TECHNOLOGY REVIEW (MINI-HTA)

PROPHYLACTIC ANTICOAGULATION IN AMBULATORY CANCER PATIENTS

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in cancer patients. Cancer patients have a four- to seven-fold increased risk of VTE compared with the general population or people without cancer; about 5% to 10% of them develop a VTE within the first year of cancer diagnosis. The risk of VTE in cancer patients is dependent on the type and stage of cancer, cancer treatment modalities and patient-related factors. The incidence of VTE is often highest in the first few months after cancer diagnosis and decreases thereafter. Cancer-associated thrombosis is the second leading cause of death in ambulatory patients receiving chemotherapy. Cancer patients with VTE have a ten-fold higher risk of death than patients with VTE alone and a four-fold higher risk of death than cancer patients without VTE. Other than higher mortality rate, VTE is associated with significant inpatient and outpatient resource utilisation, and increased all-cause healthcare costs among ambulatory cancer patients. Therefore, prophylactic anticoagulation is essential for the management of ambulatory cancer patients as it may reduce healthcare utilisation and costs in this population. Despite studies indicating the safety and efficacy of low-molecular-weight heparins (LMWH) in ambulatory cancer patients receiving chemotherapy, routine pharmacological thromboprophylaxis in this population was not recommended due to relatively low benefit-to-risk ratio and burden of daily subcutaneous injections. Direct oral anticoagulants (DOAC) such as apixaban and rivaroxaban have emerged as an alternative to LMWH due to their ease of administration and because they do not require laboratory monitoring unlike warfarin. Recent studies have suggested that DOAC may be useful for primary thromboprophylaxis in ambulatory cancer patients with validated risk assessment scores.

This technology review was requested by a clinical oncologist to review the evidence on the efficacy, safety and cost-effectiveness of prophylactic anticoagulation in ambulatory cancer patients.

Objective/ aim

To assess the efficacy, safety and cost-effectiveness of prophylactic anticoagulation in ambulatory cancer patients.

Results

A total of 981 records were identified through Ovid and PubMed interfaces, and 16 were identified from other sources. A total of eight systematic reviews and two cost-effectiveness analyses were included in this review.

a) Efficacy/Effectiveness

Good level of evidence was retrieved for the evaluation of efficacy in terms of VTE events and mortality. A total of eight systematic reviews were included, three of which were Cochrane reviews. Prophylactic anticoagulation with LWMH or DOAC were associated with significant reduction in VTE events when given to ambulatory cancer patients compared with placebo or no thromboprophylaxis. Similar benefit was observed in specific populations such as lung and pancreatic cancer patients when given prophylactic anticoagulation with LMWH. Two studies showed greater risk reduction among ambulatory cancer patients with high risk

for VTE (Khorana score ≥3), suggesting that a Khorana score risk-stratified strategy may be considered in this context. However, prophylactic anticoagulation with warfarin, UFH, LMWH or DOAC, appeared to have no effect on mortality in ambulatory cancer patients compared with placebo or no thromboprophylaxis.

b) Safety

Good level of evidence was retrieved for the evaluation of safety in terms of major bleeding, clinically relevant non-major bleeding (CRNMB), minor bleeding, thrombocytopaenia and adverse events. A total of eight systematic reviews were included, three of which were Cochrane reviews. Prophylactic anticoagulation with DOAC was not associated with significant increase in risk of major bleeding and CRNMB. As for LMWH, majority of studies showed that prophylactic anticoagulation with LMWH was not associated with significant increase in risk of major bleeding, thrombocytopaenia and adverse events. No significant increase in risk of major bleeding was observed when LMWH prophylaxis was given to specific populations such as lung and pancreatic cancer patients. As for patients with high risk for VTE (Khorana score ≥3), one study showed no significant increase in risk of major bleeding when DOAC prophylaxis was given. However, the risk of bleeding, while not reaching statistical significance, suggests caution when prophylactic anticoagulation is considered for ambulatory cancer patients.

c) Economic implication

Two cost-effectiveness analyses were included. One study evaluated the cost-utility of DOAC versus placebo for VTE prevention in ambulatory cancer patients from the health sector perspective using a Markov state-transition model over a lifetime. The DOAC thromboprophylaxis for six months appeared to be cost-effective in ambulatory cancer patients who were at intermediate-to-high risk for VTE with an incremental cost of US$1,445, QALY increase of 0.12, and an international cost-effectiveness ratio (ICER) of US$11,947 per QALY gained. The implementation of this strategy in high-risk patients with Khorana score ≥3 led to higher cost-benefit ratio with an incremental cost of US$1,103, QALY increase of 0.19 and an ICER of US$5,794 per QALY gained. Another study evaluated LMWH anticoagulation costs during four months of chemotherapy following a new cancer diagnosis and survival benefit over 24 months in ambulatory cancer patients from a United States perspective using a Markov state-transition model. Prophylactic LMWH appeared to be economically reasonable with an incremental cost of US$3,213, QALY increase of 0.0354 QALYs and an ICER of US$90,893 per QALY gained. However, the model did not include downstream VTE morbidities, of which inclusion of related costs would likely have made LMWH more cost-effective. The authors concluded that LMWH prophylaxis would remain economically reasonable if future trials confirm its suggested mortality benefit. However, in this review, LMWH prophylaxis appeared to have no mortality benefit for ambulatory cancer patients.

d) Organisational issues

The Khorana score may help clinicians in selecting patients at high risk of VTE. However, a substantial number of cancer patients with VTE may not be identified via the Khorana score risk-stratification and may, therefore, not benefit from thromboprophylaxis. Further studies are needed to ascertain the accuracy of Khorana score in discriminating between high- and low-risk patients over time using the conventional 3-point or 2-point positivity threshold as well as stratifying patients of different cancer types based on their VTE risk.

Conclusion

Based on the review, there was good level of evidence indicating that prophylactic anticoagulation with low-molecular-weight heparin (LMWH) or direct oral anticoagulant (DOAC) significantly reduced venous thromboembolism (VTE) events with no significant increase in risk of major bleeding but appeared to have no effect on mortality when given to ambulatory cancer patients. The risk of bleeding, while not reaching statistical significance, suggests caution when primary thromboprophylaxis is being considered for ambulatory cancer patients. Current evidence does not support routine thromboprophylaxis in ambulatory cancer patients. Greater risk reduction without significant increase in risk of major bleeding (two systematic reviews involving two recent DOAC trials) and higher incremental cost-effectiveness ratio (one cost-effectiveness analysis) were observed when DOAC thromboprophylaxis was given to high-risk ambulatory cancer patients, suggesting that a Khorana score risk-stratified strategy may be considered in this context. However, a substantial number of cancer patients with VTE may not be identified via the Khorana score risk-stratification and may, therefore, not benefit from thromboprophylaxis. More evidence is needed to ascertain the performance of Khorana score in selecting ambulatory cancer patients at high risk for VTE.

Methods

Electronic databases were searched through the PubMed and Ovid interface: MEDLINE (1946 to present), EBM Reviews–Cochrane Database of Systematic Reviews (2005 to 4th March 2020), EBM Reviews–Cochrane Central Register of Controlled Trials (January 2020), EBM Reviews–Database of Abstracts of Review of Effects (1st Quarter 2016), EBM Reviews–Health Technology Assessment (4th Quarter 2016), NHS economic evaluation database (1st Quarter 2016). Searches were also run in INAHTA, horizon scanning databases, FDA website and general search engine. Additional articles were identified from reviewing the references of retrieved articles. The last search was run on 5th March 2020.

Summary of efficacy outcomes for prophylactic anticoagulation in ambulatory cancer patients compared with placebo or no thromboprophylaxis.

Efficacy outcomes	Specific population	Study	Anticoagulants			
			UFH	LMWH	DOAC	Warfarin
Incidence of VTE (symptomatic/ asymptomatic DVT + PE)		Becattini 2020		*OR 0.51; 95% CI: 0.43, 0.61[a]		
				*OR 0.43; 95% CI: 0.33, 0.56[a]	*OR 0.49; 95% CI: 0.33, 0.74	
		Barbarawi 2019		*RR 0.58; 95% CI: 0.48, 0.69	*RR 0.39; 95% CI: 0.24, 0.63	
		Li 2019			*RR 0.56; 95% CI: 0.35, 0.89	
		Di Nisio 2016		*RR 0.59; 95% CI: 0.48, 0.73		
		Ben-Aharon 2014		*RR 0.56; 95% CI: 0.38, 0.81		
		Phan 2014		*OR 0.53; 95% CI: 0.41, 0.70		
	Lung cancer	Becattini 2020		*OR 0.42; 95% CI: 0.26, 0.67[a]		
		Phan 2014		*OR 0.46; 95% CI: 0.29, 0.74		
	Pancreatic cancer	Becattini 2020		*OR 0.26; 95% CI: 0.14, 0.48[a]		
		Phan 2014		*OR 0.33; 95% CI: 0.16, 0.67		
	High risk (Khorana score ≥3)	Becattini 2020		*OR 0.48; 95% CI: 0.34, 0.68[a]		
		Li 2019			*RR 0.47; 95% CI: 0.25, 0.89	
Symptomatic VTE (symptomatic DVT + PE)		Becattini 2020		*OR 0.49; 95% CI: 0.39, 0.61[a]		
		Li 2019			RR 0.58; 95% CI: 0.29, 1.13	
		Akl 2017	*RR 0.56; 95% CI: 0.47, 0.68			
		Di Nisio 2016			*RR 0.08; 95% CI: 0.01, 0.67[b]	RR 0.15; 95% CI: 0.02, 1.20
		Ben-Aharon 2014		*RR 0.46; 95% CI: 0.32, 0.67		
	Lung cancer	Ben-Aharon 2014		*RR 0.42; 95% CI: 0.25, 0.71		
		Di Nisio 2016		*RR 0.40; 95% CI: 0.20, 0.80		
	Pancreatic cancer	Ben-Aharon 2014		*RR 0.31; 95% CI: 0.18, 0.55		
		Di Nisio 2016		*RR 0.41; 95% CI: 0.23, 0.75		
Symptomatic DVT		Akl 2017	*RR 0.46; 95% CI: 0.33, 0.63			
		Kahale 2017			RR 0.07; 95% CI: 0.00, 1.32[b]	RR 0.08; 95% CI: 0.00, 1.42
Symptomatic PE		Akl 2017	*RR 0.61; 95% CI: 0.47, 0.80			
		Kahale 2017			RR 0.16; 95% CI: 0.01, 3.91[b]	RR 1.05; 95% CI: 0.07,16.58
Mortality	VTE-related	Becattini 2020		OR 0.52, 95% CI: 0.25, 1.08[a]		
		Barbarawi 2019		RR 0.62; 95% CI: 0.28, 1.34		
	All-cause (unspecified duration)	Barbarawi 2019		*RR 0.95; 95% CI: 0.91, 0.99	RR 0.93; 95% CI: 0.58, 1.48	
		Phan 2014		OR 0.97; 95 % CI 0.87, 1.08		
	All-cause (3 months)	Kahale 2017			RR 0.24; 95% CI: 0.02, 2.56[b]	
	All-cause (6 months)	Li 2019			RR 0.98; 95% CI: 0.67, 1.44	
	All-cause (12 months)	Akl 2017	RR 0.98; 95% CI: 0.93, 1.03			
		Kahale 2017				RR 0.95; 95% CI: 0.87,1.03
		Di Nisio 2016	RR 0.86; 95% CI: 0.72, 1.03	RR 0.93; 95% CI: 0.80, 1.09		
		Ben-Aharon 2014		RR 0.93; 95% CI: 0.83, 1.04		
	All-cause (24 months)	Akl 2017	RR 0.99; 95% CI: 0.96, 1.01			

CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; OR, odds ratio; PE, pulmonary embolism; RR, risk ratio; UFH, unfractionated heparin; VTE, venous thromboembolism. Statistical significance * = $p<0.05$ or CI for OR/RR not crossing the null value of 1. [a]One study comparing antithrombin with no antithrombin was included. [b]Only one study comparing apixaban with placebo was included.

Summary of safety outcomes for prophylactic anticoagulation in ambulatory cancer patients compared with placebo or no thromboprophylaxis.

Safety outcomes	Specific population	Study	Anticoagulants			
			UFH	LMWH	DOAC	Warfarin
Major bleeding[a]		Becattini 2020		OR 1.30; 95% CI: 0.98, 1.73[d]		
		Becattini 2020		OR 1.27; 95% CI: 0.93, 1.73[d]	OR 1.78; 95% CI: 0.83, 3.83	
		Barbarawi 2019		RR 1.26; 95% CI: 0.92, 1.74	RR 1.76; 95% CI: 0.83, 3.73	
		Li 2019			RR 1.96; 95% CI: 0.80, 4.82	
		Akl 2017	RR 1.30; 95% CI: 0.94, 1.79			
		Kahale 2017			RR 0.16; 95% CI: 0.01, 3.91[e]	*RR 2.93; 95% CI: 1.86, 4.62
		Di Nisio 2016		RR 1.44; 95% CI: 0.98, 2.11	RR 0.62; 95% CI: 0.06, 6.63[e]	RR 3.82; 95% CI: 0.97, 15.04[f]
		Ben-Aharon 2014		RR 1.28; 95% CI: 0.84, 1.95		
		Phan 2014		*OR 1.57; 95 % CI: 1.04, 2.37		
	Lung cancer	Di Nisio 2016		RR 1.49; 95% CI: 0.79, 2.80		
	Pancreatic cancer			RR 1.21; 95% CI: 0.58, 2.51		
	High risk (Khorana score ≥3)	Li 2019			RR 1.60; 95% CI: 0.42, 6.01	
Clinically relevant bleeding	Major + CRNMB	Di Nisio 2016	RR 2.01; 95% CI: 0.18, 21.96	*RR 3.40; 95% CI: 1.20, 9.63	RR 1.87; 95% CI: 0.23, 14.91[e]	
	Major + minor bleeding	Ben-Aharon 2014		RR 1.29; 95% CI: 0.95, 1.77		
CRNMB[b]		Li 2019			RR 1.28; 95% CI: 0.74, 2.20	
Minor bleeding[c]		Akl 2017	*RR 1.70; 95% CI: 1.13, 2.55			
		Kahale 2017			*RR 4.43; 95% CI: 0.25, 79.68[e]	*RR 3.14; 95% CI: 1.85, 5.32
		Di Nisio 2016		RR 1.23; 95% CI: 0.89, 1.70		
Thrombocytopaenia		Akl 2017	RR 0.69; 95% CI: 0.37, 1.27			
		Ben-Aharon 2014		RR 1.05; 95% CI: 0.76, 1.45		
Serious adverse events		Di Nisio 2016		RR 0.86; 95% CI: 0.70, 1.07		

CI, confidence interval; CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; OR, odds ratio; RR, risk ratio; UFH, unfractionated heparin. Statistical significance * = $p<0.05$ or CI for OR/RR not crossing the null value of 1. [a]Major bleeding is typically defined as overt bleeding associated with a fall in haemoglobin of 2 g/dL or more, or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. [b]CRNMB is typically defined as overt bleeding that does not meet the criteria for major bleeding, but is associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life. [c]Minor bleeding is typically defined as a bleeding event not matching the criteria for major bleeding or CRNMB.[22] [d]One study comparing antithrombin with no antithrombin was included. [e]Only one study comparing apixaban with placebo was included. [f]Only one study comparing warfarin with placebo was included.

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ABBREVIATION

AMED	Allied and Complementary Medicine Database
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATIII	Antithrombin III
BMI	Body Mass Index
CASP	Critical Appraisal Skills Programme
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Controlled Register of Trials
CI	Confidence interval
CINAHL	The Cumulative Index to Nursing and Allied Health Literature
CPG	Malaysian Clinical Practice Guidelines
CRNMB	Clinically relevant non-major bleeding
DVT	Deep vein thrombosis
DOAC	Direct oral anticoagulants
EHA	European Hematology Association
ESMO	European Society of Medical Oncology
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCUP	Healthcare Cost and Utilisation Project
HIT	Heparin-induced thrombocytopaenia
HITT	Heparin-induced thrombocytopaenia and thrombosis
HR	Hazard ratio
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
INR	International Normalised Ratio
ISTH	International Society for Thrombosis and Haemostasis
LE	Level of evidence
LMWH	Low-molecular-weight heparins
MA	Meta-analysis
MNCR	Malaysia National Cancer Registry
MOH	Ministry of Health
NHS	United Kingdom National Health Service
NNT	Number needed to treat
NNTB	Number needed to treat for an additional beneficial outcome
NNTH	Number needed to treat for an additional harmful outcome
OR	Odds ratio
PE	Pulmonary embolism
RCT	Randomised controlled trial
RR	Risk ratio/ relative risk
SR	Systematic review
UFH	Unfractionated heparin
US	United States
US FDA	United States Food and Drug Administration

1.0 BACKGROUND

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in cancer patients. Cancer patients have a four- to seven-fold increased risk of VTE compared with the general population or people without cancer; about 5% to 10% of them develop a VTE within the first year of cancer diagnosis.[1] A large cohort study showed that the incidence rate of first VTE in patients with active cancer was 5.8 per 100 person-years.[2] Cancer patients constitute about 20% of all patients with VTE which is estimated to be 100 cases per 100,000 population every year in the United States (US).[1,3] In Malaysia, a total of 115,238 new cancer cases were registered for the period of 2012-2016 with age standardised incidence rate of 86 cases per 100,000 male population and 102 cases per 100,000 female population.[4]

The risk of VTE in cancer patients is dependent on the type and stage of cancer, cancer treatment modalities and patient-related factors. Highest rates of VTE have been observed in pancreas, brain, stomach, lung and ovarian cancers while relatively high rates of VTE were reported in patients with kidney cancer and haematological malignancies, particularly those with lymphoma and multiple myeloma.[1,5] The risk of VTE appears to increase from localized, regional to metastatic cancer.[1] A population-based cohort study reported that the adjusted relative risk (RR) of VTE for stage 1, 2, 3 and 4 cancer was 2.9, 2.9, 7.5, and 17.1, respectively.[6] Cancer treatment modalities such as surgery, chemotherapy, hormonal therapy, antiangiogenic drugs, immunomodulatory agents, erythropoiesis-stimulating agents, blood transfusions, and central venous catheters increase the risk of VTE.[1] Older age, obesity, prolonged immobility and comorbidities are known risk factors for VTE.[1,5] The incidence of VTE is often highest in the first few months after cancer diagnosis and decreases thereafter, possibly due to the initiation of cancer treatment upon diagnosis increasing VTE risk; reduced VTE risk in treated patients who go into remission; and a considerable proportion of cancer patients eventually succumbing to the disease.[1]

Cancer-associated thrombosis is the second leading cause of death in ambulatory patients receiving chemotherapy.[7] Cancer patients with VTE have a ten-fold higher risk of death than patients with VTE alone and a four-fold higher risk of death than cancer patients without VTE.[1] Other than higher mortality rate, VTE is associated with significant inpatient and outpatient resource utilisation, and increased all-cause healthcare costs among ambulatory cancer patients. Cancer patients with VTE had approximately three times as many all-cause hospitalisations (mean 1.38 versus 0.55 per patient) and days in hospital (10.19 versus 3.37), incurring higher overall all-cause inpatient costs (mean US$21,299 versus US$7,459 per patient), outpatient costs (US$53,660 versus US$4,232 per patient), and total health care costs (US$74,959 versus US$41,691 per patient) than cancer patients without VTE. Total mean VTE-related health care costs for cancer patients with VTE were US$9,247 per patient over one year post-VTE follow-up period. Adjusted mean incremental all-cause health care costs of VTE were US$30,538 per patient for cancer overall, ranging from US$1,946 for gastric to US$38,983 for pancreatic cancer.[8] Therefore, prophylactic anticoagulation is essential for the management of ambulatory cancer patients as it may significantly reduce healthcare utilisation and costs in this population.

According to the Malaysian Clinical Practice Guidelines (CPG) on prevention and treatment of VTE published in 2013, pharmacological VTE prophylaxis should be offered to hospitalised patients with cancer and continue until the patient is no longer at increased risk of VTE. As for patients with active cancer and confirmed proximal DVT or PE, low-molecular-weight heparins (LMWH) such as enoxaparin and tinzaparin should be offered and continue to be given for six months. It is not mentioned in the CPG whether patients with active cancer receiving care in ambulatory or outpatient setting should be offered primary thromboprophylaxis to prevent VTE.[9] Despite studies indicating the safety and efficacy of LMWH in ambulatory cancer patients receiving chemotherapy, routine pharmacological thromboprophylaxis in this population was not recommended due to relatively low benefit-to-risk ratio and burden of daily subcutaneous injections.[10] Direct oral anticoagulants (DOAC) such as apixaban and rivaroxaban have emerged as an alternative to LMWH due to their ease of administration and because they do not require laboratory monitoring unlike warfarin. However, there may be an excessive bleeding risk in certain patient groups, particularly those with gastrointestinal malignancies. Recent studies have suggested that DOAC may be useful for primary thromboprophylaxis in ambulatory cancer patients with validated risk assessment scores.[11]

The American Society of Clinical Oncology (ASCO) currently recommends that clinicians may offer thromboprophylaxis with apixaban, rivaroxaban, or LMWH to selected high-risk outpatients with cancer (Khorana score ≥2 prior to starting a new systemic chemotherapy regimen), provided there are no significant risk factors for bleeding and no drug interactions (evidence quality: intermediate-to-high for apixaban and rivaroxaban, intermediate for LMWH; strength of recommendation: moderate). Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting.[12] The Scientific and Standardisation Committee (SSC) through its subcommittee Haemostasis & Malignancy of the International Society for Thrombosis and Haemostasis (ISTH) suggests the use of DOAC (apixaban and rivaroxaban) of up to six months as primary VTE prophylaxis in ambulatory cancer patients starting chemotherapy with Khorana score ≥2, no drug-drug interactions, and not at high risk for bleeding (such as patients with gastroesophageal cancers). A final treatment should be made after considering the risk of both VTE and bleeding, as well as patients' preference and values. In high-risk ambulatory cancer patients where primary thromboprophylaxis is planned but with concerns for safety of DOAC (such as in patients with concern of drug interaction or high risk of gastrointestinal bleeding), it is suggested to use LMWH.[13] Both ASCO and ISTH recommend against routine thromboprophylaxis in cancer outpatients without risk assessment and against its use in low-risk patients as defined by the Khorana score.

This technology review was requested by a clinical oncologist to review the evidence on efficacy, safety and cost-effectiveness of prophylactic anticoagulation in ambulatory cancer patients.

2.0 OBJECTIVE / AIM

To assess the efficacy, safety and cost-effectiveness of prophylactic anticoagulation in ambulatory cancer patients.

3.0 TECHNICAL FEATURES

Anticoagulants used for pharmacological prophylaxis to prevent VTE in patients with cancer include unfractionated heparin (UFH), LMWH such as dalteparin and enoxaparin, and factor Xa inhibitors such as fondaparinux, rivaroxaban and apixaban.[12]

Both UFH and LMWH inhibit thrombin (IIa) activation by binding to antithrombin III (ATIII), a peptide that inhibits several activated clotting factors. The UFH binds to and increases the activity of ATIII by inducing a conformational change to factor Xa, which ultimately leads to inhibition at factors Xa and IIa in a 1:1 ratio, in addition to some inhibition on factors IXa, XIa, XIIa. The LMWH, which also binds to ATIII, are smaller and have a higher proportional impact on factors Xa and IIa, in a 3:1 or 2:1 ratio.[14] The heparins are administered subcutaneously. The LMWH remain to be the anticoagulants of choice in the VTE prophylaxis in surgical or acutely ill, hospitalised medical cancer patients and high-risk patients undergoing ambulatory chemotherapy.[15] Studies comparing LMWH with UFH have shown that LMWH was more effective than UFH in preventing thrombosis without increasing the risk of bleeding. The LMWH are less likely to produce haematomas at injection site, heparin-induced thrombocytopaenia and thrombosis (HITT), and osteoporosis than UFH which requires complex labour intensive administration, monitoring and dose adjustment.[9] The dosing regimen for VTE prophylaxis using LMWH in patients with cancer treated in outpatient setting is either dalteparin 5,000 IU once daily or enoxaparin 40mg once daily.[12]

Fondaparinux binds to ATIII, resulting in a conformational change, thereby inhibiting factor Xa without having any effect on IIa. Fondaparinux is contraindicated in patients with renal insufficiency as it is primarily eliminated unchanged in the urine. Apixaban and rivaroxaban directly bind to the active site of factor Xa, thereby inhibiting both free and clot-associated factor Xa, in addition to inhibiting prothrombinase activity.[14] Fondaparinux is administered subcutaneously whereas apixaban and rivaroxaban are administered orally. Both apixaban and rivaroxaban have quick onset of action and short half-life which are more favourable alternatives to warfarin. Despite similar ease of oral administration and much lower cost, warfarin has delayed onset of action, drug-drug interaction and narrow therapeutic range requiring daily monitoring of international normalised ratio (INR).[9] The dosing regimen for VTE prophylaxis using factor Xa inhibitors in cancer patients treated in outpatient setting is fondaparinux 2.5mg once daily, apixaban 2.5mg twice daily or rivaroxaban 10mg once daily.[12]

Several clinical prediction scores have been developed to identify cancer patients who may benefit from primary prophylaxis given their individual risk profiles. The Khorana score was the first clinical prediction score to predict VTE risk specifically in cancer patients receiving chemotherapy in the outpatient setting (Table 1). It is the most widely utilised risk model for this population, allowing clinicians to effectively exclude low-risk patients from thromboprophylaxis and associated bleeding risks. Advantages of the Khorana score include its relative simplicity, successful validation in multiple studies, and high negative predictive value while limitations include a low positive predictive value, a need for further risk stratification (most patients are classified as intermediate risk), and lack of consistent validity in single sites of cancers.[11]

Table 1: Predictive model for chemotherapy-associated VTE in the ambulatory setting.[12,16]

Patient characteristics	**Risk score**
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecologic, bladder, testicular, renal)	1
Pre-chemotherapy platelet count ≥350 x 10^9/L	1
Haemoglobin level <10 g/dL or use of red cell growth factors	1
Pre-chemotherapy leukocyte count >11 x 10^9/L	1
BMI ≥35 kg/m^2	1
Calculate total score, adding points for each criterion in the model	
Interpretation	
High-risk score ≥ 3	
Intermediate-risk score = 1–2	
Low-risk score = 0	

BMI, body mass index. Note: Data adapted.[12]

4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE (R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to 4th March 2020
- EBM Reviews – Cochrane Central Register of Controlled Trials – January 2020
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2016
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to 4th March 2020
- EBM Reviews – Health Technology Assessment – 4th Quarter 2016
- EBM Reviews – NHS Economic Evaluation Database – 1st Quarter 2016

Other databases:

- PubMed
- INAHTA

Other website:

- USFDA

Additional articles were identified from handsearching the references of retrieved articles. General search engine was used to get additional web based information. The search was limited to English articles on humans. Appendix 1 showed the detailed search strategies. The last search was conducted on 5th March 2020.

4.2 SELECTION

Two reviewers (GYN and AS) independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection.

Inclusion criteria

Population	Adults diagnosed with cancer under ambulatory or outpatient care
Interventions	Primary thromboprophylaxis with anticoagulants
Comparators	Placebo or no thromboprophylaxis
Outcomes	i. Efficacy (incidence of VTE, mortality rate) ii. Safety (major bleeding, minor bleeding/clinically relevant non-major bleeding (CRNMB), adverse events) iii. Cost, cost-effectiveness, cost utility, cost-analysis and economic evaluation iv. Organisational – guidelines
Study design	Health Technology Assessment (HTA) reports, Systematic Review (SR) and Meta-analysis (MA), Randomised Controlled Trial (RCT)

Exclusion criteria

i. Animal / laboratory / case reports / case series / cohort studies / cross-sectional studies
ii. Narrative review
iii. Non-English articles
iv. Study population receiving inpatient care / under hospitalisation / undergoing surgery

5.0 RESULTS

A total of 981 records were identified through Ovid and PubMed interfaces, and 16 were identified from other sources (references of retrieved articles). After removal of 392 duplicates, 605 records were screened and 556 were excluded. Of these, 49 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria, 10 full text articles were included and 39 full text articles were excluded due to the study being included in SR (n=10), SR was updated (n=4), irrelevant study design (n=15), irrelevant population (n=6), irrelevant outcome (n=3) and lack of relevant outcome (n=1). The flow chart of included studies is shown in Figure 1. Evidence was graded according to the US/Canadian Preventive Services Task Force (See Appendix 2).

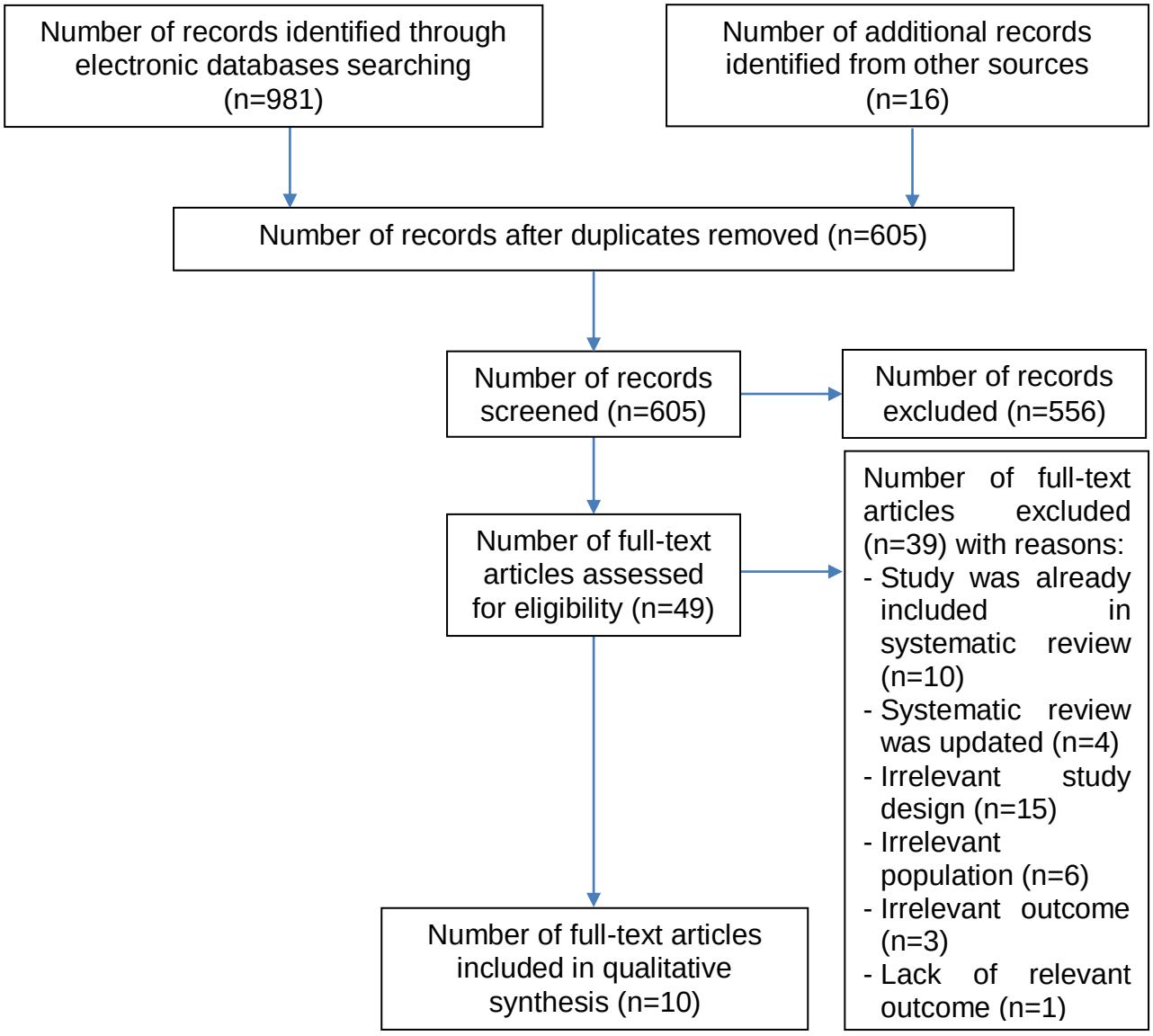

Figure 1. Flow chart of included studies

The ten full text articles finally selected for this review comprised of eight SRs and two cost-effectiveness analyses (CEAs).

Quality assessment of included studies

Both reviewers (GYN and AS) independently appraised relevant articles using the Critical Appraisal Skills Programme (CASP) checklist. Review authors' judgements involved answering "yes", "no" and "can't tell" to specific questions and discrepancies were resolved by consensus.

Overall, the studies included were of high quality. The appraisal revealed that one of the SRs mentioned assessment of quality was carried out but outcome or results of quality assessment were not reported. One of the CEAs did not consider discounting for costs and consequences.

The critical appraisal of included studies are summarised as below.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Becattini et al. 2020	Yes	Yes	Yes	Yes
Barbarawi et al. 2019	Yes	Yes	Yes	Yes
Li et al. 2019	Yes	Yes	Yes	Yes
Akl et al. 2017	Yes	Yes	Yes	Yes
Kahale et al. 2017	Yes	Yes	Yes	Yes
Di Nisio et al. 2016	Yes	Yes	Yes	Yes
Ben-Aharon et al. 2014	Yes	Yes	Yes	Yes
Phan et al. 2014	Yes	Yes	Can't tell	Yes

Figure 2a. Critical appraisal for systematic reviews.

Criteria assessed	Li et al. 2020	Pishko et al. 2012
A well-define question posed?	Yes	Yes
Comprehensive description of competing alternative given?	Yes	Yes
Effectiveness established?	Yes	Yes
Effects of intervention identified, measured and valued appropriately?	Yes	Yes
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	Yes	Yes
Costs and consequences adjusted for different times at which they occurred (discounting)?	Yes	No
Results of the evaluation?	Yes	Yes
Incremental analysis of the consequences and costs of alternatives performed?	Yes	Yes
Sensitivity analysis performed?	Yes	Yes

Figure 2b. Critical appraisal for economic evaluation studies.

5.1 EFFICACY/ EFFECTIVENESS

A total of eight SRs were included for the evaluation of efficacy.[17–24] Outcome measures include VTE and mortality.

5.1.1 Venous thromboembolism (VTE)

Eight studies showed that prophylactic anticoagulation significantly reduced VTE in ambulatory cancer patients.[17–24]

Becattini et al. (2020) conducted a SR and MA to assess the clinical benefit of antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy. Studies comparing thromboprophylaxis with anticoagulants such as warfarin, antithrombin, LMWH (certoparin, dalteparin, enoxaparin, nadroparin and semuloparin) and DOAC (apixaban and rivaroxaban) versus placebo or none were searched via Medline and Scopus up to December 2018. Primary outcome was objectively confirmed VTE and ancillary outcomes were symptomatic

VTE and fatal VTE. Sensitivity analyses were performed concerning (i) parenteral or oral anticoagulants; (ii) symptomatic VTE; (iii) fatal VTE; (iv) subgroups of patients based on the primary cancer site (lung, pancreas and breast); (v) patients considered as being at high-risk of VTE; and (vi) high-quality studies.[17, level I]

A total of 22 RCTs with 11,953 patients were included. Duration of prophylaxis ranged from four weeks to one year. The length of follow-up ranged from six weeks to one year. Anticoagulant prophylaxis significantly reduced objectively confirmed VTE [22 RCTs; n=11,953; odds ratio (OR) 0.51; 95% confidence interval (CI): 0.43, 0.61; I^2=24%] and symptomatic VTE (17 RCTs; n=10,374; OR 0.49; 95% CI: 0.39, 0.61; I^2=0%) compared with placebo or none. Anticoagulant prophylaxis did not significantly reduce fatal VTE (6 RCTs; n=4,705; OR 0.52; 95% CI: 0.25, 1.08; I^2=0%) compared with placebo or no thromboprophylaxis. The efficacy of prophylaxis in reducing VTE was consistent in all sensitivity analyses. The authors concluded that prophylaxis with oral or parenteral anticoagulants reduced the risk of VTE in ambulatory cancer patients. However, there may be conflict of interest as authors disclosed receiving fees/honorarium from pharmaceutical companies including Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, Daiichi Sankyo and LEO Pharma.[17, level I]

Barbarawi et al. (2019) conducted a SR and MA to assess the safety and efficacy of anticoagulation in VTE prophylaxis in ambulatory cancer patients. Studies comparing LMWH (dalteparin, nadroparin, enoxaparin, certoparin, bemiparin and semuloparin), DOAC (apixaban and rivaroxaban), aspirin, warfarin, and UFH with placebo were searched via PubMed/MEDLINE, Embase and Cochrane Library up to December 2018. Primary outcome was VTE events and secondary outcomes were all-cause mortality and VTE-related mortality. Sensitivity analysis of primary outcome was conducted by sequential removal of each of the involved trials and specific primary cancer site (lung and pancreas).[18, level I]

A total of 24 RCTs with 13,338 patients were included. The length of follow-up ranged from three to 24 months. Significant reduction in VTE events was seen with LMWH [risk ratio (RR) 0.58; 95% CI: 0.48, 0.69; p<0.001; I^2=0%] and DOAC (RR 0.39; 95% CI: 0.24, 0.63; p<0.001; I^2=5%) compared with placebo. Compared with placebo, LMWH significantly reduced DVT (RR 0.28; 95% CI: 0.11, 0.71; p=0.008; I^2=0%) and PE events (RR 0.57; 95% CI: 0.43, 0.75; p<0.001; I^2=0%). However, no significant reduction in DVT (RR 0.53; 95% CI: 0.26, 1.07, p=0.07; I^2=33%) and PE events (RR 0.46; 95% CI: 0.21, 1.02; p=0.06; I^2=30%) was seen with DOAC. The sensitivity analysis showed that sequential removal of each trial did not change outcome significance. The authors concluded that both LMWH and DOAC were associated with lower VTE events compared with placebo.[18, level I]

Li et al. (2019) conducted a SR and MA to assess phase III studies of DOAC versus placebo for the prevention of VTE in adult ambulatory cancer patients receiving systemic therapy. Studies were searched via Embase, MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) up to February 2019. Primary outcomes were overall VTE incidence during the first six months (including symptomatic PE and DVT, incidental PE, ultrasound-detected DVT, and VTE-related death) and secondary outcomes were symptomatic VTE (PE and DVT) incidence and all-cause mortality during the first six months. Subgroup analysis was performed for intermediate-risk (score 2) and high-risk (score ≥3) Khorana score. Sensitivity analyses included pre-planned secondary study outcomes of overall and symptomatic VTE incidence during on-treatment study period.[19, level I]

A total of two RCTs with 1,415 participants were included. The duration of prophylaxis and follow-up were 180 days. Compared with placebo, significant reduction in overall VTE incidence during first six months was seen with DOAC [(RR 0.56; 95% CI: 0.35, 0.89; *p*=0.01; I^2=26%); (absolute risk difference (ARD) −4.09%; 95% CI: −6.93, −1.24)]. However, there was no significant reduction in symptomatic VTE incidence during first six months with DOAC [(RR 0.58; 95% CI: 0.29, 1.13; *p*=0.11; I^2=44%); (ARD −2.59%; 95% CI: −6.26, +1.09)]. The sensitivity analysis showed that outcomes did not change significantly. The authors concluded that low-dose DOAC prophylaxis reduced the rate of overall VTE in high-risk cancer patients starting systemic chemotherapy. However, there may be conflict of interest as authors disclosed receiving fees/grants/support from pharmaceutical companies including Janssen, Pfizer, Bayer, Daiichi Sankyo, Boehringer Ingelheim, Bristol-Myers Squibb, Sanofi, and LEO Pharma.[19, level I]

Akl et al. (2017) updated the Cochrane review which aimed to evaluate efficacy and safety of parenteral anticoagulants in ambulatory patients with cancer undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise had no standard therapeutic or prophylactic indication for anticoagulation. Studies were searched via CENTRAL, MEDLINE, Embase, handsearching of conference proceedings, checking of references of included studies, use of the 'related citation' feature in PubMed and trial registries up to August 2017. Primary outcomes were all-cause mortality; pre-specified at 12 months, 24 months and over the duration of trial. Secondary outcomes were symptomatic DVT and PE. The certainty of evidence at the outcome level was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Subgroup analyses for patients with (1) lung cancer (either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC)) versus those with non-lung cancer; (2) patients with advanced cancer versus those with non-advanced cancer were conducted. Sensitivity analyses excluding trials at high risk of bias was carried out.[20, level I]

A total of 19 RCTs with 9,650 participants, comparing parenteral anticoagulants (UFH and LMWH) with placebo or no intervention, were included. The length of follow-up ranged from 12 to 24 months. Compared to no heparin, heparin significantly reduced symptomatic VTE [(16 RCTs; n=9,036; RR 0.56; 95% CI: 0.47, 0.68; *p*<0.0001; I^2=0%); (RD 30 fewer per 1000; 95% CI: 36 fewer to 22 fewer; high certainty of evidence)]; symptomatic DVT (14 RCTs; n=8,867; RR 0.46; 95% CI: 0.33, 0.63; *p*<0.0001; I^2=22%); and symptomatic PE (14 RCTs; n=8,867; RR 0.61; 95% CI: 0.47, 0.80; *p*=0; I^2=0%). The subgroup analysis for lung versus non-lung cancer showed that the test for subgroup difference was not statistically significant. The sensitivity analysis excluding the one study at high risk of bias, from the analyses did not change the results significantly. The authors concluded that heparin reduced symptomatic VTE in ambulatory cancer patients.[20, level I]

Kahale et al. (2017) updated the Cochrane review which aimed to evaluate the efficacy and safety of oral anticoagulants in ambulatory people with cancer undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise had no standard therapeutic or prophylactic indication for anticoagulation. Studies were searched via CENTRAL, Ovid MEDLINE, Embase, handsearching of conference proceedings; checking of references of included studies; a search for ongoing studies; and using the 'related citation' feature in PubMed up to December 2017. Primary outcome was all-cause mortality and secondary outcomes were symptomatic DVT and PE. Subgroup analyses based on the type

of oral anticoagulant and for patients with lung cancer (either SCLC or NSCLC) versus those with non-lung cancer were conducted.[21, level I]

A total of seven RCTs with 1,486 participants, comparing warfarin (six RCTs; length of follow-up: 12 months) and apixaban (one RCT; length of follow-up: three months) with placebo or no intervention, were included. Warfarin (1 RCT; n=315) appeared to have no effect on symptomatic PE [(RR 1.05; 95% CI: 0.07, 16.58; *p*=0.97); (risk difference (RD) 0 fewer per 1000; 95% CI: 6 fewer to 98 more); very low certainty evidence)] but likely decreased the incidence of symptomatic DVT [(RR 0.08; 95% CI: 0.00, 1.42; *p*=0.09); (RD 35 fewer per 1000; 95% CI: 38 fewer to 16 more); low certainty evidence] compared with no warfarin. Clinically important effect of apixaban (1 RCT; n=92) on symptomatic DVT [(RR 0.07; 95% CI: 0.00, 1.32; *p*=0.08); (RD 93 fewer per 1000, 95% CI: 100 fewer to 32 more); low certainty evidence] or symptomatic PE [(RR 0.16; 95% CI: 0.01, 3.91); (RD 28 fewer per 1000, 95% CI: 33 fewer to 97 more); low certainty evidence] could not be confirmed or excluded. The sensitivity analyses did not change the results significantly. The authors concluded that the evidence did not show a mortality benefit from oral anticoagulation in people with cancer.[21, level I] However, recent DOAC trials on apixaban and rivaroxaban were not yet available during the conduct of this Cochrane review.[25,26]

Di Nisio et al. (2016) updated the Cochrane review which aimed to assess efficacy and safety of primary thromboprophylaxis for VTE in ambulatory cancer patients receiving chemotherapy compared with placebo or no thromboprophylaxis. Studies were searched via CENTRAL and Cochrane Vascular Group Specialised Register (MEDLINE Ovid, Embase Ovid, CINAHL, AMED and through handsearching relevant journals) up to June 2016. Primary outcome was symptomatic VTE and secondary outcomes were symptomatic PE; symptomatic DVT; unsuspected (incidental) VTE; overall (symptomatic and unsuspected) VTE and one-year overall mortality. In the case of statistically significant overall estimates, clinical effect summary statistics such as the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) were calculated. Between-trial heterogeneity was explored by stratifying the main outcomes for age, type of cancer, stage of cancer (metastatic versus non-metastatic), type of major bleeding, concealment of allocation, blinding, analysis in accordance with the intention-to-treat principle, trial size and differences in the use of co-interventions in trial groups. Univariate random-effects model meta-regression was used to determine whether treatment effects were affected by these factors and by three continuous variables at trial level: dosage of intervention, treatment duration, and length of follow-up. Quality of evidence was assessed according to GRADE principles.[22, level I]

A total of 26 RCTs involving 12,352 participants with locally advanced or metastatic cancer, comparing UFH (one RCT), LMWH dalteparin, certoparin, nadroparin, enoxaparin, bemiparin (18 RCTs), ultra-low molecular weight heparin (uLMWH) semuloparin (one RCT), warfarin (5 RCTs), antithrombin (one RCT) and DOAC apixaban (one RCT) with placebo or no thromboprophylaxis, were included. The length of follow-up ranged from median 3.5 to 25 months. Significant reduction in symptomatic VTE was seen with LMWH (9 RCTs; n=3,284; RR 0.54; 95% CI: 0.38, 0.75; high-quality evidence) in the absence of heterogeneity (Tau^2=0.00) compared with no thromboprophylaxis. This corresponded to a NNTB of 30 (95% CI: 23, 56), assuming a background risk of 71 symptomatic VTE events per 1,000 patients. Thromboprophylaxis using LMWH also significantly reduced symptomatic DVT [(8 RCTs; n=5,310; RR 0.49; 95% CI: 0.35, 0.67; Tau^2=0.00); (NNTB 68; 95% CI: 53, 105); high-quality

evidence] and symptomatic PE [(7 RCTs; n=5,226; RR 0.59; 95% CI: 0.40, 0.86; Tau^2=0.00); (NNTB 174; 95% CI: 119, 510); low-quality evidence] and overall VTE by 41% [(9 RCTs; n=5,366; RR 0.59; 95% CI: 0.48, 0.73; Tau^2=0.00); (NNTB 25; 95% CI: 20, 38)]. As for incidental VTE, there was no statistically significant benefit or harm for LMWH (RR 0.66; 95% CI: 0.41, 1.08). Stratified analyses did not show any effect of LMWH type, type of cancer, dosage, or design characteristics on the RR of symptomatic VTE. No evidence was found for a linear association between treatment duration and the risk of symptomatic VTE using meta-regression analysis (p=0.514).[22, level I]

Comparing LMWH with aspirin in multiple myeloma (2 RCTs; n=781), there was no statistically significant difference in symptomatic VTE (RR 0.51; 95% CI: 0.22, 1.17; moderate-quality evidence); symptomatic DVT (RR 0.81; 95% CI: 0.32, 2.04; low-quality evidence); and symptomatic PE (RR 0.13; 95% CI: 0.02, 1.03; moderate-quality evidence). Comparing LMWH with warfarin in multiple myeloma (1 RCT; n=439), there was significant reduction in symptomatic VTE (RR 0.33; 95% CI: 0.14, 0.83; high-quality evidence) but there was no statistically significant difference in symptomatic DVT (RR 0.43; 95% CI: 0.17, 1.10; moderate-quality evidence); and symptomatic PE (RR 0.11; 95% CI: 0.01, 2.06; low-quality evidence).[22, level I]

For warfarin versus placebo or no thromboprophylaxis in breast cancer (1 RCT; n=311), there was no statistically significant difference in symptomatic VTE (RR 0.15; 95% CI: 0.02, 1.20; low-quality evidence); symptomatic DVT (RR 0.08; 95% CI: 0.00, 1.42; low-quality evidence) and symptomatic PE (RR 1.05; 95% CI: 0.07, 16.58; very low-quality evidence). For warfarin versus aspirin in multiple myeloma (1 RCT; n=440), there was no statistically significant difference in symptomatic VTE: (RR 1.50; 95% CI: 0.74, 3.04; moderate-quality evidence); symptomatic DVT (RR 1.75; 95% CI: 0.75, 4.09; moderate-quality evidence) and symptomatic PE (RR 1.00; 95% CI: 0.25, 3.95; moderate-quality evidence).[22, level I]

As for apixaban versus placebo (1 RCT; n=122). there was significant reduction in symptomatic VTE (RR 0.08; 95% CI: 0.01, 0.67; moderate-quality evidence) and symptomatic DVT (RR 0.08; 95% CI: 0.01, 0.67; moderate-quality evidence) but there was no statistically significant difference in symptomatic PE (RR 0.11; 95% CI: 0.00, 2.54; low-quality evidence). The authors concluded that primary thromboprophylaxis with LMWH significantly reduced the incidence of symptomatic VTE in ambulatory cancer patients treated with chemotherapy. Despite the encouraging results of this review, routine prophylaxis in ambulatory cancer patients could not be recommended before safety issues are adequately addressed.[22, level I]

Ben-Aharon et al. (2014) conducted a SR and MA to evaluate the impact of LMWH primary prophylaxis on VTE incidence and survival in cancer patients. Studies were searched via CENTRAL, PubMed, Clinical Trials, conference proceedings of the ASCO, American Society of Hematology (ASH), European Society of Medical Oncology (ESMO) and the European Hematology Association (EHA) up to October 2013. Primary outcome was symptomatic VTE and secondary outcomes were DVT, PE, any VTE and all-cause mortality. Subgroup analyses were performed for lung cancer and pancreatic cancer, which were regarded as cancers with a high thrombogenic potential.[23, level I]

A total of 11 RCTs involving 6,942 patients, comparing LMWH (certoparin, dalteparin, enoxaparin, nadroparin and semuloparin) with placebo or no thromboprophylaxis, were included. The length of follow-up ranged from six to 12 months. Primary prophylaxis with LMWH significantly reduced symptomatic VTE (7 RCTs; n=2,612; RR 0.46; 95% CI: 0.32, 0.67; p<0.0001; I^2=0%) with number needed to treat (NNT) 50 (95% CI: 33, 100); DVT (RR 0.35; 95% CI: 0.21, 0.61; p=0.0001; I^2=0%); PE (RR 0.49; 95% CI: 0.29, 0.84; p=0.01; I^2=0%); any VTE (10 RCTs; n=6,942; RR 0.56; 95% CI: 0.38, 0.81, I^2=36%). There were no significant variations in the effect of different LMWH in any of the outcomes. The sensitivity analysis according to risk of bias and specifically according to allocation concealment showed that VTE reduction in both trials of low risk for bias (RR 0.67; 95% CI: 0.49, 0.93) were relatively lower than those of high risk (RR 0.33; 95% CI: 0.21, 0.52). The authors concluded that LMWH reduced the incidence of symptomatic VTE and PE in patients receiving chemotherapy for cancer.[23, level I]

Phan et al. (2014) conducted a SR and MA to measure safety and efficacy of outpatient primary VTE prophylaxis in patients with solid tumours receiving chemotherapy. Studies were searched via Ovid MEDLINE, Embase, EBM reviews-Cochrane database of systematic reviews, EBM reviews-ACP journal club, EBM reviews-Database of abstracts of reviews of effects up to December 2012. Primary outcome was first VTE (asymptomatic or symptomatic; included PE and DVT) and secondary outcome was all-cause mortality. Subgroup analyses for VTE and bleeding outcomes were performed using pre-specific subgroups including drug type, multiple types of tumors and catheter–based prophylaxis.[24, level I]

A total of 11 RCTs involving 7,875 patients, comparing LMWH (certoparin, dalteparin, nadroparin and semuloparin) with placebo or no thromboprophylaxis and warfarin with placebo, were included. The lengths of follow-up for LMWH ranged from six to 12 months / median 10.5 to 19.3 months; and for warfarin, ranged from median 26 to 88 months. Significant reduction in VTE events was seen in the prophylaxis group [(11 RCTs; n=7,875; OR 0.56; 95 % CI: 0.45, 0.71; I^2=18.3%); (RD -0.02; 95 % CI -0.03, -0.01; p<0.001)]. Greater reduction was seen when LMWH prophylaxis was analysed [(9 RCTs; n=6,748; OR 0.53; 95 % CI 0.41, 0.70; I^2=12.3%); (RD -0.02; 95 % CI -0.03, -0.01)]. No single study influenced the pooled estimate and the result of a sensitivity analysis using only manuscripts with low risk of bias was not different to the main result (OR 0.54; 95 % CI 0.40, 0.73; I^2=15 %). The authors concluded that although there was a clear measurable VTE rate reduction when primary thromboprophylaxis was given to patients with cancer, improving risk stratification tools to personalize strategies might enhance VTE prevention in cancer patients.[24, level I]

5.1.1 a) Parenteral versus oral anticoagulants

Becattini et al. (2020) reported that both parenteral (11 RCTs; n=6,700; OR 0.43; 95% CI: 0.33, 0.56; I^2=0%) and oral anticoagulant prophylaxis (3 RCTs; n=1,526; OR 0.49; 95% CI: 0.33, 0.74; I^2=57%) significantly reduced the incidence of VTE. However, moderate heterogeneity was found in the analysis of studies with oral anticoagulants.[17, level I]

5.1.1 b) Lung cancer

Five studies showed that prophylactic anticoagulation significantly reduced VTE events in lung cancer.[17,18,22–24]

Becattini et al. (2020) reported that anticoagulant prophylaxis (warfarin, antithrombin, LMWH and DOAC) significantly reduced the incidence of VTE in lung cancer (3 RCTs; n=1,991; OR 0.42; 95% CI: 0.26, 0.67 I^2=0%).[17, level I]

Barbarawi et al. (2019) reported that compared with placebo, LMWH significantly reduced VTE events in lung cancer (RR 0.53; 95% CI: 0.41, 0.68, p<0.001; I^2=0%).[18, level I]

Di Nisio et al. (2016) reported that thromboprophylaxis using LMWH significantly reduced symptomatic VTE by 60% (4 RCTs; n=933; RR 0.40; 95% CI: 0.20, 0.80) compared with no thromboprophylaxis.[22, level I]

Ben-Aharon et al. (2014) reported that primary prophylaxis with LMWH significantly reduced symptomatic VTE in lung cancer (RR 0.42; 95% CI: 0.25, 0.71; p=0.001; I^2=0%) with NNT 33 (95% CI: 25, 100). The authors concluded that VTE prophylaxis should be considered for ambulatory patients with lung cancer receiving chemotherapy as the benefit of LMWH reducing the incidence of symptomatic VTE was apparent in this specific population.[23, level I]

Phan et al. (2014) reported that significant reduction in VTE events was observed with LMWH prophylaxis among patients with lung cancer (3 RCTs; n=1,926; OR 0.46; 95% CI: 0.29, 0.74; I^2=0%).[24, level I]

5.1.1 c) Pancreatic cancer

Five studies showed that prophylactic anticoagulation significantly reduced VTE events in pancreatic cancer.[17,18,22–24]

Becattini et al. (2020) reported that anticoagulant prophylaxis (warfarin, antithrombin, LMWH and DOAC) significantly reduced the incidence of VTE in pancreatic cancer (4 RCTs; n=740; OR 0.26; 95% CI: 0.14, 0.48; I^2=21%).[17, level I]

Barbarawi et al. (2019) reported that compared with placebo, LMWH significantly reduced VTE events in pancreatic cancer (RR 0.39; 95% CI: 0.24, 0.64; p<0.001; I^2=0%).[18, level I]

Di Nisio et al. (2016) reported that thromboprophylaxis using LMWH also significantly reduced symptomatic VTE by 59% (2 RCTs, n=431; RR 0.41; 95% CI: 0.23, 0.75) compared with no thromboprophylaxis.[22, level I]

Ben-Aharon et al. (2014) reported that primary prophylaxis with LMWH significantly reduced symptomatic VTE in pancreatic cancer (RR 0.31; 95% CI: 0.18, 0.55; p<0.0001; I^2=0%) with NNT 10 (95% CI: 7, 16). The authors concluded that VTE prophylaxis should be considered for ambulatory patients with pancreatic cancer receiving chemotherapy as the benefit of LMWH reducing the incidence of symptomatic VTE was apparent in this specific population.[23, level I]

Phan et al. (2014) reported that significant reduction was observed with LMWH prophylaxis among patients with pancreatic cancer (3 RCTs; n=430; OR 0.33; 95 % CI 0.16, 0.67; I^2=0%).[24, level I]

5.1.1 d) Patients at high risk (Khorana score ≥3)

Two studies showed that prophylactic anticoagulation significantly reduced VTE events in high-risk ambulatory cancer patients (Khorana score ≥3).[17,19]

Becattini et al. (2020) reported that anticoagulant prophylaxis (warfarin, antithrombin, LMWH and DOAC) significantly reduced the incidence of VTE in high-risk patients with Khorana score ≥3 (5 RCTs; n=2,167; OR 0.48; 95% CI: 0.34, 0.68; I^2=0%).[17, level I]

Li et al. (2019) conducted a subgroup analysis for patients with intermediate (score 2; n=960) and high risk (score ≥3; n=455) Khorana score. Compared with placebo, significant reduction in overall VTE incidence during first six months was seen with DOAC in patients with high risk Khorana score [(RR 0.47; 95% CI: 0.25, 0.89); (ARD −6.08%; 95% CI: −11.21, −0.95)]. No significant reduction was observed in the intermediate-risk group [(RR 0.60; 95% CI: 0.30, 1.18); (ARD −3.31%; 95% CI: −6.71, +0.09)]. The ARD was smaller in intermediate-risk group compared to high-risk group. The authors suggested that a Khorana score risk-stratified strategy should be considered for decisions regarding thromboprophylaxis to ensure the largest absolute risk reduction in the highest risk patient population.[19, level I]

5.1.2 Mortality

Seven studies showed that prophylactic anticoagulation did not significantly reduce mortality in ambulatory cancer patients.[17,19–24]

Becattini et al. (2020) reported that anticoagulant prophylaxis (warfarin, antithrombin, LMWH and DOAC) did not significantly reduced VTE-related mortality (6 RCTs; n=4,705; OR 0.52, 95% CI 0.25, 1.08; I^2=0%).[17, level I]

Barbarawi et al. (2019) reported that compared with placebo, significant reduction in all-cause mortality was seen with LMWH (RR 0.95; 95% CI: 0.91, 0.99, p=0.02; I^2=7%). However, no significant reduction was seen with DOAC (RR 0.93; 95% CI: 0.58, 1.48; p=0.76; I^2=53%). In terms of VTE-related mortality, no significant reduction was seen with LMWH compared with placebo (RR 0.62; 95% CI: 0.28, 1.34; p=0.22; I^2=0%).[18, level I]

Li et al. (2019) found that compared with placebo, there was no significant reduction in all-cause mortality during first six months with DOAC [(RR 0.98; 95% CI: 0.67, 1.44; p=0.91; I^2=54%); (ARD −0.53%; 95% CI: −6.88, +5.83)].[19, level I]

Akl et al. (2017) compared heparin (UFH and LMWH) with placebo or no intervention. Heparin did not significantly reduce all-cause mortality at 12 months [(18 RCTs; n=9,575; RR 0.98; 95% CI: 0.93, 1.03; p=0.45; I^2=31%); (RD 10 fewer per 1000; 95% CI: 35 fewer to 15 more; moderate certainty of evidence)]; all-cause mortality at 24 months [(14 RCTs; n=5,229; RR 0.99; 95% CI: 0.96, 1.01; p=0.31; I^2=27%); (RD 8 fewer per 1000; 95% CI: 31 fewer to 8 more; moderate certainty of evidence)] and all-cause mortality time-to-event analysis (15 RCTs; n=8,388; HR 0.93; 95% CI: 0.84, 1.03; p=0.18; I^2=64%). For the subgroup analysis for lung versus non-lung cancer and advanced versus non-advanced cancer, the test for subgroup difference was not statistically significant. The authors concluded that heparin appeared to have no effect on mortality at 12 months and 24 months in ambulatory cancer patients.[20, level I]

Kahale et al. (2017) reported that warfarin appeared to have no effect on mortality at six months (3 RCTs; n=964; RR 0.93; 95% CI: 0.77,1.13; *p*=0.46; I^2=6%); mortality at one year [(5 RCTs; n=1,281; RR 0.95; 95% CI: 0.87,1.03; *p*=0.21); (RD 29 fewer per 1000, 95% CI: 75 fewer to 17 more); I^2=0%; moderate certainty evidence]; mortality at two years (2 RCTs; n=528; RR 0.99; 95% CI: 0.70,1.30; *p*=0.77; I^2=93%); and mortality at five years (1 RCT; n=344; RR 0.93; 95% CI: 0.83,1.03; *p*=0.16; I^2=100%). For the subgroup analysis of lung versus non-lung cancer, the test for subgroup difference was not statistically significant. Clinically important effect of apixaban on mortality at three months could not be confirmed or excluded [(1 RCT; n=92; RR 0.24; 95% CI: 0.02, 2.56; *p*=0.24); (RD 51 fewer per 1000, 95% CI: 65 fewer to 104 more); low certainty evidence]. The authors concluded that the existing evidence does not show a mortality benefit from oral anticoagulation in people with cancer.[21, level I] However, recent DOAC trials on apixaban and rivaroxaban were not yet available during the conduct of this Cochrane review.[25,26]

Di Nisio et al. (2016) reported that there was no statistically significant difference in one-year mortality for LMWH versus no thromboprophylaxis (9 RCTs; n=3,284; RR 0.93; 95% CI: 0.80, 1.09; low-quality evidence). For UFH versus no thromboprophylaxis (1 RCT; n=277) in small cell lung cancer, the summary estimate did not conclusively rule out an increase or reduction in one-year mortality (RR 0.86; 95% CI: 0.72, 1.03; moderate-quality evidence).[22, level I]

Ben-Aharon et al. (2014) reported that there was no statistically significant benefit for LMWH in one-year mortality rates (6 RCTs, n=2,550; RR 0.93; 95% CI: 0.83, 1.04; *p*=0.18; I^2=51%) compared with placebo or no thromboprophylaxis.[23, level I]

Phan et al. (2014) reported that there was no statistically significant difference in all-cause mortality between LMWH and placebo groups (8 RCTs; n=6,374; OR 0.97; 95 % CI 0.87, 1.08; I^2=17.8 %).[24, level I]

Table 2: Summary of efficacy outcomes for prophylactic anticoagulation in ambulatory cancer patients compared with placebo or no thromboprophylaxis.

Efficacy outcomes	Specific population	Study	Anticoagulants			
			UFH	LMWH	DOAC	Warfarin
Incidence of VTE (symptomatic/ asymptomatic DVT + PE)		Becattini 2020		*OR 0.51; 95% CI: 0.43, 0.61[a]		
				*OR 0.43; 95% CI: 0.33, 0.56	*OR 0.49; 95% CI: 0.33, 0.74	
		Barbarawi 2019		*RR 0.58; 95% CI: 0.48, 0.69	*RR 0.39; 95% CI: 0.24, 0.63	
		Li 2019			*RR 0.56; 95% CI: 0.35, 0.89	
		Di Nisio 2016		*RR 0.59; 95% CI: 0.48, 0.73		
		Ben-Aharon 2014		*RR 0.56; 95% CI: 0.38, 0.81		
		Phan 2014		*OR 0.53; 95% CI: 0.41, 0.70		
	Lung cancer	Becattini 2020		*OR 0.42; 95% CI: 0.26, 0.67[a]		
		Phan 2014		*OR 0.46; 95% CI: 0.29, 0.74		
	Pancreatic cancer	Becattini 2020		*OR 0.26; 95% CI: 0.14, 0.48[a]		
		Phan 2014		*OR 0.33; 95% CI: 0.16, 0.67		
	High risk (Khorana score ≥3)	Becattini 2020		*OR 0.48; 95% CI: 0.34, 0.68[a]		
		Li 2019			*RR 0.47; 95% CI: 0.25, 0.89	
Symptomatic VTE (symptomatic DVT + PE)		Becattini 2020		*OR 0.49; 95% CI: 0.39, 0.61[a]		
		Li 2019			RR 0.58; 95% CI: 0.29, 1.13	
		Akl 2017	*RR 0.56; 95% CI: 0.47, 0.68			
		Di Nisio 2016			*RR 0.08; 95% CI: 0.01, 0.67[b]	RR 0.15; 95% CI: 0.02, 1.20
		Ben-Aharon 2014		*RR 0.46; 95% CI: 0.32, 0.67		
	Lung cancer	Ben-Aharon 2014		*RR 0.42; 95% CI: 0.25, 0.71		
		Di Nisio 2016		*RR 0.40; 95% CI: 0.20, 0.80		
	Pancreatic cancer	Ben-Aharon 2014		*RR 0.31; 95% CI: 0.18, 0.55		
		Di Nisio 2016		*RR 0.41; 95% CI: 0.23, 0.75		
Symptomatic DVT		Akl 2017	*RR 0.46; 95% CI: 0.33, 0.63			
		Kahale 2017			RR 0.07; 95% CI: 0.00, 1.32[b]	RR 0.08; 95% CI: 0.00, 1.42
Symptomatic PE		Akl 2017	*RR 0.61; 95% CI: 0.47, 0.80			
		Kahale 2017			RR 0.16; 95% CI: 0.01, 3.91[b]	RR 1.05; 95% CI: 0.07,16.58
Mortality	VTE-related	Becattini 2020		OR 0.52, 95% CI: 0.25, 1.08[a]		
		Barbarawi 2019		RR 0.62; 95% CI: 0.28, 1.34		
	All-cause (unspecified duration)	Barbarawi 2019		*RR 0.95; 95% CI: 0.91, 0.99	RR 0.93; 95% CI: 0.58, 1.48	
		Phan 2014		OR 0.97; 95 % CI 0.87, 1.08		
	All-cause (3 months)	Kahale 2017			RR 0.24; 95% CI: 0.02, 2.56[b]	
	All-cause (6 months)	Li 2019			RR 0.98; 95% CI: 0.67, 1.44	
	All-cause (12 months)	Akl 2017	RR 0.98; 95% CI: 0.93, 1.03			
		Kahale 2017				RR 0.95; 95% CI: 0.87,1.03
		Di Nisio 2016	RR 0.86; 95% CI: 0.72, 1.03	RR 0.93; 95% CI: 0.80, 1.09		
		Ben-Aharon 2014		RR 0.93; 95% CI: 0.83, 1.04		
	All-cause (24 months)	Akl 2017	RR 0.99; 95% CI: 0.96, 1.01			

CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; OR, odds ratio; PE, pulmonary embolism; RR, risk ratio; UFH, unfractionated heparin; VTE, venous thromboembolism. Statistical significance * = p<0.05 or CI for OR/RR not crossing the null value of 1. [a]One study comparing antithrombin with no antithrombin was included. [b]Only one study comparing apixaban with placebo was included.

5.2 SAFETY

A total of eight SRs were included for the evaluation of safety.[17–24] Outcome measures include major bleeding, clinically relevant non-major bleeding (CRNMB), minor bleeding, thrombocytopaenia and adverse events. Major bleeding is typically defined as overt bleeding associated with a fall in haemoglobin of 2g/dL or more, or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. As for CRNMB, it is typically defined as overt bleeding that does not meet the criteria for major bleeding, but is associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life. Minor bleeding is typically defined as a bleeding event not matching the criteria for major bleeding or CRNMB.[22]

Becattini et al. (2020) evaluated major bleeding for secondary outcome with anticoagulant prophylaxis (warfarin, antithrombin, LMWH and DOAC). There was no significant increase in risk of major bleeding with anticoagulant prophylaxis (OR 1.30; 95% CI: 0.98, 1.73; I^2=0%) compared with placebo or none. Sensitivity analysis showed that when analysis was limited to high-quality studies or those with VTE as the primary outcome, anticoagulant prophylaxis was associated with a marginally significant increase in major bleeding. The authors concluded that prophylaxis with oral or parenteral anticoagulants reduced VTE risk in ambulatory cancer patients, with an acceptable increase in major bleeding.[17, level I]

Barbarawi et al. (2019) reported that compared with placebo, no significant increase in risk of major bleeding was seen with LMWH (RR 1.26; 95% CI: 0.92, 1.74; *p*=0.16; I^2=0%) and DOAC (RR 1.76; 95% CI: 0.83, 3.73; *p*=0.14; I^2=0%). The authors concluded that the potentially protective effect of lowering VTE events for both LMWH and DOAC compared with placebo must be balanced against possible increased bleeding risk for some patients.[18, level I]

Li et al. (2019) evaluated major bleeding and CRNMB incidence during on-treatment period for safety outcomes with the use of DOAC. Compared with placebo, there was no statistically significant increase in risk of major bleeding [(RR 1.96; 95% CI: 0.80, 4.82; *p*=0.14; I^2=0%); (ARD +0.99%; 95% CI: -0.31, +2.28)] and CRNMB while on-treatment with DOAC [(RR 1.28; 95% CI: 0.74, 2.20; *p*=0.37; I^2=0%); (ARD +0.83%; 95% CI: -1.00, +2.66)]. The authors concluded that low-dose DOAC prophylaxis may increase the likelihood of bleeding in high-risk cancer patients starting systemic chemotherapy.[19, level I]

Akl et al. (2017) evaluated major bleeding, minor bleeding and thrombocytopaenia for secondary outcomes with the use of heparin (UFH and LMWH) versus no heparin. The authors commented that heparin likely increased the risks of major bleeding compared to no heparin [(18 RCTs; n=9,592; RR 1.30; 95% CI: 0.94, 1.79; *p*=0.11; I^2=0%); (RD 4 more per 1000; 95% CI: 1 fewer to 11 more; moderate certainty of evidence)]. The authors also commented that heparin likely increased the risks of minor bleeding compared to no heparin [(16 RCTs; n=9,245; RR 1.70; 95% CI: 1.13, 2.55; *p*=0.01; I^2=53%); (RD 17 more per 1000; 95% CI: 3 more to 37 more; high certainty of evidence)]. Results failed to confirm or to exclude a beneficial or detrimental effect of heparin on thrombocytopaenia (12 RCTs; n=5,832; RR 0.69; 95% CI: 0.37, 1.27; *p*=0.23; I^2=83%); RD 33 fewer per 1000; 95% CI: 66 fewer to 28 more; moderate certainty of evidence). Sensitivity analysis excluding the one

study at high risk of bias from the analyses did not change the results significantly. The authors concluded that heparin likely increased major and minor bleeding in ambulatory cancer patients.[20, level I]

Kahale et al. (2017) evaluated major bleeding, minor bleeding for secondary outcomes with the use of oral anticoagulants versus placebo or no thromboprophylaxis. Warfarin appeared to have increased risk of major bleeding [(5 RCTs; n=1,281; RR 2.93; 95% CI: 1.86, 4.62; p<0.0001); (RD 107 more per 1000, 95% CI: 48 more to 201 more); I^2=6%; moderate certainty evidence] and minor bleeding [(4 RCTs; n=863; RR 3.14; 95% CI: 1.85, 5.32; p<0.0001); (RD 167 more per 1000, 95% CI: 66 more to 337 more); I^2=21%; moderate certainty evidence]. Clinically important effect of apixaban (1 RCT; n=92) on major bleeding [(RR 0.16; 95% CI: 0.01, 3.91; p=0.26); (RD 28 fewer per 1000, 95% CI: 33 fewer to 97 more); low certainty evidence] and minor bleeding [(RR 4.43; 95% CI: 0.25, 79.68; p=0.31); (RD 0 fewer per 1000, 95% CI: 0 fewer to 8 more); low certainty evidence] could not be confirmed or excluded. The sensitivity analyses did not change the results significantly. The authors concluded that oral anticoagulation in people with cancer suggested an increased risk for bleeding.[21, level I] However, recent DOAC trials on apixaban and rivaroxaban were not yet available during the conduct of this Cochrane review.[25,26]

Di Nisio et al. (2016) evaluated major bleeding for primary outcome; and clinically relevant bleeding (major and CRNMB); minor bleeding and serious adverse event for secondary outcome. For LMWH versus no thromboprophylaxis, the difference in major bleeding was not statistically significant (13 RCTs; n=6,356; RR 1.44; 95% CI: 0.98, 2.11; low-quality evidence) in the absence of heterogeneity (Tau^2=0.00); however, there was significant increase in clinically relevant bleeding (4 RCTs; n=3,105; RR 3.40, 95% CI: 1.20, 9.63; Tau^2=0.73; moderate-quality evidence). There was no statistically significant benefit or harm for minor bleeding (RR 1.23; 95% CI: 0.89, 1.70) and serious adverse events (RR 0.86; 95% CI: 0.70, 1.07). The results of stratified analyses did not show any effect of the type of LMWH, dosage, type of cancer, definition of major bleeding, trial size, or design characteristics on the RR of major bleeding. There was no evidence for a linear association between treatment duration and the risk of major bleeding based on meta-regression analysis (p=0.751).[22, level I]

For LMWH versus aspirin in multiple myeloma (2 RCTs; n=781), there was no statistically significant difference in major bleeding (RR 0.14; 95% CI: 0.01, 2.76; low-quality evidence). For UFH versus no thromboprophylaxis in small cell lung cancer (1 RCT; n=277), there was no statistically significant difference in clinically relevant bleeding (RR 2.01; 95% CI: 0.18, 21.96; low-quality evidence); no cases of HIIT were reported. For warfarin versus placebo or no thromboprophylaxis (1 RCT; n=311), warfarin may increase the risk of major bleeding in breast cancer and SCLC (RR 3.82; 95% CI: 0.97, 15.04; low-quality evidence) with evidence of a high degree of heterogeneity (Tau^2=0.71). For warfarin versus aspirin in multiple myeloma (1 RCT; n=440), there was no statistically significant difference in major bleeding (RR 0.14; 95% CI: 0.01, 2.75; low-quality evidence). As for apixaban versus placebo (1 RCT; n=122), there was no statistically significant difference in major bleeding (RR 0.62; 95% CI: 0.06, 6.63; low-quality evidence); and clinically relevant bleeding (RR 1.87; 95% CI: 0.23, 14.91; low-quality evidence). The authors concluded that the risk of major bleeding associated with LMWH, while not reaching statistical significance, suggested caution and mandated additional studies to determine the risk-to-benefit ratio of LMWH in ambulatory cancer patients receiving chemotherapy.[22, level I]

Ben-Aharon et al. (2014) evaluated grade 3 or 4 haematological and non-haematological adverse events) for secondary outcomes which were reported in nine trials evaluating 6,595 patients. Data regarding major bleeding and clinically relevant bleeding (defined as major plus minor bleeding) were extracted. There was no significant increase in the rate of clinically relevant bleeding (RR 1.29; 95% CI: 0.95, 1.77) and major bleeding events (RR 1.28; 95% CI: 0.84, 1.95) for LMWH compared with placebo or no thromboprophylaxis. There was no significant increase in thrombocytopaenia (RR 1.05; 95% CI: 0.76, 1.45). The NNTH for serious adverse events was 100 (95% CI: 50, very large number). The authors concluded that LMWH reduced the incidence of symptomatic VTE and PE in patients receiving chemotherapy for cancer, with no apparent increase in major bleeding.[23, level I]

Phan et al. (2014) reported that there were 68 major bleeding events among 4,127 patients who received thromboprophylaxis and 40 major bleeding events in 3,748 patients who received placebo. Major bleeding events were significantly higher in thromboprophylaxis group compared to placebo group (OR 1.65; 95 % CI: 1.12, 2.44; I^2=0%). Sensitivity analysis including only studies with low risk of bias showed that the bleeding likelihood decreased (OR 1.41; 95 % CI: 0.93, 2.14; I^2=0%) and was no longer statistically significant. When only LMWH studies were grouped, the odds of major bleeding increased significantly (OR 1.57; 95 % CI: 1.04, 2.37; I^2=0%).[24, level I]

5.2.1 a) Parenteral versus oral anticoagulant

Becattini et al. (2020) reported that there was no significant increase in risk of major bleeding with parenteral (21 RCTs; n=10,713; OR 1.27; 95% CI: 0.93, 1.73; I^2=0%) or oral anticoagulant prophylaxis (3 RCTs; n=1,494; OR 1.78; 95% CI: 0.83, 3.83; I^2=0%) compared with placebo or no thromboprophylaxis.[17, level I]

5.2.1 b) Lung cancer

Barbarawi et al. (2019) reported that compared with placebo, LMWH prophylaxis did not increase the risk of major bleeding in lung cancer (RR 1.21; 95% CI: 0.68, 2.18; *p*=0.51; I^2=0%).[18, level I]

Di Nisio et al. (2016) reported that compared with no thromboprophylaxis, LMWH did not increase the risk of major bleeding in lung cancer (4 RCTs; n=3,065; RR 1.49; 95% CI: 0.79, 2.80) in the absence of statistical heterogeneity (Tau^2=0.00).[22, level I]

5.2.1 c) Pancreatic cancer

Barbarawi et al. (2019) reported that compared with placebo, LMWH prophylaxis did not increase the risk of major bleeding in pancreatic cancer (RR 1.21; 95% CI: 0.58, 2.51; *p*=0.62; I^2=0%).[18, level I]

Di Nisio et al. (2016) reported that compared with no thromboprophylaxis, LMWH did not increase the risk of major bleeding in pancreatic cancer (2 RCTs; n=433; RR 1.21; 95% CI: 0.58, 2.51) in the absence of statistical heterogeneity (Tau^2=0.00).[22, level I]

5.2.1 d) Patients at high risk (Khorana score ≥3)

Li et al. (2019) reported that there was no statistically significant increase in risk of major bleeding while on-treatment with DOAC in high-risk patients [(RR 1.60; 95% CI: 0.42, 6.01); (ARD +1.42%; 95% CI: −1.14, +3.97)].[19, level I]

Table 3: Summary of safety outcomes for prophylactic anticoagulation in ambulatory cancer patients compared with placebo or no thromboprophylaxis.

Safety outcomes	Specific population	Study	Anticoagulants			
			UFH	LMWH	DOAC	Warfarin
Major bleeding[a]		Becattini 2020		OR 1.30; 95% CI: 0.98, 1.73[d]		
		Becattini 2020		OR 1.27; 95% CI: 0.93, 1.73[d]	OR 1.78; 95% CI: 0.83, 3.83	
		Barbarawi 2019		RR 1.26; 95% CI: 0.92, 1.74	RR 1.76; 95% CI: 0.83, 3.73	
		Li 2019			RR 1.96; 95% CI: 0.80, 4.82	
		Akl 2017	RR 1.30; 95% CI: 0.94, 1.79			
		Kahale 2017			RR 0.16; 95% CI: 0.01, 3.91[e]	*RR 2.93; 95% CI: 1.86, 4.62
		Di Nisio 2016		RR 1.44; 95% CI: 0.98, 2.11	RR 0.62; 95% CI: 0.06, 6.63[e]	RR 3.82; 95% CI: 0.97, 15.04[f]
		Ben-Aharon 2014		RR 1.28; 95% CI: 0.84, 1.95		
		Phan 2014		*OR 1.57; 95 % CI: 1.04, 2.37		
	Lung cancer	Di Nisio 2016		RR 1.49; 95% CI: 0.79, 2.80		
	Pancreatic cancer			RR 1.21; 95% CI: 0.58, 2.51		
	High risk (Khorana score ≥3)	Li 2019			RR 1.60; 95% CI: 0.42, 6.01	
Clinically relevant bleeding	Major + CRNMB	Di Nisio 2016	RR 2.01; 95% CI: 0.18, 21.96	*RR 3.40; 95% CI: 1.20, 9.63	RR 1.87; 95% CI: 0.23, 14.91[e]	
	Major + minor bleeding	Ben-Aharon 2014		RR 1.29; 95% CI: 0.95, 1.77		
CRNMB[b]		Li 2019			RR 1.28; 95% CI: 0.74, 2.20	
Minor bleeding[c]		Akl 2017	*RR 1.70; 95% CI: 1.13, 2.55			
		Kahale 2017			*RR 4.43; 95% CI: 0.25, 79.68[e]	*RR 3.14; 95% CI: 1.85, 5.32
		Di Nisio 2016		RR 1.23; 95% CI: 0.89, 1.70		
Thrombocytopaenia		Akl 2017	RR 0.69; 95% CI: 0.37, 1.27			
		Ben-Aharon 2014		RR 1.05; 95% CI: 0.76, 1.45		
Serious adverse events		Di Nisio 2016		RR 0.86; 95% CI: 0.70, 1.07		

CI, confidence interval; CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; OR, odds ratio; RR, risk ratio; UFH, unfractionated heparin. Statistical significance * = $p<0.05$ or CI for OR/RR not crossing the null value of 1. [a]Major bleeding is typically defined as overt bleeding associated with a fall in haemoglobin of 2 g/dL or more, or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. [b]CRNMB is typically defined as overt bleeding that does not meet the criteria for major bleeding, but is associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life. [c]Minor bleeding is typically defined as a bleeding event not matching the criteria for major bleeding or CRNMB.[22] [d]One study comparing antithrombin with no antithrombin was included. [e]Only one study comparing apixaban with placebo was included. [f]Only one study comparing warfarin with placebo was included.

5.3 ECONOMIC IMPLICATION

A total of two CEAs were included for the evaluation of cost-effectiveness.[27,28]

Li et al. (2020) conducted a CEA to evaluate the cost-utility of low-dose DOAC versus placebo for the prevention of cancer-associated thrombosis in ambulatory cancer patients from health sector perspective using a Markov state-transition model. The target population was a hypothetical cohort of ambulatory patients with cancer aged 60 years who were considered at intermediate-to-high risk for VTE (Khorana score ≥2) without absolute contraindications for thromboprophylaxis. Transition probabilities, RRs and 95% CIs for VTE, bleeding, discontinuation, and mortality outcomes were derived from a meta-analysis[19] and relevant epidemiology studies. Direct medical costs and complications were included. All cost estimates were inflated to May 2019 US dollars using the US Consumer Price Index for all urban consumers' medical care. Direct non-medical cost, indirect cost, individual coupons or cost-assistance programmes were not considered. Utility weights were derived from published literature. Three percent yearly discounts for outcome and costs were applied based on the US rates.[27, level I]

For the base-case analysis, cumulative costs and quality adjusted life-years (QALYs) were estimated for each treatment over a lifetime with one-month cycle length to derive the incremental cost-effectiveness ratio (ICER). One-way deterministic, probabilistic and scenario sensitivity analyses were performed. Probabilistic sensitivity analysis using Monte Carlo simulation over 1000 times was performed to generate cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC). Several scenario sensitivity analyses were performed by varying the duration of intervention (six versus 12 months), treatment effect estimate (on-treatment versus intention-to-treat period), and the risk profile of the population (high risk versus intermediate risk). All data analyses were conducted using Microsoft Excel for Mac 16.17.[27, level I]

The base-case analysis showed that DOAC prophylaxis for six months was associated with 32 fewer VTEs (20 fewer PEs; 12 fewer DVTs), 11 more major bleeding events, and 21 more CRNMB events per 1000 patients in patients with cancer at intermediate-to-high risk for VTE. The intervention group had a mean total cost of US$9,899 per person, 6.51 life-years, and 4.79 QALYs. The placebo group had a mean total cost of US$8,454 per person, 6.34 life-years, and 4.67 QALYs. The incremental cost and QALY increases were US$1,445 and 0.12, respectively, with an ICER of US$11,947 per QALY gained over a lifetime.[27, level I]

The one-way sensitivity analyses showed that the key drivers of ICER variations were the RRs of DVT, PE, and major bleeding as well as drug cost. Probabilistic sensitivity analysis showed that DOAC were associated with an incremental cost increase of US$1,537, an incremental QALY increase of 0.11, and an ICER of US$14,330 per QALY. Based on CEAC, the strategy would be 94% cost-effective at threshold of US$50,000 per QALY. The scenario sensitivity analyses showed that compared with 6-month DOAC prophylaxis, 12-month DOAC prophylaxis was associated with a greater incremental cost increase (US$2,410 versus US$1,445), a

greater incremental QALY increase (0.15 versus 0.12), and an ICER of US$16,389 per QALY gained. The stratified analysis showed that selection of high-risk patients (Khorana scores ≥3) had an incremental cost increase of US$1,103, an incremental QALY increase of 0.19, with an ICER of US$5,794 per QALY gained. The selection of intermediate-risk patients (Khorana score 2) had an incremental cost increase of US$1,527, an incremental QALY increase of 0.11, and an ICER of US$15,118 per QALY gained.[27, level I]

The authors concluded that low-dose 6-month DOAC thromboprophylaxis to be cost-effective in patients with cancer who were at intermediate-to-high risk for VTE. The implementation of this strategy in patients with Khorana scores ≥3 may lead to the highest cost-benefit ratio. However, there may be conflict of interest as the authors disclosed receiving fees/grants/support from pharmaceutical companies including Janssen, Pfizer, Bayer, Daiichi Sankyo, Aspen Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, Sanofi, and LEO Pharma.[27, level I]

Pishko et al. (2012) conducted a CEA to evaluate anticoagulation costs during four months of chemotherapy following a new cancer diagnosis and survival benefit over 24 months in ambulatory cancer patients from US perspective using a Markov state-transition model with one-month cycle length. The target population was a hypothetical cohort of ambulatory patients with advanced cancer, no previous VTE and no anticoagulation indication and treated with four months of enoxaparin 40 mg subcutaneously once daily (fixed dosage). Transition probabilities, VTE risk, major and minor bleeding, mortality and other clinical parameters were obtained from a Cochrane 2011 meta-analysis and three other published studies. Pharmacy costs for enoxaparin, including syringes and needles, were based on the average wholesale prices in 2011. Hospitalisation costs were derived from 2009 Healthcare Cost and Utilisation Project (HCUP) data, and other costs were obtained from the medical literature. All costs were inflated to 2011 levels using the US Consumer Price Index. Quality-of-life measures were obtained from published studies. Discounting of the outcomes and costs was not reported.[28, level I]

The model was constructed using TreeAge Pro Suite 2009. Two treatment strategies, LMWH or no LWMH, were compared. One-way sensitivity analyses were conducted to assess the effects of varying baseline estimates (LMWH cost per month, RR of mortality, 2-year mortality risk, RR of VTE and RR of major bleed) on ICER. A two-way sensitivity analysis was conducted to assess the effect of varying both LMWH duration and RR of mortality. All parameter values were simultaneously varied 10,000 times over predefined probability distributions in a probabilistic sensitivity analysis. Patients with advanced cancer were assumed to have a two-year mortality risk of 85.9% based on Cochrane meta-analysis data, but with no other indication for prophylactic anticoagulation including hospitalisation, central venous line placement, or surgery.[28, level I]

The base-case analysis showed that the cost of 4-month LMWH prophylaxis was US$3,465 with 0.6674 QALYs while the cost of no-prophylaxis strategy was US$252 with 0.630 QALYs. The incremental cost and QALY increases were US$3,213 and 0.0354 QALYs, respectively, with an ICER of US$90,893 per QALY gained (falling

within the acceptable range of US$100,000 per QALY gained). One-way sensitivity analyses showed that LMWH prophylaxis would remain economically reasonable (cost less than US$100,000 per QALY) if two-year mortality exceeded 75%; anticoagulation costs were less than US$1,076 per month; or if LMWH relative mortality risk was less than 0.927. Results were not sensitive to variation in RR of VTE on anticoagulation, nor to major or minor bleeding risk on anticoagulation. The two-way sensitivity analysis showed that the cost of extending anticoagulation up to 24 months was acceptable only when the mortality RR was less than 0.762.[28, level I]

The probabilistic sensitivity analysis showed that using a willingness-to-pay threshold of US$100,000 per QALY gained, there was 56.1% likelihood that LMWH would be considered cost-effective in ambulatory cancer patients. If a US$75,000/QALY threshold was used, LWMH was favoured in 34.0% of model iterations; if the threshold was US$50,000 per QALY gained, there was 9.5% likelihood LMWH was favoured. However, the model did not include downstream VTE morbidities, such as recurrent VTE, post-thrombotic syndrome, chronic thromboembolic hypertension, possible heparin-induced thrombocytopaenia, and higher bleed rates from treatment dose anticoagulants for those who did develop VTE and their subsequent costs. Inclusion of these costs would likely have made LMWH more cost-effective. The authors concluded that prophylactic LMWH given to decrease cancer-related mortality, with no conventional indication, appeared to be economically reasonable if its suggested mortality benefit is confirmed in future trials.[28, level I] However, in this review, LMWH prophylaxis appeared to have no mortality benefit for ambulatory cancer patients.

5.4 ORGANISATIONAL ISSUES

The Khorana score, introduced in 2008, is the most well-known risk stratification tool used to guide the selection of cancer patients at high risk of VTE.[29] The score assigns points to five clinical and pre-chemotherapy laboratory parameters: primary tumour site (+1 or 2 points), platelet count of ≥350 x 10^9/L (+1 point), haemoglobin concentration of <10 g/dL or use of red cell growth factors (+1 point), leukocyte count of >11 x 10^9/L (+1 point), and a BMI of ≥35 kg/m^2 (+1 point) (Table 1).[12,16]

Mulder et al. (2019) conducted a SR and MA to evaluate the performance of the Khorana score in predicting VTE in ambulatory cancer patients. Studies which evaluated the Khorana score were searched via Embase and MEDLINE from January 2008 to June 2018. A total of 45 articles and eight abstracts were included, comprising 55 cohorts enrolling 34,555 ambulatory cancer patients, of whom 2,386 (6.9%) were diagnosed with VTE during follow-up. In terms of risk classification by Khorana score, 6,319 patients (19%) had a Khorana score of 0 points (low risk), 21,172 patients (64%) a score of 1 or 2 points (intermediate risk), and 5,614 patients (17%) a score of 3 or more points (high risk). The incidence of VTE in the first six months was 5.0% (95% CI: 3.9, 6.5) in low-risk patients; 6.6% (95% CI: 5.6, 7.7) in intermediate-risk patients; and 11.0% (95% CI: 8.8, 13.8) in high-risk patients, which indicates that there may be considerable residual risk in low-to-intermediate risk group. Of all patients who developed VTE in the first six months, only about one in four (23.4%; 95% CI: 18.4, 29.4) were classified as high risk, suggesting that a

substantial amount of ambulatory cancer patients may not be identified via the Khorana score, and may, therefore, not benefit from thromboprophylaxis. Difference in predicted performance across cancer types was also observed. In the high-risk group, the reported 6-month risk of VTE was considerably lower for patients with lung cancer (6.4%; 95% CI: 4.9, 8.4) and haematologic malignancies (7.1%; 95% CI: 2.6, 18.4) compared to those with gastrointestinal cancer (13.0%; 95% CI: 8.5, 19.6), urogenital cancer (18.2%; 95% CI: 8.6, 34.6), or various cancers (11.5%; 95% CI: 8.6, 15.3, lung vs. various, p=0.0008; hematologic vs. various, p=0.000), implying that the Khorana score may be less informative for patients with lung cancer or haematologic malignancies.[29] An individual patient data meta-analysis evaluating LMWH among 3,293 high-risk Khorana score patients with solid cancer from seven RCTs also found that the Khorana score was unable to stratify patients with lung cancer based on their VTE risk.[30]

Both ASCO and ISTH recommend that primary thromboprophylaxis should be given to ambulatory cancer patients starting chemotherapy with Khorana score ≥2, no significant risk factors for bleeding and no drug-drug interactions.[12,13] Mulder et al. (2019) found that applying a positivity threshold of 2-point rather than the conventional 3-point would increase the proportion of patients classified as high risk (from 17% to 47%) and the proportion of VTE events that occur in the high-risk group (from 23% to 55%) while in parallel decreasing the absolute risk of VTE in this group (from 11% to 9%). The authors commented that whether the 9% risk of VTE during the first six months is considered high enough to justify thromboprophylaxis is a matter of debate.[29] Another study by Di Nisio et al. (2019) evaluating other prediction scores for VTE such as PROTECHT, CONKO, and ONKOTEV scores alongside Khorana score reported that at the conventional 3-point positivity threshold, none of the scores discriminated between high- and low-risk patients whereas the use of a 2-point positivity threshold improved performance of all scores, capturing a higher proportion of VTE. The study also reported that the accuracy of these scores tend to decrease over time, suggesting the need of periodic re-evaluation to estimate possible variation of risk.[31]

6.0 DISCUSSION AND CONCLUSION

6.1 Efficacy/Effectiveness

Good level of evidence was retrieved for the evaluation of efficacy in terms of VTE events and mortality. A total of eight systematic reviews were included, three of which were Cochrane reviews. Prophylactic anticoagulation with LWMH or DOAC were associated with significant reduction in VTE events when given to ambulatory cancer patients compared with placebo or no thromboprophylaxis. Similar benefit was observed in specific populations such as lung and pancreatic cancer patients when given prophylactic anticoagulation with LMWH. Two studies showed greater risk reduction among ambulatory cancer patients with high risk for VTE (Khorana score ≥3), suggesting that a Khorana score risk-stratified strategy may be considered in this context. However, prophylactic anticoagulation with warfarin, UFH, LMWH or DOAC, appeared to have no effect on mortality in ambulatory cancer patients compared with placebo or no thromboprophylaxis.

6.2 Safety

Good level of evidence was retrieved for the evaluation of safety in terms of major bleeding, clinically relevant non-major bleeding (CRNMB), minor bleeding, thrombocytopaenia and adverse events. A total of eight systematic reviews were included, three of which were Cochrane reviews. Prophylactic anticoagulation with DOAC was not associated with significant increase in risk of major bleeding and CRNMB. As for LMWH, majority of studies showed that prophylactic anticoagulation with LMWH was not associated with significant increase in risk of major bleeding, thrombocytopaenia and adverse events. No significant increase in risk of major bleeding was observed when LMWH prophylaxis was given to specific populations such as lung and pancreatic cancer patients. As for patients with high risk for VTE (Khorana score ≥3), one study showed no significant increase in risk of major bleeding when DOAC prophylaxis was given. However, the risk of bleeding, while not reaching statistical significance, suggests caution when prophylactic anticoagulation is considered for ambulatory cancer patients.

6.3 Economic implication

Two cost-effectiveness analyses were included. One study evaluated the cost-utility of DOAC versus placebo for VTE prevention in ambulatory cancer patients from the health sector perspective using a Markov state-transition model over a lifetime. The DOAC thromboprophylaxis for six months appeared to be cost-effective in ambulatory cancer patients who were at intermediate-to-high risk for VTE with an incremental cost of US$1,445, QALY increase of 0.12, and an international cost-effectiveness ratio (ICER) of US$11,947 per QALY gained. The implementation of this strategy in high-risk patients with Khorana score ≥3 led to higher cost-benefit ratio with an incremental cost of US$1,103, QALY increase of 0.19 and an ICER of US$5,794 per QALY gained. Another study evaluated LMWH anticoagulation costs during four months of chemotherapy following a new cancer diagnosis and survival benefit over 24 months in ambulatory cancer patients from a United States perspective using a Markov state-transition model. Prophylactic LMWH appeared to be economically reasonable with an incremental cost of US$3,213, QALY increase

of 0.0354 QALYs and an ICER of US$90,893 per QALY gained. However, the model did not include downstream VTE morbidities, of which inclusion of related costs would likely have made LMWH more cost-effective. The authors concluded that LMWH prophylaxis would remain economically reasonable if future trials confirm its suggested mortality benefit. However, in this review, LMWH prophylaxis appeared to have no mortality benefit for ambulatory cancer patients.

6.4 Organisational issues

The Khorana score may help clinicians in selecting patients at high risk of VTE. However, a substantial number of cancer patients with VTE may not be identified via the Khorana score risk-stratification and may, therefore, not benefit from thromboprophylaxis. Further studies are needed to ascertain the accuracy of Khorana score in discriminating between high- and low-risk patients over time using the conventional 3-point or 2-point positivity threshold as well as stratifying patients of different cancer types based on their VTE risk.

6.5 Limitations

This technology review has several limitations. Non-English articles were excluded. Clinical heterogeneity in the incidence of VTE may arise from differences in study population in terms of tumour types, cancer site (single or multiple), disease stages, chemotherapy regimen, and methods for VTE detection (screening or symptomatic) which may have an impact on the evaluation of efficacy.[17,18,23,24] Some of the trials included in the systematic reviews had small sample size.[17,18,20–23] The lengths of follow-up were variable among studies included in the systematic reviews, ranging from six weeks to 88 months. There was also variability in practice in terms of type, dose, timing and duration (minimum four weeks to one year) of anticoagulant prophylaxis. Some studies were able to conduct subgroup analysis for lung and pancreatic cancers but not for other types of malignancies.[22–24] Patients with malignancy involving the brain are at high risks of both bleeding and thrombosis but this population was underrepresented in current DOAC trials (24 patients in AVERT[25] and excluded in CASSINI[26]), and whether this high-risk population could have similar outcomes remains unclear.[19] Prevention of VTE reduces morbidities such as post thrombotic syndrome and chronic thromboembolic related pulmonary hypertension which should be taken into consideration. However, all study outcomes did not include the risk of morbidity.[17–24] Results should be interpreted with caution as there may be conflicts of interest in some of the studies included in this review.[17,19,22,27] Some of the Cochrane review authors were involved as committee members for VTE-related guidelines.[20,21] One study did not declare conflicts of interest.[24]

6.6 Conclusion

Based on the review, there was good level of evidence indicating that prophylactic anticoagulation with low-molecular-weight heparin (LMWH) or direct oral anticoagulant (DOAC) significantly reduced venous thromboembolism (VTE) events with no significant increase in risk of major bleeding but appeared to have no effect on mortality when given to ambulatory cancer patients. The risk of bleeding, while not reaching statistical significance, suggests caution when primary thromboprophylaxis is being considered for ambulatory cancer patients. Current evidence does not support routine thromboprophylaxis in ambulatory cancer

patients. Greater risk reduction without significant increase in risk of major bleeding (two systematic reviews involving two recent DOAC trials) and higher incremental cost-effectiveness ratio (one cost-effectiveness analysis) were observed when DOAC thromboprophylaxis was given to high-risk ambulatory cancer patients, suggesting that a Khorana score risk-stratified strategy may be considered in this context. However, a substantial number of cancer patients with VTE may not be identified via the Khorana score risk-stratification and may, therefore, not benefit from thromboprophylaxis. More evidence is needed to ascertain the performance of Khorana score in selecting ambulatory cancer patients at high risk for VTE.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS / DIAGNOSTIC STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I	**Evidence obtained from at least one properly designed randomised controlled trial.**
II-I	**Evidence obtained from well-designed controlled trials without randomisation.**
II-2	**Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.**
II-3	**Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.**
III	**Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.**

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 04, 2020>
Search Strategy:

1 Neoplasms/ (415369)
2 Cancer*.tw. (1713737)
3 Neoplas*.tw. (256448)
4 Tumo?r*.tw. (1647998)
5 Malignan*.tw. (238571)
6 Carcinoma*.tw. (648597)
7 1 or 2 or 3 or 4 or 5 or 6 (3013073)
8 Outpatients/ (15505)
9 Outpatient*.tw. (163029)
10 Ambulatory Care/ (42450)
11 Ambulatory.tw. (76584)
12 8 or 9 or 10 or 11 (250326)
13 7 and 12 (20879)
14 Anticoagulants/ (74232)
15 Anticoagula*.tw. (90523)
16 Thromboprophyla*.tw.(4726)
17 DOAC*.tw. (1840)
18 NOAC*.tw. (2077)
19 Antithrombins/ (6256)
20 Thrombin inhibitor*.tw. (4618)
21 Antithrombin*.tw. (15708)
22 Dabigatran.tw. (4463)
23 Argatroban.tw. (1226)
24 Inogatran.tw. (41)
25 Melagatran.tw. (271)
26 Factor Xa Inhibitors/ (4418)
27 (Factor Xa adj1 inhibitor*).tw. (2204)
28 Apixaban.tw. (2945)
29 Betrixaban.tw. (149)
30 Edoxaban.tw. (1232)
31 Fondaparinux.tw. (1669)
32 Rivaroxaban.tw. (4695)
33 Heparin, Low-Molecular-Weight/ (8428)
34 (Low molecular weight adj1 heparin).tw. (10027)
35 Lmwh.tw. (4670)
36 Enoxaparin.tw. (4208)
37 Dalteparin.tw. (986)
38 Tinzaparin.tw. (405)
39 Nadroparin.tw. (422)
40 Semuloparin.tw. (19)
41 Heparin/ (53946)
42 heparin.tw. (75773)
43 Warfarin/ (19182)
44 warfarin.tw. (23435)
45 Aspirin/ (44411)
46 Aspirin.tw. (47339)
47 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (265336)
48 13 and 47 (528)
49 limit 48 to humans (448)
50 limit 49 to english language (400)

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per Ovid MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
EBM Reviews- NHS economic evaluation database	
PubMed	(((((((((NEOPLASMS[MeSH Terms]) OR Cancer*[Text Word]) OR Neoplas*[Text Word]) OR Tumo?r*[Text Word]) OR Malignan*[Text Word]) OR Carcinoma*[Text Word])) AND ((((OUTPATIENTS[MeSH Terms]) OR Outpatient*[Text Word]) OR AMBULATORY CARE[MeSH Terms]) OR Ambulatory[Text Word]))) AND ((((((((((((((((((((((((((((((ANTICOAGULANTS[MeSH Terms]) OR (Anticoagula*[Text Word])) OR (Thromboprophyla*[Text Word])) OR (DOAC[Text Word])) OR (NOAC[Text Word])) OR (ANTITHROMBINS[MeSH Terms])) OR (Thrombin inhibitor*[Text Word])) OR (Antithrombin*[Text Word])) OR (Dabigatran[Text Word])) OR (Argatroban[Text Word])) OR (Inogatran[Text Word])) OR (Melagatran[Text Word])) OR (FACTOR XA INHIBITORS[MeSH Terms])) OR (Factor Xa adj1 inhibitor*[Text Word])) OR (Apixaban[Text Word])) OR (Betrixaban[Text Word])) OR (Edoxaban[Text Word])) OR (Fondaparinux[Text Word])) OR (Rivaroxaban[Text Word])) OR (HEPARIN, LOW-MOLECULAR-WEIGHT[MeSH Terms])) OR (LMWH[Text Word])) OR (Low molecular weight adj1 heparin[Text Word])) OR (Enoxaparin[Text Word])) OR (Dalteparin[Text Word])) OR (Tinzaparin[Text Word])) OR (Nadroparin[Text Word])) OR (Semuloparin[Text Word])) OR (HEPARIN[MeSH Terms])) OR (Heparin[Text Word])) OR (WARFARIN[MeSH Terms])) OR (Warfarin[Text Word]) OR (ASPIRIN[MeSH Terms])) OR (Aspirin[Text Word]))))
INAHTA	Anticoagulants, anticoagulation, prophylactic anticoagulation, thromboprophylaxis

APPENDIX 3: EVIDENCE TABLE

Evidence table: Efficacy and safety
Question: What are the efficacy and adverse events of prophylactic anticoagulation in ambulatory cancer patients compared with placebo or no thromboprophylaxis?

Bibliographic citation	Study Type/Methods	LE	No. of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
1. Becattini C, Verso M, Muňoz A, et al. Updated meta-analysis on prevention of venous thromboembolism in ambulatory cancer patients. Haematologica. 2020;105(3):838-848.	**Systematic review and meta-analysis** **Aim:** To assess the clinical benefit of antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy. **Data source**: Medline and Scopus. RCTs up to December 2018 were included. **Quality assessment:** Jadad score and Cochrane risk of bias tool. **Primary outcome:** Objectively confirmed VTE, defined as the composite of PE and/or DVT adjudicated according to the criteria and procedures of the individual studies **Ancillary outcomes:** symptomatic VTE and fatal VTE. **Secondary outcome:** Major bleeding defined according to the criteria of the individual studies.	I	VTE as primary outcome: 14 RCTs, 8,226 patients [breast cancer (2), pancreatic cancer (2), acute lymphatic leukemia (1); multiple myeloma (1), glioma (1), lung cancer (1), multiple cancers (6)] Death as primary outcome: 8 RCTs, 3,727 patients [lung cancer (3), multiple cancers (5)]	VTE as primary outcome (n=4,331): 1. Levine (1994): warfarin; n=152 2. Mitchell (2003): antithrombin; n=25 3. Agnelli (2009): nadroparin 3800IU od; n=769 4. Perry (2010): dalteparin 5000IU od; n=99 5. Larocca (2011): enoxaparin 40mg od; n=166 6. Haas (2012): certoparin 3000IU od; n=268 7. Haas (2012): certoparin 3000IU od; n=174 8. Agnelli (2012): semuloparin 20mg od; n=1608 9. Maraveyas (2012): dalteparin; n=59 10. Levine (2012): apixaban; n=93 11. Pelzer (2015): enoxaparin 40mg od; n=160 12. Khorana (2017): dalteparin 5000 IU od; n=50	VTE as primary outcome (n=3,895): 1. Levine (1994): placebo; n=159 2. Mitchell (2003): none; n=60 3. Agnelli (2009): placebo; n=381 4. Perry (2010): placebo; n=87 5. Larocca (2011): aspirin 100mg od; n=176 6. Haas (2012): placebo; n=264 7. Haas (2012): placebo; n=177 8. Agnelli (2012): placebo; n=1604 9. Maraveyas (2012): none; n=62 10. Levine (2012): placebo; n=29 11. Pelzer (2015): none; n=152 12. Khorana (2017): none; n=48 13. Khorana (2019): placebo; n=421 14. Carrier (2019): placebo; n=275	Range for duration of follow-up: four weeks to one year. Range of duration of prophylaxis: four weeks to six months (in studies with VTE as primary outcome); four weeks to 12 months (in studies with death as primary outcome	**a) Efficacy** Incidence of VTE (VTE as primary outcome; 14 RCTs; n=8,226): Significant reduction was seen with anticoagulant prophylaxis (OR 0.45; 95% CI: 0.36, 0.56). **Incidence of VTE** (death as primary outcome; 8 RCTs; n=3,727): Significant reduction was seen with anticoagulant prophylaxis (OR 0.61; 95% CI: 0.47, 0.81; I^2=0%). **Pooled incidence of VTE** (22 RCTs; n=11,953): Significant reduction was seen with anticoagulant prophylaxis (OR 0.51; 95% CI: 0.43, 0.61; I^2=2.4%). **Incidence of VTE with parenteral anticoagulants** (VTE as primary outcome; 11 RCTs; n=6,700): Significant reduction was seen with anticoagulant prophylaxis (OR 0.43; 95% CI: 0.33, 0.56; I^2=0%). **Incidence of VTE with oral anticoagulants** (VTE as primary outcome; three RCTs; n=1,526): Significant reduction was seen with anticoagulant prophylaxis (OR 0.49; 95% CI: 0.33, 0.74; I^2=57%).	Authors disclosed receiving fees/ honorarium from pharmaceutical companies including Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, Daiichi Sankyo and LEO Pharma. No evidence of publication bias was found in individual comparisons at visual inspection of funnel plots.

	Statistical analysis: RevMan 5.3 software and StatsDirect 3.0 were used. Incidence of study outcomes and odds ratios (OR) with 95% CI:s were pooled using Mantel-Haenszel method. Cumulative and separate analyses for studies with VTE or mortality as the primary outcome were conducted. Fixed-effects models were used (absence of significant heterogeneity: Cochran χ^2 test p<0.10; I^2<50%). Sensitivity analyses were performed concerning (i) parenteral or oral anticoagulants; (ii) symptomatic VTE; (iii) fatal VTE; (iv) subgroups of patients based on the primary cancer site (lung, pancreas and breast); (v) patients considered as being at high-risk of VTE; and (vi) high-quality studies. Correction for zero cells were performed. Publication bias of primary outcome was assessed via the funnel plot.		**Inclusion:** studies not on post-operative VTE prevention; studies including at least one comparator arm not receiving anticoagulant prophylaxis; objective confirmation of non-fatal VTE	13. Khorana (2019): rivaroxaban 10mg od; n=420 14. Carrier (2019): apixaban 2.5mg bd; n=288 Death as primary outcome (n=1,890): 1. Kakkar (2004): dalteparin 5000 IU od; n=190 2. Altinbas (2004): dalteparin 5000 IU od; n=42 3. Klerk (2005): nadroparin; n=148 4. Sideras (2006): dalteparin 5000 IU od; n=68 5. van Doormaal (2011): nadroparin; n=244 6. Elit (2012): dalteparin; n=77 7. Lecumberri (2013): bemiparin 3500 IU; n=20 8. Macbeth (2015): dalteparin 5000 IU od; n=1101	Death as primary outcome (n=1,837): 1. Kakkar (2004): placebo; n=184 2. Altinbas (2004): placebo; n=42 3. Klerk (2005): placebo; n=154 4. Sideras (2006): placebo; n=70 5. van Doormaal (2011); none; n=259 6. Elit (2012): none; n=9 7. Lecumberri (2013): none; n=18 8. Macbeth (2015): none; n=1101		**Symptomatic VTE** (VTE as primary outcome; 12 RCTs; n=1,518): Significant reduction was seen with anticoagulant prophylaxis (OR 0.48; 95% CI: 0.39, 0.60; I^2=0%). **Pooled symptomatic VTE** (17 RCTs; n=10,374): Significant reduction was seen with anticoagulant prophylaxis (OR 0.49; 95% CI: 0.39, 0.61; I^2=0%). **Fatal VTE** (VTE as primary outcome; six RCTs; n=4,705) No significant reduction was seen with anticoagulant prophylaxis (OR 0.52, 95% CI: 0.25, 1.08; I^2=0%). **Incidence of VTE in lung cancer** (VTE as primary outcome; three RCTs; n=1,991): Significant reduction was seen with anticoagulant prophylaxis (OR 0.42; 95% CI: 0.26, 0.67 I^2=0%). **Incidence of VTE in pancreatic cancer** (VTE as primary outcome; four RCTs; n=740): Significant reduction was seen with anticoagulant prophylaxis (OR 0.26; 95% CI: 0.14, 0.48; I^2=21%). **Incidence of VTE in patients at estimated high risk according to Khorana score** (VTE as primary outcome; five RCTs; n=2,167): Significant reduction was seen with anticoagulant prophylaxis (OR 0.48; 95% CI: 0.34, 0.68; I^2=0%). **Incidence of VTE in high-quality studies** (VTE as primary outcome; nine RCTs; n=7,628): Significant reduction was seen with anticoagulant prophylaxis (OR 0.47; 95% CI: 0.36, 0.60; I^2=0%).	In this study, the incidence of VTE in ambulatory cancer patients treated with chemotherapy varied from 2.3% to over 30% without anticoagulant prophylaxis. Pooled incidence of major bleeding was 2% in patients randomised to anticoagulant prophylaxis, with high variability across individual studies as shown by significant heterogeneity.

							Sensitivity analysis: The efficacy of prophylaxis in reducing VTE was consistent in studies with VTE or death as primary outcome and in all sensitivity analyses. **b) Safety** **Major bleeding risk** (VTE as primary outcome): A marginally significant increase was seen with anticoagulant prophylaxis (OR 1.43; 95% CI: 1.01, 2.04). **Pooled major bleeding risk** (24 RCTs; n=12,014): No significant increase was seen with anticoagulant prophylaxis (OR 1.30; 95% CI: 0.98, 1.73; I^2=0%) **Major bleeding risk with parenteral anticoagulants** (21 RCTs; n=10,713) No significant increase was seen with anticoagulant prophylaxis (OR 1.27; 95% CI: 0.93, 1.73; I^2=0%) **Major bleeding risk with oral anticoagulants** (three RCTs; n=1,494) No significant increase was seen with anticoagulant prophylaxis (OR 1.78; 95% CI: 0.83, 3.83; I^2=0%) **Sensitivity analysis:** When analysis was limited to high-quality studies or those with VTE as the primary outcome, the use of anticoagulant prophylaxis was associated with a marginally significant increase in major bleeding. **Conclusion:** Prophylaxis with oral or parenteral anticoagulants reduces the risk of VTE in ambulatory cancer patients, with an acceptable increase in major bleeding.	

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2. Barbarawi M, Zayed Y, Kheiri B, et al. The role of anticoagulation in venous thromboembolism primary prophylaxis in patients with malignancy: A systematic review and meta-analysis of randomized controlled trials. Thromb Res. 2019.	**Systematic review and meta-analysis** **Aim:** to assess the safety and efficacy of anticoagulation in VTE prophylaxis in ambulatory cancer patients. **Data source:** PubMed/MEDLINE, Embase and Cochrane Library. RCTs up to December 2018 were included. **Quality assessment:** Cochrane risk of bias tool. **Primary outcomes:** VTE events **Secondary outcomes:** all-cause mortality and VTE-related mortality, major bleeding **Statistical analysis:** RevMan 5.3, Comprehensive Meta-analysis v3, and TSA v0.9.5.9 software were used. Mantel-Haenszel random effects model was used to report RRs and 95% CI:s; and ORs with Bayesian 95% credible intervals (CIs) for both direct and network meta-analyses using the Markov Chain Monte Carlo (MCMC) simulation. Heterogeneity was assessed using I^2 statistic. Publication bias of primary outcome was assessed via the funnel plot. Sensitivity analysis of primary outcome was conducted by sequential removal of each of the involved trials. Sensitivity analyses of primary outcome were conducted for patients with lung cancer and pancreatic cancer.	I	24 RCTs with 13,338 patients were included. Six RCTs were done on lung cancer and three RCTs were done on pancreatic cancer. **Inclusion:** RCTs that evaluated anticoagulant use as primary prevention of VTE in ambulatory cancer patients with outcomes of interest **Exclusion:** Studies that included hospitalised cancer patients, patients diagnosed with VTE at the time of randomisation, and those that did not account for the outcomes of interest	7,197 received anticoagulants [5,485 received low-molecular-weight heparin (LMWH) in 18 RCTs including dalteparin, nadroparin, enoxaparin, certoparin, bemiparin, semuloparin; 806 received direct Xa inhibitors in two trials including apixaban and rivaroxaban, 396 received aspirin, 372 received warfarin, and 138 received UFH]	6,141 received placebo	Range of follow-up: three to 24 months.	**a) Efficacy** VTE events: Significant reduction was seen with LMWH (RR 0.58; 95% CI: 0.48, 0.69; p<0.001; I^2=0%) and direct Xa inhibitors (RR 0.39; 95% CI: 0.24, 0.63; p<0.001; I^2=5%) compared with placebo. Network meta-analysis (NMA) showed that UFH, warfarin, aspirin, certoparin, and nadroparin did not lower the VTE events compared with placebo. The NMA did not show any significant difference between the other studied anticoagulants; apixaban, rivaroxaban, dalteparin, enoxaparin, bemiparin and semuloparin. **DVT events:** Compared with placebo, significant reduction was seen with LMWH (RR 0.28; 95% CI: 0.11, 0.71; p=0.008; I^2=0%); No significant reduction was seen with direct Xa inhibitors (RR 0.53; 95% CI: 0.26, 1.07, p=0.07; I^2=33%). **PE events:** Compared with placebo, significant reduction was seen with LMWH (RR 0.57; 95% CI: 0.43, 0.75; p<0.001; I^2=0%); no significant reduction was seen with direct Xa inhibitors (RR 0.46; 95% CI: 0.21, 1.02; p=0.06; I^2=30%). **All-cause mortality**: Compared with placebo, significant reduction was seen with LMWH (RR 0.95; 95% CI: 0.91, 0.99; p=0.02; I^2=7%); no significant reduction was seen with direct Xa inhibitors (RR 0.93; 95% CI: 0.58, 1.48; p=0.76; I^2=53%).	In this study, the incidence of VTE in the entire placebo group was relatively high (6.1%), and it was higher in patients with lung cancer (7.3%) and advanced pancreatic cancer (19.4%) who did not receive any anticoagulation. The authors declared no conflict of interest.

							VTE-related mortality: No significant reduction was seen with LMWH compared with placebo (RR 0.62; 95% CI: 0.28, 1.34; p=0.22; I^2=0%). **Sensitivity analysis:** Sequential removal of each trial did not change outcome significance. LMWH compared with placebo showed a significant reduction in VTE events in both lung cancer (RR 0.53; 95% CI: 0.41, 0.68, p<0.001; I^2=0%) and pancreatic cancer (RR 0.39; 95% CI: 0.24, 0.64; p<0.001; I^2=0%). **b) Safety** Major bleeding: Compared with placebo, no significant increase was seen with LMWH (RR 1.26; 95% CI: 0.92, 1.74; p=0.16; I^2=0%) and direct Xa inhibitors (RR 1.76; 95% CI: 0.83, 3.73; p=0.14; I^2=0%). The NMA showed that there was no difference between the competing treatments. **Sensitivity analysis:** Major bleeding did not increase significantly in patients who received LMWH compared with those receiving placebo in both lung cancer (RR 1.21; 95% CI: 0.68, 2.18; p=0.51; I^2=0%) and pancreatic cancer (RR 1.21; 95% CI: 0.58, 2.51; p =0.62; I^2=0%). **Conclusion:** Both LMWH and direct Xa inhibitors were associated with a lower VTE events compared with placebo. However, this potentially protective effect must be balanced against the possible increased risk of bleeding for some patients.	

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3. Li A, Kuderer NM, Garcia DA et al. Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: A systematic review and meta-analysis. J Thromb Haemost. 2019;17(12):2141-2151.	**Systematic review and meta-analysis** **Aim:** to assess phase III studies of DOAC versus placebo for the prevention of VTE in the adult ambulatory cancer patients receiving systemic therapy. **Data source:** Embase, MEDLINE, and CENTRAL. RCTs up to February 2019 were included. **Quality assessment:** Cochrane risk of bias tool. **Primary outcomes:** overall VTE incidence during the first six months (including symptomatic PE and DVT, incidental PE, ultrasound-detected DVT, and VTE-related death). **Secondary outcomes:** symptomatic VTE (PE and DVT) incidence during the first six months and all-cause mortality during the first six months. **Safety outcomes:** major bleeding and CRNMB incidence during the on-treatment period.	I	Two RCTs with 1,415 participants. Inclusion: adult ambulatory patients with cancer, prophylactic use of DOAC, and RCT. Exclusion: paediatric patients, inpatient or postoperative setting, therapeutic indication of DOAC, or non-phase III RCT.	711 patients received anticoagulants Carrier (2019): apixaban 2.5mg bd; n=291 Khorana (2019): Rivaroxaban 10mg od; n=420	704 patients received placebo Carrier (2019): n=283 Khorana (2019): n=421	Carrier (2019): 180 days Khorana (2019): 180 days	**a) Efficacy** Overall VTE incidence by six months: Compared with placebo, significant reduction was seen with DOAC [(RR 0.56; 95% CI: 0.35, 0.89; *p*=0.01; I^2=26%); (ARD −4.09%; 95% CI: −6.93, −1.24)]. a) Subgroup analysis i) High risk Khorana score ≥3 (32%): Compared with placebo, significant reduction was seen with DOAC [(RR 0.47; 95% CI: 0.25, 0.89); (ARD −6.08%; 95% CI: −11.21, −0.95)]. ii) Intermediate risk Khorana score 2 (68%): Compared with placebo, no significant reduction was seen with DOAC [(RR 0.60; 95% CI: 0.30, 1.18); (ARD −3.31%; 95% CI: −6.71, +0.09)]. ARD was smaller compared to high-risk group. **Symptomatic VTE incidence by six months:** Compared with placebo, no significant reduction was seen with DOAC [(RR 0.58; 95% CI: 0.29, 1.13; *p*=0.11; I^2=44%); (ARD −2.59%; 95% CI: −6.26, +1.09)]. **All-cause mortality by six months**: Compared with placebo, no significant reduction was seen with DOAC [(RR 0.98; 95% CI: 0.67, 1.44; *p*=0.91; I^2=54%); (ARD −0.53%; 95% CI: −6.88, +5.83)]. **Sensitivity analysis** (outcomes for the on-treatment study period): Outcomes did not change significantly. Threshold of VTE outcome occurrence above which VTE prevention outweigh harm of bleeding: Mt = 0.96 * 0.0099/0.44 = 2.2% with a range from 1.3% to 4.1% (depending on the variations of published patient preference values for bleeding versus VTE prevention). Because the 6-	Authors disclosed receiving fees/ grants/ support from pharmaceutical companies including Janssen, Pfizer, Bayer, Daiichi Sankyo, Boehringer Ingelheim, Bristol-Myers Squibb, Sanofi, and LEO Pharma. No publication bias was detected. The 6-month overall VTE incidence in the placebo arm was similarly high in both trials (37/404 or 9% in Khorana (2019) and 28/275 or 10% in Carrier (2019). Khorana (2019) excluded 4.5% of eligible patients who had pre-existing, clinically unsuspected lower extremity DVT by baseline screening ultrasound prior to study start or systemic cancer therapy. This led to lower than expected incidence of symptomatic VTE.

	Statistical analysis: RevMan 5.3 software was used. Aggregate participant data was used for the quantitative meta-analysis. RR, absolute risk difference (ARD), and 95% CI were estimated using Mantel-Haenszel random effects model (DerSimonian-Laird analysis). Heterogeneity was assessed by visual inspection and I^2 statistic. To determine the threshold at which benefit of preventing VTE outcomes is equal to harms of bleeding for medical decision-making, the expected utility theory (EUT) threshold model was used: $M_{VTE} = RV_H * H_{rx}/RRR_{VTE}$, where RV_H refers to the patient's preferences related to avoiding harms of treatment (major bleeding) versus avoiding disease outcomes (VTE), H_{rx} is the bleeding risk of low-dose DOAC, and RRR is the relative risk reduction of VTE using DOAC. For determination of RV_H, we used the standard quality of life utility studies from the general VTE literature. Subgroup analysis was performed for intermediate-risk (score 2) and high-risk (score ≥3) Khorana score. Sensitivity analyses included pre-planned secondary study outcomes of overall and symptomatic VTE incidence during on-treatment study period.						month cumulative incidence of VTE was 5.8% for symptomatic events and 9.2% for overall events, the EUT threshold result of 2.2% (1.3%-4.1%) would suggest that the benefit of treatment outweighs its risk for an average cancer patient in this study population. **b) Safety** Major bleeding while on-treatment: Compared with placebo, no statistically significant increase was seen with DOAC [(RR 1.96; 95% CI: 0.80, 4.82; *p*=0.14; I^2=0%); (ARD +0.99%; 95% CI: -0.31, +2.28)]. a) Subgroup analysis i) High risk Khorana score ≥3 (32%): Compared with placebo, no statistically significant increase was seen with DOAC [(RR 1.60; 95% CI: 0.42, 6.01); (ARD +1.42%; 95% CI: −1.14, +3.97)]. ii) Intermediate risk Khorana score 2 (68%): Compared with placebo, no statistically significant increase was seen with DOAC [(RR 1.91; 95% CI: 0.56, 6.53); (ARD +0.98%; 95% CI: −0.40, +2.36)]. ARD was smaller compared to high-risk group. **CRNMB while on-treatment:** Compared with placebo, no statistically significant increase was seen with DOAC [(RR 1.28; 95% CI: 0.74, 2.20; *p*=0.37; I^2=0%); (ARD +0.83%; 95% CI: -1.00, +2.66)]. **Conclusion:** Low-dose DOAC prophylaxis reduced the rate of overall VTE in high-risk cancer patients starting systemic chemotherapy but may increase the likelihood of bleeding. A Khorana score risk-stratified strategy should be considered for decisions regarding thromboprophylaxis to ensure the largest absolute risk reduction in the highest risk patient population.	Comparing Khorana (2019) with Carrier (2019), the 6-month symptomatic VTE incidence was 3.6% versus 3.1% in the respective DOAC arms, but 4.5% versus 7.8% in the respective control arms. More than 50% of patients in Khorana (2019) had cancer diagnoses generally considered at very high risk for VTE among solid tumours (pancreatic or gastroesophageal cancers). Pancreatic cancers may require higher doses of anticoagulant prophylaxis. Gastroesophageal cancers may pose higher risk of bleeding on DOAC. More than 50% of patients in Carrier (2019) had lymphoma and gynaecologic malignancies.

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4. Akl EA, Kahale LA, Hakoum MB, et al. Parenteral anticoagulation in ambulatory patients with cancer. Cochrane Database of Syst Rev. 2017(9).	**Systematic review and meta-analysis** **Aim:** To evaluate the efficacy and safety of parenteral anticoagulants in ambulatory patients with cancer who, typically, are undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation. **Data source:** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, handsearching of conference proceedings; checking of references of included studies; use of the 'related citation' feature in PubMed and a search for ongoing studies in trial registries. RCTs up to August 2017 were included. **Quality assessment:** Cochrane risk of bias tool. **Primary outcomes:** All-cause mortality; pre-specified at 12 months, 24 months and over the duration of the trial. **Secondary outcomes:** symptomatic DVT, PE, health-related quality of life (QoL), major bleeding, minor bleeding, thrombocytopaenia.	I	19 RCTs with 9,650 participants.	Parenteral anticoagulants: heparin (either UFH or LMWH)	Placebo or no intervention.	12-24 months	**a) Efficacy** **All-cause mortality at 12 months** (18 RCTs; n=9,575): Compared to no heparin, no significant reduction was seen with heparin [(RR 0.98; 95% CI: 0.93, 1.03; *p*=0.45; I^2=31%); (RD 10 fewer per 1000; 95% CI: 35 fewer to 15 more; moderate certainty of evidence)]. a) Subgroup analysis: i) Lung versus non-lung cancer The test for subgroup difference was not statistically significant (*p*=0.47). ii) Advanced versus non-advanced The test for subgroup difference was not statistically significant (*p*=0.56). **All-cause mortality at 24 months** (14 RCTs; n=5,229): Compared to no heparin, no significant reduction was seen with heparin [(RR 0.99; 95% CI: 0.96, 1.01; *p*=0.31; I^2=27%); (RD 8 fewer per 1000; 95% CI: 31 fewer to 8 more; moderate certainty of evidence)]. a) Subgroup analysis: i) Advanced versus non-advanced The test for subgroup difference was not statistically significant (*p*=0.97). **All-cause mortality - time-to-event analysis** (15 RCTs; n=8,388): Compared to no heparin, no significant reduction was seen with heparin (HR 0.93; 95% CI: 0.84, 1.03; *p*=0.18; I^2=64%). **Symptomatic VTE** (16 RCTs; n=9,036): Compared to no heparin, significant reduction was seen with heparin [(RR 0.56; 95% CI: 0.47, 0.68; *p*<0.0001; I^2=0%); (RD 30 fewer per 1000; 95% CI: 36 fewer to 22 fewer; high certainty of evidence)]. a) Subgroup analysis: i) Lung versus non-lung cancer The test for subgroup difference was not statistically significant (*p*=0.21). **Symptomatic DVT** (14 RCTs; n=8,867): Compared to no heparin, significant reduction was seen with heparin (RR 0.46; 95% CI: 0.33, 0.63; *p*<0.0001; I^2=22%).	All co-authors declared no conflicts of interests except for HJS who was panel member of the ASH VTE in cancer patients, Vice-Chair of the ASH VTE guidelines and played various leadership roles from 1999 until 2014 with ACCP VTE guidelines; and EAA who served on the executive committee the ACCP Antithrombotic Therapy Guidelines published in 2016.

	Statistical analysis: For time-to-event data, the log (hazard ratios (HRs)) was pooled using a random-effects model, and the generic inverse variance facility of RevMan 2014. For dichotomous data, the RR was calculated separately for each study. The certainty of evidence at the outcome level was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Heterogeneity was assessed by visual inspection of forest plots, estimation of percentage heterogeneity between trials (I^2 statistic) and formal statistical test of significance. Subgroup analyses for patients with (1) lung cancer (either SCLC or NSCLC) versus those with non-lung cancer; (2) patients with advanced cancer versus those with non-advanced cancer were conducted. Sensitivity analyses excluding trials at high risk of bias was carried out. When the primary meta-analysis of a specific outcome found a statistically significant effect, sensitivity meta-analyses were conducted to assess the risk of bias associated with missing participant data.						**Symptomatic PE** (14 RCTs; n=8,867): Compared to no heparin, significant reduction was seen with heparin (RR 0.61; 95% CI: 0.47, 0.80; *p*=0; I^2=0%). **Health-related QoL** (2 RCTs; n=2,241): Results failed to confirm or to exclude a beneficial or detrimental effect of heparin on quality of life (moderate certainty of evidence). **b) Safety** Major bleeding (18 RCTs; n=9,592): Heparin likely increased the risks compared to no heparin [(RR 1.30; 95% CI: 0.94, 1.79; *p*=0.11; I^2=0%); (RD 4 more per 1000; 95% CI: 1 fewer to 11 more; moderate certainty of evidence)]. a) Subgroup analysis: i) Lung versus non-lung cancer The test for subgroup difference was not statistically significant (*p*=0.61). **Minor bleeding** (16 RCTs; n=9,245): Heparin likely increased the risks compared to no heparin [(RR 1.70; 95% CI: 1.13, 2.55; *p*=0.01; I^2=53%); (RD 17 more per 1000; 95% CI: 3 more to 37 more; high certainty of evidence)]. **Thrombocytopaenia** (12 RCTs; n=5,832): Results failed to confirm or to exclude a beneficial or detrimental effect of heparin on thrombocytopaenia (RR 0.69; 95% CI: 0.37, 1.27; *p*=0.23; I^2=83%); RD 33 fewer per 1000; 95% CI: 66 fewer to 28 more; moderate certainty of evidence). **Sensitivity analysis:** The sensitivity analysis excluding the one study at high risk of bias, from the analyses did not change the results significantly. **Conclusion:** Heparin appears to have no effect on mortality at 12 months and 24 months. It reduces symptomatic VTE and likely increases major and minor bleeding.	

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5. Kahale LA, Hakoum MB, Tsolakian IG, et al. Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane Database of Syst Rev. 2017(12).	**Systematic review and meta-analysis** **Aim:** To evaluate the efficacy and safety of oral anticoagulants in ambulatory people with cancer undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation. **Data source:** CENTRAL (2016, Issue 1), MEDLINE (Ovid) and Embase (Ovid); handsearching of conference proceedings; checking of references of included studies; a search for ongoing studies; and using the 'related citation' feature in PubMed. RCTs up to December 2017 were included. **Quality assessment:** Cochrane risk of bias tool. **Primary outcomes:** All-cause mortality. **Secondary outcomes:** symptomatic DVT, PE, health-related QoL, major bleeding, minor bleeding.	I	Seven RCTs with 1,486 participants. **Inclusion:** RCTs assessing the benefits and harms of VKA or DOAC in ambulatory people with cancer. These participants are typically undergoing systemic anticancer therapy, possibly including chemotherapy, target therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation.	• Warfarin (6 RCTs) • Apixaban (1 RCT)	Placebo or no intervention	Warfarin: 12 months Apixaban: 3 months	**a) Efficacy** **1) VKA versus no VKA** Mortality at six months (3 RCTs; n=964): VKA appeared to have no effect on mortality at six months (RR 0.93; 95% CI: 0.77,1.13; p=0.46; I^2=6%). a) Subgroup analysis - Lung vs non-lung cancer The test for subgroup difference was not statistically significant (p=0.14). **Mortality at one year** (5 RCTs; n=1,281): VKA appeared to have no effect on mortality at one year [(RR 0.95; 95% CI: 0.87,1.03; p=0.21); (RD 29 fewer per 1000, 95% CI: 75 fewer to 17 more); I^2=0%; moderate certainty evidence]. a) Subgroup analysis - Lung vs non-lung cancer The test for subgroup difference was not statistically significant (p=1.00). **Mortality at two years** (2 RCTs; n=528): VKA appeared to have no effect on mortality at two years (RR 0.99; 95% CI: 0.70,1.30; p=0.77; I^2=93%). **Mortality at five years** (1 RCT; n=344): VKA appeared to have no effect on mortality at five years (RR 0.93; 95% CI: 0.83,1.03; p=0.16; I^2=100%). **Symptomatic VTE** (1 RCT; n=315): VKA appeared to have no effect on PE [(RR 1.05; 95% CI: 0.07, 16.58; p=0.97); (RD 0 fewer per 1000; 95% CI: 6 fewer to 98 more); very low certainty evidence)] but likely decreased the incidence of DVT [(RR 0.08; 95% CI: 0.00, 1.42; p=0.09); (RD 35 fewer per 1000; 95% CI: 38 fewer to 16 more); low certainty evidence]. **Health-related QoL:** no data were found for VKA. **2) DOAC versus no DOAC** (1 RCT; n=92): Mortality at three months: Clinically important effect of apixaban on mortality at three months could not be confirmed or excluded [(RR 0.24; 95% CI: 0.02, 2.56; p=0.24); (RD 51 fewer per 1000, 95% CI: 65 fewer to 104 more); low certainty evidence].	The inclusion of different types of cancer in the same study precluded us from conducting the subgroup analyses to explore effect modifiers such as stage of cancer. The interpretation of findings was also limited by not including data from the trials published as abstracts. All co-authors declared no conflicts of interests except for HJS who was panel member of the ASH VTE in cancer patients, Vice-Chair of the ASH VTE guidelines and played various leadership roles from 1999 until 2014 with ACCP VTE guidelines; and EAA who served on the executive committee the ACCP Antithrombotic Therapy Guidelines published in 2016.

	Statistical analysis: For dichotomous data, the RR was calculated separately for each study using RevMan 2014 and pooled using random-effects model. The certainty of evidence at the outcome level was assessed using the GRADE approach. Heterogeneity was assessed by visual inspection of forest plots, estimation of percentage heterogeneity between trials (I^2 statistic) and formal statistical test of significance. Subgroup analyses based on the type of oral anticoagulant and the characteristics of participants (type and stage of cancer, and whether participants were on cancer treatment or not) were conducted. Subgroup analyses for patients with lung cancer (either SCLC or NSCLC) versus those with non-lung cancer were also conducted. When the primary meta-analysis of a specific outcome found a statistically significant effect, sensitivity meta-analyses were conducted to assess the risk of bias associated with missing participant data.						**Symptomatic VTE:** Clinically important effect of apixaban on DVT [(RR 0.07; 95% CI: 0.00, 1.32; *p*=0.08); (RD 93 fewer per 1000, 95% CI: 100 fewer to 32 more); low certainty evidence] or PE [(RR 0.16; 95% CI: 0.01, 3.91); (RD 28 fewer per 1000, 95% CI: 33 fewer to 97 more); low certainty evidence] could not be confirmed or excluded. **Health-related QoL:** no data were found for DOAC. **b) Safety** **1) VKA versus no VKA** Major bleeding (5 RCTs; n=1,281): VKA appeared to have increased risk of major bleeding [(RR 2.93; 95% CI: 1.86, 4.62; *p*<0.0001); (RD 107 more per 1000, 95% CI: 48 more to 201 more); I^2=6%; moderate certainty evidence]. a) Subgroup analysis - Lung vs non-lung cancer The test for subgroup difference was not statistically significant (*p*=0.16). **Minor bleeding** (4 RCTs; n=863): VKA appeared to have increased risk of minor bleeding [(RR 3.14; 95% CI: 1.85, 5.32; *p*<0.0001); (RD 167 more per 1000, 95% CI: 66 more to 337 more); I^2=21%; moderate certainty evidence]. a) Subgroup analysis - Lung vs non-lung cancer The test for subgroup difference was not statistically significant (*p*=0.59). **2) DOAC versus no DOAC** (1 RCT; n=92): Major bleeding: Clinically important effect of apixaban on major bleeding could not confirmed or excluded [(RR 0.16; 95% CI: 0.01, 3.91; *p*=0.26); (RD 28 fewer per 1000, 95% CI: 33 fewer to 97 more); low certainty evidence]. **Minor bleeding:** Clinically important effect of apixaban on minor bleeding could not confirmed or excluded [(RR 4.43; 95% CI: 0.25, 79.68; *p*=0.31); (RD 0 fewer per 1000, 95% CI: 0 fewer to 8 more); low certainty evidence]. **Sensitivity analysis:** The sensitivity analyses did not change the results significantly. **Conclusion:** The existing evidence does not show a mortality benefit from oral anticoagulation in people with cancer but suggests an increased risk for bleeding.	

Bibliographic citation	Study Type/Methods	LE	No. of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
6. Di Nisio M, Porreca E, Candeloro M, et al. Primary prophylaxis for venous thrombo-embolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database of Syst Rev. 2016(12).	**Systematic review and meta-analysis** **Aim:** To assess efficacy and safety of primary thromboprophylaxis for VTE in ambulatory cancer patients receiving chemotherapy compared with placebo or no thromboprophylaxis **Data source:** CENTRAL and Cochrane Vascular Group Specialised Register (MEDLINE Ovid, Embase Ovid, CINAHL, AMED and through handsearching relevant journals). RCTs up to June 2016 were included. **Quality assessment:** Cochrane risk of bias tool. **Primary outcomes:** symptomatic VTE, major bleeding **Secondary outcomes:** Symptomatic PE; symptomatic DVT; unsuspected (incidental) VTE; overall (symptomatic and unsuspected) VTE; one-year overall mortality, clinically relevant bleeding (major and CRNMB); minor bleeding; and number of participants experiencing any serious adverse event.	I	26 RCTs involving 12,352 participants (with locally advanced or metastatic cancer) Inclusion: RCTs comparing any oral or parenteral anticoagulant or mechanical intervention to no thromboprophylaxis or placebo, or comparing two different anticoagulants.	UFH (1 RCT), LMWH dalteparin, certoparin, nadroparin, enoxaparin, bemiparin (18 RCTs), ultra-low molecular weight heparin (uLMWH) semuloparin (1 RCT), VKA warfarin (5 RCTs), antithrombin (1 RCT), oral direct factor Xa inhibitor apixaban (1 RCT)	No thrombo-prophylaxis in the form of an inactive control intervention (placebo, no treatment, standard care) or an active control intervention (a different scheme or regimen of the same intervention, a different pharmacological type of prophylaxis, a different type of non-pharmacological prophylaxis).	Median 3.5 – 25 months	**a) Efficacy** **1) Semuloparin versus placebo** (1 RCT; n=3,212): Symptomatic VTE: Semuloparin significantly reduced the risk by 64% [(RR 0.36; 95% CI: 0.22, 0.60); (NNTB 46; 95% CI: 31, 87); high-quality evidence]. **a)** Lung cancer: Semuloparin significantly reduced symptomatic VTE by 64% (9/591 versus 25/589; RR 0.36; 95% CI: 0.17, 0.76). **b)** Pancreatic cancers: Semuloparin significantly reduced symptomatic VTE by 78% (3/126 versus 14/128; RR 0.22; 95% CI: 0.06, 0.74). **Symptomatic DVT:** Semuloparin significantly reduced the risk by 68% (RR 0.32; 95% CI: 0.16, 0.63; high-quality evidence). **Symptomatic PE:** Semuloparin reduced the risk by 52% (RR 0.48; 95% CI: 0.22, 1.01; moderate-quality evidence) but was not statistically significant. **Incidental VTE:** Semuloparin did not influence incidental VTE (RR 0.14; 95% CI: 0.01, 2.76; moderate-quality evidence). **One-year mortality:** Semuloparin did not influence one-year mortality (RR 1.02; 95% CI: 0.96, 1.08; moderate-quality evidence). **2) LMWH versus no thromboprophylaxis** (9 RCTs; n=3,284) **Symptomatic VTE:** Significant reduction was seen with LMWH (RR 0.54; 95% CI: 0.38, 0.75; high-quality evidence) in the absence of heterogeneity (Tau^2=0.00). This corresponded to a NNTB of 30 (95% CI: 23, 56), assuming a background risk of 71 symptomatic VTE events per 1000 patients. **a)** Lung (4 RCTs; n=933): LMWH significantly reduced symptomatic VTE by 60% (RR 0.40; 95% CI: 0.20, 0.80). **b)** Pancreatic cancers (2 RCTs, n=431): LMWH significantly reduced symptomatic VTE by 59% (RR 0.41; 95% CI: 0.23, 0.75).	The main limiting factors were imprecision and risk of bias. The clinical trials evaluating LMWH against placebo or no thrombo-prophylaxis varied in the duration and type of LMWH, including 8 weeks to 48 months of subcutaneous dalteparin, enoxaparin, certoparin, nadroparin, or bemiparin. The dose of LMWH was prophylactic in the majority of the studies, and intermediate in one study, or therapeutic in one study. In two studies initial therapeutic LMWH was followed by intermediate doses. LMWH did not increase major bleeding when compared with no thrombo-prophylaxis, but the CIs were wide and the upper limit did not exclude a twice-as-

	Statistical analysis: Results were presented as summary RRs with 95% CI: for dichotomous variables using inverse-variance random-effects model meta-analysis. In the case of statistically significant overall estimates, clinical effect summary statistics such as the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) were calculated to express the final results of the review. Data analysis was performed using RevMan 5. Stratified analyses by type of thromboprophylaxis and funnel plot exploration were performed using STATA release 14. Between-trial heterogeneity was explored by stratifying the main outcomes for the following trial characteristics: age, type of cancer, stage of cancer (metastatic versus non-metastatic); type of major bleeding, concealment of allocation, blinding; analysis in accordance with the intention-to-treat principle; trial size; and differences in the use of co-interventions in the trial groups. Univariate random-effects model meta-regression was used to determine whether treatment effects were affected by these factors and by three continuous						**Symptomatic DVT** (8 RCTs; n=5,310): Significant reduction was seen with LMWH [(RR 0.49; 95% CI: 0.35, 0.67; Tau^2=0.00); (NNTB 68; 95% CI: 53, 105); high-quality evidence]. **Symptomatic PE** (7 RCTs; n=5,226): Significant reduction was seen with LMWH [(RR 0.59; 95% CI: 0.40, 0.86; Tau^2=0.00); (NNTB 174; 95% CI: 119, 510); low-quality evidence]. **Overall VTE** (9 RCTs; n=5,366): LMWH significantly reduced risk by 41% [(RR 0.59; 95% CI: 0.48, 0.73; Tau^2=0.00; (NNTB 25; 95% CI: 20, 38)). **Incidental VTE:** There was no statistically significant benefit or harm. (RR 0.66; 95% CI: 0.41, 1.08). **One-year mortality:** There was no statistically significant benefit or harm (RR 0.93; 95% CI: 0.80, 1.09; low-quality evidence). **Sensitivity analysis:** Stratified analyses did not show any effect of the type of LMWH, type of cancer, dosage, or design characteristics on the RR of symptomatic VTE. No evidence was found for a linear association between treatment duration and the risk of symptomatic VTE using metaregression analysis (p=0.514). **3) LMWH versus aspirin** (2 RCTs; n=781) in multiple myeloma **Symptomatic VTE:** There was no statistically significant difference (RR 0.51; 95% CI: 0.22, 1.17; moderate-quality evidence). **Symptomatic DVT:** There was no statistically significant difference (RR 0.81; 95% CI: 0.32, 2.04; low-quality evidence). **Symptomatic PE:** There was no statistically significant difference (RR 0.13; 95% CI: 0.02, 1.03; moderate-quality evidence).	high risk of bleeding with heparin. While additional studies are needed to clarify the efficacy and safety of warfarin, the bleeding concerns and the complexity of VKA management discourage the use of warfarin for primary prophylaxis in cancer patients. As renal insufficiency often complicates the course of multiple myeloma, caution should be taken in the administration and dosing of drugs such as LMWH or direct thrombin or factor Xa inhibitors with a predominant renal clearance. The lack of difference such as risk of major bleeding for semuloparin and LMWH, may be related to the small number of RCTs and small number of studied participants or events, or both, as well as the

	variables at trial level: dosage of intervention, treatment duration, and length of follow-up. Quality of evidence was assessed according to GRADE principles.						**4) LMWH versus warfarin** (1 RCT; n=439) in multiple myeloma **Symptomatic VTE:** Significant reduction was seen (RR 0.33; 95% CI: 0.14, 0.83; high-quality evidence). **Symptomatic DVT:** There was no statistically significant difference (RR 0.43; 95% CI: 0.17, 1.10; moderate-quality evidence). **Symptomatic PE:** There was no statistically significant difference (RR 0.11; 95% CI: 0.01, 2.06; low-quality evidence). **5) UFH versus no thromboprophylaxis** (1 RCT; n=277) in SCLC One-year mortality: The summary estimate did not conclusively rule out an increase or reduction (RR 0.86; 95% CI: 0.72, 1.03; moderate-quality evidence). **6) Warfarin versus placebo or no thromboprophylaxis** (1 RCT; n=311) in breast cancer **Symptomatic VTE:** There was no statistically significant difference (RR 0.15; 95% CI: 0.02, 1.20; low-quality evidence). **Symptomatic DVT:** There was no statistically significant difference (RR 0.08; 95% CI: 0.00, 1.42; low-quality evidence). **Symptomatic PE:** There was no statistically significant difference (RR 1.05; 95% CI: 0.07, 16.58; very low-quality evidence). **7) Warfarin versus aspirin** (1 RCT; n=440) in multiple myeloma **Symptomatic VTE:** There was no statistically significant difference (RR 1.50; 95% CI: 0.74, 3.04; moderate-quality evidence). **Symptomatic DVT:** There was no statistically significant difference (RR 1.75; 95% CI: 0.75, 4.09; moderate-quality evidence). **Symptomatic PE:** There was no statistically significant difference (RR 1.00; 95% CI: 0.25, 3.95; moderate-quality evidence).	absence of a true effect. All co-authors declared no conflicts of interests except for MDN who had received consultancy fees from Bayer, Grifols, and Daiichi Sankyo not related to the present review.

							8) Apixaban versus placebo (1 RCT; n=122) **Symptomatic VTE**: Significant reduction was seen with apixaban (RR 0.08; 95% CI: 0.01, 0.67; moderate-quality evidence). **Symptomatic DVT**: Significant reduction was seen with apixaban (RR 0.08; 95% CI: 0.01, 0.67; moderate-quality evidence). **Symptomatic PE:** There was no statistically significant difference (RR 0.11; 95% CI: 0.00, 2.54; low-quality evidence). **b) Safety** **1) Semuloparin versus placebo** (1 RCT; n=3,212): **Major bleeding:** The difference in major bleeding was not statistically significant (19/1589 versus 18/1583; RR 1.05, 95% CI: 0.55, 2.00; low quality of evidence). **Clinically relevant bleeding:** No significant increase in risk was seen with semuloparin (2.8% versus 2.0%; RR 1.40, 95% CI: 0.90, 2.19; moderate quality of evidence). **Serious adverse events:** Incidence of serious adverse events was similar in the semuloparin and placebo groups (26% versus 25%). Incidence of thrombocytopaenia was similar in the semuloparin and placebo groups (7.1% versus 7.6%). There was no cases of HIT. **2) LMWH versus no thromboprophylaxis** (9 RCTs; n=3,284) **Major bleeding** (13 RCTs; n=6,356): The difference was not statistically significant (RR 1.44; 95% CI: 0.98, 2.11; low-quality evidence) in the absence of heterogeneity (Tau^2=0.00). a) Lung (4 RCTs; n=3,065): There was no statistically significant higher risk of major bleeding with LMWH compared with control treatment (RR 1.49; 95% CI: 0.79, 2.80) and no evidence of statistical heterogeneity (Tau^2=0.00). b) Pancreatic cancers (2 RCTs; n=433): There was no increase in major bleeding with LMWH (RR 1.21; 95% CI: 0.58, 2.51) and no evidence of statistical heterogeneity (Tau^2=0.00).	

							Clinically relevant bleeding (4 RCTs; n=3,105): Significant increase was seen with LMWH (RR 3.40, 95% CI: 1.20, 9.63; Tau^2=0.73; moderate-quality evidence). **Minor bleeding:** There was no statistically significant benefit or harm. (RR 1.23; 95% CI: 0.89, 1.70). **Serious adverse events:** There was no statistically significant benefit or harm. (RR 0.86; 95% CI: 0.70, 1.07). **Sensitivity analysis:** The results of the stratified analyses did not show any effect of the type of LMWH, dosage, type of cancer, definition of major bleeding, trial size, or design characteristics on the RR of major bleeding. There was no evidence for a linear association between treatment duration and the risk of major bleeding based on meta-regression analysis (*p*=0.751). **3) LMWH versus aspirin** (2 RCTs; n=781) in multiple myeloma **Major bleeding:** There was no statistically significant difference (RR 0.14; 95% CI: 0.01, 2.76; low-quality evidence). **4) UFH versus no** thromboprophylaxis (1 RCT; n=277) in SCLC **Clinically relevant bleeding:** There was no statistically significant difference (RR 2.01; 95% CI: 0.18, 21.96; low-quality evidence). There were no cases of HIT. **5) Warfarin versus placebo or no thromboprophylaxis** (1 RCT; n=311) Major bleeding: VKA may increase the risk in breast cancer and SCLC (RR 3.82; 95% CI: 0.97, 15.04; low-quality evidence) with evidence of a high degree of heterogeneity (Tau^2=0.71). **6) Warfarin versus aspirin** (1 RCT; n=440) in multiple myeloma **Major bleeding:** There was no statistically significant difference (RR 0.14; 95% CI: 0.01, 2.75; low-quality evidence).	

							7) Apixaban versus placebo (1 RCT; n=122) **Major bleeding:** There was no statistically significant difference (RR 0.62; 95% CI: 0.06, 6.63; low-quality evidence). **Clinically relevant bleeding:** There was no statistically significant difference (RR 1.87; 95% CI: 0.23, 14.91; low-quality evidence). **Conclusion:** Primary thromboprophylaxis with LMWH significantly reduced the incidence of symptomatic VTE in ambulatory cancer patients treated with chemotherapy. In addition, the uLMWH semuloparin, which is not commercially available, significantly reduced the incidence of symptomatic VTE. The risk of major bleeding associated with LMWH, while not reaching statistical significance, suggest caution and mandate additional studies to determine the risk-to-benefit ratio of LMWH in this setting. Despite the encouraging results of this review, routine prophylaxis in ambulatory cancer patients cannot be recommended before safety issues are adequately addressed. Additional studies investigating targeted primary prophylaxis in people with specific types or stages of cancer associated with a higher risk of VTE are needed.	

Bibliographic citation	Study Type/Methods	LE	No. of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
7. Ben-Aharon I, Stemmer SM, Leibovici L, et al. Low molecular weight heparin (LMWH) for primary thrombo-prophylaxis in patients with solid malignancies–systematic review and meta-analysis. Acta Oncol. 2014;53(9):1230-1237.	**Systematic review and meta-analysis** **Aim:** to evaluate the impact of LMWH primary prophylaxis on VTE incidence as well as survival in cancer patients **Data source:** CENTRAL, PubMed, Clinical Trials, conference proceedings of the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Society of Medical Oncology (ESMO) and the European Hematology Association (EHA). RCTs up to October 2013 were included. **Quality assessment:** Cochrane risk of bias tool. **Primary outcomes:** symptomatic VTE **Secondary outcomes**: DVT, PE, any VTE, all-cause mortality, adverse events (grade 3 or 4 haematological and non-haematological adverse events). Regarding bleeding, data regarding major bleeding and clinically relevant bleeding (defined as major plus minor bleeding) were extracted. **Statistical analysis:** RRs and 95% CI:s for dichotomous data were estimated using the Mantel-Haenszel method and pooled according to inverse of variance method (RevMan version 5.1). Heterogeneity was assessed using χ^2-test of heterogeneity and I^2 measure of inconsistency. Random-effects model by Der Simonian and Laird method was chosen for all analyses due to different types of cancer and therefore different VTE risks. Subgroup analyses were performed for lung cancer and pancreatic cancer, which are regarded as cancers with a high thrombogenic potential. Number needed to treat (NNT) was calculated to evaluate the additive effect of	I	11 trials involving 6,942 patients Inclusion: RCTs that compared the addition of LMWH to standard chemotherapy in ambulatory cancer patients, as primary thrombo-prophylaxis.	•Nadroparin (3 RCTs) •Dalteparin (4 RCTs) •Certoparin (2 RCTs) •Enoxaparin (1 RCT) •Semulo-parin (1 RCT)	Placebo or no thromboprophylaxis	Six to 12 months	**a) Efficacy** **Symptomatic VTE** (7 RCTs; n=2,612): Primary prophylaxis with LMWH significantly reduced symptomatic VTE (RR 0.46; 95% CI: 0.32, 0.67; p<0.0001; I^2=0%) with NNT 50 (95% CI: 33, 100). a) Lung cancer: Primary prophylaxis with LMWH significantly reduced symptomatic VTE (RR 0.42; 95% CI: 0.25, 0.71; p=0.001; I^2=0%) with NNT 33 (95% CI: 25, 100). b) Pancreatic cancer: Primary prophylaxis with LMWH significantly reduced symptomatic VTE (RR 0.31; 95% CI: 0.18, 0.55; p<0.0001; I^2=0%) with NNT 10 (95% CI: 7, 16). **DVT:** Primary prophylaxis with LMWH significantly reduced DVT (RR 0.35; 95% CI: 0.21, 0.61; p=0.0001; I^2=0%). **PE:** Primary prophylaxis with LMWH significantly reduced the rate of PE (RR 0.49; 95% CI: 0.29, 0.84; p=0.01; I^2=0%). **Any VTE** (10 RCTs; n=6,942): LMWH significantly reduced any VTE (RR 0.56; 95% CI: 0.38, 0.81, I^2=36%). **Mortality at one-year** (6 RCTs, n=2,550): There was no statistically significant benefit for LMWH in one-year mortality rates (RR 0.93; 95% CI: 0.83, 1.04; p=0.18; I^2=51%). **Type of LMWH:** There were no significant variations in the effect of different LMWH in any of the outcomes. **Sensitivity analysis:** Sensitivity analysis according to risk of bias, and specifically according to allocation concealment showed similar results for VTE reduction in both trials of low risk for bias (RR 0.67; 95% CI: 0.49, 0.93) and those of high risk (RR 0.33; 95% CI: 0.21, 0.52).	The authors declared no conflicts of interests..

	LMWH on the absolute risk for VTE using the data in each arm (LMWH vs. control). Risk was calculated by multiplying the absolute risk of the control arm by (1-RR for VTE/PE/DVT).						**b) Safety** **Adverse events:** The rate of grade 3 or 4 adverse events was reported in nine trials, evaluating 6,595 patients. There was no significant increase in either the rate of clinically relevant bleeding (RR 1.29; 95% CI: 0.95, 1.77), nor in major bleeding events (RR 1.28; 95% CI: 0.84, 1.95). There was no significant increase in thrombocytopaenia (RR 1.05; 95% CI: 0.76, 1.45). The NNH for serious adverse events was 100 (95% CI: 50, very large number). **Conclusion:** LMWH reduces the incidence of symptomatic VTE and PE in patients receiving chemotherapy for cancer, with no apparent increase in major bleeding. The benefit is most apparent in pancreatic cancer and also lung cancer. VTE prophylaxis should be considered for these specific populations.	

Bibliographic citation	Study Type/Methods	LE	No. of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
8. Phan M, John S, Casanegra AI, et al. Primary venous thromboembolism prophylaxis in patients with solid tumors: a meta-analysis. J Thromb Thrombolysis. 2014;38(2):241-249.	**Systematic review and meta-analysis** **Aim:** To measure safety and efficacy of out-patient primary VTE prophylaxis in patients with solid tumors receiving chemotherapy **Data source:** Ovid MEDLINE, Embase, EBM Reviews-Cochrane database of systematic reviews, EBM Reviews-ACP journal club, EBM Reviews-Database of abstracts of reviews of effects. RCTs up to December 2012 were included. **Quality assessment:** Cochrane risk of bias tool. **Primary outcomes:** first VTE (asymptomatic or symptomatic; included PE and DVT), major bleeding **Secondary outcomes:** all-cause mortality **Statistical analysis:** Data were analysed using R META package. Heterogeneity was assessed using Q statistic and a formal test of homogeneity. The I^2 index and corresponding 95% CI were used to summarize the proportion of total variability in effect sizes due to between-study variation. The OR and RD estimates from each study were pooled by using Mantel–Haenszel fixed-effects method, inverse-variance method and random-effects model by DerSimonian and Laird. In the presence of significant heterogeneity (p<0.1), random-effects model results were presented over fixed effects model. An influence analysis estimating pooled effect sizes after leaving each study out was performed. Subgroup analyses for VTE and bleeding outcomes were performed using pre-specific subgroups including drug type, multiple types of tumours and catheter– based prophylaxis.	I	11 RCTs involving 7,875 patients. Inclusion: Malignancies included were those of the breast, lung, gastrointestinal tract (including pancreatic), ovary, head and neck, and brain. Exclusion: Haematological malignancies including leukemia, lymphoma and multiple myeloma were excluded even if the chemotherapy was administered in the ambulatory setting.	LMWH: • Dalteparin (3 RCTs) • Nadroparin (3 RCTs) • Semuloparin (1 RCT) • Certoparin (2 RCT) VKA warfarin: 2 RCTs	Placebo	LMWH Range: 6-12 months Median: 10.5 – 19.3 months Warfarin Range: 26-88 months	**a) Efficacy** **VTE events** (11 RCTs; n=7,875): Significant reduction was seen in the prophylaxis group [(OR 0.56; 95% CI: 0.45, 0.71; I^2=18.3%); (RD -0.02; 95% CI: -0.03, -0.01; p<0.001)]. Greater reduction was seen when LMWH prophylaxis was analysed [(9 RCTs; n=6,748; OR 0.53; 95% CI: 0.41, 0.70; I^2=12.3%); (RD -0.02; 95% CI: -0.03, -0.01)]. Significant reduction was observed with LMWH prophylaxis among patients with lung cancer (3 RCTs; n=1,926; OR 0.46; 95% CI: 0.29, 0.74; I^2=0%) and pancreatic cancer (3 RCTs; n=430; OR 0.33; 95% CI: 0.16, 0.67; I^2=0%). No publication bias was detected. **All-cause mortality** (8 RCTs; n=6,374; LMWH versus placebo): There was no statistically significant difference in mortality between the treatment groups (OR 0.97; 95% CI: 0.87, 1.08; I^2=17.8 %). **Sensitivity analysis:** No single study influenced the pooled estimate and the result of a sensitivity analysis using only manuscripts with low risk of bias was not different to the main result (OR 0.54; 95% CI: 0.40, 0.73; I^2=15 %).	There is a paucity of data on appropriate classification of thrombotic events in patients with cancer; therefore, the outcomes analysed are not homogeneous. The impact of specific chemotherapy agents on the incidence of VTE could not be isolated, which may change the relative efficacy of thrombo-prophylaxis. Although there are several VTE risk factors and stratification scores specific to patients with cancer, a validated risk score was not used to stratify the randomisation in any of the available trials. The authors did not declare conflicts of interest.

							b) Safety **Major bleeding**: There were 68 major bleeding events among the 4,127 patients who received thromboprophylaxis and 40 major bleeding events in 3,748 patients who received placebo. Major bleeding events were significantly higher in the intervention group (OR 1.65; 95% CI: 1.12, 2.44; I^2=0%). **Sensitivity analysis:** On a sensitivity analysis including only the studies with low risk of bias, the bleeding likelihood decreased (OR 1.41; 95% CI: 0.93, 2.14; I^2=0%) and was no longer statistically significant. When only LMWH studies were grouped, the odd of major bleeding increased significantly (OR 1.57; 95% CI: 1.04, 2.37; I^2=0%). **Conclusion:** Although there is a clearly measurable VTE rate reduction when primary thromboprophylaxis is given to patients with cancer, before anticoagulants are added to the conventional treatment of patients with cancer, more information is needed on the value of risk stratification tools to personalize prevention strategies.	

Evidence Table : Cost-effectiveness
Question : What is the cost-effectiveness of prophylactic anticoagulation in ambulatory cancer patients compared with placebo or no thromboprophylaxis?

Bibliographic citation	Study Type/Methods	LE	No. of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
1. Li A, Carlson JJ, Kuderer NM, et al. Cost-effectiveness analysis of low-dose direct oral anticoagulant (DOAC) for the prevention of cancer-associated thrombosis in the United States. Cancer. 2020.	**Cost-effectiveness analysis** **Aim:** to evaluate the cost-utility of low-dose DOAC versus placebo for the prevention of cancer-associated thrombosis in ambulatory patients with cancer using Markov state-transition model. **Target population:** hypothetical cohort of ambulatory patients with cancer aged 60 years who were considered at intermediate-to-high risk for VTE (Khorana score ≥2) without absolute contraindications for thromboprophylaxis. **Perspective:** health sector perspective **Time horizon:** 40-year lifetime horizon **Cycle length:** one month **Discount rate:** 3% **Measurement of effectiveness:** VTE events. Transition probabilities, RRs and 95% CIs for VTE, bleeding, discontinuation, and mortality outcomes were derived from a meta-analysis by Li (2019) and relevant epidemiology studies. **Cost and utility:** Direct medical costs and complications were included. All cost estimates were inflated to May 2019 US dollars using the US Consumer Price Index for all urban consumers' medical care. Utility weights were derived from published literature. **Base-case and sensitivity analyses:** for the base-case analysis, the cumulative cost and QALYs were estimated for each treatment over a lifetime time horizon. The ICER was calculated as the difference in cost over the difference in QALYs. Half-cycle correction was not performed given the short cycle length of 1 month. To highlight the model's calibration performance, clinical events at a time horizon	I	Two RCTs with 1,415 participants. **Inclusion:** adult ambulatory patients with cancer, prophylactic use of DOAC, and RCT. **Exclusion:** paediatric patients, inpatient or postoperative setting, therapeutic indication of DOAC, or non-phase III RCT.	711 patients received low-dose DOAC. Carrier (2019): apixaban 2.5mg bd; n=291 Khorana (2019): Rivaroxaban 10mg od; n=420	704 patients received placebo Carrier (2019): n=283 Khorana (2019): n=421	Carrier (2019): 180 days Khorana (2019): 180 days	**Base-case analysis:** DOAC prophylaxis for six months was associated with 32 fewer VTEs (20 fewer PEs; 12 fewer DVTs), 11 more major bleeding events, and 21 more CRNMB events per 1000 patients in patients with cancer at intermediate-to-high risk for VTE. The intervention group had a mean total cost of US$9899 per person, 6.51 life-years, and 4.79 QALYs. The placebo group had a mean total cost of US$8454 per person, 6.34 life-years, and 4.67 QALYs. The incremental cost and QALY increases were US$1445 and 0.12, respectively, with an ICER of US$11,947 per QALY gained over a lifetime. **One-way sensitivity analyses:** Key drivers of ICER variations were the RRs of PE, DVT, and major bleeding as well as drug cost. **Probabilistic sensitivity analysis:** DOAC were associated with an incremental cost increase of US$1537, an incremental QALY increase of 0.11, and an ICER of US$14,330 per QALY. As shown in CEAC, the strategy would be 94% cost-effective at the threshold of US$50,000 per QALY. **Scenario sensitivity analyses:** 1) Outcomes based on on-treatment (as-treated) instead of overall follow-up (intention-to-treat) transition probability and RR for VTE: Compared with primary analysis, DOAC was associated with a similar incremental cost increase, a greater incremental QALY increase (0.14 versus 0.12 QALYs), and an ICER of US$9896 per QALY gained.	Authors disclosed receiving fees/ grants/ support from pharmaceutical companies including Janssen, Pfizer, Bayer, Daiichi Sankyo, Aspen Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, Sanofi, and LEO Pharma. Direct non-medical cost, indirect cost, individual coupons or cost-assistance programmes were not considered.

	of six months were reported to emulate the outcomes reporting from the RCTs. One-way deterministic, probabilistic and scenario sensitivity analyses were performed. Probabilistic sensitivity analysis using Monte Carlo simulation over 1000 times was performed to generate cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC). The distributions assumed for the input parameters were γ (cost), β (utility weights and transition probability), and log-normal (RR). The standard errors were derived from the 95% CIs, and α/β parameters were estimated using the method of moments. Several scenario sensitivity analyses were performed by varying the duration of intervention (six versus 12 months), the treatment effect estimate (on-treatment versus intention-to-treat period), and the risk profile of the population (high risk versus intermediate risk). All data analyses were performed in Microsoft Excel for Mac 16.17. **Assumptions**: 1) patients existed in mutually exclusive states; 2) patients who experienced a first VTE event would transition to treatment with a therapeutic-dose of DOAC and would remain on-treatment unless VTE, bleeding, death, or discontinuation occurred; 3) patients who experienced any bleeding while on prophylaxis would all transition off DOAC after one cycle because of low tolerance of adverse effects; 4) patients who experienced a recurrent VTE or CRNMB would return to the same anticoagulant on-treatment state after 1 cycle unless death had occurred; 5) patients who experienced major bleeding would transition to an off-treatment state after 1 cycle unless death had occurred; 6) patients who were still alive after 5 years had similar VTE and mortality rates as the general non-cancer population; and 7) patients would suffer from bleeding complications and/or discontinue anticoagulant at a constant rate unrelated to cancer remission or cure.						2) Outcomes based on 12-month instead of 6-month duration of prophylaxis: Compared with primary analysis, DOAC was associated with a greater incremental cost increase (US$2410 versus US$1445), a greater incremental QALY increase (0.15 versus 0.12), and an ICER of US$16,389 per QALY gained. 3) Outcomes based on constant cancer mortality rate from year 5 and beyond instead of life-table extrapolation: Compared with primary analysis, the incremental cost difference was similar but incremental QALY difference was smaller between the DOAC and placebo arms, and the resulting ICER was higher at US$15,602 per QALY gained. 4) Outcomes based on drug pricing estimates from the Federal Supply Schedule instead of the Red Book: The lower acquisition drug cost for apixaban translated into a lower incremental cost difference of US$518, an unchanged incremental QALY difference for both arms, and an ICER of US$4283 per QALY gained. **Stratified analysis** (high-risk versus intermediate risk): The selection of patients with Khorana scores ≥3 had an incremental cost increase of US$1103, an incremental QALY increase of 0.19, with an ICER of US$5794 per QALY gained. The selection of patients with Khorana score of 2 had an incremental cost increase of US$1527, an incremental QALY increase of 0.11, and an ICER of US$15,118 per QALY gained. **Conclusion:** Low-dose DOAC thromboprophylaxis for six months appears to be cost-effective in patients with cancer who are at intermediate-to-high risk for VTE. The implementation of this strategy in patients with Khorana scores ≥3 may lead to the highest cost-benefit ratio.	

Bibliographic citation	Study Type/Methods	LE	No. of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
2. Pishko AM, Smith KJ, Ragni MV. Anticoagulation in ambulatory cancer patients with no indication for prophylactic or therapeutic anticoagulation. Thromb Haemost. 2012;108(08):303-310.	**Cost-effectiveness analysis** **Aim:** to evaluate costs and survival benefit of prophylactic anticoagulation given during four months of chemotherapy following a new cancer diagnosis in ambulatory cancer patients with no VTE history using Markov state-transition model. **Target population:** hypothetical cohort of ambulatory patients with advanced cancer, no previous VTE and no anticoagulation indication, and treated with four months of enoxaparin 40 mg subcutaneously once daily (fixed dosage). **Perspective:** US (as reported) **Time horizon**: 24-month **Cycle length:** one month **Discount rate:** Not reported **Measurement of effectiveness:** Mortality reduction. Transition probabilities, VTE risk, major and minor bleeding, mortality and other clinical parameters were obtained from a Cochrane 2011 meta-analysis and three other published studies. **Cost and utilities:** Pharmacy costs for enoxaparin, including syringes and needles, were based on the average wholesale prices in 2011. Hospitalisation costs were derived from 2009 Healthcare Cost and Utilisation Project (HCUP) data, and other costs were obtained from the medical literature. All costs were inflated to 2011 levels using the U.S. Consumer Price Index. Quality-of-life measures were obtained from published studies. **Statistical analysis:** Model was constructed using TreeAge Pro Suite 2009. Two treatment strategies, LMWH or no LWMH, were compared. One-way sensitivity analyses were conducted to assess the effects of varying baseline estimates (LMWH cost per month, RR of mortality, 2-year mortality risk, RR of VTE and RR of major bleed) on ICER. All	I	9 RCTs involving 2,857 patients with various malignancies including glioma, advanced lung, gastrointestinal and breast cancers.	1,624 patients receiving heparin (either un-fractionated heparin or LMWH)	1,219 patients receiving placebo or no intervention	Range of follow-up: two to 84 months	**Base-case analysis:** The cost of four-month LMWH prophylaxis was US$3,465 with 0.6674 QALYs. The cost of no-prophylaxis strategy was US$252 with 0.630 QALYs. The incremental cost and QALY increases were US$3,213 and 0.0354 QALYs, respectively, with an ICER of US$90,893/QALY gained (falling within the acceptable range of US$100,000/QALY gained). **One-way sensitivity analyses:** LMWH prophylaxis would remain economically reasonable (cost less than US$100,000/QALY) if two-year mortality exceeded 75%; anticoagulation costs were less than US$1,076 per month; or if LMWH relative mortality risk was less than 0.927. Results were not sensitive to variation in RR of VTE on anticoagulation, nor to major or minor bleeding risk on anticoagulation. **Two-way sensitivity analysis**: The cost of extending anticoagulation up to 24 months was acceptable only when the mortality RR was less than 0.762. **Probabilistic sensitivity analysis:** Using a willingness to pay threshold of US$100,000 per QALY gained, there was 56.1% likelihood that LMWH would be considered cost-effective in the ambulatory cancer patient. If a US$75,000/QALY threshold was used, LWMH was favoured in 34.0% of model iterations; if the threshold was US$50,000 per QALY gained, there was 9.5% likelihood LMWH was favoured. **Conclusion:** Prophylactic LMWH given to decrease cancer-related mortality, with no conventional indication, appears economically reasonable if its suggested mortality benefit is confirmed in future trials.	The data used to construct the model were based on cancer patients with varying types and stages of cancer; and varying types and durations of prophylactic anticoagulation. The model did not include downstream VTE morbidities, such as recurrent VTE, post-thrombotic syndrome, chronic thromboembolic hypertension, possible heparin-induced thrombocytopaenia, and higher bleed rates from treatment dose anticoagulants for those who do develop VTE and their subsequent costs. Inclusion of these costs, however, would likely have made LMWH more cost-effective.

	parameter values were simultaneously varied 10,000 times over predefined probability distributions in a probabilistic sensitivity analysis. A two-way sensitivity analysis was conducted to assess the effect of varying both LMWH duration and RR of mortality. **Assumptions:** Patients have advanced cancer with a two-year mortality risk of 85.9% based on Cochrane meta-analysis data, but with no other indication for prophylactic anticoagulation including hospitalisation, central venous line placement, or surgery. The cohort for each strategy enters the model in the no-bleed, no-VTE state. During each monthly Markov cycle, there are risks of VTE, minor or major bleeds, death, or of remaining in the same state. Patients stay in the bleeding state or VTE state for one month only, and then proceed to the post-bleeding or post-VTE states where they continue to be tracked in the model. Patients in any health state may also proceed to the dead state, based on the monthly likelihood of mortality in a given health state. As the model only tracked patients with no conventional indication for anticoagulation, it did not include the 10–20% of cancer patients who initially present with VTE.							