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SYSTEMATIC REVIEW

Editor's Choice — A Systematic Review and Meta-Analysis of the Efficacy and Safety of Anticoagulation in the Treatment of Venous Thromboembolism in Patients with Cancer

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WHAT THIS PAPER ADDS

This meta-analysis provides complete evidence for the relative efficacy and safety of all major anticoagulant types in the treatment of cancer related venous thromboembolism, pointing out the often insufficient and moderate quality information in the existing literature, which highlights the need for further investigations. Data from previous studies showing that low molecular weight heparins (LMWHs) are more effective than, and equally safe as vitamin K antagonists (VKAs) are confirmed. However, anti-Xa agents are more effective and much safer than VKAs. In a direct comparison, direct oral anticoagulants are better but less safe than LMWHs, although the moderate quality of the evidence calls for further research results that are eagerly awaited.

Objective/Background: The aim was to review the relative efficacy and safety of anticoagulation for managing venous thromboembolism (VTE) in patients with cancer.

Methods: A systematic review and meta-analysis was carried out. On 17 May 2018 the MEDLINE and Scopus databases were searched for randomised controlled trials (RCTs). Eligible RCTs had to be performed in patients with cancer exclusively or to report results on a subset of patients with cancer. The main study outcomes (efficacy/recurrent VTE and safety/bleeding events) were expressed as risk ratios (RR) with a 95% confidence interval (CI). The quality of evidence was assessed following the GRADE method.

Results: Twenty-three RCTs with 6980 patients were identified. Low molecular weight heparins (LMWHs) were more effective than vitamin K antagonists (VKAs) in preventing recurrent VTE (RR 0.58, 95% CI 0.45—0.75) and deep vein thrombosis (RR 0.44, 95% CI 0.29—0.69) but not pulmonary embolism (PE), bleeding, or overall mortality. Direct oral anticoagulants (DOACs) were more effective than VKAs in preventing recurrent VTE (RR 0.65, 95% CI 0.45—0.95) but not DVT, PE, overall mortality, or bleeding. However, anti-Xa DOACs were more effective (RR for VTE 0.64, 95% CI 0.42—0.97) and caused less bleeding than VKAs, although major bleeding was reduced only with DOACs not requiring initial parenteral anticoagulation (RR 0.45, 95% CI 0.21—0.97). In a direct comparison, DOACs were more effective than LMWHs in preventing VTE recurrence (RR 0.64, 95% CI 0.45—0.90) but caused more major bleeding (RR 1.75, 95% CI 1.10—2.77), with no difference in fatal bleeding and overall mortality. Quality of evidence, where sufficient, was mostly moderate or high.

Conclusion: Compared with VKAs, LMWHs and DOACs are more effective in treating VTE, but the former caused less bleeding. DOACs are more effective than LMWHs in preventing VTE recurrence but may carry a higher risk of major bleeding, pending additional information by ongoing trials.

Keywords: Anticoagulation, Cancer, Venous thromboembolism

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INTRODUCTION

Venous thromboembolism (VTE) is a common complication of cancer, and its treatment is a challenge for clinicians because of the variety of comorbidities and coexisting chemotherapeutic polypharmacy in these patients.[1] Many anticoagulant types have been used over time, while modern guidelines propose a low molecular weight heparin

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(LMWH) for acute and long-term treatment, followed by secondary prophylaxis with an oral vitamin K antagonist (VKA) after 3–6 months.[2] However, the progression of malignancy may affect the bioavailability of VKAs and in combination with any coexisting food or drug interactions may lead to recurrence of VTE related to a sub-therapeutic international normalised ratio, or bleeding related to coagulopathy.[3]

Several studies support the use of LMWHs as monotherapy for the treatment of VTE in patients with cancer because of the superiority of the LMWH regimen over standard VKA therapy,[4] with different LMWHs being used for this purpose.[5,6]

In an attempt to find a much safer and more effective treatment for VTE in patients with cancer, direct oral anticoagulants (DOACs) have been tested.[7] These are not only as effective as VKAs in treating VTE, but also do not require adjustment of their dose based on blood tests. Several studies and meta-analyses have reported a superiority in efficacy and safety of DOACs in the treatment of VTE,[8] although results in patients with malignancy are limited because of the small number of patients included. The original trials may have been underpowered for some efficacy measures or had a non-inferiority design, which makes the use of meta-analysis very important in decision making, as the latter provide a thorough assessment of the existing evidence. Additionally, a full assessment of the methodological quality of these studies and grading of the quality of evidence they provide is imperative for clinical and research purposes.

The aim of the present systematic review and meta-analysis was to study the effectiveness and safety of anticoagulant therapy in the treatment of VTE in patients with cancer, focusing on comparisons of the several types of anticoagulants.

MATERIALS AND METHODS

Search method

A literature search was conducted on 17 May 2018 of PubMed (MEDLINE database, National Library of Medicine

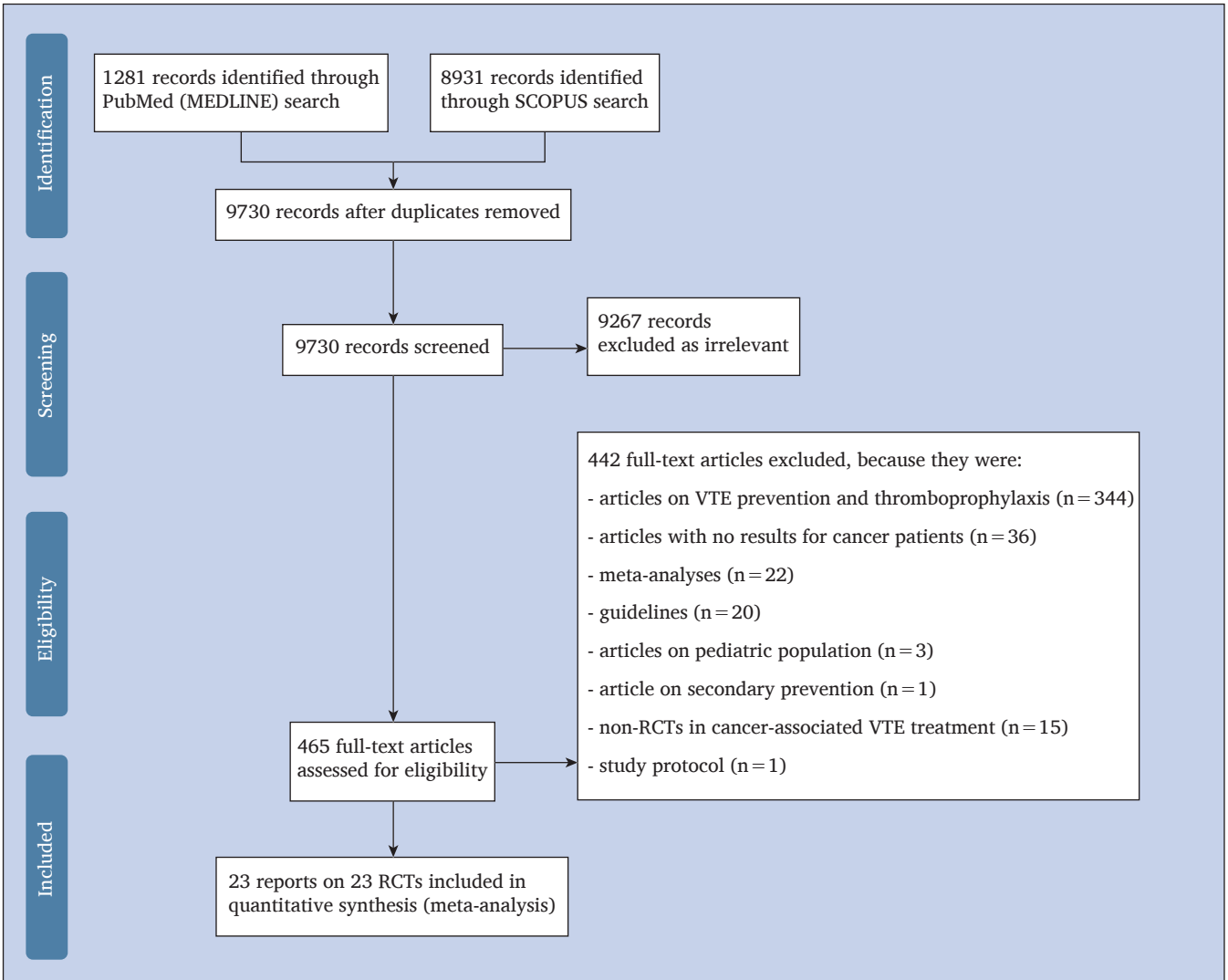


Figure 1. Study flow diagram of randomised controlled trial selection for the treatment of venous thromboembolism in cancer. VTE = Venous thromboembolism; RCT = Randomised controlled trial.

of the USA) and SCOPUS (www.scopus.com), using the following keywords for treatment of VTE in cancer: (DVT or (deep vein thrombosis) or PE or (pulmonary embolism) or VTE or (venous thromboembolism)) and (cancer or malignancy) and (treatment or heparin or (low molecular weight heparin) or (direct oral anticoagulant) or warfarin), restricted to clinical trials and articles, respectively, using the corresponding filters. The aim was to identify randomised controlled trials (RCTs) investigating the efficacy and safety of anticoagulant therapy in the treatment of VTE (deep vein thrombosis, DVT, and/or pulmonary embolism, PE) in patients with active cancer. This search was followed by a manual search of the reference list of the relevant articles to identify additional studies. Unpublished data (e.g., from the manufacturers and the authors of the included studies) were not sought, but the full text article of each RCT and its supplementary appendix were both obtained. Data from two pooled subgroup analyses of RCTs (EINSTEIN DVT-PE and RE-COVER I-II) were also used as supplementary sources.

Main outcome measures

The following information, where available, was retrieved from the RCTs: (i) efficacy, including recurrence of VTE, fatal and symptomatic pulmonary embolism (PE), and recurrent

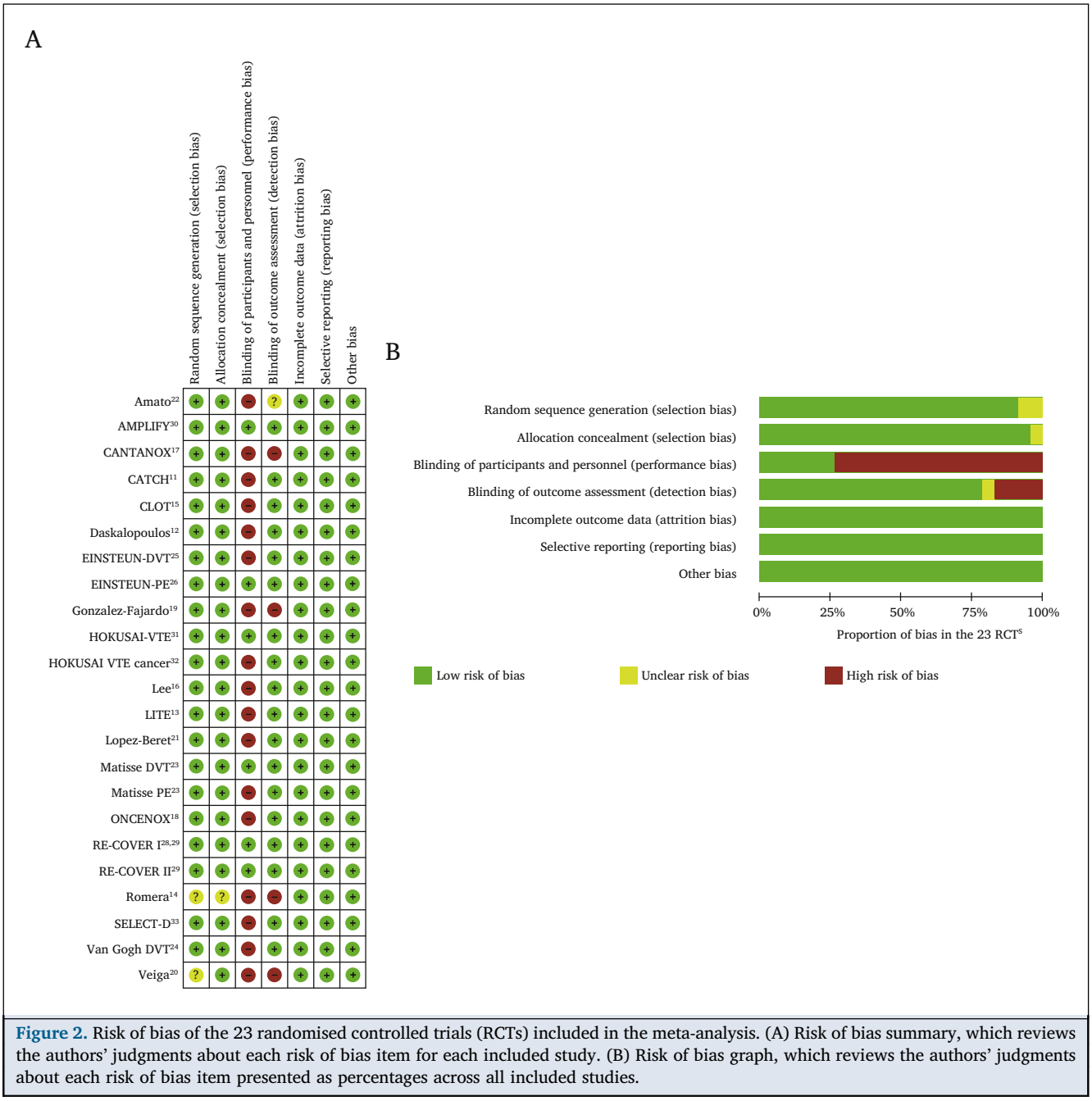


Figure 2. Risk of bias of the 23 randomised controlled trials (RCTs) included in the meta-analysis. (A) Risk of bias summary, which reviews the authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph, which reviews the authors' judgments about each risk of bias item presented as percentages across all included studies.

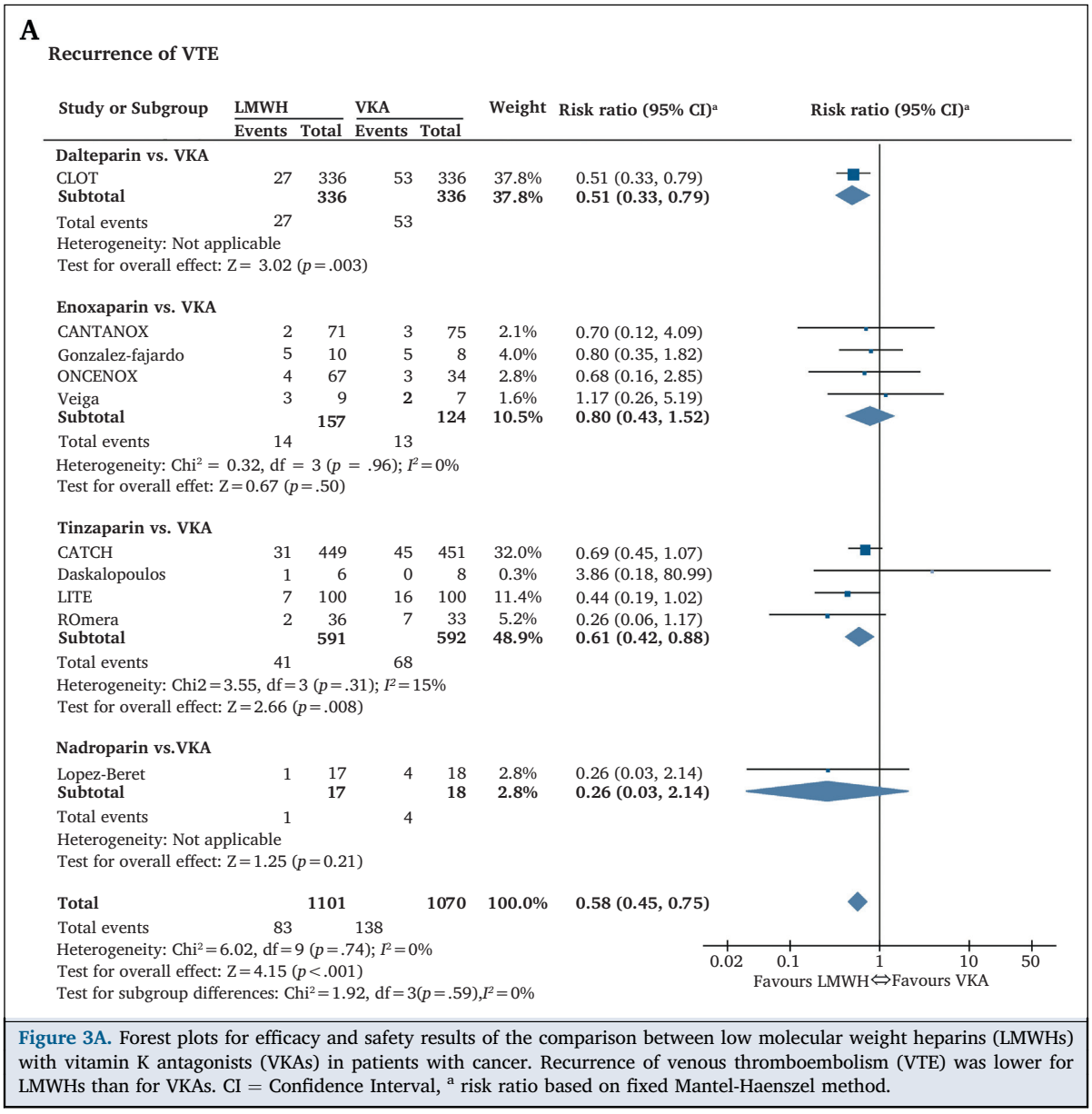


Figure 3A. Forest plots for efficacy and safety results of the comparison between low molecular weight heparins (LMWHs) with vitamin K antagonists (VKAs) in patients with cancer. Recurrence of venous thromboembolism (VTE) was lower for LMWHs than for VKAs. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

DVT; (ii) safety, including major, clinically relevant non-major, and any bleeding, and death due to bleeding, death due to PE, death due to cancer, and all cause death.

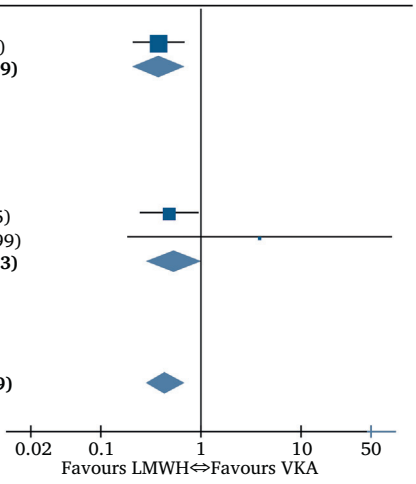
Statistics

For each RCT included in the study, raw data (number or patients who developed an end point in the intervention and control groups and total number of patients) were extracted by one of the authors (G.I.K.), and manually entered into the meta-analysis software Review Manager (RevMan, version 5.2. and 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen). All extracted data were checked against the source documents by another author (S.K.K.). RevMan performed the meta-analyses (Mantel-Haenszel method), produced forest plots, and provided inconsistency (I^2) statistics that evaluate the heterogeneity of the included studies. A non-significant p value for the Cochrane Q statistic indicates that there is no significant statistical heterogeneity between studies. An I^2 value of 0% indicates no heterogeneity, whereas larger values are consistent with increasing heterogeneity. For a statistically significant $I^2 > 50\%$, indicative of substantial heterogeneity a random effects model was chosen instead of the fixed effect model. To address potential heterogeneity because of pooling studies with different bias risks, sensitivity analyses was performed by excluding studies with a high risk of bias. In comparisons with $\geq$10 studies, a funnel plot analysis was performed to check for publication bias. For the comparison of LMWHs with VKAs, meta-regression was performed on the effect of the anti-factor Xa/anti-factor IIa activity ratio of the various LMWHs, as previously reported,[9] on risk of the various outcome measures using Comprehensive Meta-Analysis (version 3.3.070; Biostat, Eaglewood, NJ, USA), where there was sufficient evidence ($\geq$4 RCTs).

B

Recurrence of DVT

Study or Subgroup	LMWH Events	LMWH Total	VKA Events	VKA Total	Weight	Risk ratio (95% CI)[a]
Dalteparin vs. VKA						
CLOT	14	336	37	336	59.3%	0.38 (0.21,0.69)
Subtotal		**336**		**336**	**59.3%**	**0.38 (0.21, 0.69)**
Total events	14		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.20 (p = .001)						
Tinzaparin vs. VKA						
CATCH	12	449	25	451	40.0%	0.48 (0.25, 0.95)
Daskalopoulos	1	6	0	8	0.7%	3.86 (0.18, 80.99)
Subtotal		**455**		**459**	**40.7%**	**0.54 (0.28, 1.03)**
Total events	13		25			
Heterogeneity: Chi^2 = 1.71, df = 1 (p = .19); I^2 = 42%						
Test for overall effect: Z = 1.88 (p = .06)						
Total		**791**		**795**	**100.0%**	**0.44 (0.29,0.69)**
Total events	27		62			
Heterogeneity: Chi^2 = 2.27, df = 2 (p = .32); I^2 = 12%						
Test for overall effect: Z = 3.65 (p = .0003)						
Test for subgroup differences: Chi^2 = 0.63, df = 1 (p = .43), I^2 = 0%						



C

Recurrence of PE

Study or Subgroup	LMWH Events	LMWH Total	VKA Events	VKA Total	Weight	Risk ratio (95% CI)[a]
Dalteparin vs. VKA						
CLOT	13	336	16	336	43.2%	0.81 (0.40, 1.66)
Subtotal		**336**		**336**	**43.2%**	**0.81 (0.40, 1.66)**
Total events	13		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (p = .57)						
Tinzaparin vs. VKA						
CATCH	20	449	20	451	53.9%	1.00 (0.55, 1.84)
Romera	1	36	1	33	2.8%	0.92 (0.06, 14.07)
Subtotal		**485**		**484**	**56.8%**	**1.00 (0.55, 1.81)**
Total events	21		21			
Heterogeneity: Chi^2 = 0.00, df = 1 (p = .95); I^2 = 0%						
Test for overall effect: Z = 0.00 (p = 1.00)						
Total		**821**		**820**	**100.0%**	**0.92 (0.58, 1.45)**
Total events	34		37			
Heterogeneity: Chi$_2$ = 0.20, df = 2 (p = .91); I^2 = 0%						
Test for overall effect: Z = 0.36 (p = .72)						
Test for subgroup differences: Chi^2 = 0.19, df = 1 (p = .66), I^2 = 0%						

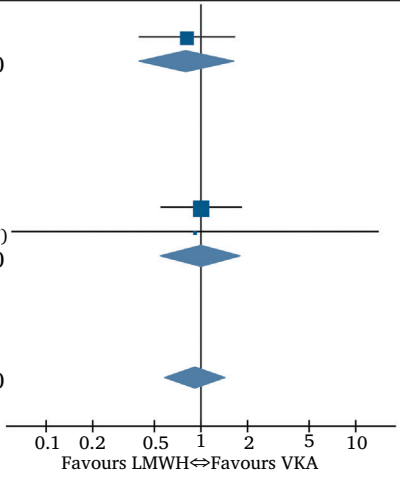


Figure 3B and C. Forest plots for efficacy and safety results of the comparison between low molecular weight heparins (LMWHs) with vitamin K antagonists (VKAs) in patients with cancer. (B) Recurrence of deep vein thrombosis (DVT) in the comparison of LMWH with VKAs. (C) Recurrence of pulmonary embolism (PE) in the comparison of LMWH with VKAs. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

Quality of evidence assessment

The RevMan risk of bias assessment tool was used to assess the methodological quality of the included studies. The system developed by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group was used to grade the quality of evidence as high, moderate, low, and very low, based on risk of bias, directness of evidence, heterogeneity, precision of effects estimates, and risk of publication bias.[10] High quality evidence indicates that further research is very unlikely to change confidence in the estimate of effect; moderate quality evidence indicates that further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; low quality evidence indicates that further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; and very low quality evidence indicates great uncertainty about the estimate. A

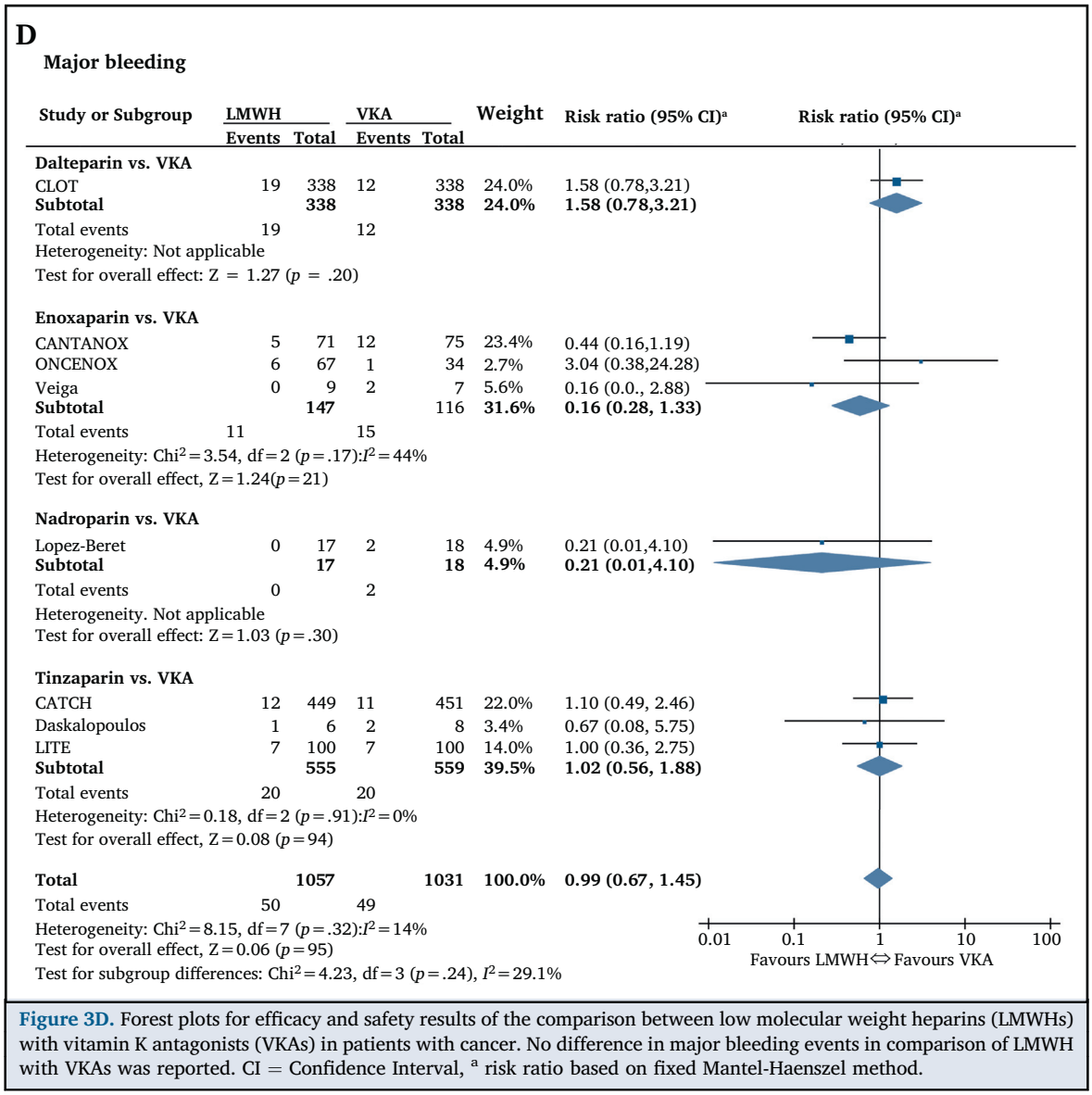


Figure 3D. Forest plots for efficacy and safety results of the comparison between low molecular weight heparins (LMWHs) with vitamin K antagonists (VKAs) in patients with cancer. No difference in major bleeding events in comparison of LMWH with VKAs was reported. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

"summary of findings" table was created using GRADE profiler (version 3.6.1), which assessed the outcome measures with results provided by $\geq$ 3 RCTs, except for the comparison of DOACs with LMWHs. The assumed control intervention risks were calculated from the mean number of events in the control groups of the included studies for each outcome.

RESULTS

Some 9730 English language records identified through the electronic database (Pubmed and SCOPUS) search were retrieved after removing duplicates. In total, 9267 were excluded after reading the abstract because they were deemed to be irrelevant. For the remaining 465 records the full text was obtained and 442 articles were excluded, 344 of them because they were VTE prevention and thromboprophylaxis studies, 22 because they were meta-analyses, 20 because they were guideline articles, 36 because no information on patients with cancer was provided, 15 because they were not RCTs, three because they were paediatric VTE trials, one study protocol, and one secondary prevention trial, which left 23 publications reporting 23 RCTs in the meta-analysis.[11–33] A PRISMA flow diagram is shown in Fig. 1. A total of 29,134 patients participated in the 23 RCTs in the treatment of VTE. Some 6923 of them were patients with cancer with VTE and were included in the meta-analysis.

The design of the included studies is shown in Table S1 (see Supplementary Material). Seven were double blind trials, 15 had an open label design, and the remaining one was a randomised prospective, single blind, parallel group trial. Of the 23 RCTs on VTE treatment in patients with cancer, 11 trials compared a LMWH with a VKA, six compared a DOAC with a VKA, two compared a DOAC with a LMWH, and four compared a synthetic pentasaccharide (fondaparinux or idraparinux) with a LMWH (enoxaparin), unfractionated heparin (UFH), or a VKA. Recurrent symptomatic VTE, defined as the composite of DVT, non-fatal PE

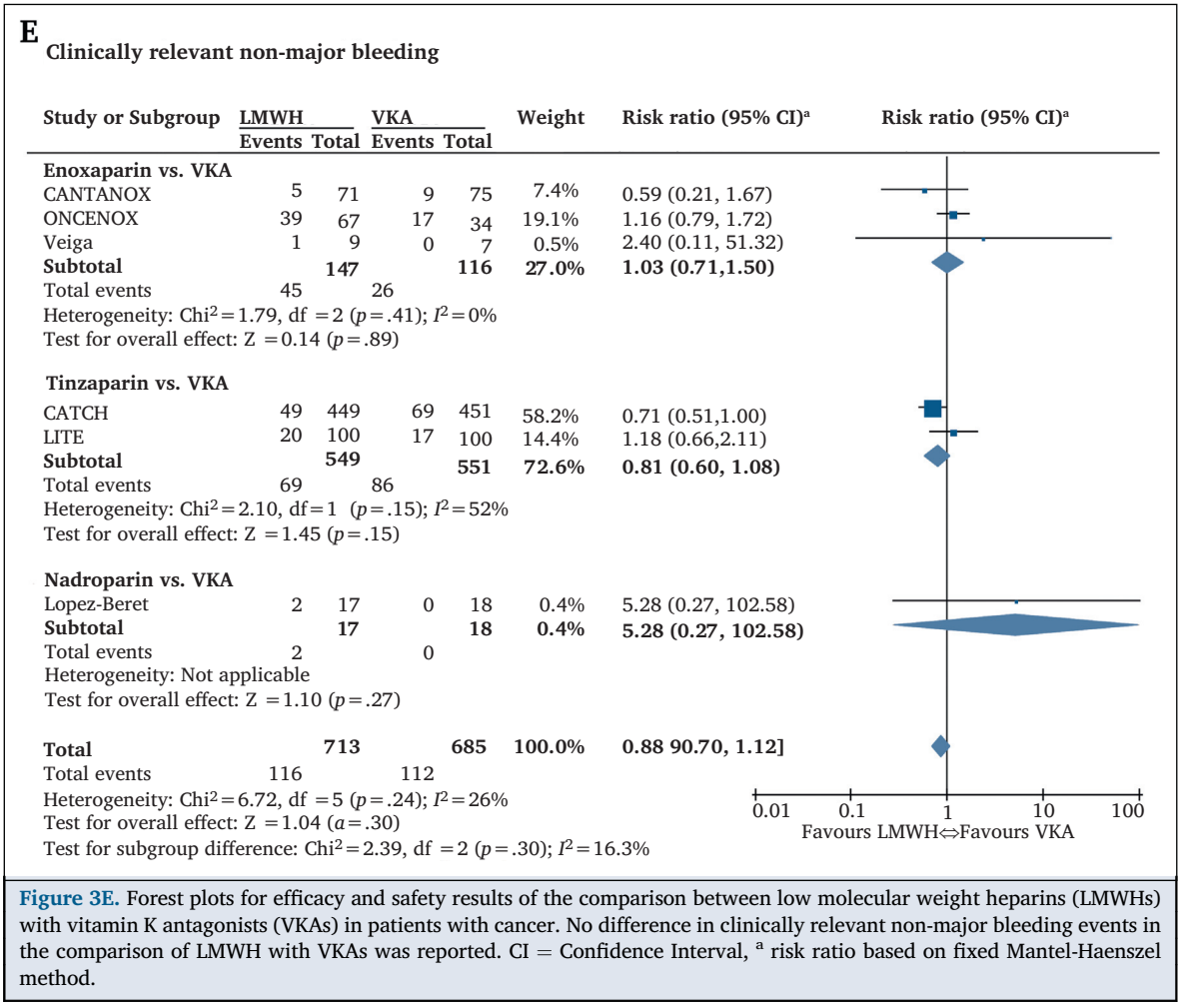


Figure 3E. Forest plots for efficacy and safety results of the comparison between low molecular weight heparins (LMWHs) with vitamin K antagonists (VKAs) in patients with cancer. No difference in clinically relevant non-major bleeding events in the comparison of LMWH with VKAs was reported. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

and fatal PE, was the most commonly used efficacy outcome. In most studies, unexplained death that could not be attributed to a documented cause and where PE was not ruled out, was classified as fatal PE and considered to be part of the primary efficacy outcome. Major bleeding and clinically relevant non-major bleeding were the most frequently used safety outcomes. Bleeding was defined as major if it was clinically overt and associated with a fall in the haemoglobin level of $\geq$20 g/L, if it led to transfusion of $\geq$2 units of red cells, if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, interruption, or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of daily life activities.

Of the 23 included RCTs, 17 had a high risk of performance bias because they there were open label studies (Fig. 2).[11–24,26,28–33] Four had a high risk of detection bias,[14,17,19,20,22] and one an unclear risk.[22] Reporting, attrition, and other bias attributes had a low risk of bias, and selection bias had a low risk except in two studies with unclear risk of selection bias. All studies provided numerical results for at least one outcome measure suitable for inclusion into the quantitative meta-analysis.

LMWHs vs. VKAs

Eleven RCTs with 2777 participants compared LMWHs with standard treatment with warfarin in patients with cancer. LMWHs were more effective than VKAs in preventing recurrence in the form of symptomatic VTE (7.5% vs. 12.9%, risk ratio [RR] 0.58, 95% confidence interval [CI] 0.45—0.75, I^2 = 0%, participants = 2,171, studies = 10 [Fig. 3A], and no evidence for publication bias on funnel plot analysis), and VTE recurrence in the form of symptomatic DVT (3.4% vs. 7.8%, RR 0.44, 95% CI 0.29—0.69, I^2 = 12%, participants = 1,586, studies = 3 [Fig. 3B]) but not PE (4.1% vs. 4.5%, RR 0.92, 95% CI 0.58—1.45, I^2 = 0%, participants = 1,641, studies = 3 [Fig. 3C]).There was no difference in major bleeding or in clinically relevant non-major bleeding in the LMWH and VKA groups (4.7% vs. 4.8%, RR 0.99, 95% CI 0.67—1.45, I^2 = 14%, participants = 2,088, studies = 8 [Fig. 3D] and 16.3% vs. 16.4%, RR 0.88, 95% CI 0.70—1.12, I^2 = 26%, participants = 1,398, studies = 6 [Fig. 3E], respectively).

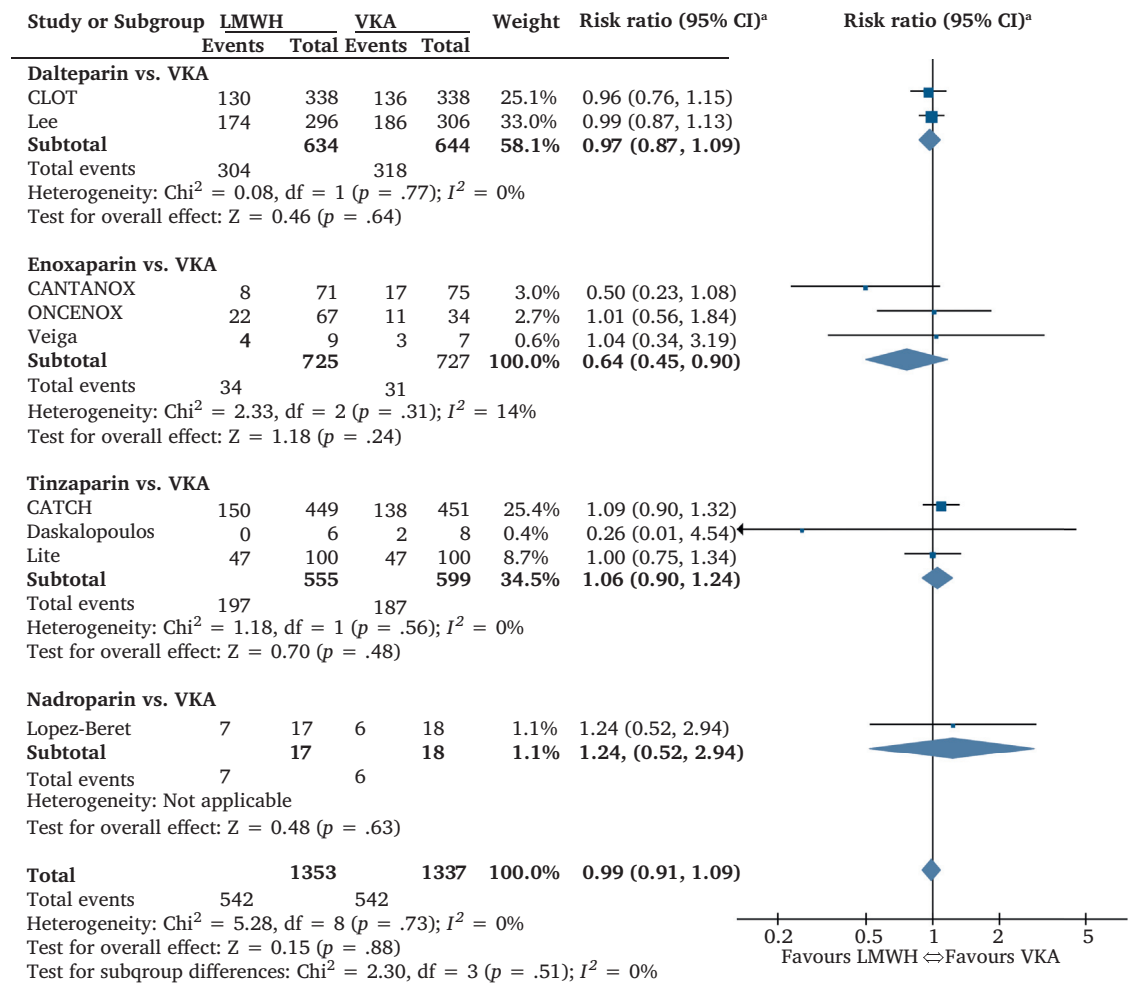


Figure 3F. Forest plots for efficacy and safety results of the comparison between low molecular weight heparins (LMWHs) with vitamin K antagonists (VKAs) in patients with cancer. No difference in overall mortality was reported. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

There was no difference in all bleeding events between LMWHs and VKAs (27.9% vs. 25.8%, RR 1.01, 95% CI 0.85—1.20, participants = 1,398, studies = 6, I^2 = 24%). There was no difference between LMWHs and VKAs in overall mortality (40.1% vs. 40.5%, RR 0.99, 95% CI 0.91—1.09, I^2 = 0%, participants = 2,690, studies = 9 [Fig. 3F]), but there was a non-significant trend for a lower risk of fatal PE and fatal bleeding in the LMWH group compared with VKAs (2.6% vs. 3.6%, RR 0.76, 95% CI 0.46—1.26, I^2 = 0%, participants = 1,891, studies = 4 [Fig. 3G] and 0.6% vs. 1.3%, RR 0.54, 95% CI 0.22—1.29, I^2 = 0%, participants = 2,054, studies = 5 [Fig. 3H], respectively).

DOACs vs. VKAs

Six RCTs on 1926 participants compared DOACs with VKAs. Compared with standard treatment with VKAs, DOACs were more effective in preventing recurrent symptomatic VTE (5.6% vs. 8.8%, RR 0.65, 95% CI 0.45—0.95, I^2 = 0%, participants = 1,486, studies = 4 [Fig. 4A]). There was a non-significant reduction of DVT (4.0% vs. 6.2%, RR 0.66, 95% CI 0.26—1.68, I^2 = 0%, participants = 335, studies = 1) but not PE (fatal or non-fatal; 1.2% vs. 0.6%, RR 1.87, 95% CI 0.17—20.46, I^2 = 0%, participants = 335, studies = 1). There was a statistically significant lower risk of major bleeding in the DOAC group compared with VKAs (2.5% vs. 4.2%, RR 0.58, 95% CI 0.35—0.99, I^2 = 11%, participants = 1,708, studies = 4 [Fig. 4B]) but only a non-significant trend for clinically relevant non-major bleeding (13.5% vs. 16.8%, RR 0.81, 95% CI 0.63—1.04, I^2 = 0%, participants = 1,341, studies = 4 [Fig. 4C]). There was no difference in overall mortality between the two groups (18.1% vs. 18.1%, RR 1.00, 95% CI 0.79—1.27, I^2 = 0%, participants = 1,197, studies = 3) or cancer deaths (19.4% vs. 21.7%, RR 0.89, 95% CI 0.61—1.29, I^2 = 0%, participants = 430, studies = 2).

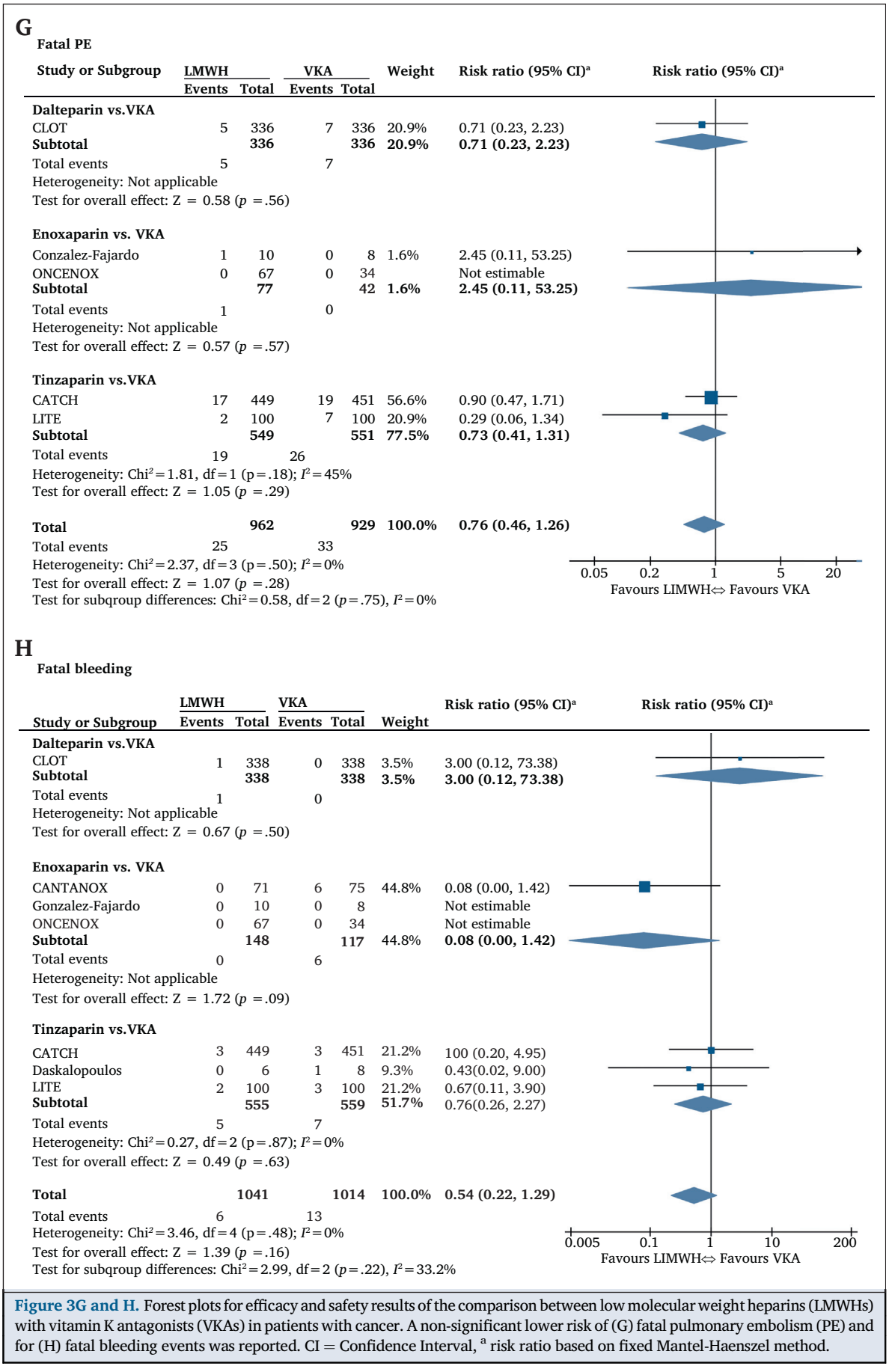


Figure 3G and H. Forest plots for efficacy and safety results of the comparison between low molecular weight heparins (LMWHs) with vitamin K antagonists (VKAs) in patients with cancer. A non-significant lower risk of (G) fatal pulmonary embolism (PE) and for (H) fatal bleeding events was reported. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

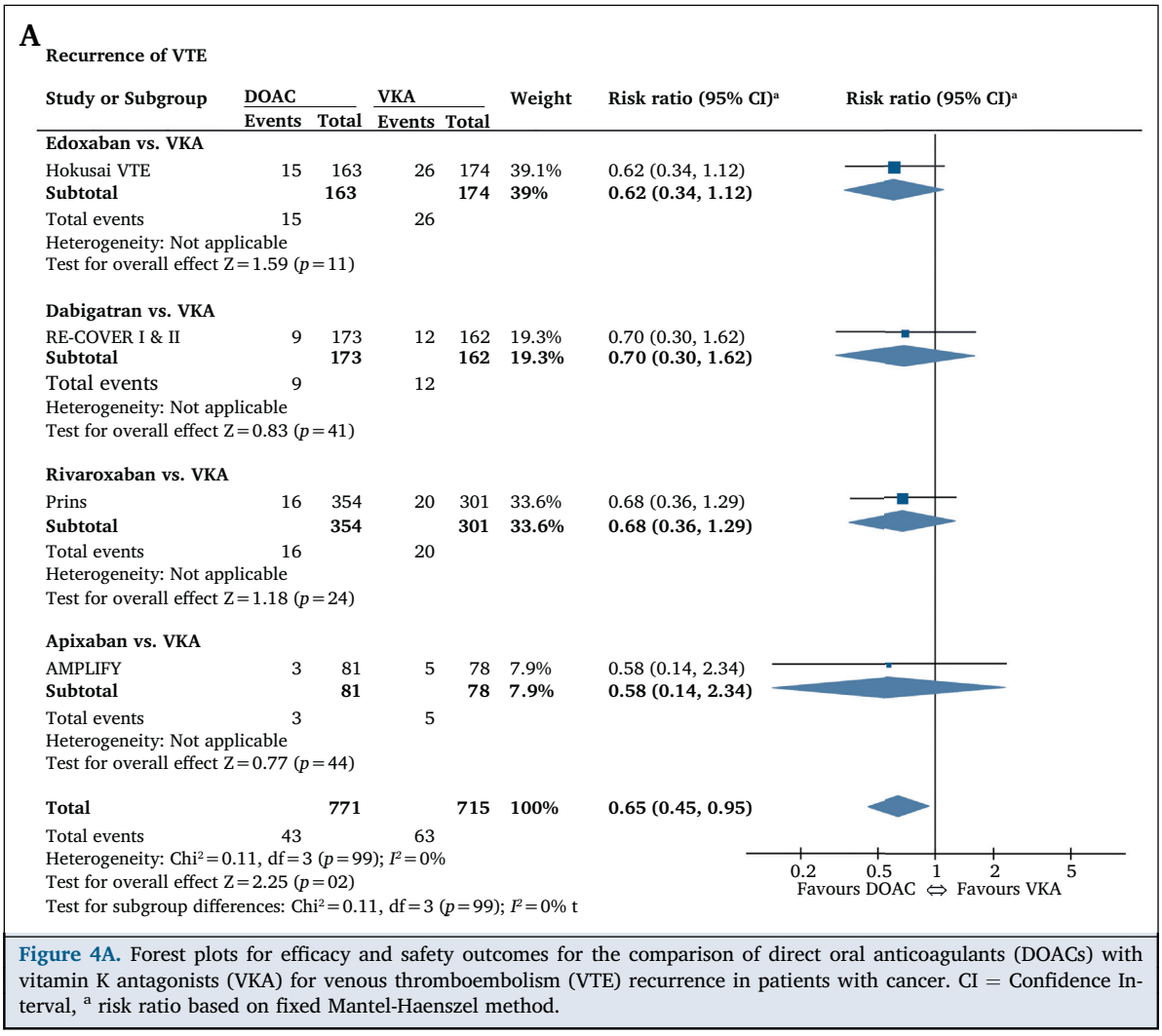


Figure 4A. Forest plots for efficacy and safety outcomes for the comparison of direct oral anticoagulants (DOACs) with vitamin K antagonists (VKA) for venous thromboembolism (VTE) recurrence in patients with cancer. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

Synthetic pentasaccharides (fondaparinux or idraparinux) vs. heparins or VKAs

In this analysis, four studies with 825 patients compared a synthetic pentasaccharide (fondaparinux or idraparinux) with UFH, enoxaparin, or a VKA. There was a non-significant difference in VTE recurrence between these two groups (10.5% vs. 12.7, RR 0.85, 95% CI 0.44—1.63, I^2 = 63%, participants = 811, studies = 4). Major bleeding occurred less frequently in the synthetic pentasaccharide group, but the difference was not significant (5.4% vs. 6.7%, RR 0.79, 95% CI 0.46—1.37, I^2 = 0%, participants = 811, studies = 4). Clinically relevant non-major bleeding had a non-significantly higher incidence in the synthetic pentasaccharide group (11.7% vs. 10.5%, RR 1.10, 95% CI 0.75—1.63, I^2 = 27%, participants = 811, studies = 4). Overall mortality was non-significantly higher for synthetic pentasaccharides (24.0% vs. 20.5%, RR 1.17, 95% CI 0.91—1.51, I^2 = 0%, participants = 825, studies = 4).

DOACs vs. LMWHs

Two RCT studies with 1452 patients compared DOACs with LMWHs. In this comparison recurrence of VTE was statistically significantly lower with DOACs compared with LMWHs (6.8% vs. 10.6% RR 0.64, 95% CI 0.45—0.90, I^2 = 0%, participants = 1,452, studies = 2 [Fig. 4D]); however, a significantly higher incidence of major bleeding in the DOAC group was observed (6.5% vs. 3.7% RR 1.75, 95% CI 1.10—2.77, I^2 = 0%, participants = 1,452, studies = 2 [Fig. 4E]). There was a non-significantly lower risk of fatal bleeding in DOAC group (0.1% vs. 0.4%, RR 0.43, 95% CI 0.06—2.90, I^2 = 0%, participants = 1,452, studies = 2). There was no statistically significant difference between DOACs and LMWHs in overall mortality (35.0% vs. 34.1%, RR 1.03, 95% CI 0.89—1.18, I^2 = 33%, participants = 1,452, studies = 2).

LMWHs, DOACs, or synthetic pentasaccharides vs. VKAs

This was a pooled analysis of these three categories testing for heterogeneity of the various outcomes. Key efficacy and safety results are presented in Fig. S1 (Supplementary Material). VTE recurrence was lower for all agents with no heterogeneity (I^2 = 0%, except pentasaccharides) or subgroup differences compared with VKAs, although it reached statistical significance only for LMWHs ($p < .001$), DOACs ($p = .02$), and, particularly, anti-Xa agents ($p = .04$).

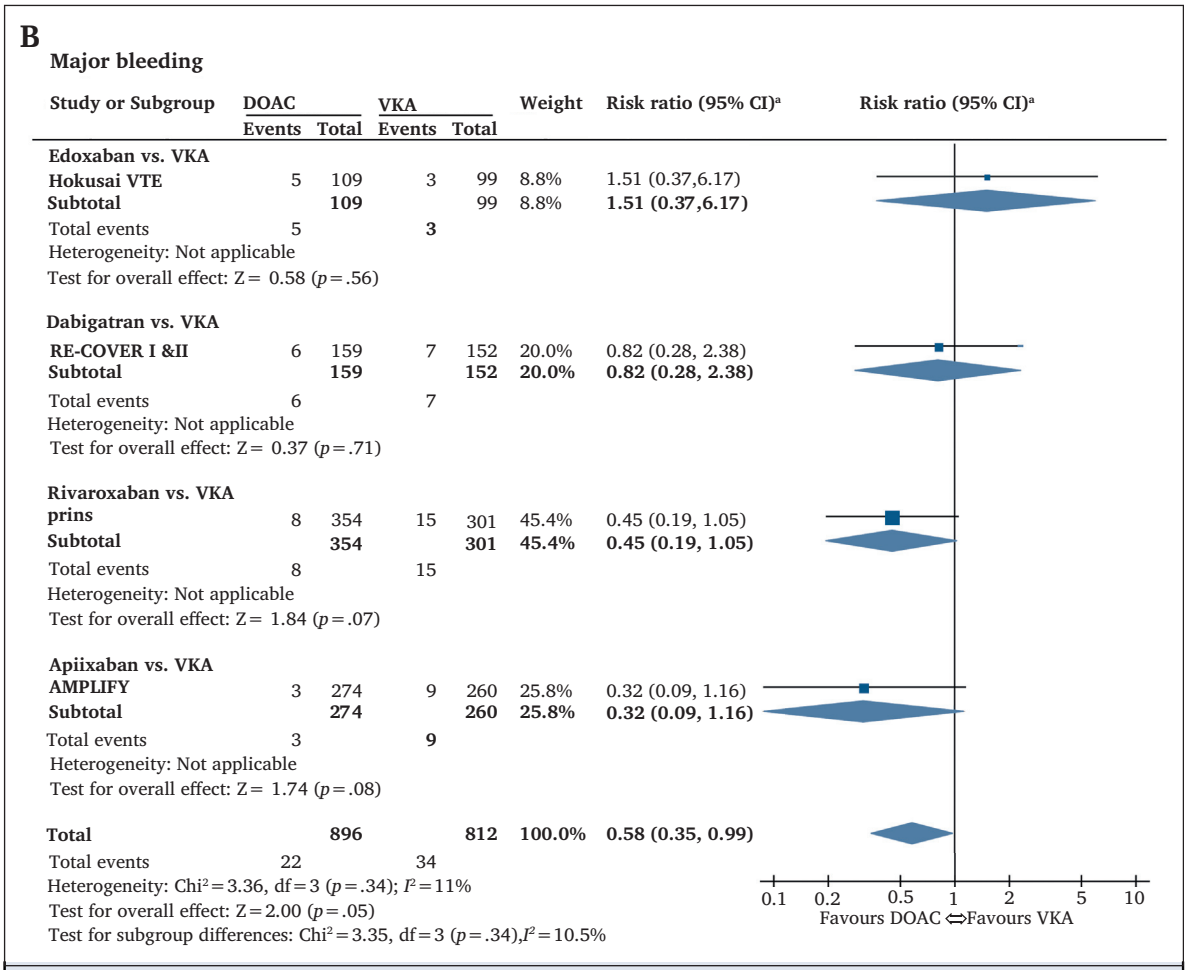


Figure 4B. Forest plots for efficacy and safety outcomes for the comparison of direct oral anticoagulants (DOACs) with vitamin K antagonists (VKA) for major bleeding events in patients with cancer. CI = Confidence Interval; VTE = venous thromboembolism [a] risk ratio based on fixed Mantel-Haenszel method.

Based on limited data, DVT recurrence was significantly lower only for LMWHs compared with VKAs ($p < .001$) with no heterogeneity, while there was no difference on PE recurrence of the various agents compared with VKAs. Major bleeding compared with VKAs was lower only for anti-Xa agents not requiring initial parenteral anticoagulation (rivaroxaban and apixaban, $p = .04$) with absence of overall heterogeneity. Clinically relevant non-major bleeding was lower only for anti-Xa agents compared with VKAs ($p = .04$) with no heterogeneity. All bleedings were lower only for anti-Xa agents compared with VKAs ($p = .05$) with no heterogeneity. No difference in overall mortality, cancer related mortality, fatal PE, and fatal bleeding across the comparisons of the various agents with VKAs was observed.

Sensitivity analysis

This was performed for the comparison of synthetic pentasaccharides with UFH or LMWH/VKA for the outcome of VTE recurrence, where a statistically significant high heterogeneity was obtained ($I^2 = 63\%$, $p = .04$). Three trials were excluded because of their high risk of bias,[22,24,26] which left for analysis one trial (Matisse DVT) with a non-significant difference between the two groups.

Quality of the evidence per GRADE system

A detailed assessment of study outcomes for the comparisons of LMWHs and DOACs with VKAs, where two or more studies were available, is given in Tables 1 and 2, respectively, and for the LMWH-DOAC comparison in Table S2 (see Supplementary Material). In all comparisons the quality of the evidence was moderate or high grade, according to Working Group grades of evidence. For the comparison of synthetic pentasaccharides with heparins or VKA, the quality of evidence was graded as low for the outcome of VTE recurrence and moderate for the outcomes of major bleeding, clinically relevant non-major bleeding, and all cause death.

Meta-regression and subgroup analyses

On meta-regression analysis there was no association between the anti-factor Xa/anti-factor IIa activity ratio of the various LMWHs on the RR of the various outcome measures, including VTE ($p = .73$, Fig. S2A [Supplementary

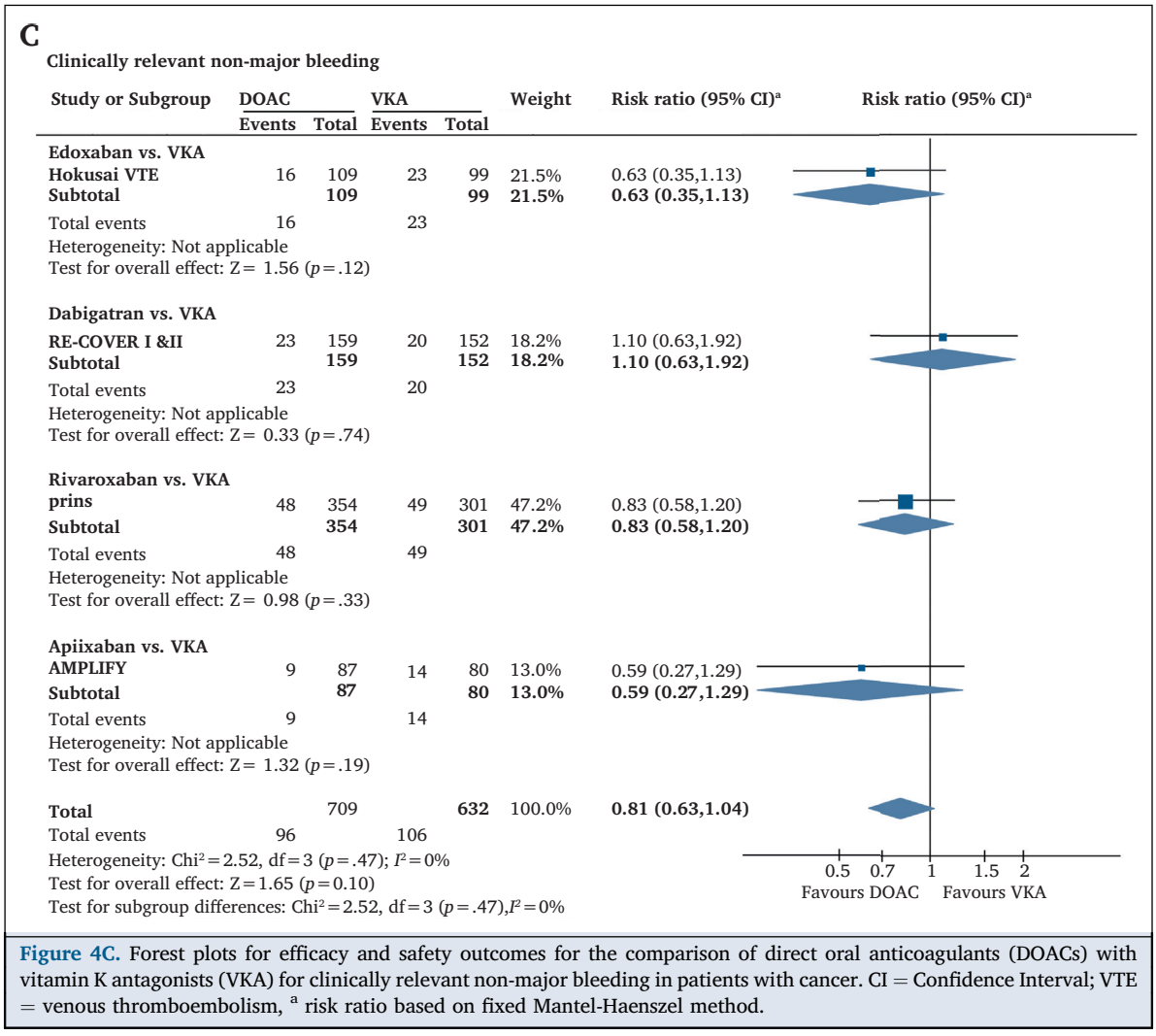


Figure 4C. Forest plots for efficacy and safety outcomes for the comparison of direct oral anticoagulants (DOACs) with vitamin K antagonists (VKA) for clinically relevant non-major bleeding in patients with cancer. CI = Confidence Interval; VTE = venous thromboembolism, [a] risk ratio based on fixed Mantel-Haenszel method.

Material]), major bleeding (p = .27, Fig. S2B [Supplementary Material]), and fatal bleeding (p = .19, Fig. S2C [Supplementary Material]). Results of subgroup analyses for anti-Xa and anti-IIa DOACs and those requiring initial parenteral anticoagulation and those not requiring it are presented in Table S3 (Supplementary Material). Anti-Xa DOACs and those not requiring initial anticoagulation (rivaroxaban and apixaban) were significantly more effective and safer compared with VKAs.

DISCUSSION

This systematic review and meta-analysis has demonstrated that in patients with cancer related VTE, both LMWHs and DOACs are more effective than VKAs in preventing recurrent events. Additionally, DOACs appear to be safer than VKAs by causing less bleeding, based on a non-significant trend. However, these efficacy and safety results were significant only when restricted to anti-Xa agents. Although the quality of evidence was graded as high for LMWHs, it was moderate for DOACs, highlighting the need for future research comparing DOACs with VKAs. Another relevant finding was that in a direct comparison, DOACs were more effective than LMWHs in preventing VTE recurrence, at the expense of major bleeding, but again the quality of evidence was graded as moderate.

Compared with recent meta-analyses on this topic,[34–36] this is to date, the largest review performed, as a result of including twice as many studies. Also, collected evidence was compiled in a pooled analysis for LMWHs, DOACs, or synthetic pentasaccharides vs. VKAs, testing for heterogeneity in the various subgroups. The indirect methodology with network meta-analysis used in some of these meta-analyses is considered a factor to downgrade the evidence using the GRADE methodology. Therefore, it was decided not to use network meta-analysis, but rather to grade the level of evidence and provide this assessment in Tables 1 and 2, and S2. Additionally, formal sensitivity and subgroup analyses, and also meta-regression analyses, were performed to study the subject further.

The natural history of malignancy is frequently complicated by an episode of VTE (DVT or PE), which may increase mortality and morbidity rates. Modern therapeutic strategies with a LMWH or DOAC are more effective in preventing VTE recurrence compared with standard therapy with VKA, but they had no effect on the overall mortality in the

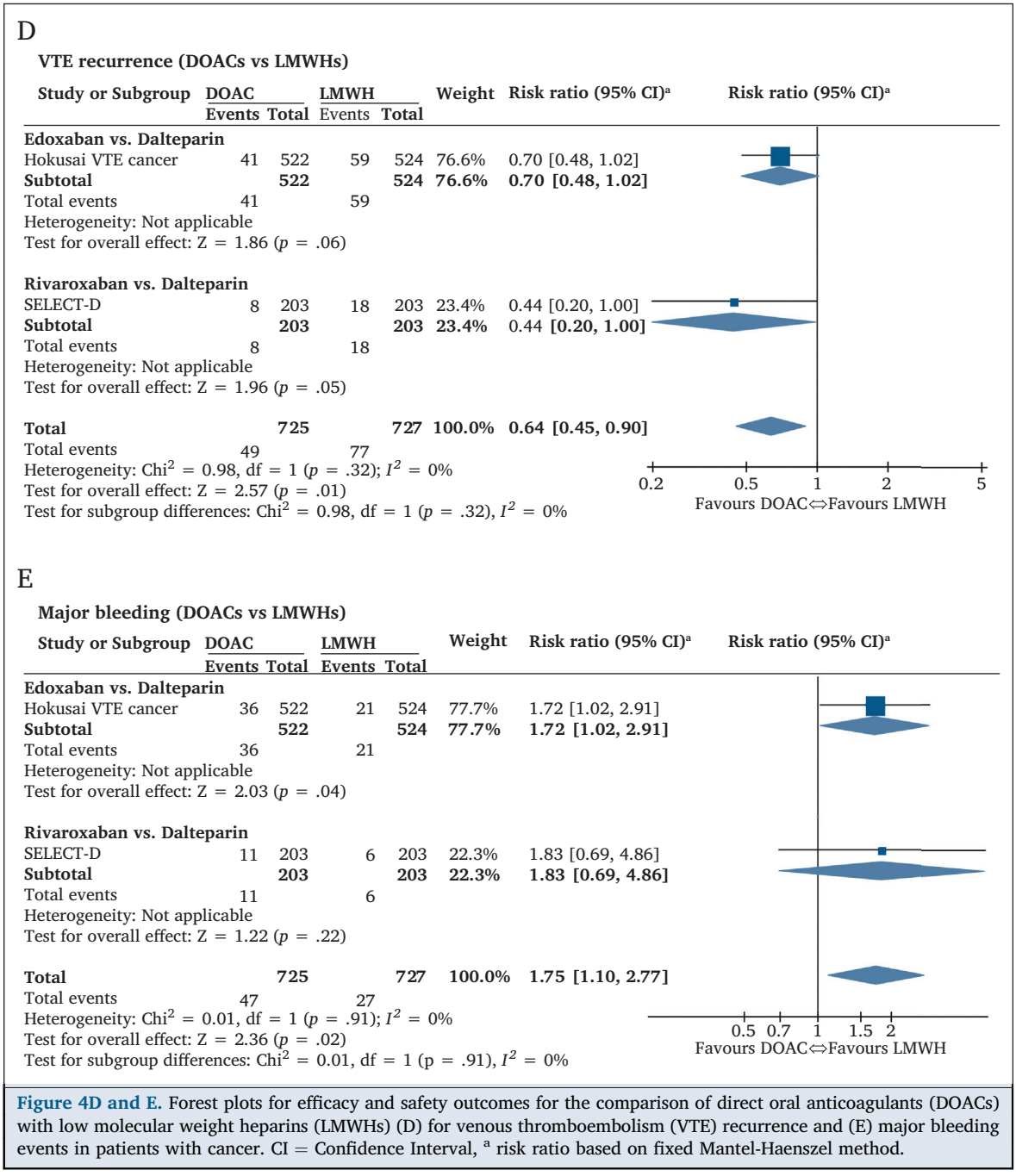


Figure 4D and E. Forest plots for efficacy and safety outcomes for the comparison of direct oral anticoagulants (DOACs) with low molecular weight heparins (LMWHs) (D) for venous thromboembolism (VTE) recurrence and (E) major bleeding events in patients with cancer. CI = Confidence Interval, [a] risk ratio based on fixed Mantel-Haenszel method.

present study. Treatment with LMWH has a lower risk of recurrent VTE than VKAs, and several studies and meta-analyses agree with these results.[37–41] Similar effects for the recurrence VTE have been described for patients with and without cancer.[41] The risk of DVT recurrence was significantly lower for LMWHs compared with VKAs, but the risk of PE recurrence was not different between LMWHs and VKAs probably because of the small number (only three) of the included trials in this outcome, as a result of lack of subgroup data in patients with malignancy in the original trials.

In the meta-analysis, recurrence rates were also lower for DOACs, particularly anti-Xa agents, compared with VKAs, with a non-significantly lower risk of DVT recurrence but not for PE. Similar results were presented by Vedovati *et al.*,[7] who reported an odds ratio of 0.63 (95% CI 0.37—1.1; I^2 = 0%) in a meta-analysis of six studies, in favour of DOACs.[7] In the present meta-analysis, the risk of recurrent VTE with DOACs was statistically significantly lower compared directly with LMWHs, with a moderate grade of evidence; to the best of the authors' knowledge, this is the first ever meta-analysis using GRADE methodology and the results imply that further work is required to raise the level of evidence. Recurrent VTE with fondaparinux was not different compared with VKAs, a result in agreement with previous studies.[42] Also, in the present study, the anti-factor Xa/anti-factor IIa activity ratio of LMWHs had no association with VTE recurrence on meta-regression analysis, with no

heterogeneity on forest plot analysis. These observations indicate that LMWH selection should not be based on the activity ratio, but rather on clinical effectiveness that is evident only for tinzaparin and dalteparin (Fig. 3A).

Safety outcomes like major bleeding occurred with the same rate in LMWHs compared with VKAs, but with a trend towards a statistically significantly lower risk for DOACs compared with VKAs. Anti-Xa agents, however, reduced clinically relevant and total bleeding compared with VKAs, in agreement with a previous meta-analysis in patients with or without cancer, where a larger sample size allowed for statistical significance to be found for both major and clinically relevant non-major bleeding.[8] In the present meta-analysis, major bleeding was reduced only for anti-Xa agents not requiring initial parenteral anticoagulation, in total agreement with what has previously been reported for unselected patients.[8] These outcomes were different to those reported by Iorio *et al.*,[43] where a reduction of major bleeding with the advantage in favour of LMWHs compared with VKAs (OR 0.45; 95% CI 0.18−1.11) was reported.[43] Carrier *et al.*[40] reported a non-significant increase in major bleeding with LMWHs compared with VKAs (RR 1.06, 95% CI 0.5−2.23), consistent with the present findings and a non-significant reduction for DOACs compared with VKAs (RR 0.78, 95% CI 0.42−1.44). There are reports of a higher incidence of gastrointestinal bleeding in patients with colorectal cancer treated with DOACs, without a statistically significant difference, in one study,[44] whereas in the recent Hokusai VTE Cancer Study the entire excess of major bleeding with edoxaban occurred in patients with gastrointestinal cancer.[45] The percentage of patients with this type of cancer in two RCTs that compared a DOAC with a VKA and provided relevant results was <10%, which may well explain the superior safety of the former agents in this comparison (Fig. 4B),[27,31] and the seemingly discrepant results of the comparison of DOACs with LMWH. The above

Table 1. Summary of findings per GRADE methodology for the comparison of low molecular weight heparins (LMWHs) with vitamin K antagonists (VKAs) in treating venous thromboembolism (VTE) in patients with cancer

Outcomes	Illustrative comparative risks		Risk ratio (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk for VKA	Corresponding risk for LMWH (95% CI)			
VTE recurrence	129 per 1000	75 per 1000 (58−97)	0.58 (0.45−0.75)	2171 (10)	⊕⊕⊕⊖ moderate[a]
Deep vein thrombosis recurrence	78 per 1000	34 per 1000 (23−54)	0.44 (0.29−0.69)	1586 (3)	⊕⊕⊕⊕ high[a,b]
PE recurrence	45 per 1000	42 per 1000 (26−65)	0.92 (0.58−1.45)	1641 (3)	⊕⊕⊕⊖ moderate[a]
All bleeding	258 per 1000	261 per 1000 (220−310)	1.01 (0.85−1.2)	1398 (6)	⊕⊕⊕⊕ high
Major bleeding	48 per 1000	47 per 1000 (32−69)	0.99 (0.67−1.45)	2088 (8)	⊕⊕⊕⊖ moderate[a]
Fatal bleeding	13 per 1000	7 per 1000 (3−17)	0.54 (0.22−1.29)	2055 (7)	⊕⊕⊕⊖ moderate[a]
Clinically relevant non-major bleeding	164 per 1000	144 per 1000 (114−183)	0.88 (0.7−1.12)	1.398 (6)	⊕⊕⊕⊖ moderate[a]
Cancer deaths	218 per 1000	242 per 1000 (201−295)	1.11 (0.92−1.35)	1348 (4)	⊕⊕⊕⊕ high
Fatal PE	36 per 1000	27 per 1000 (16−45)	0.76 (0.46−1.26)	1891 (5)	⊕⊕⊕⊖ moderate[a]
All cause deaths	405 per 1000	401 per 1000 (369−442)	0.99 (0.91−1.09)	2690 (9)	⊕⊕⊕⊕ high

The *corresponding risk* (and its 95% CI) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95% CI). Explanation of the GRADE Working Group grades of evidence is provided in methodology. VTE = venous thromboembolism; CI = confidence interval; GRADE = Grading of Recommendation, Assessment, Development and Evaluation; PE = pulmonary embolism.

[a] Downgraded because the total number of events is < 300.

[b] Upgraded because of a large effect size.

Table 2. Summary of findings per GRADE methodology for the comparison of direct oral anticoagulants (DOACs) with vitamin K antagonists (VKAs) in treating venous thromboembolism (VTE) in patients with cancer

Outcomes	Illustrative comparative risks		Risk ratio (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk for VKA	Corresponding risk for DOACs (95% CI)			
VTE recurrence	88 per 1000	57 per 1000 (40−84)	0.65 (0.45−0.95)	1486 (4)	⊕⊕⊕⊖ moderate[a]
All bleeding	236 per 1000	193 per 1000 (134−278)	0.82 (0.57−1.18)	686 (3)	⊕⊕⊕⊖ moderate[a]
Major bleeding	46 per 1000	30 per 1000 (17−51)	0.65 (0.37−1.12)	1341 (4)	⊕⊕⊕⊖ moderate[a]
Clinically relevant non-major bleeding	168 per 1000	136 per 1000 (106−174)	0.81 (0.63−1.04)	1341 (4)	⊕⊕⊕⊖ moderate[a]
All cause deaths	181 per 1000	181 per 1000 (143−230)	1 (0.79−1.27)	1197 (3)	⊕⊕⊕⊖ moderate[a]

The *corresponding risk* (and its 95% CI) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95% CI). CI = confidence interval. Explanation of the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group grades of evidence is provided in methodology.

[a] Downgraded because the total number of events is < 300.

findings indicate that DOACs, particularly anti-Xa agents, may replace LMWHs in patients with VTE as a result of non-gastrointestinal cancer, in the absence of other specific contraindication, including vomiting and hepatic failure.

There was no statistically significant difference in overall mortality rates in all group comparisons, but a non-significant trend of lower risk of fatal bleeding and fatal PE was observed in the LMWH group compared with VKAs, and a non-significant trend for less fatal bleeding with DOACs compared with LMWHs.[40] In most studies included in the present meta-analysis there were no detailed reports of the characteristics of cancer type or staging in patients with fatal bleeding or fatal PE events, in order to identify benefits between the compared treatments.

Oral anticoagulants have the disadvantage of enteral administration, which could be a problem for a number of patients with cancer with an inability to tolerate food or inability to swallow, or with other gastrointestinal motor disorders. In these cases parenteral administration of a LMWH is a simple and safe alternative therapy for VTE in patients with cancer, albeit associated with discomfort and the development of ecchymoses at the injection sites. Both DOACs and LMWHs, compared with VKAs, do not require period monitoring with blood tests and abrogate the limitation of close follow up. The management of bleeding complications with DOACs was not different from what is done with other anticoagulants,[44] and most of the new specific antidotes have now been approved for the reversal of the DOAC effect in emergency situations (idarucizumab, andexanet-alfa, aripazine).[46]

In most comparisons, quality of evidence was graded as high or moderate, but in one comparison (synthetic pentasaccharides vs. heparins or VKA) this was low; comparisons falling into the last two categories (moderate and low) require further investigation. Implications for practice include the use of LMWHs or DOACs for the treatment of VTE, PE, or DVT, in hospitalised or ambulatory patients with malignancy with a non-significant risk of recurrent VTE or bleeding events, and a simpler follow up for these patients. The advantage of oral administration of DOACs may improve compliance with the proposed therapy.

A major limitation of this systematic review and meta-analysis is that there are only few trials of VTE treatment in patients with cancer and the number of participants in these trials was relatively small. For that reason, more RCTs are needed with more participants for safety outcomes in the treatment of VTE in patients with cancer. There are a number of ongoing trials for the treatment of VTE in patients with cancer and it is expected that when their results become available in the near future, the quality of evidence may increase where at present it is insufficient.[47] Another limitation of the present study is the lack of cost effectiveness calculations, which may vary from country to country. Also, almost all RCTs have not provided a breakdown of events by cancer type to allow performance of a subgroup analysis in pursuit of patient characteristics associated with increased efficacy and safety. Additionally, there is a need for trials comparing the various anticoagulation types in extended duration anticoagulation (i.e., after the first 3–6 months) in patients with active malignancy. At present, guidelines suggest switching to VKAs.[48]

In conclusion, compared with VKAs, LMWHs, and DOACs, particularly anti-Xa agents, are more effective in treating VTE, but the latter are also safer in terms of bleeding. In a direct comparison, DOACs are more effective than LMWHs in preventing VTE recurrence and may carry a higher risk of major bleeding, based on moderate quality data. The results of ongoing trials are eagerly awaited.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.11.004.

REFERENCES

1 Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;**5**:632–4.
2 Piran S, Schulman S. Management of venous thromboembolism: an update. *Thromb J* 2016;**14**(suppl. 1):23.
3 Posch F, Konigsbrugge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. *Thromb Res* 2015;**136**:582–9.
4 Martinez-Zapata MJ, Mathioudakis AG, Mousa SA, Bauersachs R. Tinzaparin for Long-term treatment of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *Clin Appl Thromb Hemost* 2017;**24**:226–34.
5 Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost* 2003;**89**:953–8.
6 Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS. Outpatient treatment of pulmonary embolism with dalteparin. *Thromb Haemost* 2000;**83**:209–11.
7 Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. *Chest* 2014;**147**:475–83.
8 Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice – Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg* 2014;**48**:565–75.
9 Gerotziafas GT, Petropoulou AD, Verdy E, Samama MM, Elalamy I. Effect of the anti-factor Xa and anti-factor IIa activities of low-molecular-weight heparins upon the phases of thrombin generation. *J Thromb Haemost* 2007;**5**:955–62.
10 GRADE working group. What is GRADE? Available from: www.gradeworkinggroup.org.
11 Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015;**314**:677–86.

12 Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, Sfiridis P, Nikolaou A, Dimitroulis D, et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. *Eur J Vasc Endovasc Surg* 2005;**29**:638–50.
13 Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006;**119**:1062–72.
14 Romera A, Cairols MA, Vila-Coll R, Marti X, Colome E, Bonell A, et al. A randomised open label trial comparing long-term subcutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2009;**37**:349–56.
15 Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;**349**:146–53.
16 Lee AY, Rickles FR, Julian JA, Gent M, Baker RI, Bowden C, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. *J Clin Oncol* 2005;**23**:2123–9.
17 Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002;**162**:1729–35.
18 Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clin Appl Thromb Hemost* 2006;**12**:389–96.
19 Gonzalez-Fajardo JA, Arreba E, Castrodeza J, Perez JL, Fernandez L, Agundez I, et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 1999;**30**:283–92.
20 Veiga F, Escriba A, Maluenda MP, Lopez Rubio M, Margalet I, Lezana A, et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. *Thromb Haemost* 2000;**84**:559–64.
21 Lopez-Beret P, Orgaz A, Fontcuberta J, Doblas M, Martinez A, Lozano G, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc Surg* 2001;**33**:77–90.
22 Amato B, Compagna R, Rocca A, Bianco T, Milone M, Sivero L, et al. Fondaparinux vs warfarin for the treatment of unsuspected pulmonary embolism in cancer patients. *Drug Des Devel Ther* 2016;**10**:2041–6.
23 van Doormaal FF, Raskob GE, Davidson BL, Decousus H, Gallus A, Lensing AW, et al. Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. *Thromb Haemost* 2009;**101**:762–9.
24 van Doormaal FF, Cohen AT, Davidson BL, Decousus H, Gallus AS, Gent M, et al. Idraparinux versus standard therapy in the treatment of deep venous thrombosis in cancer patients: a subgroup analysis of the Van Gogh DVT trial. *Thromb Haemost* 2010;**104**:86–91.
25 The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;**363**:2499–510.
26 The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;**366**:1287–97.
27 Prins MH, Lensing AW, Brighton TA, Lyons RM, Rehm J, Trajanovic M, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol* 2014;**1**:e37–46.
28 Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;**361**:2342–52.
29 Schulman S, Goldhaber SZ, Kearon C, Kakkar AK, Schellong S, Eriksson H, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost* 2015;**114**:150–7.
30 Agnelli G, Buller HR, Cohen A, Gallus AS, Lee TC, Pak R, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost* 2015;**13**:2187–91.
31 Raskob GE, van Es N, Segers A, Angchaisuksiri P, Oh D, Boda Z, et al. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. *Lancet Haematol* 2016;**3**:e379–87.
32 Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2017;**378**:615–24.
33 Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018. JCO2018788034.
34 Li A, Garcia DA, Lyman GH, Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. *Thromb Res* 2019;**173**:158–63.
35 Sobieraj DM, Baker WL, Smith E, Sasiela K, Trexler SE, Kim O, et al. Anticoagulation for the treatment of cancer-associated thrombosis: a systematic review and network meta-analysis of randomized trials. *Clin Appl Thromb Hemost* 2018. Sep 24 (Epub ahead of print).
36 Vedovati MC, Giustozzi M, Bonitta G, Agnelli G, Becattini C. Efficacy and safety of anticoagulant agents in patients with venous thromboembolism and cancer: a network meta-analysis. *Thromb Res* 2018;**170**:175–80.
37 Che DH, Cao JY, Shang LH, Man YC, Yu Y. The efficacy and safety of low-molecular-weight heparin use for cancer treatment: a meta-analysis. *Eur J Intern Med* 2013;**24**:433–9.
38 Louzada ML, Majeed H, Wells PS. Efficacy of low-molecular-weight-heparin versus vitamin K antagonists for long term treatment of cancer-associated venous thromboembolism in adults: a systematic review of randomized controlled trials. *Thromb Res* 2009;**123**:837–44.
39 Laporte S, Bertoletti L, Romera A, Mismetti P, Perez de Llano LA, Meyer G. Long-term treatment of venous thromboembolism with tinzaparin compared to vitamin K antagonists: a meta-analysis of 5 randomized trials in non-cancer and cancer patients. *Thromb Res* 2012;**130**:853–8.
40 Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY. Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. *Thromb Res* 2014;**134**:1214–9.
41 Bochenek T, Nizankowski R. The treatment of venous thromboembolism with low-molecular-weight heparins. A meta-analysis. *Thromb Haemost* 2012;**107**:699–716.
42 Pesavento R, Amitrano M, Trujillo-Santos J, Di Micco P, Mangiacapra S, Lopez-Jimenez L, et al. Fondaparinux in the initial and long-term treatment of venous thromboembolism. *Thromb Res* 2014;**135**:311–7.
43 Iorio A, Guercini F, Pini M. Low-molecular-weight heparin for the long-term treatment of symptomatic venous thromboembolism: meta-analysis of the randomized comparisons with oral anticoagulants. *J Thromb Haemost* 2003;**1**:1906–13.

44 Schulman S, Shrum J, Majeed A. Management of bleeding complications in patients with cancer on DOACs. *Thromb Res* 2016;**140**(suppl. 1):S142–7.
45 Kraaijpoel N, Di Nisio M, Mulder FI, van Es N, Beyer-Westendorf J, Carrier M, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: results from the Hokusai VTE Cancer Study. *Thromb Haemost* 2018;**118**:1439–49.
46 Tummala R, Kavtaradze A, Gupta A, Ghosh RK. Specific antidotes against direct oral anticoagulants: a comprehensive review of clinical trials data. *Int J Cardiol* 2016;**214**:292–8.
47 McBane Ii R, Loprinzi CL, Ashrani A, Perez-Botero J, Leon Ferre RA, Henkin S, et al. Apixaban and dalteparin in active malignancy associated venous thromboembolism. The ADAM VTE Trial. *Thromb Haemost* 2017;**117**:1952–61.
48 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;**149**:315–52.

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COUP D'OEIL

Late Post-traumatic Iliac Artery Aneurysm

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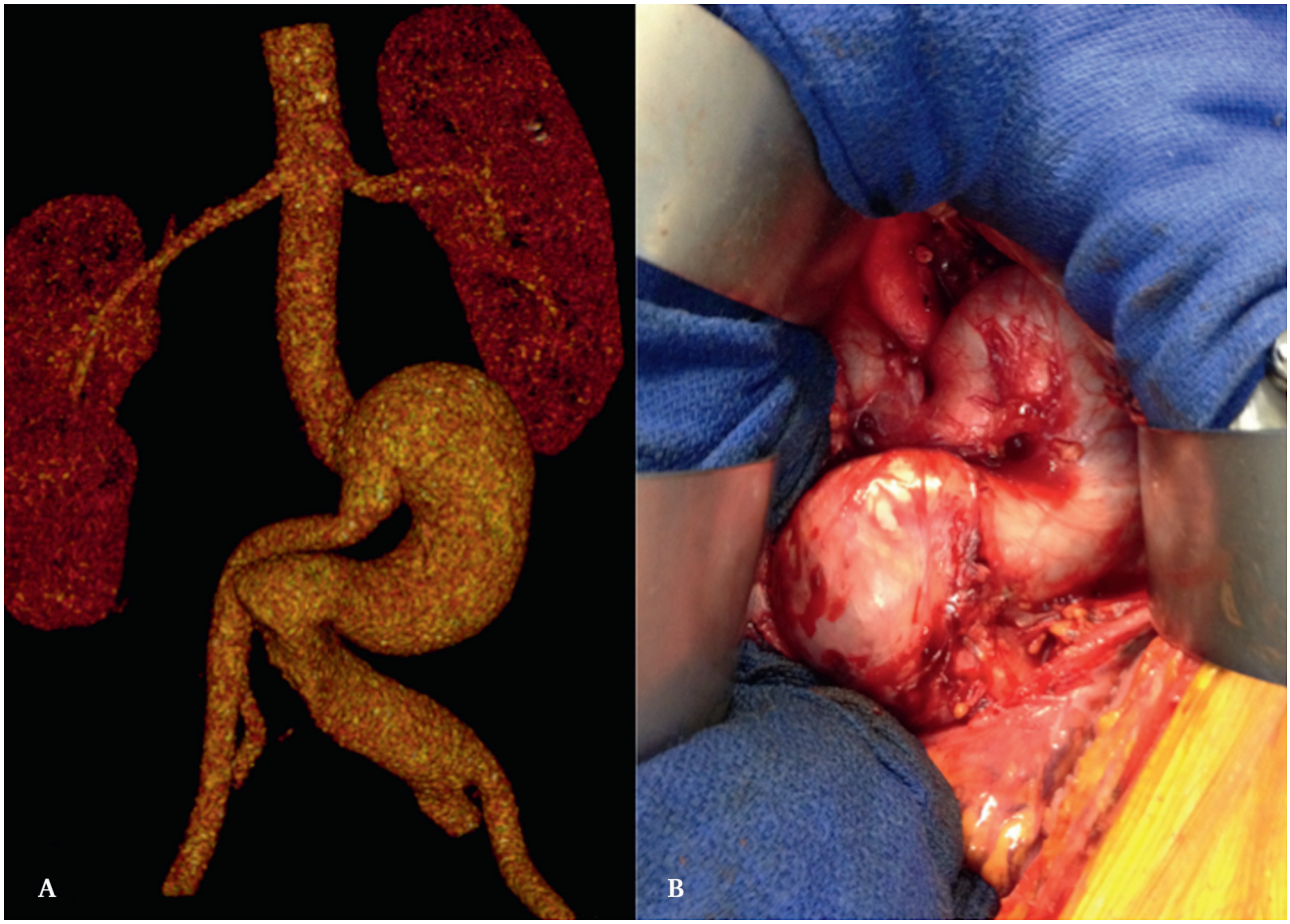

A 35 year old man with history of abdominal trauma (13 years previously) presented with a seven day history of resistant lower back pain. Computed tomography angiography revealed aneurysms of the left common, internal and proximal external iliac arteries (A). The aneurysms (B) were treated by open surgical resection and graft interposition. Intra-operative findings, as well as pathology, ruled out chronic dissection. Following blunt trauma, minimal arterial injury may result in localised weakness leading to thinning and expansion over time. Early diagnosis and rigorous follow up, often not undertaken as typified here, are key points in the management of these patients.

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