



Treatment of cancer-associated venous thromboembolism by new oral anticoagulants: a meta-analysis

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Background: The efficacy and safety of newer oral anticoagulants (NOAs) compared to vitamin K antagonist (VKA) in preventing the recurrence of venous thromboembolism (VTE) is well documented. However, it still needs to be determined whether this pattern holds when compared to the combination of low-molecular-weight heparin (LMWH) and VKA in patients with VTE and malignancy.

Methods: For this analysis, the authors searched available databases for randomized controlled trials (RCTs) comparing the NOAs with standard treatment (combination of LMWH and VKA) in patients with VTE and those comparing NOAs with LMWH only for prevention of VTE. All these RCTs included small proportion of patients with cancer. The authors then assessed the pooled treatment effects of VTE recurrence, as well as major and non-major clinically relevant bleeding in the two groups.

Results: Twelve studies met our inclusion criteria, yielding 2,054 patients. Five studies with rivaroxaban, three each with dabigatran and apixaban, and one with edoxaban compared NOAs with standard treatment. There was a non-significant reduction in VTE recurrence by the NOAs (3.95%) compared to standard treatment (5.62%) [risk ratio (RR) =0.68; 95% confidence interval (CI) =0.42–1.10; P=0.12]. The major bleeding rate with NOAs was (2.62%) compared to the corresponding rate for standard treatment (3.75%) (RR =0.66; 95% CI =0.36–1.20; P=0.17). The non-major clinically relevant bleeding rate with NOAs was (12.82%) compared to the rate for standard treatment (15.52%) (RR =0.85; 95% CI =0.65–1.10; P= 0.22). However, compared to LMWH only, both higher major (RR =2.18; 95% CI =0.32–14.80; P=0.42) and non-major clinically relevant (RR =2.39; 95% CI =0.75–7.56; P=0.14) bleeding rates were noted with NOAs use in acutely-ill hospitalized patients.

Conclusions: NOAs seem to be comparable to standard treatment in both their efficacy and safety in patients with VTE and malignancy. However, increased rates of bleeding were observed with their use compared to LMWH use in acutely-ill hospitalized patients.

Keywords: Newer oral anticoagulants (NOAs); cancer; vitamin K antagonists (VKAs); low-molecular-weight heparin (LMWH); venous thromboembolism (VTE); meta-analysis

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Introduction

The risk of venous thromboembolism (VTE) is fourfold to sevenfold in patients with malignancy compared to those without (1,2). VTE is the leading cause of mortality in patients with cancer and results in increased morbidity (3,4). It also contributes to an increased cost of care (5). The management of cancer-associated thrombosis poses many challenges due to the simultaneously increased risk of bleeding seen in patients receiving anticoagulation treatment (6,7). Given the delicate hemostatic balance in patients with cancer, the assessment of both thrombosis and bleeding risks is vital for effective management of hematological complications. The 2016 CHEST Guideline and Expert Panel Report advocates the use of low-molecular-weight heparin (LMWH) over a vitamin K antagonist (VKA) for the first three months after the diagnosis of VTE in cancer patients (Grade 2B recommendation) (8). However, a recurrence rate of VTE as high as 15% per year in cancer patients has compelled practitioners to consider indefinite anticoagulation in this population. Therefore, extended anticoagulant therapy is recommended in these patients despite the increased risks of bleeding (8).

The issues concerning the long-term use of LMWH include its feasibility, the cost of the drug, and quality of life. VKA therapy for VTE in cancer patients is suboptimal due to the twofold risk of relapse and the threefold risk of bleeding compared to the corresponding rates for non-cancer patients (9). VKA therapy for VTE in cancer patients also poses challenges in management, which include potential interactions with multiple medications along with associated difficulty in controlling the international normalized ratio (INR), thereby resulting in poor-quality anticoagulation control, as echoed by a reduced time in the therapeutic range (TTR) (10). New direct anti-Xa and anti-IIa oral anticoagulants with no recommended laboratory monitoring requirements, predictable responses, oral administration, and fixed dose regimens are attractive alternatives for the treatment of VTE in cancer patients. However, given the small proportion of cancer patients included in the trials with these newer agents, a meta-analysis specifically including cancer patients from these trials will provide more evidence of their efficacy and safety. Although these trials have proportion of patients with cancer, many of them do not specify the type of malignancy. Lack of this data demands a RCT in specific types of cancers with these new agents.

Prior meta-analyses have assessed the effectiveness

of newer oral anticoagulants (NOAs) for the secondary prevention of VTE. Our study also includes trials where NOAs were compared with LMWH for thromboprophylaxis in hospitalized patients, and a proportion of these patients had malignancy. We therefore conducted an updated meta-analysis for efficacy and safety outcomes.

Methods

Search strategy and data sources

All randomized controlled trials (RCTs) published as of April 30, 2017 were identified after conducting a search using the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Abstracts were retrieved and independently reviewed by two authors, Satyanarayana R. Vaidya and Sonu Gupta, for eligibility. We also searched the bibliographies of the original trials, the meta-analyses, and review articles. The search terms used were as follows: venous thromboembolism, cancer, malignancy, thromboprophylaxis, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, or oral factor Xa inhibitor, an oral thrombin inhibitor. The meta-analysis was conducted as per the recommendations from the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (11,12). The search algorithm is demonstrated in *Figure 1*.

Study selection

Studies which met the following inclusion criteria were included.

- (I) Randomized controlled trials
- (II) Trials comparing NOAs with low molecular weight heparin
- (III) Trials comparing NOAs with combination of LMWH or heparin and therapeutic doses of VKAs in patients with VTE,
- (IV) Trials which recruited patients with active cancer.

Observational studies, RCTs which did not include cancer patients, studies with no comparator arms were excluded. The outcomes of interest included VTE recurrence rates, major and clinically relevant bleeding.

Data extraction

The data were extracted independently by two authors, Satyanarayana R. Vaidya and Sonu Gupta, from the trials,

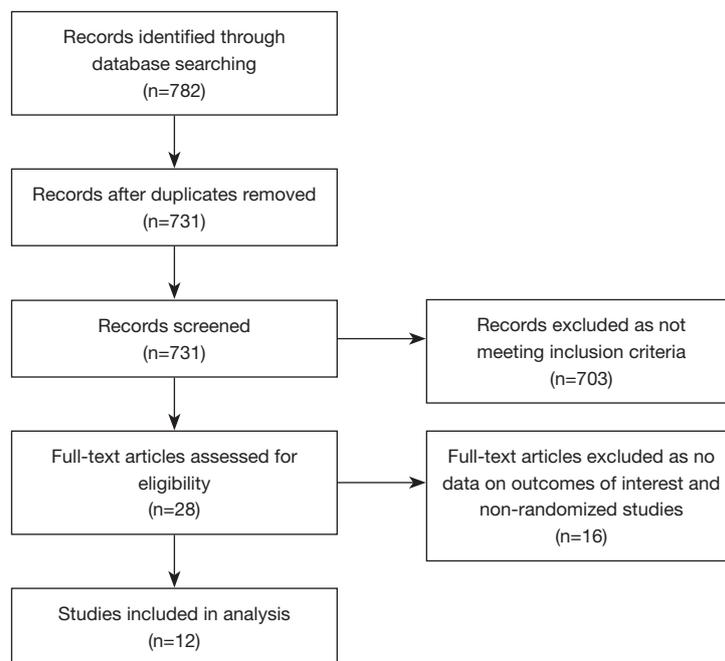


Figure 1 PRISMA flow diagram depicting search strategy.

including the year of publication, study design, sample size, mean age, sex, therapeutic indication, type of drug, dose, duration of follow-up, and number of patients with active cancer. The efficacy outcomes included the number of VTE recurrences; safety outcomes included major or clinically relevant bleeding. The characteristics of the included studies are summarized in *Table 1*.

Quality assessment

The quality of the studies was assessed by using the Jadad scale (13). A score of ≥ 3 was considered to define a high-quality study, with all twelve studies having this score.

Statistical analysis

The statistical analysis was conducted in line with the recommendations of the Cochrane Collaboration and PRISMA guidelines using Review Manager (RevMan) version 5.3 software (Cochrane, Oxford, UK). The random effects model of DerSimonian and Laird was used because of the clinical and methodological heterogeneity of the studies. The relative risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using the inverse variance method. Heterogeneity was considered as the proportion of the

total variation observed between the trials, which was due to the differences between the trials rather than a sampling error, and was assessed using the I^2 statistic. An $I^2 < 25\%$ was considered to represent low heterogeneity, and an $I^2 > 75\%$ was considered to represent high heterogeneity (14). The publication bias was estimated visually through the use of funnel plots (*Figure 2*). Inspection of the funnel plot for the outcomes for VTE did not reveal any publication bias.

Results

Our primary search yielded 782 studies. Twelve studies fulfilled our inclusion criteria and were included in the meta-analysis (15-26). These twelve studies had included active cancer patients and reported their outcomes. Of the twelve trials, five studied rivaroxaban (16,18-20,23), three studied apixaban (15,17,22), three studied dabigatran (24-26), and one studied edoxaban (21). Of the twelve studies, ten compared NOAs with standard treatment of VTE (LMWH & VKA). Two studies compared NOAs with LMWH only in acutely ill hospitalized patients. In aggregate, all the above studies included a total of 2,054 active cancer patients. The duration of follow-up ranged from one to 36 months. The study sizes ranged from 520 to 8,240 patients, with the rates of included cancer patients ranging from 2.5–9.4%.

Table 1 Characteristics of studies included

Study	Year	Study design	Study medication	Dose of medication	Control	Duration of study (months)	Number of patients randomized	Number of patients with active cancer range (%)	Time in therapeutic range (TTR) (%)	Mortality: study medication/control	Recurrent VTE: study medication/control	Clinically relevant bleeding: study medication/control	Jadad score
Agnelli <i>et al.</i> (AMPLIFY)	2013	Double blind	Apixaban	10 mg bid for 7 days followed by 5 mg bid	LMWH/VKA	6	5,395	169 (3.1)	61	1.5/1.9	2.3/2.7	4.3/9.7	5
Agnelli <i>et al.</i> (ODIXa-DVT)	2007	Double blind	Rivaroxaban	10 or 20 or 30 mg bid or 40 mg qd	LMWH/VKA	3	528	16 (3.0)	60	2.7/0.8	1.9 or 2.0 or 1.8 or 2.6 vs. 0.9	5.0 or 9.4 or 10.7 or 11.6 vs. 6.3	5
Buller <i>et al.</i> (EINSTEIN DVT)	2008	Double blind	Rivaroxaban	20 or 30 or 40 mg q daily	LMWH/VKA	3	543	51 (9.4)	50.3	3.0 or 6.0 or 1.5 vs. 3.6	2.6 or 3.6 or 1.7 vs. 6.9	5.9 or 6.0 or 2.2 vs. 8.8	5
Buller <i>et al.</i> (BOTTICELLI DOSE RANGING)	2008	Double blind	Apixaban	5 or 10 mg bid or 20 mg q daily	LMWH/VKA	3	520	37 (7.1)	57	2.3 or 0.7 or 0.8 vs. 0	2.6 or 3.2 or 1.7 vs. 2.5	8.6 or 4.5 or 8.9 vs. 7.9	5
Bauersachs <i>et al.</i> (EINSTEIN DVT)	2010	Open	Rivaroxaban	15 mg bid for 3 wks followed by 20 mg q daily	LMWH/VKA	12	3,449	207 (6.0)	57.7	2.2/2.9	2.1/3.0	8.1/8.1	5
Buller <i>et al.</i> (HOKUSA)	2013	Double blind	Heparin/edoxaban	60 mg once daily or 30 mg once daily	Heparin or LMWH/VKA	12	8,240	208 (2.5)	63.5	3.2/3.1	3.2/3.5	8.5/10.3	5
Buller <i>et al.</i> (EINSTEIN PE)	2012	Open	Rivaroxaban	15 mg bid for 3 weeks followed by 20 mg qd	LMWH/VKA	12	4,832	223 (4.6)	62.7	2.4/2.1	2.1/1.8	10.3/11.4	3
Goldhaber <i>et al.</i> (ADOPT)	2011	Double blind	Apixaban	2.5 mg bid for 30 days	Enoxaparin	1	6,528	211 (3.23)	NR	1.73/1.61	2.71/3.06	0.47/0.19	5
Cohen <i>et al.</i> (MAGELLAN)	2011	Double blind	Rivaroxaban	10 mg q daily	Enoxaparin	1	8,101	592 (7.3)	NR	0.1 vs. 0.2	3.0 vs. 3.1	2.8 vs. 1.2	4
Schulman <i>et al.</i> (RECOVER I)	2009	Double blind	Dabigatran	150 mg bid	Heparin/VKA	6	2,539	121 (4.8)	60	1.6 vs. 1.7	2.7 vs. 2.5	5.6 vs. 8.8	5
Schulman <i>et al.</i> (RECOVER II)	2014	Double blind	Dabigatran	150 mg bid	Heparin/VKA	6	2,589	100 (3.9)	57	2.0 vs. 1.9	2.3 vs. 2.2	5.0 vs. 7.9	5
Schulman <i>et al.</i> (REMEDY)	2013	Double blind	Dabigatran	150 mg bid	Heparin/VKA	6-36	2,586	119 (4.2)	65.3	1.2 vs. 1.3	1.8 vs. 1.3	5.6 vs. 10.2	5

VKA, Vitamin K antagonist; LMWH, low molecular weight heparin.

Recurrence of VTE

Twenty-nine of 733 cancer patients treated with NOAs developed VTE compared to 35 of the 622 patients treated with standard treatment. Compared to standard treatment, NOAs showed a non-significant reduction in VTE [RR

=0.68; 95% CI =0.42–1.10; P=0.12] (Figure 3). There was no heterogeneity for this outcome.

Bleeding events

Nineteen of 725 cancer patients treated with NOAs developed major bleeding compared to 23 of the 612 patients treated with standard treatment. Compared to standard treatment, NOAs showed a non-significant reduction in major bleeding (RR =0.66; 95% CI =0.36–1.20; P=0.17) (Figure 4).

Non-major clinically relevant bleeding occurred in 93 of 725 cancer patients treated with NOAs compared to 95 of 612 cancer patients treated with standard treatment. Compared to standard treatment, a non-significant reduction in clinically relevant bleeding was shown with the use of NOAs (RR =0.85; 95% CI =0.65–1.10; P=0.22) (Figure 5).

Subgroup analysis

A subgroup analysis of trials comparing anti-Xa and anti-IIa with control medications was conducted. Of the twelve trials, nine studies with anti-Xa and three with anti-IIa were analyzed. The RR for recurrent VTE showed rates of 0.67

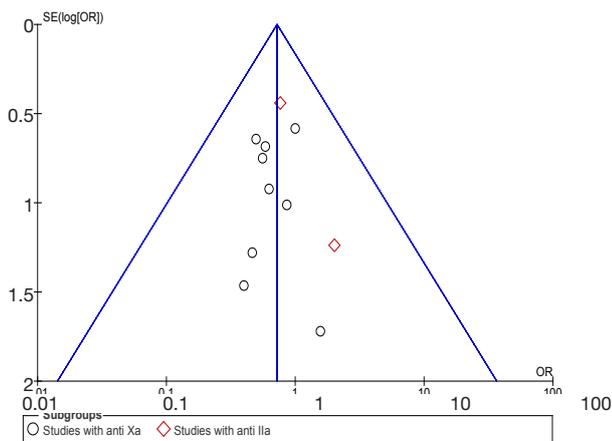


Figure 2 Funnel plot for the outcome recurrence of venous thromboembolism showing no publication bias.

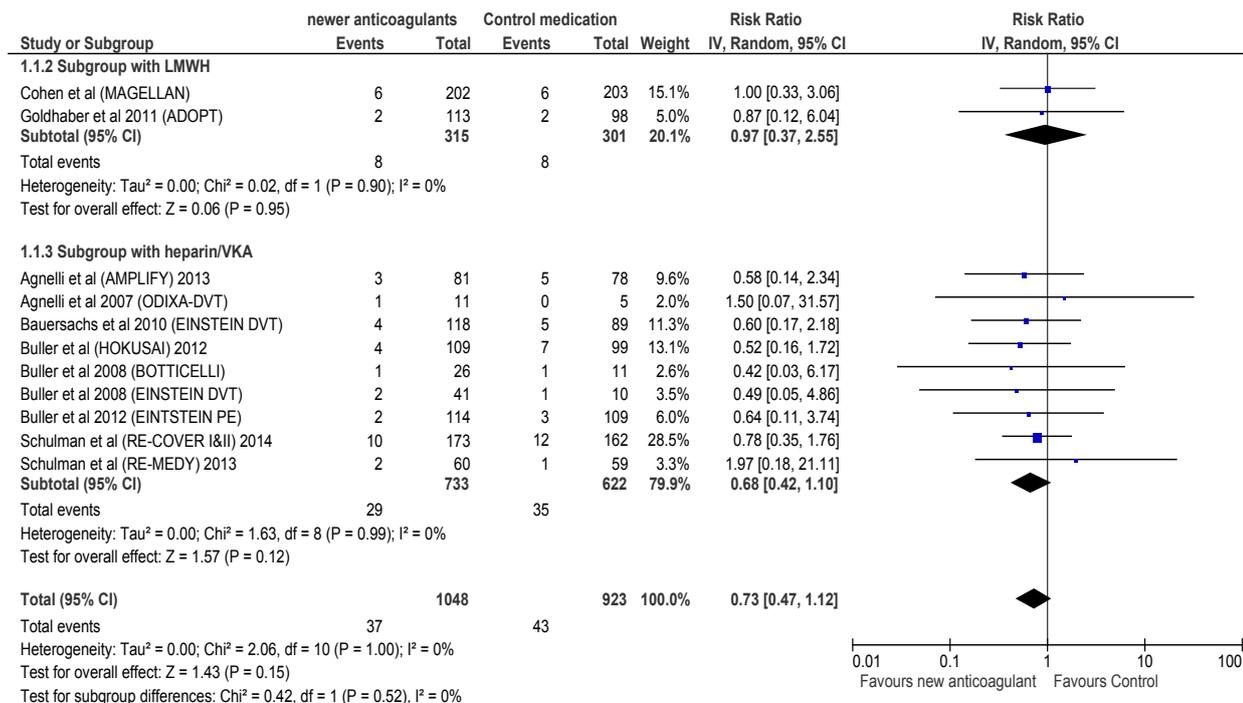


Figure 3 Forest plot for recurrence of venous thromboembolism. Summary risk ratios and 95% confidence intervals showing non-significant reduction in VTE recurrence by NOAs. VTE, venous thromboembolism; NOAs, newer oral anticoagulants.

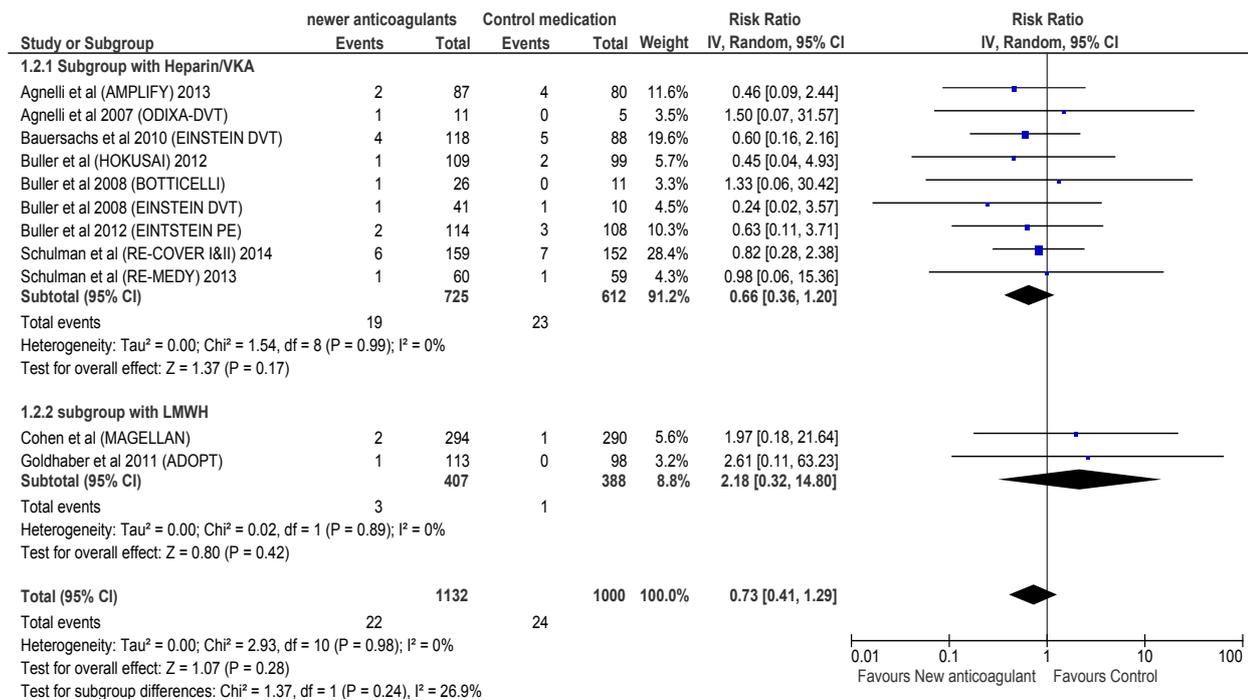


Figure 4 Forest plot for major bleeding. Summary risk ratios and 95% confidence intervals showing higher rates of bleeding with NOAs compared to LMWH. NOAs, newer oral anticoagulants; LMWH, low-molecular-weight heparin.

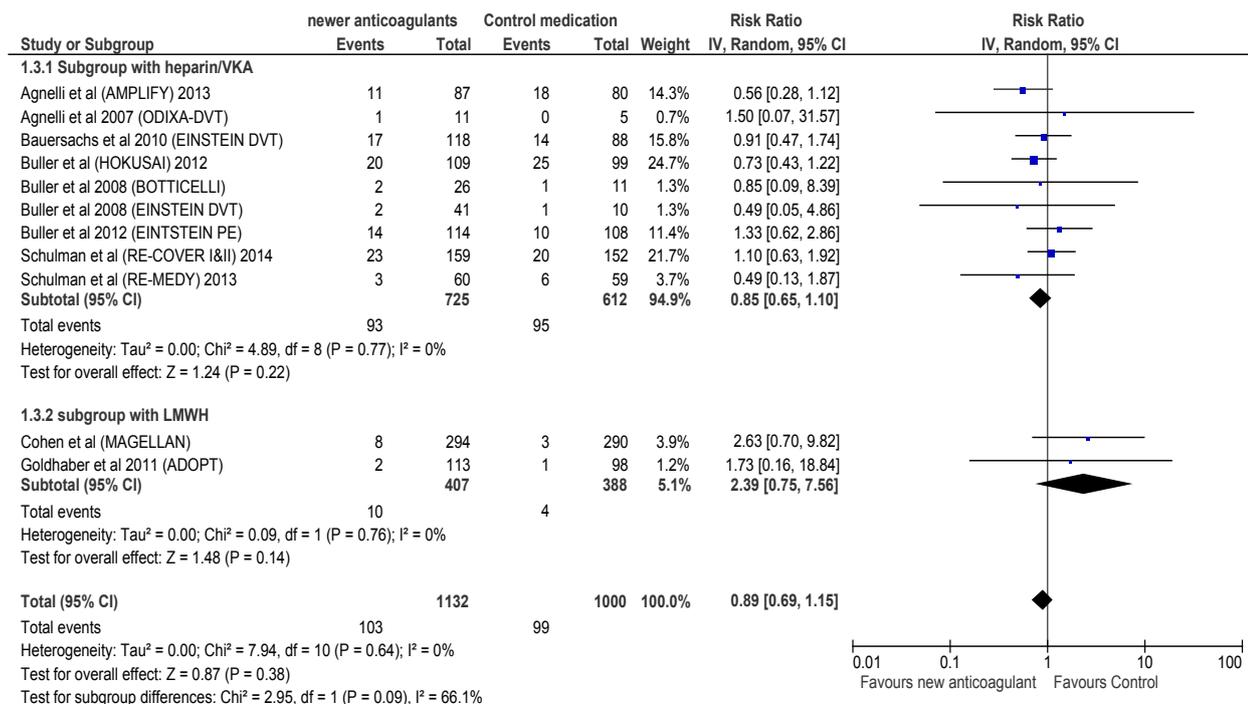


Figure 5 Forest plot for non-major clinically relevant bleeding. Summary risk ratios and 95% confidence intervals showing higher rates of bleeding with NOAs compared to LMWH. NOAs, newer oral anticoagulants; LMWH, low-molecular-weight heparin.

(95% CI =0.40–1.14) for anti-Xa and 0.86 (95% CI =0.40–1.85) for anti-IIa, respectively.

NOAs compared to LMWH only in hospitalized cancer patients

A subgroup analysis of studies showed that NOAs were comparable to LMWH in prevention of VTE in acutely ill hospitalized cancer patients. (RR =0.97; 95% CI =0.37–2.55; P=0.95). Higher major bleeding (RR =2.18; 95% CI =0.32–14.80; P=0.42) and clinically relevant bleeding (RR =2.39; 95% CI =0.75–7.56; P=0.14) rates were observed with NOAs compared to LMWH in acutely ill hospitalized cancer patients. However, the results did not reach statistical significance.

Discussion

The results of this meta-analysis of randomized trials comparing the efficacy and safety of NOAs with standard VTE treatment (heparin & VKA combination) in cancer patients suggest that NOAs are comparable in their efficacy and safety to standard treatment for VTE in cancer patients with a non-significant lower event rate. The mild reduction of both VTE and bleeding events noted was consistent across all studies. However, NOAs tend to show higher rates of bleeding compared to LMWH only in acutely ill hospitalized cancer patients.

The efficacy of NOAs in preventing the recurrence of VTE found in our study is similar to that found in a prior meta-analysis conducted by Vedovati *et al.* (27), where VTE recurred in 3.9% of cancer patients treated with NOAs as compared to 6.0% of those treated conventionally. In the randomized trial “Low Molecular Weight Heparin versus Oral Anticoagulant therapy for the prevention of recurrent Venous Thromboembolism in patients with cancer (CLOT) study”, recurrent VTE was found in 8% of patients in randomized treatment with dalteparin compared to 16% in those with oral anticoagulation treatment, which was equivalent to a 50% risk reduction. In this study, the level of anticoagulation as estimated by time in TTR was around 46%. Compared to this value, the mean TTR of conventional treatment in randomized trials with NOAs is around 59.45%. This increased intensity of anticoagulation in the conventional treatment group in randomized trials with NOAs compared to those in the CLOT study might explain the lower risk reduction of 27% found in our study.

In our analysis, the bleeding rates with NOAs were comparable to those with heparin & VKA combination in cancer patients. In a subgroup analysis of acutely ill hospitalized cancer patients, where NOAs were compared to LMWH for prevention of VTE, both major and clinically relevant bleeding rates in the NOA cohort were higher than corresponding rates among the LMWH treated group. However, in this subgroup, acutely-ill hospitalized medical patients were included, which was different from the relatively healthier patients in the randomized trials with NOAs. In a study by Decousus *et al.* on acutely ill medical patients, active gastroduodenal ulceration, prior bleeding, low platelet count, advanced age, hepatic or renal failure, the presence of a central venous catheter, rheumatic disease, and cancer were identified as risk factors upon admission and were associated with in-hospital bleeding (28). Furthermore, the median age of patients in the MAGELLAN trial (23) was around 71 years, and around 21% of patients had impaired renal function (creatinine clearance of less than 50 mL per minute), and about 7% of the patients had active cancer. Additionally, 4% had acute inflammatory or rheumatic disease. These above risk factors present at admission in these patients could have contributed to the increased rates of bleeding observed with extended thromboprophylaxis.

The inclusion of data from only randomized trials strengthens our analysis. There was no significant heterogeneity observed for all the outcomes, suggesting that the results were consistent across all studies. Conversely, our study has limitations inherent to any meta-analysis. The datasets included in our analysis were not matched for type and stage of cancer or type of VTE. Most of the studies included in the meta-analysis excluded patients with anemia, high bleed risk, thrombocytopenia, and renal failure. Therefore, the results of this study are applicable to select group of patients without the above parameters. Unfortunately, a precise definition of active cancer was not available in the various studies. These limitations support the need for ad hoc clinical trials with NOAs evaluating efficacy and safety exclusively among cancer patients.

Conclusions

NOAs seem to be comparable in efficacy and safety to conventional treatment in prevention of VTE recurrence among cancer patients. However, increased rates of bleeding were observed with their use as compared to

LMWH use in acutely-ill hospitalized patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jxym.2017.07.04>). 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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References

- Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *Jama* 2005;293:715-22.
- Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000;160:809-15.
- Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;5:632-4.
- Gussoni G, Frasson S, La Regina M, et al. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry. *Thromb Res* 2013;131:24-30.
- Khorana AA, Dalal MR, Lin J, et al. Health care costs associated with venous thromboembolism in selected high-risk ambulatory patients with solid tumors undergoing chemotherapy in the United States. *Clinicoecon Outcomes Res* 2013;5:101-8.
- Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002;100:3484-8.
- Monreal M, Falga C, Valdes M, et al. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost* 2006;4:1950-6.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016;149:315-52.
- Coleman R, MacCallum P. Treatment and secondary prevention of venous thromboembolism in cancer. *Br J Cancer* 2010;102 Suppl 1:S17-23.
- De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. *Thromb Haemost* 2013;110:1087-107.
- Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;354:1896-900.
- Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
- Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *Bmj* 2003;327:557-60.
- Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799-808.
- Agnelli G, Gallus A, Goldhaber SZ, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation* 2007;116:180-7.
- Buller H, Deitchman D, Prins M, et al. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *J Thromb Haemost* 2008;6:1313-8.
- Buller HR, Lensing AW, Prins MH, et al. A dose-ranging study evaluating once-daily oral administration

- of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. *Blood* 2008;112:2242-7.
19. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-510.
 20. Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287-97.
 21. Büller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406-15.
 22. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011;365:2167-77.
 23. Cohen AT, Spiro TE, Buller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med* 2013;368:513-23.
 24. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342-52.
 25. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013;368:709-18.
 26. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129:764-72.
 27. Vedovati MC, Germini F, Agnelli G, et al. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. *Chest* 2015;147:475-83.
 28. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011;139:69-79.

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