SYSTEMATIC REVIEW

# Factor Xa inhibitor for venous thromboembolism management in patient with cancer: a systematic review and meta-analysis [version 1; peer review: awaiting peer review]

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## Abstract

**Background:** An earlier systematic review reported no differences in the incidence of recurrent venous thromboembolism and major bleeding between factor Xa inhibitors and standard anticoagulation. The present meta-analysis aimed to assess the effectiveness of factor Xa inhibitors for the management of venous thromboembolism (VTE), specifically in patients with cancer, as there were more randomized clinical trials (RCTs) available.

**Methods:** The PubMed and Cochrane Library databases were systematically screened for all RCTs assessing factor Xa inhibitor efficacy for VTE management in cancer patients. Using RevMan 5.3, we performed a Mantel–Haenszel fixed-effects meta-analysis of the following outcomes: recurrent VTE, VTE events, and major bleeding rates.

**Results:** We identified 11 studies involving 7,965 patients. Factor Xa inhibitors were superior in preventing VTE recurrence, compared to low-molecular-weight heparin (LMWH) (OR 0.60; 95% CI 0.45–0.80; P < 0.01) and vitamin K antagonists (VKA) (OR 0.51; 95% CI 0.33–0.78; P < 0.01). As prophylaxis, factor Xa inhibitors had a similar rate of VTE compared to VKAs (OR 1.08 [95% CI 0.31–3.77]; P = 0.90) and a lower rate compared to placebo (OR 0.54 [95% CI 0.35–0.81]; P < 0.01). Major bleeding rates were higher with factor Xa inhibitors than with LMWHs (OR 1.34 [95% CI 0.83–2.18]; P = 0.23), but significantly lower than VKAs (OR 0.71 [95% CI 0.55–0.92]; P < 0.01).

**Conclusions:** Factor Xa inhibitors are effective for VTE management in patients with cancer; however, they are also associated with an increased bleeding risk compared to LMWH, but decreased when compared to VKA.

**Open Peer Review**

**Reviewer Status** *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

**Keywords**
bleeding, cancer, factor Xa inhibitor, oral anticoagulant, venous thromboembolism.

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## Introduction

Cancer patients are five times more likely to experience venous thromboembolism (VTE) than the general population.[1] Second only to cancer itself, VTE is the second most common cause of mortality in cancer patients.[2] According to previous clinical management recommendations, the typical VTE treatment in cancer patients involves the initial use of parenteral low-molecular-weight heparin (LMWH) followed by long-term use of oral vitamin K antagonists (VKA).[3] However, recent recommendations proposed factor Xa inhibitors as one of the options of the main initial treatment for VTE.[4]

Factor Xa inhibitors are preferred over LMWH and VKA because they conveniently do not require injections every day compared to LMWH, their more predictable effects, lack of monitoring or frequent repeat doses, and fewer drug interactions compared to VKA.[5] An earlier systematic review reported differences between factor Xa inhibitors and standard anticoagulation drugs in the incidence of recurrent VTE and major bleeding.[6] Based on this research, the present meta-analysis aims to evaluate the effectiveness of factor Xa inhibitors for the management of venous thromboembolism, particularly in patients with cancer.

### Ethical considerations

Ethical approval for this research was obtained from the Dr. Soetomo General Hospital Surabaya Ethical Committee in Health Research (1964/KEPK/IV/2020).

### Trial registry

UMIN Clinical Trial Registry (UMIN ID 000040346).

## Methods

We adopted the Preferred Reporting Items for Reviews and Meta-Analyses guidelines for analysis reporting.[7] Any RCTs that studied VTE rates or major bleeding, as primary or secondary outcomes, in cancer patients who received an oral factor Xa inhibitor were included. Phase II trials, trials with an antiplatelet control group, and trials using an anticoagulant as VTE post-procedure prophylaxis were excluded.

We conducted a systematic search using the PubMed and Cochrane Library databases on April 24, 2020, after gaining approval from the Institutional Review Board. As for the title, abstract, and medical subject heading, we used search terms like “cancer,” “factor Xa inhibitor,” “oral anticoagulant,” “venous thromboembolism,” “apixaban,” “rivaroxaban,” “edoxaban,” “prophylaxis,” “bleeding,” “thromboembolism,” “thromboprophylaxis,” “randomized,” and “rct.”

We screened more studies by looking at the references in the included articles. Two investigators independently selected studies, with disagreements resolved through discussion and a third investigator's opinion. Thereafter, for each report, two investigators independently extracted the following information: authors, year of publication, trial name, cancer status, sample size, dose and duration of anticoagulation, duration of patient follow-up, and outcomes for the two treatment groups where available.

We determined four comparison groups: (1) factor Xa inhibitor versus LMWH as treatment for VTE; (2) factor Xa inhibitor versus VKA as treatment for VTE; (3) factor Xa inhibitor versus placebo as prophylaxis for VTE; (4) factor Xa inhibitor versus VKA as prophylaxis for VTE. The outcomes of our meta-analysis were recurrent VTE or new VTE event rates and incidence of major bleeding. VTE events were confirmed by leg vein ultrasound scanning, D-dimer testing, or both; alternatively, clinically overt pulmonary embolism was confirmed by imaging. Major bleeding was defined as in Schulman *et al.*[8]

The Cochrane Collaboration Risk of Bias Tool was used by two independent investigators to assess the methodological quality of included studies, and the GRADE approach was employed to grade each outcome.[9,10] Any disputes were settled through discussion with a third investigator. We calculated odds ratios (ORs) for all outcomes at the longest follow-up period and used Review Manager (RevMan v5.3 2014) to apply the Mantel−Haenszel fixed-effects method. We conducted a modified intention-to-treat analysis including patients who had received ≥ 1 medication dose. We planned to a conduct sensitivity analysis by removing studies likely to be biased. The I2 statistic was used to assess statistical heterogeneity between studies. If the heterogeneity was > 50%, we applied a random-effects model for analysis.[11]

## Results

The search identified 202 citations in PubMed and 41 in the Cochrane Library, among which 43 were duplicates (Figure 1). We found 22 more studies of which we evaluated the full text. Four studies were post-procedure prophylaxis

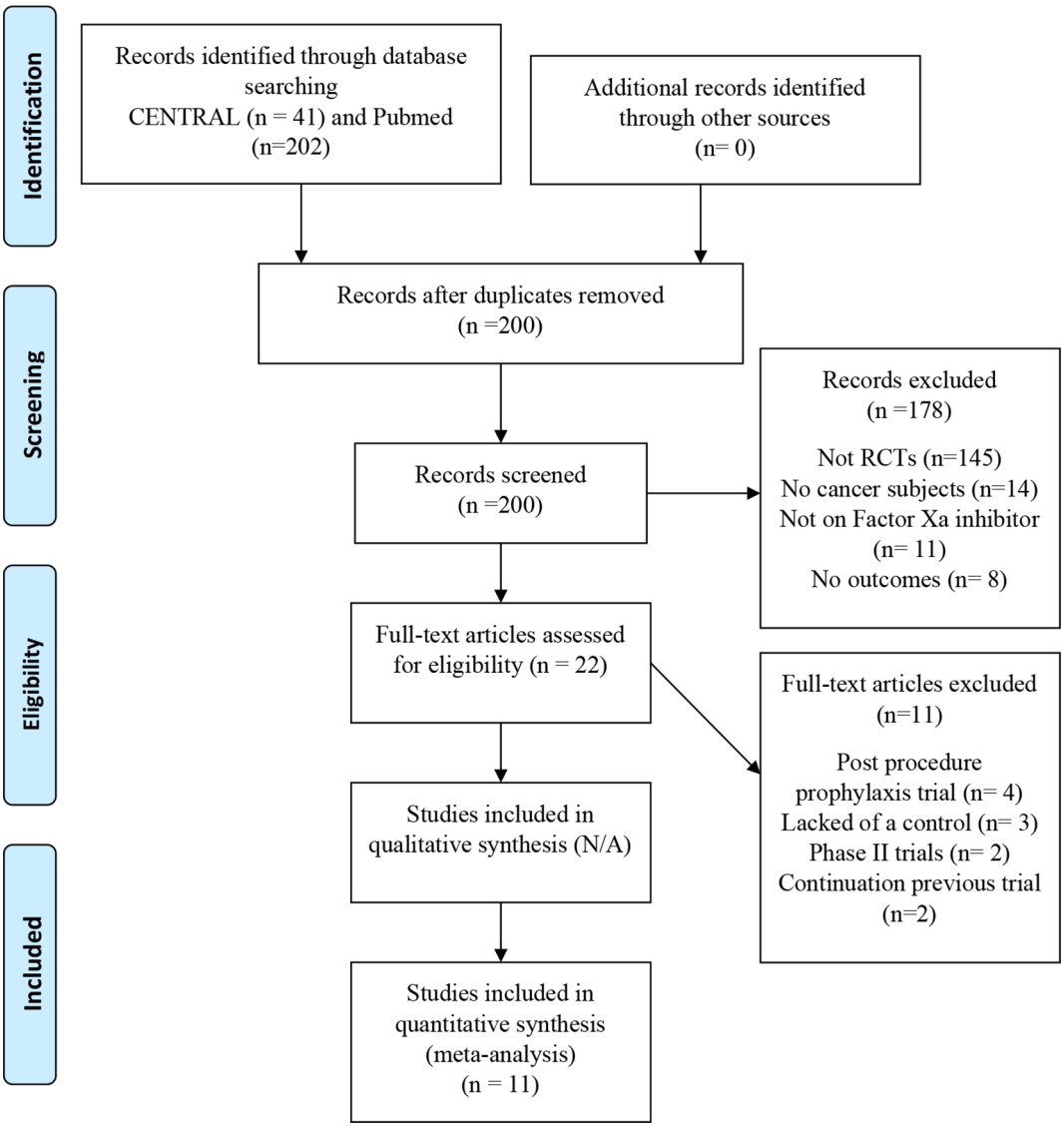


**Figure 1. PRISMA flow diagram.**

trials, three lacked a control, two were phase II trials, and two were extensions of included trials, so 11 were omitted. As a result, we could include 11 studies in our analysis.[12–22]

Table 1 lists the characteristics of the included studies. There were four trials on apixaban, four on rivaroxaban, and three on edoxaban. The study size ranged from 300 to 1,170 patients. Five studies were subgroup analyses of patients with cancer from larger primary trials.[12–16] We pooled their data only from the subgroup of patients with cancer, not all study population. One study was a pooled analysis of the subgroup of patients with cancer in "sister" trials.[17] Four trials[13,18–20] compared factor Xa inhibitors with LMWH, and three[12,14,17] compared factor Xa inhibitors with VKA as a VTE treatment. Two trials[15,16] compared factor Xa inhibitors with placebo and two[21,22] compared factor Xa inhibitors with VKA as prophylaxis of VTE. We included one trial that investigated two doses of edoxaban for VTE prophylaxis, where the outcomes of both groups were combined and analyzed as one intervention group.[16]

The risk of bias across domains is presented in Figure 2. In most studies, the randomization process, adherence to the intervention, assessment, missing outcome results, and reporting were deemed adequate. In four trials, participants were blinded. The percentage of patients not followed up ranged from 0.2% to 5.6%. All trials reported the results from modified intention-to-treat analysis.

**Table 1. The characteristics of the included trials.**

| Author | Blinding to subjects | Population | Randomized patients | Intervention | Dose | Control | Follow up period | Death | Lost to follow up |
|---|---|---|---|---|---|---|---|---|---|
| Prins et al., 2013; EINSTEIN-DVT and PE | No | Cancer patients with VTE (100% active cancer) | 597 | Rivaroxaban | 15 mg bid for 3 wk followed by 20 mg qd | Heparin/VKA | 3-12 months | 30% vs 35% | N/A |
| Agnelli et al., 2015; AMPLIFY | Yes | Cancer patients with VTE (31.6% active cancer) | 534 | Apixaban | 10 mg bid for 7 d followed by 5 mg bid | Heparin/VKA | 6 months | N/A | N/A |
| Raskob et al., 2016; HOKUSAI-VTE | Yes | Cancer patients with VTE (48% active cancer) | 771 | Edoxaban | 60 mg once daily | Heparin/VKA | 3-12 months | N/A | N/A |
| Raskop et al., 2017; HOKUSAI-VTE | No | Cancer patients with VTE (97.9% active cancer) | 1050 | Edoxaban | 60 mg once daily | Dalteparin (200 UI/kg/d during 30 days, then 150 UI/kg/d) | 12 months | 39% vs 36% | 0.8% (3 vs 5) |
| Young et al., 2017; SELECT-D | No | Cancer patients with VTE (100% active cancer) | 406 | Rivaroxaban | 15 mg bid for 3 wk followed by 20 mg qd | Dalteparin (200 UI/kg/d during 30 days, then 150 UI/kg/d) | 6 months | 75% vs 70% | 0.2% (0 vs 1) |
| McBane et al., 2018; ADAM VTE | No | Cancer patients with VTE (100% active cancer) | 300 | Apixaban | 10 mg bid for 7 d followed by 5 mg bid | Dalteparin (200 UI/kg/d during 30 days, then 150 UI/kg/d) | 6 months | 15% vs 10% | 5.6% (9 vs 7) |
| Fanola et al., 2018; ENGAGE AF-TIMI | No | Cancer patients with AF (100% active cancer) | 1153 | Edoxaban | 60 mg once daily or 30 mg once daily | VKA | > 2 years | 32% vs 30% | N/A |
| Chen et al., 2019; ROCKET AF | No | Cancer patients with AF (7.8% active cancer) | 640 | Rivaroxaban | 20 mg qd | VKA | 2 years | 10% vs 15% | N/A |
| Carrier et al., 2019; AVERT | Yes | Ambulatory patients with risk of VTE | 574 | Apixaban | 2.5 mg bid | Placebo | 6 months | 12% vs 10% | 4.3% (13 vs 11) |
| Khorana et al., 2019; CASSINI | Yes | Ambulatory patients with risk of VTE | 841 | Rivaroxaban | 10 mg qd | Placebo | 6 months | 20% vs 25% | N/A |
| Agnelli et al., 2020; CARAVAGGIO | No | Cancer patients with VTE (97.3% active cancer) | 1170 | Apixaban | 10 mg bid for 7 d followed by 5 mg bid | Dalteparin (200 UI/kg/d during 30 days, then 150 UI/kg/d) | 6 months | 23% vs 25% | 1.7% (12 vs 8) |



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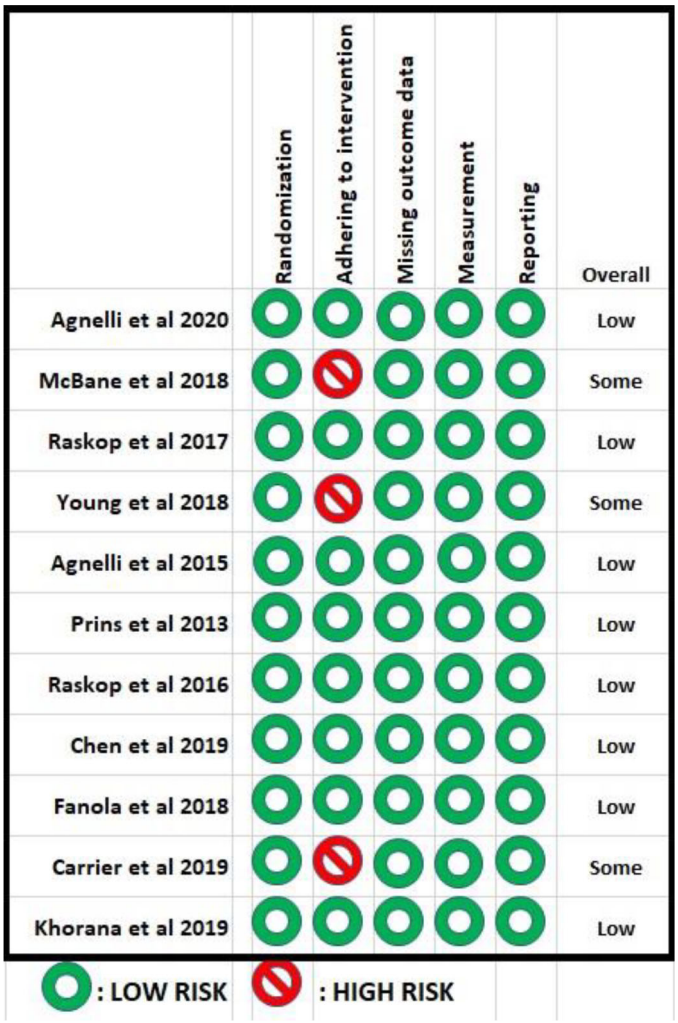


**Figure 2. Risk of bias assessment.**

The quality of evidence for each outcome analyzed using the GRADE approach is presented in Table 2. We did not downgrade from the risk of bias, inconsistency, indirectness, and imprecision aspect of all outcomes, because of a low risk of bias, no substantial heterogeneity, a large enough sample size, and narrow confidence interval (CI). We downgraded one level for the major bleeding outcome because the funnel plot of major bleeding outcome suggested publication bias (Figure 3).

Seven studies involving 4,771 patients reported VTE recurrence (Table 2). Recurrence occurred in 4.9% (117/2,399) of patients allocated to factor Xa inhibitors, 9.1% (132/1,445) allocated to LMWHs, and 6.9% (64/927) of those allocated to VKAs. In comparison (Figure 4), the reduction of the risk of VTE recurrence with factor Xa inhibitors compared to LMWH was acceptable (four trials; OR 0.60; 95% CI 0.45–0.80; $P < 0.01$), without substantial heterogeneity ($I2 = 26\%$; $P = 0.26$). VTE recurrence rates were lower in patients treated with factor Xa inhibitors compared to patients treated using VKAs (three trials; OR 0.51; 95% CI 0.33–0.78; $P < 0.01$), without substantial heterogeneity ($I2 = 0\%$; $P = 0.37$).

Three studies, including 2,056 patients, reported the incidence of new VTE after anticoagulant prophylaxis. The factor Xa inhibitor group had a 4.1% (42/1,021) VTE occurrence rate, while the VKA and placebo groups each had 1.45% (5/355) and 9.6% (65/680), respectively. According to the meta-analysis shown in Figure 5, there were similar VTE incidences in the factor Xa inhibitor and the VKA groups (one trial; OR = 1.08 [95% CI, 0.31–3.77]; $P = 0.90$); however, the heterogeneity analysis could not be applied. The estimated effect of factor Xa inhibitors on VTE incidence compared to placebo showed a statistically significant reduction (two trials; OR = 0.54 [95% CI, 0.35–0.81]; $P < 0.01$), without substantial heterogeneity ($I2 = 31\%$; $P = 0.23$).

**Table 2. Summary of findings.**

| | No of studies | Total participants | Pooled OR (95% CI) | P | I2 (P) | GRADE |
|---|---|---|---|---|---|---|
| Recurrence | | | | | | High |
| vs LMWH | 4 | 2890 | 0.60 (0.45, 0.80) | 0.0004 | 26% (0.26) | |
| vs VKA | 3 | 1881 | 0.51 (0.33, 0.78) | 0.002 | 0% (0.37) | |
| New VTE | | | | | | High |
| vs VKA | 1 | 684 | 1.08 (0.31, 3.77) | 0.90 | N/A | |
| vs Placebo | 2 | 1372 | 0.54 (0.35, 0.81) | 0.003 | 31% (0.23) | |
| Major bleeding | | | | | | Moderate |
| vs LMWH | 4 | 2890 | 1.34 (0.83, 2.18) | 0.23 | 28% (0.25) | |
| vs VKA | 5 | 3703 | 0.71 (0.55, 0.92) | 0.009 | 0% (0.72) | |
| vs Placebo | 2 | 1372 | 1.98 (0.88, 4.44) | 0.10 | 0% (0.96) | |

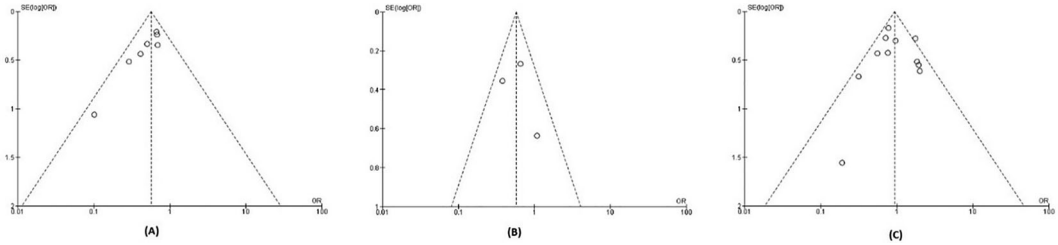


**Figure 3. Funnel plot of (A) recurrent VTE outcome; (B) new VTE outcome; (C) major bleeding outcome.**

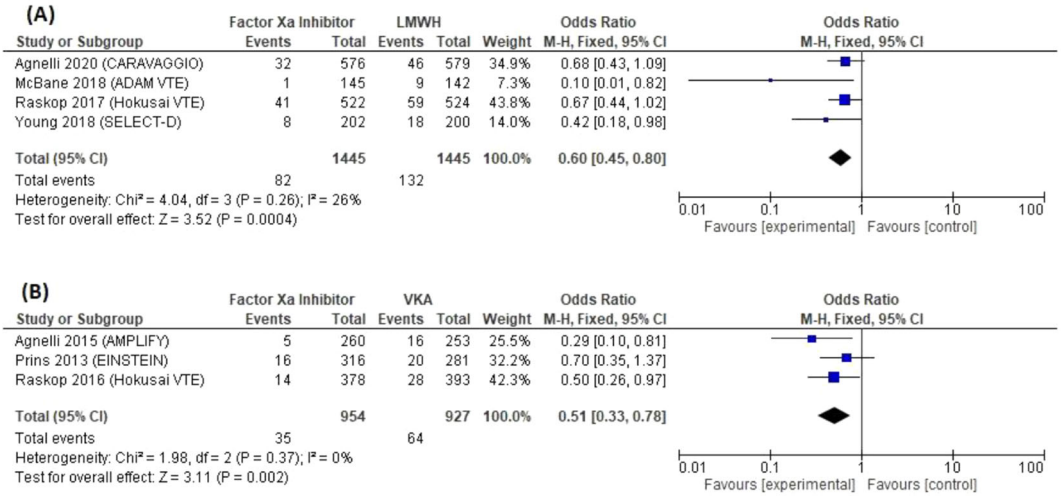


**Figure 4. Forest plot of recurrent VTE outcome.**

Eleven studies, including 7,965 patients, reported major bleeding (Table 2). Major bleeding occurred in 5.5% (231/4,178) of patients allocated to factor Xa inhibitors, 3.6% (52/1445) to LMWHs, 8.1% (134/1,662) to VKAs and 1.3% (9/680) to placebo. According to the meta-analysis shown in Figure 6, the acceptable increase of risk cannot be confirmed from the description of major bleeding with factor Xa inhibitors compared to LMWH, as based on an OR of 1.34 (95% CI, 0.83–2.18) with a P = 0.23, which is not statistically significant. However, factor Xa inhibitors significantly reduced the risk of major bleeding compared to VKAs (five trials; OR = 0.71 [95% CI, 0.55–0.92]; P = 0.009), without substantial heterogeneity (I2 = 0%; P = 0.72). The risk of major bleeding was higher with factor Xa inhibitors versus placebo

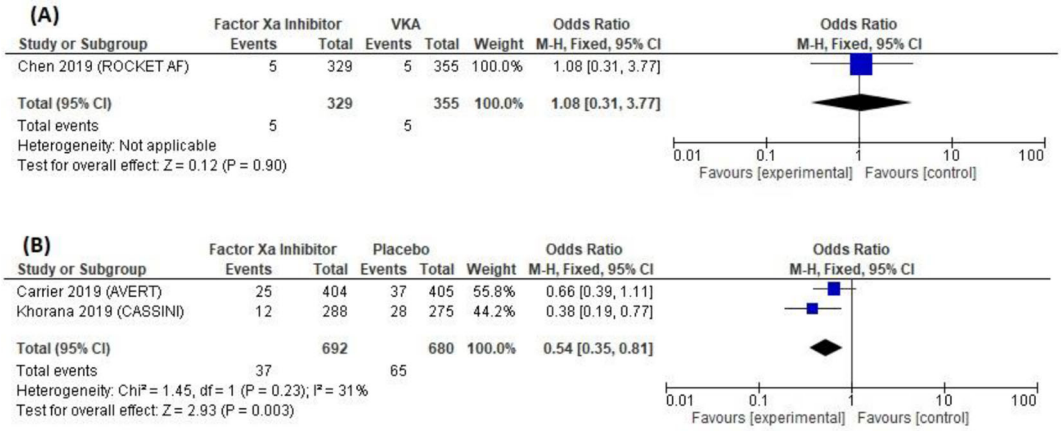


**Figure 5. Forest plot of new VTE outcome.**

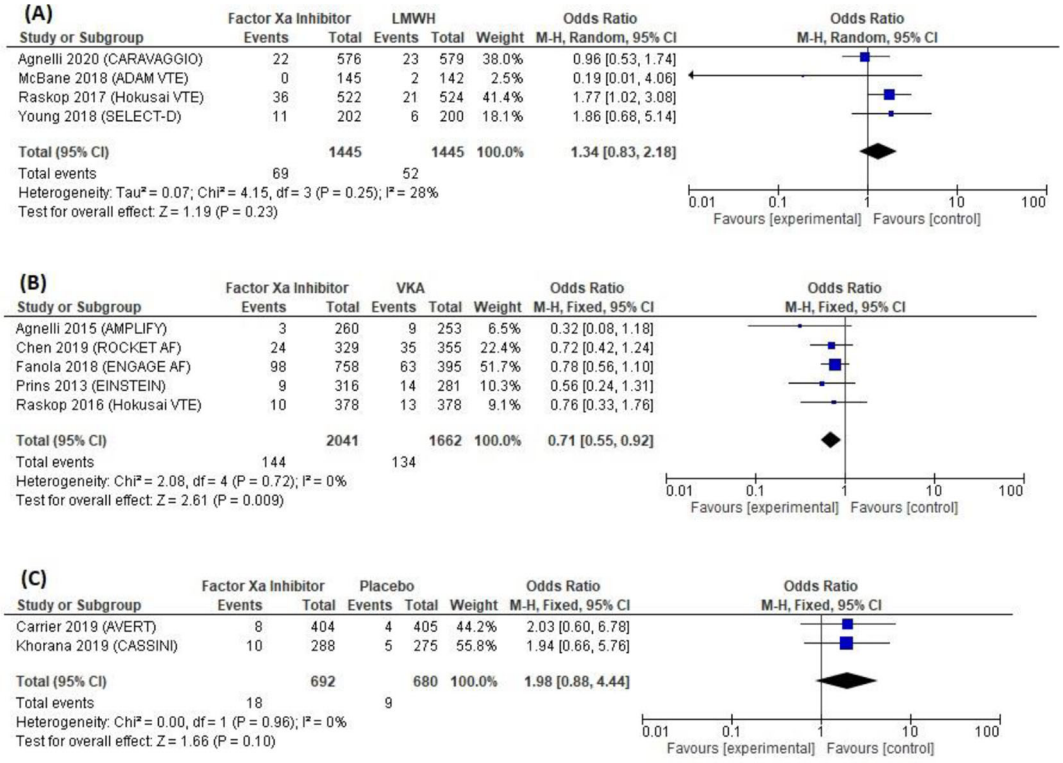


**Figure 6. Forest plot of major bleeding outcome.**

(two trials; OR = 1.98 [95% CI, 0.88–4.44]; P = 0.10) but not statistically significant, without substantial heterogeneity (I2 = 0%; P = 0.96).

## Discussion

The aim of this meta-analysis was to determine the efficacy and safety of factor Xa inhibitors for VTE treatment in cancer patients. Recurrence was 4.9%, 9.1%, and 6.9 % for the factor Xa inhibitor, LMWH, and VKA groups, respectively. All were lower than the findings of a retrospective cohort study which reported an incidence of 13.1%, 17.6%, and 17.9%, respectively.[23] Our review of four studies involving over 4,771 patients found that factor Xa inhibitors were associated with a lower risk of VTE recurrence when compared to LMWH, and even lower when compared to VKA. This result was consistent with a recent meta-analysis which combined data from RCTs and retrospective cohort studies.[24]

Another finding in our meta-analysis in terms of safety profiles was that factor Xa inhibitors were associated with an increased risk of bleeding when compared to LMWH, but a lower risk when compared to VKA. This result is in line with the findings of other systematic reviews.[24–26] However, another meta-analysis found a significantly higher incidence of bleeding (two trials, OR= 2.72 [95% CI: 1.05–7.01]; P= 0.039) with factor Xa inhibitors, relative to LMWH.[27] Importantly, the bleeding outcome in comparison to LMWH was the result of pooled data from nonspecific cancer patients. The results of the analysis of major bleeding in comparison to LMWH were mainly influenced by those of the HOKUSAI VTE Cancer trial and the recent CARAVAGGIO trial.[28,29] Both had different results: the former showed significantly higher bleeding in the edoxaban group while the second showed similar major bleeding events between groups.

Our meta-analysis also provided information about the efficacy of factor Xa inhibitors as prophylaxis, which suggested that, compared to placebo, it can significantly reduce VTE incidence. According to a recent clinical practice guideline, high-risk cancer outpatients can receive thromboprophylaxis with a factor Xa inhibitor or LMWH, in the absence of major risk factors for bleeding.[30] The high cost and the pain of daily LMWH injections was avoided with the factor Xa inhibitor regimen.

With respect to factor Xa inhibitors and LMWH, the inclusion of the CARAVAGGIO trial, with highly rigorous evidence, increased the accuracy of the estimated outcomes. There are a number of limitations to the current meta-analysis: the majority of the data corresponded to subgroup or post-hoc analyses. Further, the following variables were not controlled for: cancer stage, type of cancer, follow-up period. While most of the included studies evaluated patients for six months, the optimal duration of anticoagulation treatment was not evaluated to achieve an agreement. Finally, despite our systematic electronic database search and our investigation of the references in the included studies, we may have missed relevant studies.

## Conclusion

Factor Xa inhibitors are effective for VTE management in patients with cancer; however, they are also associated with an increased bleeding risk compared to LMWH, but decreased when compared to VKA.

## Data availability statement

***Underlying data***

All data underlying the results are available as part of the article and no additional source data are required.

***Reporting guidelines***[8]

Figshare: PRISMA checklist for 'Factor Xa inhibitor for venous thromboembolism management in Patients with cancer: a systematic review and meta-analysis'. https://doi.org/10.6084/m9.figshare.16590086.v3[31]



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