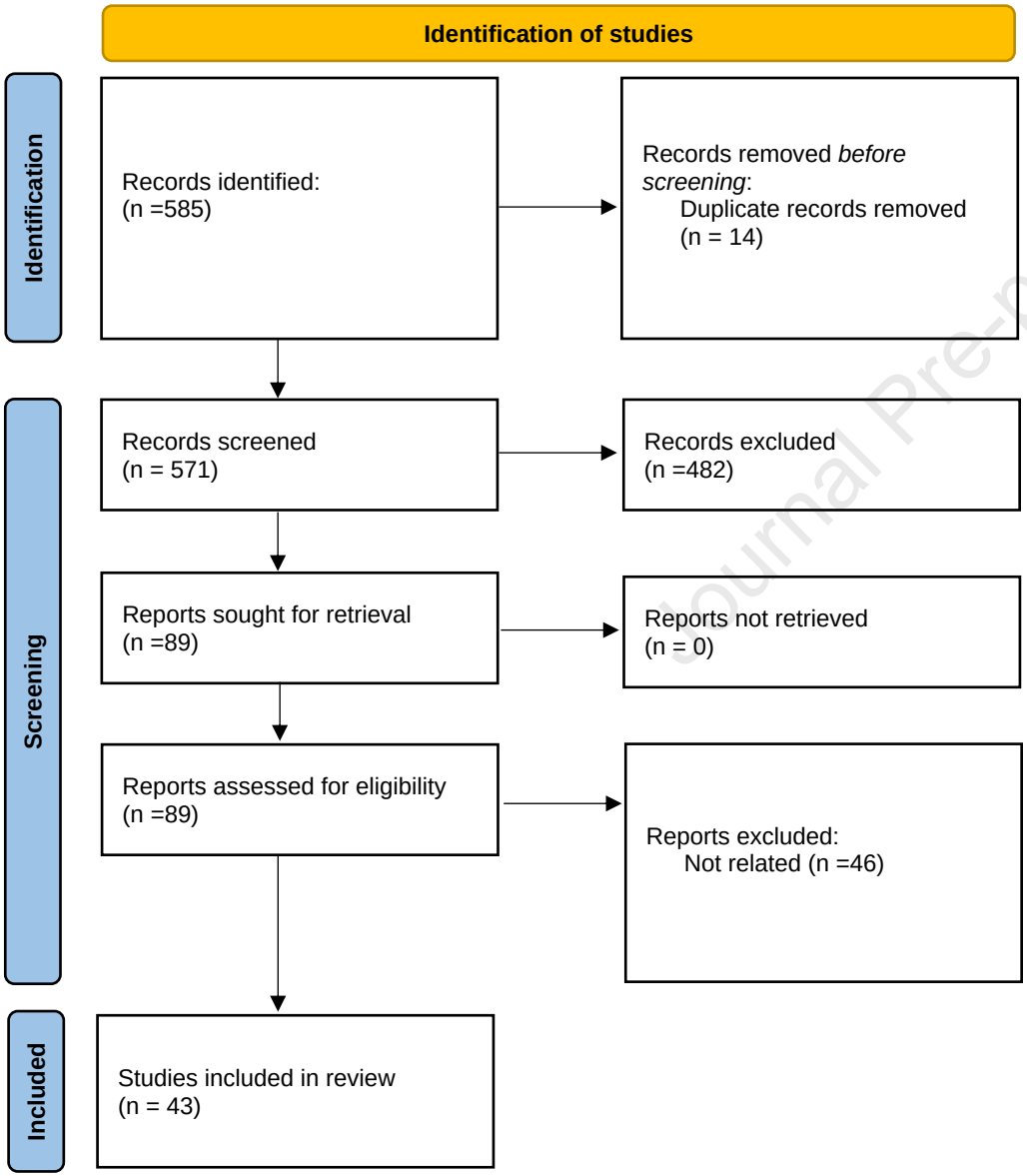
"ticlopidine"[MeSH Terms] OR "ticlopidine"[All Fields] OR "ticlid"[All Fields]) OR ("tirofiban"[MeSH Terms] OR "tirofiban"[All Fields]) OR ("tirofiban"[MeSH Terms] OR "tirofiban"[All Fields] OR "aggrastat"[All Fields]) OR ("abciximab"[MeSH Terms] OR "abciximab"[All Fields]) OR ("abciximab"[MeSH Terms] OR "abciximab"[All Fields] OR "reopro"[All Fields]) OR ("cilostazol"[MeSH Terms] OR "cilostazol"[All Fields]) OR "asa"[All Fields] OR ("antithrombotic"[All Fields] OR "antithrombotics"[All Fields]) OR ("heparin"[MeSH Terms] OR "heparin"[All Fields] OR "heparine"[All Fields] OR "heparins"[All Fields] OR "heparin s"[All Fields] OR "heparinate"[All Fields] OR "heparinated"[All Fields] OR "heparines"[All Fields] OR "heparinic"[All Fields] OR "heparinisation"[All Fields] OR "heparinised"[All Fields] OR "heparinization"[All Fields] OR "heparinize"[All Fields] OR "heparinized"[All Fields] OR "heparinizing"[All Fields]) OR ("enoxaparin"[MeSH Terms] OR "enoxaparin"[All Fields] OR "enoxaparine"[All Fields] OR "enoxaparin s"[All Fields] OR "enoxaparins"[All Fields]) OR ("enoxaparin"[MeSH Terms] OR "enoxaparin"[All Fields] OR "enoxaparine"[All Fields] OR "lovenox"[All Fields] OR "enoxaparin s"[All Fields] OR "enoxaparins"[All Fields]) OR "tpa"[All Fields] OR ("tissue plasminogen activator"[MeSH Terms] OR ("tissue"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "tissue plasminogen activator"[All Fields]) OR ("reperfusate"[All Fields] OR "reperfusates"[All Fields] OR "reperfuse"[All Fields] OR "reperfused"[All Fields] OR "reperfusing"[All Fields] OR "reperfusion"[MeSH Terms] OR "reperfusion"[All Fields] OR "reperfusions"[All Fields] OR "reperfusive"[All Fields]) OR "endovascular"[All Fields] OR ("dalteparin"[MeSH Terms] OR "dalteparin"[All Fields]) OR ("nadroparin"[MeSH Terms] OR "nadroparin"[All Fields] OR "nadroparine"[All Fields]) OR ("reviparin"[Supplementary Concept] OR "reviparin"[All Fields] OR "reviparine"[All Fields]) OR ("parnaparin"[Supplementary Concept] OR "parnaparin"[All Fields]) OR ("certoparin"[Supplementary Concept] OR "certoparin"[All Fields]) OR ("tinzaparin"[MeSH Terms] OR "tinzaparin"[All Fields]) OR ("bemiparin"[Supplementary Concept] OR "bemiparin"[All Fields]) OR ("warfarin"[MeSH Terms] OR "warfarin"[All Fields] OR "warfarin s"[All Fields] OR "warfarinization"[All Fields] OR "warfarinized"[All Fields] OR "warfarins"[All Fields]) OR ("warfarin"[MeSH Terms] OR "warfarin"[All Fields] OR "coumadin"[All Fields] OR "warfarin s"[All Fields] OR "warfarinization"[All Fields] OR "warfarinized"[All Fields] OR "warfarins"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields] OR "dabigatran s"[All Fields]) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields]) OR ("apixaban"[Supplementary Concept] OR "apixaban"[All Fields] OR "apixaban s"[All Fields]) OR ("edoxaban"[Supplementary Concept] OR "edoxaban"[All Fields]) OR ("apixaban"[Supplementary Concept] OR "apixaban"[All Fields] OR "eliquis"[All Fields] OR "apixaban s"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields] OR "pradaxa"[All Fields] OR ("dabigatran"[All Fields] AND "etexilate"[All Fields]) OR "dabigatran etexilate"[All Fields]) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields] OR "xarelto"[All Fields]) OR ("edoxaban"[Supplementary Concept] OR "edoxaban"[All Fields] OR "savaysa"[All Fields]) OR ("tissue plasminogen activator"[MeSH Terms] OR ("tissue"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "tissue plasminogen activator"[All Fields] OR "alteplase"[All Fields]) OR ("urokinase type plasminogen activator"[MeSH Terms] OR ("urokinase type"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "urokinase type plasminogen activator"[All Fields] OR "urokinase"[All Fields] OR "urokinases"[All Fields]) OR ("streptokinase"[MeSH Terms] OR "streptokinase"[All Fields] OR "streptokinases"[All Fields]) OR ("aur protein staphylococcus aureus"[Supplementary Concept] OR "aur protein staphylococcus aureus"[All Fields] OR "staphylokinase"[All Fields]) OR ("monteplase"[Supplementary Concept] OR "monteplase"[All Fields]) OR ("pamiteplase"[Supplementary Concept] OR "pamiteplase"[All Fields]) OR ("lanoteplase"[Supplementary Concept] OR "lanoteplase"[All Fields]) OR ("reteplase"[Supplementary Concept] OR "reteplase"[All Fields]) OR "tenectaplase"[All Fields] OR ("tenecteplase"[MeSH Terms] OR "tenecteplase"[All Fields]) OR ("salivary plasminogen activator alpha 1 desmodus rotundus"[Supplementary Concept] OR "salivary plasminogen activator alpha 1 desmodus rotundus"[All Fields] OR "desmoteplase"[All Fields]) OR

("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR "anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields])) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "cva"[All Fields] OR ("brain ischaemia"[All Fields] OR "brain ischemia"[MeSH Terms] OR ("brain"[All Fields] AND "ischemia"[All Fields]) OR "brain ischemia"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR ("cerebral"[All Fields] AND "vascular"[All Fields] AND "accident"[All Fields]) OR "cerebral vascular accident"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR ("cerebrovascular"[All Fields] AND "accident"[All Fields]) OR "cerebrovascular accident"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields])) AND

**COVID-19 terms:**

("coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "coronavirinae*"[All Fields] OR "coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "wuhan*"[All Fields] OR "hubei*"[All Fields] OR "Huanan"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "nCoV2019"[All Fields] OR "nCoV-2019"[All Fields] OR "COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "covid19"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "covid"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "corvid"[All Fields] OR "corvids"[All Fields] OR "HCoV-19"[All Fields] OR "HCoV19"[All Fields] OR "CoV"[All Fields] OR "2019 novel*"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "ncov"[All Fields] OR "n-cov"[All Fields] OR "SARS-CoV-2"[All Fields] OR "SARSCoV-2"[All Fields] OR "SARSCoV2"[All Fields] OR "SARS-CoV2"[All Fields] OR "SARSCov19"[All Fields] OR "SARS-Cov19"[All Fields] OR "SARS-Cov-19"[All Fields] OR "Ncovor"[All Fields] OR "ncorona*"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR ("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]))

**Appendix 2. The PRISMA diagram for STROKE/TIA*.**



***A note: One study was added subsequently, at the finalization stage (Dmytriw AA, Ghozy S, Sweid A, et al. International controlled study of revascularization and outcomes following COVID-positive mechanical thrombectomy. Eur J Neurol. 2022.). The study revealed findings similar to the initially included studies, thus not influencing the respective recommendation.**

**SECTION III. ATRIAL FIBRILLATION**

**PICO Questions for Atrial Fibrillation**

**Atrial fibrillation terms:**

("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields] OR "a-fib"[All Fields] OR (("atrialisation"[All Fields] OR "atrialization"[All Fields] OR "atrialized"[All Fields] OR "atrially"[All Fields] OR "heart atria"[MeSH Terms] OR ("heart"[All Fields] AND "atria"[All Fields]) OR "heart atria"[All Fields] OR "atrial"[All Fields]) AND ("tachycardia"[MeSH Terms] OR "tachycardia"[All Fields] OR "tachycardias"[All Fields] OR "tachycardia s"[All Fields])) OR (("atrialisation"[All Fields] OR "atrialization"[All Fields] OR "atrialized"[All Fields] OR "atrially"[All Fields] OR "heart atria"[MeSH Terms] OR ("heart"[All Fields] AND "atria"[All Fields]) OR "heart atria"[All Fields] OR "atrial"[All Fields]) AND ("tachyarrhythmia s"[All Fields] OR "tachycardia"[MeSH Terms] OR "tachycardia"[All Fields] OR "tachyarrhythmia"[All Fields] OR "tachyarrhythmias"[All Fields]))) AND

**Antiplatelet/Antithrombosis terms:**

("antiplatelet"[All Fields] OR "antiplatelets"[All Fields] OR "platelet aggregation inhibitors/administration and dosage"[MeSH Major Topic] OR "platelet aggregation inhibitors/pharmacology"[MeSH Terms] OR "Platelet Aggregation Inhibitors"[Supplementary Concept] OR ("aspirin"[MeSH Terms] OR "aspirin"[All Fields] OR "aspirins"[All Fields] OR "aspirin s"[All Fields] OR "aspirine"[All Fields]) OR ("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "clopidogrel s"[All Fields]) OR ("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "plavix"[All Fields] OR "clopidogrel s"[All Fields]) OR ("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel s"[All Fields]) OR ("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "effient"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel s"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields] OR "brilinta"[All Fields]) OR ("dipyridamol"[All Fields] OR "dipyridamole"[MeSH Terms] OR "dipyridamole"[All Fields]) OR ("dipyridamol"[All Fields] OR "dipyridamole"[MeSH Terms] OR "dipyridamole"[All Fields] OR "persantin"[All Fields] OR "persantine"[All Fields]) OR ("eptifibatide"[MeSH Terms] OR "eptifibatide"[All Fields] OR "integrilin"[All Fields]) OR ("eptifibatide"[MeSH Terms] OR "eptifibatide"[All Fields]) OR ("cangrelor"[Supplementary Concept] OR "cangrelor"[All Fields]) OR ("cangrelor"[Supplementary Concept] OR "cangrelor"[All Fields] OR "kengreal"[All Fields]) OR ("ticlopidin"[All Fields] OR "ticlopidine"[MeSH Terms] OR "ticlopidine"[All Fields]) OR ("ticlopidin"[All Fields] OR "ticlopidine"[MeSH Terms] OR "ticlopidine"[All Fields] OR "ticlid"[All Fields]) OR ("tirofiban"[MeSH Terms] OR "tirofiban"[All Fields]) OR ("tirofiban"[MeSH

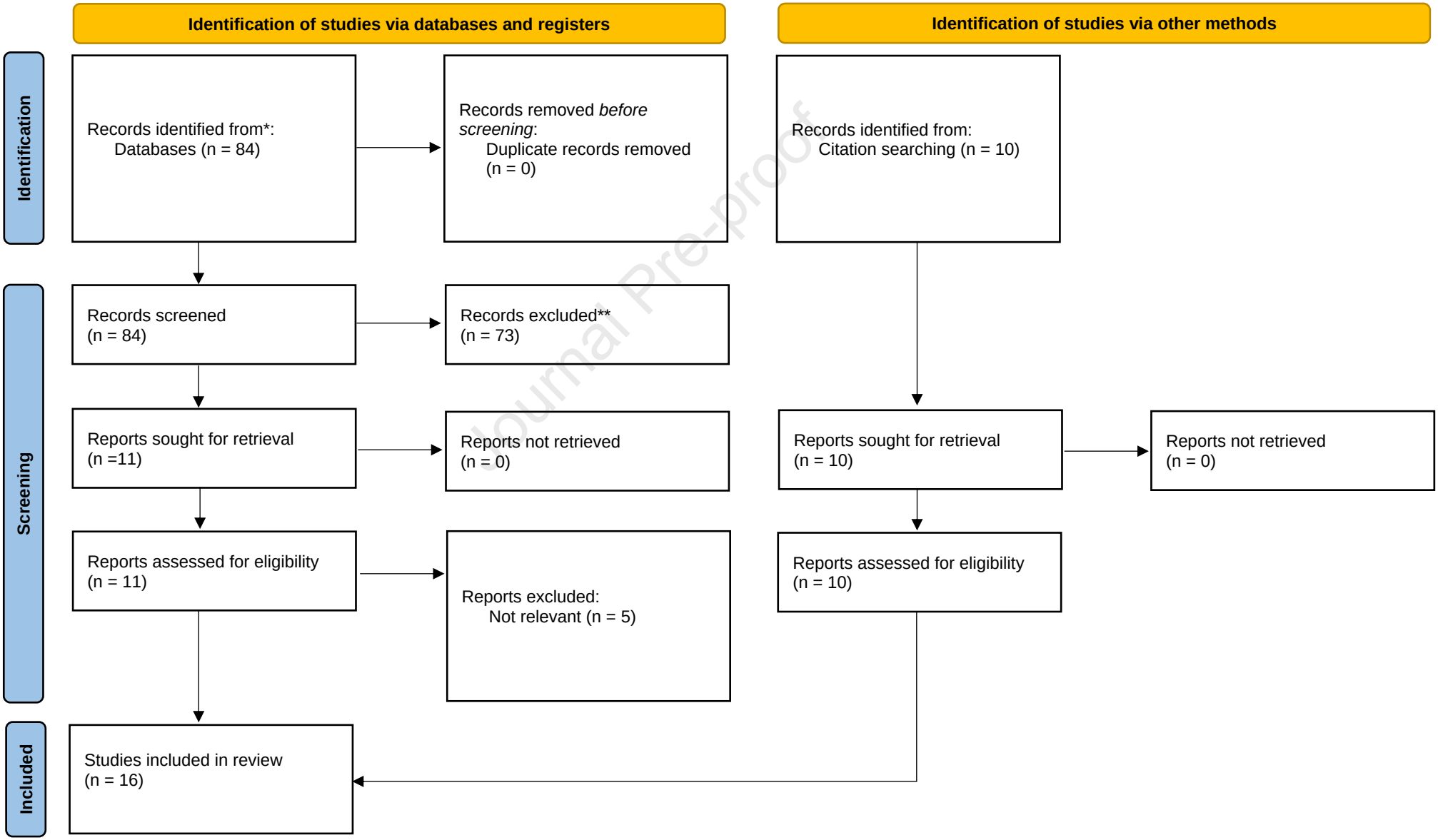
Terms] OR "tirofiban"[All Fields] OR "aggrastat"[All Fields]) OR ("abciximab"[MeSH Terms] OR "abciximab"[All Fields]) OR ("abciximab"[MeSH Terms] OR "abciximab"[All Fields] OR "reopro"[All Fields]) OR ("cilostazol"[MeSH Terms] OR "cilostazol"[All Fields]) OR "asa"[All Fields] OR ("antithrombotic"[All Fields] OR "antithrombotics"[All Fields]) OR ("heparin"[MeSH Terms] OR "heparin"[All Fields] OR "heparine"[All Fields] OR "heparins"[All Fields] OR "heparin s"[All Fields] OR "heparinate"[All Fields] OR "heparinated"[All Fields] OR "heparines"[All Fields] OR "heparinic"[All Fields] OR "heparinisation"[All Fields] OR "heparinised"[All Fields] OR "heparinization"[All Fields] OR "heparinize"[All Fields] OR "heparinized"[All Fields] OR "heparinizing"[All Fields]) OR ("enoxaparin"[MeSH Terms] OR "enoxaparin"[All Fields] OR "enoxaparine"[All Fields] OR "enoxaparin s"[All Fields] OR "enoxaparins"[All Fields]) OR ("enoxaparin"[MeSH Terms] OR "enoxaparin"[All Fields] OR "enoxaparine"[All Fields] OR "lovenox"[All Fields] OR "enoxaparin s"[All Fields] OR "enoxaparins"[All Fields]) OR "tpa"[All Fields] OR ("tissue plasminogen activator"[MeSH Terms] OR ("tissue"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "tissue plasminogen activator"[All Fields]) OR ("reperfusate"[All Fields] OR "reperfusates"[All Fields] OR "reperfuse"[All Fields] OR "reperfused"[All Fields] OR "reperfusing"[All Fields] OR "reperfusion"[MeSH Terms] OR "reperfusion"[All Fields] OR "reperfusions"[All Fields] OR "reperfusive"[All Fields]) OR "endovascular"[All Fields] OR ("dalteparin"[MeSH Terms] OR "dalteparin"[All Fields]) OR ("nadroparin"[MeSH Terms] OR "nadroparin"[All Fields] OR "nadroparine"[All Fields]) OR ("reviparin"[Supplementary Concept] OR "reviparin"[All Fields] OR "reviparine"[All Fields]) OR ("parnaparin"[Supplementary Concept] OR "parnaparin"[All Fields]) OR ("certoparin"[Supplementary Concept] OR "certoparin"[All Fields]) OR ("tinzaparin"[MeSH Terms] OR "tinzaparin"[All Fields]) OR ("bemiparin"[Supplementary Concept] OR "bemiparin"[All Fields]) OR ("warfarin"[MeSH Terms] OR "warfarin"[All Fields] OR "warfarin s"[All Fields] OR "warfarinization"[All Fields] OR "warfarinized"[All Fields] OR "warfarins"[All Fields]) OR ("warfarin"[MeSH Terms] OR "warfarin"[All Fields] OR "coumadin"[All Fields] OR "warfarin s"[All Fields] OR "warfarinization"[All Fields] OR "warfarinized"[All Fields] OR "warfarins"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields] OR "dabigatran s"[All Fields]) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields]) OR ("apixaban"[Supplementary Concept] OR "apixaban"[All Fields] OR "apixaban s"[All Fields]) OR ("edoxaban"[Supplementary Concept] OR "edoxaban"[All Fields]) OR ("apixaban"[Supplementary Concept] OR "apixaban"[All Fields] OR "eliquis"[All Fields] OR "apixaban s"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields] OR "pradaxa"[All Fields] OR ("dabigatran"[All Fields] AND "etexilate"[All Fields]) OR "dabigatran etexilate"[All Fields]) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields] OR "xarelto"[All Fields]) OR ("edoxaban"[Supplementary Concept] OR "edoxaban"[All Fields] OR "savaysa"[All Fields]) OR ("tissue plasminogen activator"[MeSH Terms] OR ("tissue"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "tissue plasminogen activator"[All Fields] OR "alteplase"[All Fields]) OR ("urokinase type plasminogen activator"[MeSH Terms] OR ("urokinase type"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "urokinase type plasminogen activator"[All Fields] OR "urokinase"[All Fields] OR "urokinases"[All Fields]) OR ("streptokinase"[MeSH Terms] OR "streptokinase"[All Fields] OR "streptokinases"[All Fields]) OR ("aur protein staphylococcus aureus"[Supplementary Concept] OR "aur protein staphylococcus aureus"[All Fields] OR "staphylokinase"[All Fields]) OR ("monteplase"[Supplementary Concept] OR "monteplase"[All Fields]) OR ("pamiteplase"[Supplementary Concept] OR "pamiteplase"[All Fields]) OR ("lanoteplase"[Supplementary Concept] OR "lanoteplase"[All Fields]) OR ("reteplase"[Supplementary Concept] OR "reteplase"[All Fields]) OR "tenectaplase"[All Fields] OR ("tenecteplase"[MeSH Terms] OR "tenecteplase"[All Fields]) OR ("salivary plasminogen activator alpha 1 desmodus rotundus"[Supplementary Concept] OR "salivary plasminogen activator alpha 1 desmodus rotundus"[All Fields] OR "desmoteplase"[All Fields]) OR ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields] OR

"anticoagulate"[All Fields] OR "anticoagulated"[All Fields] OR "anticoagulating"[All Fields] OR "anticoagulation"[All Fields] OR "anticoagulations"[All Fields] OR "anticoagulative"[All Fields])) AND

**COVID-19 terms:**

("coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "coronavirinae*"[All Fields] OR "coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "wuhan*"[All Fields] OR "hubei*"[All Fields] OR "Huanan"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "nCoV2019"[All Fields] OR "nCoV-2019"[All Fields] OR "COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "covid19"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "covid"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "corvid"[All Fields] OR "corvids"[All Fields] OR "HCoV-19"[All Fields] OR "HCoV19"[All Fields] OR "CoV"[All Fields] OR "2019 novel*"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "ncov"[All Fields] OR "n-cov"[All Fields] OR "SARS-CoV-2"[All Fields] OR "SARSCoV-2"[All Fields] OR "SARSCoV2"[All Fields] OR "SARS-CoV2"[All Fields] OR "SARSCov19"[All Fields] OR "SARS-Cov19"[All Fields] OR "SARS-Cov-19"[All Fields] OR "Ncovor"[All Fields] OR "ncorona*"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR ("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]))

**Appendix 2. The PRISMA diagram for atrial fibrillation.**



**SECTION IV. SYSTEMIC THROMBOSIS/THROMBOEMBOLISM**

**PICO Questions for Peripheral Artery Disease**

**PAD/Limb Ischemia terms:**

((((("extremities"[MeSH Terms] OR "extremities"[All Fields] OR "extremity"[All Fields] OR "extremity s"[All Fields]) AND ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischaemias"[All Fields] OR "ischemias"[All Fields])) OR ("peripheral arterial disease"[MeSH Terms] OR ("peripheral"[All Fields] AND "arterial"[All Fields] AND "disease"[All Fields]) OR "peripheral arterial disease"[All Fields] OR ("peripheral"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "peripheral artery disease"[All Fields] OR ("peripheral arterial disease"[MeSH Terms] OR ("peripheral"[All Fields] AND "arterial"[All Fields] AND "disease"[All Fields]) OR "peripheral arterial disease"[All Fields]) OR ("pathog dis"[Journal] OR "pad"[All Fields]) OR (("peripheral"[All Fields] OR "peripherally"[All Fields] OR "peripherals"[All Fields] OR "periphereal"[All Fields] OR "peripheric"[All Fields] OR "peripherically"[All Fields]) AND ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischaemias"[All Fields] OR "ischemias"[All Fields])) OR (("extremities"[MeSH Terms] OR "extremities"[All Fields] OR "limb"[All Fields]) AND ("ischaemia"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischaemias"[All Fields] OR "ischemias"[All Fields])))) AND

**Anticoagulation/antithrombotic/surgery terms:**

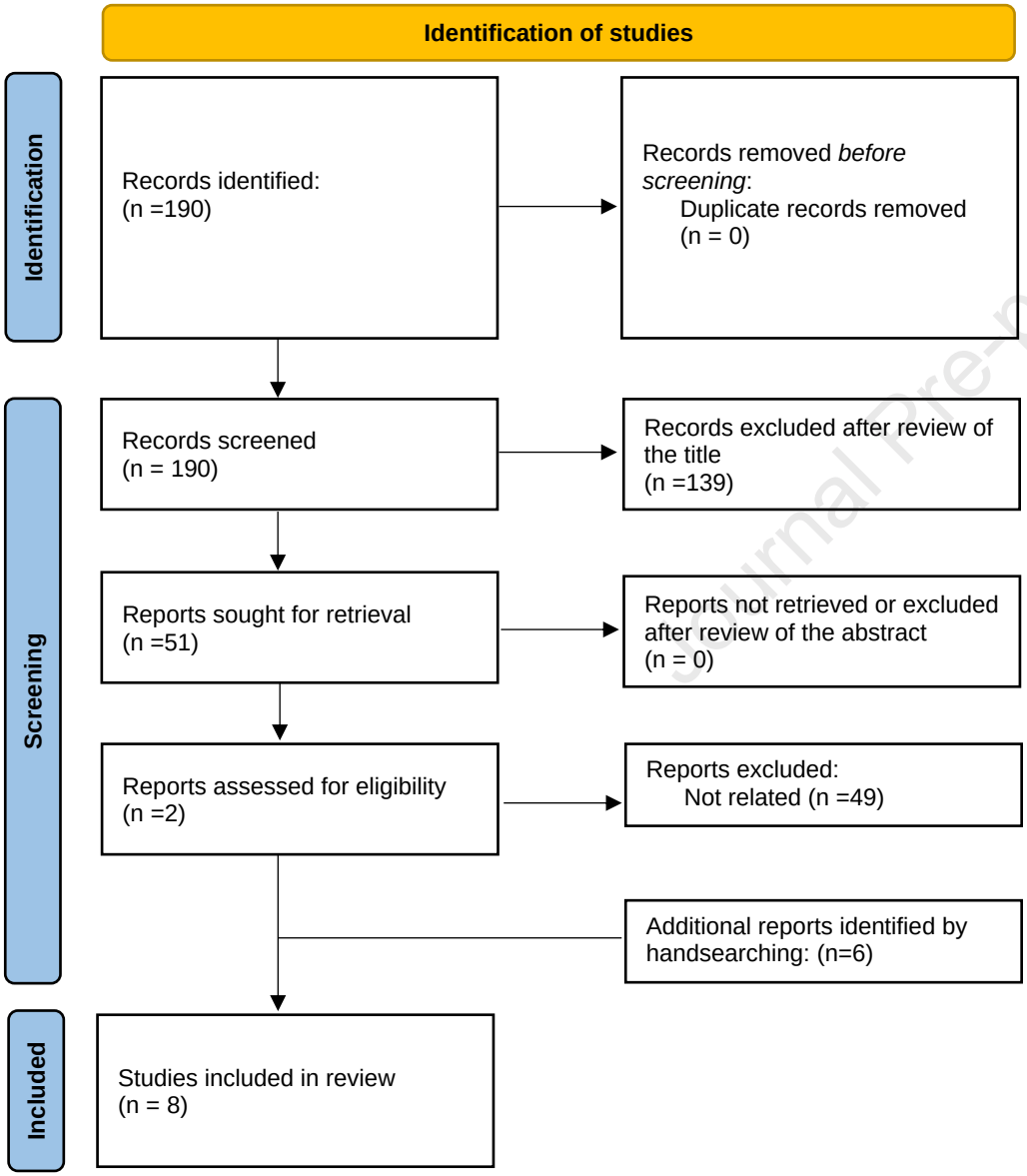
("stent s"[All Fields] OR "stentings"[All Fields] OR "stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields] OR "stented"[All Fields] OR "stenting"[All Fields] OR ("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgerys"[All Fields] OR "surgeries"[All Fields]) OR ("endarterectomy"[MeSH Terms] OR "endarterectomy"[All Fields] OR "endarterectomies"[All Fields]) OR ("revascularisation"[All Fields] OR "revascularisations"[All Fields] OR "revascularise"[All Fields] OR "revascularised"[All Fields] OR "revascularising"[All Fields] OR "revascularization"[All Fields] OR "revascularizations"[All Fields] OR "revascularize"[All Fields] OR "revascularized"[All Fields] OR "revascularizes"[All Fields] OR "revascularizing"[All Fields]) OR "dilitation"[All Fields] OR ("dilatable"[All Fields] OR "dilatated"[All Fields] OR "dilatating"[All Fields] OR "dilatation"[MeSH Terms] OR "dilatation"[All Fields] OR "dilatations"[All Fields] OR "dilate"[All Fields] OR "dilation"[All Fields] OR "dilations"[All Fields] OR "dilatative"[All Fields] OR "dilatator"[All Fields] OR "dilatators"[All Fields] OR "dilated"[All Fields] OR "dilates"[All Fields] OR "dilating"[All Fields] OR "dilator"[All Fields] OR "dilators"[All Fields]) OR

("amputate"[All Fields] OR "amputated"[All Fields] OR "amputating"[All Fields] OR "amputation"[MeSH Terms] OR "amputation"[All Fields] OR "amputations"[All Fields] OR "amputed"[All Fields]))

**COVID-19 terms:**

("coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "coronavirinae*"[All Fields] OR "coronavirus*"[All Fields] OR "coronovirus*"[All Fields] OR "wuhan*"[All Fields] OR "hubei*"[All Fields] OR "Huanan"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "nCoV2019"[All Fields] OR "nCoV-2019"[All Fields] OR "COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "covid19"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "covid"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "corvid"[All Fields] OR "corvids"[All Fields] OR "HCoV-19"[All Fields] OR "HCoV19"[All Fields] OR "CoV"[All Fields] OR "2019 novel*"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "ncov"[All Fields] OR "n-cov"[All Fields] OR "SARS-CoV-2"[All Fields] OR "SARSCoV-2"[All Fields] OR "SARSCoV2"[All Fields] OR "SARS-CoV2"[All Fields] OR "SARSCov19"[All Fields] OR "SARS-Cov19"[All Fields] OR "SARS-Cov-19"[All Fields] OR "Ncovor"[All Fields] OR "ncorona*"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR ("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]))

**Appendix 2. The PRISMA diagram for SYSTEMIC THROMBOSIS/THROMBOEMBOLISM.**



**Antithrombotic therapy in arterial thrombosis and thromboembolism in COVID-19:**

**CHEST Expert Panel Report**

**SUPPLEMENTAL FILE**

Authors: Tatjana Potpara[1,2], MD, PhD, Dominick J Angiolillo [3], MD, PhD, Behnood Bikdeli[4-7], MD, MS, Davide Capodanno[8], Oana Cole[9], Angel Coz Yataco[10], Gheorghe-Andrei Dan[11], Stephanie Harrison[12], Jonathan M. Iaccarino[13] MD MS, Lisa K. Moores[14], George Ntaios[15], MD, MSc, PhD, Gregory Y.H. Lip[16].

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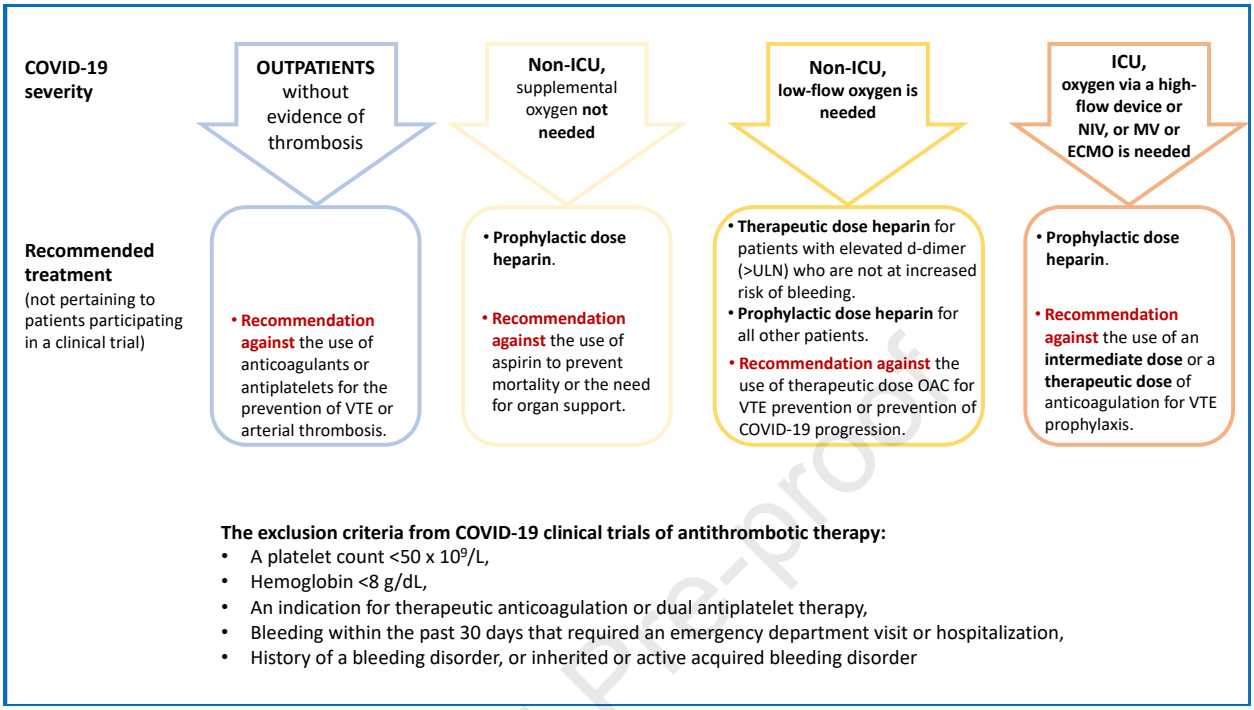
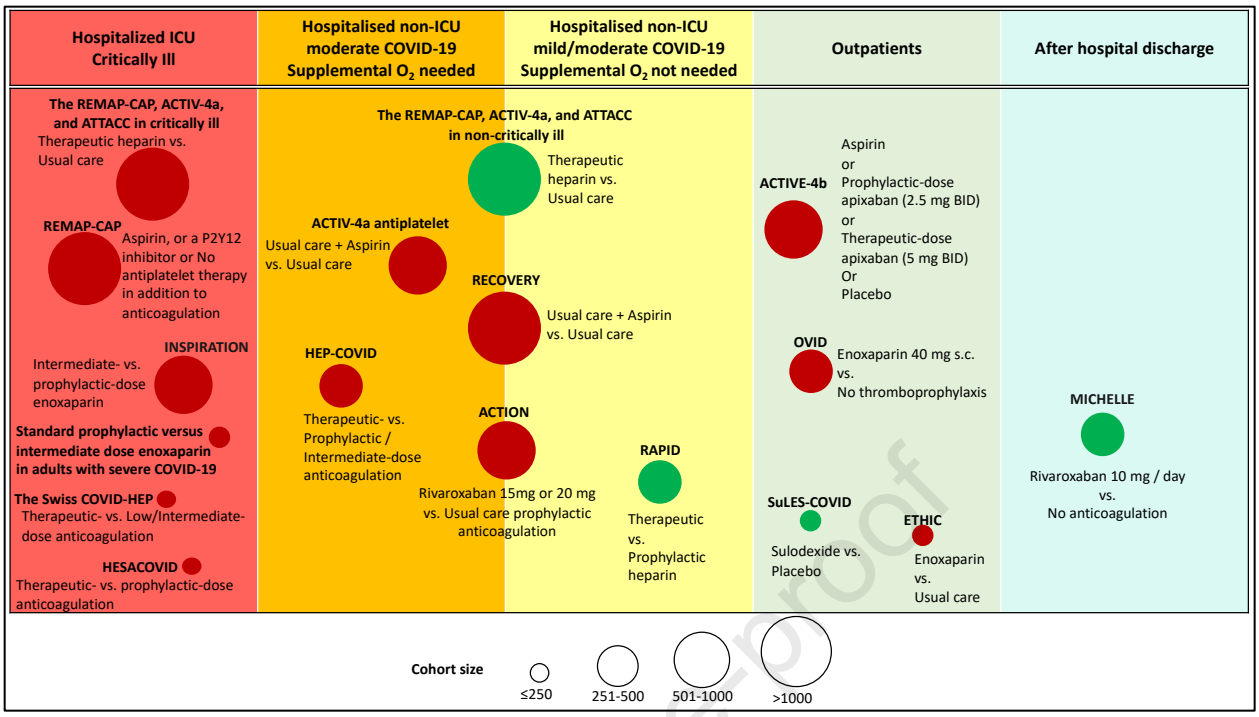
**e-Figure 1. A summary of published guidelines for the management of COVID-19-related coagulopathy and prevention of VTE[1-8] (see e-Table 1 for a more detailed summary).**




ICU, intensive care unit; VTE, venous thromboembolism; OAC, oral anticoagulant; NIV, noninvasive ventilation; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

**e-Figure 2. Published RCTs of antithrombotic therapy in patients with COVID-19 (see e-Table 1 for additional information)[9-25].**




In summary, only in *hospitalized non-ICU COVID-19 patients*, therapeutic-dose heparin reduced mortality compared with prophylactic-dose heparin, and in *post-discharge patients at high risk for VTE*, rivaroxaban 10mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis (green-colored studies).

RCT, randomized clinical trial; ICU, Intensive care unit; $O_2$, oxygen.

**e-Table 1. Published randomized clinical trials of antithrombotic therapy in patients with COVID-19.**

| **Note: An indication for therapeutic anticoagulation or dual antiplatelet therapy were among exclusion criteria in all trials below.** | |
|---|---|
| **CRITICALLY ILL/HOSPITALIZED ICU/SEVERE COVID-19 patients** | |
| **The REMAP-CAP, ACTIV-4a, and ATTACC trial:** Multiplatform, open-label RCT of therapeutic anticoagulation in critically ill, hospitalized patients with COVID-19 in 9 countries[25]. | |
| **Interventions:** | **Interpretation:** |
| Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 536).<br>Usual care (n = 567). | An initial strategy of therapeutic dose heparin was not associated with a greater probability of survival to hospital discharge or a greater number of days free of organ support compared with usual care. |

| | |
|---|---|
| | The probability of inferiority of therapeutic dose heparin to usual care thromboprophylaxis regarding these outcomes was high. |
| **The REMAP-CAP:** Effect of Antiplatelet Therapy on Survival and Organ Support–Free Days in Critically Ill Patients With COVID-19 A Randomized Clinical Trial[10]. | |
| **Interventions:**<br>Open-label aspirin (n = 565),<br>A P2Y12 inhibitor (n = 455), or<br>No antiplatelet therapy (control; n = 529),<br>in addition to anticoagulation thromboprophylaxis in critically ill adult patients | **Interpretation:**<br>Treatment with an antiplatelet agent, compared with no antiplatelet agent, had a low likelihood of providing improvement in the number of organ support-free days within 21 days. |
| **The INSPIRATION trial:** Open-label RCT of intermediate-dose versus prophylactic-dose anticoagulant in patients in intensive care with COVID-19 in Iran[11]. | |
| **Interventions:**<br>Intermediate-dose anticoagulation: enoxaparin 1 mg/kg daily (n = 276).<br>Prophylactic-dose anticoagulation (n = 286). | **Interpretation:**<br>Intermediate-dose anticoagulation did not significantly reduce VTE and ATE, the need for ECMO, or mortality.<br>Although the difference was nonsignificant, patients who received intermediate-dose anticoagulation had more bleeding events than patients who received usual care. |
| **Standard versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial[12]** | |
| **Interventions:**<br>(In COVID-19 patients requiring admission to ICU and/or having laboratory evidence of coagulopathy)<br>Intermediate dose enoxaparin (n = 87).<br>Standard prophylactic dose enoxaparin (n = 86). | **Interpretation:**<br>There was no significant difference in the safety or efficacy of standard prophylactic dose vs. weight-adjusted intermediate dose enoxaparin in preventing death or thrombosis at 30 days in hospitalized patients with severe COVID-19. |
| **Therapeutic anticoagulation to prevent thrombosis, coagulopathy, and mortality in severe COVID-19: The Swiss COVID-HEP randomized clinical trial[13].** | |
| **Interventions:**<br>Therapeutic anticoagulation versus low-dose anticoagulation in acutely ill participants or intermediate-dose anticoagulation in critically ill participants, with enoxaparin or unfractionated heparins in acutely ill medical COVID-19 patients with D-dimer >1000 ng/ml or critically ill COVID-19 patients. (n=159). | **Interpretation:**<br>Among patients with severe COVID-19 treated with corticosteroids and with exclusion of pulmonary embolism at hospital admission for most, risks of mortality, thrombotic outcomes, and DIC were low at 30 days. The lack of benefit of therapeutic anticoagulation was too imprecise for definite conclusions. |
| **The HESACOVID trial: Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial[14].** | |

| **Interventions:** | **Interpretation:** |
|---|---|
| Therapeutic enoxaparin (n=10) vs.<br>Standard anticoagulant thromboprophylaxis (n=10)<br>in COVID-19 patients requiring mechanical ventilation. | Therapeutic enoxaparin improves gas exchange and decreases the need for mechanical ventilation in severe COVID-19. |
| **HOSPITALIZED NON-ICU/MODERATE COVID-19/SUPPLEMENTARY $O_2$ NEEDED** | |
| **The ACTIVE-4a trial: Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: A randomized clinical trial[15]** | |
| **Interventions:** | **Interpretation:** |
| Usual care plus aspirin 150 mg/day (n = 7351).<br>Usual care (n = 7541). | The use of a P2Y12 inhibitor in addition to a therapeutic dose heparin did not result in an increased odds of improvement in organ support-free days within 21 days during hospitalization, compared with a therapeutic dose heparin only in non-critically ill patients hospitalized for COVID-19.<br>Major bleeding events were infrequent and comparable between the study arms. |
| **The HEP-COVID trial:** Open-label RCT of therapeutic heparin in high-risk, hospitalized patients with COVID-19 in the United States[16] | |
| **Interventions:** | **Interpretation:** |
| Therapeutic LMWH until hospital discharge or primary endpoint met (n = 129).<br>Usual care of prophylactic or intermediate-dose LMWH until hospital discharge or primary endpoint met (n = 124). | Compared to usual care, therapeutic LMWH reduced the incidence of VTE, ATE, and death.<br>For patients not in the ICU, therapeutic LMWH significantly reduced thrombotic events and did not increase major bleeding. |
| **The REMAP-CAP, ACTIV-4a, and ATTACC:** Multiplatform, open-Label RCT of therapeutic anticoagulation in non-critically ill, hospitalized patients with COVID-19 in 9 countries[9]. | |
| **Interventions:** | **Interpretation:** |
| Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 1190).<br>Usual care (n = 1054). | Therapeutic heparin increased organ support-free days and decreased the number of patients requiring organ support.<br>Therapeutic heparin did not significantly affect hospital length of stay or the number of major thrombosis events or deaths.<br>Major bleeds occurred 1% more frequently in therapeutic arm. |
| **The RECOVERY trial:** Aspirin in patients admitted to hospital with COVID-19: A randomized, controlled, open-label, platform trial[17] | |
| **Interventions:** | **Interpretation:** |
| Usual care plus aspirin 150 mg/day (n = 7351).<br>Usual care (n = 7541). | Aspirin use was not associated with reduction in 28-day mortality or the risk of progression to invasive mechanical ventilation or death but was associated with a small |

| | |
|---|---|
| | increase in the rate of being discharged alive within 28 days. |
| **The ACTION trial:** Open-label RCT of therapeutic oral anticoagulation (Rivaroxaban) in hospitalized patients with COVID-19 in Brazil[18] | |
| **Interventions:**<br>Therapeutic anticoagulation for 30 days:<br>Rivaroxaban 15 mg or 20 mg daily; if clinically unstable, enoxaparin 1 mg/kg twice daily or UFH (n = 311).<br>Usual care prophylactic anticoagulation with enoxaparin or UFH during hospitalization (n = 304). | **Interpretation:**<br>Compared with usual care, therapeutic rivaroxaban did not reduce mortality, hospital duration, oxygen use duration, or thrombosis.<br>Patients who received therapeutic rivaroxaban had more clinically relevant nonmajor bleeding than those who received usual care.<br>The longer duration of therapy in the rivaroxaban arm may have influenced the difference in bleeding events. |
| **HOSPITALIZED NON_ICU/MILD-to-MODERATE COVID-19/SUPPLEMENTAL $O_2$ NOT NEEDED** | |
| **The RAPID trial:** Open-label RCT of therapeutic heparin in moderately ill, hospitalized patients with COVID-19 in 6 countries[19]. | |
| **Interventions:**<br>Therapeutic UFH or LMWH for 28 days or until discharge or death (n = 228).<br>Prophylactic UFH or LMWH for 28 days or until discharge or death (n = 237). | **Interpretation:**<br>Compared to prophylactic heparin, therapeutic heparin reduced mortality (a secondary endpoint) but had no effects on the composite primary endpoint of ICU admissions or the need for NIV or MV, or death up to 28 days.<br>Major bleeding and VTE were not different in the therapeutic and prophylactic arms. |
| **OUTPATIENTS WITH COVID-19** | |
| **The ACTIV 4b trial:** Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: A randomized clinical trial[20]. | |
| **Interventions:**<br>(In symptomatic but clinically stable outpatients with COVID-19 for 45 days)<br>Aspirin 81 mg/day (n = 164)<br>Prophylactic-dose apixaban 2.5 mg twice daily (n = 165)<br>Therapeutic-dose apixaban 5 mg twice daily (n = 164)<br>Placebo (n = 164) | **Interpretation:**<br>Treatment with aspirin or apixaban did not reduce a composite of all-cause mortality, venous and arterial thrombosis including stroke and myocardial infarction, or hospitalization for cardiovascular or pulmonary cause, compared with placebo in symptomatic clinically stable outpatients with COVID-19. |
| **The OVID trial:** Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19: a randomized, open-label, parallel-group, multicenter, phase 3 trial[21]. | |

| **Interventions:** | **Interpretation:** |
|---|---|
| Subcutaneous enoxaparin 40 mg once daily (n=234) for 14 days versus standard of care (no thromboprophylaxis, n=238) in outpatient patients ≥50 years with acute COVID-19 with respiratory symptoms or body temperature higher than 37·5°C. | Thromboprophylaxis with enoxaparin does not reduce early hospitalizations and deaths. |
| **The SuLES-COVID trial:** Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomized Controlled Trial[22]. | |
| **Interventions:** | **Interpretation:** |
| Participants with high risk for severe clinical progression received sulodexide (oral 1,000 LRU/d; n=124) or placebo (n=119) for 21 days. | Treatment with sulodexide, when provided within 3 days of clinical onset, improved their clinical outcomes. Although the results should be confirmed. |
| **The ETHIC trial:** Thromboprophylactic low-molecular-weight heparin versus standard of care in unvaccinated, at-risk outpatients with COVID-19: an open-label, multicenter, randomized, controlled, phase 3b trial[23]. | |
| **Interventions:** | **Interpretation:** |
| Subcutaneous enoxaparin for 21 days (40 mg once daily if they weighed <100 kg and 40 mg twice daily if they weighed ≥100 kg); n=105 or standard of care (n=114) in participants ≥30 years who had not received a COVID-19 vaccine and had symptomatic, confirmed COVID-19 in the outpatient setting plus at least one risk factor for severe disease within 9 days of symptom onset. | Prophylaxis with low-molecular-weight heparin had no benefit for at-risk outpatients with COVID-19. |
| **AFTER HOSPITAL DISCHARGE** | |
| **The MICHELLE trial:** Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalization for COVID-19: An open-label, multicenter, randomized, controlled trial[24]. | |
| **Interventions:** | **Interpretation:** |
| (At hospital discharge, following the in-hospital standard dose heparin thromboprophylaxis in COVID-19 patients at increased risk for VTE)<br>Rivaroxaban 10 mg/day (n = 160).<br>No anticoagulation (n = 160). | In patients at high risk for VTE discharged after hospitalization for COVID-19, thromboprophylaxis with rivaroxaban 10mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis. |

COVID-19, Coronavirus disease 2019; ICU, intensive care unit; RCT, randomized clinical trial; UFH, unfractionated heparin; LMWH, low molecular weight heparin; VTE, venous thromboembolism; ATE, arterial thromboembolism; ECMO, extracorporeal membrane oxygenation; DIC, disseminated intravascular coagulation; NIV, noninvasive ventilation; MV, mechanical ventilation.

**SECTION I. ACUTE CORONARY SYNDROME**

From the search results, n=92 citations were screened, and n=6 addressing ACS in patients with COVID-19 were identified. Studies relevant for the specific research question are shown in Tables 2 and 3.

**e-Table 2. Studies of relevance for patients with ACS and COVID-19.**

| Study | Year | Design | Cohort size | Study Aim | Main endpoint(s) | Main finding(s) |
|---|---|---|---|---|---|---|
| Russo et al.[26] | 2020 | Observational | N=192 | To evaluate the potential association between antithrombotic therapy and ARDS or in-hospital mortality. | ARDS, death during hospitalization | Both unadjusted and adjusted regression analyses showed no difference in the risk of ARDS at admission, or death during hospitalization, between patients treated or not with antiplatelets or anticoagulants.<br>The adjusted RRs during hospitalization between patients who received antecedent antiplatelet or anticoagulant agents vs. those who did not:<br>A) For antiplatelet drugs<br>aRR 0.58, 95% CI 0.38-1.14, p=0.17 for ARDS,<br>aRR 0.51, 95% CI 0.21-1.15, p=0.11 for death<br>B) For anticoagulants<br>aRR 1.24, 95% CI 0.56-2.08, p=0.47 for ARDS,<br>aRR 1.15, 95% CI 0.29-2.57, p=1.00 for death. |
| Rashid et al.[27] | 2021 | Observational | N=517 | To characterize the presenting profile and outcomes of patients hospitalized with ACS and COVID-19 infection. | Use of DAPT | Patients with COVID-19 were less likely to receive dual antiplatelet medication (76.3% vs 88.0%; p<0.001). |

ACS, acute coronary syndromes; ARDS, acute respiratory distress syndrome; aRR, adjusted Relative Risk; CI, Confidence Interval; DAPT, dual antiplatelet therapy.

**e-Table 3. Studies addressing stent thrombosis in COVID-19 patients.**

| Study, author(s) | Year | Design | Cohort size | Study aim | Main endpoints | Main findings |
|---|---|---|---|---|---|---|
| Elkholy et al.[28] | 2021 | Case report | 1 | To present subacute ST despite adequate DAPT | Explore reasons for subacute ST in COVID-19 patient on adequate DAPT | COVID-19-related thrombogenicity likely to be the cause of subacute ST |
| Prieto-Lobato et al.[29] | 2020 | Case series | 4 | Presentation of 1 acute and 3 delayed ST cases | Explore a case series of ST and the investigation into possible mechanisms | SARS-CoV-2 hypercoagulable state may lead to increased incidence of ST in the presence of other biological and mechanical risk factors |
| Tan et al.[30] | 2021 | Multicenter observational cohort study | 111 | To describe the incidence of arterial and venous thrombotic events in ICU COVID-19 patients in Singapore | Incidence and prevalence of thrombotic and bleeding events in ICU COVID-19 patients | Higher rate of arterial (9.9%, 95%CI: 5.6 – 16.9%) rather than venous (1.8%, 95% CI: 0.5-6.3%) thrombotic events in critically ill COVID-19 patients; Throughout hospitalization, venous thrombotic events were 6.3% (95%CI: 3.1-12.5%), versus arterial, 11.7% (95%CI: 7-19%) |
| Rapkiewicz et al.[31] | 2020 | Case series | 7 | Provide mechanistic insights into hypercoagulability seen with | Present findings from autopsies of COVID-19 patients from a New York | Platelet-rich thrombi in the pulmonary, hepatic, renal, and cardiac |

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| | | | | COVID-19 disease | academic medical center | microvasculature at autopsy of COVID-19 patients, regardless of the coagulation status |

ST, stent thrombosis; DAPT, dual antiplatelet therapy; ICU, intensive care unit; CI, confidence interval.

**SECTION II. STROKE/TIA**

From the search results, 571 citations were screened, and 43 addressing stroke/TIA in patients with COVID-19 were identified. Studies relevant for the specific research question are shown in Tables 4 and 5.

**e-Table 4. Systematic reviews showing that patients with COVID-19 and previous cerebrovascular disease have higher risk of COVID-19 severity and mortality.**

| Study, author(s) | Year | Design | Cohort size | Study aim | Main endpoints | Main findings |
|---|---|---|---|---|---|---|
| Fang et al.[32] | 2020 | Systematic review and meta-analysis (61 articles included) | 5756 | To evaluate the associations of epidemiological, comorbidity factors with the severity and prognosis of COVID-19 | Severity and prognosis of COVID-19 | Cerebrovascular disease was associated with higher severity of COVID-19 (RR: 2.77, 95%CI:1.70-4.52) and higher mortality (RR: 4.55, 95%CI:2.60-7.94) |
| Noor et al.[33] | 2020 | Meta-analysis (58 articles included) | 6069 | To find the prevalence of mortality among hospitalized COVID-19 infected patients and associated risk factors for death | Mortality | Cerebrovascular disease was associated with higher mortality (RR: 2.75, 95%CI:1.54-4.89) |

COVID-19, Coronavirus disease 2019; RR, Relative Risk; CI, Confidence Interval.

**e-Table 5. Studies assessing outcomes after endovascular treatment in COVID-19 patients.**

| Study, author(s) | Year | Design | Cohort size | Study aim | Main endpoints | Main findings |
|---|---|---|---|---|---|---|
| Marto JP, et al. [European Stroke Journal 2022, Vol. 7(1S) 3–545, abstr] | 2022 | Multicenter cohort study | 15128 (853 patients with COVID-19 and 14275 contemporaneous non-COVID-19 patients who were treated with intravenous thrombolysis or EVT) | To evaluate the safety and disability outcomes of revascularization treatments in patients with ischemic stroke and COVID-19 | - symptomatic intracerebral hemorrhage<br>- symptomatic subarachnoid hemorrhage<br>- mortality at 3 months<br>- 3-month modified Rankin score | Patients with COVID-19 had higher rate of symptomatic hemorrhagic transformation (OR 1.58; 95% CI 1.18–2.12), any symptomatic intracranial hemorrhage (OR 1.60; 95% CI 1.32–1.94), 24-hour mortality (OR 2.45; 95% CI 2.04–2.93), 3-month mortality (OR 1.87; 95% 1.44–2.44), and worse 3-month modified Rankin score (OR 1.49; 95% 1.22–1.82) |
| Al-Smadi et al.[34] | 2021 | Systematic review and meta-analysis | 65 | To assess outcomes of endovascular thrombectomy for large vessel occlusions in COVID-19 patients | - TICI ≥ 2b<br>- Re-occlusion of the initially affected artery<br>- post-procedural hemorrhage | - TICI ≥ 2b was reported in 83.1% (n = 54) of cases<br>- The rate of early cerebral re-occlusion was 8.2%<br>- the rate of post-procedural hemorrhage was 4.1% |

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| Sweid et al.[35] | 2020 | Case series | 16 | To present a case series of COVID-19 patients with acute cerebrovascular pathologies | - TICI ≥ 2b<br>- symptomatic intracranial hemorrhage | - TICI ≥ 2b was reported in all cases<br>- the rate of symptomatic intracranial hemorrhage was 13.6% |
| Pezzini A, et al.[36] | 2021 | Case series | 18 | To report outcomes of COVID-19 patients who underwent reperfusion therapies for acute ischemic stroke | - Complete recanalization<br>- symptomatic intracranial hemorrhage | - 55.6% of patients achieved complete recanalization<br>- the rate of symptomatic intracranial hemorrhage was 11.1% |
| Cagnazzo F, et al.[37] | 2021 | Cohort study | 93 | To study early outcomes after mechanical thrombectomy in patients with COVID-19 | - Successful / complete recanalization<br>- symptomatic intracranial hemorrhage | - The rates of successful and complete recanalization were 79.6% and 43%, respectively<br>- the rate of symptomatic intracranial hemorrhage was 5.4% |
| Dmytriw A, et al.[38] | 2022 | Cross sectional, international multicenter retrospective study | 697 patients with acute LVO (302 COVID-19; 395 non-COVID-19) | To determine if a significant association exists between COVID-19 status with revascularization and | Co-primary outcomes were: 1) optimal revascularization defined as modified Thrombolysisin Cerebral Infarction (mTICI) grade 3; 2) unfavorable | - procedure-related complication rate was higher among COVID-19 patients (26.6% vs. 10.0%; p<0.001)<br>- No significant difference in |

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| | | | | functional outcomes following thrombectomy for large vessel occlusion, after adjustment for potential confounding factors | functional outcome at discharge and 90 days defined as modified Rankin Scale (mRS) score 3-6; 3) mortality at 90 days. Secondary outcomes were: 1) symptomatic intracerebral hemorrhage (sICH) defined as reduction in the National Institute of Health Stroke Scale (NIHSS) by four points in association with any hemorrhage, at the judgment of the treating clinician; 2) NIHSS 24 hours following MT. | sICH (6.6% vs. 5.6%; p=0.683)<br>- Poor functional outcome (mRS 3-6) at discharge was more frequent in the COVID-19 group (37.1% vs. 9.6%; p<0.001)<br>- favorable functional outcome (mRS 0-2) at 90-day follow-up was less frequent in COVID-19 vs. non-COVID-19 (10.6% vs 59.0%; p< 0.001) patients<br>- mortality rate was higher in the COVID-19 group (42.0% vs. 19.1; p≤0.001) |

COVID-19, Coronavirus disease 2019; RR, Relative Risk; CI, Confidence Interval; TICI, Thrombolysis in cerebral infarction scale.

**SECTION III. ATRIAL FIBRILLATION**

From the search results, 84 citations were screened. Of these, three case-series[39-41] and three single-center or multicenter observational studies were identified as addressing the research question[42-44]. No RCTs were identified which addressed the research question. Studies relevant for the specific research question are shown in Supplemental Table S6.

**e-Table 6. Studies assessing outcomes for patients COVID-19 and atrial fibrillation receiving anticoagulation treatment.**

| Study, author(s) | Year | Design | Cohort size | Study aim | Main endpoints | Main findings |
|---|---|---|---|---|---|---|
| Denas, et al.[42] | 2021 | Cohort study | 4697 (559 in receiving anticoagulation for AF and 559 not receiving anticoagulation after propensity-score matching). | To compare outcomes among people aged ≥65 years, who were receiving anticoagulation for AF and a propensity score matched group of patients who were not receiving anticoagulation. | - All-cause mortality<br>- Hospital admission<br>- ICU admission | All-cause mortality was significantly lower among patients receiving anticoagulation (26.5% vs. 32.2%; risk ratio 0.82, 95%CI 0.68-0.99), but on time-to-event analysis the risk of all-cause mortality was not statistically significantly lower (HR 0.81, 95%CI 0.65-1.01, p = 0.054).<br>There was no difference in risk of hospital admission (risk ratio 1.01, 95%CI 0.92-1.10) and intensive care unit admission (risk ratio 1.06, 95%CI 0.72-1.56). |
| Flam, et al.[43] | 2021 | Cohort study | 459,402 (103,703 NOAC users with AF; 36,875 with AF not using NOACs; 355,699 non- | To assess whether ongoing NOAC use was associated with outcomes | - Hospital admission<br>- Composite of ICU admission and mortality | - Compared to people with AF or people with major CVD not receiving NOACs, NOAC use was not associated with reduced risk |

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| | | | users with major CVD) | with laboratory-confirmed COVID-19. | | of hospital admission for COVID-19 (adjusted HR [95% confidence interval] 1.00 [0.75-1.33] and aHR 0.94 [0.80-1.10], or ICU admission or death due to COVID-19 (aHRs 0.76 [0.51-1.12], and 0.90 [0.71-1.15], respectively). |
| Fumagalli, et al.[44] | 2022 | Cohort study | 806 | To evaluate mortality-related factors in AF patients aged ≥60 years in-hospital with COVID-19. | - In-hospital mortality | - Use of VKAs or NOACs at admission or persistence of OAC during hospitalization was associated with lower odds of in-hospital mortality (ORs [95% confidence intervals]: 0.16 [0.03-0.84] for VKAs vs no OAC, 0.22 [0.08-0.56] for NOACs vs no OAC and 0.05 [0.01-0.24] for persistence of OAC vs OAC discontinuation during hospitalization, respectively). |

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| Mazzitelli, et al.[41] | 2020 | Case series | 3 | To report three cases of major bleeding which occurred in patients with COVID-19 prescribed anticoagulant treatment for paroxysmal AF | - Major bleeding | - Major bleeding reported in all cases |
| Al-Abbas, et al.[39] | 2021 | Case study | 1 | To report the case of a patient with COVID-19 and new-onset AF | - | - |
| Di Tano, et al.[40] | 2020 | Case study | 1 | To report the case of a patient with chronic atrial fibrillation who was hospitalized for severe COVID-19 pneumonia. | - | - |

AF, atrial fibrillation; CI, Confidence Interval; COVID-19, Coronavirus disease 2019; CVD, cardiovascular disease; HR, hazard ratio; ICU, intensive care unit; NOAC, non-vitamin-K-antagonist oral anticoagulant; OR, odds ratio; VKA, vitamin-K-antagonist.

**SECTION IV. SYSTEMIC THROMBOSIS/THROMBOEMBOLISM**

From the search results, n=190 citations were screened, and n=8 addressing systemic thrombosis/thromboembolism in patients with COVID-19 were identified. Studies relevant for the specific research question are shown in Supplemental Table S7.

**e-Table 7. Studies assessing outcomes after endovascular treatment in COVID-19 patients**

| Study, author(s) | Year | Design | Cohort size | Study aim | Main endpoints | Main findings |
|---|---|---|---|---|---|---|
| Goldman et al.[45] | 2020 | Retrospective propensity-matched analysis | 48 patients (16 with COVID-19 and 32 without COVID-19) | To assess the severity of clot burden in patients with versus without COVID-19 who have lower extremity arterial thrombosis assessed by CT angiography of the abdomen with lower extremity run-off | Thrombus burden, assessed by three imaging-based scoring systems | Patients with COVID-19 and lower extremity arterial thrombosis, had a larger clot burden (P<0.001) and worse clinical outcomes compared with those without COVID-19. |
| Li et al.[46] | 2020 | Retrospective observational study | 65 patients (15 included during the pandemic, and 50 from the pre-COVID-19 period) | To assess the severity of illness at the time of surgery in patients with peripheral arterial disease prior to versus early during the COVID-19 pandemic | Rutherford classification of peripheral arterial disease and perioperative complications | Fewer patients presented during the pandemic, but a larger proportion of them presented with Rutherford class 4-6 (P=0.04), and had perioperative complications (P=0.02) compared with those who presented prior to the pandemic |
| Bellosta et al.[47] | 2020 | Single-center Retrospective observational study | 20 patients with COVID-19 and acute limb events | To describe the clinical presentation and outcomes of patients with COVID-19 and acute limb events | No pre-specified endpoints. Clinical presentation, therapies, and outcomes were described | The relative frequency of cases with acute limb events was higher than historical controls. Of 17 patients undergoing revascularization, success was achieved in only 12 cases, which was less than the expected success based on historical experience. |
| Smolderen et al.[48] | 2021 | Retrospective observational study from large health system in the United States | 3830 patients with COVID-19 (including 693 with history of peripheral arterial disease) | To assess the association between peripheral arterial disease and outcomes of patients with COVID-19 | Mortality and major adverse cardiovascular events | Peripheral arterial disease was a predictor for both mortality and major adverse cardiovascular events in bivariate analysis. Results were consistent multiple sets of multivariable adjusted models. |
| Jongkind et al.[49] | 2022 | Scoping review | 114 relevant articles (298 patients for | To review the clinical studies for management of acute | NA | The evidence was slim with most of the publications being case |

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| | | | mortality analysis) | limb ischemia in patients with COVID-19 | | reports or small case series. The authors concluded that most recommendations from pre-COVID-19 era should be continued with three revisions, to consider appropriate testing and protection against COVID-19, to extend CT angiography images to involve the entire aorta and iliac vessels, and to prefer local/regional anesthesia for procedures. |
| Attisani et al.[50] | 2021 | Systematic review | 36 articles with a total of 194 patients | To assess the clinical characteristics and 30-day outcomes of patients with COVID-19 who developed acute limb events | Location of ischemia, treatment patterns, 30-day mortality | Most patients were men, with a median age of 60 years. Many of them lacked the traditional risk factors and were already on some form of antiplatelet therapy. Technical success rate for revascularization was lower than expected (68%) and mortality rate was as high as 35%. |
| Vo et al.[51] | 2022 | retrospective multicenter observational study | 26 patients with COVID-19 and acute arterial thrombosis | To assess patient characteristics, treatment, and outcomes of patients with COVID-19 and peripheral arterial thrombosis | Patient characteristics, treatment patterns, mortality | predominant presentation was a lower limb ischemia (N=23). Limb salvage rate was lower than in non-COVID-19 patients. Overall mortality rate was 31%. |
| Barco et al.[52] | 2021 | Single center retrospective study | 22 patients with COVID-19 and acute limb-threatening ischemia | To assess the treatment pattern and clinical outcomes in patients with COVID-19 and acute limb-threatening ischemia | Risk of amputation after revascularization, mortality | 18 patients underwent surgical revascularization, and 4 underwent percutaneous revascularization. Three patients died from acute respiratory distress syndrome. There were 2 major and 1 minor |

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