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Supplementary Material

Direct Oral Anticoagulants for Treatment of Venous Thromboembolism Associated with Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

There is uncertainty about the choice of anticoagulation therapy in patients with malignancy and venous thromboembolism (VTE). While low-molecular weight heparin (LMWH) remains the current standard, direct oral anticoagulants (DOACs) have emerged as an appealing alternative option. The primary objective of this analysis was to compare the efficacy and safety of DOACs versus LMWH in patients with malignancy and VTE. The secondary objective was to compare the safety and efficacy of the different DOACs. An online search of PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov from inception until April 2020 was conducted. Four RCTs encompassing 2,907 patients, (50.5% men and mean age of 65.7 ± 10.5) were selected. At a mean follow up of 12 months, moderate certainty evidence showed no differences between DOAC and LMWH in VTE recurrence (HR, 0.54 [CI 0.23 to 1.28], I^2 = 56%, p=0.23), in major bleeding (HR, 1.38 [CI 0.45 to 4.22], I^2 = 33%, p=0.21) or clinically relevant non-major bleeding (CRNMB) (HR, 1.77 [CI 0.49 to 6.40], I^2 = 73.9%, p=0.087). There was no difference between the DOACs when compared to each other. In conclusion, DOACs are an acceptable alternative to LMWHs for the treatment of VTE in patients with malignancy.

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Appendix Table 1: Search strategy.

Database	Search Terms	Filters	Number of hits
Cochrane Central Register of Controlled Trials (Issue 4 of 12, April 2020), MEDLINE, PubMed, ClinicalTrials.gov	(clot or VTE or thrombosis or thromboembolism) AND ((cancer or malignancy or tumor) AND (LMWH OR enoxaparin OR dalteparin OR heparin) AND (DOAC OR NOAC OR Apixaban OR edoxaban or rivaroxaban or dabigatran))	None	282

Appendix Table 2: GRADE Summary of Findings Table.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)		
VTE recurrence (follow up: median 6 months)												
4	randomized trials	not serious	Serious [a]	not serious	not serious	none	82/1446 (5.7%)	132/1448 (9.1%)	**HR 0.54** (0.23 to 1.28)	41 fewer per 1,000 (from 69 fewer to 24 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Major Bleeding (follow up: median 6 months)												
4	randomized trials	not serious	Serious [a]	not serious	not serious	none	69/1446 (4.8%)	52/1448 (3.6%)	**HR 1.38** (0.45 to 4.22)	13 more per 1,000 (from 20 fewer to 107 more)	⨁⨁⨁◯ MODERATE	CRITICAL
CRNMB (follow up: median 6 months)												
4	randomized trials	not serious	serious [a]	not serious	not serious	none	162/1446 (11.2%)	107/1448 (7.4%)	**HR 1.77** (0.49 to 6.40)	53 more per 1,000 (from 37 fewer to 314 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; HR: Hazard Ratio; DOAC: direct oral anticoagulant; LMWH: low-molecular-weight heparin; a: Unexplained Heterogeneity noted amongst the trials. Some malignancies were excluded in different trials which poses a risk for heterogeneity as patients have different bleeding (safety) outcomes based on the type of malignancy they have.

(It is providing summary of findings for each of the included studies and the quality of evidence rating for each of the three outcomes analyzed in this analysis)

Developed using GRADEpro (Link)

Appendix Table 3: Baseline characteristics of the included studies.

Trial and Patient Characteristics								
RCTs	**Hokusai-VTE cancer N=1050**		**SELECT-D N=406**		**ADAM-VTE N=300**		**Caravaggio N=1155**	
Trial design	Non-inferiority		Pilot		Superiority		Non-inferiority	
Follow up	12 months		24 months		6 months		7 months	
Eligibility criteria	Adult patients with cancer were eligible for inclusion in the trial if they had acute symptomatic or incidentally detected VTE. Low-molecular-weight heparin given for at least 6 months.		Patients with active cancer (solid and hematologic malignancies) presenting with a primary objectively confirmed VTE, either symptomatic lower-extremity proximal DVT, symptomatic PE, or incidental PE.		Adult patients with confirmed active cancer and cancer associated VTE including brain metastasis patients.		Consecutive adults with cancer who had a newly diagnosed symptomatic or incidental proximal lower-limb DVT or PE were eligible to participate in the trial.	
Primary outcome measures	Composite measure of recurrent VTE or major bleeding within 12 months after randomization		VTE recurrence in the 6 months after randomization		Major bleeding		VTE recurrence in the 6 months after randomization	
Cancers excluded	• basal cell • skin SCC		• basal cell • skin SCC		-		• basal cell • skin SCC • primary brain tumor • intracerebral metastases • acute leukemia	
Agent type	DOAC	LMWH	DOAC	LMWH	DOAC	LMWH	DOAC	LMWH
Study arms	Edoxaban	Dalteparin	Rivaroxaban	Dalteparin	Apixaban	Dalteparin	Apixaban	Dalteparin
Number of subjects	522	524	203	203	150	150	576	579
Age, years (mean ± SD or median (25-75th percentile)	64.3 ± 11.0	63.7 ± 11.7	67 (34-87)	67 (22-87)	64.4 ± 11.3	64 ± 10.8	67.2 ± 11.3	67.2 ± 10.9
Male gender (%)	53.1	50.2	57	48	48	48.7	50.7	47.7
Dosing	Dalteparin for at least 5 days followed by Edoxaban 60 mg once daily for 6 to 12 months	200 IU/kg once daily first 30 days followed by 150 IU/kg daily	15 mg twice daily for 3 weeks followed by 20 mg once daily for 2 to 6 months	200 IU/kg once daily first 30 days followed by 150 IU/kg daily	10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months	200 IU/kg once daily first 30 days followed by 150 IU/kg daily	10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months	200 IU/kg once daily first 30 days followed by 150 IU/kg daily

RCTs: Randomized clinical trials; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; VTE: venous thromboembolism; SCC: squamous-cell carcinoma skin.

Appendix Table 4: Definition of major outcomes as per the included studies.

Hokusai-VTE cancer	SELECT-D	The ADAM-VTE Trial	Caravaggio
DVT: non-compressible vein segment on ultrasonography or an intra-luminal filling defect on venography, CT venography or MRI venography, located in the inferior vena cava (IVC), the iliac vein, the common femoral vein, the femoral or the popliteal vein. **Recurrent VTE:** symptomatic new DVT or PE, incidental new DVT or PE involving segmental or more proximal pulmonary arteries, or fatal PE or unexplained death for which PE could not be ruled out as the cause. **Incidental venous thromboembolism:** thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of VTE. **Symptomatic PE recurrence:** New intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of > 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), or a new non–high-probability perfusion defect associated with DVT as documented by ultrasound or venography.	**DVT Recurrence:** new, non-compressible venous segment or a substantial increase (4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography. **Symptomatic PE recurrence:** New intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of > 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), or a new non–high-probability perfusion defect associated with DVT as documented by ultrasound or venography. **Incidental PE:** Incidentally diagnosed PE on CT when imaging performed, usually for staging of cancer. **Fatal PE:** objective diagnostic testing, autopsy, or death, which could not be attributed to any other cause.	**Thrombus**: the qualifying thrombus could be an acute lower extremity or upper extremity (jugular, innominate, subclavian, axillary, brachial) DVT, PE, splanchnic (hepatic, portal, splenic, mesenteric, renal, gonadal), or cerebral vein thrombosis confirmed by appropriate cross-section imaging. **Recurrent DVT**: thrombus confirmed by duplex ultrasonography, venography, CT, or MRI. **Recurrent PE**: confirmed by CT, MR, conventional pulmonary angiography, or VQ imaging. **Fatal PE**: objective diagnostic testing, autopsy, or death that could not be attributed to a documented cause and for which PE/DVT could not be ruled out (unexplained death). **Incidental VTE recurrence** had to be identified on surveillance- related imaging. In order to be classified as a recurrent event, there had to be a new filling defect evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.	**DVT:** the evidence of one or more filling defects at compression ultrasonography, venography, CT venography or MR venography involving at least the popliteal vein or more proximal veins. **PE**: One or more among: an intra-luminal filling defect at CT pulmonary angiography, an intra-luminal filling defect, or a new sudden cut-off of vessels more than 2.5 mm in diameter at pulmonary angiogram, a perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/ perfusion lung scan (VQ scan), in unsuspected PE, there must be one or more filling defect in segmental or more-proximal arteries at chest CT pulmonary angiography.
Major bleeding: overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death, in accordance with the criteria of the International Society on Thrombosis and Hemostasis. **CRNMB**: A bleeding event will be classified as a clinically relevant non-major bleeding event if it is overt (i.e. is symptomatic or visualized by examination) not meeting the criteria for major bleeding, requires medical attention or is associated with discomfort for the subject such as pain, or impairment of activities of daily life.	**Major bleeding:** acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the hemoglobin level of 20 g/L over a 24-hour period, transfusion of two or more units of packed red cells, bleeding at a critical site or fatal bleeding. **CRNMB**: Acute, clinically overt episodes, such as wound hematoma, bruising, gastrointestinal bleeding, hemoptysis, hematuria, or epistaxis, that did not meet the criteria for major bleeding but were associated with medical intervention, unscheduled physician contact, interruption of study drug or discomfort or impairment of activities of daily life.	**Major bleeding**: overt bleeding plus a hemoglobin decrease of ≥2 gram per decileter; or transfusion of ≥2 units of packed red blood cells; or intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intraarticular, intramuscular with compartment syndrome, or fatal bleeding **CRNMB:** overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact with the health care team, or temporary anticoagulant cessation.	**Major Bleeding**: acute clinically overt bleeding associated with one or more of the following: a decrease in the hemoglobin level of at least 2 g per deciliter, a transfusion of 2 or more units of red cells, bleeding occurring at a critical site, bleeding resulting in surgical intervention, or fatal bleeding, all occurring during the trial-drug period through 72 hours after the last dose was administered. **CRNMB:** Acute, clinically overt episodes, such as wound hematoma, bruising, GI bleeding, hemoptysis, hematuria, or epistaxis, that did not meet the criteria for major bleeding but were associated with medical intervention, unscheduled physician contact, interruption of study drug or discomfort or impairment of activities of daily life.

Cancer: Cancer other than basal-cell or SCC that was active or had been diagnosed within the previous 2 years and was objectively confirmed. **Active cancer:** cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 months before randomization; or hematologic cancer that was not in complete remission.	**Active cancer:** cancer (other than basal-cell or SCC) in the previous 6 months, any treatment for cancer within the previous 6 months, recurrent or metastatic cancer, or cancer not in complete remission (hematologic malignancy).	**Active cancer:** cancer on cross-sectional or positron emission tomography imaging, metastatic disease, and/or cancer-related surgery, chemotherapy, or radiation therapy within the prior six months.	**Cancer** defined as: Cancer other than basal-cell or SCC of the skin, primary brain tumor, known intracerebral metastases, or acute leukemia were eligible to participate in the trial. **Active cancer** was defined as cancer that had been diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrollment or during 6 months before randomization, or recurrent locally advanced or metastatic cancer.

CRNMB: Clinically relevant non-major bleeding; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; SCC: squamous-cell carcinoma skin.

Appendix Table 5: Checklist as per the Preferred Reporting System of Systematic Review and Meta-analysis (PRISMA) Guidelines.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online Supplement (eTable 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5 Online Supplement (eFigure 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6 Online Supplement (eTable 2)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Online Supplement (eTable-3)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Online Supplement (eFigure-1)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	All figures have outcomes as per individual studies
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	eTable 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Appendix Table 6: Individual Randomized clinical trials assessing the efficacy and safety of DOACs.

Outcomes: Randomized clinical trials assessing the efficacy and safety of direct oral anticoagulants in the treatment of cancer associated thrombosis				
RCTs	**Hokusai-VTE cancer**	**SELECT-D**	**ADAM-VTE**	**Caravaggio**
Primary outcome measures	Composite of recurrent VTE or major bleeding within 12 months after randomization	VTE recurrence in the 6 months after randomization	Major bleeding	VTE recurrence in the 6 months after randomization
Primary outcome results	Edoxaban: 12.8% (67/522) Dalteparin: 13.5% (71/524) HR, 0.97; 95% CI, 0.70 - 1.36 P=0.006 for non-inferiority; P=0.87 for superiority	Rivaroxaban: 4% (8/203), 95% CI, 2 – 9 Dalteparin: 11% (18/203), 95% CI, 7 - 16 HR,0.43; 95% CI, 0.19 - 0.99	Apixaban: 0% (0/145) Dalteparin: 1.4% (2/142) HR not estimable P value 0.138	Apixaban: 5.6 % (32/576) Dalteparin: 7.9% (46/579) HR, 0.63; 95% CI, 0.37 - 1.07 P<0.001 for non-inferiority
Major secondary outcomes	**Recurrent VTE** Edoxaban: 7.9% (41/522) Dalteparin: 11.3% (59/524) HR, 0.71; 95% CI, 0.48 - 1.06, p-value 0.09 (Difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2) **Major bleeding** Edoxaban: 6.9% (36/522) Dalteparin: 4.0% (21/524) HR, 1.77; 95% CI, 1.03 – 3.04, p-value 0.04 (Difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6). ---------- **Death from any cause** Edoxaban: 39.5% (206/522) Dalteparin: 36.6% (192/524) HR, 1.12; 95% CI, 0.92 - 1.37 **CRNMB** Edoxaban: 14.6% (76/522) Dalteparin: 11.1% (58/524) HR, 1.38; 95% CI, 0.98 - 1.94	**Major bleeding** Rivaroxaban: 6% (11/203), 95% CI, 3-11 Dalteparin: 4% (6/203), 95% CI, 2 – 8 HR,1.83; 95 % CI,0.68 - 4.96 **CRNMB** Rivaroxaban: 13%, (25/203), 95% CI, 9 – 19 Dalteparin: 4%, (7/203), 95% CI, 2 – 9 HR, 3.76; 95% CI, 1.63 - 8.69	**VTE recurrence** Apixaban: 0.7% (1/145) Dalteparin: 6.3% (9/142) HR 0.099, 95% CI, 0.013-0.78, p value .0281 **CRNMB** Apixaban: 6.2% (9/145) Dalteparin: 4.2% (7/142) **Composite of Major bleeding + CRNMB** Apixaban: 6.2% Dalteparin: 6.3% **Mortality** Apixaban: 16% (23/145) Dalteparin: 11% (15/145))	**Major bleeding** Apixaban: 3.8% (22/576) Dalteparin: 4.0% (23/579) HR, 0.82; 95% CI, 0.4–1.69, p-value 0.6 **Recurrent VTE or major bleeding** Apixaban: 8.9%, (51/576) Dalteparin: 11.4%, (66/579) HR, 0.7; 95% CI, 0.45–1.07 **CRNMB** Apixaban: 9%, (52/576) Dalteparin: 6%, (35/579) HR, 1.42; 95% CI, 0.88–2.30 **Death from any cause** Apixaban: 23.4%, (135/576) Dalteparin: 26.4%, (153/579) HR, 0.82; 95% CI, 0.62–1.09

RCTs: Randomized clinical trials; CRNMB: clinically relevant non-major bleeding; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; VTE: venous thromboembolism; CI: confidence interval; HR: Hazard Ratio.

Appendix Table 7: Outcomes included in the pooled analysis.

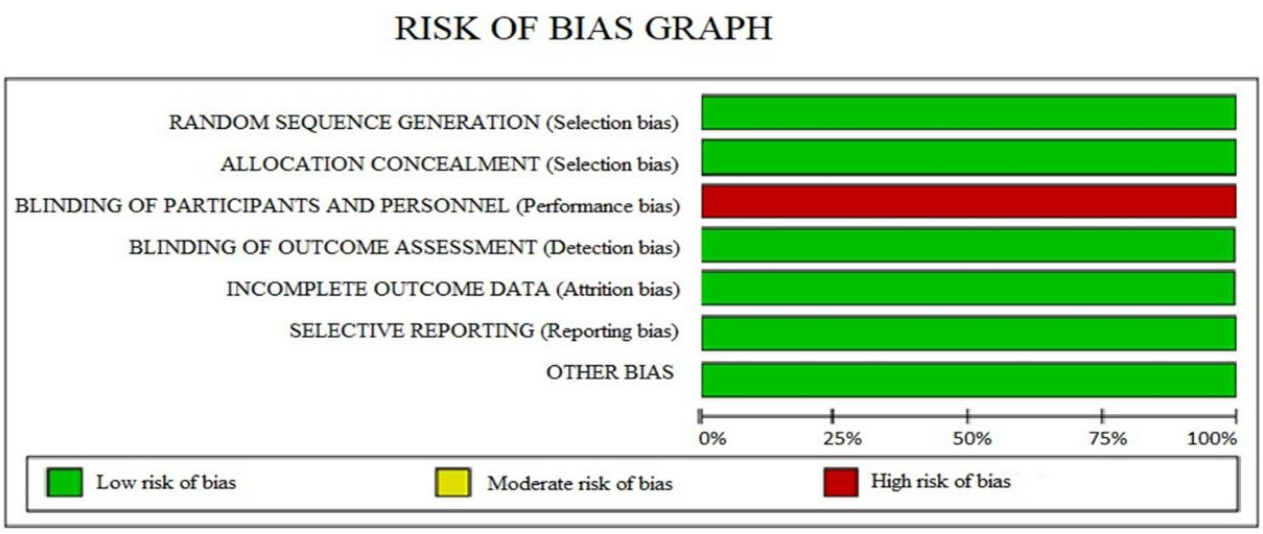
	Edoxaban	**Dalteparin**	**Rivaroxaban**	**Daltaparin**	**Apixaban**	**Daltaparin**	**Apixaban**	**Dalteparin**	**Events/Total**	
									DOAC	**LMWH**
VTE Recurrence	7.9% (41/522)	11.3% (59/524)	4% (8/203)	11% (18/203)	0.7% (1/145)	6.3% (9/142)	5.6 % (32/576)	7.9% (46/579)	82/1446	132/1448
HR	HR, 0.71; 95% CI, 0.48 - 1.06, p-value 0.09		HR,0.43; 95% CI,0.19 - 0.99		HR 0.099, 95% CI (0.013-0.78), p value .0281		HR, 0.63; 95% CI, 0.37 - 1.07 P<0.001		HR 0.54 (0.23-1.28)	
Major bleeding	6.9% (36/522)	4.0% (21/524)	6% (11/203)	**4**% (6/203)	0% (0/145)	1.4% (2/142)	3.8% (22/576)	4.0% (23/579)	69/1446	52/1448
HR	HR, 1.77; 95% CI, 1.03 – 3.04, p-value 0.04		HR,1.83; 95 %CI,0.68 - 4.96		HR not estimable, P value 0.138		HR, 0.82; 95% CI, 0.4– 1.69, p-value 0.6		HR 1.38 (0.45-4.22)	
CRNMB	14.6% (76/522)	11.1% (58/524)	13% (25/203)	4% (7/203)	6.2% (9/145)	4.2% (7/142)	9% (52/576)	6% (35/579)	162/1446	107/1448
HR	HR, 1.38; 95% CI, 0.98 - 1.94		HR, 3.76; 95% CI, 1.63 - 8.69		-		HR, 1.42; 95% CI (0.88–2.30)		HR 1.77 (0.49-6.4)	

CRNMB: clinically relevant non-major bleeding; DOAC: direct oral anticoagulant; LMWH: low-molecular-weight heparin; VTE: venous thromboembolism.; CI: confidence interval; HR: Hazard Ratio.

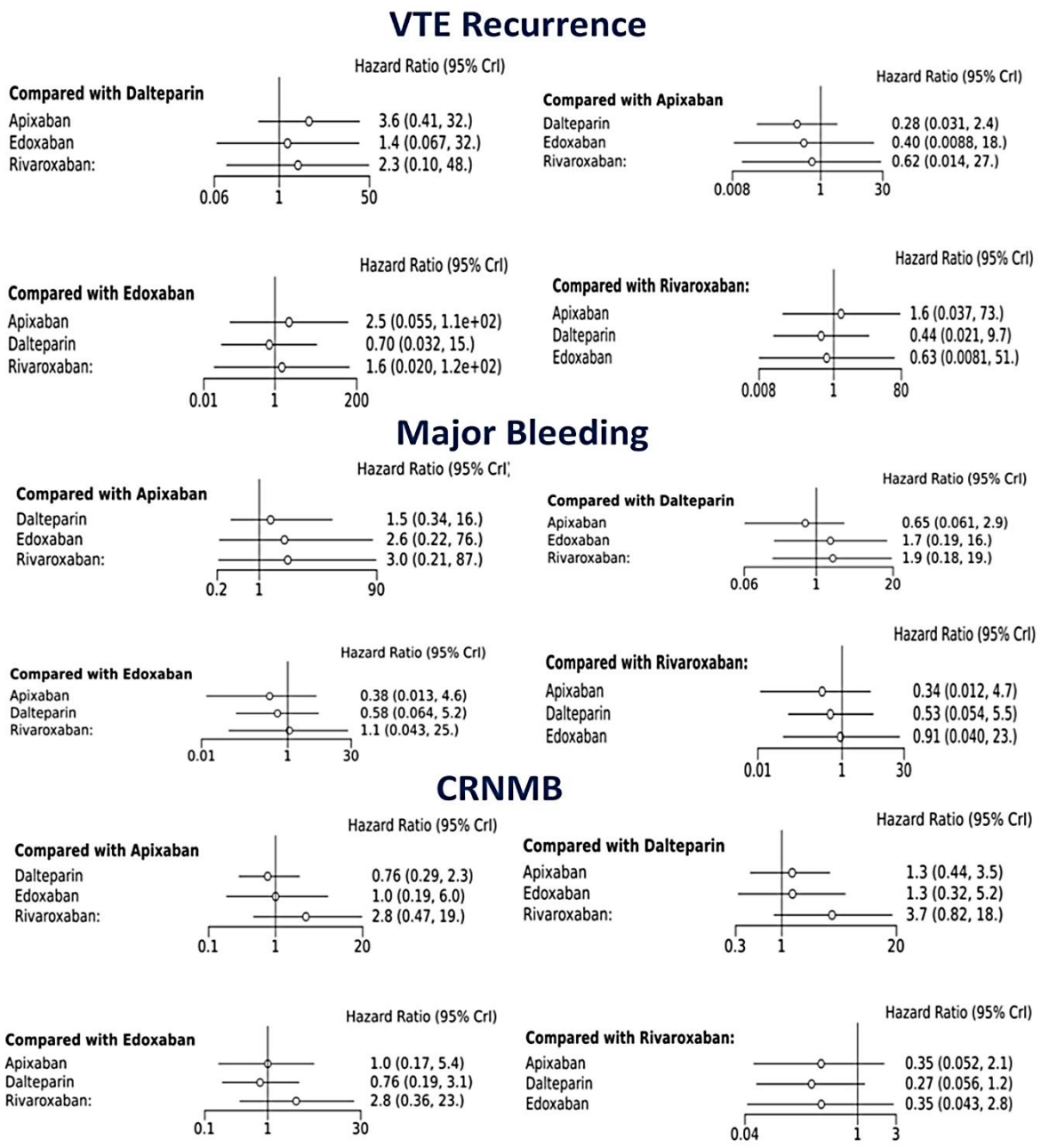
A

Trial	Hokusai-VTE cancer	SELECT-D	ADAM-VTE	Caravaggio
Year	2018	2018	2019	2020
Random sequence generation (selection bias)	Low	Low	Low	Low
Allocation concealment (selection bias)	Low	Low	Low	Low
Blinding of participants, personnel and outcome assessors (blinding)	High	High	High	High
Incomplete outcome date (attrition bias)	High (427/1050 because of death primarily)	High (176/406 from death, adverse event and withdrawal))	High (95//300 death, withdrawal)	High (374/1170 death, withdrawal)
Selective reporting (reporting bias)	unclear	unclear	unclear	unclear
Other bias	unclear	Small sample size	Small sample size	unclear

B



Appendix Figure 1: A) Risk of bias summary table: review authors' judgements about each risk of bias item for each included study and **B)** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Appendix Figure 2: Forest Plots showing the network meta-analysis of the three outcomes and each drug compared amongst each other including hazard ratios (HR) and 95% confidence

VTE Rank probabilities table

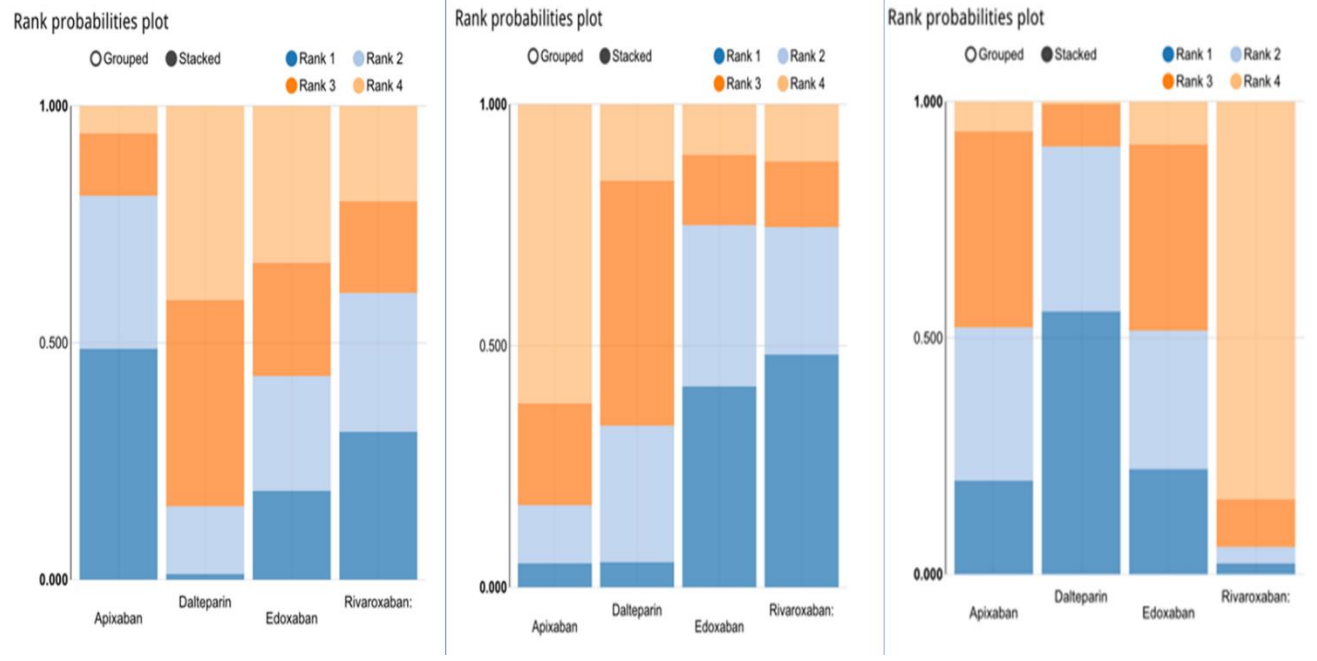
	Rank 1	Rank 2	Rank 3	Rank 4
Apixaban	0.488	0.323	0.132	0.058
Dalteparin	0.012	0.143	0.435	0.410
Edoxaban	0.188	0.242	0.239	0.331
Rivaroxaban:	0.312	0.293	0.193	0.202

Major Bleeding Rank probabilities table

	Rank 1	Rank 2	Rank 3	Rank 4
Apixaban	0.050	0.120	0.211	0.619
Dalteparin	0.052	0.282	0.508	0.158
Edoxaban	0.416	0.334	0.146	0.105
Rivaroxaban:	0.482	0.264	0.136	0.119

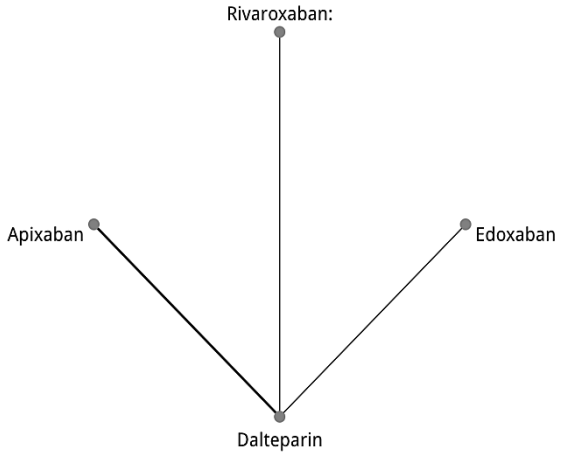
CRNMB Rank probabilities table

	Rank 1	Rank 2	Rank 3	Rank 4
Apixaban	0.198	0.324	0.415	0.063
Dalteparin	0.556	0.349	0.090	0.005
Edoxaban	0.223	0.293	0.394	0.091
Rivaroxaban:	0.023	0.035	0.101	0.841



Appendix Figure 3: Rank probabilities representation of VTE recurrence, Major Bleeding and CRNMB.

Rank probabilities representations for all three outcomes. The probabilities of each intervention to be the best are calculated (1st in the rank 1 is the best and last i.e. 4th in the rank is the worst). Rank probabilities add up to one both within a rank-over-treatments (columns) and within a treatment-over-ranks (rows). Apixaban has 48.8% probability to be the best drug with least vte recurrence (1st in the rank), followed by Rivaroxaban. This same scenario is represented graphically below each table where each drug has a probability to be a part of the 1st, 2nd, 3rd, 4th positions.



Appendix Figure 4: Network of the Bayesian Network Meta-analysis.
Nodes represent the interventions in the network and lines are showing direct available comparisons between pairs of interventions. Thickness of arms corresponds to the number of studies for each comparison.