An Updated Systematic Review and Meta-Analysis of The Safety and Efficacy of Factor Xa Inhibitors Versus Low Molecular Weight Heparin Therapy for Treatment of Cancer Associated Venous Thromboembolism

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Abstract

Background

Patients with cancer-related venous thromboembolism (CA-VTE) have discovered Factor Xa inhibitors to be an effective intervention in recent decades. However, the greater bleeding risk involved with Factor Xa inhibitors than with low molecular weight heparin (LMWH) has now been substantiated in non-randomized studies as well as randomized control trials (RCT), albeit ambiguously, and this raises concerns for patients with CA-VTE.

Aims

We aim to pool data from all relevant studies reporting results for recurrent VTE, bleeding and mortality related to bleeding in CA-VTE patients undergoing treatment with Factor Xa inhibitors versus LMWH.

Methods

PubMed and Scopus databases were queried from inception through last week of March, 2022 for all RCT and non-randomized studies comparing the efficacy of Factor Xa inhibitors versus LMWH in patients with CA-VTE, on recurrence of VTE, clinically relevant non-major bleeding (CRNMB) and major bleeding events and mortality related to bleeding. A random-effects model was used and risk ratios (RR) with 95% confidence intervals (CI) were reported.

Results

Fourteen non-randomized studies and six RCTs were included in our analysis. The total participants were 17,781. Our pooled analysis demonstrated that in non-randomized studies, Factor Xa inhibitors, compared to LMWH, had a significantly lower risk of recurrence of VTE (RR: 0.70 [0.60, 0.80]; p = 0.00001; I2 = 0%) and a significantly higher risk of overall bleeding (RR: 1.51 [1.10, 2.07]; p = 0.01; I^2 = 59%), however, no significant difference in the risk of bleeding-related mortality was observed between Xa inhibitors and LMWH (RR: 0.99 [0.34, 2.92]; p = 0.99; I^2 = 0%). In RCTs, Factor Xa inhibitors, compared to LMWH, had a significantly lower risk of recurrence of VTE (RR: 0.65 [0.49, 0.85]; p = 0.002; I^2 = 3%) and a significantly higher risk bleeding (RR: 1.35 [1.02, 1.80]; p = 0.04; I^2 = 37%). However, no significant difference in the risk of bleeding-related mortality was observed between Factor Xa inhibitors and LMWH (RR: 0.33 [0.07, 1.43]; p = 0.14; I^2 = 0%). Furthermore, our pooled analysis demonstrated that there was no significant difference in the risk of overall bleeding in GI malignancies, between Factor Xa inhibitors and LMWH (RR: 1.39 [0.86, 2.26]; p = 0.18; I^2 = 58%), risk of CRNMB (RR: 1.52 [0.80, 2.88]; p = 0.20; I^2 = 56%), and the risk of major bleeding (RR: 1.29 [0.66, 2.48]; p = 0.46; I^2 = 46%).

Conclusion

Our results show that in the context of CA-VTE, Factor Xa inhibitor therapy may be a safe, effective, and realistic alternative to LMWH.

Introduction

Venous thromboembolism is a serious medical complication which has recently been on the rise.[1]–[4] Cancer associated venous thromboembolism(CA-VTE) is particularly concerning, with 15% of patients with cancer presenting with at least one episode of CA-VTE.[5], [6] Patients with cancer are 4–7 times more likely to present with VTE than the general population.[7]–[10] VTE, alongside infection, is also the leading cause of mortality in patients with cancer after the cancer itself.[11] This situation is further complicated by specific types of cancer malignancies such as gastrointestinal(GI) cancers which are prone to bleeding from the mucosa overlying the luminal tumours, making them particularly concerning groups in the case of administration of anti-coagulant therapies.[12], [13]

The formerly standard treatment for CA-VTE has been parenteral low molecular heparin (LMWH). Factor Xa inhibitors, which are also known as direct oral anti-coagulants (DOACs) offer a potentially practical alternative and have recently emerged as a potential alternative. Whilst their efficacy and safety profile has been elucidated to a degree in the past,[14] new data has come to light, which may present with meaningfully different results. As such, we felt the need to update the previous meta-analysis, which concluded its search in October 2020, including the more recent findings, to evaluate these outcomes more conclusively. Use of Factor Xa inhibitor therapy has been highlighted as a potential alternative to LMWH in short-term treatment of CA-VTE by the American Society of Haematology 2021 guidelines.[15] The evidence to this end, however, is of low or moderate certainty, largely due to the limited power and number of studies in previous meta-analyses. The new studies that have been published which may help improve the degree of certainty to this end by providing a larger body of evidence to refer to. Additionally, the limited degree of data in the case of evaluating gastrointestinal malignancies, especially in consideration of the fact that new evidence has come to light which we have reason to believe may meaningfully change the results to this end, provides an additional reason for our updating the previous analysis.

Through our analysis we seek to fill this gap in the literature by conclusively evaluating the comparative efficacy and safety profiles of these two potential treatment options for CA-VTE. We aim to pool data from all relevant studies reporting results for recurrent VTE, bleeding and mortality related to bleeding in CA-VTE patients undergoing treatment with Factor Xa inhibitors versus LMWH.

Methods

Data Sources and Search Strategy

The data, analytic techniques, and study materials utilized in this investigation are provided in the paper and as supplementary data to allow for the replication of the results or replication of the research strategy. This systematic review and meta-analysis adheres to guidelines of Preferred Reporting Items for Systematic review and Meta-Analysis [16]. Approval from the Institutional Review Board was not required as the data used in the study is publicly available. Medline and Scopus databases were searched from inception until March 2022. Detailed search strategies for each database are provided in **Supplementary Table S1**. Other relevant sources for data were references of reviews and editorials from prominent medical journals.

Study Selection

All retrieved articles were transferred to Endnote X7 (Clarivate Analytics, PA), to check for, and remove duplicates. Initially, title and abstract of the remaining articles were assessed. Subsequently, full text of the remaining articles was evaluated to find relevant articles according to the inclusion criteria. The screening process was independently conducted by two reviewers (TM and AMR), and to settle any discrepancies, a senior reviewer (TJS) was consulted. All randomized controlled trials (RCT) or non-randomized studies including adult patients with cancer, and undergoing treatment with Factor Xa inhibitors versus low molecular weight heparin (LMWH), and if they reported quantitative safety and efficacy data for intervention and control groups. Studies were excluded if they were systematic reviews, narrative reviews, case reports or editorials.

Data Extraction and Quality Assessment

Data was extracted from the studies that were included according to the inclusion criteria, by two independent reviewers (TM and AMR). Any discrepancies were resolved by consensus and by consulting the senior reviewer (TJS). We evaluated the treatment efficacy by the rate of recurrent venous thromboembolism (VTE). which was a combination of recurrent deep venous thrombosis (DVT) and recurrent pulmonary embolism (PE). We evaluated the rate of overall bleeding, which was a combination of clinically relevant non-major bleeding (CRNMB) events and major bleeding events, as defined by International Society of Thrombosis and Haemostasis [17]. Two independent reviewers (TM and AMR) assessed the quality of the included studies using the Cochrane Risk-of-Bias Tool for Randomized Trials (ROB-2) [18] and the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) [19].

Statistical Analysis

We performed a meta-analysis using Review Manager (Version 5.3; Cochrane Collaboration; London, United Kingdom). Summary estimates of recurrence of VTE, DVT, PE and overall bleeding, CRNMB, major bleeding, and fatal bleeding events were calculated. Risk ratio (RR) and 95% confidence interval (CI) were calculated for each study, which were subsequently pooled using a random-effects model. Forest plots were generated to visually analyse the pooled results. Subgroup analysis for overall bleeding, CRNMB and major bleeding events was conducted for gastrointestinal malignancies. Forest plots reported effect sizes for non-randomized studies and RCTs separately. Heterogeneity was assessed using Higgins I^2 statistic, where a value of I^2 = 25–50% was considered mild, 50–75% was considered moderate, and

above 75% was considered severe [20]. Visual inspection of funnel plots was performed to assess publication bias. A p-value of < 0.05 was considered significant in all cases.

Results

Literature Search, Baseline Characteristics, and Quality Assessment

Initial, our systematic review yielded 1,521 studies. After initial screening of titles and abstracts, 782 studies were excluded. Full text review of the remaining studies resulted in exclusion of 719 studies. Therefore, 20 studies were included in our analysis. Characteristics of the included studies are given in **Supplementary Table S2**. The total number of participants was 17,781. The total number of female participants was 8,970. The mean age of the participants was 64.6 years. The mean study duration was 51 months. Summary of the quality assessment of the included studies is provided in **Supplementary Table S3 and S4.**

Results of the Meta-analysis

Recurrence of VTE: Out of 20 selected studies, 13 non-randomized studies reported results on recurrence of VTE (Factor Xa inhibitors, total participants, 5369, events, 283; LMWH, total participants, 8292, events, 555). Our pooled analysis demonstrated that Factor Xa inhibitors had a significantly lower risk of recurrence of VTE (RR: 0.70 [0.60, 0.80]; p = 0.00001; I^2 = 0%; Fig. 2), compared to LMWH. Out of 20 selected studies, 5 RCTs reported results on recurrence of VTE (Factor Xa inhibitors, total participants, 1520, events, 86; LMWH, total participants, 1532, events, 138). Our pooled analysis demonstrated that Factor Xa inhibitors had a significantly lower risk of recurrence of VTE (RR: 0.65 [0.49, 0.85]; p = 0.002; I^2 = 3%; Fig. 2) compared to LMWH.

Recurrence of DVT: Out of 20 selected studies, 7 non-randomized studies reported results on recurrence of DVT (Factor Xa inhibitors, total participants, 1027, events, 29; LMWH, total participants, 966, events, 44). Our pooled analysis demonstrated that there was no significant difference in the risk of recurrence of DVT between Factor Xa inhibitors and LMWH (RR: 0.61 [0.33, 1.13]; p = 0.12; I^2 = 9%; **Supplementary Figure S1**). Out of 20 selected studies, 6 RCTs reported results on recurrence of DVT (Factor Xa inhibitors, total participants, 1570, events, 40; LMWH, total participants, 1582, events, 74). Our pooled analysis demonstrated that Factor Xa inhibitors had a significantly lower risk of recurrence of DVT (RR: 0.58 [0.40, 0.85]; p = 0.006; I^2 = 0%; **Supplementary Figure S1**) compared to LMWH.

Recurrence of PE: Out of 20 selected studies, 6 non-randomized studies reported results on recurrence of PE (Factor Xa inhibitors, total participants, 926, events, 32; LMWH, total participants, 940, events, 42). Our pooled analysis demonstrated that there was no significant difference in the risk of recurrence of PE between Factor Xa inhibitors and LMWH (RR: 0.77 [0.47, 1.29]; p = 0.33; I^2 = 4%; **Supplementary Figure S2**). Out of 20 selected studies, 5 RCTs reported results on recurrence of PE (Factor Xa inhibitors, total participants, 1520, events, 51; LMWH, total participants, 1532, events, 72). Our pooled analysis

demonstrated that there was no significant difference in the risk of recurrence of PE between Factor Xa inhibitors and LMWH (RR: 0.72 [0.51, 1.03]; p = 0.07; I^2 = 0%; **Supplementary Figure S2**).

Overall bleeding: Out of 20 selected studies, 12 non-randomized studies reported results for bleeding (Factor Xa inhibitors, total participants, 1921, events, 238; LMWH, total participants, 2098, events, 205). Our pooled analysis demonstrated that Factor Xa inhibitors had a significantly higher risk of overall bleeding (RR: 1.51 [1.10, 2.07]; p = 0.01; I^2 = 59%; Fig. 3), compared to LMWH. Out of 20 selected studies, 6 RCTs reported results for bleeding (Factor Xa inhibitors, total participants, 1570, events, 224; LMWH, total participants, 1582, events, 166). Our pooled analysis demonstrated that Factor Xa inhibitors had a significantly higher risk of overall bleeding (RR: 1.35 [1.02, 1.80]; p = 0.04; I^2 = 37%; Fig. 3) compared to LMWH.

Clinically relevant non-major bleeding (CRNMB): Out of 20 selected studies, 10 non-randomized studies reported results for CRNMB (Factor Xa inhibitors, total participants, 5185, events, 600; LMWH, total participants, 8095, events, 993). Our pooled analysis demonstrated that there was no significant difference in the risk of CRNMB between Factor Xa inhibitors and LMWH (RR: 1.25 [0.91, 1.71]; p = 0.17; I^2 = 77%; **Supplementary Figure S3**). Out of 20 selected studies, 6 RCTs reported results for CRNMB (Factor Xa inhibitors, total participants, 1570, events, 173; LMWH, total participants, 1582, events, 118). Our pooled analysis demonstrated that Factor Xa inhibitors had a significantly higher risk of CRNMB (RR: 1.48 [1.12, 1.94]; p = 0.005; I^2 = 17%; **Supplementary Figure S3**) compared to LMWH.

Major bleeding: Out of 20 selected studies, 14 non-randomized studies reported results for major bleeding (Factor Xa inhibitors, total participants, 5843, events, 250; LMWH, total participants, 8786, events, 392). Our pooled analysis demonstrated that there was no significant difference in the risk of major bleeding between Factor Xa inhibitors and LMWH (RR: 1.10 [0.80, 1.51]; p = 0.57; I^2 = 56%; **Supplementary Figure S4**). Out of 20 selected studies, 6 RCTs reported results on clinically relevant non-major bleeding (Factor Xa inhibitors, total participants, 1570, events, 72; LMWH, total participants, 1582, events, 59). Our pooled analysis demonstrated that there was no significant difference in the risk of major bleeding between Factor Xa inhibitors and LMWH (RR: 1.18 [0.75, 1.86]; p = 0.47; I^2 = 24%; **Supplementary Figure S4**).

Bleeding-related mortality: Out of 20 selected studies, 4 non-randomized studies reported results for bleeding-related mortality (Factor Xa inhibitors, total participants, 320, events, 9; LMWH, total participants, 361, events, 8). Our pooled analysis demonstrated that there was no significant difference in the risk of bleeding-related mortality between Factor Xa inhibitors and LMWH (RR: 0.99 [0.34, 2.92]; p = 0.99; I^2 = 0%; **Supplementary Figure S5**). Out of 20 selected studies, 4 RCTs reported results on bleeding-related mortality (Factor Xa inhibitors, total participants, 1375, events, 1; LMWH, total participants, 1390, events, 7). Our pooled analysis demonstrated that there was no significant difference in the risk of bleeding-related mortality between Factor Xa inhibitors and LMWH (RR: 0.33 [0.07, 1.43]; p = 0.14; I^2 = 0%; **Supplementary Figure S5**).

Bleeding in GI malignancies: Out of 20 selected studies, 4 non-randomized studies reported results for bleeding in GI malignancies (Factor Xa inhibitors, total participants, 383, events, 74; LMWH, total participants, 537, events, 88). Our pooled analysis demonstrated that there was no significant difference in the risk of overall bleeding in GI malignancies, between Factor Xa inhibitors and LMWH (RR: 1.39 [0.86, 2.26]; p = 0.18; I^2 = 58%; **Supplementary Figure S6**). Out of 20 selected studies, 4 non-randomized studies reported results for CRNMB in GI malignancies (Factor Xa inhibitors, total participants, 383, events, 43; LMWH, total participants, 537, events, 52). Our pooled analysis demonstrated that there was no significant difference in the risk of CRNMB in GI malignancies, between Factor Xa inhibitors and LMWH (RR: 1.52 [0.80, 2.88]; p = 0.20; I^2 = 56%; **Supplementary Figure S7**). Out of 20 selected studies, 4 non-randomized studies reported results for major bleeding in GI malignancies (Factor Xa inhibitors, total participants, 383, events, 37; LMWH, total participants, 537, events, 39). Our pooled analysis demonstrated that there was no significant difference in the risk of major bleeding in GI malignancies, between Factor Xa inhibitors and LMWH (RR: 1.29 [0.66, 2.48]; p = 0.46; I^2 = 46%; **Supplementary Figure S8**).

Discussion

Through this pooled analysis of 17, 781 patients, this study seeks to compare the efficacy and safety profiles of Factor Xa inhibitors in comparison to the current standard of care in the treatment of CA-VTE, LMWH. We found risk of recurrent VTE events to be significantly higher for LMWH therapy than Factor Xa inhibitors. No significant difference was found between LMWH and Factor Xa inhibitor treatment in bleeding mortality or major bleeding events. Risk of non-major bleeding events was higher for Factor Xa inhibitors in RCTs evaluating this outcome, but not in their non-randomised counterparts. All bleeding complications for GI malignancies, a subgroup of particular interest due to their increased risk of bleeding events due to their propensity to bleed from the mucosa overlying the luminal tumours,[12], [13] were demonstrably similar for both LMWH and Factor Xa inhibitor therapies.

Our study updates the findings formerly elucidated by Hussain et al[14], in light of more recent trials such as the ones conducted by Mokadem et al[21] and the one by Houghton et al[22] which presented findings which we suspected would materially alter results. Mokadem et al found there to be no significant difference between risk of major or non-major bleeding in Factor Xa inhibitors vs LMWH, while Houghton et al was a trial conducted in GI patients and found there to be no significant difference in bleeding events, major or non-major, between the administration of Factor Xa inhibitors or LMWH. Particularly in the case of GI bleeding outcomes, we presented with results different from our predecessors which served to further highlight the safety and efficacy of DOAC therapy in comparison to LMWH administration. Whilst most of the results were not materially altered, we did manage to reproduce the findings demonstrated previously and further verify their veracity in a more updated context.

Through our analysis we demonstrated that the risk of recurrent VTE events was significantly lower with Factor Xa inhibitor administration than with LMWH. This was observed in both RCTs and NRSs, which, combined with the consistency of this finding with the previous meta-analysis to this end, goes towards

establishing its fidelity and demonstrates the efficacy of Factor Xa inhibitors in the treatment of cancer associated VTE. A decreased risk of recurrent VTE events directly translates to potential for a more optimistic prognostic outlook for these patients.

Risk of recurrent PE was not significantly different for Factor Xa inhibitors or LMWH. This finding was consistent across randomised and non-randomised control trials. Risk of recurrent DVT in Factor Xa inhibitor administration was significantly lower than that in LMWH in RCTs, but not in NRSs. These findings are consistent with those of Hussain et al and lead us to believe that, in light of the abovementioned results of total VTE event significance and risk of PE non-significance, the result presented in the non-randomised studies is either due to the bias stemming from the non-randomised nature of the observational trials or a statistical anomaly resulting from a lack of data to this end, one which would be rectified by higher power studies to this end. Since RCTs are fundamentally considered to be more reliable than non-randomised trials, with the RCTs in our analysis also considering a greater number of total DVT events than the observational studies and having, as such, a larger, more reliable sample, in addition to the fact that it would be consistent with the other results of our study, as highlighted above, we have decided to focus on the RCT results as the more ones for our study.

This study highlights the increased risk of non-major bleeding complications in patients assigned to factor Xa inhibitors than their LMWH counterparts. This finding was non-significant in the non-randomised studies but was significant in the RCTs. The RCT findings will be considered the more reliable of the two for reasons mentioned above. Overall risk of bleeding was significantly increased in Factor Xa inhibitors in comparison to LMWH, in both NRSs and RCTs. We also found there not to be a significant increase in risk of major bleeding events as a result of Factor Xa inhibitors compared to LMWH. This was perceived in both observational studies and RCTs, a finding at odds with our predecessors, which serves to further verify the viability of this intervention as a safe alternative to the traditional administration of LMWH. In light of our other findings in regard to overall and non-major bleeding events mentioned above, we can conclude that the increased risk of non-major bleeding events is well-established and majorly contributes to the perceived increase in risk of overall bleeding events from this intervention. The risk of fatal bleeding was not significantly different in either intervention, a finding consistent with previous studies to this end[15]. This serves to further establish the safety profile of Factor Xa inhibitors as a suitable alternative to LMWH.

Factor Xa inhibitors have also not presented with an increased risk of bleeding complications compared to LMWH in patients with GI malignancies. This finding is contradictory to our predecessors and is especially useful as concerns of safety in these populations more vulnerable to bleeding complications were amongst the most compelling reasons against the use of Factor Xa inhibitors as alternatives to LMWH therapies. Our study puts these concerns to rest and provides evidence in favour of administration of Factor Xa inhibitors as a safe and efficacious alternative therapy in these populations. To this end, more evidence is needed to make a recommendation to revise the current standard of care for these patients. These findings do, however present some promising preliminary results, opening avenues for future research and potential treatment guideline revision recommendations in future.

In addition to the increased efficacy of Factor Xa inhibitors compared to LMWH, they can also be administered orally, as opposed to LMWH which is administered parenterally. This is a significant stride forward in terms of patient adherence to prescription and quality of care provided to patients.[23], [24] Adoption of factor Xa inhibitors as standard practice for CA-VTE treatment would provide a cheaper, more convenient and significantly more comfortable alternative to routine parenteral administration of LMWH. Factor Xa inhibitors act directly to inhibit factor Xa in the coagulation cascade. As such, their mechanism of action is far more predictable, making it so they also do not require regular laboratory monitoring and present with fewer drug interactions than do their counterparts.[25], [26] This is particularly valuable in the case of CA-VTE as these patients are likely undergoing courses of chemotherapy or other medications in conjunction. LMWH on the other hand, acts on factors IIa, Xa, and to a lesser degree, IXa and XIIa. This indirect mechanism of action makes it necessary for extensive laboratory monitoring to ensure the INR remains within the therapeutic range. Factor Xa inhibitors would, as such, not only be safer but be far more comfortable, convenient, and practical for these patients, significantly improving the quality of care provided to them. Factor Xa inhibitors are, as such, also more useful for outpatient use than LMWH, which find their primary use in inpatients.[27]

While our results were largely consistent with previous findings and included mostly high-quality studies, our study did nonetheless present with some limitations. Firstly, due to the paucity of data, the outcomes for GI malignancies could not be verified to a satisfactory degree. Owing to the small sample size and limited quantity of the studies evaluating these populations, the results cannot be exhaustively verified or rigorously authenticated. Next, not enough data could be found to compare the many different Factor Xa inhibitors to elucidate the best one for the treatment of CA-VTE. Lastly, while our study explored efficacy in the form of VTE event recurrence and safety in the form of bleeding events in patients, these findings do not necessarily translate to a meaningful quality of life improvement for patients. These were not outcomes explored in our study. More data is needed highlighting the quality-of-life changes in patients on Factor Xa inhibitors as opposed to LMWH therapies. Further analysis is also needed to establish whether this increased efficacy translates over to better prognostic outcomes for patients in the form of decreased mortality or morbidity.

Further research is needed exploring the potential role of Factor Xa inhibitors in patients suffering from GI malignancies. Paucity of data to this end has limited the fidelity of this analysis, and more high-powered RCTs are required in this particular subgroup to provide a more meaningful result. Additional research is also needed to highlight the most effective Factor Xa inhibitor for the treatment of CA-VTE. Direct comparison is needed to this end in the form of high-power RCTs, which could form the basis of future guideline revision recommendations. Lastly, it is necessary to explore whether the increased efficacy of Factor Xa inhibitors over LMWH translates over to improve quality-of-life and prognostic outcomes for patients.

Conclusion

Our analysis highlights Factor Xa inhibitor therapy as a safe, efficacious, and practical alternative to parenteral LMWH administration for the treatment of CA-VTE. However, more research is warranted for patients with GI malignancies to evaluate efficacy of Factor Xa inhibitors better, and to determine the impact on quality-of-life in this population.

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28. **Online Supplementary Data**
29. **Supplementary Table S1**: **Search strategy**
30. **Supplementary Table S2**: **Baseline characteristics of the included studies**
31. Supplementary Table **S3**: **Risk of Bias in Randomized Controlled Trials**
32. Supplementary Table **S4**: **Risk of Bias in Non-randomized Studies**
33. Supplementary Figure **S1: Forest plot showing results of Factor Xa inhibitors vs LMWH on recurrence of DVT**
34. Supplementary Figure **S2: Forest plot showing results of Factor Xa inhibitors vs LMWH on recurrence of PE**
35. Supplementary Figure **S3**: **Forest plot showing results of Factor Xa inhibitors vs LMWH on clinically relevant non-major bleeding events**
36. Supplementary Figure **S4: Forest plot showing results of Factor Xa inhibitors vs LMWH on major bleeding events**
37. Supplementary Figure **S5: Forest plot showing results of Factor Xa inhibitors vs LMWH on bleeding-related mortality events**
38. Supplementary Figure **S6: Forest plot showing results of Factor Xa inhibitors vs LMWH on overall bleeding events in GI malignancies**
39. Supplementary Figure **S7: Forest plot showing results of Factor Xa inhibitors vs LMWH on clinically relevant non-major bleeding events in GI malignancies**
40. Supplementary Figure **S8: Forest plot showing results of Factor Xa inhibitors vs LMWH on major bleeding events in GI malignancies**
41. **Supplementary Table S1**: **Search strategy**

Figures

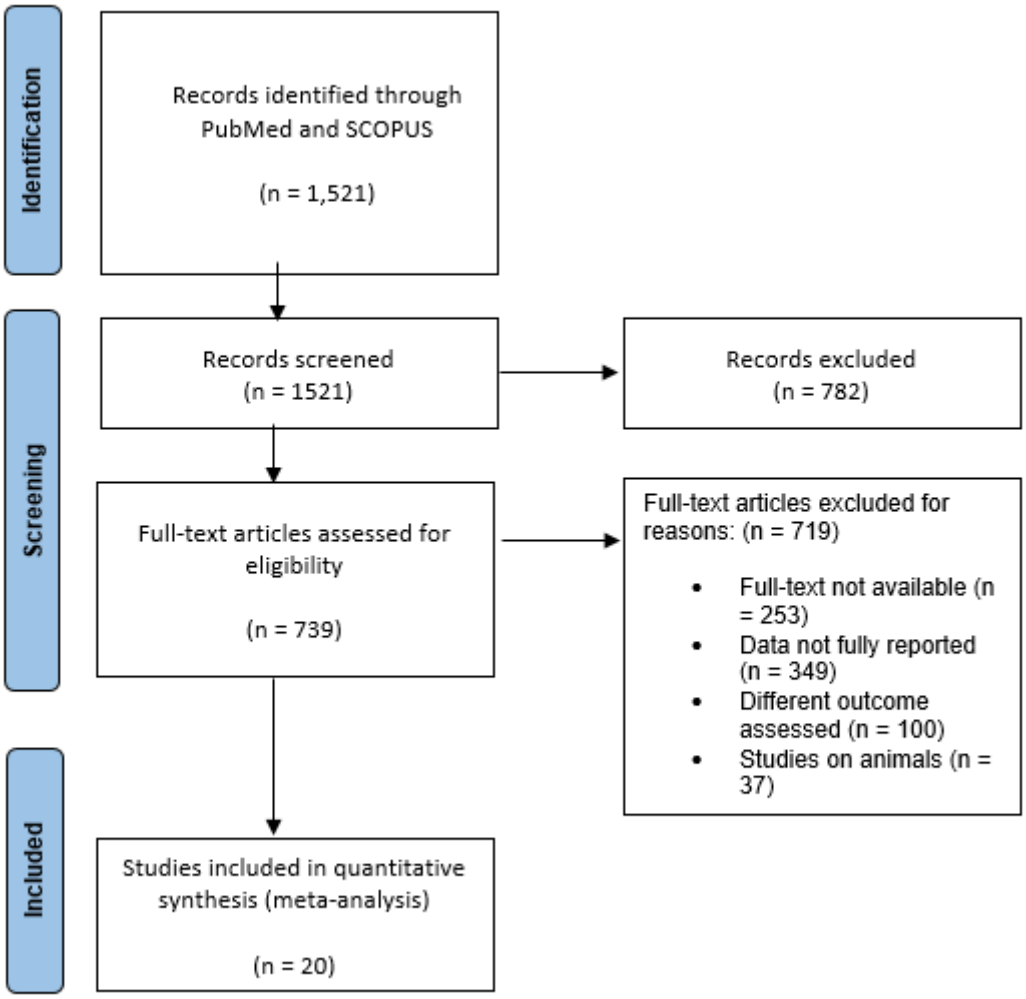

Figure 1

PRISMA flowchart summarizing study selection process

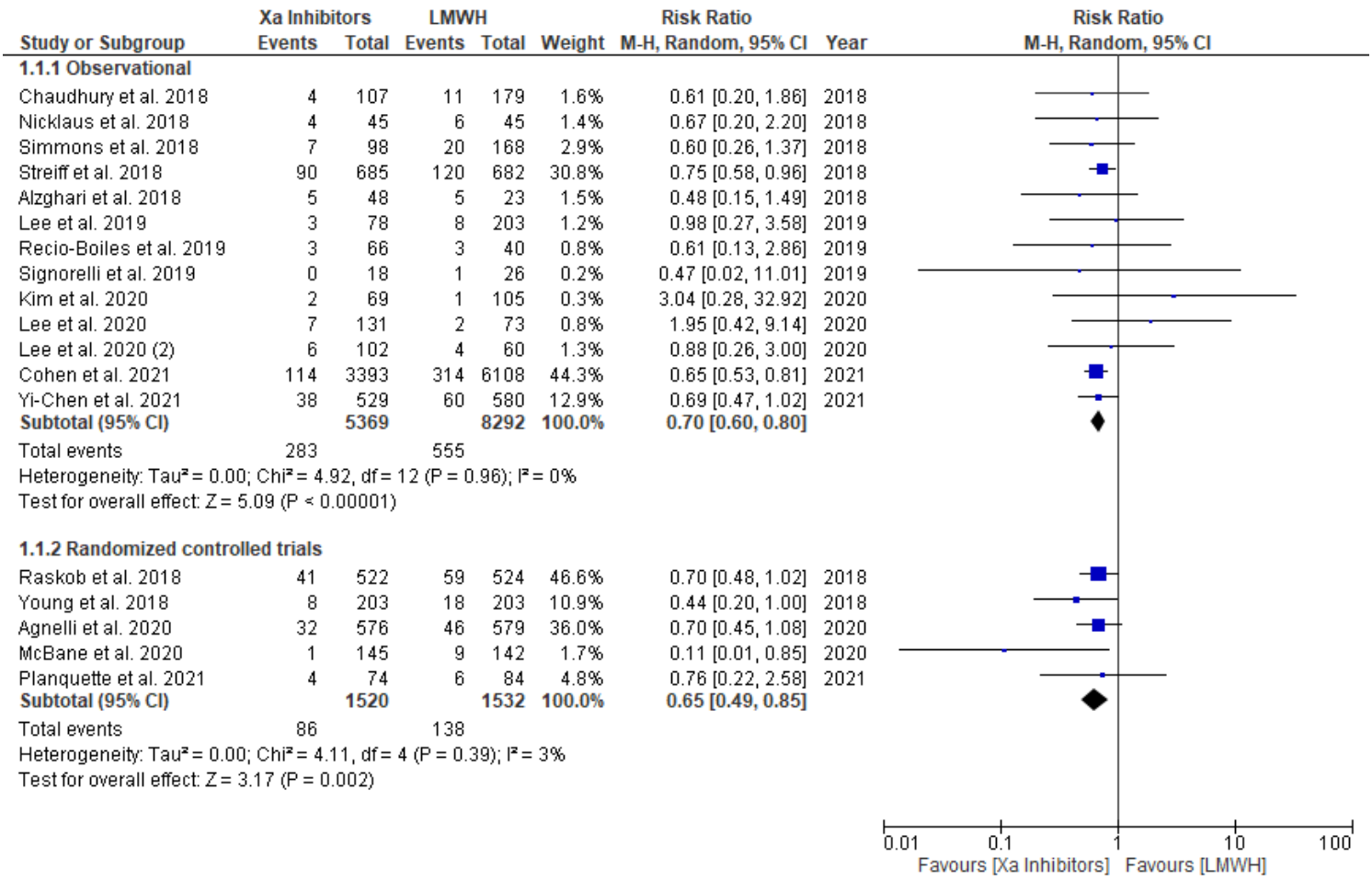

Figure 2

Forest plot showing results of Factor Xa inhibitors vs LMWH on recurrence of VTE

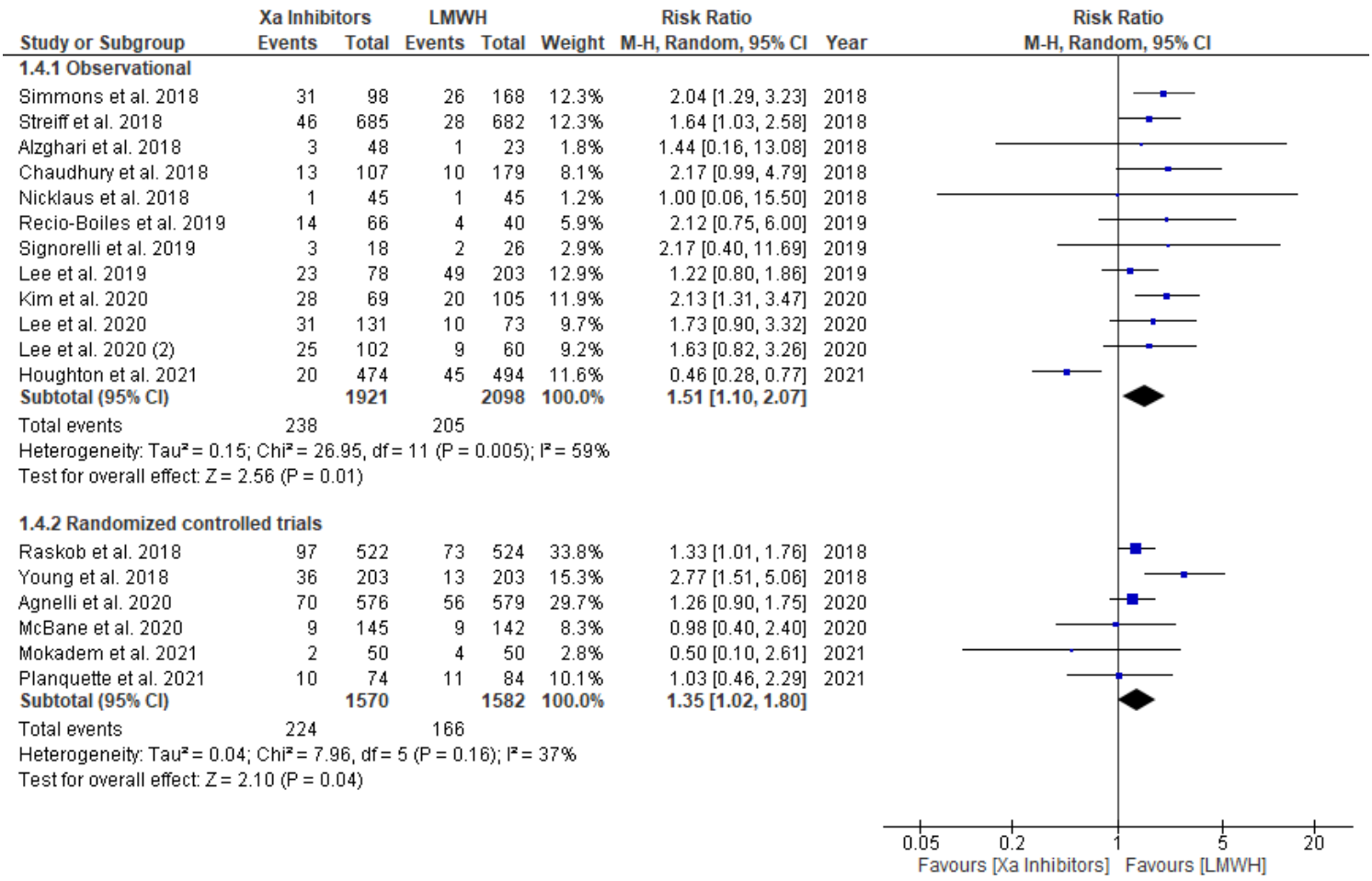

Figure 3

Forest plot showing results of Factor Xa inhibitors vs LMWH on overall bleeding events

Supplementary Files

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- SupplementaryInformation.docx