Supplementary Table 1. Timeline summary of recommendations of ASCO and ISTH guidelines regarding the Khorana score for the use of thromboprophylaxis in ambulatory cancer patients

Year	Studies and guideline/guidance recommendations	Quality of evidence	Strength of recommendation
2007	**ASCO guideline**[51] Routine prophylaxis with an antithrombotic agent is not recommended	*Not reported*	*Not reported*
2008	**Khorana risk score developed**[10] The Khorana risk score for cancer-associated VTE is proposed, which classifies patients at low risk (0 points); intermediate risk (1-2 points); or high risk (≥3 points).		
2012	**Post-hoc analyses in LMWH prophylaxis trials in cancer patients** PROTECHT post-hoc analysis[40], Khorana score ≥3 (n=115): ARR 6.6%, NNT 15 SAVE-ONCO post hoc analysis[52], Khorana score ≥3 (n=550): ARR 4%, NNT 25		
2013	**ASCO guideline**[53]***** Based on limited RCT data, clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy.	*Moderate*	*Weak*
2014	**ISTH guidance**[13]***** We suggest that, in the absence of available clinical trials, cancer patients with solid tumors and a Khorana Score of ≥ 3 starting or receiving systemic therapy should be prescribed outpatient thromboprophylaxis, except for those with contraindications to anticoagulation or a diagnosis of primary brain tumor.	*Based on expert opinions and best available evidence.*	*weaker guidance statement*
2017	**PHACS trial, LMWH vs. observation**[54] Khorana score ≥3 (n=98): ARR 9%, NNT 12 Study remained underpowered due to not meeting pre-defined sample size		
2018	**AVERT & CASSINI trials, DOACs vs. placebo** AVERT[14] (apixaban), Khorana score ≥2 (n=563): ARR 6%, NNT 17 CASSINI[15] (rivaroxaban), Khorana score ≥2 (n=841): ARR 2.6%, NNT 35		
2019	**ASCO guideline**[8] High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding and no drug interactions.	*intermediate to high for apixaban and rivaroxaban, intermediate for LMWH*	*Moderate*
2019	**ISTH guidance**[9] We suggest the use of apixaban or rivaroxaban as primary thromboprophylaxis in ambulatory cancer patients starting chemotherapy with Khorana score ≥2 in patients with no drug-drug interactions and not at high risk for bleeding.	*Based on expert opinions and best available evidence.*	*weaker guidance statement*

Abbreviations: ASCO: American Society of Clinical Oncology; ISTH: international Society on Thrombosis and Haemostasis; VTE: venous thromboembolism; LMWH: low-molecular-weight heparin; RCT: Randomized controlled trial; ARR: absolute risk reduction; NNT: number needed to treat; DOAC: direct oral anticoagulant

*For the sake of the size of the table, two commonly used guidelines and guidance documents are used, instead of all guidelines

Supplementary Table 2. PRISMA Checklist

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.	3/4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	4/5
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.	4, supp Table 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp Table 3
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).	4/5
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
Summary measures	13	State the principal summary measures (e.g., relative risk, difference in means).	5/6
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.	6/7
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).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
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.	8
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.	Table 2
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).	9
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.	Figure 1, 3 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supp Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supp Table 3
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).	12/13
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).	14/15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
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

Supplementary table 3. Search strategy

Medline search 30th April 2020

1	neoplasms[mesh] OR malignan*[tiab] OR neoplasm*[tiab] OR cancer[All Fields] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR "Medical Oncology"[MeSH] OR "Hematologic Neoplasms"[MeSH] **(n=4510391)**
2	"Thrombosis"[MeSH] OR "pulmonary embolism"[MeSH] OR thrombos*[tiab] OR thrombot*[tiab] OR thromboemboli*[tiab] OR phlebothrombosis[All Fields] OR "deep vein thrombosis"[All Fields] OR pulmonary emboli*[All Fields] OR venous thromboembolic event*[All Fields] **(n= 295352)**
3	Anticoagulants[Mesh] OR Factor Xa inhibitors[MeSH Terms] OR dabigatran[MeSH Terms] OR rivaroxaban[MeSH Terms] OR Heparin, Low-Molecular-Weight[MeSH Terms] OR heparin[MeSH Terms] OR Coumarins [MeSH Terms] OR anticoagulants[tiab] OR DOAC*[tiab] OR NOAC*[tiab] OR apixaban*[tiab] OR betrixaban*[tiab] OR edoxaban*[tiab] OR rivaroxaban*[tiab] OR dabigatran*[tiab] OR ximelagatran*[tiab] OR LMWH[tiab] OR low-molecular-weight heparin[tiab] OR dalteparin*[tiab] OR enoxaparin*[tiab] OR nadroparin*[tiab] OR tinzaparin*[tiab] OR parnaparin*[tiab] OR danaparoid*[tiab] OR reviparin*[tiab] OR bemiparin*[tiab] OR semuloparin*[tiab] OR fondaparinux*[tiab] OR vitamin K antag*[tiab] OR warfarin[tiab] OR acenocoumarol[tiab] OR phenprocoumon[tiab] **(n= 179022)**
4	Khorana[All Fields] OR scor*[tiab] OR stratif*[tiab] OR predict*[tiab] **(n= 2440470)**
5	prophyla*[tiab] OR thromboprophyla*[tiab] **(n= 165994)**
6	(randomized controlled trial*.pt. OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh])) **(n= 4121050)**
7	"Infant"[Mesh] OR "child"[MeSH Terms] **(n= 2452047)**

8	1 AND 2 AND 3 AND 4 AND 5 AND 6 NOT 7 **(n=165)**

Embase search 30th April 2020

1	exp neoplasm/ OR malignan*.ti,ab OR neoplasm*'.ti,ab OR cancer* OR cancer*.ti,ab OR carcinoma*.ti,ab OR adenocarcinoma*.ti,ab OR tumour*.ti,ab OR tumor*.ti,ab OR exp Medical Oncology/ OR exp Hematologic Neoplasms/ **(n= 7300811)**
2	exp Thrombosis/ or exp pulmonary embolism/ or thrombos*.ti,ab. or thrombot*.ti,ab. or thromboemboli*.ti,ab. or phlebothrombosis.mp. or deep vein thrombosis.mp. or pulmonary emboli*.ti,ab. or venous thromboembolic event*.mp. **(n= 538777)**
3	exp anticoagulants/ or exp factor xa inhibitors/ or exp dabigatran/ or exp rivaroxaban/ or exp heparin, low-molecular-weight/ or exp heparin/ or exp coumarins/ or anticoagulants.ti,ab or DOAC*.ti,ab. or NOAC*.ti,ab or apixaban*.ti,ab. or betrixaban*.ti,ab. or edoxaban*.ti,ab. or rivaroxaban*.ti,ab. or dabigatran*.ti,ab. or ximelagatran*.ti,ab. or LMWH.ti,ab. or low-molecular-weight heparin.ti,ab. or exp dalteparin/ or exp enoxaparin/ or exp nadroparin/ or exp tinzaparin/ or dalteparin*.ti,ab or enoxaparin*.ti,ab or nadroparin*.ti,ab. or tinzaparin*.ti,ab or parnaparin*.ti,ab. or danaparoid*.ti,ab. or reviparin*.ti,ab or bemiparin.ti,ab or semuloparin.ti,ab or fondaparinux.ti,ab or vitamin k antag*.ti,ab. or warfarin.ti,ab or acenocoumarol.ti,ab or phenprocoumon.ti,ab **(n= 721306)**
4	Khorana.mp. or scor$.tw. or stratif$.tw. or predict$.tw. or exp prediction/ **(n= 3519821)**
5	prophyla*.ti,ab. or thromboprophyla*.ti,ab. **(n= 262593)**
6	randomized controlled trial*.ti,ab. or controlled clinical trial*.ti,ab. or randomized*.ti,ab. OR placebo*.ti,ab. or drug therapy*.ti,ab. or randomly*.ti,ab. or trial*.ti,ab. OR groups*.ti,ab. not (exp animals/ not exp humans/) **(n= 3947072)**
6	exp Infant/ or exp child/ **(n= 2994493)**

7	1 and 2 and 3 and 4 and 5 not 6 **(n= 1076)**
8	Limit 7 to exclude medline journals **(n=99)**

Cochrane CENTRAL trial database 30th April 2020

1	MeSH descriptor: [Neoplasms] explode all trees or MeSH descriptor: [Medical Oncology] explode all trees or MeSH descriptor: [Hematologic Neoplasms] explode all trees or (malignan* OR neoplasm* OR cancer* OR carcinoma* OR adenocarcinoma* OR tumour* OR tumor*):ti,ab,kw **(n= 213373)**
2	MeSH descriptor: [Venous Thrombosis] explode all trees or MeSH descriptor: [Pulmonary Embolism] explode all trees or (thrombos* OR thrombot* OR thromboemboli*):ti,ab,kw or (phlebothrombosis OR "deep vein thrombosis" OR pulmonary emboli* OR venous thromboembolic event*) **(n=27334)**
3	MeSH descriptor: [Anticoagulants] explode all trees or MeSH descriptor: [Factor Xa Inhibitors] explode all trees or MeSH descriptor: [Dabigatran] explode all trees or MeSH descriptor: [Rivaroxaban] explode all trees or MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees or MeSH descriptor: [Heparin] explode all trees or MeSH descriptor: [Coumarins] explode all trees or (anticoagulants OR DOAC* OR NOAC* OR apixaban* OR betrixaban* OR edoxaban* OR rivaroxaban* OR dabigatran* OR ximelagatran* OR LMWH OR low-molecular-weight heparin OR dalteparin* OR enoxaparin* OR nadroparin* OR tinzaparin* OR parnaparin* OR danaparoid* OR reviparin* OR bemiparin* OR semuloparin* OR fondaparinux* OR vitamin K antag* OR warfarin OR acenocoumarol OR phenprocoumon):ti,ab,kw **(n=17596)**
4	(Khorana) or (scor* OR stratif* OR predict*):ti,ab,kw **(n=332293)**
5	(prophyla* OR thromboprophyla*):ti,ab,kw **(35646)**
6	MeSH descriptor: [Infant] explode all trees or MeSH descriptor: [Child] explode all trees **(n= 18552)**
7	1 and 2 and 3 and 4 and 5 not 6 **(n= 91)**

Supplementary Table 4. Summary of findings table of thromboprophylaxis in cancer patients with an intermediate risk, intermediate-to-high risk or high risk of venous thromboembolism according to the Khorana score. Sensitivity analysis restricted to double blind placebo-controlled studies without high risk of bias.

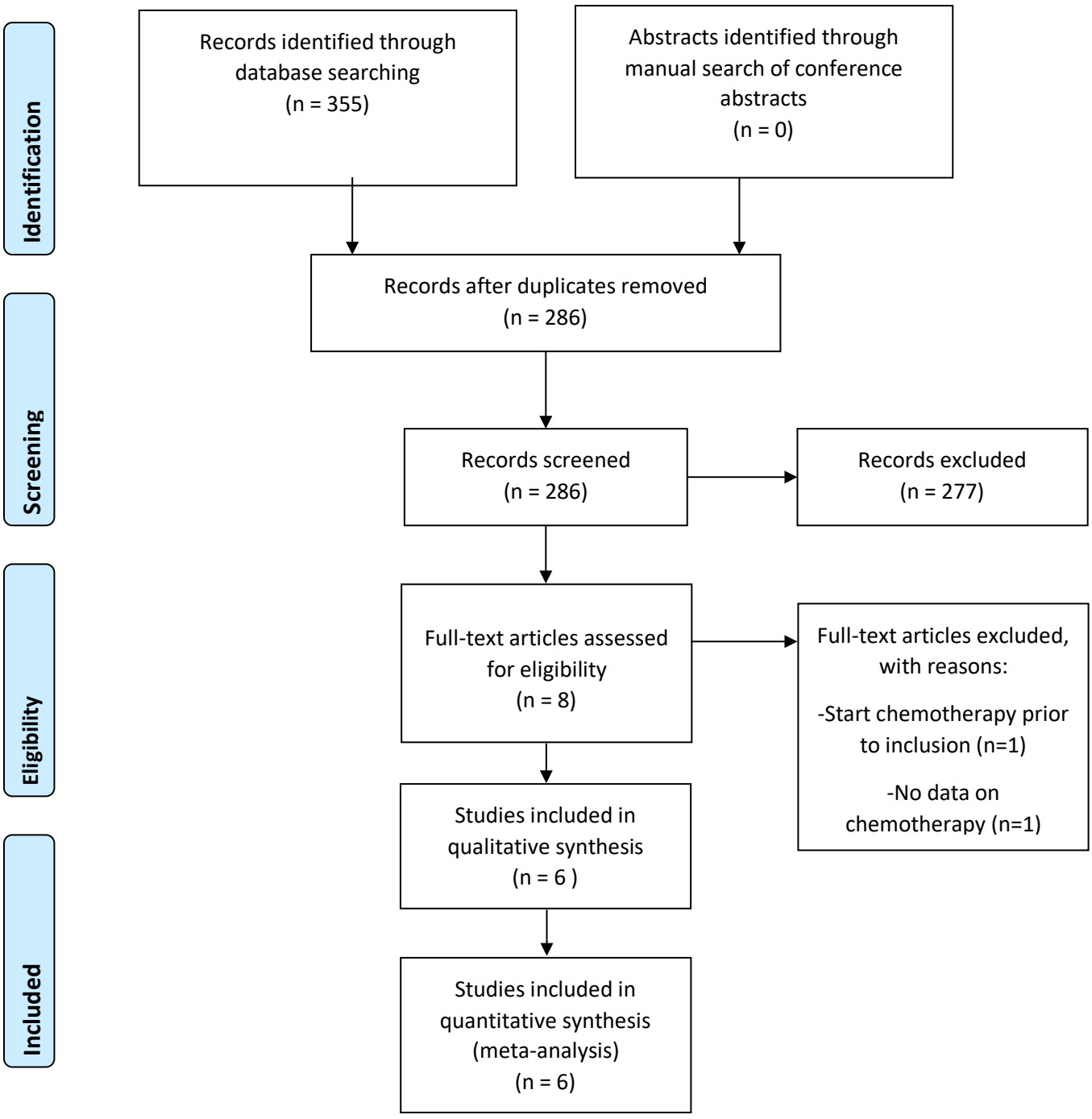
Study outcomes at 6 months	№ of patients (studies)	Certainty of the evidence (GRADE)	Relative risk (95% CI)	Anticipated absolute effects		
				Risk without thromboprophylaxis*	Risk difference with thromboprophylaxis (95% CI)	NNT/NNH
Intermediate-to-high risk of VTE (Khorana score 2 or higher)						
Venous thromboembolism	2,966 (3 RCTs)	⊕⊕⊕⊕ *(HIGH)*	0.52 (0.33 to 0.77)	8.3%	-4.0% (-5.6 to -1.9)	NNT 25 (18 to 53)
Major bleeding	2,923 (3 RCTs)	⊕⊕⊕◯ *(MODERATE)*	1.27 (0.64 to 3.04)	1.2%	0.3% (-0.4 to 2.5)	NNH 334 (NNH 40 to NNT 250)
All-cause mortality	2,966 (3 RCTs)	⊕⊕⊕◯ *(MODERATE)*	0.87 (0.76 to 1.09)	24.7%	-3.2% (-5.9 to 2.2)	NNT 32 (NNT 17 to NNH 46)
Intermediate risk of VTE (Khorana score 2)†						
Venous thromboembolism	1,942 (3 RCTs)	⊕⊕⊕⊕ *(HIGH)*	0.55 (0.24 to 0.96)	7.1%	-3.2% (-5.4 to -0.3)	NNT 32 (19 to 333)
Major bleeding	1,911 (3 RCTs)	⊕⊕⊕◯ *(MODERATE)*	1.27 (0.53 to 3.96)	1.0%	0.3% (-0.5 to 3.0)	NNH 334 (NNH 34 to NNT 200)
High risk of VTE (Khorana score 3 or higher)†						
Venous thromboembolism	1,016 (3 RCTs)	⊕⊕⊕⊕ *(HIGH)*	0.48 (0.28 to 0.82)	11.1%	-5.8% (-8.0 to -2.0)	NNT 18 (13 to 50)
Major bleeding	1,005 (3 RCTs)	⊕⊕⊕◯ *(MODERATE)*	1.13 (0.43 to 3.66)	1.6%	0.2% (-0.9 to 4.3)	NNH 500 (NNH 24 to NNT 112)

*__The risk of VTE in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). The assumed risk is derived from a systematic review on VTE incidences in different Khorana scores by Mulder *et al.* Haematologica. 2019; 104(6).

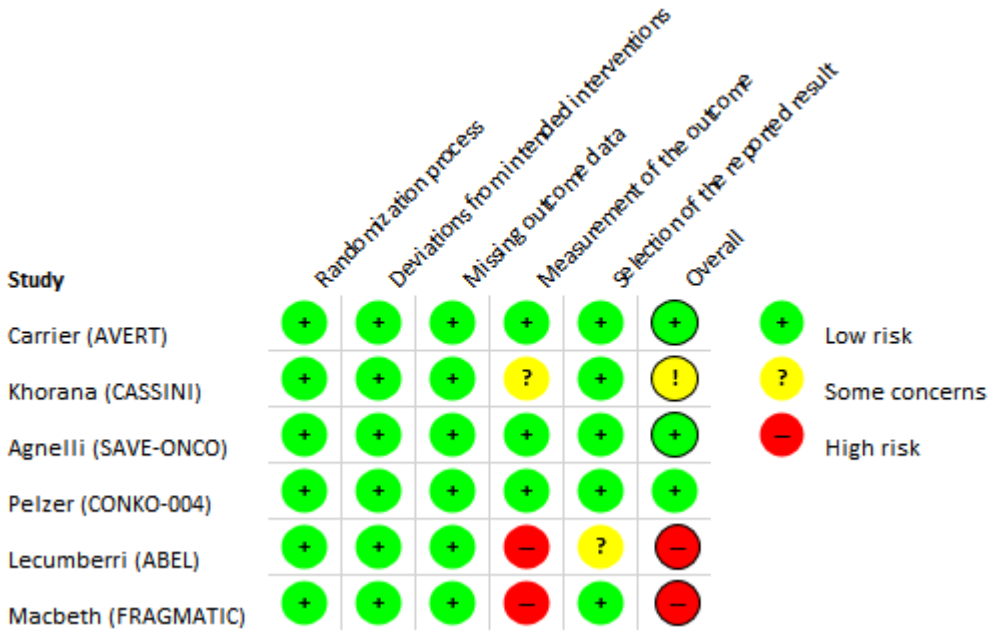
†All-cause mortality was not calculated for the groups with Khorana score 2 and 3 separately since 2 out of 3 trials did not report these data.

Abbreviations: CI: Confidence interval; **NNH:** number needed to harm; **NNT:** number needed to treat; **RCT:** Randomized controlled trial; **RR:** Risk ratio; **VTE:** venous thromboembolism

Supplementary Figure 1. PRISMA Flow Chart of study selection



Supplementary Figure 2. Risk of bias assessment



Studies: Carrier[14], Khorana[15], Agnelli[28], Pelzer[29], Lecumberri[30], Macbeth[31]

Supplementary Figure 3. Funnel plot of included studies