Evidence Brief: Anticoagulation for Hospitalized Adults with COVID-19

March 2022

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

Recommended citation: Mackey K, Young S, Oakes M, Arastu A, Maldonado E, Anderson J, Parr NJ. Evidence Brief: Anticoagulation for Hospitalized Adults with COVID-19. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-199; 2022.

AUTHORS

Author roles, affiliations, and contributions to the present report (using the CRediT taxonomy) are summarized in the table below.

Author	Role and Affiliation	Report Contribution
Katherine Mackey, MD, MPP	Clinician Investigator, Evidence Synthesis Program (ESP) Coordinating Center, Portland VA Health Care System Portland, OR	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Supervision
Sarah Young, MPH	Research Associate, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Investigation, Methodology, Writing – original draft, Writing – review & editing, Project administration
Michael Oakes, MD	Investigator, Department of Internal Medicine, Oregon Health & Science University (OHSU) Portland, OR	Investigation
Asad Arastu, MD	Investigator, Department of Internal Medicine, OHSU Portland, OR	Investigation
Edward Maldonado, MD	Investigator, Department of Internal Medicine, OHSU Portland, OR	Investigation
Johanna Anderson, MPH	Senior Research Associate, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Methodology, Investigation, Supervision
Nicholas J. Parr, PhD, MPH	Associate Director, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Supervision

This report was prepared by the Evidence Synthesis Program Coordinating Center located at the **Portland VA Health Care System**, directed by Mark Helfand, MD, MPH, MS and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the VA Health Services Research and Development Service (HSR&D) for an Evidence Brief on the benefits and harms of antithrombotic treatments for adults with COVID-19 to inform Veterans Health Administration (VHA) clinical policies and practices.

ACKNOWLEDGMENTS

The authors are grateful to Kathryn Vela, MLIS for literature searching; Payten Sonnen for data abstraction efforts and editorial and citation management support; Mark Helfand, MD, MPH, MS and Devan Kansagara, MD, MCR for critical feedback on drafts of the present report; and the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Joe Francis, MD
Chief Improvement & Analytics Officer
VA Central Office

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix D in Supplemental Materials for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of

their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

TABLE OF CONTENTS

TABLES AND FIGURES

EXECUTIVE SUMMARY

Key Findings

- Intermediate-dose anticoagulation (doses between those used for prophylaxis and treatment of diagnosed thrombotic disease) may be associated with a small mortality benefit compared to standard thromboprophylaxis among hospitalized adults with COVID-19 but does not appear to reduce the risk of thrombotic events. In contrast, therapeutic-dose anticoagulation may reduce the risk of thrombotic events but does not appear to reduce mortality. Our confidence in these findings is low, primarily due to study methodological inconsistencies and limitations.
- COVID-19-specific evidence on bleeding risk is limited but sufficient to conclude that higher doses of anticoagulation are likely associated with a dose-dependent increase in bleeding risk among hospitalized adults with COVID-19.
- Important gaps exist in the evidence regarding anticoagulation use among hospitalized adults with COVID-19. No studies have directly compared intermediate and therapeutic-dose anticoagulation among adults with different disease severity. Some trends in the evidence suggest that adults with less severe disease may benefit from higher anticoagulation doses but whether mortality benefits, if any, outweigh potential harms remains unclear. Future research is needed to better understand if and when higher-dose anticoagulation is beneficial.

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease COVID-19, can lead to profound inflammation and a prothrombotic state. At the beginning of the pandemic, observational data and anecdotal reports on the risk of thrombotic complications in COVID-19 prompted some clinicians, hospitals, and health systems to modify their approaches to prophylactic anticoagulation in the inpatient setting by using higher than standard doses. Several randomized controlled trials (RCTs) have recently been published, adding to extensive observational data from the first 18 months of the pandemic. We aimed to synthesize available evidence on the benefits and harms of intermediate-dose and therapeutic-dose anticoagulation compared to standard thromboprophylaxis among hospitalized adults with COVID-19 and to examine whether benefits and harms vary by medication, patient characteristics, or disease factors.

Background

The Evidence Synthesis Program Coordinating Center is responding to a request from Department of Veterans Affairs Health Services Research and Development Service (HSR&D) for an Evidence Brief on the benefits and harms of anticoagulation strategies among adults with COVID-19. Findings from this Evidence Brief will be used to inform VA clinical policies and practices.

Methods

To identify studies, we searched MEDLINE® and the WHO Global Literature on Coronavirus Disease database, and other sources through October 12, 2021. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See the Methods section and our PROSPERO protocol for full details of our methodology.

We included 2 RCTs and 23 cohort studies of intermediate-dose anticoagulation and 6 RCTs and 22 cohort studies of therapeutic-dose anticoagulation. Table ES-1 presents descriptions of the intervention and comparison conditions.

Table ES-1. Descriptions of Interventions and Comparator

Intervention	Definition	Example
Intermediate-dose anticoagulation	Anticoagulation doses in between therapeutic doses and standard thromboprophylaxis	Enoxaparin 40mg twice daily
Empiric therapeutic-dose anticoagulation	Medications and doses typically used for treatment of diagnosed thrombotic disease	Enoxaparin 1mg/kg twice daily
Comparator	**Definition**	**Example**
Standard thromboprophylaxis	Medications and doses considered standard of care for thromboprophylaxis among adults hospitalized with medical illness	Enoxaparin 40mg daily

Overall, we synthesized studies using a "best evidence" approach, meaning that we focused on the studies most germane to our Key Questions and of the highest methodological quality. Reported results for mortality and bleeding outcomes were synthesized quantitatively using random-effects meta-analyses, while results for thrombotic events were narratively synthesized due to inconsistencies in outcome definitions and other study features. Table ES-2 summarizes findings. Intermediate-dose anticoagulation does not appear to reduce the risk of thrombotic events but may provide a small mortality benefit compared to standard thromboprophylaxis. In contrast, therapeutic-dose anticoagulation may reduce the risk of thrombotic events compared to standard thromboprophylaxis but does not appear to offer a mortality benefit. Our confidence in these findings is low due to study methodological limitations, with the most notable limitation being that some participants did not receive the same anticoagulation dose as their assigned group and/or were exposed to different doses during the study period. Although mostly consistent, results were imprecise for some outcomes.

Table ES-2. Summary of Findings

Outcome	Intervention	Evidence	Summary of Findings
Mortality	Intermediate-dose anticoagulation	2 RCTs 15 Cohorts	Low SOE: Mortality risk may be reduced
	Therapeutic-dose anticoagulation	6 RCTs 18 Cohorts	Low SOE: Mortality risk may be similar
Thrombotic events	Intermediate-dose anticoagulation	2 RCTs 18 Cohorts	Low SOE: Risk of thrombotic events may be similar
	Therapeutic-dose anticoagulation	6 RCTs 10 Cohorts	Low SOE: Risk of thrombotic events may be reduced
Bleeding events	Intermediate-dose anticoagulation	2 RCTs 16 Cohorts	Low[a] SOE: Bleeding risk is increased
	Therapeutic-dose anticoagulation	6 RCTs 12 Cohorts	Low[a] SOE: Bleeding risk is increased

Note. [a]Low confidence in evidence specific to COVID-19.
Abbreviation. SOE=strength of evidence.

In terms of harms, when considered alongside extensive pre-pandemic evidence linking higher anticoagulation doses to increased bleeding risk, available COVID-19-specific evidence is sufficient to conclude that higher doses of anticoagulation are likely associated with a dose-

dependent increase in bleeding risk among hospitalized patients with COVID-19. This risk is likely comparable to bleeding risks with anticoagulation among adults hospitalized with other medical illnesses.

We observed a trend across studies suggesting that mortality benefits of higher anticoagulation doses, if any, may be more likely in adults with lower disease severity. However, no RCT to date has directly compared intermediate-dose anticoagulation to therapeutic-dose anticoagulation among adults with both non-critical and critical illness. Therefore, questions remain regarding whether possible benefits of higher anticoagulation doses are due to the dose itself or timing. In other words, evidence to date has not addressed whether intermediate-dose anticoagulation initiated earlier in the disease course (*ie*, among those with moderate disease) would confer equivalent benefits as therapeutic-dose anticoagulation. Given the dose-dependent risks associated with anticoagulation, determining the incremental benefit of intermediate-dose compared to therapeutic-dose anticoagulation, if any, should be a priority of future research.

The evidence included in this review has several important limitations. First, cohort studies were limited by high potential for unmeasured confounders, and in some cases, inadequate or lack of statistical adjustment techniques and lack of accounting for co-interventions or other factors affecting clinical care. Second, results of both RCTs and cohort studies could be skewed by patients' receipt of different anticoagulation doses during the study period in both intervention and comparison groups. Third, some studies—including the largest RCTs—used composite primary outcomes with different components, limiting the ability to compare primary outcomes across studies. Fourth, most trials evaluated heparin or low molecular weight heparin (LMWH) rather than other forms of anticoagulation such as direct oral anticoagulants (DOACs). Findings are therefore most clinically applicable to patients who might receive heparin or LMWH anticoagulation and not other forms of anticoagulation. Finally, most studies were conducted in early 2020, and it is possible that clinical practices have evolved in the interim and findings from this evidence base are less relevant now. The incidence of thrombotic complications in COVID-19 could also be different with new variants or shifts in the age distribution of affected patients. Limitations of our review methods include single review at the abstract screening level, which could have led to missing eligible studies, and sequential review for study selection, data abstraction, and quality assessment (in contrast to dual independent review for all steps).

In summary, intermediate-dose anticoagulation does not appear to reduce the risk of thrombotic events but may provide a small mortality benefit compared to standard thromboprophylaxis. In contrast, therapeutic-dose anticoagulation may reduce the risk of thrombotic events compared to standard thromboprophylaxis but does not appear to offer a mortality benefit. Although limited, COVID-19-specific evidence on bleeding risk is sufficient to conclude that higher doses of anticoagulation are likely associated with a dose-dependent increase in bleeding risk among hospitalized patients with COVID-19. Our confidence in these findings is low, and the evolving and currently incomplete understanding of any potential benefits of higher-dose anticoagulation must be weighed against known potential harms. An important evidence gap to address in future research is whether the benefits of higher anticoagulation doses, if any, depend more on when anticoagulation is initiated (*ie*, earlier in the disease course when disease is moderate and not severe or critical) or the dose itself.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center is responding to a request from the VA Health Services Research and Development Service (HSR&D) for an Evidence Brief on the benefits and harms of antithrombotic treatments for adults with COVID-19. Findings from this Evidence Brief will be used to inform Veterans Health Administration (VHA) clinical policies and practices.

BACKGROUND

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease COVID-19, can lead to a profound inflammatory and prothrombotic state and may be associated with a higher risk of thrombotic complications than other viral illnesses.[1] Most adults who are hospitalized due to medical illness in US settings receive low-dose anticoagulation (*ie*, thromboprophylaxis) as part of standard in-hospital care to prevent venous thromboembolism (VTE), namely deep vein thrombosis (DVT) and pulmonary embolism (PE). In the first waves of the COVID-19 pandemic, anecdotal reports of high VTE rates among hospitalized patients, as well as speculation that microthrombi formation might explain the rapid decline witnessed in some patients, led to concern that standard thromboprophylaxis dosing was inadequate.[2,3] In response, many clinicians, hospitals, and health systems changed their approach to inpatient anticoagulation for adults with COVID-19 by using higher than standard prophylactic doses (termed "intermediate," "intensified," "escalated," or "subtherapeutic" dosing, and hereafter referred to as intermediate-dose anticoagulation), or empirically starting therapeutic-dose anticoagulation.

Whether the benefits of higher anticoagulation dosing, if any, outweigh potential harms such as increased bleeding risk has been an ongoing area of research during the pandemic. Results of several randomized controlled trials (RCTs) evaluating inpatient anticoagulation dosing in COVID-19 have recently been published. These trials add to the large evidence base generated in the first 18 months of the pandemic (composed largely of observational studies) from hospitals and health systems describing their experience with modified anticoagulation strategies. The aim of this report was to synthesize available evidence on the benefits and harms of intermediate-dose anticoagulation and empiric use of therapeutic anticoagulation compared to standard thromboprophylaxis among hospitalized adults with COVID-19 and examine whether benefits and harms vary by medication dose or timing, patient characteristics, or disease factors.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42020224256.

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

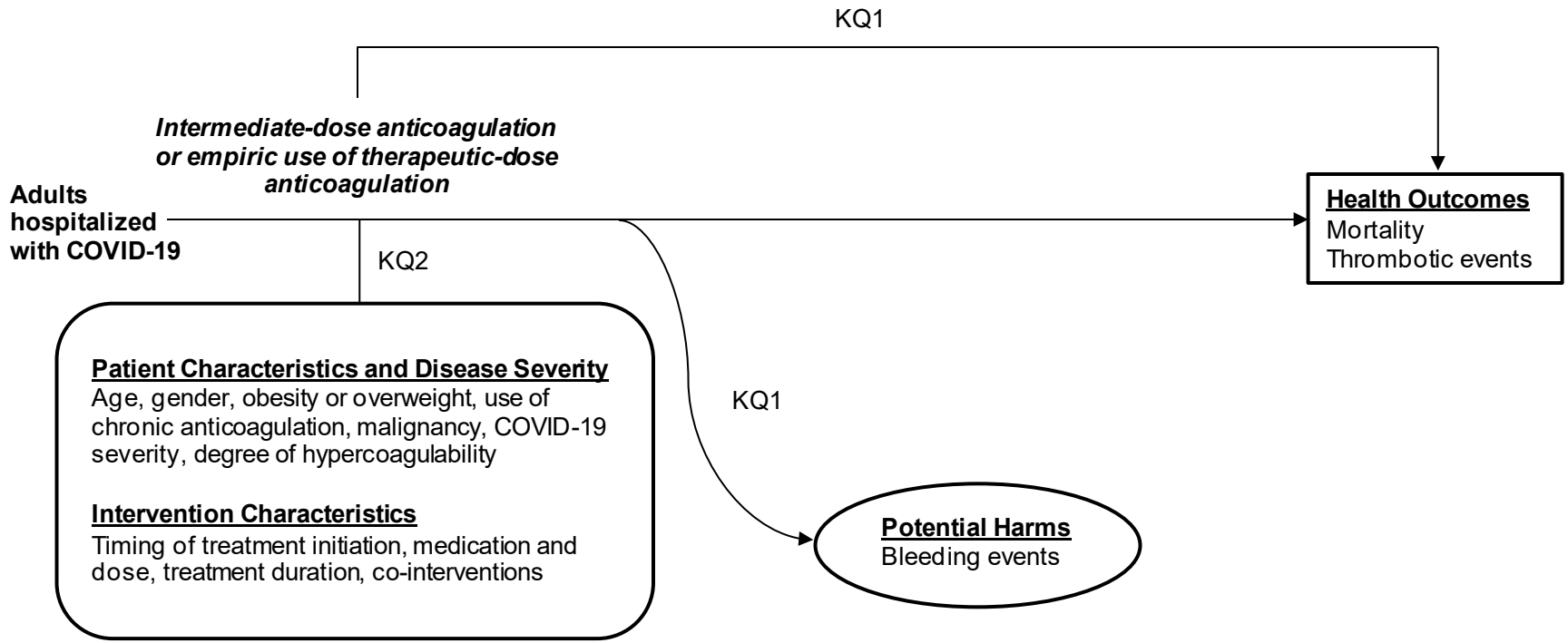
KQ1: What are the benefits and harms of intermediate-dose anticoagulation and empiric use of therapeutic anticoagulation compared to standard thromboprophylaxis in adults with COVID-19?

KQ2: Do these benefits and harms vary by medication type or dose, timing, patient characteristics, COVID-19 disease severity, or degree of hypercoagulability based on laboratory analysis?

ANALYTIC FRAMEWORK

The analytic framework shown in Figure 1 provides a conceptual overview of this review. The population of interest was adults hospitalized with COVID-19. Eligible outcomes included thrombotic events, mortality, and treatment harms (Key Question 1). Whether benefits and/or risks of the intervention differ by patient characteristics (*eg*, age, gender, COVID-19 severity, obesity or overweight, use of chronic anticoagulation, malignancy), COVID-19 severity, degree of hypercoagulability based on laboratory analysis, or treatment protocol (*eg*, medication type or dose timing of treatment initiation) was also of interest (Key Question 2).

Figure 1. Analytic Framework



ELIGIBILITY CRITERIA

We included studies that met the following criteria:

***P**opulation*	Adults with viral reverse transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection or clinically diagnosed COVID-19
***I**ntervention*	Intermediate-dose anticoagulation or empiric use of therapeutic-dose anticoagulation (*ie*, in the absence of diagnosed thrombus)
***C**omparator*	Standard thromboprophylaxis
***O**utcomes*	• *Benefits:* Thrombotic events, mortality • *Harms:* Bleeding complications
***T**iming*	Any
***S**etting*	Hospital
***S**tudy Design*	Randomized control trials (RCTs), cohort studies, case-control studies, and systematic reviews

DATA SOURCES AND SEARCHES

To identify articles relevant to the key questions, a research librarian searched Ovid MEDLINE and the WHO Global Literature on Coronavirus Disease database through October 12, 2021, using terms for *COVID-19* and *thrombosis* (see Appendix A in Supplemental Materials for complete search strategies). Additional citations were identified from hand-searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. We included studies that reported intervention and comparator medications and dosages and excluded studies that lacked this detail for the intervention (*eg*, studies that described intermediate-dose anticoagulation without stating the medication name or dose). Titles, abstracts, and full-text articles were reviewed by 1 investigator and checked by another. All disagreements were resolved by consensus or discussion with a third investigator.

DATA ABSTRACTION AND ASSESSMENT

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. We organized studies according to intervention type (intermediate or therapeutic anticoagulation dosage) and population (moderately ill or severely/critically ill participants). We defined "standard thromboprophylaxis" as anticoagulants prescribed according to pre-COVID-19 era guidelines for VTE prevention among adults hospitalized with medical illness.[4] We defined "treatment-dose anticoagulation" as anticoagulants prescribed at doses typically used for treatment of diagnosed thrombus or thromboembolic disease[5,6] but used empirically in the case of COVID-19 (*eg*, without imaging-confirmed thrombotic disease). We defined "intermediate-dose anticoagulation" as doses in between standard thromboprophylaxis and typical treatment doses. A practicing clinician (KM) reviewed all studies to confirm the

classification of interventions as either therapeutic or intermediate anticoagulation, considering the medications and doses used as well as the classifications used by study authors. If doses were adjusted for body weight or renal function, we assumed that these adjustments were made appropriately and remained consistent with dosing intent (intermediate, therapeutic, or standard thromboprophylaxis dosing). We defined moderate COVID-19 as requiring hospital admission, but not major organ support, mechanical ventilation, or intensive care unit (ICU)-level care. We defined severe or critical COVID-19 as requiring major organ support, mechanical ventilation, or ICU-level care.

The internal validity (risk of bias) of each included study was rated using the Cochrane ROB-2[7] tool for RCTs and ROBINS-I[8] tool for controlled observational studies. All data abstraction and internal validity ratings were first completed by 1 investigator and then checked by another; disagreements were resolved by consensus or discussion with a third investigator. We graded the strength of the evidence for each outcome based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[9] This approach provides a rating of confidence in reported findings based on study methodology (design, quality, and risk of bias), consistency across studies (whether effects are in the same direction and have a consistent magnitude), and directness (whether assessed outcomes are clinically important to patients and providers). Confidence ratings also incorporate the precision of findings (*eg*, confidence intervals) when this information is available.

For this review, we applied the following general algorithm for strength of evidence ratings: *high confidence* in evidence consisting of multiple, large trials with low risk of bias and consistent, direct, and precise findings; *moderate confidence* in evidence consisting of multiple trials with low to unclear risk of bias and consistent, direct, and precise findings; and *low confidence* in evidence consisting of a single trial or multiple small trials in addition to observational studies, with unclear to high risk of bias and/or inconsistent, indirect, or imprecise findings. *Insufficient* evidence consisted of a single trial or few observational studies with unclear or high risk of bias, or no available studies.

SYNTHESIS

Overall, we synthesized studies using a "best evidence" approach, meaning that we focused on the studies most germane to our Key Questions and of the highest methodological quality.[10] Reported results for mortality and bleeding outcomes were synthesized quantitatively, while results for thrombotic events were narratively synthesized due to inconsistencies in outcome definitions and other study features. Outcomes were reported as hazard, odds, or risk ratios, and studies varied in whether reported ratios were adjusted for patient characteristics and/or study methodological factors. Adjustments were typically implemented through covariate controls (*eg*, using multiple logistic regression analysis) or propensity score-based methods for matching during group assignment. Estimates from groups matched on patient characteristics were treated as adjusted. For quantitative synthesis of mortality outcomes, we only included adjusted estimates; most bleeding estimates were unadjusted and all estimates were included in meta-analyses.

When no ratio was reported or studies reported unadjusted odds ratios, risk ratios were calculated directly from reported outcome events. One study[11] reported bleeding outcomes among patients receiving standard thromboprophylaxis ($n = 83$) together with a small number of patients

receiving no anticoagulation ($n = 6$). Reported adjusted odds ratios were converted to risk ratios using the square-root transformation[12,13] and pooled with risk ratios. When studies reported no events in 1 group, a standard continuity correction of 0.5 was applied to all counts. This correction was not well performing for 1 effect estimate[14] (comparing bleeding events in patients receiving standard thromboprophylaxis or intermediate-dose anticoagulation) due to substantial imbalance in group sizes and low outcome prevalence. A correction of 0.4 was better performing and was used for this effect estimate only. Any study reporting no events in both groups was excluded from meta-analyses.[15]

Hazard ratios and risk ratios were synthesized separately using random-effects meta-analyses. All synthesized ratios represent a comparison between standard thromboprophylaxis and intermediate- or therapeutic-dose anticoagulation, with ratios less than 1 indicating benefits (*ie* reduced risk) for intermediate- or therapeutic-dose anticoagulation compared to standard thromboprophylaxis and ratios greater than 1 indicating greater risk compared to standard thromboprophylaxis. In a small number of cases, studies reported outcomes at multiple timepoints; in general, we included only the longest-term estimate in analyses (*eg*, when both 30- and 90-day all-cause mortality were reported, only the 90-day estimate was synthesized).

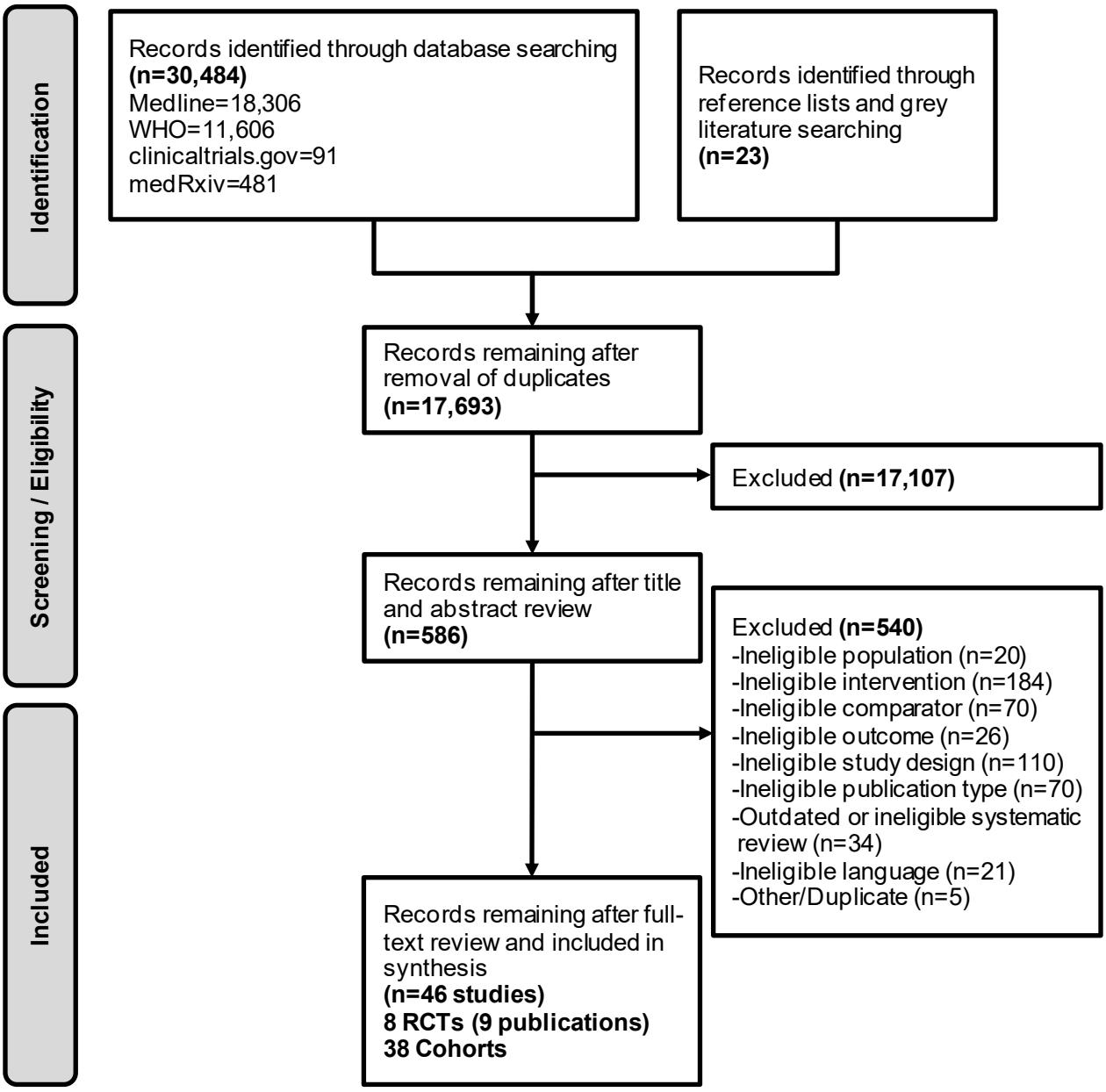
Results of meta-analyses are reported as overall hazard or risk ratios accompanied by 95% confidence intervals (CIs), and statistical significance was evaluated at a significance level of .05. Heterogeneity was estimated using the restricted maximum-likelihood estimator and is reported and evaluated using 95% prediction intervals (PIs).[16,17] Use of the Knapp-Hartung adjustment[18] was planned for all analyses, but was employed only in models pooling risk ratios. For models synthesizing hazard ratios, the very small number of available studies led to difficulty in calculating plausible CIs and PIs when the adjustment was used. Consequently, measures of statistical significance and heterogeneity for overall hazard ratios should be interpreted with caution, as they may not fully account for statistical uncertainty. Meta-analyses were conducted using the *metafor*[19] package for R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 2) summarizes the results of the study selection process (full list of excluded studies available in Appendix B in Supplemental Materials).

Figure 2. Literature Flowchart



Abbreviations. RCT=Randomized Control Trial; WHO=World Health Organization.

LITERATURE OVERVIEW

Our search identified 17,693 potentially relevant articles. From 586 articles remaining after title and abstract screening, we included 45 studies (8 open-label RCTs[20-27] and 37 cohort studies[11,14,28-61]). Table 1 provides an overview of studies according to population and intervention, and Tables 2-3 describe detailed study characteristics.

The most frequently studied anticoagulant was low molecular weight heparin (LMWH), followed by unfractionated heparin (UFH), direct oral anticoagulants (DOACs), and vitamin K antagonist (VKAs). Among observational studies, patient factors cited as influencing clinical decisions to use intermediate-dose or empiric therapeutic-dose anticoagulation included an elevated D-dimer level (a laboratory test quantifying fibrin-degradation products released in the blood with breakdown of clots), need for supplement oxygen or ICU-level care, a history of prior thrombotic disease or cancer, and/or other comorbidities. Many observational studies ascribed decisions to institutional protocols or discretion of the treating clinician or team or provided no information about how anticoagulant medications and doses were chosen.

Table 1. Overview of Study Populations and Interventions

	Intermediate-dose anticoagulation	Therapeutic-dose anticoagulation
Severe or critically-ill participants	2 RCTs[24,27]; 11 cohorts[11,35,36,40,43,47,55-57,59,61] (Total N = 3,517)	2 RCTs[20,22], 8 cohorts[11,28,34-37,40,48] (Total N = 5,605)
Moderately-ill participants	2 cohorts[51,52] (Total N = 551)	2 RCTs[21,25], 1 cohort[52] (Total N = 2,911)
Participants with mixed disease severity	10 cohorts[14,29-31,38,39,41,45,46,49] (Total N = 7,146)	2 RCTs[23,26], 13 cohorts[14,32,33,38,39,41,42,44,50,53,54,58,60] (Total N = 14,573)

Notes. [a]The number of studies in this table exceeds the total number of included studies because some studies evaluated both intervention types.
[b]Moderate COVID-19 was defined as requiring hospital admission, but not major organ support, mechanical ventilation, or ICU-level care. Severe or critical COVID-19 was defined as requiring major organ support, mechanical ventilation, or intensive care unit (ICU)-level care.
Abbreviation. N=number of participants.

Table 2. Studies Comparing Intermediate-dose Thromboprophylaxis to Standard Thromboprophylaxis

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Intermediate-dose Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
RCTs						
Bikdeli and Sadehipour, 2020[27,62] (INSPIRATION) *Iran*	7/29/20-11/19/20	562	Median age: 62[d] Female: 42% Median BMI: 27[d] Malignancy: NR Chronic AC use: 0%[e]	Severe or critically ill	Enoxaparin 1mg/kg daily	Enoxaparin (dose NR)
Perepu, 2021[24] *US*	4/26/20-1/6/21	173	Median age: 64 Female: 44% Median BMI: 31 Malignancy: 12 Chronic AC use: 0%[e]	Severe or critically ill	Enoxaparin 1mg/kg daily if BMI<30 or 0.5mg/kg twice daily if BMI ≥30	Enoxaparin 40mg daily if BMI<30 or 30-40mg twice daily if BMI ≥30
Cohorts						
Arachchillage, 2021[29] *UK*	4/10/20-4/23/20	171	Mean age: 65 ±16 Female: 40% Mean BMI: 27[d] Malignancy: 11% Chronic AC use: 0%[e]	Mixed; Severe or critically ill 17%	Enoxaparin 40-120mg twice daily or 40mg daily if <50 kg, tinzaparin 175 IU/kg daily, or UFH infusion if CrCl <20mL/min	Enoxaparin 40mg daily
Atallah, 2020[11] *UAE*	3/1/20-5/29/20	188	Median age: 49 (40-61) Female: 18% Median BMI: 26 (24-31) Malignancy: 4% Chronic AC use: 2%	Severe or critically ill	Enoxaparin 40mg twice daily	Enoxaparin 40mg daily
Avruscio[30] *Italy*	3/4/20-4/30/20	85	Mean age: 67[d] Female: 28% Mean BMI: 27[d] Malignancy: 12% Chronic AC use: NR	Mixed; Severe or critically ill 48%	Enoxaparin 60-80mg daily or 60mg twice daily, fondaparinux 5mg daily, or UFH infusion (target aPTT 60s and an activated clotting time 180–200s)	Enoxaparin 40mg or fondaparinux 2.5mg daily

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Intermediate-dose Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Benito, 2020[31] *Spain*	3/9/20-4/15/20	76	Mean age: 63[d] Female: 33% Mean BMI: 27[d] Malignancy: 9% Chronic AC use: NR	Mixed; Severe or critical 33%	Enoxaparin 100 IU/kg, bemiparin 75-80 IU/kg, or tinzaparin 100 IU/kg daily	Enoxaparin 4,000 IU, bemiparin 3,500 IU, or tinzaparin 4,500 IU daily
Gabara, 2021[35] *Spain*	3/1/20-4/30/20	201	Mean age: 62 Female: 29% Mean BMI: NR Malignancy: NR Chronic AC use: 8%	Severe or critical	Enoxaparin 1mg/kg daily or 60mg daily if >80kg; tinazaparin 75 IU/kg daily or 50 IU/kg daily if >90kg; bemiparin 5,000 IU daily, or fondaparinux 5mg daily	Enoxaparin 40mg, tinzaparin 4,500 IU, bemiparin 3,500 IU, or fondaparinux 2.5mg daily
Halaby, 2021[36] *US*	1/1/20-5/30/20	443	Median age: 66 (55-75) Female: 43% Mean BMI: 31 (±10) Malignancy: 16% Chronic AC use: 14%	Severe or critical	Enoxaparin 0.5 mg/kg twice daily or 40mg twice daily if BMI <40, or SC heparin 7,500 3 times daily	Enoxaparin ≤40mg daily or 40mg twice daily if BMI ≥40, SC heparin ≤5,000 IU 2-3 times daily, apixaban 2.5mg twice daily, rivaroxaban 10mg daily, betrixaban 80-160mg daily, fondaparinux 2.5mg daily, or UFH infusion for patients on CCRT
Hsu, 2020[38] *US*	2/27/20-4/24/20	468	Median age: 60[d] Female: 45% Mean BMI: NR Malignancy: NR Chronic AC use: NR	Mixed	LMWH 40mg twice daily or SC heparin 7,500 units 3 times daily	LMWH 40mg daily, SC heparin 5,000 IU 3 times daily, or apixaban 2.5 mg twice daily
Jiménez-Soto, 2021[39] *Mexico*	3/12/20-7/15/20	321	Mean age: 54[d] Female: 33% BMI>30: 80% intervention vs 75% comparator Malignancy: NR Chronic AC use: 0%[e]	Mixed; 17% Severe or critical	Enoxaparin 0.5 mg/kg or 40mg twice daily	Enoxaparin 40mg daily

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Intermediate-dose Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Jonmarker, 2020[40] *Sweden*	3/1/20-4/30/20	152	Median age: 61 (52–69) Female: 18% Median BMI: 28 (26-33) Malignancy: 6% Chronic AC use: 6%	Severe or critical	Tinzaparin >4,500 IU but <175 IU/kg or dalteparin >5,000 IU but <200 IU/kg daily	Tinzaparin 2,500-4,500 IU or dalteparin 2,500-5,000 IU daily
Kessler, 2020[14] *Switzerland*	4/1/20-5/6/20	270	Mean age: 70[d] Female: 39% Mean BMI: NR Malignancy: 7% Chronic AC use: 7%	Mixed; Severe or critical 28%	Enoxaparin 40-80mg twice daily, SC heparin 5,000 3 times daily, or UFH infusion (target anti-Xa ≤ 0.4 IU/ml or 0.3–0.5 IU/ml)	Enoxaparin 40mg daily or SC heparin 5,000 IU twice daily
Kumar, 2020[41] *US*	3/1/20-2/5/21	4,645	Median age: 66[d] Female: 48% Mean BMI: 30[d] Malignancy: 13% Chronic AC use: NR	Mixed	Enoxaparin 1mg/kg daily	Enoxaparin 0.5mg/kg daily or SC heparin 5,000 IU 2-3 times daily
Lavinio, 2021[43] *Europe (multiple sites)*	2/26/20-5/30/20	852	Median age: 66 (37-85) Female: 20% Mean BMI: NR; Obese: 28% Malignancy: 7% Chronic AC use: 17%	Severe or critical	Enoxaparin 40-80mg twice daily, fondaparinux (dose NR), or UFH infusion (target ratio 1.5-2.5)	NR, assumed to be LMWH or heparin[f]
Martinelli, 2020[45] *Italy*	3/9/20-4/7/20	278	Median age: 59 (49-67) Female: 35% Median BMI: 28 (25-30) Malignancy: NR Chronic AC use: 0%[e]	Mixed; Severe or critical 15%	Enoxaparin 0.7 mg/kg twice daily or 1 mg/kg daily	Enoxaparin 40mg daily

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Intermediate-dose Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Meizlish, 2021[46] *US*	3/1/20-6/30/20	382[h]	Median age: NR; Age >60: 61% Female: 49% Median BMI: NR; Obese: 43% Malignancy: NR Chronic AC use: NR	Mixed	Enoxaparin ≥0.4 and < 0.7 mg/kg twice daily or SC heparin 7,500 IU at any frequency if BMI <40	Enoxaparin 30-40mg at a weight-adjusted concentration of <0.7 mg/kg daily, enoxaparin 30-40mg at a weight-adjusted concentration of <0.4 mg/kg twice daily, SC heparin 5,000 IU up to 3 times daily, or SC heparin 5,000 or 7,500 IU up to 3 times daily if BMI ≥40
Moll, 2021[47] *US*	3/7/20-6/1/20	94	Mean age: 62 ±16 Female: 43% Mean BMI: 30 ±7 Malignancy: 6% (hematologic only) Chronic AC use: NR	Severe or critical	Enoxaparin 40mg twice daily or SC heparin 7,500 IU 3 times daily	Enoxaparin 40mg daily or SC heparin 5,000 IU 2-3 times daily
Paolisso, 2020[49] *Italy*	3/1/20-4/10/20	450	Median age: 67 (55-79) Female: 37% Median BMI: 26 (24-30) Malignancy: 11% Chronic AC use: 0%[e]	Mixed; Severe or critical 16%	Enoxaparin 40-60mg twice daily	Enoxaparin 40-60mg daily
Pesavento, 2020[51] *Italy*	2/26/20-4/6/20	324	Median age: 71 (59-82) Female: 44% Mean BMI: 28 ±4 Malignancy: <1% Chronic AC use: 0%[e]	Moderate	Enoxaparin (median daily dose 120mg) or fondaparinux (dose NR)	Enoxaparin 40mg daily, fondaparinux 2.5mg daily, or SC heparin 5,000 IU 3 times daily
Pieralli, 2021[52] *Italy*	3/21/20-5/25/20	227	Mean age: 72 ±13 Female: 43% Mean BMI: NR, Obese: 11% Malignancy: 9% Chronic AC use: NR	Moderate	Enoxaparin 60-80mg daily	Enoxaparin 20-40mg or fondaparinux 1.5-2.5mg daily

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Intermediate-dose Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Stessel, 2020[55] *Belgium*	3/13/20-4/20/20	72	Mean age: 67[d] Female: 32% Mean BMI: 26[d] Malignancy: NR Chronic AC use: NR	Severe or critical	Nadroparin 3,800 IU twice daily	Nadroparin 2,850 IU daily
Taccone, 2020[56] *Belgium*	3/10/20-4/30/20	49	Median age: 61 (57-66) Female: 30% Mean BMI: NR; Obese: 40% Malignancy: 13% Chronic AC use: NR	Severe or critical	Enoxaparin 40mg twice daily or UFH infusion 1,500-2,200 IU/hr[i]	Enoxaparin 40mg daily
Tacquard, 2021[57] *France*	3/21/20-4/10/20	538	Median age: 63 (55-71) Female: 28% Median BMI: 29 (26-33) Malignancy: 7% Chronic AC use: 7%	Severe or critical	LMWH >6,000 daily or UFH infusion ≥ 200 IU/kg or resulting in anti-Xa ≥ 0.3 IU/l	LMWH 4,000-6,000 IU daily or UFH infusion <200 IU/kg or resulting in 0.1 ≤ anti-Xa < 0.3 IU/l
Voicu, 2020[59] *France*	3/11/20-12/10/20	93	Median age: 63 (56-71) Female: 31% Median BMI: 29 (25-32) Malignancy: NR Chronic AC use: 0%[e]	Severe or critical	Enoxaparin 40mg twice daily	Enoxaparin 40mg daily or UFH 15,000 IU daily
Zermatten, 2020[61] *Switzerland*	2/28/20-4/26/20	100	Median age: 64 (56-73) Female: 26% Mean BMI: NR; Obese: 18% Malignancy: 3% Chronic AC use: 8%	Severe or critical	Enoxaparin 40-60mg twice daily or UFH infusion 200 IU/kg/24h	Enoxaparin 40mg or UFH 5,000 IU twice daily if CrCl<30 ml/min

Notes. [a] BMI reported in kg/m2.
[b] Moderate COVID-19 defined as requiring hospital admission, but not major organ support, mechanical ventilation, or ICU-level care. Severe or critical COVID-19 defined as requiring major organ support, mechanical ventilation, or ICU-level care.
[c] Dosing as reported by each study. Doses were typically adjusted for weight and renal function and not all possible doses are reported in this table. Detailed UFH infusion protocols including target activated partial thromboplastin time (aPTT) or anti-factor Xa activity were not reported in all studies.
[d] Weighted average calculated by ESP reviewers.
[e] Study excluded adults on chronic anticoagulation or indication for therapeutic-dose anticoagulation at the time of hospitalization.

[f] Includes 19 (2.2%) patients with contraindications to anticoagulation at the time of ICU admission who received no heparin.
[h] N is for the propensity score-matched group. The overall study cohort consisted of 2785 participants.
[i] 6/18 (33%) patients in the higher intensity group received therapeutic UFH.
Abbreviations. AC=anticoagulation; AE=adverse events; aPTT= activated partial thromboplastin time; BMI=body mass index; CCRT=continuous renal replacement therapy; CrCl = creatinine clearance; DOAC=direct oral anticoagulants; LMWH=low molecular weight heparin; ICU=intensive care unit; INR=international normalized ratio; IU=international units; N=number of participants; NR=not reported; TE=thrombotic Events; VKA=vitamin K antagonist; ROB=risk of bias; UAE=United Arab Emirates; UFH=unfractionated heparin; US=United States.

Table 3. Studies Comparing Therapeutic Anticoagulation to Standard Thromboprophylaxis

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Therapeutic Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
RCTs						
Goligher, 2021[20] (ATTACC/ACTIV-4a/REMAP-CAP) *Multiple*[d]	4/21/20-12/19/20	1098[e]	Mean age: 61[f] Female: 30% Median BMI: 30 Malignancy: NR Chronic AC use: NR	Severe or critical	Enoxaparin 1mg/kg twice daily or 1.5mg/kg daily, dalteparin 100 IU/kg twice daily or 200 IU/kg daily, tinazaparin 175 anti-Xa units/kg daily, or UFH infusion (dose NR)	Enoxaparin 40mg daily, dalteparin 5000 units daily, tinazaparin 75 anti-Xa units/kg or 4500 units daily (whichever is higher), or UFH 5000 units 2-3 times daily[g]
Lawler, 2021[21] (ATTACC/ACTIV-4a/REMAP-CAP) *Multiple*[h]	4/21-20-1/22/21	2219[e]	Mean age: 59[f] Female: 41% Median BMI: 30 Malignancy: NR Chronic AC use: NR	Moderate	Enoxaparin 1mg/kg twice daily or 1.5mg/kg daily, dalteparin 100 IU/kg twice daily or 200 IU/kg daily, tinazaparin 175 anti-Xa units/kg daily, or UFH infusion (dose NR)	Enoxaparin 40mg daily, dalteparin 5000 units daily, tinazaparin 75 anti-Xa units/kg or 4500 units daily (whichever is higher), or UFH 5000 units 2-3 times daily[i]
Lemos, 2020[22] *Brazil*	4/1/20-7/31/20	20	Mean age: 57[f] Female: 20% Mean BMI: 34[d] Malignancy: 0% Chronic AC use: 0%[j]	Severe or critical[k]	Enoxaparin 1mg/kg twice daily or UFH if CrCl <10mL/min (targeted to aPTT ratio 1.5-2)	SC heparin 5000 IU 3 times daily or enoxaparin 40mg daily if <120mg; SC heparin 7500 IU 3 times daily or enoxaparin 40mg twice daily if weight >120kg
Lopes, 2021[23] (ACTION) *Brazil*	6/24/20-2/26/21	615	Mean age: 57 ±14 Female: 40% Mean BMI: 30 Malignancy: 0%[l] Chronic AC use: 0%[j]	Mixed, Severe or critical 7%	Rivaroxaban 20mg daily, enoxaparin 1mg/kg twice daily, or UFH infusion (target anti-Xa 0·3–0·7 IU/mL or aPTT 1·5–2·5 times the mean normal value)	Enoxaparin or heparin (doses NR)
Sholzberg, 2021[25] (RAPID) *Multiple*[m]	5/29/21-4/12/21	465	Mean age: 60 Female: 43% Mean BMI: 30 Malignancy: 7% Chronic AC use: 0%[j]	Moderate	Dalteparin, enoxaparin, tinzaparin, or UFH (doses NR)	Dalteparin, enoxaparin, tinzaparin, fondaparinux, or UFH (doses NR)

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Therapeutic Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Spyropoulos, 2021[26] (HEP-COVID) *US*	5/8/20-5/14/21	253	Mean age: 67 Female: 46% Mean BMI: 31[f] Malignancy: 12% Chronic AC use: 0%[j]	Mixed; Severe or critical 33%	Enoxaparin 1mg/kg or 0.5mg/kg twice daily depending on CrCl	Enoxaparin ≤40mg daily, 30-40mg twice daily, or 0.5 mg/kg twice daily[n]
Cohorts						
Al-Samkari, 2021[28] *US*	3/4/20-4/11/20	2809	Median age: 61 (53-71) Female: 36% Mean BMI: 30[f] Malignancy: 4% Chronic AC use: 0%[j]	Severe or critical	UFH, LMWH, bivalirudin, argatroban, fondaparinux or DOAC, within 2 days of ICU admission (doses NR)	Enoxaparin 40mg daily, SC heparin 5,000 units 2-3 times daily[o]
Atallah, 2020[11] *UAE*	3/1/20-5/29/20	188	Mean age: 49 Female: 18% Median BMI: 26 Malignancy: NR Chronic AC use: 2%	Severe or critical	UFH infusion per PE protocol (target aPTT 60-85s) or DOAC	Enoxaparin 40mg daily
Canoglu, 2020[32] *Turkey*	3/11/20-4/31/20	154	Median age: 60 Female: 38% Median BMI: NR Malignancy: NR Chronic AC use: 0%[j]	Mixed	Enoxaparin 1mg/kg twice daily	Enoxaparin 0.5 mg/kg twice daily
Copur, 2021[54] *Turkey*	3/11/20-4/11/20	115	Mean age: 67 Female: 50% Mean BMI: NR Malignancy: NR Chronic AC use: NR	Mixed	LMWH 1mg/kg twice daily	LMWH 40mg daily

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Therapeutic Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Elmelhat, 2020[33] *UAE*	3/1/20-5/31/20	52	Mean age: 47 (±10.4) Female: 20% Median BMI: 26 (24-31) Malignancy: NR Chronic AC use: NR	Mixed; Severe or critical 51%	Enoxaparin 1 mg/kg twice daily	Enoxaparin 40mg daily
Ferguson, 2020[34] *US*	3/15/20-5/8/20	141	Mean age: 64[f] Female: 45% Mean BMI: 31[f] Malignancy: NR Chronic AC use: NR	Severe or critical	UFH, LMWH 1 mg/kg twice daily or 1.5mg/kg daily, or DOAC	Enoxaparin 30-40mg daily, enoxaparin 0.5 mg/kg twice daily, or SC heparin 5000 units 2 or 3 times daily.
Gabara, 2021[35] *Spain*	3/1/20-4/30/20	201	Mean age: 62 Female: 29% Mean BMI: NR Malignancy: NR Chronic AC use: 8%	Severe or critical	Enoxaparin 1mg/kg twice daily or 1.5 mg/kg daily; tinazaparin 175 IU/kg daily; bemiparin 115 IU/kg daily; or fondaparinux 5mg daily if <50kg, 7.5mg daily if 51-100kg, or 10mg daily if >100kg	Enoxaparin 40mg, tinzaparin 4,500 IU, bemiparin 3,500 IU, or fondaparinux 2.5mg daily
Halaby, 2021[36] *US*	1/1/20-5/30/20	443	Median age: 66 (55-75) Female: 43% Mean BMI: 31 ±10 Malignancy: 16% Chronic AC use: 14%	Severe or critical	UFH, argatroban, bivalirudin, enoxaparin 1 mg/kg twice daily or 1.5mg/kg daily, fondaparinux ≥5mg daily, warfarin, apixaban 5-10mg twice daily, rivaroxaban 15mg twice daily or 20mg daily, or dabigatran 150mg twice daily	Enoxaparin ≤40mg daily or 40mg twice daily if BMI ≥40, SC heparin ≤5,000 IU 2-3 times daily, apixaban 2.5mg twice daily, rivaroxaban 10mg daily, betrixaban 80-160mg daily, fondaparinux 2.5mg daily, or UFH for patients on CCRT
Helms, 2021[37] *France*	3/3/20-5/30/20	179	Median age: 62 (51-70) Female: 27% Median BMI: 30 (26-34) Malignancy: 5% Chronic AC use: 0%[j]	Severe or critical	LMWH 100mg IU/kg daily based on actual weight without exceeding 10,000 IU/12 hours or UFH 500 IU/kg daily if CrCl <30 mL/min	LMWH up to 6000 IU twice daily in obese patients or UFH 200 IU/kg daily if CrCl <30 mL/min

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Therapeutic Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Hsu, 2020[38] *US*	2/27/20-4/24/20	468	Age: 60[f] Female: 45% BMI: NR Malignancy: NR Chronic AC use: NR	Mixed	UFH, LMWH 1mg/kg twice daily, dose-adjusted warfarin with a target INR 2-3, apixaban 5mg twice daily, or rivaroxaban 20mg daily	LMWH 40mg daily, SC heparin 5000 units 3 times daily, or apixaban 2.5mg twice daily
Jiménez-Soto, 2021[39] *Mexico*	3/12/20-7/15/20	321	Mean age: 54[f] Female: 33% BMI>30: 86% in intervention group and 75% in comparator group Malignancy: NR Chronic AC use: 0%[j]	Mixed	Enoxaparin 1mg/kg twice daily	Enoxaparin 40mg daily
Jonmarker, 2020[40] *Sweden*	3/1/20-4/30/20	152	Median age: 61 (52–69) Female: 18% BMI: 28 (26-33) Malignancy: 6% Chronic AC use: 6%	Severe or critical	Tinzaparin (≥ 175 IU/kg of body weight or dalteparin ≥ 200 IU/kg of body weight	Tinzaparin 2,500-4,500 IU or dalteparin 2,500-5,000 IU daily
Kessler, 2020[14] *Switzerland*	4/1/20-5/6/20	270	Mean age: 70[f] Female: 39% BMI: NR Malignancy: 7% Chronic AC use: 7%	Mixed	Enoxaparin (dose NR), UFH infusion (target anti-Xa 0.3–0.7 U/ml), DOAC, or VKA (target INR 2.5 ±0.5)	Enoxaparin 40mg daily or SC heparin 5,000 IU twice daily
Kumar, 2020[41] *US*	3/1/20-2/5/21	4,645	Median age: 66[f] Female: 48% Mean BMI: 30[f] Malignancy: 13% Chronic AC use: NR	Mixed	Enoxaparin 1mg/kg twice daily, UFH infusion, DOAC, or warfarin	Enoxaparin 0.5mg/kg daily or SC heparin 5,000 IU 2-3 times daily

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Therapeutic Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Kuno, 2021[42] *US*	3/1/20-3/30/21	2,533	Mean age: 65[f] Female: 44% Mean BMI: NR Malignancy: 8% Chronic AC use: NR	Mixed	Apixaban, dabigatran, rivaroxaban, edoxaban, warfarin, enoxaparin UFH, or argatroban (doses NR)	Enoxaparin or heparin (doses NR)
Lynn, 2020[44] *US*	3/15/20-5/31/20	402	Mean age NR; Age >60:57% Female: 46% Mean BMI NR: BMI >30: 95% Malignancy: 5% Chronic AC use: NR	Mixed; Severe or critical 27%	UFH, enoxaparin 1mg/kg twice daily or 1.5mg/kg daily, or DOAC	NR
Motta, 2020[48] *US*	4/1/20-4/25/20	374	Mean age: 65 ±18 Female: 41% Mean BMI: 29 ±8 Malignancy: 12% Chronic AC use: 0%[j]	Severe or critical	UFH (target aPTT 70-110s) or LMWH 1mg/kg twice daily or 1.5mg/kg daily or twice daily titrated to anti-Xa 0.6–1 IU/mL or daily titrated to 1–2 IU/mL, started at admission	LMWH 30-40mg daily or SC heparin 5000mg 3 times daily
Patel, 2020[50] *US*	3/9/20-6/26/20	1716	Age >60: 48% Female: 45% Mean BMI NR: BMI >30: 45% Malignancy: 10% Chronic AC use: NR	Mixed	NR[p]	NR[p]
Pieralli, 2021[52] *Italy*	3/21/20-5/25/20	227	Mean age: 72 ±13 Female: 43% Mean BMI: NR, Obese: 11% Malignancy: 9% Chronic AC use: NR	Moderate	Enoxaparin 120-160mg daily, fondaparinux 5-10mg daily, VKA, or DOAC	Enoxaparin 20-40mg or fondaparinux 1.5-2.5mg daily

Author, Year *Country*	Study Period	N	Patient Characteristics[a]	Disease Severity[b]	Intervention: Therapeutic Anticoagulation[c]	Comparator: Standard Thromboprophylaxis[c]
Qin, 2020[53] *China*	1/10/20-2/28/20	749	Mean age: 60 (±15) Female: 52% Mean BMI: NR; Mean weight in kg: 65 (±11) Malignancy: NR Chronic AC use: NR	Mixed	LMWH 100 IU/kg twice daily	LMWH 3,000–5,000 IU daily
Vaughn, 2021[58] *US*	3/7/20-6/17/20	1351	Median age: 64[f] Female: 48% Median BMI: NR Malignancy: NR Chronic AC use: 0%[j]	Mixed; Severe or critical 30%	Enoxaparin, UFH, apixaban, edoxavan, rivaroxaban, warfarin (doses NR)	LMWH, fondaparinux, apixaban, or UFH (doses NR)[q]
Yu, 2021[60] *US*	3/5/20-5/15/20	929	Mean age: 62[f] Female: 44% Mean BMI: 29 Malignancy: 8% Chronic AC use: 0%[j]	Mixed	Enoxaparin 1mg/kg twice daily, apixaban ≥ 5mg twice daily, UFH infusion, or fondaparinux ≥ 5mg once daily	"Low dose prophylactic AC"

Notes. [a] BMI reported in kg/m2.
[b] Moderate COVID-19 defined as requiring hospital admission, but not major organ support, mechanical ventilation, or ICU-level care. Severe or critical COVID-19 defined as requiring major organ support, mechanical ventilation, or ICU-level care.
[c] Dosing as reported by each study. Doses were typically adjusted for weight and renal function and not all possible doses are reported in this table. Detailed UFH infusion protocols including target activated partial thromboplastin time (aPTT) or anti-factor Xa activity were not reported in all studies.
[d] UK, US, Canada, Brazil, Ireland, Netherlands, Australia, Nepal, Saudi Arabia, Mexico.
[e] N is for the total number of participants randomized to receive the intervention or usual care, not all of whom were included in the primary analysis.
[f] Weighted average calculated by ESP reviewers.
[g] Participants in the comparator group received standard low dose thromboprophylaxis (72%) or enhanced intermediate dose thromboprophylaxis (27%).
[h] UK, US, Canada, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain.
[i] Participants in the comparator group received standard low dose thromboprophylaxis (41%) or enhanced intermediate dose thromboprophylaxis (51%). Data not available for all participants.
[j] Adults on chronic anticoagulation or indication for therapeutic-dose anticoagulation at the time of hospitalization were excluded.
[k] Presumed ICU, as all patients required mechanical ventilation.
[l] Patients with active cancer were excluded.
[m] Brazil, Canada, Ireland, Saudi Arabia, UAE, and US.
[n] 61% received standard prophylaxis doses and 39% received intermediate-dose anticoagulation.
[o] The control group received at least standard thromboprophylaxis, 8 centers (12%) transitioned to higher-than-standard doses for some or all patients with COVID-19 during the study period based on criteria such as D-dimer or empirical dose escalation. The control group also included patients who received therapeutic AC after 2 days (intention to treat analysis).

[p] Specific medications and doses not reported for intervention and comparison groups but are presumed to be standard dosing for therapeutic or prophylactic anticoagulation, respectively. Anticoagulants used at the study location were: apixaban, argatroban, bivalirudin, dabigatran, dalteparin, edoxaban, enoxaparin, fondaparinux, heparin, rivaroxaban, and warfarin.
[q] Some patients in the comparator group received intermediate-dose anticoagulation. The study authors categorized anticoagulation dosing by intent (i.e. treatment or prophylaxis).
Abbreviations. AE=adverse events, aPTT= activated partial thromboplastin time, BMI=body mass index, CCRT=continuous renal replacement therapy, CrCl = creatinine clearance, DOAC=direct oral anticoagulants, LMWH=low molecular weight heparin, ICU=intensive care unit, INR= international normalized ratio, IU=international units; N=number of participants, NR=not reported, TE=thrombotic Events, VKA=vitamin K antagonist, ROB=risk of bias, UAE=United Arab Emirates, UFH=unfractionated heparin, US=United States.

MORTALITY

Intermediate-dose anticoagulation, but not therapeutic-dose anticoagulation, may provide a small mortality benefit compared to standard thromboprophylaxis. However, our confidence in these findings is low, and future research is needed to better understand if and when higher-dose anticoagulation is beneficial.

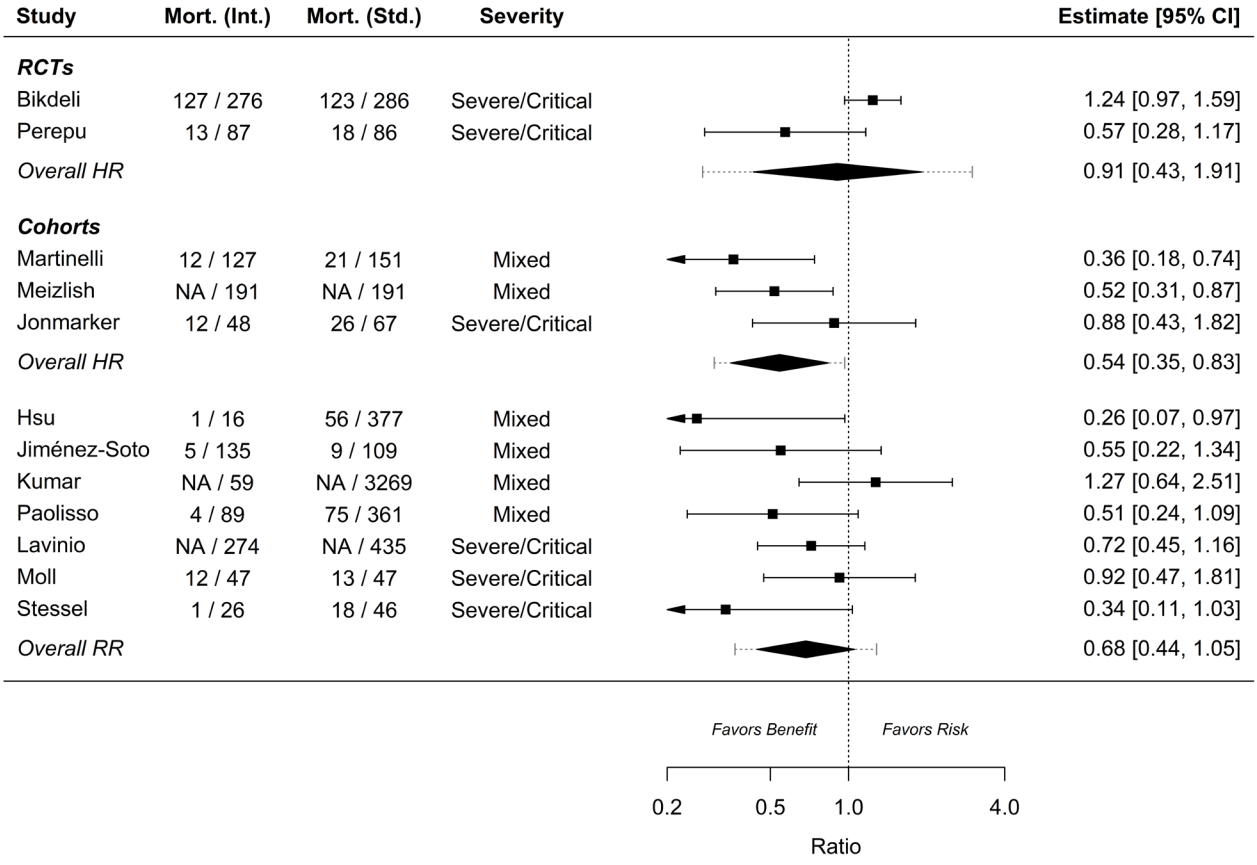
Intermediate-Dose Anticoagulation Compared to Standard Thromboprophylaxis

We identified 2 open-label RCTs reported in 3 publications[24,27,62] comparing the effects of intermediate-dose anticoagulation and standard thromboprophylaxis on mortality. One trial was conducted among 562 hospitalized adults in Iran[27,62] (the INSPIRATION trial) and the other among 173 hospitalized adults in the US (Perepu et al).[24] Both trials included adults requiring ICU-level care and Perepu et al also included non-ICU patients with coagulopathy (defined as a modified ISTH Overt Disseminated Intravascular Coagulation [DIC] score ≥3). Both trials compared intermediate-dose enoxaparin (1mg/kg daily or 0.5mg/kg twice daily for BMI ≥30) to standard thromboprophylaxis with enoxaparin. After accounting for site effects, the INSPIRATION trial did not identify a significant difference in 30-day all-cause mortality (OR = 1.20, 95% CI [0.84, 1.72]) or 90-day all-cause mortality (HR = 1.24, 95% CI [0.97, 1.59]), or the primary outcome, a composite of thrombotic events, treatment with extracorporeal membrane oxygenation (ECMO), and 90-day all-cause mortality (HR = 1.21, 95% CI [0.95, 1.55]). Perepu et al also did not identify a significant difference in 30-day all-cause mortality with intermediate-dose anticoagulation (HR = 0.57, 95% CI [0.28-1.17] in the intention-to-treat population). While neither trial had statistically significant results, we note that the direction of effect estimates differed between these 2 trials (results in the INSPIRATION trial favored risk and results in Perepu et al favored benefit). When estimates were pooled (Figure 2), the overall HR was nonsignificant but was in the direction of benefit (overall HR = 0.91, 95% CI [0.43, 1.91]).

We identified 15 cohort studies[29,35,38-41,43,45-47,49,51,55,57,59] evaluating mortality among adults who received intermediate-dose anticoagulation compared to standard thromboprophylaxis (see Appendix C in the Supplemental Materials for all study results). Ten of these cohort studies provided adjusted estimates[38-41,43,45-47,49,55] and, notably, the direction of pooled adjusted estimates (Figure 2) is consistent with Perepu et al,[24] suggesting a decreased risk of mortality with intermediate-dose anticoagulation compared with standard thromboprophylaxis (overall HR = 0.54, 95% CI [0.35, 0.83], $k = 3$; overall RR = 0.68, 95% CI [0.44, 1.05], $k = 7$). The overall HR was significant ($p = .005$) and the overall RR approached significance ($p = .052$) (importantly, as noted in the Methods section, the HR model did not employ the Knapp-Hartung adjustment, which may have led to an inaccurately small p-value). Moreover, in virtually all cases, study-level adjusted effect estimates were consistently in the direction of benefit associated with intermediate-dose anticoagulation. Heterogeneity in these estimates was limited (HR 95% PI [0.30, 0.97]; RR 95% PI [0.37, 1.28]).

We considered factors that might explain the difference in the direction of mortality effect estimates between the INSPIRATION trial[27,62] and Perepu et al.[24] We identified no major methodological concerns in either trial. Both trials were conducted over similar time periods relative to the start of the pandemic, making it unlikely that meaningful differences existed in general COVID-19 inpatient management between the 2 trial settings.

Figure 2. Forest Plot of Mortality Hazard and Risk of Intermediate-dose Anticoagulation vs Standard Thromboprophylaxis



Notes. Mortality event counts represented as number of patients who died / total analytic group size; NA denotes studies that did not report mortality event counts. Heterogeneity represented as gray error bars corresponding to 95% prediction intervals. Models pooling hazard ratios did not employ Knapp-Hartung adjustment (see Methods section).
Abbreviations. CI=confidence interval; HR=hazard ratio; Int=intermediate dose; Mort=mortality; RCT=randomized controlled trial; RR=risk ratio; Std=standard dose.

One possible explanation for the trend towards reduced mortality risk with intermediate-dose anticoagulation in Perepu et al[24] could be the inclusion of patients with less severe disease (those with coagulopathy but not requiring ICU-level care). As shown in Figure 2, risk estimates from cohorts that included patients with mixed disease severity often indicated relatively large benefit with intermediate-dose anticoagulation, while estimates from cohorts of severe or critically-ill patients were more inconsistent but generally indicated small or no differences in risk between groups. This pattern suggests that a mortality benefit of intermediate-dose anticoagulation, if any, may be more likely in those with lower disease severity. Finally, the absolute difference in deaths in the INSPIRATION trial[27,62] was small (deaths in the intermediate-dose group = 127; deaths in the standard thromboprophylaxis group = 123), raising the possibility that differences between groups were due to chance rather than a causal effect of intermediate-dose anticoagulation.

In summary, consistency in the direction of effect estimates across pooled results from 2 RCTs[24,27,62] and 10 adjusted cohorts[38-40,43,45-47,49,55,41] suggests a possible mortality benefit with intermediate-dose anticoagulation compared to standard thromboprophylaxis among adults hospitalized with COVID-19. Potential benefits may be more likely among those with less severe

disease. Our confidence in these findings is low and additional trial data is needed to draw stronger conclusions. This evidence is currently inadequate to serve as a basis for clinical decision-making but provides a rationale for further study.

Therapeutic Anticoagulation Compared to Standard Thromboprophylaxis

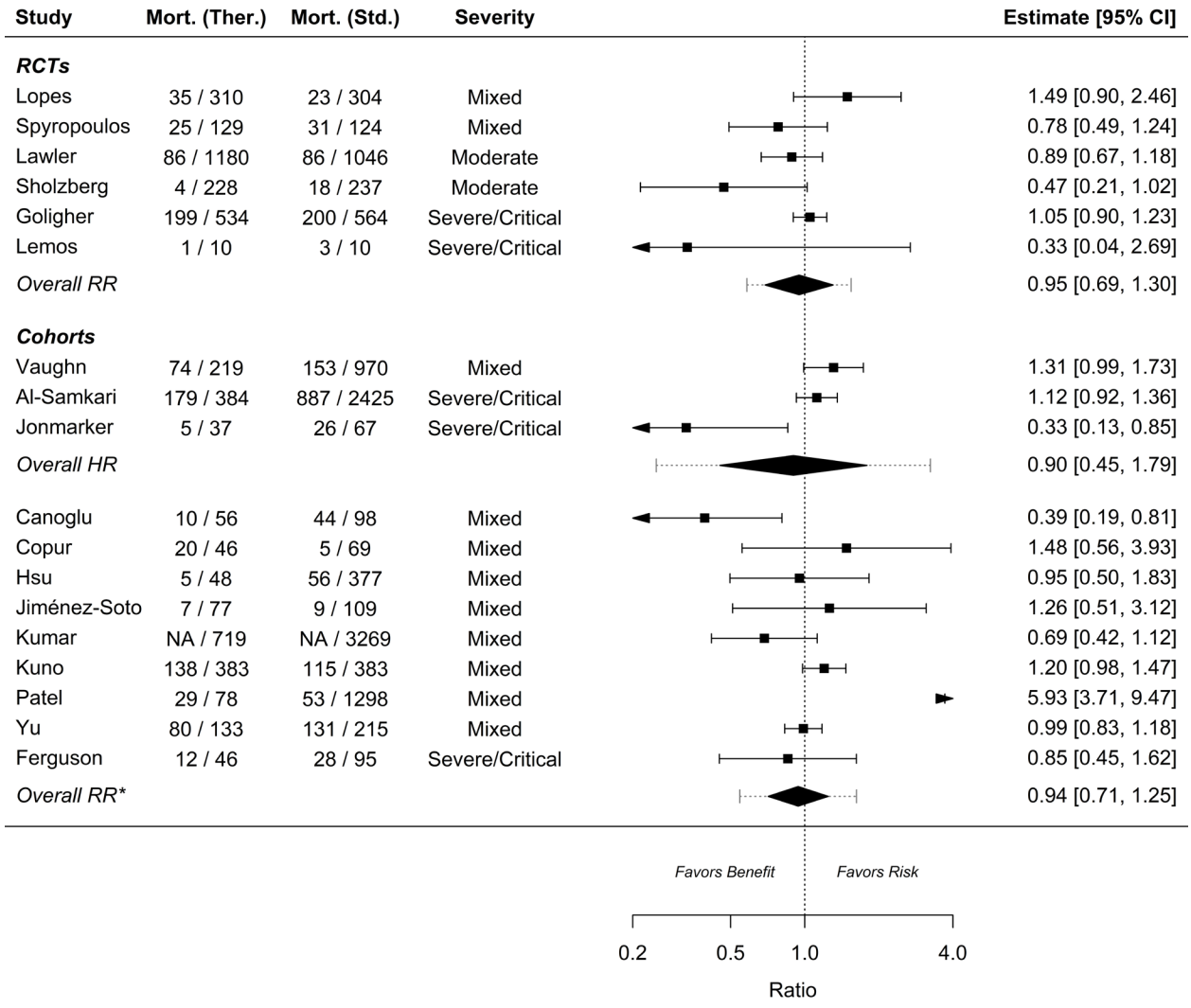
We identified 6 RCTs (4 trials[22,23,25,26] and 2 sub-studies[20,21] of the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial) comparing the effects of therapeutic-dose anticoagulation and standard thromboprophylaxis on mortality.

In the large ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial,[20,21] adults in the intervention group received therapeutic doses of enoxaparin, dalteparin, tinazaparin, or UFH and those in the comparison group received prophylactic doses of these medications (Table 3). This trial was the only one that analyzed outcomes separately for non-critically ill and critically ill adults, reporting results as adjusted odds ratios with credible intervals based on use of Bayesian analyses. In the non-critically ill group,[21] those receiving therapeutic anticoagulation had *greater* odds of survival to hospital discharge compared to standard thromboprophylaxis, although this difference was not statistically significant (adjusted OR = 1.21, 95% credible interval [0.87, 1.68]). The trial was stopped because predefined criteria for *superiority* were met, with the study finding a probable benefit in a composite outcome of survival to hospital discharge and days free of organ support. In contrast, critically ill patients had *lower* odds of survival to hospital discharge (adjusted OR = 0.88, 95% credible interval [0.67, 1.16]).[20] This part of the trial was also stopped, in this case due to *futility* in terms of the composite outcome. The risk of in-hospital death with therapeutic-dose anticoagulation compared with usual care was not significantly different for non-critically ill patients (RR = 0.89, 95% CI [0.67, 1.18]) compared with critically ill patients (RR = 1.05, 95% CI [0.90, 1.23]) based on overlap of confidence intervals (Figure 3).

Among the other 4 trials, the multi-national RAPID trial[25] conducted among 465 moderately-ill adults found a lower risk of all-cause mortality at 28 days among the group receiving therapeutic heparin (OR = 0.22, 95% CI [0.07, 0.65], $p = 0.006$), although this difference was not statistically significant when converted to a risk ratio for the purpose of meta-analysis (Figure 3). The remaining 3 trials[22,23,26] did not identify a significant difference in mortality risk with therapeutic anticoagulation compared to standard thromboprophylaxis. Pooled RCT results ($k = 6$) suggest no difference in mortality risk between patients receiving therapeutic dose anticoagulation and those receiving standard dose thromboprophylaxis (overall RR = 0.95, 95% CI [0.69, 1.30]), as shown in Figure 3.

We identified 18 cohort studies[28,32-35,37-42,44,48,50,53,54,58,60] evaluating mortality among adults who received therapeutic-dose anticoagulation compared to standard thromboprophylaxis. Adjusted estimates from 12 of these cohorts[28,32,34,38-42,50,54,58,60] suggest no or potentially small differences in mortality risk between dosages (overall HR = 0.90, 95% CI [0.45, 1.79], $k = 3$; overall RR = 1.13, 95% [0.64, 2.01], $k = 9$), as also shown in Figure 3. The cohort study results support the overall findings from RCTs of no or little difference in mortality risk with therapeutic anticoagulation compared to standard thromboprophylaxis.

Figure 3. Forest Plot of Mortality Hazard and Risk of Therapeutic-dose Anticoagulation vs Standard Thromboprophylaxis



Notes. Mortality event counts represented as number of patients who died / total analytic group size. Heterogeneity represented as gray error bars corresponding to 95% prediction intervals. Models pooling hazard ratios did not employ Knapp-Hartung correction (see Methods section). Asterisk (*) indicates overall risk ratio for cohort studies excludes 1 severely outlying study [50].
Abbreviations. CI=confidence interval; HR=hazard ratio; Mort=mortality; RR=risk ratio; RCT=randomized controlled trial; Std=standard dose; Ther=therapeutic dose.

Limited heterogeneity was present among RCTs (95% PI [0.58, 1.54]), while substantial heterogeneity occurred among cohorts reporting hazard ratios (95% PI [0.25, 3.24]) and risk ratios (95% PI [0.21, 6.20]). Additionally, although the overall risk ratio from cohort studies suggests a potentially increased risk with therapeutic anticoagulation, as shown in Figure 3, this finding may be the result of influence from an inconsistent and outlying estimate from 1 study.[50] This observational study had a severe imbalance in group size (therapeutic-dose group = 78, standard thromboprophylaxis group = 1298), and when removed, the overall estimate is consistent with other pooled results (Overall RR = 0.94, 95% CI [0.71, 1.25]) and heterogeneity was considerably reduced (95% PI [0.54, 1.62]).

Individual studies varied considerably in baseline patient severity, sample size, and among cohort studies, treatment and control group size (Table 3 and Figure 3). These factors may influence estimates through, for example, prognostic imbalance, which can lead to inconsistent or spurious observed effects especially in small studies. For example, the largest RCT analyses,[20,21,42] which are less susceptible to prognostic imbalance, provide estimates close to 1 (no difference between groups) despite dissimilar patient severity, while the 4 smaller RCTs [22,23,25,26] provide estimates that are considerably larger and inconsistent. Additionally, with the exception of 2 studies in moderately-ill patients, estimates varied in both magnitude and direction among studies with similar patient severity, suggesting an unclear relationship between severity of patients receiving treatment-dose anticoagulation and mortality risk.

Our confidence in these results is low due to the inconsistency described above, as well as study methodological limitations. In both RCTs and cohort studies, participants were often exposed to more than 1 anticoagulation medication. Moreover, participants in the same group (intervention or comparison group) did not always receive the same type of anticoagulation dose. For example, 22.4% of critically ill intervention group patients in the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial[20] received lower doses than therapeutic anticoagulation and 59.6% in the usual care group received higher doses than standard thromboprophylaxis at post-randomization day 1. Similarly, among non-critically ill patients in this trial,[21] 20.4% in the intervention group and 28.3% in the comparison group received lower than therapeutic or higher than standard prophylaxis anticoagulation doses, respectively. In the HEP-COVID trial,[26] 39% of comparison group participants received intermediate-dose anticoagulation rather than standard thromboprophylaxis. Dose changes during the study period and receipt of different anticoagulation medications and doses within intervention and comparison groups could influence observed between-group differences in outcomes.

In summary, therapeutic-dose anticoagulation does not appear to provide a mortality benefit compared to standard thromboprophylaxis based on pooled RCT estimates, which are further supported by estimates from cohort studies, although our confidence in findings remains low.

THROMBOTIC EVENTS

Therapeutic anticoagulation, but not intermediate-dose anticoagulation, may be associated with reduced occurrence of thrombotic events compared to standard thromboprophylaxis.

Twenty studies (the INSPIRATION and Perepu et al trials[24,27,62] and 18 cohorts[11,29-31,35,38-41,43,45,47,52,55-57,59,61]) evaluated thrombotic events among patients who received intermediate-dose anticoagulation compared to those who received standard thromboprophylaxis (Appendix C in the Supplemental Materials). Results suggest that the risk of thrombotic events with intermediate-dose anticoagulation compared to standard thromboprophylaxis is similar, although as with mortality outcomes, the direction of effect estimates differed between the 2 trials. In the INSPIRATION trial,[27,62] the risk of DVT or PE was similar in both groups (HR = 0.93, 95% CI [0.48, 1.76]). Perepu et al also found no statistically significant difference between groups (OR = 1.79, 95% CI [0.51, 6.25], $p > 0.99$), but the effect estimate was in the direction of benefit. Like mortality outcomes, divergent findings between these 2 trials may be due to inclusion of patients with less severe disease in Perepu et al. The overall finding of no significant difference in thrombotic event risk between groups receiving intermediate-dose anticoagulation and standard

thromboprophylaxis is supported by results of 7 cohort studies[11,30,38,41,45,47,56,57] providing risk estimates, which were mostly consistent in finding no difference.

Sixteen studies (6 RCTs[20-23,25,26] and 10 cohorts[11,35,37-41,48,52,58]) evaluated thrombotic events among patients who received therapeutic-dose anticoagulation compared to those who received standard thromboprophylaxis (Appendix C in the Supplemental Materials). Results suggest that the risk of thrombotic events may be lower with treatment-dose anticoagulation. This finding was consistent across RCTs with the exception of a small trial[22] of 20 participants, in which thrombotic event rates were the same (20%) in both the intervention and control groups. Among 3 cohorts that reported risk estimates, two[11,37] found that therapeutic-dose anticoagulation was associated with a lower risk of thrombotic events compared to standard thromboprophylaxis. The exception was a US cohort study of 4,645 adults with a mix of disease severity which found no difference in venous thromboembolism risk with therapeutic-dose anticoagulation compared to standard thromboprophylaxis.[41] However, more than half (129/251) of first in-hospital venous thromboembolism events were diagnosed within 24 hours of admission, a timeline which makes the correlation of any anticoagulation dose with thrombotic event outcomes less plausible and is a serious a methodological limitation of this study.

Our confidence in findings related to the risk of thrombotic events for both intermediate-dose anticoagulation and therapeutic anticoagulation is low. Studies varied considerably in how thrombotic events were defined (*eg*, defined as all thrombotic events, only venous thromboembolism, or only PE or DVT) and measured. In most studies, diagnostic imaging was obtained based on clinical symptoms and signs, rather than as part of a screening protocol. However, it is likely that clinical decisions regarding which patients to test for thrombotic complications were highly contextual and influenced not only by patient characteristics but by hospital protocols and culture as well as available staff and imaging resources. In RCTs (which were open-label) and cohort studies, awareness of anticoagulation dose may have also influenced decisions to obtain diagnostic imaging.

BLEEDING RISK

Both intermediate- and therapeutic-dose anticoagulation may be associated with increased risk of bleeding compared to standard thromboprophylaxis, with the risk level appearing to be dose-dependent.

Nineteen studies (the INSPIRATION and Perepu et al trials[24,27,62] and 17 cohorts[11,14,29,30,35,36,38-40,43,45,47,49,51,52,56,59]) evaluated bleeding outcomes with intermediate-dose anticoagulation compared to standard thromboprophylaxis (Appendix C in the Supplemental Materials). Synthesizing effect estimates from 3 studies providing hazard ratios and 15 studies reporting or providing data to calculate risk ratios suggests that use of intermediate-dose anticoagulation may be associated with increased bleeding (overall HR = 1.80, 95% CI [0.22, 14.44], $k = 3$; overall RR = 1.28, 95% CI [0.92, 1.78], $k = 15$). However, these overall estimates were not statistically significant, and in the case of the overall hazard ratio, were imprecisely estimated (wide confidence interval). No heterogeneity was present in the overall risk estimate (95% PI [0.92, 1.78]), while substantial heterogeneity occurred among hazard ratios (95% PI [0.04, 82.05]).

Nineteen studies (6 RCTs[20-23,25,26] and 13 cohorts[11,14,33-40,44,52,60]) evaluated bleeding outcomes with therapeutic-dose anticoagulation compared to standard thromboprophylaxis (Appendix C in

the Supplemental Materials). Synthesizing effect estimates from these studies suggests that use of therapeutic-dose anticoagulation is associated with increased bleeding risk compared to standard thromboprophylaxis (overall RR = 2.18, 95% CI [1.59, 2.98], k = 18), a finding which was statistically significant ($p < .001$). A post hoc analysis of data from RCTs only also suggests increased risk (overall RR = 1.69, 95% CI [0.84, 3.41], k = 6), although in this case the finding was nonsignificant. Substantial heterogeneity was present among risk ratios (95% PI [1.02, 4.65]). The single cohort study[36] reporting a hazard ratio also observed an increased risk of bleeding among patients receiving therapeutic-dose anticoagulation (adjusted HR = 1.55, 95% CI [0.88, 2.73]), compared with patients receiving standard-dose anticoagulation (groups were statistically balanced on indicators of disease severity and dialysis history). Although this effect was not statistically significant, when variation in anticoagulation intensity over time was accounted for, a larger and significant risk of bleeding was found for patients receiving therapeutic-dose anticoagulation (adjusted HR = 2.59, 95% CI [1.20, 5.57]).

We have low confidence in these estimates, which are primarily derived from cohort studies with unclear or high risk of bias. In contrast to mortality results, most reported bleeding results were unadjusted, increasing risk of confounding. Bleeding events were also rare, limiting the ability of studies to detect differences between groups. In the INSPIRATION trial, for example, 7/276 (2.5%) and 4/286 (1.4%) participants in the intervention and control groups experienced major bleeding, respectively, although bleeding was fatal for 3 patients receiving intermediate-dose anticoagulation.[27] Similarly, in the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial, major bleeding occurred in 20/529 (3.8%) and 13/562 (2.3%) of critically ill adults receiving therapeutic-dose anticoagulation and standard thromboprophylaxis, respectively, and was overall less common among non-critically ill adults.[20,21]

DISCUSSION

Many hospitals and health systems have adopted novel approaches to anticoagulation management for patients with COVID-19 that differ from pre-pandemic guideline-recommended thromboprophylaxis for adults hospitalized with medical illness. To inform VHA clinical policies and practices, the aim of this review was to synthesize evidence (based on a literature search through October 12, 2021) on the benefits and harms of intermediate-dose and therapeutic-dose anticoagulation compared to standard thromboprophylaxis among adults hospitalized with COVID-19.

Intermediate-dose anticoagulation (doses between those used for prophylaxis and treatment of diagnosed thrombotic disease) does not appear to reduce the risk of thrombotic events but may provide a small mortality benefit compared to standard thromboprophylaxis. In contrast, therapeutic-dose anticoagulation may reduce the risk of thrombotic events compared to standard thromboprophylaxis but does not appear to offer a mortality benefit. Our confidence in these findings is low due to study methodological limitations, with the most notable limitation being that some participants did not receive the same anticoagulation dose as their assigned group and/or were exposed to different doses during the study period. Although mostly consistent, results were imprecise (wide confidence intervals) for some outcomes. In terms of harms, when considered alongside extensive pre-pandemic evidence linking higher anticoagulation doses to increased bleeding risk, available COVID-19-specific evidence is sufficient to conclude that higher doses of anticoagulation are likely associated with a dose-dependent increase in bleeding risk among hospitalized patients with COVID-19 comparable to adults hospitalized with other medical illnesses.[4,6] Several other reviews have been conducted on this topic (based on a March 2, 2022 search of the COVID-19 review repository, www.covid19reviews.org). Our conclusions are largely consistent with those of a recent systematic review and meta-analysis of the same RCTs that we included.[63]

Results of the ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial provide an example of the nuance involved in estimating benefits and harms of anticoagulation approaches in COVID-19 and the important knowledge gaps that still exist. In this large trial, separate analyses for non-critically ill and critically ill participants who received therapeutic-dose anticoagulation had divergent findings, suggesting possible benefit for non-critically ill participants but potential harms for those who were critically ill (based on a composite outcome of hospital survival and days free of organ support). Likewise, findings from this evidence synthesis suggest a mortality benefit compared to standard thromboprophylaxis, if any, may be more likely in those with lower disease severity. However, no RCT to date has directly compared intermediate-dose anticoagulation to therapeutic-dose anticoagulation among adults with both non-critical and critical illness. Therefore, questions remain regarding whether possible benefits of higher anticoagulation doses are due to the dose itself or timing. In other words, evidence to date has not addressed whether intermediate-dose anticoagulation initiated earlier in the disease course (*ie*, among those with moderate disease) would confer equivalent benefits as therapeutic-dose anticoagulation. Given the dose-dependent risks associated with anticoagulation, determining the incremental benefit of intermediate-dose compared to therapeutic-dose anticoagulation, if any, should be a priority of future research.

Although not the focus of this review, a well-conducted retrospective cohort study[64] of standard thromboprophylaxis among 4,297 US Veterans with COVID-19 receiving care in VHA hospitals

from March 1 to July 31, 2020 found that thromboprophylaxis was associated with a reduced risk of receiving therapeutic anticoagulation after the first 24 hours of hospital admission (HR = 0.81, 95% CI [0.73, 0.90]), a proxy measure for diagnosed thrombotic events and/or clinical worsening. This study also found that initiation of thromboprophylaxis within the first 24 hours of admission was associated with a decreased risk of 30-day mortality (HR = 0.73, 95% CI [0.66, 0.81]) compared to not receiving thromboprophylaxis. Results of this VHA study attest to use of standard thromboprophylaxis as a sound clinical approach to management of hospitalized adults with COVID-19, an approach that is consistent with current NIH guidelines[65] recommending use of prophylactic-dose heparin for hospitalized adults who do not have a contraindication and who are not receiving therapeutic heparin.

CURRENT GUIDELINES

National Institutes of Health (NIH) clinical guidelines regarding use of antithrombotic therapies in patients with COVID-19[65] (updated February 24, 2022) recommend use of therapeutic-dose heparin (but not oral anticoagulants) for hospitalized adults who require low-flow oxygen but not ICU-level care, who have a D-dimer value above the upper limit of normal, and do not have increased bleeding risk. For adults who require ICU-level care, NIH guidelines recommend against using intermediate or therapeutic anticoagulation doses.

NIH guidance is similar to current recommendations from the American Society of Hematology (ASH), which has released a *draft* statement (as of December 16, 2021) suggesting use of therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness.[66] For those with critical illness, ASH has published a statement suggesting use of prophylactic-intensity over intermediate-intensity anticoagulation.[67] In a living guidance document,[68] the World Health Organization (WHO) suggests administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing and, unlike NIH and ASH, does not provide separate guidance for non-critically ill and critically-ill patients (as of November 23, 2021). See Appendix E for an overview of relevant recommendations from NIH as well as other key scientific groups and clinical societies.

LIMITATIONS

The evidence included in this review has several important limitations. First, methodological issues of cohort studies limit our confidence in findings. These issues include high potential for unmeasured confounders (patients at higher risk of thrombotic events and/or poor outcomes are more likely to be prescribed higher doses of antithrombotic medications), inadequate or lack of statistical adjustment techniques, and lack of accounting for co-interventions (use of COVID-19 therapies that may influence outcomes) or other factors affecting clinical care (such as nurse-to-patient ratios). Second, results of included RCTs and cohort studies could be skewed by patients' receipt of different anticoagulation medications and doses during the study period, either by design (*ie,* studies allowed for treatment changes based on clinical judgement) or factors external to the study such as a change in hospital policies. Also, in our effort to include all relevant findings, we included studies in which a portion of the patients in either the intervention or comparison group did not receive the same anticoagulation dosing. We have identified these studies in the footnotes of Tables 2 and 3. Third, some studies including the largest RCTs used composite primary outcomes with different components, limiting the ability to compare primary outcomes across studies. Fourth, most included trials evaluated heparin or LMWH, with the

exception of 2 trials[23,25] of therapeutic-dose anticoagulation (ACTION and RAPID) that included participants receiving DOACs. Findings are therefore most clinically applicable to patients who might receive heparin or LMWH anticoagulation rather than other forms of anticoagulation, with the caveat that published trial data is insufficient to recommend one type of anticoagulant over another (trials were not designed to address this clinical question). Finally, most studies were conducted in early 2020, and it is possible that clinical practices have evolved in the interim and findings from this evidence base are less relevant now. The incidence of thrombotic complications in COVID-19 could also be changing with the arrival of new variants or shifts in the age distribution of affected patients.

Limitations of our methods include single review at the abstract screening level, which could have led to missing eligible studies, and sequential review for study selection, data abstraction, and quality assessment (in contrast to dual independent review for all steps). Another limitation is our scope, with a narrow focus on comparisons of intermediate- and therapeutic-dose anticoagulation to standard thromboprophylaxis in the inpatient setting and not on comparisons of standard thromboprophylaxis with other novel antithrombotic strategies in COVID-19 or use of anticoagulation in the outpatient setting.

RESEARCH IN PROGRESS

We identified 12 ongoing trials, including two[69,70] that are complete but do not yet have published results (Appendix E in Supplemental Materials). Both of these completed trials are small (fewer than 200 participants) and compared thrombotic events with intermediate-dose anticoagulation to standard thromboprophylaxis. Among trials that are currently recruiting, 2 will investigate mortality with intermediate and therapeutic-dose anticoagulation compared to standard thromboprophylaxis.[71,72]

CONCLUSIONS

Intermediate-dose anticoagulation does not appear to reduce the risk of thrombotic events but may provide a small mortality benefit compared to standard thromboprophylaxis. In contrast, therapeutic-dose anticoagulation may reduce the risk of thrombotic events compared to standard thromboprophylaxis but does not appear to offer a mortality benefit. Although limited, COVID-19-specific evidence on bleeding risk is sufficient to conclude that higher doses of anticoagulation are likely associated with a dose-dependent increase in bleeding risk among adults hospitalized with COVID-19. Our confidence in these findings is low, and the evolving and currently incomplete understanding of any potential benefits of higher-dose anticoagulation must be weighed against known potential harms. An important gap in the existing evidence is whether the benefits of higher anticoagulation doses, if any, depend more on when anticoagulation is initiated (*ie*, earlier in the disease course when disease is moderate and not severe or critical) or the dose itself. This question could be addressed in a trial directly comparing benefits of harms of intermediate-dose anticoagulation compared to both therapeutic-dose anticoagulation and standard thromboprophylaxis doses.

REFERENCES

1. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75(23):2950-2973.
2. Poor HD, Ventetuolo CE, Tolbert T, et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. *Clinical and Translational Medicine.* 2020;13:13.
3. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *The Lancet Haematology.* 2020;7(5):e362-e363.
4. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Advances.* 2018;2(22):3198-3225.
5. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv.* 2018;2(22):3257-3291.
6. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest.* 2021;160(6):e545-e608.
7. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343.
8. Sterne JA, Hernán MA, McAleenan A, Reeves BC, Higgins JP. Assessing risk of bias in a non-randomized study. In: *Cochrane Handbook for Systematic Reviews of Interventions.*2019:621-641.
9. Berkman N, Lohr K, Ansari M, McDonagh M, Balk E, Whitlock E. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ publication no. 13 (14)-EHC130-EF. *Rockville Agency for Healthcare Research and Quality.* 2013.
10. Slavin RE. Best evidence synthesis: an intelligent alternative to meta-analysis. *J Clin Epidemiol.* 1995;48(1):9-18.
11. Atallah B, Sadik ZG, Salem N, et al. The impact of protocol-based high-intensity pharmacological thromboprophylaxis on thrombotic events in critically ill COVID-19 patients. *Anaesthesia.* 2020;12:12.
12. VanderWeele TJ. On a Square-Root Transformation of the Odds Ratio for a Common Outcome. *Epidemiology.* 2017;28(6):e58-e60.
13. VanderWeele TJ. Optimal approximate conversions of odds ratios and hazard ratios to risk ratios. *Biometrics.* 2020;76(3):746-752.
14. Kessler C, Stricker H, Demundo D, et al. Bleeding prevalence in COVID-19 patients receiving intensive antithrombotic prophylaxis. *J Thromb Thrombolysis.* 2020;50(4):833-836.
15. Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. *Cochrane handbook for systematic reviews of interventions.* 2019:143-176.
16. Borenstein M, Higgins JPT, Hedges LV, Rothstein HR. Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. *Research Synthesis Methods.* 2017;8(1):5-18.

17. Parr NJ, Schweer-Collins ML, Darlington TM, Tanner-Smith EE. Meta-analytic approaches for examining complexity and heterogeneity in studies of adolescent development. *Journal of adolescence.* 2019;77:168-178.
18. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Statistics in Medicine.* 2003;22(17):2693-2710.
19. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *2010.* 2010;36(3):48.
20. Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med.* 2021;385(9):777-789.
21. Lawler PR, Goligher EC, Berger JS, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *N Engl J Med.* 2021;385(9):790-802.
22. Lemos ACB, do Espirito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thromb Res.* 2020;196:359-366.
23. Lopes RD, Furtado RH, Macedo AVS, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *The Lancet.* 2021.
24. Perepu US, Chambers I, Wahab A, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: a multi-center, open-label, randomized controlled trial. *Journal of Thrombosis and Haemostasis.* 2021;19(9):2225-2234.
25. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *Bmj.* 2021;375.
26. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med.* 2021;181(12):1612-1620.
27. Bikdeli B, Talasaz AH, Rashidi F, et al. Intermediate-Dose versus Standard-Dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to the Intensive Care Unit: 90-Day Results from the INSPIRATION Randomized Trial. *Thromb Haemost.* 2022;122(1):131-141.
28. Al-Samkari H, Gupta S, Karp Leaf R, et al. Thrombosis, bleeding, and the effect of anticoagulation on survival in critically ill patients with COVID-19 in the United States. *Research and Practice in Thrombosis and Haemostasis.* 2020;4(SUPPL 2).
29. Arachchillage DR, Shi C, Saliu D, et al. Efficacy safety and of D-dimer, weight, and renal function-adjusted thromboprophylaxis in patients with coronavirus disease 2019 (COVID-19). Paper presented at: Seminars in Thrombosis and Hemostasis2021.
30. Avruscio, Giampiero, Camporese, et al. COVID-19 and Venous Thromboembolism in Intensive Care or Medical Ward. *Clin Transl Sci.* 2020.
31. Benito N, Filella D, Mateo J, et al. Pulmonary Thrombosis or Embolism in a Large Cohort of Hospitalized Patients With Covid-19. *Frontiers in Medicine.* 2020.
32. Canoglu K, Saylan B. Therapeutic dosing of low-molecular-weight heparin may decrease mortality in patients with severe COVID-19 infection. *Annals of Saudi Medicine.* 2020;40(6):462-468.
33. Elmelhat A, Elbourai E, Dewedar H, et al. Comparison between Prophylactic versus Therapeutic Doses of Low-Molecular-Weight Heparin in Severely Ill Coronavirus

Disease 2019 Patients in Relation to Disease Progression and Outcome. *Dubai Medical Journal.* 2020.
34. Ferguson J, Volk S, Vondracek T, Flanigan J, Chernaik A. Empiric therapeutic anticoagulation and mortality in critically ill patients with respiratory failure from SARS-CoV-2: A retrospective cohort study. *Journal of Clinical Pharmacology.* 2020;03:03.
35. Gabara C, Solarat B, Castro P, et al. Anticoagulation strategies and risk of bleeding events in critically ill COVID-19 patients. *Med.* 2021.
36. Halaby R, Cuker A, Yui J, et al. Bleeding risk by intensity of anticoagulation in critically ill patients with COVID-19: A retrospective cohort study. *Journal of Thrombosis and Haemostasis.* 2021.
37. Helms J, Severac F, Merdji H, et al. Higher anticoagulation targets and risk of thrombotic events in severe COVID-19 patients: bi-center cohort study. *Annals of Intensive Care.* 2021;11(1):1-8.
38. Hsu A, Liu Y, Zayac AS, Olszewski AJ, Reagan JL. Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia. *Thromb Res.* 2020.
39. Jiménez-Soto R, Aguilar-Soto M, Rodríguez-Toledo CA, Camiro-Zúñiga A, Demichelis R. The impact of different prophylactic anticoagulation doses on the outcomes of patients with COVID-19. *Thromb Res.* 2021;202:14-16.
40. Jonmarker S, Hollenberg J, Dahlberg M, et al. DOSING OF THROMBOPROPHYLAXIS AND MORTALITY IN CRITICALLY ILL COVID-19 PATIENTS. *Critical Care.* 2020.
41. Kumar G, Patel D, Odeh T, et al. Incidence of Venous Thromboembolism and Effect of Anticoagulant Dosing in Hospitalized COVID-19 Patients. *Journal of hematology.* 2021.
42. Kuno T, So M, Takahashi M, Egorova NN. Prophylactic versus therapeutic anticoagulation for survival of patients with COVID-19 on steroid. *Journal of thrombosis and thrombolysis.* 2021:1-7.
43. Lavinio A, Ercole A, Battaglini D, et al. Safety profile of enhanced thromboprophylaxis strategies for critically ill COVID-19 patients during the first wave of the pandemic: observational report from 28 European intensive care units. *Critical Care.* 2021;25(1):1-10.
44. Lynn L, Reyes JA, Hawkins K, et al. The effect of anticoagulation on clinical outcomes in novel Coronavirus (COVID-19) pneumonia in a U.S. cohort. *Thromb Res.* 2020;197:65-68.
45. Martinelli I, Ciavarella A, Abbattista M, et al. Increasing dosages of low-molecular-weight heparin in hospitalized patients with Covid-19. *Intern.* 2021;03:03.
46. Meizlish ML, Goshua G, Liu Y, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a propensity score-matched analysis. *Am J Hematol.* 2021;21:21.
47. Moll M, Zon RL, Sylvester KW, et al. Intermediate versus standard dose heparin prophylaxis in COVID-19 ICU patients: A propensity score-matched analysis. *Thromb Res.* 2021;203:57-60.
48. Motta JK, Ogunnaike RO, Shah R, et al. Clinical Outcomes With the Use of Prophylactic Versus Therapeutic Anticoagulation in Coronavirus Disease 2019. *Critical Care Explorations.* 2020;2(12):e0309.
49. Paolisso P, Bergamaschi L, D'Angelo EC, et al. Preliminary Experience With Low Molecular Weight Heparin Strategy in COVID-19 Patients. *Frontiers in Pharmacology.* 2020;11:1124.

50. Patel NG, Bhasin A, Feinglass, Joseph M., Angarone MP, Cohen ER, Barsuk JH. Mortality, Critical Illness, and Mechanical Ventilation among Hospitalized Patients with COVID-19 on Therapeutic Anticoagulants. *Thrombosis Update.* 2020.
51. Pesavento R, Ceccato D, Pasquetto G, et al. The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: the Padua province experience. *J Thromb Haemost.* 2020;21:21.
52. Pieralli F, Pomero F, Giampieri M, et al. Incidence of deep vein thrombosis through an ultrasound surveillance protocol in patients with COVID-19 pneumonia in non-ICU setting: A multicenter prospective study. *Plos one.* 2021;16(5):e0251966.
53. Qin W, Dong F, Zhang Z, et al. Low molecular weight heparin and 28-day mortality among patients with coronavirus disease 2019: A cohort study in the early epidemic era. *Thromb Res.* 2021;198:19-22.
54. Çopur B, Surme S, Sayılı U, et al. Comparison of standard prophylactic and preemptive therapeutic low molecular weight heparin treatments in hospitalized patients with COVID-19. *Bratislava Medical Journal.* 2021;122:626-630.
55. Stessel B, Vanvuchelen C, Bruckers L, et al. Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study. *Thromb Res.* 2020;194:209-215.
56. Taccone FS, Gevenois PA, Peluso L, et al. Higher Intensity Thromboprophylaxis Regimens and Pulmonary Embolism in Critically Ill Coronavirus Disease 2019 Patients. *Crit Care Med.* 2020;48(11):e1087-e1090.
57. Tacquard C, Mansour A, Godon A, et al. Impact of high dose prophylactic anticoagulation in critically ill patients with COVID-19 pneumonia. *Chest.* 2021;16:16.
58. Vaughn VM, Yost M, Abshire C, et al. Trends in Venous Thromboembolism Anticoagulation in Patients Hospitalized With COVID-19. *JAMA netw.* 2021;4(6):e2111788-e2111788.
59. Voicu S, Chousterman BG, Bonnin P, et al. Increased anticoagulation reduces proximal deep vein thrombosis in mechanically ventilated COVID-19 patients: Venous thrombosis prevention & COVID-19. *Journal of Infection.* 2020;20:20.
60. Yu B, Gutierrez VP, Carlos A, et al. Empiric use of anticoagulation in hospitalized patients with COVID-19: a propensity score-matched study of risks and benefits. *Biomarker research.* 2021;9(1):1-11.
61. Zermatten MG, Pantet O, Gomez F, et al. Utility of D-dimers and intermediate-dose prophylaxis for venous thromboembolism in critically ill patients with COVID-19. *Thromb Res.* 2020;196:222-226.
62. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *Jama.* 2021;325(16):1620-1630.
63. Reis S, Popp M, Schmid B, et al. Safety and Efficacy of Intermediate-and Therapeutic-Dose Anticoagulation for Hospitalised Patients with COVID-19: A Systematic Review and Meta-Analysis. *J.* 2021;11(1):57.
64. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *Bmj.* 2021;372.

65. Antithrombotic Therapy in Patients With COVID-19. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/. Published 2022. Updated Febraury 24, 2022. Accessed March 2, 2022.
66. ASH Guidelines on Use of Anticoagulation in Patients with COVID-19. American Society of Hematology. https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19. Published 2021. Updated December 16, 2021. Accessed March 2, 2022.
67. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: May 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients. *Blood Advances.* 2021;5(20):3951-3959.
68. Organization WH. COVID-19 clinical management: living guidance, 25 January 2021. World Health Organization. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Published 2021. Updated January 25, 2021. Accessed July 19, 2021.
69. Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19 (IMPROVE). NCT04367831. https://clinicaltrials.gov/ct2/show/NCT04367831. Published 2021. Updated September 29, 2021. Accessed 2022, March 2.
70. Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients (X-Covid 19). https://www.clinicaltrials.gov/ct2/show/NCT04366960. Published 2021. Updated June 8, 2021. Accessed 2022, March 2.
71. ANTIcoagulation in Severe COVID-19 Patients (ANTICOVID). https://www.clinicaltrials.gov/ct2/show/NCT04808882. Published 2021. Updated July 14, 2021. Accessed 2022, March 2.
72. Standard vs High Prophylactic Doses or Anticoagulation in Patients With High Risk of Thrombosis Admitted With COVID-19 Pneumonia (PROTHROMCOVID). Hospital Universitario Infanta Leonor. https://clinicaltrials.gov/ct2/show/NCT04730856. Published 2022. Updated June 4, 2021. Accessed March 2, 2022.