Thrombosis Research 181 (2019) 36–45

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

The role of anticoagulation in venous thromboembolism primary prophylaxis in patients with malignancy: A systematic review and meta-analysis of randomized controlled trials

Mahmoud Barbarawi[a,*], Yazan Zayed[a], Babikir Kheiri[a], Inderdeep Gakhal[a], Owais Barbarawi[b], Areeg Bala[a], Ahmad Alabdouh[c], Ahmed Abdalla[d], Fatima Rizk[e], Ghassan Bachuwa[a], Khalil Katato[f]

[a] Department of Internal Medicine, Hurley Medical Center, Michigan State University, Flint, MI, USA
[b] Department of Internal medicine, Mutah University, Al-Karak, Jordan
[c] Department of Internal Medicine, Saint Agnes Hospital, Baltimore, MD 21229, USA
[d] Division of Hematology and Oncology, St. John Hospital, Grosse Pointe Woods, MI, USA
[e] Michigan State University, College of Osteopathic Medicine, East Lansing, MI, USA
[f] Division of Hematology and Oncology, Hurley Medical Center, Michigan State University, Flint, MI, USA

ARTICLE INFO

Keywords:
Anticoagulant
Low-molecular-weight heparin
Direct oral anticoagulant
Cancer
Meta-analysis

ABSTRACT

Background: Venous thromboembolism (VTE) is a common cause of morbidity and mortality among patients with cancer. As such, we conducted a meta-analysis of randomized controlled trials (RCTs) that evaluated anticoagulants as primary prophylaxis against VTE in cancer patients.

Methods: Pubmed/MEDLINE, Embase, and the Cochrane Library were screened for all RCTs that used anticoagulation therapy in cancer patients for primary prevention of VTE. The primary outcomes were VTE events. Secondary outcomes included all-cause mortality, VTE-related mortality and major bleeding. A random effects model was used to report the risk ratios (RR) with 95% confidence intervals (CIs), and odds ratios (ORs) with Bayesian 95% credible intervals for both direct and network meta-analyses, respectively.

Results: Twenty-four RCTs were included totaling 13,338 patients (7197 received anticoagulation and 6141 received placebo). The mean age ranged between 54.6 and 68.1 years, with 50.5% male. Compared with placebo, low-molecular-weight heparin (LMWH) or direct Xa inhibitors were associated with lower VTE events (RR 0.58; 95%CI 0.48–0.69, $P < 0.001$) and (RR 0.39; 95%CI 0.24–0.63, $p < 0.001$), respectively. LMWH was associated with decreased VTE and all-cause mortality when compared with placebo ($P < 0.05$). Regarding safety outcomes, LMWH and direct Xa inhibitors were not associated with increased risks of major bleeding ($P > 0.05$) when compared with placebo. Results regarding VTE events and major bleeding were consistent in both lung and pancreatic cancers.

Conclusions: 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.

1. Introduction

Over the past several decades, the life-expectancy for patients diagnosed with cancer has improved dramatically, largely due to advanced chemotherapy and radiation treatments [1,2]. Patients with an active cancer, especially lung, pancreatic, or hematological malignancies, are deemed to be in a hypercoagulable state and have a high incidence of venous thromboembolism (VTE), particularly, those who are receiving chemotherapy. VTE among these patients carries a high morbidity and mortality, thus means to decrease VTE events can be greatly beneficial [3–6]. Thus, treating patients with malignancy via anticoagulation may be beneficial after weighing the risk of bleeding associated with anticoagulation therapy [7].

While it is recommended that hospitalized patients with cancer should receive VTE prophylaxis, routine use of thromboprophylaxis in ambulatory patients with cancer is still controversial [8]. Various

* Corresponding author at: Department of Internal Medicine, Hurley Medical Center, Michigan State University, One Hurley Plaza, Flint, MI 48503, USA.
E-mail address: MBarbar1@hurleymc.com (M. Barbarawi).

https://doi.org/10.1016/j.thromres.2019.07.007
Received 2 April 2019; Received in revised form 7 July 2019; Accepted 12 July 2019
Available online 16 July 2019

scoring systems have been created and utilized to individually identify patients at high risk for VTE [9,10]. For example, the Khorana score has been used in various randomized controlled trials (RCTs) and has proven helpful as patients who have a score of ≥2 are deemed high risk of VTE during the first 6 months of initiating chemotherapy [10,11]. Many RCTs studying parental thromboprophylaxis, such as low molecular weight heparin (LMWH), for ambulatory patients with cancer have been conducted and have shown a modest absolute rate reduction of VTE—this was, however, associated with increased risk of bleeding [12]. This has precluded the current guideline from recommending its use in clinical practice except in patients with multiple myeloma receiving dexamethasone or anti-angiogenic drugs, as they are at very high risk of VTE [8]. Recently, there has been a growing interest in the use of direct oral anticoagulants (DOACs) as a means of preventing VTE in patients with malignancy, due to their convenience and ease of administration [11,13]. Thus, we performed a meta-analysis aiming to combine all of the available RCTs regarding VTE prophylaxis in ambulatory cancer patients in order to assess the safety and efficacy of anticoagulation in these patients.

2. Methods

2.1. Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed to conduct this meta-analysis [14]. The meta-analysis was registered with the International prospective register of systematic reviews (PROSPERO ID: CRD42019120799). The following databases: Pubmed/MEDLINE, Cochrane Library, and Embase were screened for related trials by two authors (B.K. and Y.Z.) with the input of principle investigator (M.B.) from inception to December 16, 2018. The following keywords MeSH terms: “Cancer”; “malignancy”; “deep vein thrombosis”; “pulmonary embolism”; “venous thromboembolism”; “Prophylaxis”; “prevention”; and “Primary.” There were no language restrictions. The references of the included trials and published meta-analyses and systematic reviews were also assessed for further potential trials to include.

2.2. Eligibility criteria

Only RCTs that evaluated anticoagulant use as primary prevention of VTE in ambulatory cancer patients with the outcomes of interest qualified to be included in this analysis. Studies that included hospitalized cancer patients, patients diagnosed with VTE at the time of randomization, and those that did not account for the outcomes of interest were excluded.

2.3. Data extraction

Two investigators (I.G.) and (A.B.) extracted relevant data independently into a predesigned data collection table. Any discrepancies between investigators were resolved by an independent investigator (O.B.).

2.4. Quality assessment

To conduct quality assessment and to assess the risk of bias in the included RCTs, The Cochrane Collaboration's tool was used for random sequence generation, allocation concealment, blinding of participants and health-care personnel, blinded outcome assessment, completeness of outcome data, evidence of selective reporting, or other biases (eFig. 1 in Supplement 1).

2.5. Outcomes of interest

The primary outcome was the incidence of VTE. Secondary outcomes included incidence of deep vein thrombosis (DVT), pulmonary embolism (PE), all-cause mortality, VTE-related mortality, and major bleeding events. The longest available follow-up was used for each trial in this analysis.

2.6. Statistical analysis

Risk ratios (RRs) and 95% confidence intervals (CIs) on the bases of the Mantel-Haenszel random-effects model were used to present the results. The I^2 statistic was used to assess for heterogeneity. Publication bias of the primary outcome was evaluated by assessing the funnel plot. Sensitivity analysis of the primary outcome was conducted by sequential removal of each of the involved trials. Sensitivity analyses of the primary outcome were conducted for patients with lung cancer and pancreatic cancer. For the network analysis, random effects for the consistency model were reported as odds ratios (ORs) and Bayesian 95% credible intervals (CIs) using the Markov Chain Monte Carlo (MCMC) simulation; this was performed with little informative prior distributions and likelihood functions to derive the posterior distribution of the parameters.

Our analyses were conducted using Review Manager (RevMan) version 5.3, Comprehensive Meta-analysis v3, and TSA v0.9.5.9 software.

3. Results

After reviewing 4718 studies from the databases, 4694 studies were excluded. Twenty-four RCTs were included in the final analysis (eFig. 2 in Supplement 1) [10,11,13,15–35]. Twenty-four RCTs totaled 13,338 patients, of whom, 6141 received placebo, 5485 received LMWH, 806 received direct Xa inhibitors, 396 received aspirin, 372 received warfarin, and 138 received unfractionated heparin. The mean age ranged between 54.6 and 68.1, with 50.5% male. Follow-up durations were variable between the included trials, ranging 2–24 months. Eighteen trials compared LMWH with placebo, of these, nine used dalteparin [10,15,17,19,21,22,24,31,34] three used nadroparin [16,20,33], three used enoxaparin [23,26,27], one trial used certoparin [35], one trial used bemiparin [25], and one trial used semuloparin [18]. One trial compared enoxaparin, warfarin and aspirin [28], one trial compared unfractionated heparin with placebo [32], and one trial compared warfarin with placebo [30]. Three trials were included in the direct Xa inhibitors analysis, two of them compared apixaban with placebo [11,29], and one compared rivaroxaban with placebo [13]. Six trials were done on lung cancer patients [15,16,18,24,25,35], while three were done on patients with pancreatic cancer [17,22,23]. The characteristics of the included trials and their patients' demographic features are displayed in Table 1 and Table 2. The various types of cancers studied in each trial are demonstrated in eTable 1 in Supplement 1.

3.1. Primary outcome

There was a significant reduction of VTE with the use of either LMWH or direct Xa inhibitors when compared with placebo (RR 0.58; 95% CI 0.48–0.69, $P < 0.001$; $I^2 = 0\%$) and (RR 0.39; 95% CI 0.24–0.63, $P < 0.001$; $I^2 = 5\%$), respectively (Fig. 1 and Fig. 2). Publication bias was assessed by analysis of the funnel plot (eFig. 3–4 in Supplement 1). Sensitivity analysis was performed by removing each trial sequentially and did not change the outcome significance. Network meta-analysis showed that unfractionated heparin, warfarin, aspirin, certoparin, and nadroparin did not lower the VTE events compared with placebo. Furthermore, the network analysis did not show any significant difference between the other studied anticoagulants; apixaban, rivaroxaban, dalteparin, enoxaparin, bemiparin and semuloparin (eFig. 5 in Supplement 1).

Table 1
Characteristics of the involved trials.

Study name/last author, year of publication	Number of patients		Study period	Type of anticoagulation used/dose/duration of anticoagulation	Study follow-up (months) for both VTE events and survival	Primary outcome
	Anticoagulant	Placebo				
Lebeau, 1994	138	139	1985–1988	Heparin calcium (500 IU/kg/day)/5 weeks	VTE: 24 Survival: 33	Overall survival and rate of partial or complete response to chemotherapy
Levine, 1994	152	159	1989–1992	Warfarin (1 mg/day)/6 weeks	VTE: 12 Survival: 12	VTE and arterial thrombosis
Altinbas, 2004	42	42	1998–2001	Dalteparin (5000 U/daily)/18 weeks	VTE: Median 10 (range 2–33) Survival: 12	Response to treatment.
FAMOUS/Kakkar, 2004	190	184	1995–2001	Dalteparin (5000 IU/day)/1 year or until the patient died, which ever occurred sooner	VTE: 12 Survival: 12	All-cause mortality
MALT/Klerk, 2005	148	154	1996–2003	Nadroparin (9500 U/mL) according to patient's weight: 0.4 mL for those weighing < 50 kg, 0.6 mL for those weighing between 50 and 70 kg, and 0.8 mL for those weighs in g > 70 kg twice daily during the initial 14 days of treatment and once daily thereafter for another 4 weeks	VTE: 12 Survival: 12	All-cause mortality
Sideras, 2006	44	70	1998–2001	Dalteparin (5000 IU/day)/6 months	VTE: 12 months Survival: 12	Overall survival
PROTECHT/Agnelli, 2009	779	387	2003–2007	Nadroparin (3800 IU/day)/for the duration of chemotherapy or up to a maximum of 120 days (± 10 days)	VTE: 12 Survival: 12	Composite of symptomatic venous or arterial thromboembolic events
PRODIGE/Perry, 2010	90	87	2002–2006	Dalteparin (5000 IU/day)/6 months	VTE: 6 Survival: 12	Symptomatic DVT or pulmonary embolism
Palumbo, 2011	439	Aspirin 220	2006–2009	ASA (100 mg/day), warfarin (1.25 mg/day), enoxaparin (40 mg/day)/During the three cycles of induction therapy in the younger patients and during the first six cycles of induction therapy in the elderly patients.	VTE: 6 Survival: 6	Composite of symptomatic DVT, PE, arterial thrombosis, any acute cardiovascular event (acute myocardial infarction or stroke), or sudden, otherwise unexplained death
Van Doormaal, 2011	244	259	2006–2008	Nadroparin (body weight–adjusted therapeutic doses; < 50 kg, 3800 IU/twice daily; 50–70 kg, 11,400 IU/day; > 70 kg, 15,200 IU/day)/2 weeks. Followed by half-therapeutic doses (< 50 kg, 3800 IU/day; 50–70 kg, 5700 IU/day; > 70 kg, 7600 IU/day) for 4 weeks. After these initial 6 weeks, patients in the nadroparin group were eligible for repeated cycles of nadroparin for a maximum of six cycles	VTE: median 10.5 Survival: median 10.5	All-cause mortality
Ellit, 2012	77	9	2005–2008	Dalteparin (50, 100, 150 IU/kg/day) Started within 7 days before first 21 days cycle and continued till day 21 of cycle 3	VTE: 7 days after the 6th cycle. Survival: 7 days after the 6th cycle.	Response to treatment
Larocca, 2012	166	Aspirin 167	2007–2009	Enoxaparin (40 mg/day), asparin (100 mg/day)/during the 4 cycles of lenalidomide plus low-dose dexamethasone therapy and the 6 cycles of melphalan-prednisone-lenalidomide consolidation	VTE: 6 Survival: 6	Composite of symptomatic DVT, PE, arterial thrombosis, any acute cardiovascular event (acute myocardial infarction or stroke), or sudden, otherwise unexplained, death
Levine, 2012	95	30	2006–2008	Apixaban (5 mg, 10 mg or 20 mg/day)/12 weeks	VTE: 3	Major bleeding or clinically relevant non-major bleeding
Maraveyas, 2012	59	62	2003–2009	Dalteparin (weight-adjusted schedule as described by the CLOT investigators; 200 IU/kg/day/4 weeks. Followed by a stepdown to 150 IU/kg/8 weeks)	VTE: median of 19.3. Survival: median of 19.3.	VTE event.
SAVE-ONCO/Agnelli, 2012	1589	1583	–	Semuloparin (20 mg/day)/a minimum of 3 months	VTE: 3 Survival: 12	Composite of any symptomatic DVT, any nonfatal PE, and death related to VTE
TOPIC-1/Haas, 2012	174	179	1999–2004	Certoparin (3000 IU/day)/6 months.	VTE: 6 Survival: 6	VTE including symptomatic or asymptomatic

(*continued on next page*)

Table 1 (*continued*)

Study name/last author, year of publication	Number of patients		Study period	Type of anticoagulation used/dose/duration of anticoagulation	Study follow-up (months) for both VTE events and survival	Primary outcome
	Anticoagulant	Placebo				
TOPIC-2/Haas, 2012	273	274	1999–2004	Certoparin (3000 IU/day)/6 months.	VTE: 6 Survival: 6	VTE including symptomatic or asymptomatic
Vadhan-Raj, 2013	38	37	NA	Dalteparin (5000 IU/day)/16 weeks	VTE: 3 Survival: 3	VTE event
ABEL/Lecumberri, 2013	20	18	2005–2010	Bemiparin (3500 IU/day)/26 weeks	VTE: 24 Survival: 24	Progression free survival
MICROTEC/Zwicker, 2013	23	43	NA	Enoxaparin (40 mg/day)/2 months	VTE: 2 months Survival: NA	VTE events
CONKO-004/Pelzer, 2015	160	152	2004–2009	Enoxaparin (40 mg/day)/3 months	VTE: 3 Survival: NA	Symptomatic VTE events
FRAGMATIC/Macbeth, 2016	1101	1101	2007–2011	Dalteparin (5000 IU/day)/24 weeks	VTE: 12 Survival: 23.1	Overall survival
PHACS/Khorana, 2017	50	48	2009–2013	Dalteparin (5000 IU/day)/12 weeks	VTE: 3 Survival: NA	VTE events
AVERT/Carrier, 2018	291	283	2014–2018	Apixaban (2.5 mg twice daily)/6 months	VTE: 6 Survival: 7 or death	VTE events
CASSINI/Khorana, 2019	420	421	NA	Rivaroxaban (10 mg/day)/up to 6 months	VTE: 6 Survival: 6	The composite of proximal deep-vein thrombosis in the lower limb, or upper limb, pulmonary embolism, and death from venous thromboembolism.

Abbreviations: ABEL: Adjuvant bemiparin in small cell lung cancer; AVERT: Apixaban for the prevention of venous thromboembolism in high-Risk ambulatory cancer patients; CASSINI: Rivaroxaban thromboprophylaxis in high-risk ambulatory cancer patients receiving systemic therapy; CONKO: Charité – Onkologie; FAMOUS: Fragmin advanced malignancy outcome study; DVT: Deep venous thrombosis; FRAGMATIC: The effect of fragmin added to standard therapy in patients with lung cancer; MALT: Low molecular weight heparin on survival in patients with advanced malignancy; MICROTEC: Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor bearing microparticles; PE: Pulmonary embolism; PHACS: Prophylaxis of high-risk ambulatory cancer patients study; PRODIGE: Randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma; SAVE-ONCO: Evaluation of AVE5026 in the prevention of venous thromboembolism in cancer patients undergoing chemotherapy; TOPIC-1: low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer; TOPIC-2: low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in inoperable, late-stage non–small-cell lung cancer; VTE: Venous thromboembolism.

Table 2
Demographic features of patients in the included trials.

Study name/last author, year of publication	No. of patients	Age, year mean (SD) or median (IQR)	No. of male	Weight or BMI. Value in mean (SD) or median (IQR)	Khorana score	No. of patients with the ECOG performance-status score.		No. previous VTE	Time since cancer diagnosis till randomization, value in mean (SD) or median (IQR)
						0–1	≥2		
Lebeau, 1994	Heparin 138	< 50 year: 21[a] 50–59 year: 49 60–69 year: 49 70–81 year: 19	120	–	–	–	–	–	–
	Placebo 139	< 50 year: 20[a] 50–59 year: 55 60–69 year: 39 70–81 year: 25	132	–	–	–	–	–	–
Levine, 1994	Warfarin 152	–	–	–	–	123	136	0	–
	Placebo 159	–	–	–	–	29	22	2	–
Altinbas, 2004	Dalteparin 42	57.5 (34–74)	33	–	–	29	13	–	–
	Placebo 42	58 (37–75)	35	–	–	29	13	–	–
FAMOUS/Kakkar, 2004	Dalteparin 190	62.0 (53.8–68.4)	77	–	–	–	–	–	–
	Placebo 184	60.9 (52.4–69.4)	84	–	–	–	–	–	–
MALT/Klerk, 2005	Nadroparin 148	63 (36–86)	77	Weight 71 (40–135)	–	–	–	–	17 (7–41) months
	Placebo 154	64 (28–83)	81	Weight 69 (43–96)	–	–	–	–	16 (5–39) months
Sideras, 2006	Dalteparin 24	33–50: 4[a] 51–86: 20	12	–	–	22	2	1	–
	Placebo 26	33–50: 4[a] 51–86: 22	11	–	–	23	3	1	–
PROTECHT/Agnelli, 2009	Nadroparin 769	62·1 (10·3)	372	BMI 25·4 (4·4)	–	–	–	12	–
	Placebo 381	63·7 (9·2)	183	BMI 25·2 (4·2)	–	–	–	6	–
PRODIGE/Perry, 2010	Dalteparin 99	57 (30–81)[b]	61	–	–	–	–	–	–
	Placebo 87	55 (26–77) [b]	50	–	–	–	–	–	–
Palumbo, 2011	Aspirin 220	61 (IQR 55–66)	117	–	–	–	–	2	–
	Warfarin 220	60 (IQR 54–66)	115	–	–	–	–	2	–
	Enoxaparin 219	62 (IQR 55–66)	130	–	–	–	–	1	–
Van Doormaal, 2011	Nadroparin 244	65 (10)	197	Weight 74.3 (15.5)	–	–	–	–	Prostate cancer: 4.3 (3.7) year NSCLC: 0.1 (0.1) year Pancreatic cancer: 0.1 (0.2) year
	Placebo 259	65 (9.8)	206	Weight 73.2 (14.2)	–	–	–	–	Prostate cancer: 4.6 (3.8) year NSCLC: 0.1 (0.4) year Pancreatic cancer: 0.2 (0.3) year
Ellit, 2012	Dalteparin (50 IU) 26	58 (34, 73)	0	Weight > 40 kg	–	22	4	1	–
	Dalteparin (100 IU) 25	60 (38, 72)	0		–	22	3	0	–
	Dalteparin (150 IU) 26	64 (44, 74)	0		–	23	2	3	–
	Placebo 9	62 (42, 70)	0	Weight > 40 kg	–	6	3	0	–
Larocca, 2012	Enoxaparin 166	58 IQR (52–62)	99	–	–	–	–	0	–
	Aspirin 176	57 IQR (51–61)	87	–	–	–	–	0	–
Levine, 2012	Apixaban (5 mg) 32	57 (41–67)	15	–	–	30	2	–	< 1 year: 20[a] 1–2 year: 3 > 2 year: 9
	Apixaban (10 mg) 30	60 (39–76)	13	–	–	23	5	–	< 1 year: 17[a] 1–2 year: 1 > 2 year: 12
	Apixaban (20 mg) 33	64 (25–86)	20	–	–	30	3	–	< 1 year: 22[a] 1–2 year: 3 > 2 year: 8
	Placebo 30	59 (20–82)	15	–	–	27	2	–	< 1 year: 17[a] 1–2 year: 5 > 2 year: 8
Maraveyas, 2012	Dalteparin 60	62 (40–79)	36	–	–	–	–	–	–
	Placebo 63	66 (43–82)	36	–	–	–	–	–	–
SAVE-ONCO/Agnelli, 2012	Semuloparin 1608	59.8 (10.6)	974	BMI 24.9 (5.1)	–	1465	141	32	–
	Placebo 1604	59.4 (10.6)	956	BMI 24.7 (4.9)	–	1478	124	37	–
TOPIC-1/Haas, 2012	Certoparin 174	54.6 (10.3)	0	BMI 27.0 (4.9)	–	–	–	–	3.2 (0–21.7) years[b]
	Placebo 178	56.6 (11.0)	0	BMI 27.5 (5.7)	–	–	–	–	3.1 (0–18.7) years[b]
TOPIC-2/Haas, 2012	Certoparin 273	60.8 (9.5)	227	BMI 24.7 (4.1)	–	–	–	–	0.3 years[b]
	Placebo 273	60.3 (10.0)	227	BMI 24.6 (4.2)	–	–	–	–	0.4 years[b]
Vadhan-Raj, 2013	Dalteparin 38	52	41	–	–	–	–	–	–

(*continued on next page*)

Table 2 (*continued*)

Study name/last author, year of publication	No. of patients	Age, year mean (SD) or median (IQR)	No. of male	Weight or BMI. Value in mean (SD) or median (IQR)	Khorana score	No. of patients with the ECOG performance-status score.		No. previous VTE	Time since cancer diagnosis till randomization, value in mean (SD) or median (IQR)
						0–1	≥2		
	Placebo 37			–	–	–	–	–	–
ABEL/Lecumberri, 2013	Bemiparin 20	61.1 (7.5)	17	Weight 74.1 (12.1)	–	20	0	0	–
	Placebo18	64.5 (10.0)	16	Weight 77.1 (20.1)	–	17	1	0	–
Zwicker, 2013	Enoxaparin (High TFMP) 23	68.1 (46.6–80.1)	14	BMI 23.8 (16.6–31.6)	–	22	1	–	–
	Observation (High TFMP) 11	67.5 (28.8–78.7)	5	BMI 23.8 (20.0–34.4)	–	8	3	–	–
	Observation (Low TFMP) 32	62.8 (42.7–83.8)	19	BMI 26.3 (19.0–48.7)		31	1	–	–
CONKO-004/Pelzer, 2015	Enoxaparin 160	62 (32–81)	91	BMI 24.3 (15.2–43.0)					
	Placebo 152	63 (27–83)	94	BMI 23.8 (16–39.2)					
FRAGMATIC/ Macbeth, 2016	Dalteparin 1101	65 (59–71)	661	BMI 25.6 (22.9–29.0)	–	937	164	–	21 (15–29) days
	Placebo 1101	64 (58–71)	656	BMI 25.8 (22.7–29.1)	–	926	163	–	21 (15–29) days
PHACS/Khorana, 2017	Dalteparin 50	60 (10)	29	–	Median 3	39	6	4	–
	Observation 48	58 (12)	24	–	Median 3	40	6	2	–
AVERT/Carrier, 2018	Apixaban 291	61.2 (12.4)	121	Weight 80.0 (22.3)	2: 186 3: 78 4: 26 5: 1 6: 0	186	32	9	–
	Placebo 283	61.7 (11.3)	119	Weight 82.6 (21.4)	2: 190 3: 68 4: 24 5: 1 6: 0	188	29	8	–
CASSINI/Khorana, 2019	Rivaroxaban 420	63 (23–87)	222	–	< 2: 5 2: 281 3: 106 4: 26 ≥5: 2	152	25	13	–
	Placebo 421	62 (28–88)	206	–	< 2: 3 2: 295 3: 96 4: 25 ≥5: 2	177	26	2	–

Abbreviations: ABEL: Adjuvant bemiparin in small cell lung cancer; AVERT: Apixaban for the prevention of venous thromboembolism in high-Risk ambulatory cancer patients; BMI: Body mass index; CASSINI: Rivaroxaban thromboprophylaxis in high-risk ambulatory cancer patients receiving systemic therapy; CONKO: Charité – Onkologie; FAMOUS: Fragmin advanced malignancy outcome study; ECOG: Eastern cooperative oncology group; FRAGMATIC: The effect of fragmin added to standard therapy in patients with lung cancer; IQR: Interquartile range; MALT: Low molecular weight heparin on survival in patients with advanced malignancy; MICROTEC: Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor bearing microparticles; PHACS: Prophylaxis of high-risk ambulatory cancer patients study; PRODIGE: Randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma; SAVE-ONCO: Evaluation of AVE5026 in the prevention of venous thromboembolism in cancer patients undergoing chemotherapy; SD: Standard deviation; TOPIC-1: low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer; TOPIC-2: low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in inoperable, late-stage non–small-cell lung cancer; VTE: Venous thromboembolism.

[a] Number of patients.

[b] Mean (minimum – maximum).

3.2. Secondary outcomes

Compared with placebo, LMWH significantly lowered the incidence of PE and DVT events (RR 0.57; 95% CI 0.43–0.75, P < 0.001; I^2 = 0%) and (RR 0.28; 95% CI 0.11–0.71, P = 0.008; I^2 = 0%), respectively (Fig. 1). Direct Xa inhibitors trended a lower incidence of PE and DVT compared with placebo (RR 0.46; 95% CI 0.21–1.02, P = 0.06; I^2 = 30%) and (RR 0.53; 95% CI 0.26–1.07, P = 0.07; I^2 = 33%), respectively, however, this trend did not reach statistical significance (Fig. 2).

With regard to mortality, LMWH demonstrated a significant reduction in all-cause mortality compared with placebo (RR 0.95; 95% CI 0.91–0.99, P = 0.02; I^2 = 7%), however not VTE-related mortality (RR 0.62; 95% CI 0.28–1.34, P = 0.22; I^2 = 0%) (Fig. 1). In contrast, direct Xa inhibitors showed no significant difference in all-cause mortality (RR 0.93; 95% CI 0.58–1.48, P = 0.76; I^2 = 53%).

Regarding safety outcomes, LMWH and direct Xa inhibitors did not significantly increase the risk of major bleeding when compared to placebo (RR 1.26; 95% CI 0.92–1.74, P = 0.16; I^2 = 0%) and (RR 1.76; 95% CI 0.83–3.73, P = 0.14; I^2 = 0%), respectively (Fig. 1 and Fig. 2) The network meta-analysis showed that there is no difference between the competing treatments (eFig 6 in Supplement 1).

3.3. Sensitivity analysis

Our sensitivity analysis according to the type of cancer was performed on both lung and pancreatic cancer. LMWH compared with placebo showed a significant reduction in VTE events in both lung and pancreatic cancer (RR 0.53; 95% CI 0.41–0.68, P < 0.001; I^2 = 0%) and (RR 0.39; 95% CI 0.24–0.64, P < 0.001; I^2 = 0%), respectively. Furthermore, major bleeding did not increase significantly in patients who received LMWH compared with those receiving placebo in both lung and pancreatic cancer (RR 1.21; 95% CI 0.68–2.18, P = 51; I^2 = 0%) and (RR 1.21; 95% CI 0.58–2.51, P = 0.62; I^2 = 0%),

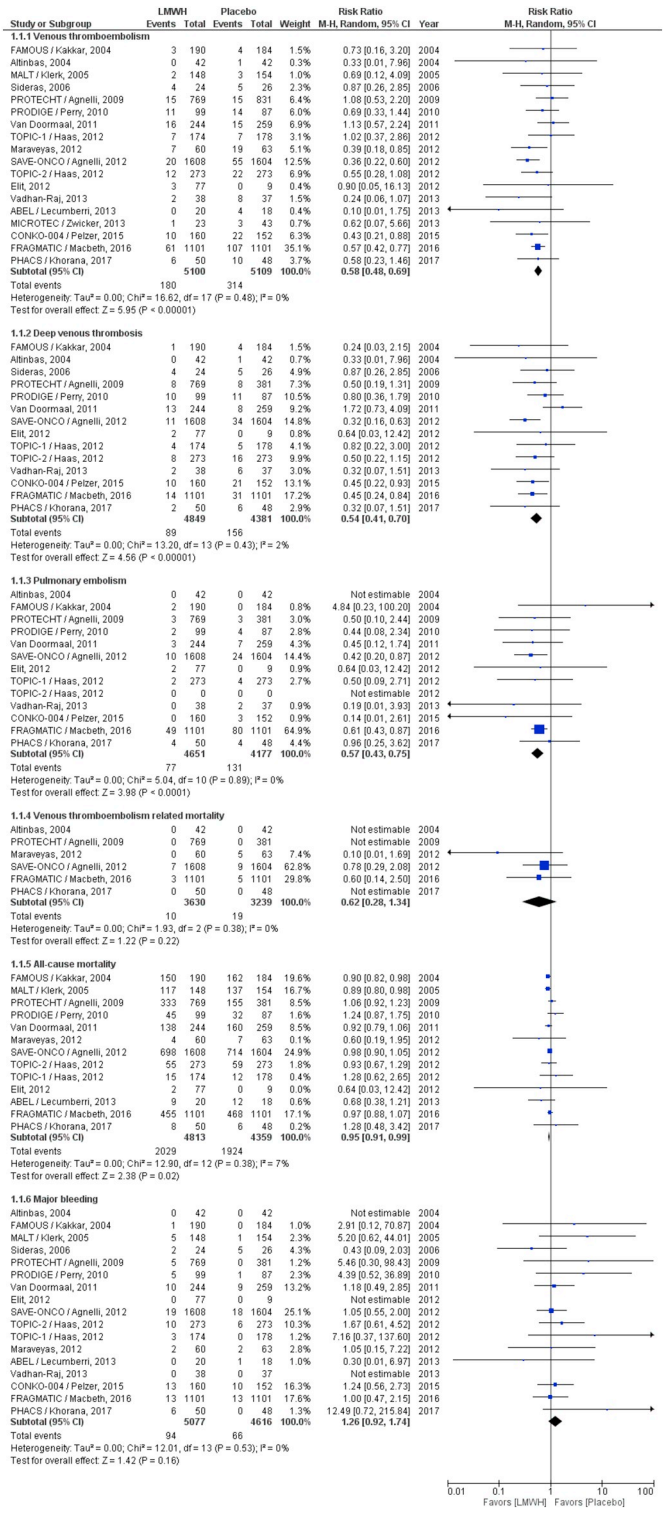

Fig. 1. Forest plot demonstrating the results of the primary and secondary outcomes of low molecular weight heparin.

respectively (eFig 7 and eFig 8 in Supplement 1).

4. Discussion

This comprehensive meta-analysis included 24 RCTs [10,11,13,15–35], and has established the following findings: First, use of either direct Xa inhibitors or parenteral LMWH as primary VTE prophylaxis for ambulatory cancer patients was associated with lower VTE and PE events when compared to placebo. This protective effect was consistent between different classes of direct Xa inhibitors and LMWH, with exceptions being certoparin and nadroparin. Second, LMWH, was associated with lower DVT events and decreased all-cause mortality compared with placebo. Finally, both LMWH and direct Xa inhibitors were associated with comparable bleeding rates compared with placebo, and this was consistent between different classes of LMWH and direct Xa inhibitors.

Our results showed that LMWH significantly reduced the number of VTE events, including DVT and PE, and this was consistent with the previously published meta-analyses and systematic reviews [12,36]. These results were consistent with the involved trials. This beneficial effect of the LMWH has been recognized by the American Society of Clinical Oncology (ASCO), however, they did not recommend LMWH as primary VTE prophylaxis [8], as the incidence of VTE were quite low in the placebo group of two large RCTs, 3.9% in PROTCHET (Prophylaxis of Thromboembolism during Chemotherapy) and 3.4% in SAVE-ONCO (Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy) [16,18]. In our pooled analysis, the incidence of VTE in the entire placebo group was quit high (6.1%), and it was higher in patients with lung cancer and advanced pancreatic cancer (APC) who did not receive any anticoagulation (7.3% and 19.4% respectively). This highlights the importance of primary VTE prophylaxis, especially in patients with pancreatic cancer.

Among the studied subgroups, patients with APC have shown to benefit more from anticoagulation (RR 0.39, number needed to treat (NNT) = 8) than patients with lung cancer (RR 0.53, NNT = 28). This data from RCTs is an important illustration that should be taken into consideration regarding the guidelines that recommend only VTE prophylaxis in multiple myeloma patients receiving dexamethasone or anti-angiogenic medications based on observational studies [8]..

The network meta-analysis shows that certoparin and nadroparin are the only LMWH agents that did not lower the VTE events. Perhaps, the extended time frame between cancer diagnosis and starting the anticoagulant was long (3.2 years) in TOPIC-1 (low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer). This may lead to overlooking the vital time associated with the greatest risk of increased thrombosis, which is the first few months after cancer diagnosis [35,37]. Furthermore, using low dose of certoparin in both TOPIC-1 and TOPIC-2 (low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in inoperable, late-stage non–small-cell lung cancer) may have affected the efficacy of certoparin in reducing the VTE events [35]. Nadroparin has been used in three trials, two of which were designed to study the survival benefit of nadroparin in patients with cancer, and anticoagulation was given for only 6 weeks [20,33]. This short duration may be insufficient to show the protective effect of nadroparin, and raises the possibility of a latent-time effect of nadroparin, as shown in the PROTCHET trial which used nadroparin for 4 months without showing a significant reduction in VTE events [16]..

The novel finding of our analysis is that direct Xa inhibitors were associated with lower VTE events compared with placebo. Furthermore, we found that direct Xa inhibitors led to less VTE events compared to LMWH. Although our analysis of the direct Xa inhibitors usage was heterogeneous regarding the medications used, both fondaparinux [13] and apixaban [11,29] were found to have a similar RR of about 0.4 for lowering the VTE events.

Our analysis indicated a significantly lower mortality rate in patients who received LMWH compared with placebo. The network analysis showed a consistent result regardless of the LMWH types. Although none of the included trials was powered enough to measure outcomes like all-cause mortality, the largest two trials FRAGMATIC (The effect of fragmin added to standard therapy in patients with lung cancer) and SAVE-ONCO showed a trend of lower mortality in the LMWH arm [18,24]. Furthermore, our results dispute previous findings

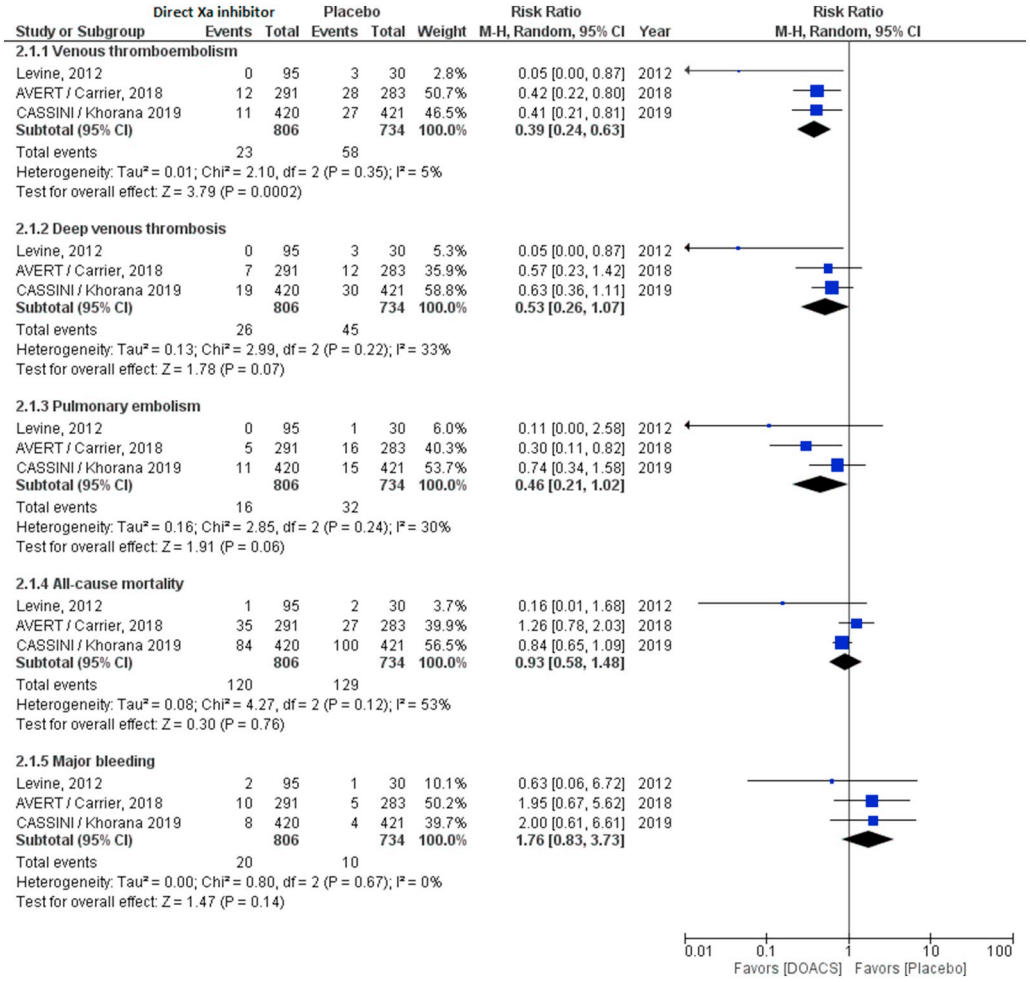

Fig. 2. Forest plot demonstrating the results of the primary and secondary outcomes of direct Xa inhibitors.

that showed only a marginal improvement in survival (RR 0.99; 95% CI 0.96 to 1.01) [38]. The reason behind this survival benefit is unclear and could be related to a proposed synergistic effect of the LMWH with the chemotherapy [39] or antimetastatic effect [24], but could not be attributed to lower VTE events according to our analysis. In contrast, direct Xa inhibitors did not show significant survival benefit, though they did trend towards a lower mortality association. This lack of benefit may be related to the small number of patients included in our analysis; thus further powered trials are needed.

The safety of anticoagulation must always be carefully considered in cancer patients as they have a high risk of bleeding due to neovascularization [40] and thrombocytopenia, especially those receiving chemotherapy [18,41,42]. The overall incidence of major bleeding was similar between the anticoagulation group (LMWH and direct Xa inhibitors), and the placebo group. These findings are consistent with the previously published Cochrane review [38], which highlighted the safety of the direct Xa inhibitors in cancer and suggesting direct Xa inhibitors as a priority therapy used in cancer patients based on the ease and convenience of use [38]. Our network analysis did not study differences between the various classes of LMWH and direct Xa inhibitors.

4.1. Limitations

This analysis has several limitations. First, although our analysis showed lower mortality in LMWH and did not show the same results with direct Xa inhibitors, none of the involved trials were large enough to measure mortality as an outcome. Furthermore, all of the patients were ambulatory, and they died outside of the hospitals from proposed disease progression, thus it is very difficult to predict the impact of VTE-related mortality in this population [16]. There were much lower numbers of patients in the warfarin, aspirin, and UFH groups, thus, it is hard to draw a conclusion about these medications. Furthermore, the warfarin doses that were used in the involved trials were very low to have predictable effect from it [43]. Second, the involved trials used different classes of LMWH and direct Xa inhibitors, however, our network meta-analysis did not analyze difference between these classes. Finally, the involved trials were heterogeneous in the included population regarding cancer type, and most of the included trials did not do sub-group analyses according to the cancer type. To overcome this limitation, we performed sensitivity analyses for patients with lung and pancreatic cancers. Moreover, the involved trials excluded a significant group of patients who have coagulopathy or thrombocytopenia, as they are at high risk of bleeding, however, a dose-adjusted therapy according to the platelet level can be used to treat patients with platelet of $\geq 30 \times 10^9$ [44].

5. Conclusions

Anticoagulation therapy with both LMWH and direct Xa inhibitors of various classes are associated with lower VTE events when compared with placebo. Furthermore, this protective effect is associated with comparable safety profiles of both LMWH and direct Xa inhibitors, as both therapies showed no increased risk of major bleeding when compared with placebo.

Declaration of Competing Interest

The author(s) declared that they have no potential conflicts of interest regarding research, authorship, and/or publication of this article.

Acknowledgements

All data generated or analyzed during this study are included in this article.

Author contributions

Drs MB, YZ, BK, and OB contributed to conception, design, data analysis, and writing the manuscript. Drs IG, AB, AA, AA and FR contributed in literature search, data collection and editing the manuscript. Drs GB and KK contributed to the editing and revision of the manuscript.

Compliance with ethical standards

Ethical approval

This study does not contain any animal or human participants.

Informed consent

Not applicable.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.07.007.

References

[1] M.A. Lichtman, Battling the hematological malignancies: the 200 years' war, Oncologist. 13 (2008) 126–138, https://doi.org/10.1634/theoncologist.2007-0228.

[2] V.T.J. DeVita, E. Chu, A history of cancer chemotherapy, Cancer Res. 68 (2008) 8643–8653, https://doi.org/10.1158/0008-5472.CAN-07-6611.

[3] M.B. Streiff, Association between cancer types, cancer treatments, and venous thromboembolism in medical oncology patients, Clin. Adv. Hematol. Oncol. 11 (2013) 349–357.

[4] A.A. Khorana, C.W. Francis, E. Culakova, N.M. Kuderer, G.H. Lyman, Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy, J. Thromb. Haemost. 5 (2007) 632–634, https://doi.org/10.1111/j.1538-7836.2007.02374.x.

[5] H.T. Sorensen, L. Mellemkjaer, J.H. Olsen, J.A. Baron, Prognosis of cancers associated with venous thromboembolism, N. Engl. J. Med. 343 (2000) 1846–1850, https://doi.org/10.1056/NEJM200012213432504.

[6] H.-M.M.B. Otten, J. Mathijssen, H. ten Cate, M. Soesan, M. Inghels, D.J. Richel, M.H. Prins, Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon, Arch. Intern. Med. 164 (2004) 190–194, https://doi.org/10.1001/archinte.164.2.190.

[7] J.W. Blom, J.P.M. Vanderschoot, M.J. Oostindier, S. Osanto, F.J.M. van der Meer, F.R. Rosendaal, Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study, J. Thromb. Haemost. 4 (2006) 529–535, https://doi.org/10.1111/j.1538-7836.2006.01804.x.

[8] G.H. Lyman, K. Bohlke, A.A. Khorana, N.M. Kuderer, A.Y. Lee, J.I. Arcelus, E.P. Balaban, J.M. Clarke, C.R. Flowers, C.W. Francis, L.E. Gates, A.K. Kakkar, N.S. Key, M.N. Levine, H.A. Liebman, M.A. Tempero, S.L. Wong, M.R. Somerfield, A. Falanga, Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014, J. Clin. Oncol. 33 (2015) 654–656, https://doi.org/10.1200/JCO.2014.59.7351.

[9] N. van Es, M. Di Nisio, G. Cesarman, A. Kleinjan, H.-M. Otten, I. Mahe, I.T. Wilts, D.C. Twint, E. Porreca, O. Arrieta, A. Stepanian, K. Smit, M. De Tursi, S.M. Bleker, P.M. Bossuyt, R. Nieuwland, P.W. Kamphuisen, H.R. Buller, Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study, Haematologica. 102 (2017) 1494–1501, https://doi.org/10.3324/haematol.2017.169060.

[10] A.A. Khorana, C.W. Francis, N.M. Kuderer, M. Carrier, T.L. Ortel, T. Wun, D. Rubens, S. Hobbs, R. Iyer, D. Peterson, A. Baran, K. Kaproth-Joslin, G.H. Lyman, Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial, Thromb. Res. 151 (2017) 89–95, https://doi.org/10.1016/j.thromres.2017.01.009.

[11] M. Carrier, K. Abou-Nassar, R. Mallick, V. Tagalakis, S. Shivakumar, A. Schattner, P. Kuruvilla, D. Hill, S. Spadafora, K. Marquis, M. Trinkaus, A. Tomiak, A.Y.Y. Lee, P.L. Gross, A. Lazo-Langner, R. El-Maraghi, G. Goss, G. Le Gal, D. Stewart, T. Ramsay, M. Rodger, D. Witham, P.S. Wells, Apixaban to prevent venous thromboembolism in patients with cancer, N. Engl. J. Med. 380 (2018) 711–719, https://doi.org/10.1056/NEJMoa1814468.

[12] M. Di Nisio, E. Porreca, M. Candeloro, M. De Tursi, I. Russi, A.W. Rutjes, Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy, Cochrane Database Syst. Rev. 12 (2016) CD008500, , https://doi.org/10.1002/14651858.CD008500.pub4.

[13] A.A. Khorana, G.A. Soff, A.K. Kakkar, S. Vadhan-Raj, H. Riess, T. Wun, M.B. Streiff, D.A. Garcia, H.A. Liebman, C.P. Belani, E.M. O'Reilly, J.N. Patel, H.A. Yimer, P. Wildgoose, P. Burton, U. Vijapurkar, S. Kaul, J. Eikelboom, R. McBane, K.A. Bauer, N.M. Kuderer, G.H. Lyman, Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer, N. Engl. J. Med. 380 (2019) 720–728, https://doi.org/10.1056/NEJMoa1814630.

[14] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P.A. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, J. Clin. Epidemiol. 62 (2009) e1–34, https://doi.org/10.1016/j.jclinepi.2009.06.006.

[15] M. Altinbas, H.S. Coskun, O. Er, M. Ozkan, B. Eser, A. Unal, M. Cetin, S. Soyuer, A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer, J. Thromb. Haemost. 2 (2004) 1266–1271, https://doi.org/10.1111/j.1538-7836.2004.00871.x.

[16] G. Agnelli, G. Gussoni, C. Bianchini, M. Verso, M. Mandala, L. Cavanna, S. Barni, R. Labianca, F. Buzzi, G. Scambia, R. Passalacqua, S. Ricci, G. Gasparini, V. Lorusso, E. Bonizzoni, M. Tonato, Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study, Lancet. Oncol. 10 (2009) 943–949, https://doi.org/10.1016/S1470-2045(09)70232-3.

[17] X. Zhou, G.R. Varadhachary, J. Milind, D. Fogelman, R. Shroff, C.E. Bueso-Ramos, M. Nguyen, X. Wang, R.A. Wolff, J.L. Abbruzzese, M.J. Overman, Randomized controlled trial of dalteparin for primary thromboprophylaxis for venous thromboembolism (VTE) in patients with advanced pancreatic cancer (APC): risk factors predictive of VTE, Blood. 122 (2013) 580 http://www.bloodjournal.org/content/122/21/580.

[18] G. Agnelli, D.J. George, A.K. Kakkar, W. Fisher, M.R. Lassen, P. Mismetti, P. Mouret, U. Chaudhari, F. Lawson, A.G.G. Turpie, Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer, N. Engl. J. Med. 366 (2012) 601–609, https://doi.org/10.1056/NEJMoa1108898.

[19] K. Sideras, P.L. Schaefer, S.H. Okuno, J.A. Sloan, L. Kutteh, T.R. Fitch, S.R. Dakhil, R. Levitt, S.R. Alberts, R.F. Morton, K.M. Rowland, P.J. Novotny, C.L. Loprinzi, Low-molecular-weight heparin in patients with advanced cancer: a phase 3 clinical trial, Mayo Clin. Proc. 81 (2006) 758–767, https://doi.org/10.4065/81.6.758.

[20] F.F. van Doormaal, M. Di Nisio, H.-M. Otten, D.J. Richel, M. Prins, H.R. Buller, Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer, J. Clin. Oncol. 29 (2011) 2071–2076, https://doi.org/10.1200/JCO.2010.31.9293.

[21] J.R. Perry, J.A. Julian, N.J. Laperriere, W. Geerts, G. Agnelli, L.R. Rogers, M.G. Malkin, R. Sawaya, R. Baker, A. Falanga, S. Parpia, T. Finch, M.N. Levine, PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma, J. Thromb. Haemost. 8 (2010) 1959–1965, https://doi.org/10.1111/j.1538-7836.2010.03973.x.

[22] A. Maraveyas, J. Waters, R. Roy, D. Fyfe, D. Propper, F. Lofts, J. Sgouros, E. Gardiner, K. Wedgwood, C. Ettelaie, G. Bozas, Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer, Eur. J. Cancer. 48 (2012) 1283–1292, https://doi.org/10.1016/j.ejca.2011.10.017.

[23] U. Pelzer, B. Opitz, G. Deutschinoff, M. Stauch, P.C. Reitzig, S. Hahnfeld, L. Muller, M. Grunewald, J.M. Stieler, M. Sinn, T. Denecke, S. Bischoff, H. Oettle, B. Dorken, H. Riess, Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial, J. Clin. Oncol. 33 (2015) 2028–2034, https://doi.org/10.1200/JCO.2014.55.1481.

[24] F. Macbeth, S. Noble, J. Evans, S. Ahmed, D. Cohen, K. Hood, D. Knoyle, S. Linnane, M. Longo, B. Moore, P.J. Woll, W. Appel, J. Dickson, D. Ferry, C. Brammer, G. Griffiths, Randomized phase III trial of standard therapy plus low molecular weight heparin in patients with lung cancer: FRAGMATIC trial, J. Clin. Oncol. 34 (2016) 488–494, https://doi.org/10.1200/JCO.2015.64.0268.

[25] R. Lecumberri, G. Lopez Vivanco, A. Font, E. Gonzalez Billalabeitia, A. Gurpide, J. Gomez Codina, D. Isla, A. Galan, I. Bover, M. Domine, V. Vicente, R. Rosell, E. Rocha, Adjuvant therapy with bemiparin in patients with limited-stage small cell lung cancer: results from the ABEL study, Thromb. Res. 132 (2013) 666–670, https://doi.org/10.1016/j.thromres.2013.09.026.

[26] A. Larocca, F. Cavallo, S. Bringhen, F. Di Raimondo, A. Falanga, A. Evangelista, M. Cavalli, A. Stanevsky, P. Corradini, S. Pezzatti, F. Patriarca, M. Cavo, J. Peccatori, L. Catalano, A.M. Carella, A.M. Cafro, A. Siniscalchi, C. Crippa, M.T. Petrucci, D. Ben Yehuda, E. Beggiato, T.C. Di Toritto, M. Boccadoro, A. Nagler, A. Palumbo, Aspirin

or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide., Blood. 119 (2012) 933–9; quiz 1093. doi:10.1182/blood-2011-03-344333.
[27] J.I. Zwicker, H.A. Liebman, K.A. Bauer, T. Caughey, F. Campigotto, R. Rosovsky, S. Mantha, C.M. Kessler, J. Eneman, V. Raghavan, H.-J. Lenz, A. Bullock, E. Buchbinder, D. Neuberg, B. Furie, Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study), Br. J. Haematol. 160 (2013) 530–537, https://doi.org/10.1111/bjh.12163.
[28] A. Palumbo, M. Cavo, S. Bringhen, E. Zamagni, A. Romano, F. Patriarca, D. Rossi, F. Gentilini, C. Crippa, M. Galli, C. Nozzoli, R. Ria, R. Marasca, V. Montefusco, L. Baldini, F. Elice, V. Callea, S. Pulini, A.M. Carella, R. Zambello, G. Benevolo, V. Magarotto, P. Tacchetti, N. Pescosta, C. Cellini, C. Polloni, A. Evangelista, T. Caravita, F. Morabito, M. Offidani, P. Tosi, M. Boccadoro, Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial, J. Clin. Oncol. 29 (2011) 986–993, https://doi.org/10.1200/JCO.2010.31.6844.
[29] M.N. Levine, C. Gu, H.A. Liebman, C.P. Escalante, S. Solymoss, D. Deitchman, L. Ramirez, J. Julian, A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer, J. Thromb. Haemost. 10 (2012) 807–814, https://doi.org/10.1111/j.1538-7836.2012.04693.x.
[30] M. Levine, J. Hirsh, M. Gent, A. Arnold, D. Warr, A. Falanga, M. Samosh, V. Bramwell, K.I. Pritchard, D. Stewart, Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer, Lancet (London, England). 343 (1994) 886–889.
[31] A.K. Kakkar, M.N. Levine, Z. Kadziola, N.R. Lemoine, V. Low, H.K. Patel, G. Rustin, M. Thomas, M. Quigley, R.C.N. Williamson, Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS), J. Clin. Oncol. 22 (2004) 1944–1948, https://doi.org/10.1200/JCO.2004.10.002.
[32] B. Lebeau, C. Chastang, J.M. Brechot, F. Capron, B. Dautzenberg, C. Delaisements, M. Mornet, J. Brun, J.P. Hurdebourcq, E. Lemarie, Subcutaneous heparin treatment increases survival in small cell lung cancer. “Petites Cellules” Group, Cancer. 74 (1994) 38–45.
[33] C.P.W. Klerk, S.M. Smorenburg, H.-M. Otten, A.W.A. Lensing, M.H. Prins, F. Piovella, P. Prandoni, M.M.E.M. Bos, D.J. Richel, G. van Tienhoven, H.R. Buller, The effect of low molecular weight heparin on survival in patients with advanced malignancy, J. Clin. Oncol. 23 (2005) 2130–2135, https://doi.org/10.1200/JCO.2005.03.134.
[34] L.M. Elit, A.Y. Lee, S. Parpia, L.L. Swystun, P.C. Liaw, P. Hoskins, D.H. Julian, J.A. Julian, M.N. Levine, Dalteparin low molecular weight heparin (LMWH) in ovarian cancer: a phase II randomized study, Thromb. Res. 130 (2012) 894–900, https://doi.org/10.1016/j.thromres.2012.09.010.
[35] S.K. Haas, M. Freund, D. Heigener, L. Heilmann, B. Kemkes-Matthes, G.-F. von Tempelhoff, N. Melzer, A.K. Kakkar, Low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer or stage III/IV lung cancer, Clin. Appl. Thromb. Hemost. 18 (2012) 159–165, https://doi.org/10.1177/1076029611433769.
[36] M. Verso, G. Gussoni, G. Agnelli, Prevention of venous thromboembolism in patients with advanced lung cancer receiving chemotherapy: a combined analysis of the PROTECHT and TOPIC-2 studies, J. Thromb. Haemost. 8 (2010) 1649–1651, https://doi.org/10.1111/j.1538-7836.2010.03901.x.
[37] J.W. Blom, C.J.M. Doggen, S. Osanto, F.R. Rosendaal, Malignancies, prothrombotic mutations, and the risk of venous thrombosis, JAMA. 293 (2005) 715–722, https://doi.org/10.1001/jama.293.6.715.
[38] E.A. Akl, L.A. Kahale, M.B. Hakoum, C.F. Matar, F. Sperati, M. Barba, V.E.D. Yosuico, I. Terrenato, A. Synnot, H. Schunemann, Parenteral anticoagulation in ambulatory patients with cancer, Cochrane Database Syst. Rev. 9 (2017) CD006652, , https://doi.org/10.1002/14651858.CD006652.pub5.
[39] F. Icli, H. Akbulut, G. Utkan, B. Yalcin, D. Dincol, A. Isikdogan, A. Demirkazik, H. Onur, F. Cay, A. Buyukcelik, Low molecular weight heparin (LMWH) increases the efficacy of cisplatinum plus gemcitabine combination in advanced pancreatic cancer, J. Surg. Oncol. 95 (2007) 507–512, https://doi.org/10.1002/jso.20728.
[40] K.A. Mander, J.W. Finnie, Tumour angiogenesis, anti-angiogenic therapy and chemotherapeutic resistance, Aust. Vet. J. 96 (2018) 371–378, https://doi.org/10.1111/avj.12747.
[41] O. Annibali, M. Napolitano, G. Avvisati, S. Siragusa, Incidence of venous thromboembolism and use of anticoagulation in hematological malignancies: critical review of the literature, Crit. Rev. Oncol. Hematol. 124 (2018) 41–50, https://doi.org/10.1016/j.critrevonc.2018.02.003.
[42] P. Prandoni, A.W.A. Lensing, A. Piccioli, E. Bernardi, P. Simioni, B. Girolami, A. Marchiori, P. Sabbion, M.H. Prins, F. Noventa, A. Girolami, Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis, Blood. 100 (2002) 3484–3488, https://doi.org/10.1182/blood-2002-01-0108.
[43] M. Mak, C. Lam, S.J. Pineda, M. Lou, L.Y. Xu, C. Meeks, C. Lin, R. Stone, K. Rodgers, G. Mitani, Pharmacogenetics of warfarin in a diverse patient population., J. Cardiovasc. Pharmacol. Ther. (2019) 1074248419843530. doi:10.1177/1074248419843530.
[44] M. Napolitano, G. Saccullo, M. Marietta, M. Carpenedo, G. Castaman, E. Cerchiara, A. Chistolini, L. Contino, V. De Stefano, A. Falanga, A.B. Federici, E. Rossi, R. Santoro, S. Siragusa, V. De Stefano, A. Falanga, A. Tosetto, G. Avvisati, M. Carpenedo, A.B. Federici, M. Marietta, M. Napolitano, E. Rossi, C. Santoro, G. Castaman, E. Cerchiara, A. Chistolini, L. Contino, M.G. Mazzucconi, I. Nichele, L. Russo, R. Santi, R.C. Santoro, S. Siragusa, G. Tagariello, Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus., Blood Transfus. 17 (2019) 171–180. doi:10.2450/2018.0143-18.