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Direct oral anticoagulants for cancer associated venous thromboembolisms: a systematic review and network meta-analysis

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MAIN TEXT

INTRODUCTION

Malignancy is a hypercoagulable state, with over 15% of patients developing deep vein thromboses (DVT) and pulmonary embolism (PE) [1]. Treatment of malignancy with chemotherapy, hormone therapy and indwelling central venous access catheters can also increase the risk of venous thromboembolism (VTE) [2]. Thrombotic events in patients with malignancy are associated with poor outcomes, including significantly higher mortality rate compared to patients without VTE [3]. Treatment of VTE in this population can be challenging due to a three to four-fold increased risk of bleeding complications and recurrence compared to patients without malignancy [4, 5]. In addition, anticoagulation treatment can be further complicated by requirement for procedures, comorbidities and medication interactions.

Until recently, subcutaneous low molecular weight heparin (LMWH) was considered the standard treatment for malignancy associated VTE [6, 7]. Randomized controlled trials (RCTs) had demonstrated superior efficacy to vitamin K antagonists in preventing recurrent VTE with similar rates of major bleeding [8, 9]. However, long term adherence with subcutaneous LMWH is highly variable, ranging between 19 to 70% [10], and can be associated with higher healthcare costs compared to other anticoagulants [11].

Direct oral anticoagulants (DOACs) are fixed-dose alternatives for the treatment of VTE, avoiding the need for subcutaneous injection and dose monitoring [12]. DOACs are the preferred first-line VTE treatment for non-malignancy associated VTE, in the absence of severe renal impairment. [6] In recent years, several RCTs have compared the efficacy and safety of DOACs and LMWH in malignancy associated VTE [13-16]. Several guidelines now recommend DOACs as an alternative to LMWH for preventing recurrence of malignancy associated VTE in carefully selected patients [17-20]. Further contributing to the evidence in this field, a major clinical trial was recently published comparing the efficacy and safety of apixaban with LMWH [16]. This systematic review and meta-analysis aims to collate the most recent RCT data on the efficacy (recurrent VTE) and safety (bleeding) of DOACs compared to LMWH for the treatment of VTE in patients with malignancy.

METHODS

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21].

Data sources / Literature search

A comprehensive systematic literature search was conducted using MEDLINE (starting 1946, via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1) and EMBASE (starting 1980, via Ovid) from inception to 1st of April 2020. The results were filtered for studies conducted on humans. There were no language restrictions. A hand search of the conference proceedings of the American Society of Clinical Oncology, the American Society of Haematology, American Thoracic Society and European Respiratory Society annual meetings from 2017 to 2019 were also performed. Reference lists of included studies and review articles

were examined for additional studies. The full search strategy is available in Supplementary Table 1.

Study eligibility criteria and selection

Two review authors (CS and JA) independently screened the titles and abstracts of identified article citations for potential eligibility. Full text manuscripts were obtained for articles considered potentially eligible by at least one review author. The two review authors then independently screened the full-text manuscripts for eligibility based on the following inclusion criteria: 1) randomized controlled trials, 2) patients of any age with cancer and acute symptomatic or incidentally found PE or DVT diagnosed using an objective diagnostic test, 3) the intended duration of anticoagulation treatment for a minimum of six months, and 4) comparison of any DOAC with any sub-cutaneous LMWH. Disagreements between the reviewers were resolved by consensus with a third reviewer (GK). The study selection decisions were recorded on EndNote referencing management software version X9 (Thomson Reuters, Philadelphia, PA, USA).

Data extraction and quality assessment

Two reviewers (CS and GK) independently extracted data from the selected studies. Disagreements were resolved by consensus or by consulting a third reviewer (JA). The quality of the included studies was assessed using the Cochrane Risk of Bias Tool [22]. Two reviewers (CS and GK) independently assessed the methodological quality of studies and resolved any disagreements by discussion. Publication bias was assessed by identification of unpublished studies in trial registries, and comparison of reported outcomes with published protocols.

Outcome measures

The co-primary outcomes for this review were recurrent VTE and major bleeding at six-months from randomisation in patients treated with DOACs compared to LMWH. We accepted the trial authors' definitions of the above outcomes used in the included studies, which are summarised in Supplementary Table 2. Secondary outcomes included 1) combined major or clinically relevant non-major bleeding (CRNMB) and 2) all-cause mortality. Predefined subgroups for analysis included major bleeding in patients with gastrointestinal and genitourinary malignancy. The reviewers contacted the study authors for study domains that were unclear.

Statistical analysis

Pooled proportions, risk ratio (RR), and risk difference (RD) along with 95% confidence intervals for each dichotomous outcome were calculated using the raw numbers provided in the manuscripts. The primary meta-analyses were performed using the Mantel-Haenszel method with a random effects model to estimate pooled effect sizes.

A complete-case analysis approach was used in the meta-analyses, where the participants considered to have missing data were excluded [23, 24]. We considered patients who were 'lost to follow-up', 'withdrew consent', 'outcome not assessable' and 'did not receive intended treatment' categories most likely had missing participant data. Sensitivity meta-analysis including all intention-to-treat participants were conducted for outcomes with statistically significant effects to assess the risk of bias associated with missing participant data. Indirect comparisons were generated between treatments by conducting network meta-analyses (multivariate random-effects meta-regression) using the frequentist method [25, 26]. Data was set up in pairs and network plots were generated. League tables are presented to show the relative treatment effects for all possible pairwise comparisons estimated in network meta-

analyses. The relative ranking of the different treatment modalities for each outcome were estimated using the P score [27].

Heterogeneity between trials was assessed by visual inspection of forest plots and by estimation of the percentage heterogeneity between trials (I^2 statistic) [24]. The Chi^2 test was performed to determine if the observed differences in results are compatible with chance alone. A p value of 0.10 was used to determine statistical significance in heterogeneity as the number of studies in the meta-analyses were expected to be low [24]. The certainty in evidence at the outcome level was assessed using the GRADE approach [28] for the primary outcomes. Forest plots of direct comparative RRs were generated using the Cochrane Review Manager 5.3 software [29]. Network meta-analysis was performed in network "meta" and "mvmeta" packages in STATA 16.1 (StataCorp, Texax, USA).

RESULTS

The systematic literature search resulted in 5464 records. A total of 5224 titles and/or abstracts were screened after removing duplicates. A total of 106 records were selected for detailed review, of which 102 studies were excluded for not meeting the inclusion criteria. Four prospective RCTs with 2907 patients were included in the quantitative synthesis [13-16]. The PRISMA flow chart is shown in Figure 1.0. The network meta-analysis plot is shown in Supplementary Figure 1.

All four trials compared DOACs to dalteparin in treatment of malignancy associated acute VTE. The treatment duration was six months in three studies [14-16] and up to 12 months in one study [13]. Six-month follow-up outcome data was extracted from the supplementary tables of the single study of longer duration. Outcome definitions were uniform across the studies, with all reporting recurrent VTE, major bleeding, CRNMB and all-cause mortality. One of the trials

had a composite primary outcome of recurrent VTE and major bleeding [13]. Study design characteristics are summarized in Table 1.0. Detailed study inclusion and exclusion criteria and outcome definitions are summarized in in Supplementary Table 2.

The treatment arm DOACs included apixaban, edoxaban and rivaroxaban. Two studies used apixaban 10mg twice daily for the first 7 days followed by 5mg twice daily [15, 16]. The treatment arm in Raskob et al consisted of edoxaban at a fixed dose of 60mg once daily after five days of lead-in therapeutic LMWH [13]. Young et al used rivaroxaban 15mg twice daily for three weeks followed by 20mg daily thereafter [14]. The control group in all four trials received dalteparin 200mg IU per kilogram of body weight once daily for 30 days followed by 150mg IU per kilogram once daily. Forest plots of pooled outcome comparisons (direct analysis) between DOACs and LMWH are shown in Figure 2.0.

Recurrent VTE and Major Bleeding

The overall risk of recurrent VTE was lower in the DOACs group compared to dalteparin group (RR 0.63, 95% CI 0.44 to 0.91; RD 31 fewer per 1000, 95% CI 50 fewer to 12 fewer; high certainty evidence) (Figure 2A). There was low degree of heterogeneity (I^2 = 28%, p = 0.25)). Sensitivity analysis is detailed in Supplementary Table 3. Major bleeding events were recorded in 62 (4.5%) patients in the DOAC group and 48 (3.4%) in the LMWH group. There was no statistically significant difference in risk of major bleeding at six months follow-up between DOACs and LMWH (RR 1.31, 95% CI 0.83 to 2.07; RD 10 more per 1000, 95% CI 4 fewer to 24 more; moderate certainty evidence) (Figure 2B). There was a low degree of heterogeneity (I^2 = 22%, p = 0.28).

In the indirect comparison, there was no significant difference in the incidence of recurrent VTE or major bleeding between the DOACs compared to dalteparin (Figure 3). The ranking

probabilities analysis showed that apixaban had the highest probability of being the treatment with the greatest reduction in recurrent VTE, followed by rivaroxaban, edoxaban, and LMWH. Low molecular weight heparin had the highest probability of being the treatment with the lowest likelihood of major bleeding, followed by apixaban, edoxaban and rivaroxaban (Supplementary Table 4).

Secondary outcomes

A statistically significant higher risk of combined major or CRNMB was seen with DOACs (n = 198, 14.2%) compared to LMWH (n = 134, 9.6%) (RR 1.52, 95% CI 1.09 to 2.12; RD 47 more per 1000, 95% CI 22 more to 71 more; low certainty evidence) (Figure 2C). There was a moderate degree of heterogeneity (I^2 = 51%, p = 0.11). Sensitivity meta-analyses showed that the estimate remained significant across all three stringent assumptions (Supplementary Table 3).

There was no difference in all-cause mortality at six months between the DOAC and LMWH treatment groups following a malignancy associated VTE (RR 1.0, 95% CI 0.84 to 1.18; RD 22 fewer deaths per 1000, 95% CI 34 fewer to 30 more; I^2 33%). There was no significant difference in the risk of all-cause mortality in the indirect analysis either.

Subgroup analysis – major bleeding in gastrointestinal and genitourinary malignancy

A total of 1063 (36.7%) of patients had gastrointestinal (n = 750, 25.9%) and genitourinary (n = 313, 10.8%) malignancy at baseline. The majority of the major bleeding events occurred in these two subgroups (n = 66/110, 60%). One study was excluded from the subgroup analysis as major bleeding events were not recorded in either study groups [15]. Pooled analysis of the three remaining studies did not show a significant difference in the risk of major bleeding with

DOACs compared to LMWH in gastrointestinal (RR 2.14, 95% CI 0.79 to 5.81) or genitourinary (RR 3.03, 95% CI 0.82 to 11.21) malignancy.

In the indirect treatment analysis of patients with gastrointestinal malignancy, edoxaban was associated with a higher relative risk of major bleeding compared to LMWH (RR 5.51, 95% CI 1.66 – 8.27). Neither apixaban nor rivaroxaban demonstrated a significant difference compared to LMWH (RR 1.11, 95% CI 0.49 – 2.48 and RR 1.67, 95% CI 0.57 – 4.86 respectively). In patients with genitourinary malignancy, a difference in the risk of major bleeding was not seen between the agents.

Qualitative assessment

The overall risk of bias was low. None of the included studies blinded the participants. However, all studies had a blinded and independent adjudication process for outcome assessment. Risk of bias assessment table is shown in Supplementary Figure 2. There was high degree of certainty in the evidence for recurrent VTE and major bleeding in the direct comparison. Certainty of evidence was low for the secondary outcomes due to significant imprecision. The summary of findings and GRADE Working Group grades of evidence for the indirect comparison are provided in Supplementary Table 5. There was no inconsistency in the network models for any of the outcome measures. In the influence analysis, the overall effect sizes in recurrent VTE and major bleeding did not change significantly after removing each individual study from the analysis. However, the RR of combined major or CRNMB between DOACs and LMWH became non-significant when the Raskob et al study [13] was removed from the analysis.

DISCUSSION

This systematic review and network meta-analysis pooled all randomized controlled trial evidence on the efficacy and safety of DOACs in malignancy associated VTE compared to LMWH. The main findings were that DOACs resulted in a statistically significant 37% reduction in risk of recurrent VTE with similar rates of major bleeding compared to LMWH in patients with malignancy associated VTE. However, the benefits were tempered by an increased risk of combined major or CRNM bleeding with DOACs compared to LMWH. While no mortality difference was demonstrated between either anticoagulation strategy, our analysis focused on the shorter treatment duration of six months which perhaps influenced this outcome. Nevertheless, the results of this meta-analysis strengthen the evidence to support DOACs as an acceptable alternative treatment option in selected patients with malignancy associated VTE. Furthermore, the majority of patients included in the meta-analysis had metastatic disease and were receiving active treatment, which makes the results more generalizable to real-world clinical practice.

A strength of our meta-analysis is the incorporation of the recent RCT by Agnelli et al, which included over 1100 patients assigned to either apixaban or LMWH [16]. A third of patients in this study had either lung or colorectal malignancy, which are traditionally regarded as highly thrombogenic [30, 31]. Given this increased VTE risk, their primary outcome demonstrating non-inferiority of apixaban compared to LMWH in preventing recurrent VTE is highly relevant.

Findings of this study highlight the importance of appropriate patient selection and careful risk-benefit assessment in patients with high risk of bleeding. Patients with gastrointestinal and genitourinary malignancy are recognized to have higher risk of bleeding complications, and in our analyses over 60% of major bleeding events occurred in these patient groups. Although the pooled analysis did not show a statistically significant difference in the risk of major bleeding in DOACs compared to LMWH, there were differences in the bleeding rates between

individual trials. Raskob et al and Young et al reported higher risk of major bleeding in patients with gastrointestinal malignancy with edoxaban and rivaroxaban respectively. Sub-analyses by bleeding site in Raskob et al suggest possible direct effects of edoxaban on the gastrointestinal tract. [13]. In contrast, Agnelli et al found no additional bleeding risk in gastrointestinal cancers with apixaban although as conceded by the authors, analysis of bleeding outcomes was not a prespecified endpoint [16]. These results are consistent with data showing apixaban having lower risk of gastrointestinal bleeding in patients without cancer compared to other DOACs [32].

Another challenging area is the management of VTE anticoagulation in patients with primary brain tumors or intracranial metastases. Agnelli et al excluded patients with brain lesions (primary or metastases) and the other three studies had low numbers of patients [16]. Given the small numbers, the authors are unable to comment on the efficacy and safety of DOACs in this patient population.

The results of our meta-analysis are consistent with the findings of several other recent studies which pooled the outcomes of currently published RCTs on this topic [33-35]. A strength of our study is the network analysis, which enabled indirect comparison of outcome data between all four treatments (edoxaban, rivaroxaban, apixaban and LMWH). This analysis suggested a trend towards reduced risk of recurrent VTE across all DOACs compared with LMWH. Among the DOACs, apixaban demonstrated the greatest effect on recurrent VTE prevention. A breakdown of DOACs by risk ratio for combined major or CRNMB suggests more favourable outcomes with apixaban although by itself, no difference was seen when compared to LMWH. Pooling data across three out of four studies where bleeding events were accurately captured, our network analysis also showed no difference in gastointestinal or genitourinary bleeding comparing DOACs and LMWH. Again, of the DOACs studied, apixaban emerged as being

least likely to be associated with major bleeding in gastrointestinal and genitourinary malignancy.

We intentionally chose six-months as the anticoagulation treatment duration as beyond this period, cancer mortality may impact VTE treatment effects. While the pooled risk of major bleeding complications between DOACs and LMWH was non-significant at six months follow-up, results from McBane et al [15] demonstrated increased risk of major bleeding with longer duration of anticoagulation. Long-term anticoagulation extension studies in non-malignant VTE suggest a divergence in bleeding risk between DOACs and LMWH with longer durations of anticoagulation, perhaps also influenced by choice of DOAC [36]. With improving survival, extended anticoagulation for VTE beyond six months is increasingly common in modern oncology [17, 37], however no studies have evaluated strategies (such as dose reduction) to mitigate bleeding risk in this situation. Such an approach is now routine in non-malignant VTE [38], and warrants further study in malignancy associated VTE.

A strength of our meta-analysis is the incorporation of the recent RCT by Agnelli et al, which included over 1100 patients assigned to either apixaban or LMWH [16]. A third of patients in this study had either lung or colorectal malignancy, which are traditionally regarded as highly thrombogenic [30, 31]. Given this increased VTE risk, their primary outcome demonstrating non-inferiority of apixaban compared to LMWH in preventing recurrent VTE is highly relevant.

There are several limitations to this meta-analysis. Only a small number of trials met the inclusion criteria, therefore the network meta-analysis has high imprecision. There were minor differences in the definitions of outcomes used in each trial, as summarized in the Supplementary Table 2, which may have contributed to heterogeneity in outcomes. The authors are unable to comment on the efficacy and safety of other available DOACs, such as

dabigatran, in this patient population. Dalteparin has become the LMWH of choice in comparative studies due to the CLOT trial demonstrating a statistically significant difference in reduction of recurrent VTE compared to warfarin [8]. There were insufficient patient numbers to evaluate additional subgroups.

CONCLUSION

In summary, high certainty evidence suggests that DOACs results in significantly lower risk of recurrent VTE at six months, compared to LMWH, in patients with malignancy. Direct oral anticoagulants appear to be non-inferior to LMWH with respect to major bleeding including in patients with gastrointestinal and genitourinary malignancy, although there was a small but significant increase in combined major or CRNMB. Apixaban seems to result in lower risk of bleeding compared to rivaroxaban and edoxaban, although the certainty of these comparisons is low. Future studies should investigate the efficacy and safety of longer duration of anticoagulation in this patient population and consider other important subgroups such as patients with cerebral malignancy.

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FIGURE LEGENDS

Figure 1.0: PRISMA flow diagram

Figure 2.0: Forest plots of pooled outcome comparisons between DOACs and LMWH at six months follow-up for (A) recurrent VTE, (B) major bleeding, (C) major or clinically relevant non-major bleeding and (D) all-cause mortality.

Figure 3. League tables of indirect comparison of outcomes between treatments. A) A) Recurrent VTE, B) Major bleeding, C) Major or CRNMB

Risk ratios (95% CIs) represent comparators (rows) vs references (columns).

CRNMB = clinically relevant non-major bleeding.

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Table 1.0: Summary of the study characteristics of included studies

Study	Design	Patient type	Treatment duration and follow-up	Outcomes	Patient characteristics		
					Characteristic	DOAC	LMWH
Raskob et al 2018 (HOKUSAI) [13]	Randomized open-label non-inferiority multicentre clinical trial	Adults with active cancer and acute symptomatic or incidentally found PE and/or DVT	At least 6 months, and up to 12 months.	• Recurrent VTE • Death from any cause • Major bleeding • CRNMB • Recurrent DVT • Recurrent PE • Event-free survival	Drug	Edoxaban	Dalteparin
					Number of patients*	522	524
					Age/ years (SD)	64.3 (11.0)	63.7 (11.7)
					Female gender/ n (%)	245 (46.9)	261 (49.8)
					PE / n (%)	328 (62.8)	329 (62.8)
					Active Ca / n (%)	513 (98.3)	511 (97.5)
					Metastatic Ca / n (%)	274 (52.5)	280 (53.4)
Young et al 2018 (SELECT-D) [14]	Randomized open-label multicentre pilot trial	≥18 years of age, with active cancer and acute symptomatic or incidentally found PE and/or DVT	Treatment: 6 months Follow-up: 24 months	• Recurrent VTE • Major bleeding • CRNM bleeding	Drug	Rivaroxaban	Dalteparin
					Number of patients†	203	203
					Patient age/ years (range)	67 (34-87)	67 (22 -87)
					Female gender/ n (%)	105 (51.7)	87 (42.9)
					PE / n (%)	145 (71.4)	150 (73.9)
					Active Ca / n (%)	203 (100)	203 (100)
					Metastatic Ca / n(%)	118 (58)	118 (58)
McBane et al 2019 (ADAM VTE) [15]	Randomized open-label superiority multicentre clinical trial	≥18 years of age with active cancer and acute VTE	6 months	• Major bleeding • CRNMB • Minor bleeding • Recurrent VTE • Arterial thrombosis • Mortality	Drug	Apixaban	Dalteparin
					Number of patients †	150	150
					Patient age/ years (SD)	64.4 (11.3)	64.0 (10.8)
					Female gender/ n (%)	78 (52.0)	77 (51.3)
					PE / n (%)	81 (55.1)	75 (50.7)
					Active Ca / n (%)	150 (100)	150 (100)
					Metastatic Ca / n(%)	96 (65.3)	97 (66.0)
Agnelli et al 2020 (CARAVAGGIO) [16]	Randomized open-label non-inferiority	Adults with cancer and acute symptomatic or	6 months	• Recurrent VTE • Major bleeding • CRNMB • Mortality	Drug	Apixaban	Dalteparin
					Number of patients*	576	579
					Patient age/ years (range)	67.2 (11.3)	67.2 (10.9)

	multicentre clinical trial	incidentally found PE and/or DVT		• Event free survival	Female gender/ n (%)	284 (49.3)	303 (52.3)
					PE / n (%)	304 (52.8)	334 (57.7)
					Active Ca / n (%)	559 (97.0)	565 (97.6)
					Metastatic Ca / n(%)	389 (67.5)	396 (68.4)

* number of patients included in the trials' intention to treat primary analyses, † number of patients enrolled and randomized, Ca = cancer, LMWH = low molecular weight heparin, PE = pulmonary embolism, DVT = deep vein thrombosis, SD = standard deviation, CRNMB = clinically relevant non-major bleeding.

Figure 1.0: PRISMA flow diagram

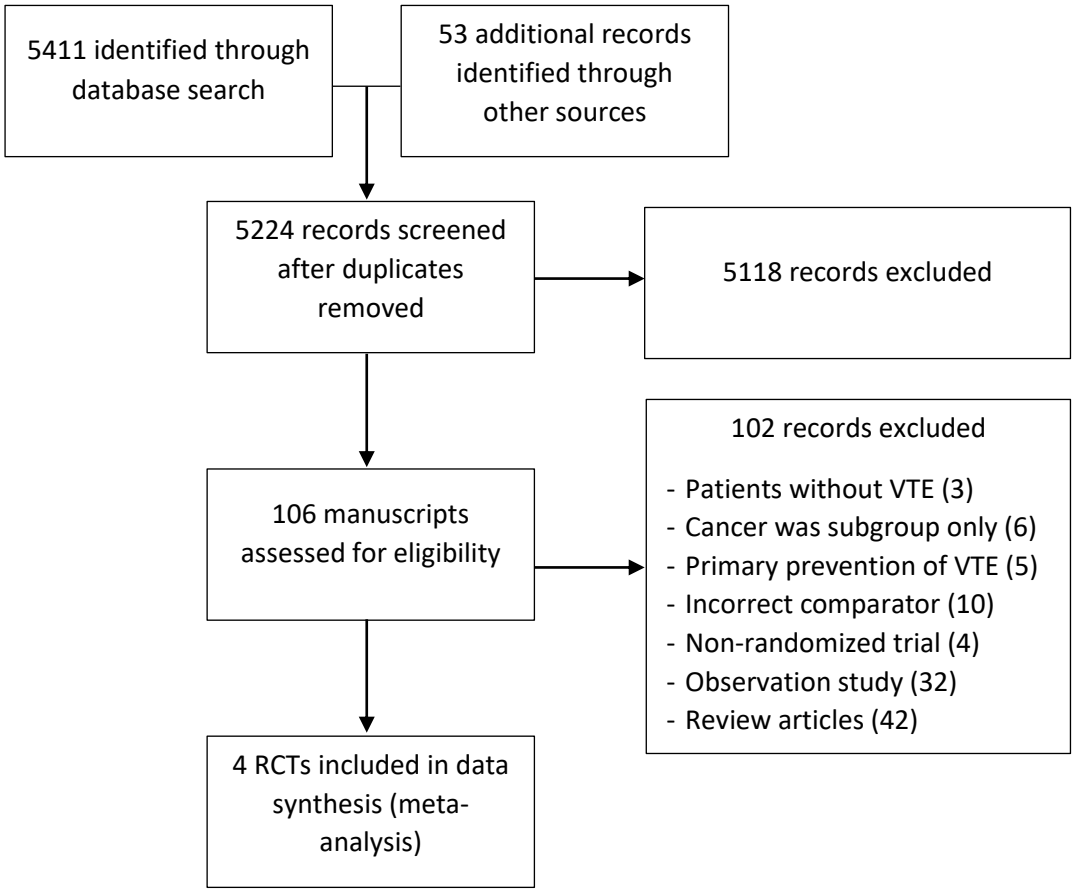
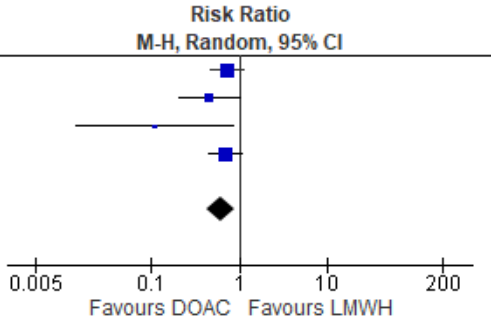


Figure 2.0: Forest plots of pooled outcome comparisons between DOACs and LMWH at six months follow-up for (A) recurrent VTE, (B) major bleeding, (C) major or clinically relevant non-major bleeding and (D) all-cause mortality.

A

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob et al 2018 (HOKUSAI)	34	509	46	507	40.6%	0.74 [0.48, 1.13]
Young et al 2018 (SELECT-D)	8	183	18	187	16.7%	0.45 [0.20, 1.02]
McBane et al 2019 (ADAM VTE)	1	136	9	135	3.1%	0.11 [0.01, 0.86]
Agnelli et al 2020 (CARAVAGGIO)	32	564	46	571	39.6%	0.70 [0.46, 1.09]
Total (95% CI)		**1392**		**1400**	**100.0%**	**0.63 [0.44, 0.91]**
Total events	75		119			

Heterogeneity: Tau² = 0.04; Chi² = 4.14, df = 3 (P = 0.25); I² = 28%
Test for overall effect: Z = 2.48 (P = 0.01)

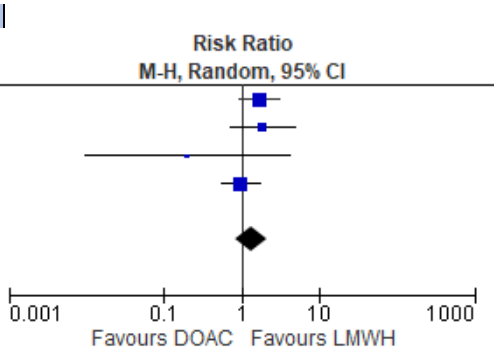


B

Rivaroxaban

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob et al 2018 (HOKUSAI)	29	509	17	507	39.2%	1.70 [0.95, 3.05]
Young et al 2018 (SELECT-D)	11	183	6	187	18.3%	1.87 [0.71, 4.96]
McBane et al 2019 (ADAM VTE)	0	136	2	135	2.2%	0.20 [0.01, 4.10]
Agnelli et al 2020 (CARAVAGGIO)	22	564	23	571	40.3%	0.97 [0.55, 1.72]
Total (95% CI)		**1392**		**1400**	**100.0%**	**1.31 [0.83, 2.07]**
Total events	62		48			

Heterogeneity: Tau² = 0.05; Chi² = 3.84, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 1.18 (P = 0.24)



C

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob et al 2018 (HOKUSAI)	83	509	56	507	35.5%	1.48 [1.08, 2.02]
Young et al 2018 (SELECT-D)	36	183	19	187	19.2%	1.93 [1.16, 3.19]
McBane et al 2019 (ADAM VTE)	9	136	9	135	10.9%	0.99 [0.41, 2.42]
Agnelli et al 2020 (CARAVAGGIO)	70	564	56	571	34.4%	1.27 [0.91, 1.76]

1.70 (95% CI 0.89 – 3.25)	**Edoxaban**		
1.87 (95% CI 0.68 – 5.16)	1.10 (95% CI 0.33 - 3.67)	**Rivaroxaban**	
0.91 (95% CI 0.11 – 7.44)	0.53 (95% CI 0.06 – 4.83)	0.48 (95% CI 0.55 – 5.00)	**Apixaban**

C) Major or CRNMB

Dalteparin			
1.48 (95% CI 1.08 – 2.02)	**Edoxaban**		
2.83 (95% CI 1.55 – 5.16)	1.92 (95% CI 0.97 – 3.78)	**Rivaroxaban**	
1.23 (95% CI 0.90 – 1.68)	0.83 (95% CI 0.53 – 1.30)	0.43 (95% CI 0.22 – 0.85)	**Apixaban**

Risk ratios (95% CIs) represent comparators (rows) vs references (columns).
CRNMB = clinically relevant non-major bleeding.