Original Article

Primary prophylaxis for venous thromboembolism in ambulatory cancer patients: a systematic review and network meta-analysis

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Background: Ambulatory cancer patients carry a high risk of venous thromboembolism (VTE). However, the optimal prophylaxis strategy remains controversial. This meta-analysis compared the effectiveness and safety of apixaban, rivaroxaban, low molecular weight heparin (LMWH), semuloparin, aspirin, and warfarin for the prevention of VTE in ambulatory cancer patients.

Methods: A systematic review and network meta-analysis was performed. PubMed, the Cochrane Central Register of Controlled Trails (CENTRAL) and EMBASE electronic databases were searched from inception to 26 April 2019. In the meta-analysis, 19 randomized controlled trials (RCTs) in ambulatory cancer patients administrated venous thromboprophylaxis agents were included. The primary outcome was the risk of VTE. Safety outcomes included the occurrence of major-bleeding. Two investigators identified the studies and performed data extraction. A network meta-analysis was performed and agents were ranked using cumulative ranking (SUCRA) probabilities.

Results: We identified 19 studies, including 11,430 patients comparing 10 interventions. Compared to placebo controls, apixaban (5 mg) showed the highest efficacy for the prevention of VTE [odds ratio (OR) 0.36, 95% confidence interval (CI): 0.18–0.71, SUCRA=69.5] and was more effective than LMWH (OR 0.5, 0.39–0.63; SUCRA=52.1) or warfarin (OR 0.75, 95% CI: 0.35–1.59; SUCRA=25.6). Moreover, the safety of apixaban (5 mg) (OR 1.41, 95% CI: 0.33–5.93; SUCRA=58.5) was higher than LMWH (OR 1.96, 95% CI: 0.99–3.86; SUCRA=44.1) or warfarin (OR 3.06, 95% CI: 1.03–9.08; SUCRA=29.1). There were no significant differences between placebo and experimental groups in terms of patient deaths.

Conclusions: Anticoagulation therapies in ambulatory cancer patients can significantly reduce the risk of VTE. However, this protective effect was associated with a significantly increased risk of major bleeding. Apixaban at the appropriate dose can decrease the risk of VTE without increasing the bleeding risk. These findings require validation in larger study cohorts.

Keywords: Venous thromboembolism (VTE); ambulatory cancer patients; new oral anticoagulants; low molecular weight heparin (LMWH); warfarin; net clinical benefit

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Introduction

Venous thromboembolism (VTE) is a frequent complication encountered in cancer patients which is related to the cancer itself or as a result of surgery and chemotherapy (1,2). The risk of mortality increases as tumor-associated VTE not only leads to fatal thromboembolism events but increases the risk of distant metastases (3-5). Ambulatory patients undergoing chemotherapy often carry a high risk of VTE, which can be high to 30% in those with metastatic or advanced malignancies (6). However, public health efforts have focused on thromboprophylaxis in a short-term setting including hospitalization and major surgery, whilst cancer therapy delivered in the outpatient setting has been ignored (7). For instance, in the updated National Comprehensive Cancer Network (NCCN) Guidelines, all hospitalized patients with active or clinically suspected tumors are recommended to be administered prophylactic anticoagulant therapy throughout their hospital stay without contraindications. However, no recommendations for VTE prevention in ambulatory cancer patients were provided due to their potential risks and limited treatment benefits (8).

Primary prophylaxis for VTE in Ambulatory Cancer Patients have received intense research attention. An array of studies have evaluated the efficacy and safety of anticoagulants in ambulatory patients with cancer and identified that prophylaxis with anticoagulants reduced the risk of VTE by ~50%, with no significant increase in the risk of major bleeding (9). Di Nisio *et al.* and Akl *et al.* both found that low molecular weight heparin (LMWH) significantly reduces the incidence of VTE and increased the risk of bleeding (10,11). In addition, with the introduction and widespread use of direct oral anticoagulants (DOACs) in VTE, the prospect of DOACs is rapidly evolving due to the convenience and ease of administration. Some DOACs were found to significantly lower the risk of VTE amongst ambulatory cancer patients with insignificant increases in the risk of bleeding (12). However, comparison of the effectiveness between different classes of anticoagulants are rarely reported, limiting practical recommendations for the prevention of VTE in ambulatory cancer patients despite the range of anticoagulation drugs available. Thus, we conducted a network meta-analysis of randomized studies to compare the effectiveness and safety of current anticoagulant regimens from both direct and indirect evidence in ambulatory patients.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-47).

Methods

A network meta-analyses was used to compare treatments regarding efficacy and safety with direct and indirect evidence of randomized controlled trials (RCTs) (13,14). A frequentist approach with multivariate random effects meta-analysis was used to compare the relative efficacy and safety of candidate strategies to prevent VTE (15-17). Multiple treatments were compared using direct and indirect evidence to provide precise estimates and direct evidence (18). Typical thromboprophylaxis in clinical practice included DOACs, warfarin and LMWH.

Protocols were established in PROSPERO (CRD42019134462) and the network meta-analyses was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for healthcare, by combining systematic reviews and previous network meta-analyses (19). We followed appropriate research approaches defined in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting the comparison between direct and indirect treatments. We referred to the network meta-analysis for healthcare decisions (20).

Data sources and research

Using controlled vocabulary elements with keywords, we searched PubMed, CENTRAL, and EMBASE electronic databases from inception to the 26th of April 2019 for original reports of RCTs (*Figure S1*). We collected reference lists of the review articles and identified other suitable trials. Studies were reviewed according to title and abstract to exclude those that did not match the research question. Studies were independently assessed by two reviewers. A third reviewer was used to resolve disputes.

Study selection

Study inclusion criteria: (I) randomized controlled trials (RCTs); (II) adults (aged ≥18 years) ambulatory cancer patients; (III) no obvious thromboembolism; (IV) candidate chemoprevention agents, namely apixaban (5 mg, 10 mg, or 20 mg per day), rivaroxaban, LMWH (prophylactic dosing), semuloparin, aspirin, warfarin alone or combination;

(V) a follow-up period of ≥3 months. Exclusion criteria were: (I) hospitalized cancer patients; (II) objectively confirmed venous or arterial thromboembolism at the time of randomization; (III) trials of drugs that are no longer available; (IV) those that did not account for the outcomes of interest.

Data extraction

Data on the primary efficacy outcomes were extracted from studies reporting the composite of objectively confirmed symptomatic or asymptomatic VTE including deep-vein thrombosis and pulmonary embolism diagnosed via the eligibility criteria (computed tomography or routine ultrasonographic testing). Safety outcomes included the rate of major bleeding, clinically relevant non-major bleeding (CRNMB) and all-cause mortality. The occurrence of major bleeding followed the guidelines of the International Society on Thrombosis and Hemostasis (ISTH; bleeding leading to hemoglobin levels ≥2 g per deciliter, transfusion of ≥2 units of packed red blood cells, bleeding that occurs at a critical site (intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitonea, or fatal bleeding) during the intervention period (21). All-cause mortality and clinically relevant non-major bleeding (CRNMB) were defined as overt bleeding that does not meet the criteria for major bleeding but is associated with medical interventions, unscheduled contact with a physician, interruption or discontinuation of study drugs, or discomfort or impairment of activities during daily living (22).

Data synthesis and statistical analysis

The Mantel-Haenszel random-effects model was used to calculate the odds ratio (OR) and 95% confidence intervals (CIs) of the efficacy of the prevention of VTE and the major bleeding events in direct meta-analysis with RevMan v5.3 (23). The I^2 statistic was applied to assess statistical heterogeneity, indicating substantial heterogeneity for values over 50% (24). A sensitivity analysis was performed to evaluate the strength of the pooled ORs by exclusion of non-double-blind randomized controlled trials or exclusion of studies with observational periods ≤6 months. When comparing efficacy and safety outcomes, a frequentist framework and random-effects model for Stata v15.1 was employed. The SUCRA ranged from 100 (high likelihood of therapeutic success) to 0 (high likelihood of therapeutic failure) to estimate the probability of each individual treatment related to efficiency and primary safety outcomes.

Results

Characteristics and risk of bias of the included trials

Using the search strategy, 3,185 unique citations were identified and 19 RCTs were included comparing 9 different interventions namely: rivaroxaban, apixaban 5 mg, apixaban 10 mg, apixaban 20 mg, LMWH, semuloparin, aspirin, warfarin and placebo groups (*Figure 1*) (25-43). A total of 19 trails were performed from 1984 to 2019 consisting of 11,430 patients, of which 897 were exposed to DOACs, 5,673 to traditional anticoagulation therapy and 4,878 placebo controls. All trials were randomized with a follow-up period of 3 months. Sixteen of the trails were multi-center (25-39,42), and 8 were double blind (25,26,28-31,36,37). In 17 of the studies, different candidate agents were compared to placebos in two arm trails. One study compared different apixaban doses to placebos forming a four-arm trial (27). A single study included 3 candidate agents without placebos that were compared in a three-arm trail (43). *Table 1* summarizes the characteristics of the included studies and presents the data suitable for the network meta-analysis. *Figure 2* shows the direct comparison and network of trials (for primary efficiency outcomes of VTE prevention and safety outcomes of major-bleeding events).

Pairwise meta-analysis

For the primary outcome of efficacy, the results of pairwise meta-analysis showed that apixaban 5 mg (OR 0.36, 95% CI: 0.18–0.71), LMWH (OR 0.50, 95% CI: 0.40–0.64) and semuloparin (OR 0.35, 95% CI: 0.21–0.59) significantly reduced the risk of VTE compared to placebo groups. Other interventions for preventing VTE reduced the risk compared to placebos but the differences lacked significance. Rivaroxaban (OR 0.66, 95% CI: 0.39–1.11), apixaban 10 mg (OR 0.13, 95% CI: 0.01–2.6), apixaban 20 mg (OR 0.12, 95% CI: 0.01–2.36) and warfarin (0.08, 0.00–1.39) were commonly used anticoagulant drugs (*Figure S2A*).

For major bleeding events, LMWH (OR 1.74, 95% CI: 1.07–2.84) and warfarin (OR 4.66, 95% CI: 1.92–11.31) were significantly related to a higher risk. For the comparison of DOACs with placebo controls, apixaban

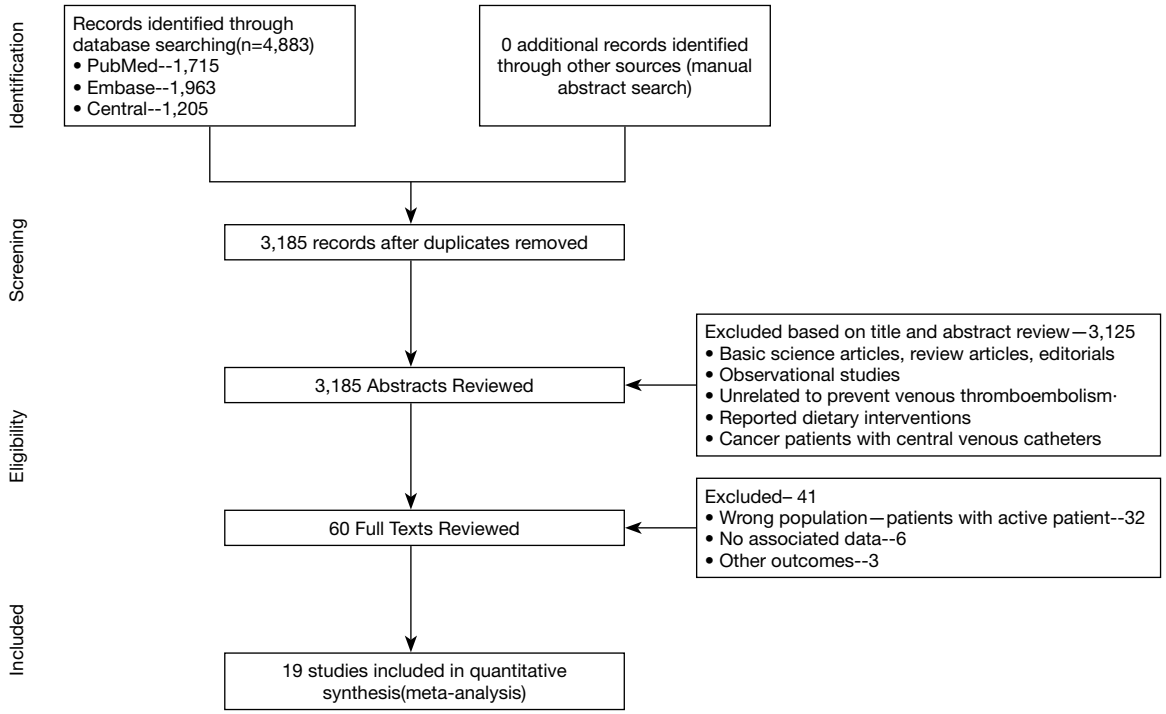

Figure 1 Flow diagram of the selection criteria.

Table 1 Characteristics of trials included in review of chemoprevention of venous thromboembolism in individuals with ambulatory cancer patients

Study	Design	Study group	Efficacy outcomes (VTE)	Safety		
				Major bleding	Bleeding	Death
Khorana, 2019, (25)	Multi-center, double blind, placebo controlled, parallel, randomized, 180 days	Placebo	37 [421]	4 [404]	8 [404]	100 [421]
		Rivaroxaban	25 [420]	8 [405]	11 [405]	84 [420]
Carrier, 2019, (26)	Multi-center, double blind, placebo controlled, parallel, randomized, 180 days	Placebo	28 [275]	5 [275]	15 [275]	27 [275]
		Apixaban 2.5 mg	12 [288]	10 [288]	21 [288]	35 [288]
Levine, 2012, (27)	Multi-center, double blind, placebo controlled, parallel, randomized, 12 weeks	Placebo	3 [29]	1 [29]	0 [29]	NA
		Apixaban 5 mg	0 [32]	0 [32]	1 [32]	NA
		Apixaban 10 mg	0 [29]	0 [29]	1 [29]	NA
		Apixaban 20 mg	0 [32]	2 [32]	2 [32]	NA
Kakkar, 2004, (28)	Multi-center, double blind, placebo controlled, parallel, randomized, 1 year	Placebo	5 [184]	0 [184]	5 [184]	NA
		LMHW (Dalteparin)	4 [190]	1 [190]	8 [190]	NA
Agnelli, 2009, (29)	Multi-center, double blind, placebo controlled, parallel, randomized, 12 months	Placebo	15 [381]	0 [381]	30 [381]	155 [381]
		LMHW (Nadroparin)	15 [769]	5 [769]	57 [769]	333 [769]

Table 1 (*Continued*)

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Study	Design	Study group	Efficacy outcomes (VTE)	Safety		
				Major bleding	Bleeding	Death
Perry, 2010, (30)	Multi-center, placebo controlled, parallel, randomized, 6 months	Placebo	13 [87]	0 [87]	NA	11 [87]
		LMHW (Dalteparin)	9 [99]	3 [99]	NA	18 [99]
Haas, 2012, (31)	Multi-center, double blind, placebo controlled, parallel, randomized, 6 months	Placebo	29 [441]	6 [451]	17 [451]	NA
		LMHW (Certoparin)	19 [442]	13 [447]	33 [447]	NA
Maraveyas, 2012, (32)	placebo controlled, parallel, randomized, 12 weeks	Placebo	17 [60]	2 [62]	2 [62]	4 [62]
		LMHW (Dalteparin)	7 [59]	2 [59]	5 [59]	7 [59]
Lecumberri, 2013, (33)	Multi-center, placebo controlled, parallel, randomized, 26 weeks	Placebo	4 [18]	1 [18]	4 [18]	12 [18]
		LMHW (Bemiparin)	0 [20]	0 [20]	2 [20]	9 [20]
Pelzer, 2015, (34)	Multi-center, single blind, placebo controlled, parallel, randomized, 3 months	Placebo	22 [152]	10 [152]	NA	NA
		LMHW (Enoxaparin)	10 [160]	13 [160]	NA	NA
Macbeth, 2016, (35)	Multi-center, placebo controlled, parallel, randomized, 24 weeks	Placebo	107 [434]	8 [434]	6 [434]	NA
		LMHW (Dalteparin)	61 [431]	12 [431]	50 [431]	NA
Khorana, 2017, (36)	Multi-center, single blind, placebo controlled, parallel, randomized, 12 weeks	Placebo	10 [48]	1 [48]	1 [48]	NA
		LMHW (Dalteparin)	6 [50]	7 [50]	3 [50]	NA
Agnelli, 2012, (37)	Multi-center, double blind, placebo controlled, parallel, randomized, 1 year	Placebo	55 [1,604]	18 [1,583]	14 [1,583]	185 [1,583]
		Semuloparin	20 [1,608]	19 [1,589]	26 [1,589]	193 [1,589]
Palumbo, 2011, (43)	Multi-center, parallel, randomized, 6 months	LMHW (Enoxaparin)	11 [219]	0 [219]	3 [219]	NA
		Aspirin	14 [220]	3 [220]	6 [220]	NA
		Warfarin	18 [220]	0 [220]	1 [220]	NA
Larocca, 2012, (38)	Multi-center, parallel, randomized, 12 months	LMHW (Enoxaparin)	2 [166]	0 [166]	1 [166]	NA
		Aspirin	4 [176]	0 [176]	0 [176]	NA
Levine, 1994, (39)	Multi-center, double blind, placebo controlled, parallel, randomized, 3 years	Placebo	6 [159]	2 [159]	3 [159]	99 [159]
		Warfarin	0 [152]	1 [152]	7 [152]	87 [152]
Chahinian, 1989, (40)	Placebo controlled, Parallel, randomized, 6 months	Placebo	NA	0 [84]	3 [84]	68 [84]
		Warfarin	NA	7 [100]	29 [100]	74 [100]
Zacharski, 1984, (41)	Placebo controlled, Parallel, randomized, 12 months	Placebo	NA	20 [208]	NA	141 [208]
		Warfarin	NA	88 [210]	NA	138 [210]
Maurer, 1997, (42)	Multi-center, placebo controlled, parallel, randomized, 8 months	Placebo	NA	3 [168]	27 [168]	48 [168]
		Warfarin	NA	12 [176]	73 [176]	47 [176]

VTE, venous thromboembolism; NA, no available.

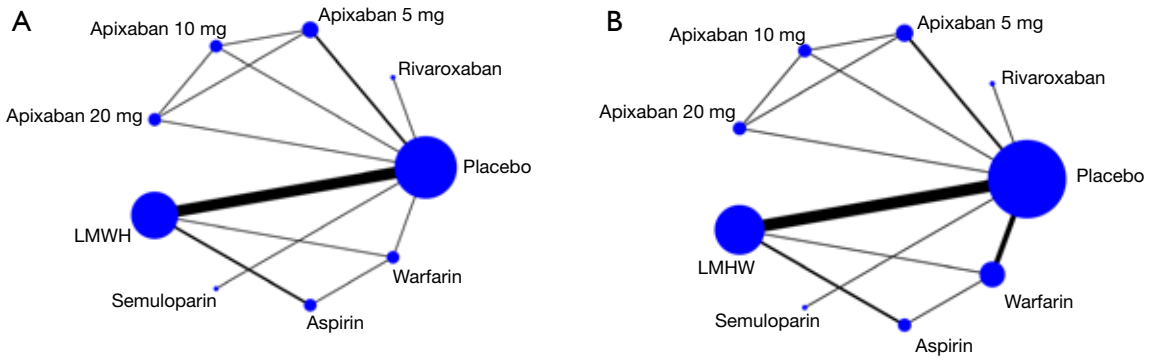

Figure 2 Network diagram of included trials and strength of comparison for (A) venous thrombosis, and (B) major bleeding events. The size of the nodes and thickness of the edges were weighted according to the number of studies evaluating and comparing each treatment, respectively.

5 mg (OR 1.43, 95% CI: 0.36–5.64) and rivaroxaban (OR 2.02, 95% CI: 0.60–6.57) increased the risk of bleeding but the effects were not significant (*Figure S2B*). Warfarin (OR 3.66, 95% CI: 2.34–5.7) significantly increased the risk of CRNMB, but DOACs (OR 1.48, 95% CI: 0.87–2.51) did not significantly increase the risk. There were no significant differences in all-cause mortality between LMWH (OR 1.14, 95% CI: 0.8–1.62), warfarin (OR 0.85, 95% CI: 0.67–1.08) and DOACs (OR 0.96, 95% CI: 0.62–1.49) compared to placebo controls (*Figure S2C,D*).

Network meta-analysis and efficacy outcomes

As shown in *Figures 3* & *4* (the data of *Figure 4* are based on *Figure S3*), anticoagulant prophylaxis in ambulatory cancer patients could effectively reduce the incidence of VTE compared to placebo groups. The anti-thrombosis effects of apixaban improved regardless of dose. However, only apixaban (5 mg) showed a significant effect (OR 0.36, 95% CI: 0.18–0.71; SUCRA=69.5). Apixaban at 10 mg (OR 0.15, 95% CI: 0.01–2.96; SUCRA=77.9) or 20 mg (OR 0.14, 95% CI: 0.01–2.68; SUCRA=78.2) had modest but non-significant effects on the rate of VTE occurrence. Similarly, rivaroxaban (OR 0.66, 95% CI: 0.39–1.11) and warfarin (OR 0.75, 95% CI: 0.35–1.59) non-significantly reduced the risk of VTE. Notably, both LMWH (OR 0.5, 95% CI: 0.39–0.63; SUCRA=52.1) and semuloparin (OR 0.35, 95% CI: 0.21–0.59; SUCRA=71.4) significantly prevented VTE.

Safety outcomes

Compared to placebo controls, the lowest safety ranking was observed for aspirin (OR 9.65, 95% CI: 1.1–84.36; SUCRA=9.4), followed by warfarin (OR 3.06, 95% CI: 1.03–9.08; SUCRA=29.1), apixaban at 20 mg (OR 2.43, 95% CI: 0.27–21.78; SUCRA=40.4), rivaroxaban (OR 2.02, 95% CI: 0.39–10.41; SUCRA=41.8), LMWH (OR 1.96, 95% CI: 0.99–3.86; SUCRA=44.1), and apixaban at 5 mg (OR 1.41, 95% CI: 0.33–5.93; SUCRA=58.5) (*Figure 3*).

LMWH (OR 2.25, 95% CI: 1.13–4.47) and warfarin (OR 3.49, 95% CI: 1.33–9.15) significantly increased the risk of CRNMB compared to placebo controls. As the dose of apixaban increased, the risk of CRNMB increased: 5 mg (OR 1.54, 95% CI: 0.36–6.63), 10 mg (OR 2.03, 95% CI: 0.13–3.1), and 20 mg (OR 3.17, 95% CI: 0.25–39.66). For DOACs agents, rivaroxaban (OR 1.38, 95% CI: 0.24–7.99) and apixaban (5 mg) had comparable effects (*Figure S4A*). No significant differences between placebo and experimental groups in terms of patient deaths were observed (*Figure S4B*).

Sensitivity analysis

Sensitivity analyses are shown in *Figures S4* & *S5*. The data were comparable to the primary outcome data. The criteria for sensitivity analysis were: (I) the exclusion of non-double-blind randomized controlled trials; (II) the exclusion of studies with observation times ≤6 months. Under the first

Major bleeding events

Efficacy in prevention of venous thromboembolism

Placebo	2.02 (0.39 to 10.41)	1.41 (0.33 to 5.93)	0.5 (0.02 to 13.76)	2.43 (0.27 to 21.78)	1.96 (0.99 to 3.86)	1.05 (0.29 to 3.81)	9.65 (1.1 to 84.36)	3.06 (1.03 to 9.08)
0.66 (0.39 to 1.11)	Rivaroxaban	0.7 (0.08 to 6.19)	0.25 (0.01 to 10.03)	1.2(0.08 to 18.66)	0.97 (0.16 to 5.73)	0.52 (0.06 to 4.2)	4.79 (0.32 to 72.63)	1.52 (0.21 to 10.86)
0.36 (0.18 to 0.71)	0.55 (0.23 to 1.3)	Apixaban 5 mg	0.36 (0.01 to 11.26)	1.73 (0.16 to 19.03)	1.39 (0.28 to 6.97)	0.75 (0.11 to 5.15	6.86 (0.52 to 90.55)	2.17 (0.39 to 12.09)
0.15 (0.01 to 2.96)	0.23 (0.01 to 4.72)	0.42 (0.02 to 8.66)	Apixaban 10mg	4.84 (0.18 to 127.64)	3.9 (0.13 to 114.51)	2.1 (0.06 to 73.19)	19.22 (0.37 to 1007.55)	6.09 (0.19 to 199.21)
0.14 (0.01 to 2.68)	0.21 (0.01 to 4.27)	0.38 (0.02 to 7.85)	0.91 (0.02 to 47.21)	Apixaban 20 mg	0.81 (0.08 to 8.01)	0.43 (0.03 to 5.52)	3.98 (0.18 to 87.02)	1.26 (0.11 to 14.62)
0.5 (0.39 to 0.63)	0.76 (0.42 to 1.34)	1.37 (0.67 to 2.82)	3.31 (0.17 to 65.89)	3.65 (0.18 to 72.44)	LMWH	0.54 (0.13 to 2.3)	4.93 (0.57 to 42.49)	1.56 (0.42 to 5.83)
0.35 (0.21 to 0.59)	0.54 (0.26 to 1.13)	0.98 (0.42 to 2.31)	2.37 (0.11 to 48.81)	2.61 (0.13 to 53.67)	0.72 (0.41 to 1.26)	Semuloparin	9.17 (0.74 to 114.08)	2.91 (0.54 to 15.64)
0.63 (0.3 to 1.35)	0.96 (0.38 to 2.43)	1.75 (0.63 to 4.86)	4.21 (0.19 to 91.5)	4.64 (0.21 to 100.61)	1.27 (0.62 to 2.64)	1.78 (0.71 to 4.47)	Aspirin	0.32 (0.03 to 2.95)
0.75 (0.35 to 1.59)	1.14 (0.45 to 2.86)	2.07 (0.75 to 5.73)	4.98 (0.23 to 108.07)	5.49 (0.25 to 118.83)	1.51 (0.73 to 3.11)	2.11 (0.84 to 5.27)	1.18 (0.59 to 2.39)	Warfarin

Figure 3 Comparative efficacy of chemoprevention for venous thromboembolism and the safety of major bleeding events in the network meta-analysis. Comparisons should be read from left to right. Odds ratio (95% credible interval) for comparisons are in cells in common between column-defining and row-defining treatment. A bold font indicates that the number is statistically significant. For the risk of venous thromboembolism, odds ratio <1 favor row-defining treatment. For the risk of major bleeding events: odds ratio <1 favor column- defining treatment.

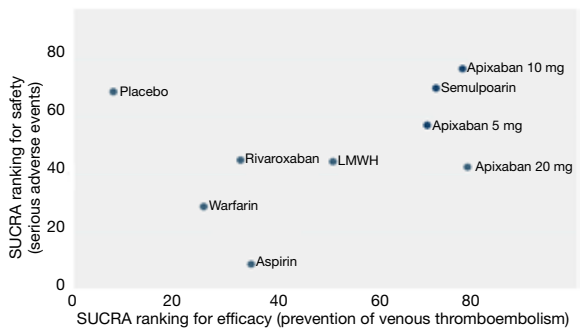

Figure 4 SUCRA rankings for efficacy and safety outcomes (range 100=treatment has high likelihood of being, 0=treatment with a high likelihood of a redcued efficacy). For efficacy outcomes, higher scores indicate an improved prevention of venous thromboembolism. For serious adverse event outcomes, higher scores=safer treatments with lower risk of serious adverse events. These data are based on *Figure S3*.

criteria, for the prevention of VTE in each group, apixaban 5 mg (OR 0.36, 95% CI: 0.18–0.71) and LMWH (OR 0.59, 95% CI: 0.38–0.91) were significantly superior. For safety outcomes, LMWH (OR 2.47, 95% CI: 1.02–6.01) significantly increased the risk of major-bleeding events (*Figure S5A*). All agents increased the risk of CRNMB compared to placebo controls without significant effects (*Figure S5B*). When applying the second rule, apixaban 5 mg (OR 0.38, 95% CI: 0.19–0.77) and LMWH (OR 0.52, 95% CI: 0.41–0.67) influenced the efficacy. LMWH (OR 2.51, 95% CI: 1.03–6.1) and increased the risk of major-bleeding events (*Figure S6*).

Quality of the evidence and risk of bias

In general, there were no serious risks of bias or inconsistency in the included studies (*Figures S7,S8*).

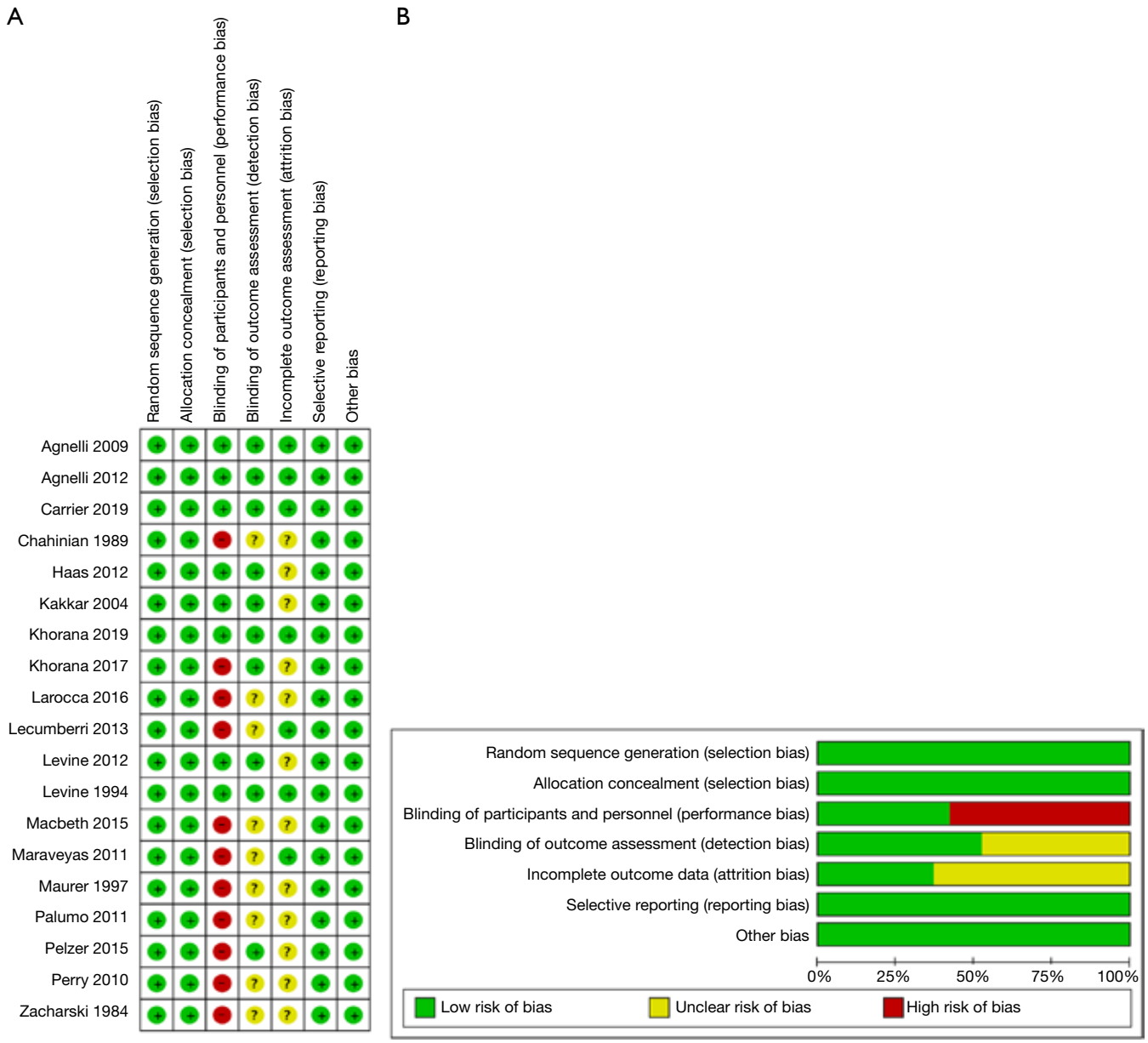

Figure 5 Quality assessment of the included studies. Overall (A) and study-level risk of bias (B), using the Cochrane's risk of bias assessment tool. Studies were deemed to have high, low or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding, and the method of addressing the incomplete data, selective reporting, and other biases. The reviewer's judgments of each risk of bias are shown as percentages across all included studies.

Following several comparisons, the 95% CI was cross-unified, leading to data inaccuracies. Using direct and independent evidence, we were confident that apixaban at 5 mg (OR 0.36, 95% CI: 0.18–0.71) and LMWH (OR 0.5, 95% CI: 0.39–0.63) prevented VTE in comparison to placebo controls.

The risk of bias of each included study was evaluated using the Cochrane Collaboration. Random sequence generation and allocation concealment were used to estimate selection bias, participant blinding, personnel to

performance bias, blinding of the outcome for detection bias, incomplete outcome data to attrition bias, selective reporting to reporting and other forms of bias (23). The included studies had low bias overall, suggesting the quality of the included trials was high (*Figure 5*).

Discussion

In this network meta-analysis and systematic review, nine protocols for the primary prevention of VTE in ambulatory cancer patients were assessed. The effectiveness and safety of the various regimens were compared regarding: (I) the efficacy of VTE prevention; (II) major-bleeding events; (III) CRNMB; and (IV) all-cause mortality. According to our analysis, anticoagulant prophylaxis effectively reduced the incidence of VTE and did not significantly increase all-cause mortality. Compared to warfarin and LMWH, apixaban had significant effects on the reduction of thrombosis without increasing the risk of major-bleeding events.

Previous studies compared anticoagulation regimens for active cancer patients (44,45). The probability of developing VTE in ambulatory cancer patients is nearly 5-fold higher than non-tumor patients and the risk of recurrent VTE is 2–9 fold higher (46,47). As the survival time of cancer patients gradually rises, the risk of developing VTE increases (48). In our analysis, anticoagulant prophylaxis in ambulatory cancer patients effectively reduced the incidence of VTE, thereby improving the quality of life of the patients. Compared to warfarin, apixaban effectively prevented VTE in a manner comparable to LMWH. Apixaban at 5 and 20 mg doses and LMWH increased the risk of major-bleeding events whilst the risk of major-bleeding decreased in those receiving apixaban at 10 mg per day. Considering heterogeneity between the outcomes, disparities in the study population and the accuracy of follow-up may explain these discrepancies. Thus, apixaban at the appropriate dose may decrease the risk of VTE without increasing the bleeding risk, but this requires validation in larger study cohorts. Semuloparin significantly prevented VTE (OR 0.35, 95% CI: 0.21–0.59) and increased the risk of major-bleeding events (OR 1.05, 95% CI: 0.29–3.81), but this drug is not commonly available in the clinical and belongs to the group of LMWHs. It is therefore not recommended for future use.

The compliance with medication is vital for ambulatory cancer patients. Anticoagulant prophylaxis with LMWH or warfarin requires frequent blood tests that increase the cost of therapy, enhance patient discomfort, and reduce thromboprophylaxis compliance. Thus, the use of DOACs to prevent VTE are recommend by doctors in the clinic (49). In this meta-analysis, we did not include all DOACs approved by the US Food and Drug Administration including dabigatran etexilate and edoxaban tosylate. The comparison of the effects of each group to prevent VTE requires further assessment. However, we observed good efficacy and high safety of the DOACs which may suggest better compliance. Although the Apixaban (5 mg) group showed the highest prevention of VTE and the lowest risk of major bleeding events, the recommended dosage cannot be administered based on the group sizes. Aspirin is used as an antiplatelet agent in clinical practice and is frequently compared to LMWH in RCTs. Aspirin prevents VTE, but the risk of major bleeding was the highest amongst all included agents. However, some have suggested that the use of aspirin to prevent VTE lowers the risk of bleeding (50). This article included two articles related to aspirin and no direct comparison to placebo groups were performed. To assess the efficacy and safety of aspirin to prevent VTE, further studies are now required.

Our study had some limitations. The meta-analysis was dependent on the quality of the included studies. Although sensitivity analysis did reveal significant bias, some outcome data were absent. Some studies included screening based DVT whilst others did not, which may increase heterogeneity. Because the time factor in the included studies was also insufficient, only the therapeutic effects and safety of the various drugs were compared.

The study also has several strengths. First, we performed a thorough literature search to provide an exhaustive analysis of the available evidence. Secondly, our goal was to provide an OR and the effectiveness and safety of treatments to support clinical decision making. This is the only article to compare the therapeutic effects of various anticoagulant drugs in ambulatory cancer patients. Finally, we provided assessments of direct and network comparisons to consider direct and indirect evidence. This helps describe comparative data from previous systematic reviews in this area.

Conclusions

Based on the analysis of existing clinical RCTs, we identified a range of compounds that can prevent VTE in ambulatory cancer patients. When a risk assessment for thrombosis in ambulatory cancer patients is performed and patients are deemed an intermediate-to-high risk,

we recommend anticoagulant prophylaxis. Amongst the commonly used anticoagulant drugs, apixaban improved the thromboprophylaxis effects and lowered the risk of major-bleeding events. Apixaban also does not require the detection of blood indicators, thereby reducing patient discomfort. We thus recommend that apixaban at the appropriate dose may decrease the risk of VTE without increasing the bleeding risk. This now requires validation in larger study cohorts.

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Footnote

Reporting Checklist: The authors have completed the PRISMA Reporting Checklist. Available at http://dx.doi.org/10.21037/apm-20-47

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-47). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Pubmed:

#1	Pulmonary embolism [MeSH Terms] OR Pulmonary Embolisms OR Embolism, Pulmonary OR Embolisms, Pulmonary OR Pulmonary Thromboembolisms OR Pulmonary Thromboembolism OR Thromboembolism, Pulmonary OR Thromboembolisms, Pulmonary
#2	Venous thrombosis [MeSH Terms] OR Phlebothrombosis OR Phlebothromboses OR Thrombosis, Venous OR Thromboses, Venous OR Venous Thromboses OR Deep Vein Thrombosis OR Deep Vein Thromboses OR Thromboses, Deep Vein OR Vein Thromboses, Deep OR Vein Thrombosis, Deep OR Deep-Venous Thrombosis OR Deep-Venous Thromboses OR Thromboses, Deep-Venous OR Thrombosis, Deep-Venous OR Deep-Vein Thrombosis OR Deep-Vein Thromboses OR Thromboses, Deep-Vein OR Thrombosis, Deep-Vein OR Thrombosis, Deep Vein OR Deep Venous Thrombosis OR Deep Venous Thromboses OR Thromboses, Deep Venous OR Thrombosis, Deep Venous OR Venous Thromboses, Deep OR Venous Thrombosis, Deep
#3	venous thromboembolism [MeSH Terms] OR Thromboembolism, Venous
#4	Apixaban OR dabigatran OR edoxaban OR rivaroxaban OR direct oral anticoagulant OR new oral anticoagulant OR direct anti Xa OR direct anti IIa OR direct thrombin inhibitor
#5	"Heparin, Low-Molecular-Weight"[Mesh Terms] OR Heparin, Low Molecular Weight OR LMWH OR Low Molecular Weight Heparin OR Low-Molecular-Weight Heparin OR dalteparin OR tinzaparin OR enoxaparin OR nadroparin
#6	"Warfarin"[Mesh Terms] OR 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one OR Apo-Warfarin OR Aldocumar OR Gen-Warfarin OR Warfant OR Coumadin OR Marevan OR Warfarin Potassium OR Potassium, Warfarin OR Warfarin Sodium OR Sodium, Warfarin OR Coumadine OR Tedicumar OR Antivitamin K OR acenocoumarol OR phenprocoumon OR coumadin
#7	randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title /Abstract]
#8	((#1 OR #2 OR #3) AND (#4 OR #5 OR #6)) AND # 7

Total: 1715 articles

Embase:

#1	'lung embolism'/exp OR 'pulmonary embolisms':ab,ti OR 'embolism, pulmonary':ab,ti OR 'embolisms, pulmonary':ab,ti OR 'pulmonary thromboembolisms':ab,ti OR 'pulmonary thromboembolism':ab,ti OR 'thromboembolism, pulmonary':ab,ti OR'thromboembolisms, pulmonary':ab,ti
#2	'vein thrombosis'/exp OR 'Phlebothrombosis':ab,ti OR 'Phlebothromboses':ab,ti OR 'Thrombosis, Venous':ab,ti OR 'Thromboses, Venous':ab,ti OR 'Venous Thromboses':ab,ti OR 'Deep Vein Thrombosis':ab,ti OR 'Deep Vein Thromboses':ab,ti OR 'Thromboses, Deep Vein':ab,ti OR 'Vein Thromboses, Deep':ab,ti OR 'Vein Thrombosis, Deep':ab,ti OR 'Deep-Venous Thrombosis':ab,ti OR 'Deep-Venous Thromboses':ab,ti OR 'Thromboses, Deep-Venous':ab,ti OR 'Thrombosis, Deep-Venous':ab,ti OR 'Deep-Vein Thrombosis':ab,ti OR 'Deep-Vein Thromboses':ab,ti OR 'Thromboses, Deep-Vein':ab,ti OR 'Thrombosis, Deep-Vein':ab,ti OR 'Thrombosis, Deep Vein':ab,ti OR 'Deep Venous Thrombosis':ab,ti OR 'Deep Venous Thromboses':ab,ti OR 'Thromboses, Deep Venous':ab,ti OR 'Thrombosis, Deep Venous':ab,ti OR 'Venous Thromboses, Deep':ab,ti OR 'Venous Thrombosis, Deep':ab,ti
#3	'venous thromboembolism'/exp OR Thromboembolism, Venous
#4	Apixaban:ab,ti OR dabigatran:ab,ti OR edoxaban:ab,ti OR rivaroxaban:ab,ti OR 'direct oral anticoagulant':ab,ti OR 'new oral anticoagulant':ab,ti OR 'direct anti Xa':ab,ti OR 'direct anti IIa':ab,ti OR 'direct thrombin inhibitor':ab,ti
#5	'low molecular weight heparin'/exp OR 'Heparin, Low Molecular Weight':ab,ti OR LMWH OR 'Low Molecular Weight Heparin':ab,ti OR 'Low-Molecular-Weight Heparin':ab,ti OR dalteparin:ab,ti OR tinzaparin:ab,ti OR enoxaparin:ab,ti OR nadroparin:ab,ti
#6	'warfarin'/exp OR '4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one':ab,ti OR 'Apo-Warfarin':ab,ti OR Aldocumar:ab,ti OR 'Gen-Warfarin':ab,ti OR Warfant:ab,ti OR Coumadin:ab,ti OR Marevan:ab,ti OR 'Warfarin Potassium':ab,ti OR 'Potassium, Warfarin':ab,ti OR 'Warfarin Sodium':ab,ti OR 'Sodium, Warfarin':ab,ti OR Coumadine:ab,ti OR Tedicumar:ab,ti OR Antivitamin K:ab,ti OR acenocoumarol:ab,ti OR phenprocoumon:ab,ti OR coumadin:ab,ti
#7	'randomized controlled trial'/exp
#8	((#1 OR #2 OR #3) AND (#4 OR #5 OR #6)) AND # 7

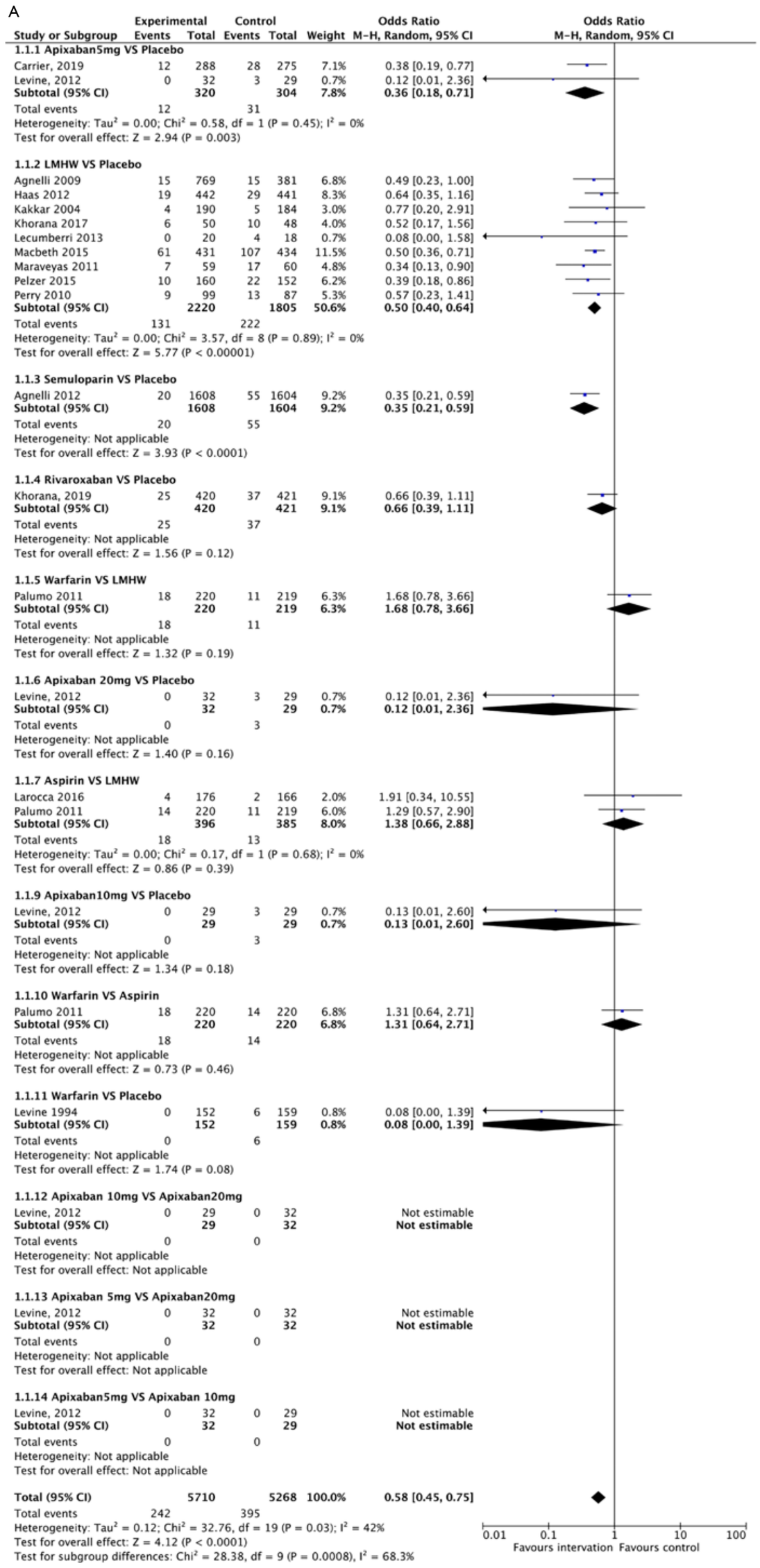
Total: 1963 articles

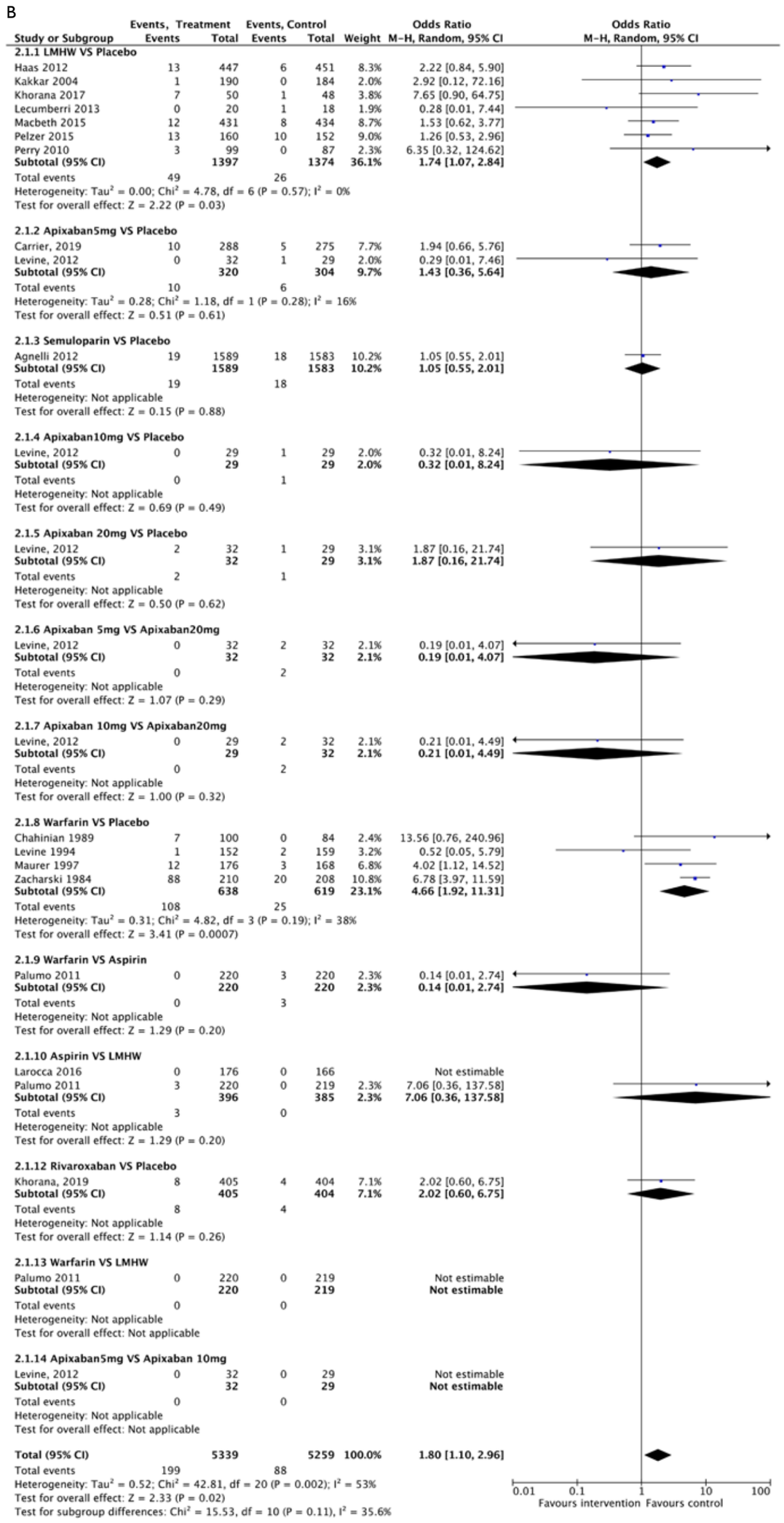
Central:

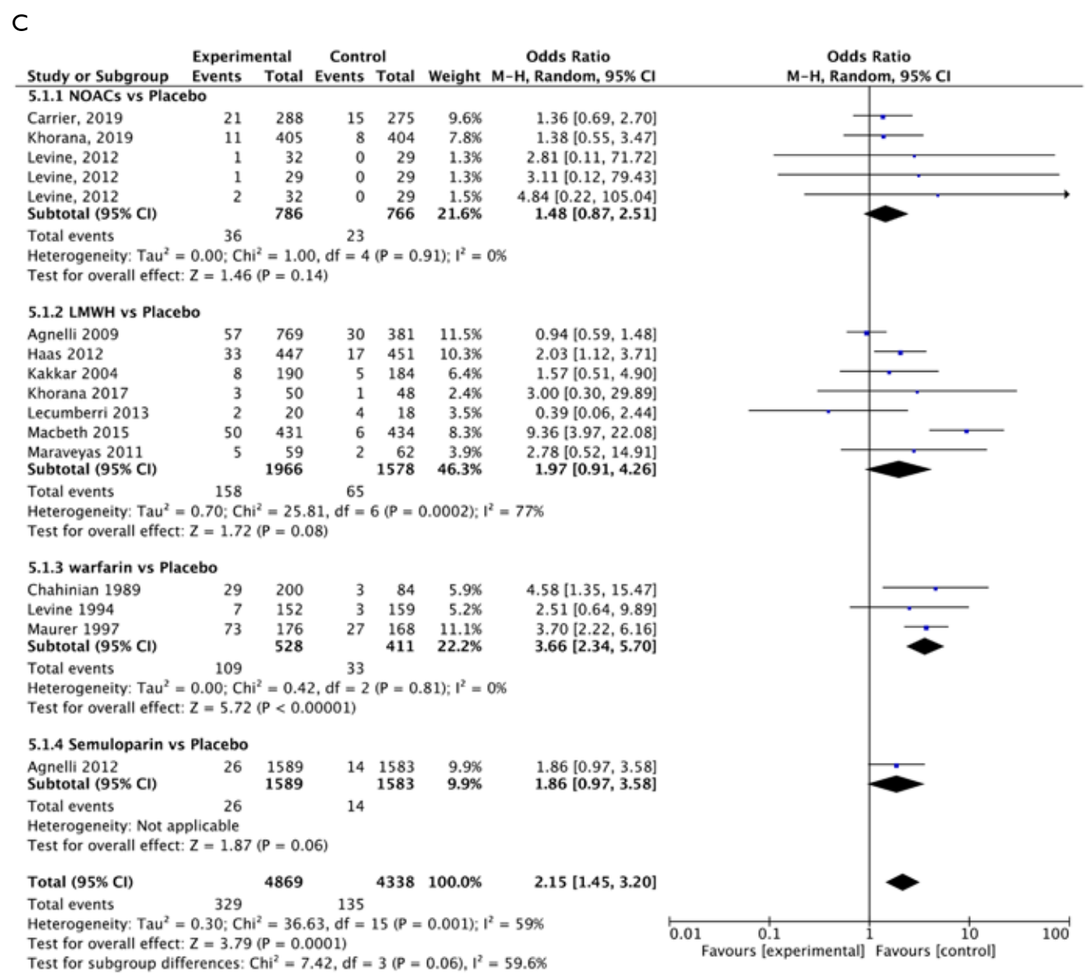
#1	MeSH descriptor: [Venous Thrombosis] explode all trees
#2	MeSH descriptor: [Pulmonary Embolism] explode all trees
#3	MeSH descriptor: [Venous Thromboembolism] explode all trees
#4	(Apixaban OR dabigatran OR edoxaban OR rivaroxaban OR direct oral anticoagulant OR new oral anticoagulant OR direct anti Xa OR direct anti IIa OR direct thrombin inhibitor):ti,ab,kw
#5	MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees OR (Heparin, Low Molecular Weight OR LMWH OR Low Molecular Weight Heparin OR Low-Molecular-Weight Heparin OR dalteparin OR tinzaparin OR enoxaparin OR nadroparin):ti,ab,kw
#6	MeSH descriptor: [Warfarin] explode all trees OR (Apo-Warfarin OR Aldocumar OR Gen-Warfarin OR Warfant OR Coumadin OR Marevan OR Warfarin Potassium OR Potassium, Warfarin OR Warfarin Sodium OR Sodium, Warfarin OR Coumadine OR Tedicumar OR Antivitamin K OR acenocoumarol OR phenprocoumon OR coumadin):ti,ab,kw
#7	(#1 OR #2 OR #3) AND (#4 OR #5 OR #6)

Total: 1205 articles

Figure S1 Search strategy. There are the keywords searched in PubMed, the Cochrane Central Register of Controlled Trails (CENTRAL), and EMBASE electronic database from inception to 26 April 2019 for original reports of RCTs.







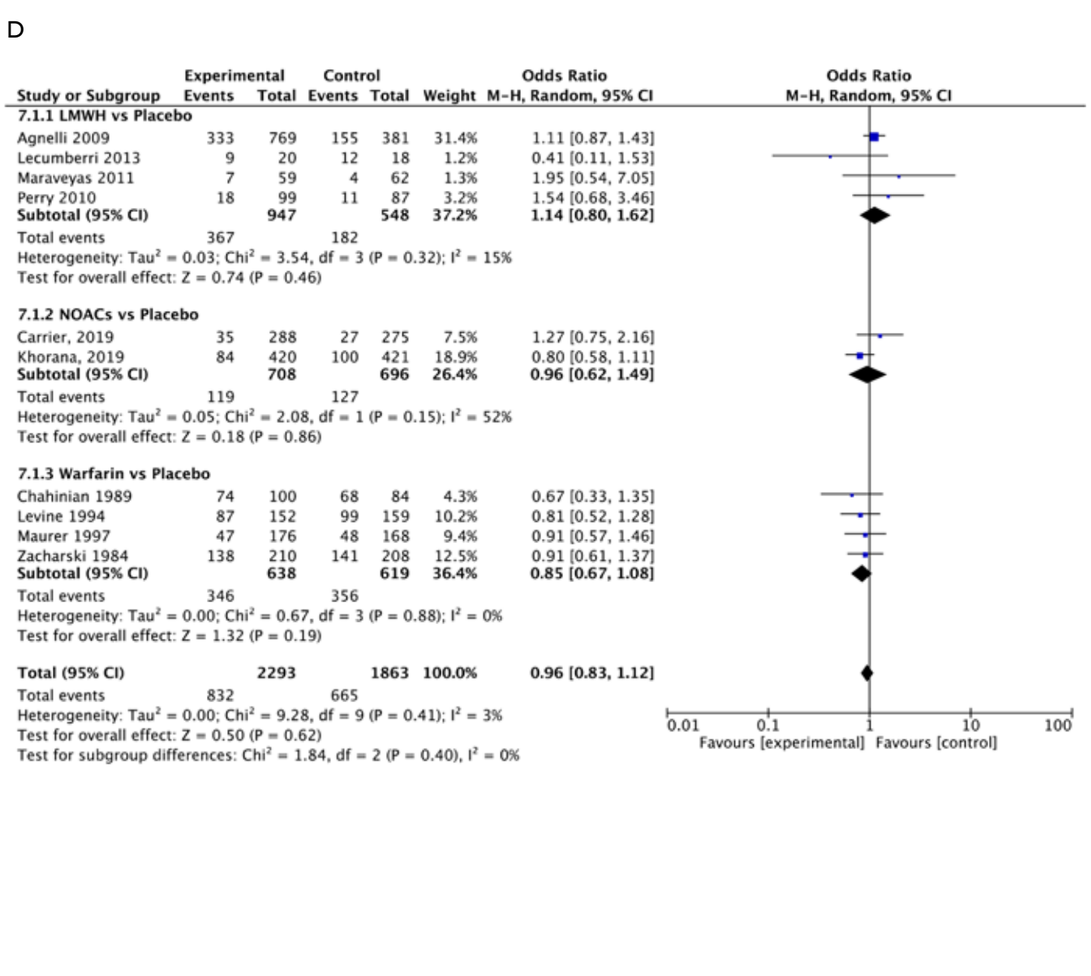


Figure S2 Direct meta-analysis of chemoprevention agents for (A) the prevention of venous thrombosis, (B) major bleeding events, (C) clinically relevant non-major bleeding events, and (D) all-cause mortality. Direct meta-analysis used M-H random effects model.

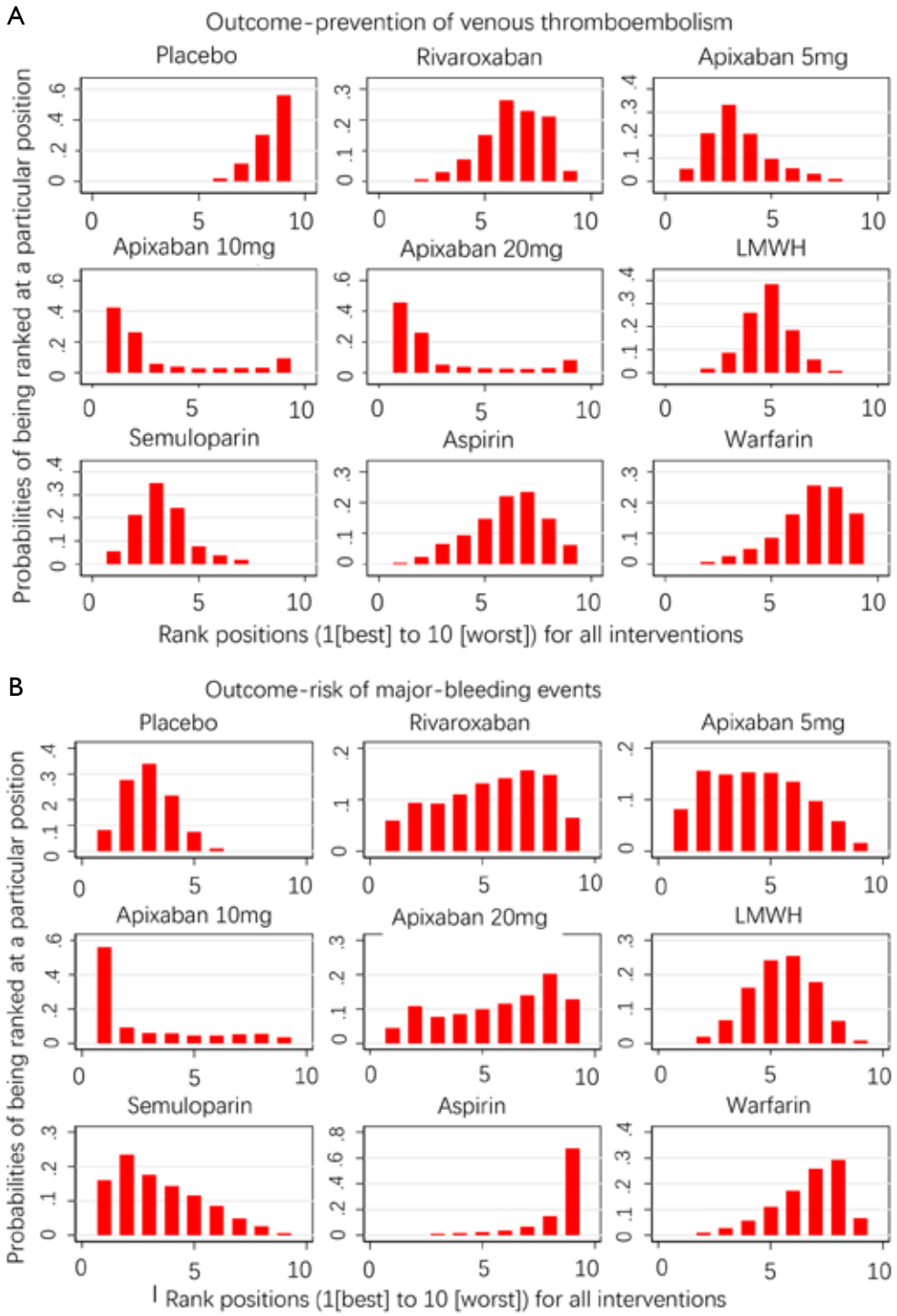


Figure S3 Renkograms demonstrating the probability of each intervention being ranked at all positions for (A) preventing venous thrombosis (B) risk of major bleeding events. This visually depicts the uncertainty in the ranking distribution of agents.

A

Clinically relevant non-major bleeding events

Placebo	1.38 (0.24 to 7.99)	1.54 (0.36to 6.63)	2.03 (0.13 to 3.1)	3.17 (0.25 to 39.66)	2.25 (1.13 to 4.47)	1.86 (0.38 to 9.09)	4.56 (0.82 to 25.37)	**3.49 (1.33 to 9.15)**
	Rivaroxaban	1.11 (0.12 to 10.58)	1.47 (0.06 to 36.75)	2.29 (0.11 to 48.54)	1.63 (0.26 to 10.3)	1.35 (0.13 to 13.91)	3.3 (0.29 to 37.29)	2.52 (0.35 to 18.01)
		Apixaban 5mg	1.32 (0.1 to 17.06)	2.06 (0.2 to 21.52)	1.46 (0.29 to 7.3)	1.21 (0.14 to 10.44)	2.96 (0.31 to 28.28)	2.26 (0.39 to 13.11)
			Apixaban 10mg	1.56 (0.12 to 19.71)	1.11 (0.07 to 18.32)	0.92 (0.04 to 21.42)	2.24 (0.09 to 56.25)	1.71 (0.09 to 30.96)
				Apixaban 20mg	0.71 (0.05 to 9.72)	0.59 (0.03 to 11.62)	1.44 (0.07 to 30.64)	1.1 (0.07 to 16.53)
					LMHW	0.83 (0.15 to 4.66)	2.03 (0.39 to 10.48)	1.55 (0.5 to 4.83)
						Semuloparin	2.45 (0.24 to 25.3)	1.87 (0.29 to 11.96)
							Aspirin	0.76 (0.12 to 4.69)
								Warfarin

B

All-cause mortality

Placebo	0.8 (0.58 to 1.11)	1.27 (0.75 to 2.16)	1.13 (0.9 to 1.42)	1.04 (0.84 to 1.30)	0.85 (0.67 to 1.08)
	Rivaroxaban	1.58 (0.85 to 2.96)	1.41 (0.94 to 2.10)	1.30 (0.88 to 1.93)	1.06 (0.71 to 1.59)
		Apixaban 5 mg	0.89 (0.5 to 1.59)	0.82 (0.46 to 1.46)	0.67 (0.37 to 1.20)
			LMWH	0.93 (0.68 to 1.27)	0.75 (0.54 to 1.05)
				Semuloparin	0.81 (0.59 to 1.12)
					Warfarin

Figure S4 Comparative safety of clinically relevant non-major bleeding events (A) and all-cause mortality (B) in network meta-analysis. Comparisons should be read from left to right. Odds ratio (95% credible interval) for comparisons are in cells in common between column-defining and row-defining treatment. Bold cells are significant. Odds ratio <1 favor column- defining treatment.

A

Major-bleeding events

Efficacy in prevention of venous thromboembolism

Placebo	2.02 (0.6 to 6.75)	1.6 (0.57 to 4.49)	0.5 (0.02 to 11.57)	2.41 (0.35 to 16.66)	**2.47 (1.02 to 6.01)**	1.05 (0.55 to 2.01)	0.52 (0.05 to 5.79)
0.66 (0.39 to 1.11)	Rivaroxaban	0.8 (0.16 to 3.89)	0.25 (0.01 to 7.18)	1.2 (0.12 to 11.69)	1.23 (0.27 to 5.49)	0.52 (0.13 to 2.06)	0.26 (0.02 to 3.83)
0.36 (0.18 to 0.71)	0.55 (0.23 to 1.3)	Apixaban 5mg	0.31 (0.01 to 7.82)	1.5 (0.19 to 11.82)	1.54 (0.4 to 6.00)	0.66 (0.19 to 2.22)	0.32 (0.02 to 4.46)
0.15 (0.01 to 2.96)	0.23 (0.01 to 4.72)	0.42 (0.02 to 8.66)	Apixaban 10mg	4.84 (0.22 to 105.04)	4.95 (0.19 to 130.04)	2.11 (0.09 to 52.31)	1.04 (0.02 to 54.81)
0.14 (0.01 to 2.68)	0.21 (0.01 to 4.27)	0.38 (0.02 to 7.85)	0.91 (0.02 to 47.21)	Apixaban 20mg	1.02 (0.12 to 8.6)	0.44 (0.06 to 3.35)	0.22 (0.01 to 4.74)
0.59 (0.38 to 0.91)	0.9 (0.45 to1.78)	1.64 (0.73 to 3.67)	3.94 (0.19 to 80.19)	4.34 (0.21 to 88.17)	LMWH	0.43 (0.14 to 1.28)	0.21 (0.02 to 2.75)
0.35 (0.21 to 0.59)	0.54 (0.26 to 1.13)	0.98 (0.42 to 2.31)	2.37 (0.11 to 48.81)	2.61 (0.13 to 53.67)	0.6 (0.31 to 1.18)	Semuloparin	0.49 (0.04 to 6.00)
0.08 (0.00 to 1.39)	0.12 (0.01 to 2.21)	0.21 (0.01 to 4.16)	0.52 (0.01 to 32.75)	0.57 (0.01 to 36.02)	0.13 (0.01 to 2.43)	0.22 (0.01 to 4.09)	Warfarin

B

Clinical non-major bleeding events

Placebo	1.38 (0.44 to 4.32)	1.44 (0.57 to 3.63)	1.9 (0.18 to 19.92)	2.96 (0.36 to 24.61)	1.37 (0.78 to 2.38)	1.86 (0.73 to 4.75)	2.51 (0.55 to 11.54)
	Rivaroxaban	1.04 (0.24 to 4.52)	1.38 (0.1 to 18.72)	2.14 (0.19 to 23.72)	0.99 (0.28 to 3.51)	1.35 (0.31 to 5.89)	1.82 (0.27 to 12.19)
		Apixaban 5mg	1.32 (0.14 to 12.66)	2.06 (0.27 to 15.49)	0.95 (0.33 to 2.77)	1.29 (0.35 to 4.81)	1.74 (0.29 to 10.36)
			Apixaban 10mg	1.56 (0.17 to 13.95)	0.72 (0.06 to 8.01)	0.98 (0.08 to 12.28)	1.32 (0.08 to 21.72)
				Apixaban 20mg	0.46 (0.05 to 4.11)	0.63 (0.06 to 6.37)	0.85 (0.06 to 11.52)
					LMWH	1.36 (0.46 to 4.05)	1.83 (0.36 to 9.32)
						Semuloparin	1.35 (0.22 to 8.06)
							Warfarin

Figure S5 Network meta-analysis for (A) prevention of venous thromboembolism and major bleeding events, (B) clinical non-major bleeding events after excluding studies with no double blind.

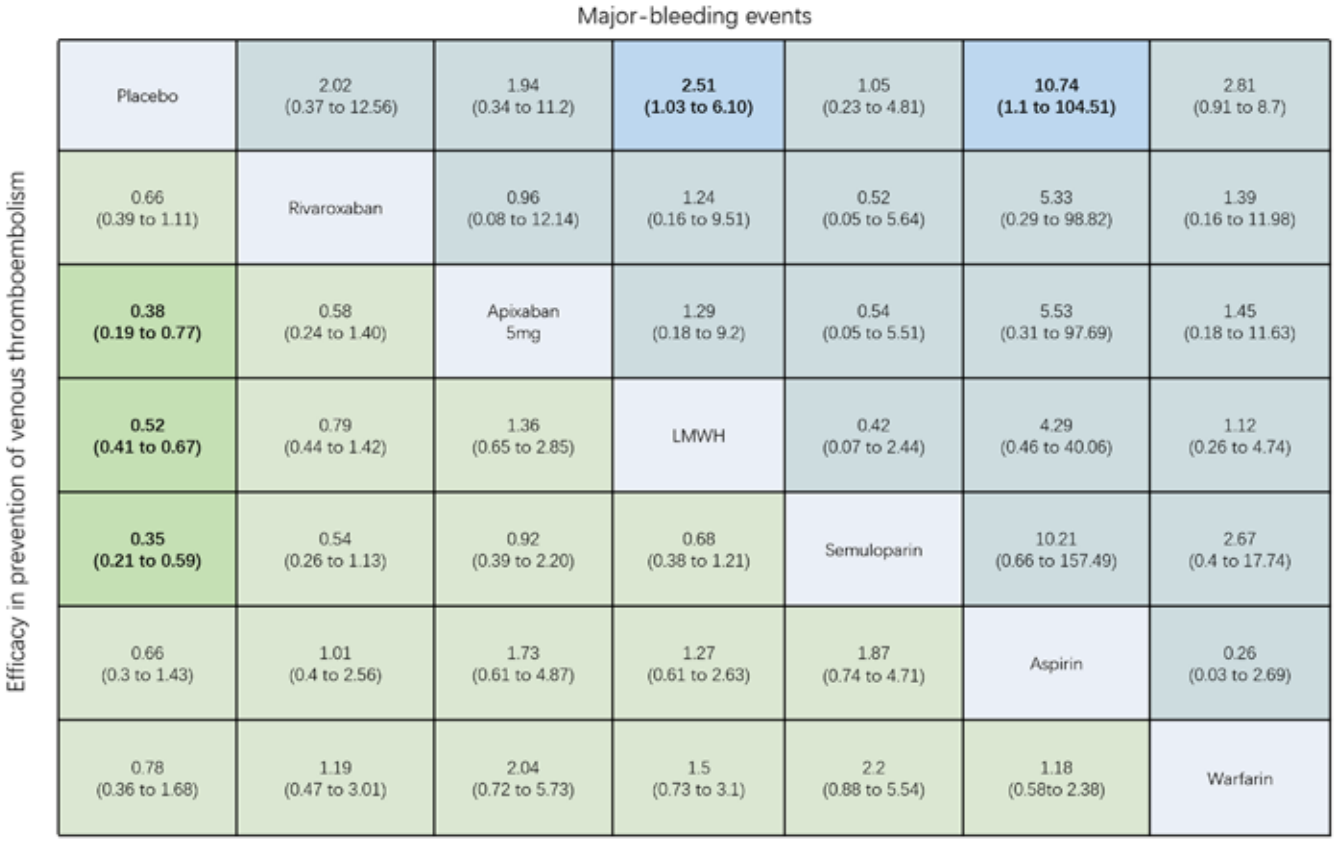


Figure S6 Network meta-analysis for prevention of venous thromboembolism and major bleeding events after excluding studies with less than 6 months of observation.

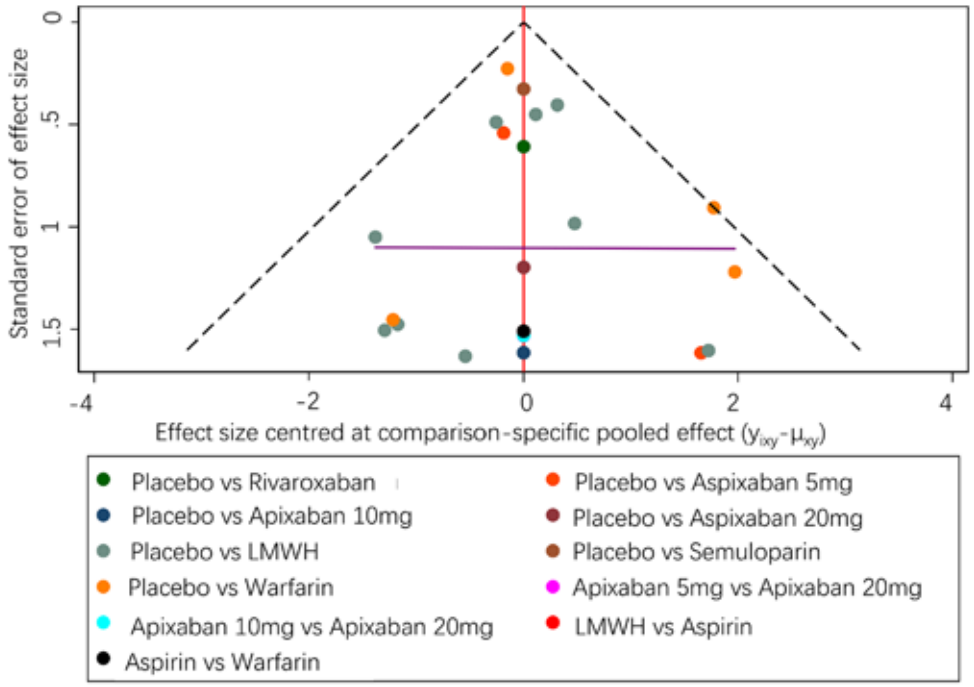


Figure S7 Small-study effects assessed via comparison-adjusted network funnel plots. In this presentation, all studies are centered on the summary effect estimate of their respective comparisons [μXY (logOR for present study)] which is represented by the vertical red line. Individual study-level effect size is represented by yiXY [where X and Y are two study agents]. The green line represents linear regression of the comparison specific differences yi - μXY on the standard error of yi. Outer dotted lines indicate the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity (logOR ± 1.96*standard error).

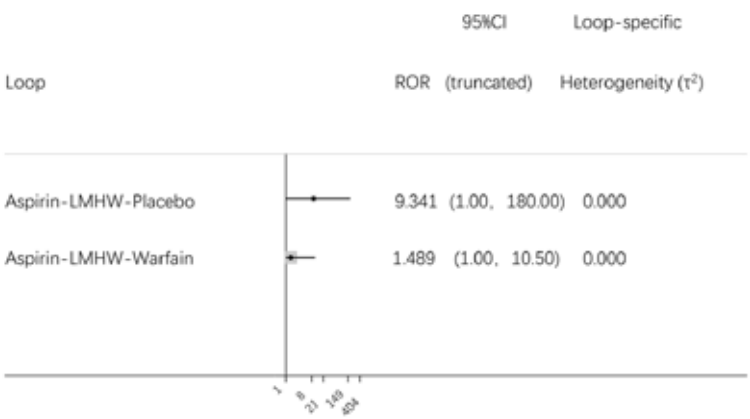


Figure S8 The Consistency test of network meta-analysis.