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Efficacy and safety of primary thromboprophylaxis for the prevention of venous thromboembolism in patients with cancer and a central venous catheter: A systematic review and meta-analysis

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ABSTRACT

Background: Venous thromboembolism (VTE) is a leading cause of mortality in patients with cancer and is associated with significant morbidity and healthcare expenditure. The risk of VTE is increased following the insertion of a central venous catheter (CVC) for chemotherapy delivery and supportive care. The risks and benefits of primary thromboprophylaxis in patients with cancer and CVC are unclear.

Objective: We sought to assess the rates of VTE and bleeding complications and to determine the efficacy and safety of primary thromboprophylaxis in adult patients with cancer and a CVC.

Methods: A systematic search of MEDLINE, EMBASE, and all EBM was conducted. Randomized controlled trials (RCTs) of adult patients with cancer and a CVC receiving primary thromboprophylaxis compared to observation/placebo were included. The primary efficacy and safety outcomes were total VTE and major bleeding episodes, respectively.

Results: A total of 12 RCTs (3545 patients) were included in the analysis. The total rates of VTE were significantly lower in patients receiving thromboprophylaxis compared to those not receiving primary prevention (7.6% *vs.* 13%; Odds Ratio (OR) 0.51, 95% CI 0.32–0.82, $p < 0.01$). The rates of major bleeding complications were not higher in patients receiving thromboprophylaxis (0.9% *vs.* 0.6%; OR 1.12, 95% CI 0.29–4.40, $p = 0.87$).

Conclusions: Primary thromboprophylaxis significantly reduced the risk of VTE without increasing the risk of major bleeding complications in patients with cancer and CVC. Future studies are needed to confirm these findings.

1. Introduction

Venous thromboembolism (VTE), commonly defined as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common complication in patients with cancer [1]. The occurrence of VTE is a leading cause of mortality in this patient population and is also associated with significant morbidity and healthcare expenditure [2,3]. The risk of VTE is increased in cancer patients that received systemic therapy. The placement of a central venous catheter (CVC) for chemotherapy delivery may increase the risk further by causing vessel endothelial injury and tissue factor exposure leading to a localized or systemic hypercoagulable state [4].

Primary thromboprophylaxis has been shown to be effective and safe in ambulatory patients with cancer initiating systemic therapy [5]. Randomized controlled trials (RCTs) have demonstrated that primary thromboprophylaxis with direct oral anticoagulants (DOACs) or low-molecular weight heparins (LMWHs) decreases the rate of VTE without significantly increasing the risk of major bleeding complications [6,7]. The American Society of Hematology currently suggests considering pharmacological primary thromboprophylaxis in ambulatory patients with cancer at high risk of VTE [8]. The current body of evidence, however, is limited in terms of recommendations specifically for

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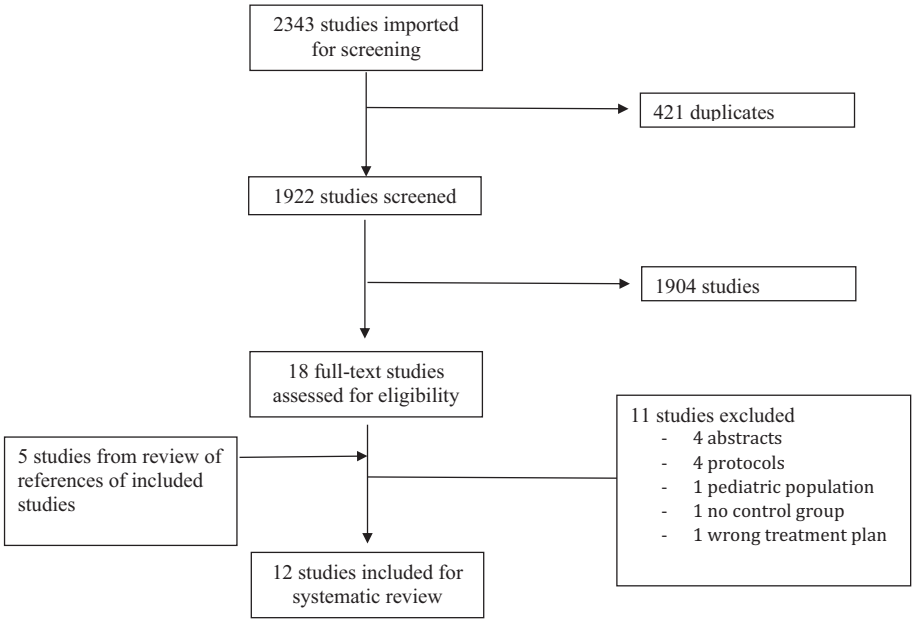

Fig. 1. PRISMA flow.

patients with cancer and CVCs. Patients with CVCs only accounted for a small subgroup in the most recent trials assessing the use of primary thromboprophylaxis in ambulatory patients with cancer receiving systemic therapy [6,7]. As such, there is a need for further investigation in this specific patient population. In this systematic review and meta-analysis, we sought to assess the current state of knowledge on the safety and efficacy of primary thromboprophylaxis in adult patients with cancer and a CVC.

2. Methods

The systematic review methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. We registered our protocol with the Open Science Framework (https://osf.io/hb5g6).

2.1. Data sources and searches

We conducted a comprehensive search of MEDLINE, EMBASE, and all Evidence Based Medicine from inception until December 30, 2020 using the OVID interface. The search strategy used a combination of MeSH and clinical content terms (See template in on-line appendix eFig. 1).

2.2. Study selection

We included all RCTs that compared pharmacological primary thromboprophylaxis to observation or placebo in cancer patients (≥16 years old) who had a CVC and reported on VTE outcomes. Exclusion criteria were observational studies, cross sectional studies, case reports, studies done on pediatric patients or patients with no active cancer, and those that did not report the VTE outcomes.

Studies were screened using the Covidence software for systematic reviews (Melbourne, Australia). Titles were directly imported into Covidence from the search databases and duplicates were removed. Two reviewers (A. L. and W. B.) independently screened the titles and abstracts of all identified citations. The same reviewers subsequently independently assessed full texts of the selected articles following screening. All disagreements were resolved by joint discussion.

Data Extraction, Outcome Measures, and Quality Assessment.

Two reviewers (A. L. and W. B.) independently extracted the data using the same format; findings were checked for agreement and the proper corrections were made. Extracted information included intervention and control characteristics (anticoagulation type, duration, and follow-up period), baseline characteristics (age, sex, cancer type, location, and staging), chemotherapy, CVC characteristics (type, location), and outcome measures. The primary efficacy outcome measure was VTE. VTE was defined as objectively confirmed, incidental or symptomatic catheter-related thrombosis (CRT), distal or proximal limb deep vein thrombosis (DVT), pulmonary embolism (PE) (segmental vessel or more proximal), other VTE (unusual site thrombosis). The primary safety outcome measure was major bleeding episodes. Major and clinically relevant non-major bleeding (CRNMB) were defined as per the International Society on Thrombosis and Haemostasis or as per the individual study definition [10,11]. Secondary outcomes included CRT, minor bleeding and overall mortality. Minor bleeding was defined as bleeding events not meeting the definitions for major and CRNMB events.

Two reviewers (A. L. and W. B.) independently evaluated the risk of bias using the Cochrane Risk of Bias Tool for RCTs. Seven domains were assessed, and each was assigned high risk, low risk, or unclear risk. Unclear risk was assigned when the information provided in the study transcript was insufficient for the reviewers to be absolutely certain on risk.

2.3. Data synthesis and analysis

The primary and secondary outcomes were reported, and pooled rates were estimated using aggregate participant data. Odds Ratio (OR) and 95% confidence interval (CI) were estimated using the Mantel-Haenszel random effects model (DerSimonian-Laird analysis) [12]. Subgroup analyses were done based on anticoagulants (DOAC, vitamin K antagonist [VKA], or LMWH). The I^2 statistic was used to assess for heterogeneity between studies. An I^2 below 30% was determined as non-significant heterogeneity, an I^2 between 30 and 70% as moderate heterogeneity and an I^2 greater than 70% as considerable heterogeneity. The meta-analysis was performed using Review Manager 5.4.1 (Copenhagen).

Table 1
Baseline characteristics of the included studies.

Study	Anticoagulation type	Anticoagulation dose (daily)	Anticoagulation duration (days)	Control type	Patients N	Age (mean)	Male (%)	Cancer type (%)[&]					CVC type (%)	
								Breast	Lung	Pancreatic	Hematological	Genitourinary	PICC	Port-a-cath
Bern et al. 2006	Warfarin	1 mg	90	Observation	121	58.3	71 (58.5)	14 (11.6)	11 (9.1)	4 (3.3)	NR	NR	NR	121 (100)
Carrier et al. 2019	Apixaban	2.5 mg (twice daily) PO	180	Placebo	215	58.9	79 (36.4)	NR	16 (7.4)	45 (20.9)	43 (20)	2 (0.9)	NR	NR
Couban et al. 2005	Warfarin	1 mg PO	90	Placebo	255	52[#]	152 (60)	10 (3.9)	5 (2.0)	NR	168 (65.9)	2 (0.8)	67 (26)	46 (18)
Heaton et al. 2002	Warfarin	1 mg	90	Observation	102	43	60 (59)	NR	NR	NR	NR	NR	10 (9.8)	NR
Ikesaka et al. 2020	Rivaroxaban	10 mg PO	90	Observation	105	60.8	33 (31)	19 (18)	NR	10 (9.5)	NR	NR	82 (78)	23 (22)
Karthaus et al. 2006	Dalteparin	5000 IU SC	112	Saline	439	55.9	182 (41)	NR	NR	NR	43 (9.8)	NR	NR	NR
Khorana et al. 2019	Rivaroxaban	10 mg PO	180	Placebo	424	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lavau-Denes et al. 2013	Dalteparin[$]	recommended dose for prevention SC	90	-	273	61	162 (59)	27 (10)	29 (11)	12 (4.4)	NR	21 (7.7)	173 (63)	0
	Warfarin[$]	1 mg PO	90	-	269	60	165 (61)	32 (12)	32 (12)	14 (5.2)	NR	18 (6.7)	169 (63)	0
Monreal et al. 1996	Fragmin	2500 IU	90	Observation	33	55	17 (52.4)	6 (18.2)	NR	NR	NR	NR	NR	33 (100)
Niers et al. 2007	Nadroparin	2850 IU SC	21	placebo	113	57.5	62 (55)	NR	NR	NR	113 (100)	NR	NR	NR
Verso et al. 2005	Enoxaparin	40 mg SC	42	Undefined	385	59.3	177 (46)	68 (18)	7 (1.8)	9 (2.3)	33 (8.6)	28 (7.3)	341 (89)	NR
Young et al. 2009	Warfarin	1 mg or dose adjusted (INR 1.5–2.0) PO	NR	-	812	60.5	499 (61.4)	64	NR	NR	NR	NR	NR	NR

CVC: central venous catheter; NR: not reported; PICC: peripherally inserted central catheter; PO: *Per os*; SC: subcutaneous.
#Reported as median.
$Use the same control population.
&Cancer type was recorded in the table only if 4 or more studies reported that type of cancer.
-Control not specified.

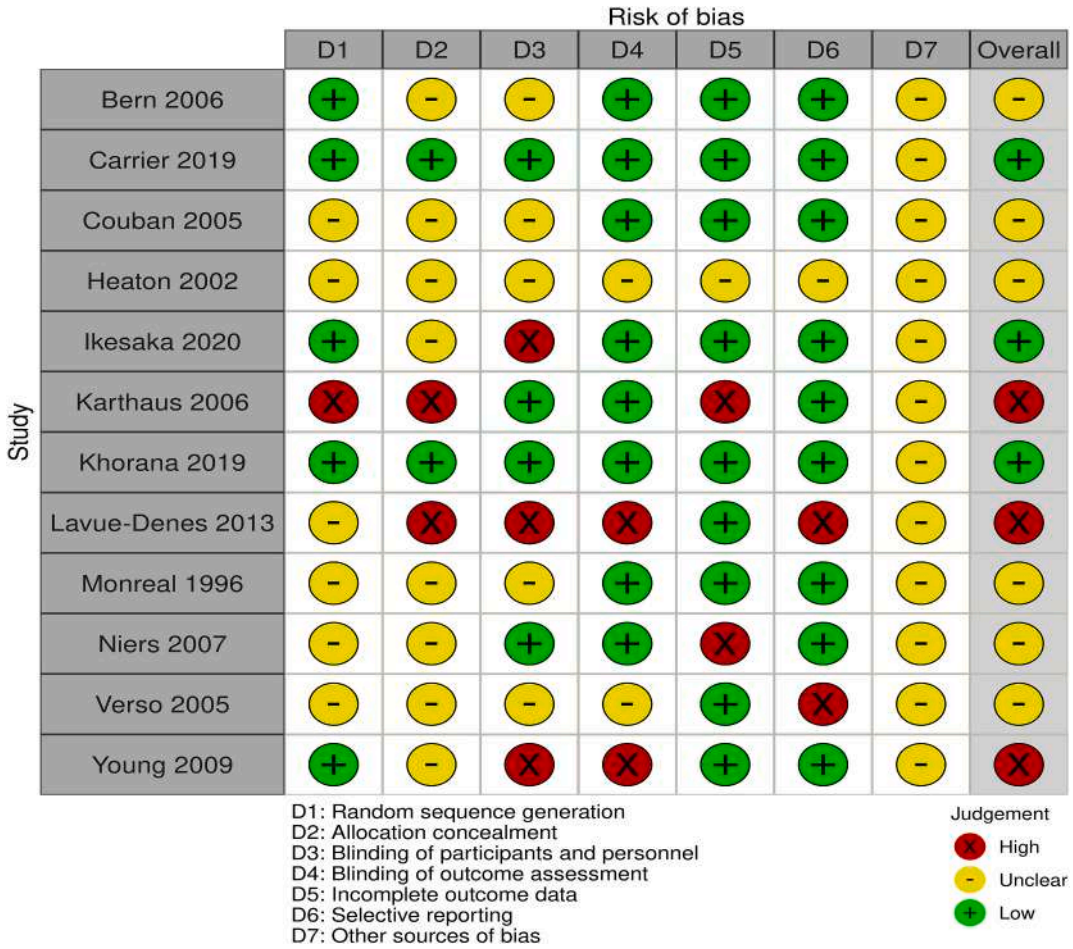

Fig. 2. Quality assessment.

3. Results

Overall, 1922 article records were screened and [6,7,11,13–22] RCTs were eventually included in the systematic review (see Fig. 1). A total of 3545 patients with cancer and a CVC were included. Baseline characteristics of the included trials are depicted in Table 1. Of the studies included, three used a DOAC, five used a VKA, and five used LMWH (of these, one study used both VKA and LMWH). Patient populations had an average age of approximately 60 years old for all studies and there were no notable differences in the proportion of each sex included. The most common types of cancers were hematological, lung, and breast. Of the studies that reported CVC type, a PICC line was used most often.

Most included RCTs were classified as low risk or unclear risk (insufficient information provided to ascertain low risk) in all categories (see Fig. 2). Six studies were open-label [13,15,16,18,19,22], although the outcomes were adjudicated by an independent adjudication committee blinded to treatment. A total of three studies were found to be at a high-risk to bias (Fig. 2).

The primary and secondary outcomes are reported in Table 2. The total rates of VTE were significantly lower in patients receiving primary thromboprophylaxis compared to those not receiving primary prevention (7.6% *vs.* 13%; OR 0.51, 95% CI 0.32–0.82, $p < 0.01$, $I^2 = 52\%$, Fig. 3). The rates of total CRT were also lower in patients receiving thromboprophylaxis compared to those not receiving primary prevention (6.3% *vs.* 9.1%; OR 0.67, 95% CI 0.45–0.99, $p = 0.04$, $I^2 = 45\%$, Fig. 4). Out of the eight studies reporting bleeding complications [6,14,17,19–21,23,24], three reported no major bleeding episodes [19,25,26]. There was no significant differences in the rates of major bleeding (0.9% *vs.* 0.7%; OR 1.12, 95% CI 0.29–4.40, $p = 0.87$, $I^2 = 32\%$. Fig. 5) or CRNMB bleeding events (8.9% *vs.* 5.4%; OR 1.28, 95% CI 0.81–2.04, $p = 0.29$, $I^2 = 0\%$, Fig. 6). Patients receiving primary thromboprophylaxis did however, have a higher rate of minor bleeding episodes (4.6% *vs.* 1.6%; OR 2.53, 95% CI 1.12–5.74, $p = 0.03$, $I^2 = 24\%$, Fig. 7). Nine studies reported overall mortality. There was no difference in overall mortality between the two treatment groups (5.3% *vs.* 6.1%; OR 0.97, 95% CI 0.65–1.44, $p = 0.88$, $I^2 = 0$, Fig. 8). Funnel plots for each outcome show no evidence of publication bias (data not shown). Subgroup analysis based on the type of anticoagulants (VKA, LMWH or DOAC) did not significantly alter the results for the primary and secondary outcome measures (data not shown).

4. Discussion

Our systematic review and meta-analysis suggest that primary thromboprophylaxis is associated with a favorable risk-benefit ratio in patients with cancer and CVC. Primary thromboprophylaxis significantly reduced the risk of VTE and CRT without increasing the risk of major bleeding complications.

Our results are consistent with previous systematic reviews assessing the efficacy and safety of primary thromboprophylaxis in this patient population. A previously published meta-analysis reported a significant reduction in symptomatic VTE and CRT for patients receiving primary thromboprophylaxis with risk ratios (RR) of 0.61 (95% CI: 0.42 to 0.88) and 0.43 (95% CI: 0.22 to 0.81), respectively [23,24]. Our systematic review also reported a lower rate of VTE and CRT in patients receiving thromboprophylaxis with ORs of 0.51 (95% CI 0.32–0.82) and 0.67 (95% CI 0.45–0.99), respectively. Overall, our meta-analysis adds to the

Table 2
Primary and secondary outcomes measures.

Study	Follow Up Period (days)	Study Arm	DVT (%)	PE (%)	Symptomatic CRT (%)	Asymptomatic CRT (%)	Total CRT (%)	VTE (%)	Major Bleeding (%)	CRNMB (%)	Minor Bleeding (%)	Mortality (%)
Bern et al. 2006	90	Control	NR	NR	NR	NR	15 (24.6)	NR	NR	NR	NR	14 (30)
		Intervention	NR	NR	4	NR	4 (6.7)	NR	NR	NR	NR	12 (20)
Carrier et al. 2019	140	Control	11 (12)	6 (6.7)	NR	NR	NR	17 (19)	2 (2.2)	6 (6.7)	NR	2 (2.2)
		Intervention	4 (3.2)	2 (1.6)	NR	NR	NR	6 (4.8)	2 (1.6)	13 (10)	NR	1 (0.8)
Couban et al. 2005	90	Control	3 (2.4)	NR	5 (0.04)	NR	5 (0.04)	NR	3 (2.4)	NR	3 (2.4)	21 (17)
		Intervention	1 (0.7)	NR	6 (4.6)	NR	6 (4.6)	NR	0	NR	5 (3.8)	22 (17)
Heaton et al. 2002	90	Control	NR	NR	NR	NR	5 (9.8)	NR	NR	NR	NR	NR
		Intervention	NR	NR	NR	NR	8 (15.7)	NR	NR	NR	NR	NR
Ikesaka et al. 2020	90	Control	NR	1 (1.9)	NR	NR	2 (3.8)	5 (9.4)	0	2 (3.8)	NR	NR
		Intervention	NR	0	NR	NR	2 (3.8)	3 (5.8)	1	2 (3.8)	NR	NR
Karthaus et al. 2006	112	Control	1 (0.7)	0	5 (3.4)	6 (4.1)	11 (7.6)	12 (8.3)	1 (0.7)	20 (14)	NR	1 (0.7)
		Intervention	3 (1.0)	1 (0.3)	10 (3.4)	10 (3.4)	20 (6.8)	24 (8.2)	1 (0.3)	49 (16.7)	NR	4 (1.4)
Khorana et al. 2019	140	Control	NR	NR	NR	NR	5 (2.4)	NR	NR	NR	NR	NR
		Intervention	NR	NR	NR	NR	1 (0.5)	NR	NR	NR	NR	NR
Lavau-Denes et al. 2013[$]	90	Control	7 (5.2)	1 (0.7)	9 (6.7)	NR	20 (15)	27 (0.2)	NR	NR	NR	8 (5.9)
		Intervention (LMWH)	1 (0.7)	0	3 (2.2)	NR	14 (10)	15 (11)	NR	NR	NR	7 (5.1)
		Control	7 (5.2)	1 (0.7)	9 (6.7)	NR	20 (15)	27 (0.2)	NR	NR	NR	8 (5.9)
		Intervention (Warfarin)	1 (0.7)	0	0	NR	8 (6.0)	9 (6.7)	NR	NR	NR	8 (6.0)
Monreal et al. 1996	90	Control	NR	NR	NR	NR	8 (53.3)	NR	0	0	NR	2 (11.8)
		Intervention	NR	NR	NR	NR	1 (5.9)	NR	0	0	NR	1 (5.9)
Niers et al. 2007	NR	Control	NR	NR	1 (1.8)	3 (5.3)	4 (7.0)	NR	0	2 (3.5)	2 (3.5)	NR
		Intervention	NR	NR	0	7 (13)	7 (13)	NR	0	2 (3.6)	5 (8.9)	NR
Verso et al. 2005	90	Control	NR	NR	6 (3.1)	22 (11)	28 (14)	NR	0	0	7 (3.6)	2 (1.0)
		Intervention	NR	NR	2 (1.0)	20 (10)	22 (12)	NR	0	0	12 (6.3)	5 (2.6)
Young et al. 2009	NR	Control	NR	NR	NR	NR	24 (5.9)	38 (9.4)	1 (0.2)	NR	1 (0.2)	NR
		Intervention	NR	NR	NR	NR	24 (5.9)	30 (7.3)	3 (0.7)	NR	14 (3.4)	NR

DVT: deep vein thrombosis; PE: pulmonary embolism; CRT: catheter-related thrombosis; VTE: venous thromboembolism; CRNMB: clinically relevant non-major bleeding; NR: not reported.
$Use the same control population.

literature by including additional studies, and more specifically, studies assessing DOACs in patients with cancer and CVC. Our current review also provides a more precise estimate of major bleeding and other bleeding complications, which will be used by clinicians to counsel patients on the safety of primary thromboprophylaxis in this patient population.

The rates of major bleeding episodes were not higher in patients receiving primary thromboprophylaxis. This is important and reassuring for clinicians as studies evaluating the management of acute cancer-associated thrombosis have previously reported a higher rate of major bleeding complications among patients receiving DOACs [25,26]. Although the benefit of primary thromboprophylaxis in ambulatory patients with cancer initiating systemic therapy has now been established [8], its role specifically in patients with CVC has been controversial. Clinical practice guidelines are currently not recommending routine use of primary thromboprophylaxis in this patient population [8,27]. These guideline recommendations are based on unclear risk benefit ratio of primary thromboprophylaxis for patients with cancer and CVC. Our study will inform clinicians and clinical practice guideline experts and help inform the decision-making process to tailor primary thromboprophylaxis for these patients.

There are some limitations to our systematic review that should be noted. The pooled meta-analysis should be interpreted carefully because some pooled estimates reported moderate levels of statistical heterogeneity. This is most likely due to the RCTs using different drugs (DOACs, VKAs, LMWHs) and different lengths of the intervention (between 21

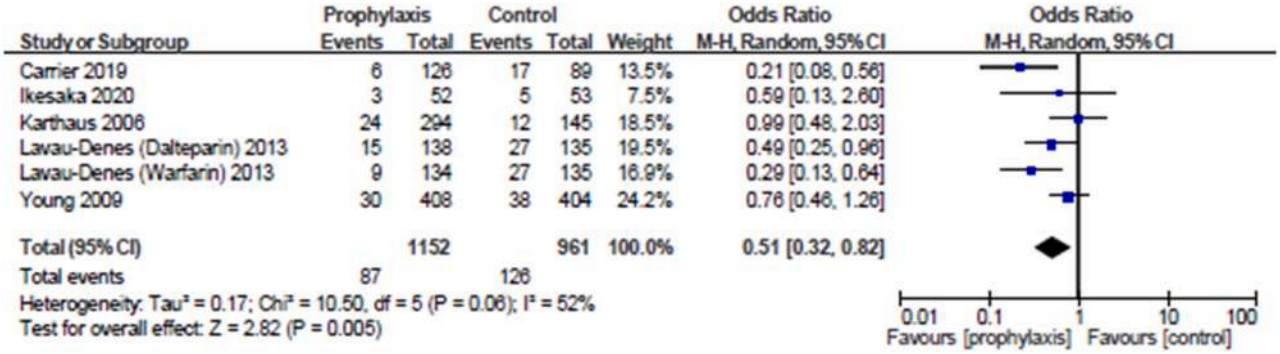

Fig. 3. Forest plot of meta-analysis for total venous thromboembolism outcome.

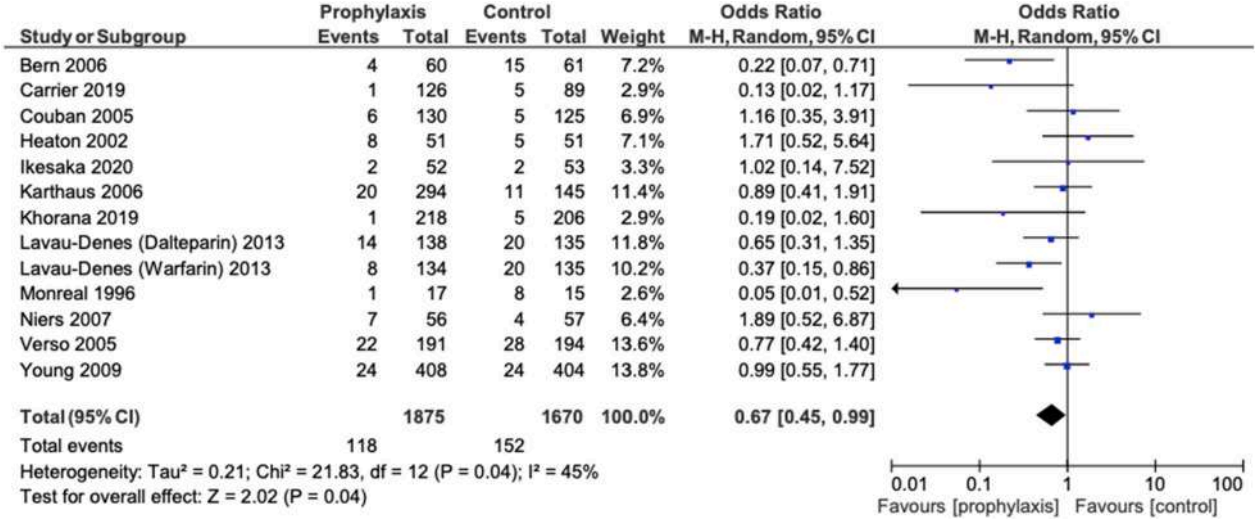

Fig. 4. Forest plot of meta-analysis for catheter-related thrombosis outcome.

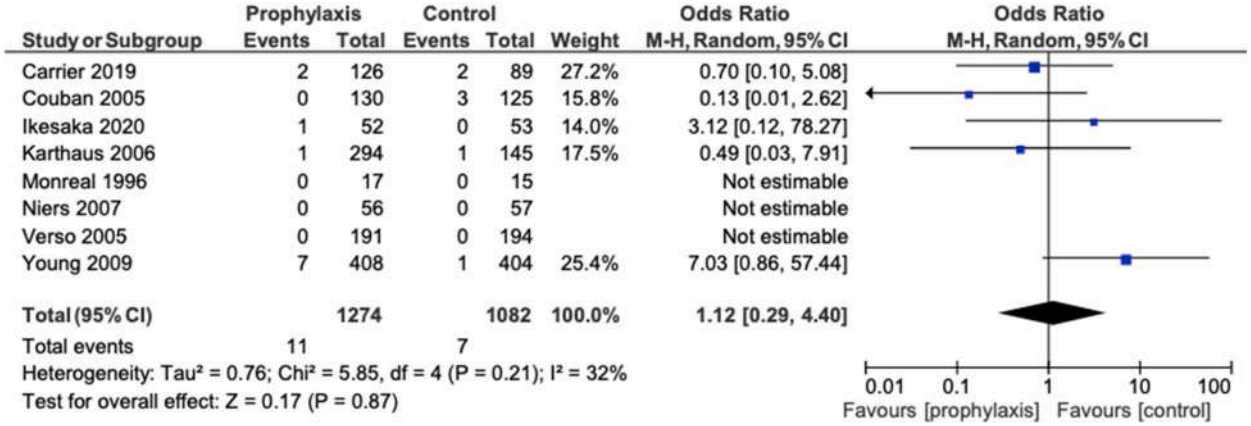

Fig. 5. Forest plot of meta-analysis for major bleeding events.

and 180 days). The studies have also included populations with different cancer types and CVC types. Secondly, CRT included a combination of symptomatic and screening detected events. Additionally, the definitions of total bleeding events were different between studies. Studies reported any combination of major bleeding, CRNMB, and minor bleeding which introduced heterogeneity into this statistic. Another important limitation is that we included two studies using data from the subgroup of patients with CVC in the main studies not designed to particularly assess patients with cancer and a CVC [6,8]. Lastly, an overarching limitation of this systematic review and meta-analysis is the lack of standardization in outcome definitions from one study to the other. Future studies should aim to report all types of thrombosis and safety outcomes based on standardized definitions and to include a homogenous patient population.

In conclusion, primary thromboprophylaxis significantly reduced the risk of VTE and CRT without increasing the risk of major bleeding complications in patients with cancer and CVC. Future studies are desperately needed to confirm these findings.

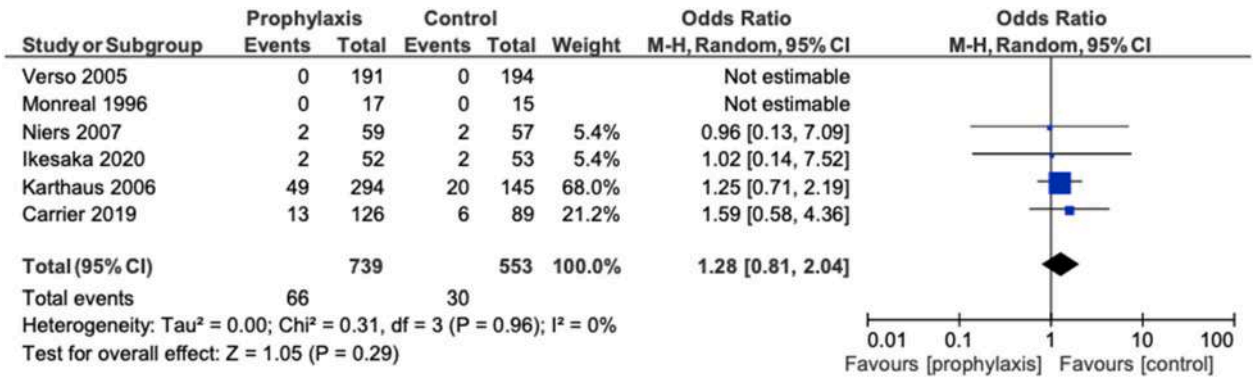

Fig. 6. Forest plot of meta-analysis for clinically relevant non-major bleeding events.

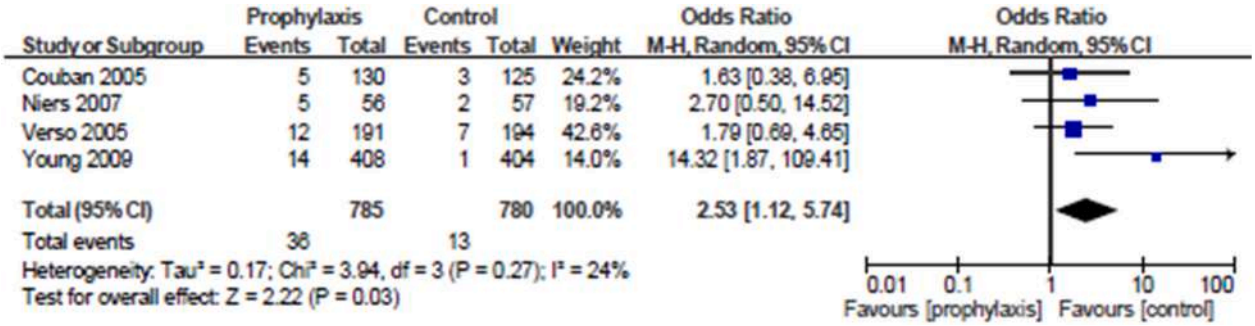

Fig. 7. Forest plot of meta-analysis for minor bleeding events.

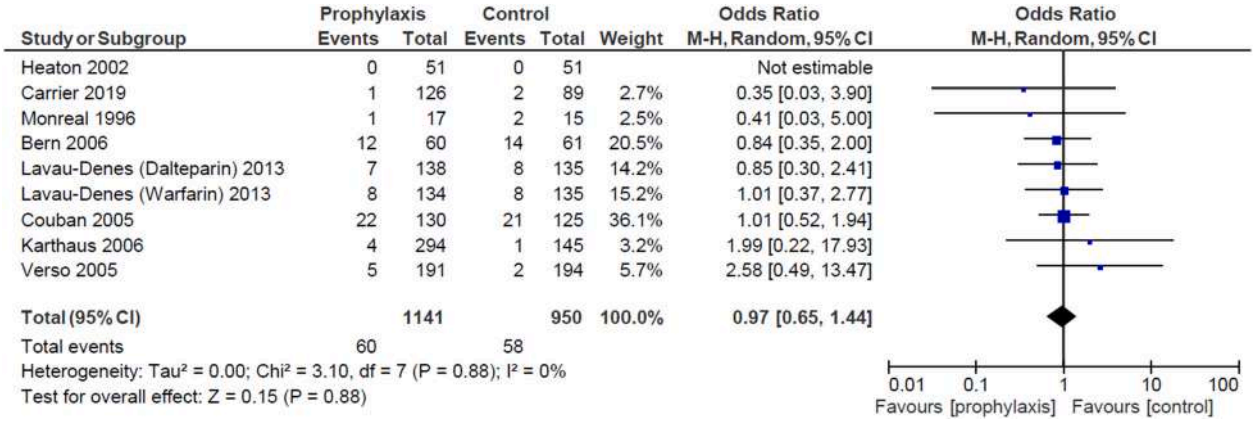

Fig. 8. Forest plot of meta-analysis for mortality.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.10.012.

CRediT authorship contribution statement

A Li and W Brandt contributed equally to study design, data extraction, statistical analysis, and wrote the manuscript. C Brown provided critical revision of the manuscript.

TF Wang, R Ikesaka, A Delluc, and P Wells interpreted data and provided critical revision of the manuscript. M Carrier was responsible for the study conception and planning and provided key revisions to the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

M Carrier has received research funding from BMS, Pfizer, and Leo Pharma. He has also received honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma. T-F. Wang reports advisory board honoraria from Servier and grants from Leo Pharma. R Ikesaka reports advisory board honoraria from Leo Pharma and Sanofi. P Wells has received research funding from.

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