ASCO® Guidelines

Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: ASCO Clinical Practice Guideline Update

Data Supplement

Table of Contents

DATA SUPPLEMENT 1: EVIDENCE TABLES 3

Clinical question 1: Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis? 3

Table 1.1 Characteristics of included meta-analysis 3

Table 1.2 Results of included meta-analysis 3

Clinical Question 2: Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy? 4

Table 2.1 Characteristics of included meta-analyses 4

Table 2.2: Results of included meta-analyses 5

Table 2.3 Characteristics of included RCTs 7

Table 2.4 Results of included RCTs 8

Table 2.5 RCT Quality Assessments 8

Clinical Question 3: Should patients with cancer undergoing surgery receive peri-operative VTE prophylaxis? 10

Table 3.1 Characteristics of included meta-analyses 10

Table 3.2 Results of included meta-analyses 11

Table 3.3 Characteristics of included RCTs 12

Table 3.4 Results of included RCTs 13

Table 3.5 RCT Quality Assessments 13

Clinical Question 4: What is the best method of treatment for patients with cancer with established VTE to prevent recurrence? 15

Table 4.1 Characteristics of included meta-analyses 15

Table 4.2 Results of included meta-analyses 16
Table 4.3 Characteristics of included RCTs 19
Table 4.4 Results of included RCTs 20
Table 4.5 RCT Quality Assessments 21
Clinical Question 5: Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival? 22
Table 5.1 Characteristics of included meta-analyses 22
Table 5.2 Results of included meta-analyses 23
Table 5.3 Characteristics of included RCT 24
Table 5.4 Results of included RCT 24
Table 5.5 RCT Quality Assessments 25
Clinical Question 6: What is known about risk prediction and awareness of VTE among patients with cancer? 26
Table 6.1 Study Characteristics- VTE risk assessment in ambulatory or hospitalized patients with mixed cancer types 26
Table 6.2 Results- VTE risk assessment in ambulatory or hospitalized patients with mixed cancer types 27
Table 6.3 Study Characteristics- VTE risk assessment in ambulatory patients with individual cancer types 28
Table 6.4 Results- VTE risk assessment in ambulatory patients with individual cancer types 29
DATA SUPPLEMENT 2: SEARCH STRATEGIES 32
DATA SUPPLEMENT 3. QUOROM DIAGRAMS 34
DATA SUPPLEMENT 4: PREVIOUS AND CURRENT RECOMENDATIONS 36

DATA SUPPLEMENT 1: EVIDENCE TABLES

Clinical question 1: Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

Table 1.1 Characteristics of included meta-analysis

Author year	Population	Anticoagulants					Outcomes				
		DOACs	VKAs	LMWH	Fondaparinux	Unfranctionated heparin	VTE rincidence	Major bleeding	Other bleeding	Mortality	Quality of life
Carrier 2014[1]	Hospitalized patients with cancer who received anticoagulant therapy or placebo. Identified from three RCTs that reported results for cancer subgroup.			√	√		√				

Abbreviations: DOAC, direct oral anticoagulants (dabigatran, apixaban; rivaroxaban, edoxaban); VKA, vitamin K antagonists (warfarin); LMWH, low-molecular-weight heparin (dalteparin, enoxaparin, tinzaparin);

Table 1.2 Results of included meta-analysis

Author year	Comparison	VTE		Survival		Major Bleeding		Other bleeding	
		Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)
Carrier 2014[1]	Thromboprophy-laxis vs placebo	3/307	RR 0.91 (0.21-4.0)	NR	NR	NR	NR	NR	NR

Abbreviations: VTE, venous thromboembolism; CI confidence interval; RR, relative risk; NR not reported;

Clinical Question 2: Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

Table 2.1 Characteristics of included meta-analyses

Author year	Anticoagulants						Cancer types		Outcomes				
	DOACs	VKAs	LMWH	Fondaparinux	Unfranctionated heparin	Any	Solid tumors	Hematologic	VTE rincidence	Major bleeding	Other bleeding	Mortality	Quality of life
Thein 2018[2]			✓				Lung cancer		✓	✓	✓	✓	
Fuentes 2017[3]		✓	✓		✓		Lung cancer		✓		✓	✓	
Di Nisio 2016[4]	✓ a	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Tun 2016[5]			✓				Advanced pancreatic		✓	✓			
Ben-Aharon 2014[6]			✓				✓		✓	✓	✓	✓	

Abbreviations: DOAC, direct oral anticoagulants (dabigatran, apixaban; rivaroxaban, edoxaban); VKA, vitamin K antagonists (warfarin); LMWH, low-molecular-weight heparin (dalteparin, enoxaparin, tinzaparin); NR, not reported

a Included one Phase II dose-finding study of apixaban with fewer than 50 participants per arm. Results not presented here.

Table 2.2: Results of included meta-analyses

Author year	Comparison	VTE		PE		DVT		Mortality		Major Bleeding		Other bleeding	
		Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)
Thein 2018[2]	LMWH vs no prophylaxis	6/4315	RR 0.51 (0.40-0.65)	NR	NR	NR	NR	2/NR	HR 1.02 (0.94-1.11)	4/3065	RR 1.47 (0.79-2.75)	4/2873	RR 3.35 (2.09-5.06) a
Fuentes 2017[3]	Any anticoagulation strategy (VKA, LMWH, or UFH) vs no prophylaxis	NR	NR	NR	NR	NR	NR	8/3819	OR 0.75 (0.58-0.96)	NR	NR	8/3708	OR 3.06 (1.64-5.72) b
	Warfarin vs no prophylaxis	NR	NR	NR	NR	NR	NR	3/586	OR 0.75 (0.47-1.21)	NR	NR	3/560	OR 5.42 (3.48-8.45) b
	LMWH vs no prophylaxis	5/4051	OR 0.50 (0.38-0.66)	NR	NR	NR	NR	4/2956	OR 0.74 (0.49-1.11)	NR	NR	4/2871	OR 2.03 (0.78-5.25) b
Di Nisio 2016[4]	Semuloparin vs placebo	1/3212	RR 0.36 (0.22-0.60)	1/3212	RR 0.48 (0.22-1.01)	1/3212	RR 0.32 (0.16-0.63)	1/3212	RR 1.02 (0.96-1.08)	1/3172	RR 1.05 (0.55-2.0)	1/3172	RR 1.40 (0.90-2.19) c
	LMWH vs no thromboprophyalxis	9/3284	RR 0.54 (0.38-0.75)	7/5226	RR 0.59 (0.40-0.86)	8/5310	RR 0.49 (0.35-0.67)	8/2304	RR 0.93 (0.80-1.09)	13/6356	RR 1.44 (0.98-2.11)	4/3105	RR 3.40 (1.20-9.63) c
	LMWH vs aspirin	2/781	RR 0.51 (0.22-1.17)	2/781	RR 0.13 (0.02-1.03)	2/781	RR 0.81 (0.32-2.04)	NR	NR	2/781	RR 0.14 (0.01-2.76)	NR	NR
	LMWH vs VKA	1/439	RR 0.33 (0.14-0.83)	1/439	RR 0.11 (0.01-2.06)	1/439	RR 0.43 (0.17-1.10)	NR	NR	NR	NR	NR	NR
	UFH vs no thromboprophylaxis	NR	NR	NR	NR	NR	NR	1/277	RR 0.86 (0.72-1.03)	NR	NR	1/277	RR 2.01 (0.18-21.96) c
	VKA vs no thromboprophylaxis	1/311	RR 0.15 (0.02-1.2)	1/311	RR 1.05 (0.07-16.58)	1/311	RR 0.08 (0-1.42)	NR	NR	4/994	RR 3.82 (0.97-15.04)	NR	NR
	VKA vs aspirin	1/440	RR 1.50 (0.74-3.04)	1/440	RR 1.00 (0.25-3.95)	1/440	RR 1.75 (0.75-4.09)	NR	NR	1/440	RR 0.14 (0.01-2.75)	NR	NR
Tun 2016[5]	LMWH vs control	4/738	RR 0.18 (0.08-0.39)	NR	NR	NR	NR	NR	NR	2/433	RR 1.25 (0.48-3.31)	NR	NR
Ben-Aharon 2014[6]	LMWH vs control	7/4812	RR 0.46 (0.32-0.67)	6/6123	RR 0.49 (0.29-0.84)	4/4470	RR 0.35 (0.21-0.61)	6/2550	RR 0.93 (0.82-1.04)	9/6595	RR 1.28 (0.84-1.95)	9/6595	RR 1.29 (0.95-1.77) c

Abbreviations: VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CI confidence interval; RR, relative risk; NR not reported; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

a Clinically relevant non-major bleeding
b Total bleeding
c Clinically relevant bleeding (major and clinically relevant non-major bleeding)

Table 2.3 Characteristics of included RCTs

Author, year	Number of patients randomized	Population	Experimental treatment	Control treatment	Treatment duration
Khorana 2019[7]	841	Ambulatory cancer patients initiating new systematic regimen, with Khorana Score ≥ 2	Rivaroxaban 10 mg once daily	Placebo	6 months
Carrier 2018[8]	574	Ambulatory cancer patients initiating chemotherapy, with Khorana Score ≥ 2.	Apixaban 2.5 mg twice daily	Placebo	6 months

Table 2.4 Results of included RCTs

Author, year	Comparison	VTE		Mortality†		Major bleeding		Clinically relevant non-major bleeding	
		% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)
Khorana 2019[7]	Rivaroxaban vs placebo	*To day 180:* 6%/8.8% *On treatment:* 2.6%/6.4%	*To day 180:* HR 0.66 (0.40-1.09) *On treatment*: HR 0.40 (0.20-0.80)	20.0%/23.8%	HR 0.83 (0.62-1.11)	2.0%/1.0%	HR 1.96 (0.59-6.49)	2.7%/2.0%	HR 1.34 (0.54-3.32)
Carrier 2018[8]	Apixaban vs placebo	*To day 180* 4.2%/10.2% *On treatment* 1.0%/7.3%	*To day 180* HR 0.41 (0.26-0.65) *On treatment* HR 0.14 (0.05-0.42)	12.2%/9.8%	HR 1.29 (0.98-1.71)	*To day 180* 3.5%/1.8% *On treatment* 2.1%/1.1%	*To day 180* HR 2.00 (1.01-3.95) *On treatment* HR 1.89 (0.39-9.24)	*To day 180* 7.3%/5.5%	*To day 180* HR 1.28 (0.89-1.84)

Abbreviations: VTE, venous thromboembolism; Int, intervention arm; cont, control arm; CI, confidence interval; HR, hazard ratio; NR, not reported.

† Death from any cause

Table 2.5 RCT Quality Assessments

Author year	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intention to Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias*
Khorana 2019[7]	√	√	?	Prior VTE more common in intervention arm	√	√	√	√	--	Low-to-intermediate

Author year	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intention to Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias*
Carrier 2018[8]	√	√	?	√	√	√	√	11 patients excluded from analysis	--	Low-to-intermediate

NOTE: **√**, indicates criteria were met; -, indicates criteria were not met; ?, indicates insufficient detail, not reported, and/or uncertain if the criteria were met.

* Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.

Clinical Question 3: Should patients with cancer undergoing surgery receive peri-operative VTE prophylaxis?

Table 3.1 Characteristics of included meta-analyses

Author year	Anticoagulants					Surgery			Questions addressed				Outcomes				
	DOACs	VKAs	LMWH	Fondaparinux	Unfractionated heparin	Any	Craniotomy	Abdominal or pelvic	Other	With versus without pharmacologic prophylaxis	LMWH vs UFH	Extended versus conventional prophylaxis	Mechanical prophylaxis	VTE rincidence	Major bleeding	Other bleeding	Mortality	Quality of life
Felder 2018[9]			✓					✓				✓ ≥ 14 days versus in-hospital period only		✓	✓	✓		
Matar 2018[10]			✓	✓	✓	✓					✓			✓	✓	✓	✓	
Fagarasanu 2016[11]			✓					✓				✓ 2-6 weeks vs ≤ 2 weeks		✓	✓		✓	
Alsheri 2016[12]			✓		✓		✓			✓	✓		✓	✓	✓	✓		

Abbreviations: DOAC, direct oral anticoagulants (dabigatran, apixaban; rivaroxaban, edoxaban); VKA, vitamin K antagonists (warfarin); LMWH, low-molecular-weight heparin (dalteparin, enoxaparin, tinzaparin); NR, not reported

Table 3.2 Results of included meta-analyses

Author year	Comparison	VTE		PE		DVT		Mortality		Major Bleeding		Other bleeding	
		Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Interventi on versus control (95% CI)
Felder 2018[9] a	Extended vs conventional thrmobprophylaxis	7/1728	OR 0.38 (0.26-0.54)	NR	NR	7/1728	OR 0.39 (0.27-0.55)	NR	NR	NR	NR	7/2239	OR 1.10 (0.67-1.81)
Matar 2018[10]	LMWH vs UFH	NR	NR	14/5588	RR 0.49 (0.17-1.47)	8/2250	RR 0.67 (0.27-1.69) b	8/4260	RR 0.82 (0.63-1.07)	9/3473	RR 1.01 (0.69-1.48)	2/1194	RR 1.01 (0.76-1.33)
	LMWH vs fondaparinux	3/1806	RR 2.51 (0.89-7.03)	1/116	RR 3.13 (0.13-74.64)	NR	NR	NR	NR	3/2339	RR 0.74 (0.45-1.23)	2/398	RR 0.83 (0.34-2.05)
Fagarasanu 2016[11]	Extended vs conventional prophyalxis c	3/1045	RR 0.43 (0.21-0.88)	3/1045	RR 0.20 (0.01-4.18) d	3/1045 2/820	Proximal RR 0.33 (0.10-1.03) Distal RR 0.63 (0.32-1.22)	3/1214	RR 0.91 (0.41-2.03)	3/1351	RR 1.20 (0.31-4.58)	NR	NR
Alsheri 2016[12]	UFH vs placebo	2/203	RR 0.27 (0.10-0.73)	NR	NR	NR	NR	NR	NR	2/NR	RR 1.20 (0.36-3.95)	5/NR	Combined major/minor bleeding: RR 2.02 (1.14-3.58)
	LMWH plus mechanical prophylaxis vs UFH plus mechanical prophylaxis	2/202	RR 1.78 (0.66-4.79)	NR	NR	NR	NR	NR	NR				
	LMWH plus mechanical prophylaxis vs mechanical prophylaxis alone	3/705	RR 0.62 (0.46-0.82)	NR	NR	NR	NR	NR	NR				
	Mechanical prophylaxis vs placebo	3/153	RR 0.31 (0.09-1.10)	NR	NR	NR	NR	NR	NR				

Abbreviations: VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CI confidence interval; OR, odds ratio; RR, relative risk; HR, hazard ratio; NR not reported; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin;

A 5 of 7 trials enrolled cancer patients only. Only 1 trial (Vedovati 2014) included minimally invasive surgery. Primary outcome was VTE within 30 days after surgery. Bleeding outcome was major or minor bleeding within 90 days of surgery.

b Symptomatic

c Results reported here are for RCTs only. There were no statistically significant differences between RCT results and cohort study results.

d Based on two events from one trial.

Table 3.3 Characteristics of included RCTs

Author, year	Number of patients randomized	Population	Experimental treatment	Control treatment	Treatment duration
Jung 2018[13]	682	Patients undergoing gastrectomy for gastric adenocarcinoma	Intermittent pneumatic compression plus LMWH	Intermittent pneumatic compression alone	Until hospital discharge
Song 2015[14]	111	Adults undergoing esosphagectomy for esophageal cancer.	LMWH BID Nadroparin 4100 AxaIU q12h	LMWH QD Nadroparin 4100 AxaIU qd	Start: 6 hours after esophagectomy End: 7th day after surgery or upon bleeding
Vedovati 2014[15]	225	Adults undergoing laparascopic surgery for colorectal cancer.	4 weeks of VTE prophylaxis with LMWH	1 week of VTE prophylaxis with LMWH	1 or 4 weeks.

Table 3.4 Results of included RCTs

Author, year	Comparison	VTE		Mortality		Major bleeding		Other bleeding	
		% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)
Jung 2018[13]	Intermittent pneumatic compression with vs without LMWH	0.6/3.6	RD 2.97 (0.81-5.12) *P* for non-inferiority=0.81	NR	NR	8.5/1.2	*P* < 0.001	0.6/0.0	*P* < 0.001
Song 2015[14]	LMWH BID vs LMWH QD	0/9.1%	*P* = 0.03	0/0	--	0/0	--	0/0	--
Vedovati 2014[15]*	LMWH: 4 weeks vs 1 week	0/9.7%	*P* = 0.001	0/0	NR	0/0.9%	NR	0.9%/0	NR

Abbreviations: VTE, venous thromboembolism; Int, intervention arm; cont, control arm; CI, confidence interval; RD, risk difference; NR, not reported.

*Reported results are from 4-week after surgery.

Table 3.5 RCT Quality Assessments

Author year	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intention to Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias*
Jung 2018[13]	✓	✓	✓	✓/-	--	✓	✓	✓	--	Intermediate
Song 2015[14]	✓	✓	?	✓	✓	✓	?	?	✓	Intermediate-high
Vedovati 2014[15]	✓	✓	?	✓	Outcome assessors were blinded	✓	✓	?	✓	Intermediate

NOTE: **√**, indicates criteria were met; -, indicates criteria were not met; ?, indicates insufficient detail, not reported, and/or uncertain if the criteria were met.

* Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.

Abbreviations: RCT, randomized controlled trial

Clinical Question 4: What is the best method of treatment for patients with cancer with established VTE to prevent recurrence?

Table 4.1 Characteristics of included meta-analyses

Author year	Anti-coagulants					Outcomes Assessed				
	DOACs	VKAs	LMWH	Fondaparinux	Unfractionated heparin	Recurrent VTE	Major bleeding	Other bleeding	Mortality	Quality of life
Kahale 2018[16]	✓	✓	✓			✓	✓	✓	✓	
Li 2018[17]	✓		✓			✓	✓	✓	✓	
Hakoum 2018[18]			✓	✓	✓	✓	✓	✓	✓	
Brunetti 2017[19]	✓	✓				✓		✓		
Martinez-Zapata 2017[20]		✓	✓			✓	✓	✓	✓	
Rojas-Hernandez 2017[21]		✓	✓				✓ Intra-cranial			
Posch 2015[22] a	✓	✓	✓			✓	✓			
Vedovati 2015[23]	✓	✓				✓	✓	✓		
Larsen 2014[24]	✓	✓				✓	✓			
Carrier 2014[25]	✓	✓				✓	✓			
Prins 2014[26]	✓	✓				✓	✓	✓	✓	
Gomez-Outes 2014[27]	✓	✓				✓		✓		
van Es 2014[28]	✓	✓				✓	✓			

Abbreviations: DOAC, direct oral anticoagulants (dabigatran, apixaban; rivaroxaban, edoxaban); VKA, vitamin K antagonists (warfarin); LMWH, low-molecular-weight heparin (dalteparin, enoxaparin, tinzaparin); PE, pulmonary embolism

a Network meta-analysis with indirect comparisons between DOACs and LMWH.

Table 4.2 Results of included meta-analyses

Author year	Comparison	Recurrent VTE		Mortality		Major Bleeding		Other bleeding	
		Number of studies/ number of patients	Effect estimate (95% CI)	Number of studies/ number of patients	Effect estimate (95% CI)	Number of studies/ number of patients	Effect estimate (95% CI)	Number of studies/ number of patients	Effect estimate (95% CI)
Kahale 2018[16]	LMWH vs VKA	5/1781	RR 0.58 (0.43-0.77)	5/1747	RR 1.00 (0.88-1.13)	4/1712	RR 1.09 (0.55-2.12)	4/1712	RR 0.78 (0.47-1.27) a
	DOAC vs VKA	4/1022	RR 0.66 (0.33-1.31)	4/1031	RR 0.93 (0.71-1.21)	4/1030	RR 0.77 (0.38-1.57)	4/1030	RR 0.84 (0.58-1.22) a
Li 2018[17]	DOAC vs LMWH	2/1452	RR 0.65 (0.42-1.01)	2/1452	RR 1.03 (0.85-1.26)	2/1452	RR 1.74 (1.05-2.88)	2/1452	RR2.31 (0.85-6.28) b
Hakoum 2018[18]	LMWH vs UFH	3/422	RR 0.69 (0.27-1.76)	5/418	RR 0.66 (0.40-1.10)	NR	NR	NR	NR
	Fondaparinux vs heparin (UFH and LMWH)	1/477	RR 0.93 (0.56-1.54)	1477	RR 1.25 (0.86-1.81)	1/477	RR 0.82 (0.40-1.66)	1/477	RR 1.53 (0.88-2.66) a
	Dalteparin vs tinzaparin	1/113	RR 0.44 (0.09-2.16)	1/113	RR 0.86 (0.43-1.73)	1/113	RR 2.19 (0.20-23.42)	1/113	RR 0.82 (0.30-2.21) a
Brunetti 2017[19]	DOAC vs VKA	7/1251	OR 0.67 (0.40-1.15)	NR	NR	NR	NR	6/1116	OR 0.83 (0.60-1.15) c
	DOAC vs LMWH (inpatient)	2/701	OR 0.96 (0.52-1.75)	NR	NR	NR	NR	2/703	OR 2.72 (1.05-7.01) c
Martinez-Zapata 2017[20]	Tinzaparin vs VKA	3/1169	RR 0.67 (0.46-0.99)	3/1169	RR 1.09 (0.91-1.30)	2/1100	RR 1.06 (0.56-1.99)	1/900	RR 0.71 (0.51-1.00) b
Rojas-Hernandez 2017[21]	LMWH vs VKA	NR	NR	NR	NR	3/1119	RR 0.49 (0.10-2.33) [d]	NR	NR
Posch 2015[22]	LMWH vs VKA	6/2078	RR 0.60 (0.45-0.79)	NR	NR	5/2020	RR 1.07 (0.66-1.73)	NR	NR

Author year	Comparison	Recurrent VTE		Mortality		Major Bleeding		Other bleeding	
		Number of studies/ number of patients	Effect estimate (95% CI)	Number of studies/ number of patients	Effect estimate (95% CI)	Number of studies/ number of patients	Effect estimate (95% CI)	Number of studies/ number of patients	Effect estimate (95% CI)
	DOAC vs VKA	4/1164	RR 0.65 (0.38-1.09) RR 1.08 (0.59-1.95)	NR	NR	4/1145	RR 0.72 (0.39-1.35) RR 0.67 (0.31-1.46)	NR	NR
	DOAC vs LMWH [e]	NA	Adjusted for VTE risk in VKA arms: RR 0.71 (0.14-3.51)	NR	NR	NA	Adjusted for bleeding risk in VKA arms: RR 0.40 (0.15-1.19)	NR	NR
Vedovati 2015[23]	DOAC vs VKA	6/1132	OR 0.63 (0.37-1.10)	NR	NR	6/1114	OR 0.77 (0.41-1.44)	6/1114	OR 0.85 (0.62-1.18) f
Larsen 2014[24]	DOAC vs VKA	4/759	OR 0.56 (0.28-1.13)	NR	NR	3/636	OR 0.88 (0.57-1.35)	NR	NR
Carrier 2014[25]	DOAC vs VKA	4/1132	RR 0.66 (0.39-1.11)	NR	NR	4/1114	RR 0.78 (0.42-1.44)	NR	NR
	LMWH vs VKA	5/1178	RR 0.52 (0.36-0.74)	NR	NR	4/1120	RR 1.06 (0.5-2.23)	NR	NR
Prins 2014[26]	Rivaroxaban vs enoxaparin with VKA	2/655	HR 0.67 (0.35-1.30)	2/655	HR 0.93 (0.64-1.35)	2/651	HR 0.42 (0.18-0.99)	2/651	HR 0.80 (0.54-1.20) f
Gomez-Outes 2014[27]	DOAC vs VKA	5/859	RR 0.62 (0.31-1.20)	NR	NR	NR	NR	3/636	RR 0.89 (0.62-1.27) g
van Es 2014[28]	DOAC vs VKA	NR/1581	RR 0.57 (0.36-0.91)	NR	NR	NR/1582	RR 0.77 (0.44-1.33)	NR	NR

Abbreviations: VTE venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist; CI confidence interval; OR, odds ratio; MD, mean difference; HR, hazard ratio; NR not reported; NA, not applicable.

a minor bleeding
b clinically relevant non-major bleeding

c Type of bleeding not specified
d Intracranial hemorrhage, assessed at 3 and 6 months
e Indirect comparison from network meta-analysis
f Clinically relevant bleeding
g Composite of major and clinically relevant non-major bleeding

Table 4.3 Characteristics of included RCTs

Author, year	Number of patients randomized	Population	Experimental treatment	Control treatment	Treatment duration	Non-inferiority margin
Young 2018[29]	406	Cancer patients with symptomatic or incidental PE or symptomatic lower extremity proximal DVT	**Rivaroxaban** 15 mg twice daily for 3 weeks, then 20 mg once daily	Dalteparin 200 IU/kg daily for 1 month and 150 IU/kg daily thereafter	6 months	NA
Raskob, 2017[30]	1050	Cancer patients (active cancer or diagnosed in previous 2 years) with acute symptomatic or incidental VTE.	LMWH for ≥ 5 days followed by oral **edoxaban** 60 mg once daily	LMWH for ≥ 5 days followed by sc dalteparin 200 IU/kg daily for 30 days and 150 IU/kg daily thereafter	6-12 months Median: 211 days in edoxaban arm and 184 days in control arm.	Upper limit of 95% CI for HR < 1.5 For composite outcome of recurrent VTE and major bleeding
Woodruff 2016[31] Subgroup analysis of patients with renal impairment in the CLOT trial	162	Patients with cancer, VTE, and baseline renal impairment (creatinine clearance < 60 ml/min)	**Dalteparin** 200 IU/kg daily for 1 month and 150 IU/kg daily thereafter	Dalteparin 200 IU/kg for ≥ 5 days, overlapped with and followed by once daily VKA	6 months	NA

Abbreviations: VTE, venous thromboembolism; LMWH, low molecular weight heparin; sc, subcutaneous; INR, international normalized ratio;

Table 4.4 Results of included RCTs

Author, year	Comparison	Recurrent VTE		Mortality		Major bleeding		Other bleeding		Composite of VTE recurrence or major bleeding	
		% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)
Young 2018[29]	Rivaroxaban vs dalteparin	4/11	HR 0.43 (0.19-0.99)	OS at 6 months: 75/70	NR	6/4	HR 1.83 (0.68-4.96)	13/4	HR 3.76 (1.63-8.69) a	NR	NR
Raskob, 2017[30]	Edoxaban vs dalteparin	7.9/11.3	HR 0.71 (0.48-1.06)	39.5/36.6	HR 1.12 (0.92-1.37)	6.9/4.0	HR 1.77 (1.03-3.04)	14.6/11.1	HR 1.38 (0.98-1.94) a	12.8/13.5	HR 0.97 (0.70-1.36) Non-inferiority *P* = 0.006
Woodruff 2016[31]	Dalteparin vs VKA	2.7/17	HR 0.15 (0.03-0.65)	48.6/48.9	NR	9.5/6.9	HR 1.29 (0.43-3.83)	20.3/24.1	HR 0.78 (0.40-1.52) b	NR	NR

Abbreviations: VTE, venous thromboembolism; Int, intervention arm; cont, control arm; CI, confidence interval; RD, risk difference; HR, hazard ratio; OS, overall survival.

a clinically relevant non-major bleeding

b major or non-major clinically relevant bleeding

Table 4.5 RCT Quality Assessments

Author year	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intention to Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias*
Young 2018[29]	✓	✓	--	✓	--	✓	✓	✓	--	Low to intermediate
Raskob, 2017[30]	✓	✓	✓	✓	--	✓	✓	1046/1050 analyzed	--	Low
Woodruff 2016[31]	Subgroup analysis of CLOT trial									

NOTE: **√**, indicates criteria were met; -, indicates criteria were not met; ?, indicates insufficient detail, not reported, and/or uncertain if the criteria were met.

* Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.

Abbreviations: RCT, randomized controlled trial

Clinical Question 5: Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?

Table 5.1 Characteristics of included meta-analyses

Author year	Anticoagulants					Cancer types				Outcomes				
	DOACs	VKAs	LMWH	Fondaparinux	Unfranctionated heparin	Solid tumors	Lymphoma	Multiple myeloma	Other	VTE incidence	Major bleeding	Other bleeding	Mortality	Quality of life
Kahale 2017[32]	✓	✓				✓	✓	✓		✓	✓	✓	✓	
Akl 2017[33]			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Yu 2016[34]			✓		✓	✓ Lung				✓	✓	✓	✓	

Abbreviations: DOAC, direct oral anticoagulants (dabigatran, apixaban; rivaroxaban, edoxaban); VKA, vitamin K antagonists (warfarin); LMWH, low-molecular-weight heparin (e.g. dalteparin, enoxaparin, tinzaparin); NR, not reported

Table 5.2 Results of included meta-analyses

Author year	Comparison	VTE		Mortality		Major Bleeding		Other bleeding		Quality of life	
		Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)	Number of studies/ number of patients	Intervention versus control (95% CI)
Kahale 2017[32]	DOAC vs no prophylaxis	1/92	RR 0.16, (0.01 to 3.91) (PE) RR 0.07 (0.00 to 1.32) (DVT)	1/92	At 3 months: RR 0.24, (0.02 to 2.56)	1/92	RR 0.16 (0.01 to 3.91)	1/92	RR 4.43 (0.25 to 79.68) a	NR	NR
	VKA vs. no prophylaxis	1/311	RR 1.05, (0.07-16.58) (PE) RR 0.08, (0.00 to 1.42) (DVT)	5/1281	At 12 months: RR 0.95 (0.87-1.03) b	5/1281	RR 2.93, (1.86 to 4.62)	4/863	RR 3.14 (1.85-5.32) a	NR	NR
Akl 2017[33]	Heparin vs. no prophylaxis	16/9036	RR 0.56 (0.47-0.68)	18/9575 14/5229	At 12 months: RR 0.98 (0.93-1.03) c At 24 months: RR 0.99 (0.96-1.01)	18/9592	RR 1.30 (0.94-1.79)	16/9245	RR 1.70 (1.13-2.55) a	2/2241	No significant difference between arms.
Yu 2016[34]	Heparin vs no prophylaxis e	4/933	RR 0.46 (0.27-0.80)	4/568	HR 0.71 (060-0.84)	4/863	RR 1.43 (0.59-3.45)	4/947	RR 1.53 (0.96-2.45)	NR	NR

Abbreviations: CI confidence interval; OR, odds ratio; RR, relative risk; HR, hazard ratio; NR not reported; PE, pulmonary embolism; DVT, deep vein thrombosis;
a Minor bleeding
b Subgroup with lung cancer: 4 studies, 837 patients, RR 0.95, 95% CI (0.85, 1.05). Subgroup without lung cancer: 2 studies, 444 patients, RR 0.95, 95% CI (0.81, 1.10)
c Subgroup with lung cancer: 6 studies, 3204 patients, RR 0.89, 95% CI (0.73-1.08). Subgroup without lung cancer: 7 studies, 1564 patients, RR 0.95, 95% CI (0.88, 1.03)
d Total bleeding
e Intervention was LMWH in five studies and UFH in one study.

Table 5.3 Characteristics of included RCT

Author, year	Number of patients randomized	Population	Experimental treatment	Control treatment	Treatment duration
Ek 2017[35]	390	Newly diagnosed small-cell lung cancer	Enoxaparin 1 mg/kg sc daily	No enoxaparin	Started on day 1 of chemotherapy and continued until the 21st day of the last chemotherapy cycle.

Abbreviations: VTE, venous thromboembolism; LMWH, low molecular weight heparin; sc, subcutaneous; INR, international normalized ratio;

Table 5.4 Results of included RCT

Author, year	Comparison	VTE		OS		PFS		Bleeding (total)	
		% Int/cont	Effect estimate (95% CI)	Median (months) Int/cont	Effect estimate (95% CI)	Median (months) Int/cont	Effect estimate (95% CI)	% Int/cont	Effect estimate (95% CI)
Ek 2017[35]	Enoxaparin vs no enoxaparin	2.5/8.5	HR 0.31 (0.11-0.84)	10.6/11.3	HR 1.11 (0.89-1.38) a	5.8/6.9	HR 1.18 (0.95-1.46)	15/4 b	NR

Abbreviations: VTE, venous thromboembolism; Int, intervention arm; cont, control arm; CI, confidence interval; OS, overall survival; PFS, progression-free survival; HR, hazard ratio;

a Among patients with limited disease (N=150): HR 1.17, 95% CI 0.80-1.70. Among patients with extensive disease (N=227): HR 1.07, 95% CI 0.82-1.40
b Fatal bleeding occurred in 3 patients in the enoxaparin arm and 1 patient in the control arm.

Table 5.5 RCT Quality Assessments

Author year	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intention to Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias*
Ek 2017[35]	✓	✓	?	✓	--	✓	✓	377/390 patients analyzed	✓	Intermediate

NOTE: **√**, indicates criteria were met; -, indicates criteria were not met; ?, indicates insufficient detail, not reported, and/or uncertain if the criteria were met.

* Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.

Abbreviations: RCT, randomized controlled trial

Clinical Question 6: What is known about risk prediction and awareness of VTE among patients with cancer?

Table 6.1 Study Characteristics- VTE risk assessment in ambulatory or hospitalized patients with mixed cancer types

Source	Study design	Sample Size	Duration of Follow-up	Study population
Pabinger 2018[36]	Prospective Model development and validation	Development: 1423 Validation: 832	6 months	Development: Vienna Cancer and Thrombosis Study. Solid tumors (excluding primary brain tumors) or lymphoma. Validation: Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism (MICA). Ambulatory patients with advanced solid cancer. Scheduled for chemotherapy within 7 days of study entry or had started chemotherapy in the previous 3 months.
Parker 2018[37]	Retrospective	1398	Median length of stay: 6 days (range 1-144)	Adult cancer patients hospitalized for medical reasons.
Patell 2017[38]	Retrospective	2780	Median length of stay: 5 days (range 0-152)	Hospitalized patients with a solid tumor or hematologic malignancy. 65% received anticoagulation on day of admission.
Posch 2016[39]	Prospective	1685	2 years	Most common cancer types were lung, lymphoma, brain, and breast.
Lustig 2015[40]	Prospective	580	3 months	Newly diagnosed, ambulatory cancer patients (cancer treatment not reported)
Holh Moinat 2014[41]	Prospective	1097	3 months	Adults with cancer and insertion of a central venous port.

Table 6.2 Results- VTE risk assessment in ambulatory or hospitalized patients with mixed cancer types

Source	Risk scores	Distribution of patients by score	Risk of VTE by score
Pabinger 2018[36]	Model based on tumor site risk category and continuous D-dimer concentration	C indices of model incorporating tumor site and D-dimer: CATS: 0.66, 95% CI 0.63-0.67 MICA: 0.68, 95% CI 0.62-0.74 C indices of KRS: CATS: 0.61, 95% CI 0.51-0.70 MICA: 0.56, 95% CI 0.50-0.63	
Parker 2018[37]	KRS ≥ 3 KRS 1-2 KRS 0	11.9% 58.4% 29.7%	5.4% 3.2% 1.4% High-risk vs low-risk: OR 3.9, 95% CI 1.4-11.2
Patell 2017[38]	KRS ≥ 3 KRS 1-2 KRS 0 KRS 2-5 KRS 0-1	13% 62% 25% 37% 63%	6% 4% 3% High risk vs low risk: OR 2.52, 95% CI 1.31-4.86 5% 3% High risk vs low risk: OR 1.82, 95% CI 1.23-2.69
Posch 2016[39]	KRS ≥ 3 KRS 2 KRS 1 KRS 0	NR NR NR NR	HR 6.47, 95% CI 2.99-14.00 HR 4.63, 95% CI 2.20-9.75 HR 3.23, 95% CI 1.53-6.81 Reference category
Lustig 2015[40]	KRS ≥ 2 KRS <2	25% 75%	11% 4%
Hohl Moinat[41] a	KRS ≥ 3	9.3%	OR 3.50, 95% CI 1.00-12.30

Abbreviations: VTE, venous thromboembolism; KRS, Khorana risk score; HR, hazard ratio; OR, odds ratio; NR, not reported;
a Primary outcomes was catheter-related VTE (occlusive deep vein thrombosis in the arm or isolated pulmonary embolism of unknown origin) at 3 months.

Table 6.3 Study Characteristics- VTE risk assessment in ambulatory patients with individual cancer types

Source	Study design	Sample Size	Duration of Follow-up	Study population
Rupa-Matysek 2018	Retrospective	118	Median 14 months	Lung cancer, undergoing outpatient chemotherapy
Fuentes 2018[42]	Retrospective	112	At least 5 weeks (median 21.3 months)	Gastric cancer (79.5% receiving chemotherapy)
Kuderer 2018[43]	Prospective	1980	6 months	Lung cancer patients initiating a new systemic cancer therapy (84% with NSCLC).
Rupa-Matysek 2017[44]	Retrospective	428	4.7 months (median)	Patients receiving chemotherapy for newly diagnosed diffuse large B cell lymphoma or Hodgkin lymphoma
Bezan 2017[45]	Retrospective	657 derivation, 349 validation	1 year	Testicular germ cell tumors (56% of derivation cohort had not had chemotherapy at baseline)
Wang 2017[46]	Retrospective	270	> 1 month	Hepatocellular carcinoma. 36% of patients received chemotherapy.
Santi 2017[47]	Pooled analysis of Phase II and Phase III trials	1717 (1189 with Khorana score)	6 months	Non-Hodgkin's lymphoma. Planned treatment was autologous stem cell transplant (27% of patients), conventional chemotherapy (67% of patients), and chemotherapy plus lenalidomide (6% of patients). All patients received rituximab.
Ramos 2017[48]	Retrospective	943	NR	Metastatic urothelial carcinoma and variant histology, treated with chemotherapy.
Kruger 2017[49]	Retrospective	172	NR	Advanced pancreatic cancer and palliative chemotherapy
Mansfield 2016[50]	Retrospective	719	15.2 months (median)	Lung cancer. 37.6% received chemotherapy.
Srikanthan 2015[51]	Retrospective	216 derivation, 108 validation	NR	Disseminated germ cell tumors treated with chemotherapy
Muñoz-Martin 2014[52]	Retrospective	84	NR	Pancreatic cancer treated with chemotherapy

Abbreviations: NSCLC, non-small cell lung cancer; NR, not reported

Table 6.4 Results- VTE risk assessment in ambulatory patients with individual cancer types

Source	Risk scores	Distribution of patients by score	Risk of VTE by score
Rupa-Matysek 2018[53]	KRS ≥ 3	13%	13%
	KRS <1-2	87%	17.5%
	PROTECHT high	52%	17.7%
	PROTECHT lower	48%	16.1%
	CONKO high	22%	15.4%
	CONKO lower	78%	17.4%
	COMPASS-CAT high	71%	23.8%
	COMPASS-CAT lower	29%	0
Fuentes 2018[42]	KRS ≥ 3	52.7%	15%
	KRS 1-2	47.3%	7.6%
			P = 0.17
	PLR high	30.4%	8.8%
	PLR low	69.6%	12.8%
			P = 0.8
	NLR high	50.9%	10.5%
	NLR low	49.1%	12.7%
			P = 0.8
Kuderer 2018[43]	KRS ≥ 3	15.1%	5.4%,
	KRS 2	30.4%	6.5%
	KRS 1	44.5%	6.4%
	KRS Unknown	10.1%	5.0%
			P = 0.98
Rupa-Matysek 2017[44]	KRS ≥ 3	15%	17%
	KRS 1-2	85%	15%
			P = 0.59

Source	Risk scores	Distribution of patients by score	Risk of VTE by score		
Bezan 2017[45]a	KRS 3	1.5%	0		
	KRS 2	12.8%	13.3%		
	KRS 1	85.7%	4%		
			P = 0.002		
	Stage IIIA-IIIC	11%	21.4%		
	Stage IIC	3%	14.3%		
	Stage 1S-IIB	13%	5.9%		
	Stage IA-IB	72%	1.7%		
			P < 0.0001		
Wang 2017[46]	KRS 3	0.7%			
	KRS 2	5.2%			
	KRS 1	25.9%	KRS > 0: 8.1%		
	KRS 0	68.1%	KRS = 0: 4.9%		
			HR 1.83, 95% CI 0.81-1.45		
Santi 2017[47] b	KRS ≥ 3	12%	6.6%		
	KRS 2	30%	4.5%		
	KRS 1	58%	2.2%		
			P = 0.012		
Ramos 2017[48]	KRS ≥ 3	17%	Overall 13%	Early (< 3 mos) 8%	Late (> 3 mos) 4.9%
	KRS 1-2	83%	9.2%	4%	5.3%
			P = 0.15	*P* = 0.04	*P* = 0.89
Kruger 2017[49]	KRS > 2	38%	19%		
	KRS 2	62%	12%		
			P = 0.4		
	CONKO > 2	38%	19%		
	CONKO 2	62%	11%		
			P = 0.41		
	aPTT ratio < median	55%	18%		
	aPTT ratio > median	45%	8%		
			P = 0.17		
Mansfield 2016[50]c	KRS ≥ 3	15%	12.4%		
	KRS 1-2	85%	12.1%		

Source	Risk scores	Distribution of patients by score	Risk of VTE by score
			P = 0.21
Srikanthan 2015[51] d	KRS ≥ 3	8%	44%
	KRS 1-2	88%	NR
	Unknown	4%	NR
			P < 0.001
	RPLN > 5 cm	27%	22%
	RPLN ≤ 5 cm	73%	5%
			P = 0.001
Muñoz-Martin 2014[52]	KRS ≥ 3	57%	37.5%
	KRS 2	43%	33%
			NS

Abbreviations: VTE, venous thromboembolism; KRS, Khorana risk score; PLR, Platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio;; aPTT, activated partial thromboplastin time; NS, not significant; HR, hazard ratio; NR, not reported; RPLN, retroperitoneal lymph node;

a Results are from the derivation cohort. In the validation cohort, results for the association between stage and VTE risk were similar.
b Any grade VTE. Includes superficial vein thrombosis.
c. 61 patients were missing KRS score.
d. Results are from the derivation cohort. In the validation cohort, risk of VTE was not significantly associated with KRS or retroperitoneal lymph node size.

DATA SUPPLEMENT 2: SEARCH STRATEGIES

Publication dates included: August 14, 2014-December 5, 2018

- Initial search: January 5, 2018
- Updated search: December 5, 2018

VTE prophylaxis and treatment

("Venous Thromboembolism"[Mesh] OR “Venous Thromboembolism"[tiab] OR “venous thrombosis”[Mesh] OR “venous thrombosis”[tiab] OR “Venous Thromboses”[tiab] OR “Phlebothrombosis”[tiab] OR “Phlebothromboses”[tiab] OR "Upper Extremity Deep Vein Thrombosis"[Mesh] OR “Deep Vein Thrombosis”[tiab] OR “Deep Vein Thromboses”[tiab] OR “Deep-Venous Thrombosis”[tiab] OR “Deep-Venous Thromboses”[tiab] OR “Thrombosis, Deep-Venous” OR “Deep Venous Thrombosis”[tiab] OR “Deep Venous Thromboses”[tiab] OR “Thrombosis, Deep Venous”[tiab] OR “Venous Thrombosis, Deep”[tiab] OR “Deep-Vein Thrombosis”[tiab] OR “Deep-Vein Thromboses”[tiab] OR "Pulmonary Embolism"[Mesh] OR “Pulmonary Embolism”[tiab] OR “Pulmonary Embolisms”[tiab] OR “Pulmonary Emboli”[tiab] OR “Pulmonary Thromboembolisms”[tiab] OR “Pulmonary Thromboemboli”[tiab] OR “Pulmonary Thromboembolism”[tiab])

AND

("antiplatelet therapy"[tiab] OR "Aspirin"[Majr] OR “Aspirin”[tiab] OR “Anticoagulants”[Mesh] OR "Heparin"[Mesh] OR “Heparin”[tiab] OR "Heparin, Low-Molecular-Weight"[Mesh] OR “low molecular weight heparin” OR "Dalteparin"[Mesh] OR “dalteparin”[tiab] OR “Fragmin”[tiab] OR "Enoxaparin"[Mesh] OR “enoxaparin”[tiab] OR “Lovenox”[tiab] OR "tinzaparin"[tiab] OR “Innohep”[tiab] OR “fondaparinux”[tiab] OR “Arixtra”[tiab] OR “Vitamin K antagonist”[tiab] OR "Warfarin"[Mesh] OR “warfarin”[tiab] OR “Coumadin”[tiab] OR “dabigatran”[tiab] OR dabigatran[Mesh] OR “Pradaxa”[tiab] OR “apixaban”[tiab] OR “Eliquis”[tiab] OR “rivaroxaban”[tiab] OR “Xarelto”[tiab] OR “edoxaban”[tiab])

AND

cancer[sb]

AND

English[la]

AND

"Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Practice Guideline" [Publication Type] OR systematic[sb] OR randomly[tiab] OR randomized[tiab] OR meta-analysis[tiab] OR trial[ti]

VTE risk prediction

Cancer[sb]

AND

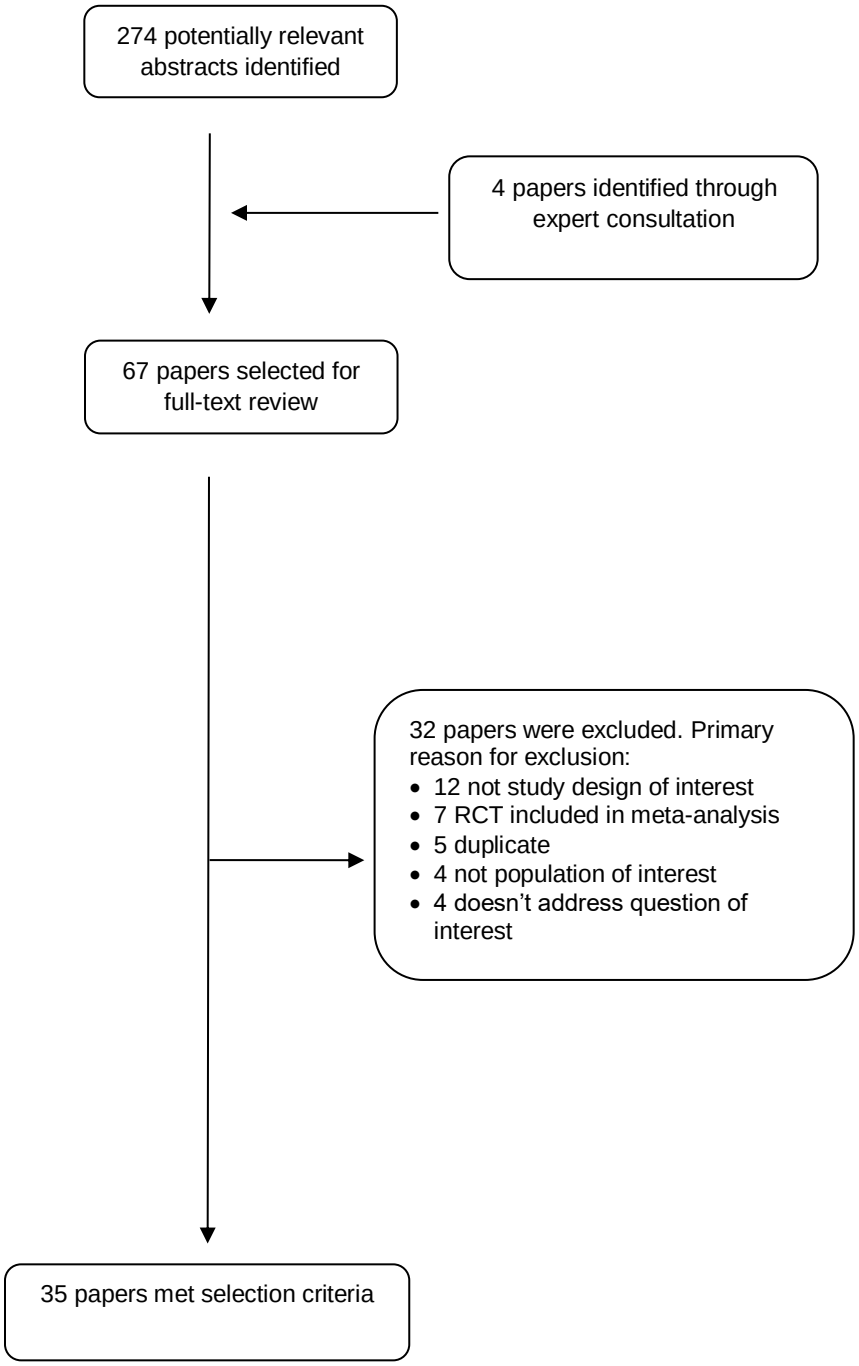
Venous thromboembolism

AND

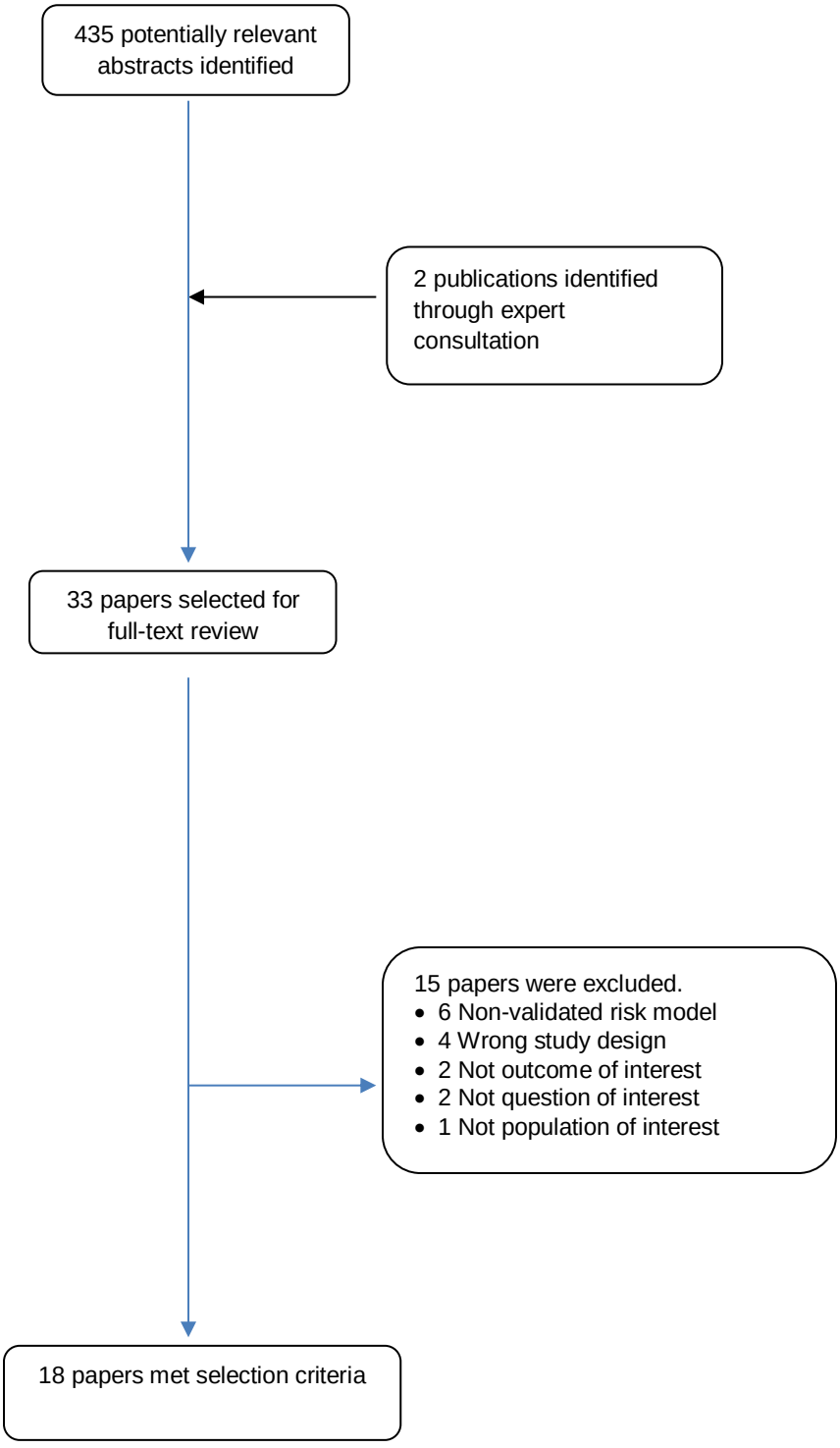
"Risk Assessment"[Mesh] OR “risk assessment”[tiab] OR “score”[tiab] OR "Validation Studies" [Publication Type] OR “risk prediction”[tiab] OR “risk stratification”[tiab]

DATA SUPPLEMENT 3. QUOROM DIAGRAMS

VTE Prophylaxis and Treatment



VTE Risk Assessment



DATA SUPPLEMENT 4: PREVIOUS AND CURRENT RECOMENDATIONS

2013/2015 Recommendations	Type of Recommendation, Strength of Evidence, Strength of Recommendation	2018 Recommendations	Type of Recommendation, Quality of Evidence, Strength of Recommendation
Inpatient			
1.1 Hospitalized patients who have active malignancy with acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.	Type: evidence based; strength of evidence: strong; strength of recommendation: strong	1.1 Hospitalized patients who have active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
1.2 Hospitalized patients who have active malignancy without additional risk factors may be considered for pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.	Type: evidence based; strength of evidence: moderate; strength of recommendation: strong	1.2 Hospitalized patients who have active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.	Type: (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Moderate)
1.3 Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion, or in patients undergoing stem cell/ bone marrow transplantation.	Type: informal consensus; strength of evidence: Insufficient; strength of recommendation: moderate	1.3 Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem-cell/bone marrow transplantation.	Type: Informal consensus; Evidence quality: Insufficient; Strength of recommendation: Moderate.

Outpatient			
2.1 Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients.	Type: evidence based; strength of evidence: moderate; strength of recommendation: strong	2.1 Routine pharmacologic thromboprophylaxis should not be offered to all cancer outpatients.	Type: Evidence based; Evidence quality: intermediate to high; Strength of recommendation: Strong
2.2 Based on limited RCT data, clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy. Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms, as well as dose and duration of prophylaxis in this setting.	Type: evidence based; strength of evidence: moderate; strength of recommendation: weak.	2.2. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban or low-molecular-weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions. 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.	Type: Evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: Moderate
2.3 Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should	Type: evidence based; strength of evidence: moderate; strength of recommendation: strong	2.3. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong

receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.		aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.	
Perioperative			
3.1 All patients with malignant disease undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis with either UFH or LMWH unless contraindicated because of active bleeding or a high bleeding risk.	Type: evidence based; strength of evidence: strong; strength of recommendation: strong.	3.1 All patients with malignant disease undergoing major surgical intervention should be offered pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) or LMWH unless contraindicated because of active bleeding, or high bleeding risk, or other contraindications.	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
3.2 Prophylaxis should be commenced preoperatively.	Type: evidence based; strength of evidence: moderate; strength of recommendation: moderate.	3.2 Prophylaxis should be commenced preoperatively.	Type: Evidence based; Evidence quality: intermediate; Strength of recommendation: Moderate
3.3 Mechanical methods may be added to pharmacologic thromboprophylaxis, but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because of	Type: evidence based; strength of evidence: moderate; strength of recommendation: strong.	3.3 Mechanical methods may be added to pharmacologic thromboprophylaxis but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because of active bleeding or high bleeding risk.	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong

active bleeding or high bleeding risk.			
3.4 A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients.	Type: informal consensus; strength of evidence: moderate; strength of recommendation: moderate.	3.4 A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients.	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
3.5 Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7-10 days. Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors as listed in Table 3. In lower risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis considering the individual patient.	Type: evidence based; strength of evidence: strong; strength of recommendation: strong to moderate	3.5 Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 to 10 days. Extended prophylaxis with LMWH for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis.	Type: Evidence based; Evidence quality: High; Strength of recommendation: Moderate to Strong

Treatment and Secondary Prophylaxis			
4.1 LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the cancer patient with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance < 30 mL/min).	Type: evidence based; strength of evidence: strong; strength of recommendation: strong.	4.1. Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance < 30 mL/min).	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
4.2 For long term anticoagulation, LMWH for at least 6 months is preferred due to improved efficacy over Vitamin K antagonists. Vitamin K antagonists are an acceptable alternative for long-term therapy if LMWH is not available.	Type: evidence based; strength of evidence: strong; Strength of recommendation: strong	4.2 For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKA). VKA are inferior, but may be utilized if LMWH or direct oral anticoagulants (DOAC) are not accessible. There is an increase in major bleeding risk with DOAC, particularly observed in GI and potentially GU malignancies. Caution with DOAC is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a DOAC.	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
4.3 Anticoagulation with LMWH or Vitamin K antagonist beyond the initial 6 months may be considered for select patients with	Type: informal consensus; strength of evidence: insufficient; strength of recommendation: weak to moderate.	Anticoagulation with LMWH, DOAC, or VKA beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak to Moderate

active cancer, such as those with metastatic disease or those receiving chemotherapy.		Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile.	
4.4 The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy (see Table 4). It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal therapy with LMWH.	Type: informal consensus; strength of evidence: weak to moderate; strength of recommendation: moderate.	4.4 Based on expert opinion in the absence of randomized trial data, uncertain short-term benefit, and mounting evidence of long-term harm from filters, the insertion of a vena cava filter should not be offered to patients with established or chronic thrombosis (VTE diagnosis more than 4 weeks ago) nor to patients with temporary contraindications to anticoagulant therapy (e.g. surgery). There also is no role for filter insertion for primary prevention or prophylaxis of PE or DVT due to its long-term harm concerns. It may be offered to patients with absolute contraindications to anticoagulant therapy in the acute treatment setting (VTE diagnosis within the past 4 weeks) if the thrombus burden was considered life-threatening. Further research is needed.	Type: Informal consensus; Evidence quality: Low to Intermediate; Strength of recommendation: Moderate

		4.5 The insertion of a vena cava filter may be offered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal anticoagulant therapy. This is based on the panel's expert opinion given the absence of a survival improvement, a limited short-term benefit, but mounting evidence of the long-term increased risk for VTE.	Type: Informal consensus; Evidence quality: Low to Intermediate; Strength of recommendation: Weak
4.5 For patients with primary CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications.	Type: informal consensus; strength of evidence: moderate; strength of recommendation: strong.	4.6 For patients with primary or metastatic central nervous system malignancies and established VTE, anticoagulation as described for other patients with cancer should be offered, although uncertainties remain about choice of agents and selection of patients most likely to benefit.	Type of recommendation: informal consensus; quality of evidence: low; strength of recommendation: moderate
4.6 Use of novel oral anticoagulants for either prevention or treatment of VTE in cancer patients is not recommended at this time.	Type of: informal consensus; strength of evidence: insufficient; strength of recommendation: strong	N/A	N/A
4.7 Based on consensus, incidental PE and DVT should be treated in the same manner as symptomatic VTE. Treatment of splanchnic or	Type: informal consensus; strength of evidence: insufficient; strength of recommendation: moderate	4.7 Incidental pulmonary embolism and deep vein thrombosis should be treated in the same manner as symptomatic VTE, given their similar clinical outcomes compared to cancer patients with symptomatic events.	(Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate)

visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.			
		4.8 Treatment of isolated subsegmental pulmonary embolism or splanchnic or visceral vein thrombi diagnosed incidentally should be offered on a case-by-case basis, considering potential benefits and risks of anticoagulation.	Type: Informal consensus; Evidence quality: Insufficient; Strength of recommendation: Moderate
Anticoagulation and Survival			
5.1 Anticoagulants are not recommended to improve survival in patients with cancer without VTE.	Type: informal consensus; strength of evidence: weak to moderate; strength of recommendation: moderate	5 Anticoagulant use is not recommended to improve survival in patients with cancer without VTE.	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
5.2 Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.	Type: informal consensus; strength of evidence: weak to moderate; strength of recommendation: moderate		

Risk Assessment			
6.1 Based on consensus, the Panel recommends that cancer patients should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. Individual risk factors, including biomarkers or cancer site, do not reliably identify cancer patients at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool (Table 5).	Type: informal consensus; strength of evidence: moderate; strength of recommendation: strong.	There is substantial variation in risk of VTE between individual cancer patients and cancer settings. Patients with cancer should be assessed for VTE risk initially and periodically thereafter, particularly when starting systemic antineoplastic therapy or at the time of hospitalization. Individual risk factors, including biomarkers or cancer site, do not reliably identify patients with cancer at high risk of VTE. In the ambulatory setting among patients with solid tumors treated with systemic therapy, risk assessment can be conducted based on a validated risk assessment tool (Khorana score, Table 2).	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong
6.2 Based on consensus, the Panel recommends that oncologists educate patients regarding VTE, particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic anti-neoplastic therapy.	Type of recommendation: informal consensus; Strength of evidence: insufficient; Strength of recommendation: strong.	6.2 Oncologists and members of the oncology team should educate patients regarding VTE, particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy.	(Type: Informal consensus; Evidence quality: Insufficient; Strength of recommendation: Strong)

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