Systematic Review/Meta-analysis

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Factor Xa inhibitors versus low-molecular-weight heparin for preventing coagulopathy following COVID-19: a systematic review and meta-analysis of randomized controlled trials

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Background: Hospitalized patients with COVID-19 have shown a significant occurrence of thromboembolism and a heightened risk of death. It remains unclear whether factor Xa inhibitors are superior to enoxaparin in this context. Hence, there is a need for a direct comparison to assess the preventive effects and safety of factor Xa inhibitors versus enoxaparin in hospitalized COVID-19 patients.

Methods: MEDLINE, Embase, and Cochrane Central databases were searched for randomized controlled trials (RCTs) or retrospective studies that compared the effectiveness or safety of factor Xa inhibitors and enoxaparin in preventing thromboembolism in hospitalized patients with COVID-19. Embolic incidence, incidence of bleeding, and all-cause mortality were among the outcomes of interest. Mantel–Haenszel weighted random-effects model was used to calculate relative risks (RRs) with 95 percent CIs.

Results: The analysis included six RCTs and two retrospective studies containing 4048 patients. Meta-analysis showed a statistically significant reduction among patients on factor Xa inhibitors compared with low-molecular-weight heparin (LMWH) in the embolic incidence [risk ratio (RR) 0.64 (95%, CI 0.42, 0.98); $P = 0.04$, $I^2 = 12\%$]. Upon subgroup analysis by type of study design, no significant reductions were noted in patients on factor Xa inhibitors in RCTs (RR: 0.62; 95% CI: 0.33–1.17; $P = 0.14$) or observational studies (RR: 0.53; 95% CI: 0.23–1.26; $P = 0.15$) when compared with enoxaparin Factor Xa inhibitors were not significantly associated with incidence of bleeding [RR 0.76 (95% CI 0.36, 1.61); $P = 0.47$, $I^2 = 0\%$] or all-cause mortality (RR: 0.81; 95% CI: 0.48–1.36; $P = 0.43$). Consistent results were obtained upon subgroup analysis by the type of study design.

Conclusion: Factor Xa inhibitors are more effective than enoxaparin in preventing thromboembolism among patients with COVID-19 who are not acutely ill and are hospitalized. Additional rigorous RCTs comparing factor Xa inhibitors with enoxaparin are warranted.

Keywords: coagulopathy, covid-19, factor Xa, heparin, molecular weight

Introduction

Concerns regarding the detrimental ramifications of the global COVID-19 have increased since the outbreak of the epidemic began. Thrombosis is a critical component in the understanding of COVID-19, with its mechanisms primarily involving complement activation, endothelial inflammation, thrombin production, platelet and leukocyte recruitment, and the induction of innate and adaptive immune responses in patients[1]. It is frequently accompanied by a sequence of embolic events and elevated d-dimer levels[2]. Patients with COVID-19 may experience a high incidence of thromboembolic events, according to a number of studies. Despite a poor prognosis, non-intensive care unit patients continue to have a high incidence of Venous thromboembolism (VTE). Moreover, among COVID-19 patients, thrombotic events have emerged as a significant cause of mortality[3]. According to reports, thromboembolism may substantially elevate the risk of

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mortality. It appears that anticoagulation is the most effective treatment for patients with COVID-19 in order to enhance survival rates and prevent thromboembolism[4].

Pharmacological thromboprophylaxis was administered in greater proportions in response to the severity of COVID-19. Heparins and vitamin K antagonists (VKAs) have been the cornerstones of anticoagulant therapy and prevention for potentially fatal thromboembolic events[5]. Although their impact is substantial, they are not without their limitations. For instance, the administration of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) beyond the hospital environment is impractical due to the necessity of injections or infusions[6]. In addition, monitoring is necessary for UFH due to its brief half-life and unpredictable plasma concentrations. Furthermore, the interaction between VKA and warfarin has significantly increased the risk of hemorrhage as a result of environmental influences and drug interactions[7]. A novel class of oral anticoagulants was thankfully approved in 2010 for the prevention of thrombotic stroke, venous thromboembolism, and pulmonary embolism in patients with nonvalvular atrial fibrillation[8]. Following this, these factor Xa inhibitors evolved progressively into two classes: direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (dabigatran)[9]. Due to the greater predictability of their pharmacokinetic and pharmacodynamic properties in comparison to warfarin, regular monitoring of their anticoagulant effect was unnecessary. In contrast to conventional oral anticoagulants (VKAs), factor Xa inhibitors exhibit superior efficacy and safety with regard to hemorrhage control and prevention of VTE[10].

Heparin, an anticoagulant, was associated with a decreased risk of in-hospital mortality among COVID-19 patients who were hospitalized, according to multiple studies[6]. Hospitalized patients with COVID-19 are particularly vulnerable to thromboembolism, with studies indicating a substantial occurrence of VTE even among non-critically ill individuals. Anticoagulation therapy has emerged as a cornerstone in the management of COVID-19 to mitigate thrombotic risks and improve survival outcomes. Anticoagulants such as heparins and vitamin K antagonists have been widely utilized; however, their limitations, including the need for injections and monitoring, have prompted the exploration of alternative therapies. Whether factor Xa inhibitors are superior anticoagulant activity compared to LMWH, particularly enoxaparin, in hospitalized patients with COVID-19 remains uncertain. Hence, we undertook a systematic review and meta-analysis to evaluate the safety and effectiveness of factor Xa inhibitors in comparison to enoxaparin in assessing the prevention of thromboembolism among hospitalized patients with COVID-19.

HIGHLIGHTS

- Factor Xa inhibitors show promise as an alternative to low-molecular-weight heparin in preventing COVID-19-related coagulopathy.
- Our analysis consistently reveals a significant reduction in coagulopathy risk with factor Xa inhibitors compared to low-molecular-weight heparin, offering valuable insights for anticoagulant selection in COVID-19 management.
- This study underscores the potential of factor Xa inhibitors as targeted interventions for preventing COVID-19-associated coagulopathy, suggesting a shift towards more tailored and effective anticoagulant strategies in clinical practice.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A466) guidelines and the Risk of Bias in Systematic Reviews and assessment of multiple systematic reviews (AMSTAR, Supplemental Digital Content 2, http://links.lww.com/MS9/A467) 2 were both followed when doing this meta-analysis[11,12]. The International Prospective Register of Systematic Reviews (PROSPERO), maintained by the National Institute for Health Research (NIHR), contains information about this study. Since the information was accessible to the general public, institutional review board (IRB) approval was not necessary.

Data sources and search strategy

MEDLINE, EMBASE and Cochrane CENTRAL were comprehensively searched from inception through July 2021 by two independent reviewers (L.A. and K.Q.). We extracted studies based on abstracts and titles. A full-text appraisal was sought when required. We included the following search terms in our study: ('Direct Oral Anticoagulants' OR 'DOAC' OR 'Factor Xa Inhibitor' OR 'rivaroxaban' OR 'apixaban' OR 'edoxaban' OR 'dabigatran') AND ('Heparin' OR 'Low Molecular Weight Heparin' OR 'LMWH' OR 'unfractionated heparin' OR 'UFH' OR 'Enoxaparin') AND ('COVID-19' OR '2019 nCoV Disease' OR 'coronavirus disease 2019' OR 'novel coronavirus' OR 'SARS-CoV-2').

Study selection

The selection process for potentially relevant published studies involved a comprehensive review of the entire manuscript. The inclusion criteria for the meta-analysis focused on studies that examined the efficacy or safety of anticoagulation in patients with COVID-19. The specific selection criteria were as follows: (1) Randomized controlled trials (RCTs) were the primary focus, but retrospective studies were also considered when RCTs were insufficient. (2) Studies involving hospitalized patients aged 18 years or older with confirmed COVID-19 were included. (3) Studies that compared the effectiveness or safety of factor Xa inhibitors with that of heparin (LMWH or UFH) for preventive treatment were included. (4) Treatment studies specifically targeting patients after experiencing embolism were excluded as they did not address the prevention of embolism. (5) Duplicate publications, review articles, editorials, case reports, and animal experiments were excluded. There were no restrictions based on patient nationality or ethnicity. The decision to include or exclude published studies was carried out independently by two researchers, with any disagreements resolved through discussion until a consensus was reached or by consulting a third author. All articles were then uploaded to Endnote Reference Library (Version X7.5; Clarivate Analytics) software to remove any duplicates.

Data extraction and assessment of study quality

Two reviewers (L.A. and K.Q.) independently extracted from the selected studies, including characteristics of the studies, patient demographics, summary events, number of events, sample sizes and treatment type. Summary events were also extracted for outcomes of interest, and risk ratios (RRs) with 95% CIs were calculated from them. The following data were extracted: study design, publication year, number of test and control groups, age of test subjects and dose of test drugs. The quality of studies across six categories [selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias] was evaluated using the Cochrane Risk of Bias Tool (CRBT).

Statistical analysis

RevMan (version 5.3; Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration) was used for all statistical calculations. We pooled RRs with 95% CI with Mantel–Haenszel (MH) random-effects weighted methods. We assessed heterogeneity across studies by using Higgins I^2. Recurrent thrombosis events were stratified into subgroups based on the type of blood vessel involved (venous or arterial) to minimize the risk of bias. Egger's regression test was conducted to evaluate the risk of publication bias. Due to the small number of studies, we did not evaluate publication bias using funnel plots.

Results

Literature search and characteristics of included studies

Of the 510 articles that were found initially, 6 RCTs and 2 retrospective studies containing 4048 patients were finalized for this analysis[13–20]. PRISMA flow diagrams describe the literature search and research selection procedure (Fig. 1). Of the 510 articles that were found initially, 6 RCTs and 2 retrospective

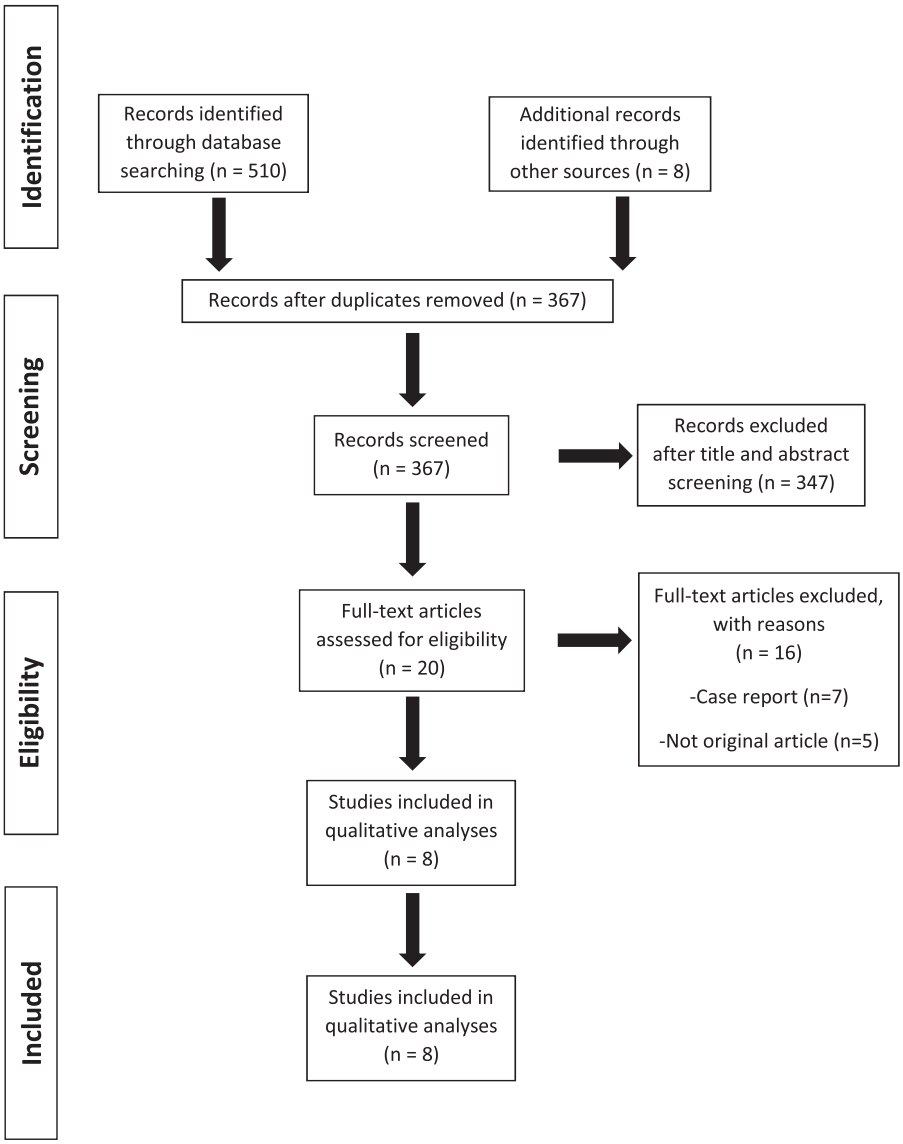

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram of study identification for meta-analysis.

Table 1

Baseline characteristics of included studies.

References	Country	Study design	Patients of group	Regimens	Total patients
Olivera *et al.*[13]	Spain	Retrospective Study	118	Edoxaban	232
			114	Enoxaparin	
Kumar *et al.*[14]	India	RCT	115	Rivaroxaban	228
			113	Enoxaparin	
ACTION[15]	Brazil	RCT	310	Rivaroxaban	614
			304	Enoxaparin or UFH	
Appiah[16]	USA	Retrospective Study	75	Apixaban	162
			87	Enoxaparin	
Mohammed *et al.*[17]	Egypt	RCT	58	Rivaroxaban	124
			66	Enoxaparin	
FREEDOM COVID[19]	USA	RCT	1121	Apixaban	2257
			1136	Enoxaparin	
COVID-PREVENT[18]	Germany	RCT	55	Rivaroxaban	111
			56	Enoxaparin	
MICHELLE[20]	Brazil	RCT	160	Rivaroxaban	320
			160	Enoxaparin	

RCT, randomized controlled trial; UFH, unfractionated heparin.

studies containing 4048 patients were finalized for this analysis. Table 1 lists the demographic and baseline characteristics. Egger's regression test was not significant for publication bias (t = 1.24, P = 0.820), as also depicted by the Funnel Plot (Fig. 2). The assessment of risk of bias in RCTs and observational studies are provided in Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A468 and Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A468 respectively.

Embolic incidence

Seven studies reported the effect of factor Xa inhibitors on embolic incidence. Meta-analysis revealed a statistically significant reduction in the risk of embolism among patients hospitalized for COVID-19 who received factor Xa inhibitors compared to those receiving enoxaparin (RR: 0.64; 95% CI: 0.42–0.98; P = 0.04). However, it is important to note that subgroup analyses by study design did not show significant reductions in embolic incidence for factor Xa inhibitors in either RCTs (RR: 0.62; 95% CI: 0.33–1.17; P = 0.14) or observational studies (RR: 0.53; 95% CI: 0.23–1.26; P = 0.15) when compared with enoxaparin. (Fig. 3)

Incidence of bleeding

Eight studies reported the effect of factor Xa inhibitors on the incidence of bleeding. Factor Xa inhibitors did not significantly

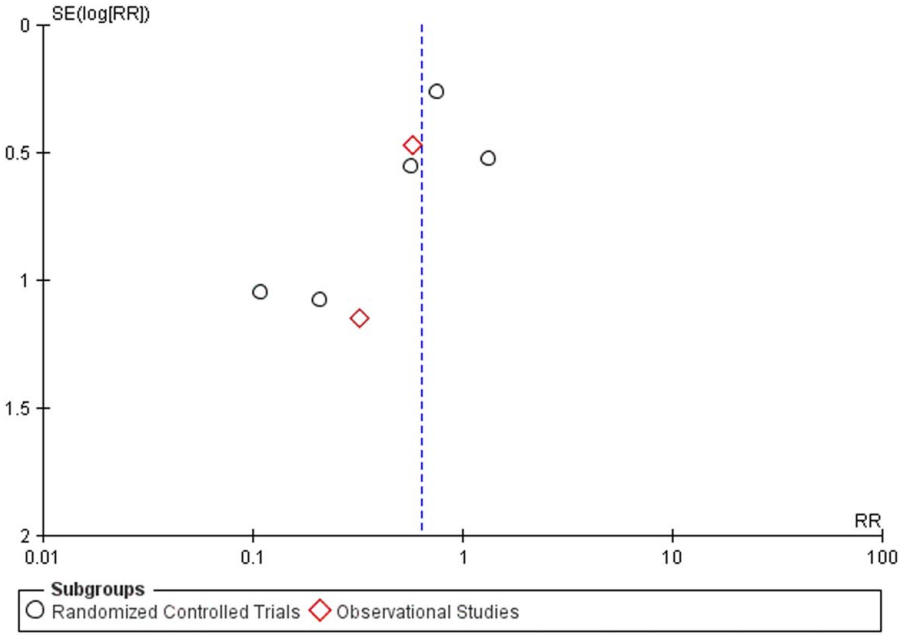

Figure 2. Funnel plot showing risk of publication bias for the outcome of embolic incidence.

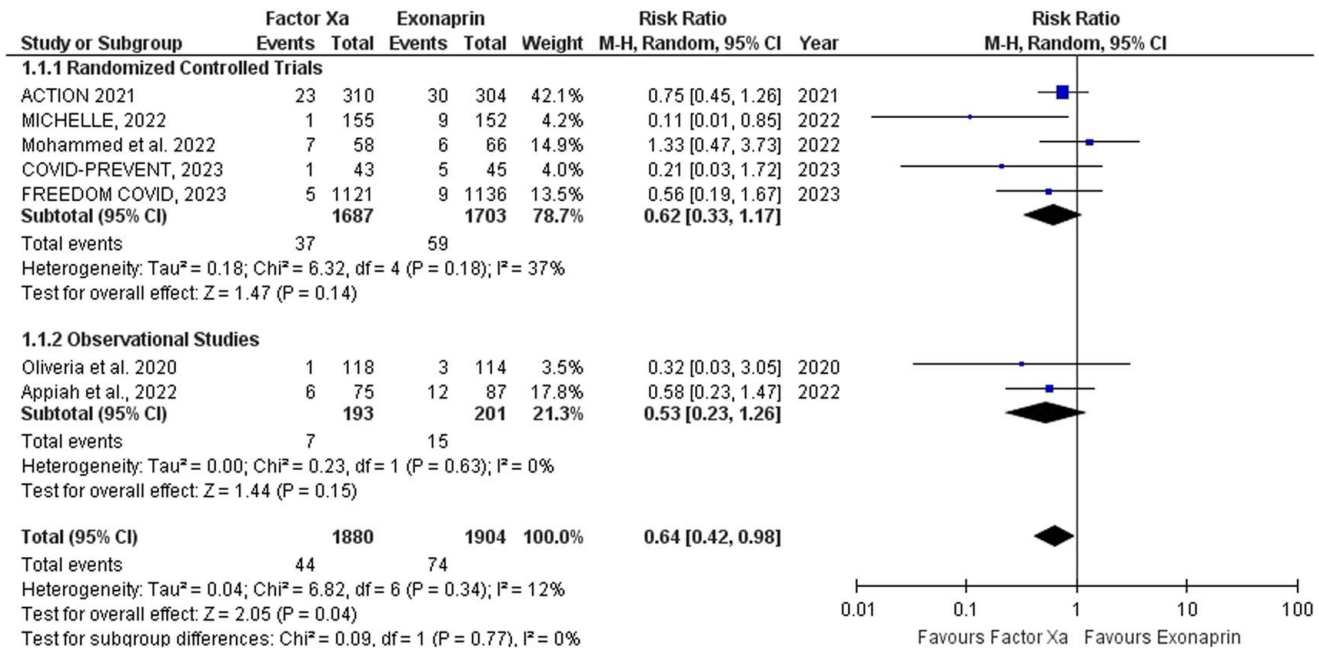

Figure 3. Forest plot showing results of factor Xa inhibitors versus enoxaparin on embolic incidence.

reduce the risk of bleeding in patients hospitalized for COVID-19 (RR: 0.76; 95% CI: 0.36–1.61; $P = 0.47$) when compared with enoxaparin. Subgroup analyses by study design also did not show significant differences in bleeding incidence between factor Xa inhibitors and enoxaparin groups. No significant reductions were noted in patients on factor Xa inhibitors in RCTs (RR: 1.33; 95% CI: 0.74–2.40; $P = 0.34$) or in observational studies (RR: 0.22; 95% CI: 0.02–2.03; $P = 0.18$) when compared with enoxaparin. (Fig. 4)

All-cause mortality

Six studies reported the effect of factor Xa inhibitors on all-cause mortality. Our meta-analysis did not find a significant difference

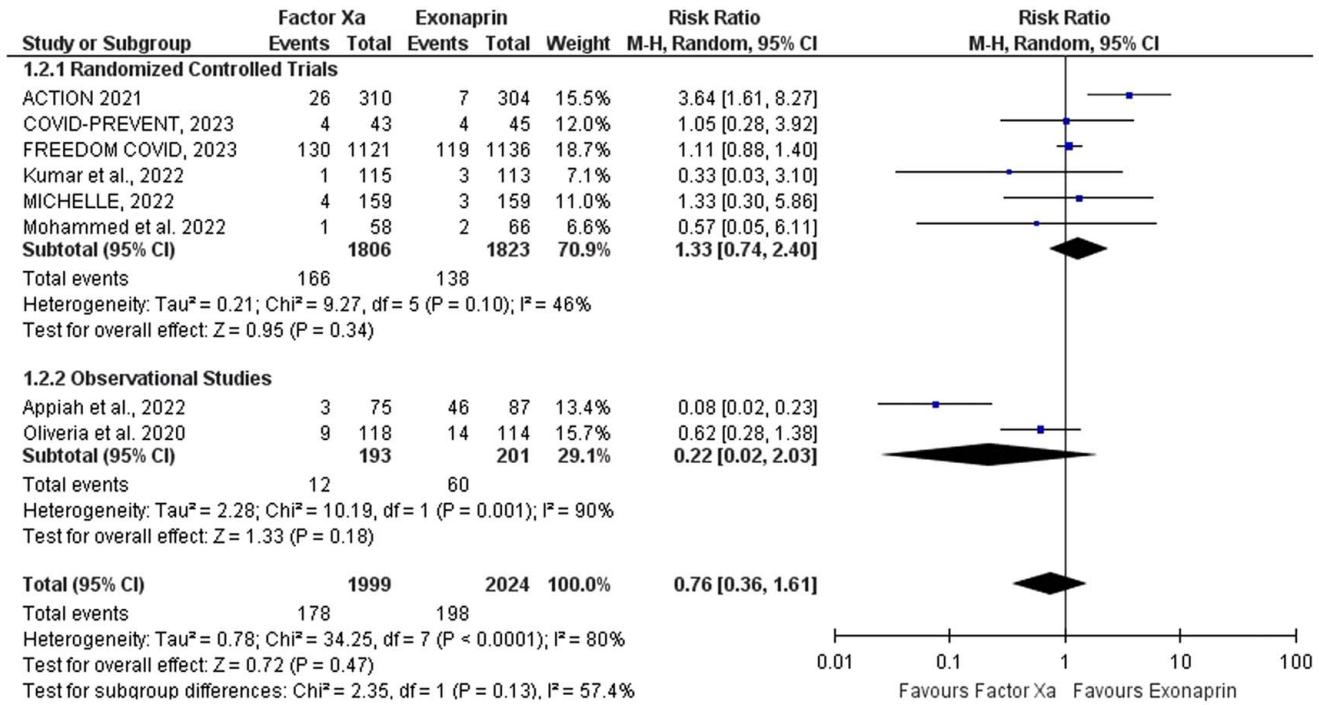

Figure 4. Forest plot showing results of apixaban versus low-molecular-weight heparin on incidence of bleeding.

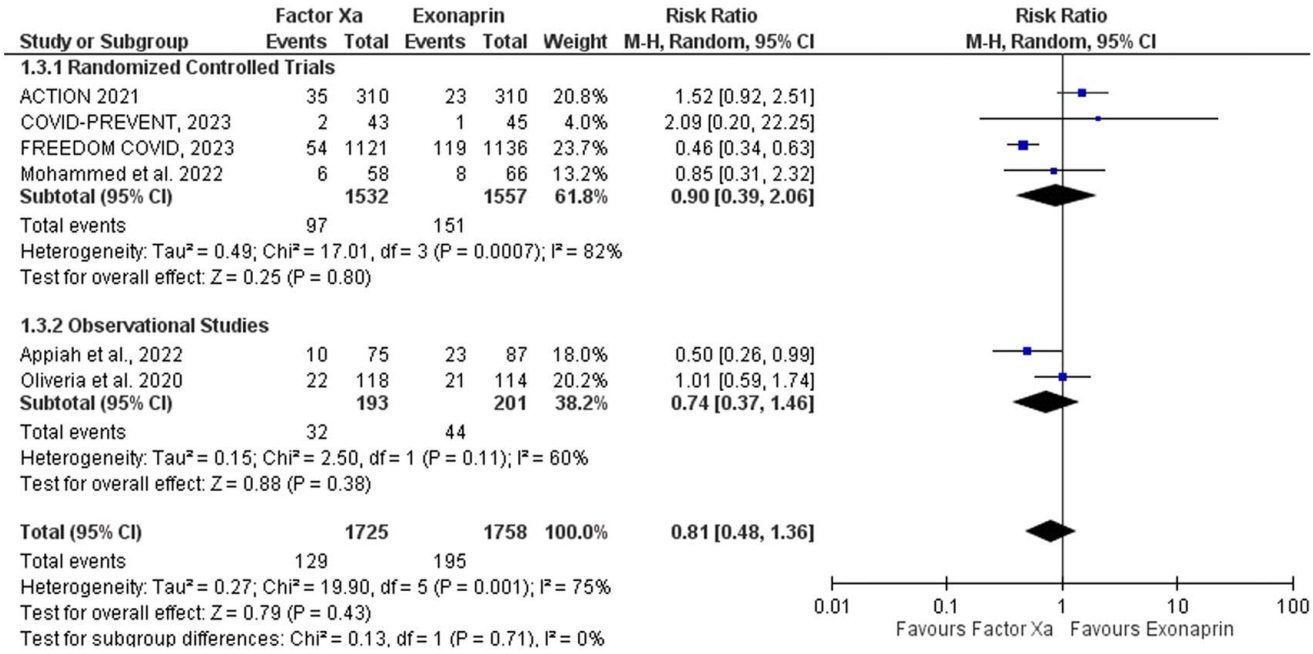

Figure 5. Forest plot showing results of apixaban versus low-molecular-weight heparin on all-cause mortality

in all-cause mortality between patients receiving factor Xa inhibitors and those receiving enoxaparin (RR: 0.81; 95% CI: 0.48–1.36; $P = 0.43$). Subgroup analyses by study design also showed consistent results across RCTs (RR: 0.90; 95% CI: 0.39–2.06; $P = 0.80$) and observational studies (RR: 0.74; 95% CI: 0.37–1.46; $P = 0.43$). (Fig. 5)

Discussion

Patients with COVID-19 may benefit from receiving prophylactic doses of anticoagulant therapy. Historically, the utilization of anticoagulants, primarily heparin, has been shown to decrease overall mortality in COVID-19 patients while they are admitted to the hospital[21]. Contrary to preventative anticoagulation, administering therapeutic anticoagulation to COVID-19 patients who are hospitalized not only did not lead to a decrease in mortality during their hospital stay but also raised the likelihood of experiencing significant bleeding. Prophylactic dosages of anticoagulants are likely preferable in non-critically unwell COVID-19 patients, mostly due to the increased risk of bleeding associated with therapeutic levels[22].

Recently, LMWH, particularly enoxaparin, has demonstrated effective anticoagulation properties and has been endorsed for use in COVID-19 patients who are hospitalized[23]. Nevertheless, preliminary evidence indicates that individuals with COVID-19 have a significantly increased susceptibility to thrombosis, even when they are administered conventional or escalated dosages of thromboprophylaxis with LMWH or UFH. The issue of heparin tolerance or resistance has emerged as a persistent challenge in the administration of anticoagulant medication for COVID-19, further complicating the monitoring process[24]. Furthermore, it is important to acknowledge that administering heparin to hospitalized COVID-19 patients as a preventive measure against blood clotting may increase the risk of heparin-induced thrombocytopenia, a potentially life-threatening complication. This complication could potentially interact with the thrombocytopenia syndrome caused by the COVID-19 vaccine[25].

Alternatively, the utilization of factor Xa inhibitors may improve the issue. Factor Xa inhibitors are promising alternatives for treating thromboembolic disease due to their ability to selectively and reversibly inhibit certain processes. Rivaroxaban is presently the predominant factor Xa inhibitor, with dabigatran and apixaban following suit in terms of usage frequency[26]. A cost-benefit study revealed that the use of factor Xa inhibitors led to a lower number of deaths caused by bleeding. Furthermore, it has been shown that factor Xa inhibitors have reduced expenses compared to enoxaparin when used for both prevention and treatment. Owing to their widely recognized pharmacokinetic and pharmacodynamic properties, factor Xa inhibitors offer numerous benefits over enoxaparin and vitamin K antagonists (VKA), such as improved safety and tolerance. As a result, factor Xa inhibitors have increasingly become the preferred medications for treating atrial fibrillation and venous thromboembolism[27]. Hence, it is necessary to assess their effectiveness and safety in COVID-19 patients in comparison to the conventional preventive administration of heparin.

Toubasi and colleagues indicated that prior utilization of factor Xa inhibitors resulted in decreased mortality and severity in individuals with COVID-19. Furthermore, it provided evidence supporting the advantages of DOAC utilization in enhancing the results of various medical conditions[28]. Conversely, a meta-analysis conducted by Dai *et al.*[29] revealed that the utilization of DOACs did not exhibit any correlation with a decreased likelihood of mortality among patients with COVID-19. Hence, a dispute persists, and there is insufficient evidence to substantiate either stance. Furthermore, a thorough examination of thromboembolic events is required to provide a more comprehensive demonstration of efficacy.

The scope of our meta-analysis encompassed COVID-19 patients who were admitted to hospitals, with the majority of them being in stable health states rather than critically ill. The findings of our study revealed that factor Xa inhibitors showed significantly superior efficacy in preventing thromboembolic events compared to heparin, particularly enoxaparin. Based on a careful evaluation of the expenses and advantages, it appears that factor Xa inhibitor therapy is adequate for non-critically unwell individuals with COVID-19.

When it comes to safety, bleeding is a primary negative outcome that occurs during the anticoagulation procedure. It is widely recognized that being exposed to large amounts of anticoagulant medication can cause bleeding incidents, which frequently lead to a fatal conclusion[30]. The findings of the current meta-analysis indicate that there was no statistically significant disparity in the occurrence of bleeding among hospitalized patients with COVID-19 who received preventive medication. However, factor Xa inhibitors had a more favorable trend in terms of lower bleeding risk compared to the group that received heparin. Furthermore, there were no significant changes observed in the results. factor Xa inhibitors appear to be a superior choice due to their convenience and lack of monitoring.

Our research has examined the overall death rate in COVID-19 patients who received factor Xa inhibitors as a potential intervention. The findings indicate that factor Xa inhibitors had a comparable impact on the mortality rate of COVID-19 patients who were administered in-hospital preventative anticoagulant therapy, as compared to enoxaparin. The limited inclusion of severely ill patients may be associated with the severity of COVID-19.

Nevertheless, our study does have several limitations. Initially, we identified a total of five studies, consisting of two retrospective studies and three RCTs. The available data may not provide enough evidence to establish the effectiveness and safety of factor Xa inhibitors preventative treatment, necessitating the necessity for future RCTs. Furthermore, it is necessary to incorporate additional studies with a similar time frame completed during hospitalization to ensure consistency and reduce treatment bias. Regrettably, the scarcity of data in the research we examined prevents us from conducting additional comparison analysis in other areas, such as drug interactions, viral load, and inflammatory index.

Conclusion

Our research indicates that among patients with COVID-19 who are not acutely ill and are hospitalized, factor Xa inhibitors are more effective than enoxaparin in preventing thromboembolism. Factor Xa inhibitors exhibit a reduced propensity for bleeding and comparable fatality rates to enoxaparin in patients with mild to moderate conditions. It appears that uncomplicated factor Xa inhibitor therapies are adequate for these patients. Additional rigorous RCTs comparing factor Xa inhibitors with enoxaparin are required to substantiate this theory across multiple dimensions.

Ethical approval

Not applicable.

Consent

Not applicable.

Source of funding

Not applicable.

Author contribution

L.A. and K.Q. conceived the idea and designed the study. M.U., A.A. collected the data and analyzed it. F.K. and U.E. drafted the manuscript. P.S., S.M. conducted literature search and created the illustrations. L.H. and S.J. revised the manuscript critically.

Conflicts of interest disclosure

The authors declare no conflict of interests.

Research registration unique identifying number (UIN)

1. Name of the registry: National Institute for Health Research (NIHR) International prospective register of systematic reviews (PROSPERO)
2. Unique Identifying number or registration ID: CRD42023443681
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=443681

Guarantor

Sayed Jawad.

Data availability statement

All the data used in this study are publicly available in the trials, which are referenced in the bibliography.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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