Anticoagulation in patients with cancer: an overview of reviews

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Abstract: Introduction. Relative benefits and harms of anticoagulants are required for judgments regarding appropriate anticoagulation in patients with cancer. **Objectives.** To review the benefits and harms of anticoagulants for prophylactic, therapeutic, and survival improvement indications in patients with cancer. **Patients and methods.** Overview of 6 systematic reviews of anticoagulation in cancer following the Cochrane Collaboration and Grading of Recommendations Assessment, Development and Evaluation methodology. **Results.** Central venous catheters thromboprophylaxis with heparin or warfarin does not significantly reduce the incidence of symptomatic deep vein thrombosis (DVT) (relative risk [RR] 0.43, 95% CI 0.18–1.06 and RR 0.62, 95% CI 0.30–1.27 respectively). For perioperative thromboprophylaxis, low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) have similar effects on mortality (RR 0.89, 95% CI 0.61–1.28) and morbidity outcomes. For the initial treatment of venous thromboembolism (VTE), LMWH compared with UFH reduces mortality at 3 months (RR 0.71, 95% CI 0.52–0.98). For the long-term treatment of VTE, LMWH compared with vitamin K antagonists reduces VTE recurrence (hazard ratio [HR] 0.47, 95% CI 0.32–0.71) but not mortality (HR 0.96, 95% CI 0.81–1.14). As interventions to improve survival, warfarin suggests a survival benefit at 6 months in the subgroup of small cell lung cancer (SCLC) (RR 0.69, 95% CI 0.50–0.96) while heparin suggests a survival benefit in patients with cancer in general (HR 0.77, 95% CI 0.65–0.91) and in those with limited SCLC in particular (HR 0.56, 95% CI 0.38–0.83). **Conclusions.** In patients with cancer, current evidence does not support routine use of thromboprophylaxis for central venous catheters or a specific anticoagulant for perioperative thromboprophylaxis. Anticoagulants may improve survival, but more data will be useful in deciding which subgroups benefit most.

Key words: anticoagulation, cancer, heparin, vitamin K antagonists

INTRODUCTION

Patients with cancer have a 4 to 6-fold increased risk of venous thromboembolism (VTE) compared with the general population [1-4]. An increased risk for VTE is also present in patients undergoing surgery for cancer compared to patients undergoing surgery for benign diseases [5,6]. In addition, patients with cancer who require long-term central venous catheters (CVC) to receive chemotherapy, transfusions, parenteral nutrition, or antibiotics are at increased risk of thrombosis [2]. At the same time, thromboembolic complications in patients with cancer can lead to significant morbidity and mortality [7]. Indeed, patients with cancer and VTE have a higher risk of death than patients with cancer alone or with VTE alone [8,9].

The relative benefits and harms of anticoagulants in patients with cancer differ from patients without cancer [10]. Thromboprophylaxis might be less effective in patients with cancer due to the prothrombotic state associated with malignancy [11,12]. Patients with cancer treated for VTE have higher thrombosis recurrence rates and more hemorrhagic complications compared to patients without cancer treated for VTE [13,14]. On the other hand, low-molecular-weight heparin (LMWH) may have a survival advantage over unfractionated heparin (UFH) in the treatment of deep vein thrombosis (DVT) but only in the subgroup of cancer patients [15].

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Table 1. Overview of reviews. Table for brief description of systematic reviews summarized in the overview

Review	Population	Interventions of interest
CVC thromboprophylaxis	Patients with cancer and a CVC but no clinical evidence of VTE	LMWH, fondaparinux, UFH, VKA, ximelagatran
Perioperative thromboprophylaxis	Patients with cancer undergoing surgery	LMWH, fondaparinux, UFH
Initial anticoagulation for VTE	Patients with cancer and VTE	LMWH, fondaparinux, UFH
Long-term anticoagulation for VTE	Patients with cancer and VTE	LMWH, VKA, ximelagatran
Oral anticoagulation for survival benefit	Patients with cancer but without clinical evidence of VTE	VKA
Parenteral anticoagulation for survival benefit	Patients with cancer but without clinical evidence of VTE	LMWH, UFH

CVC – central venous catheters, LMWH – low-molecular-weight heparin, UFH – unfractionated heparin, VKA – vitamin K antagonists, VTE – venous thromboembolism

The difference between patients with cancer and patients without cancer in terms of survival advantage with specific types of anticoagulants might be related to an antitumoral effect of anticoagulation. Experimental studies found that anticoagulants such as warfarin have an inhibitory effect on tumor growth and metastasis [16] and that a longer oral anticoagulation of patients with a first episode of venous thromboembolism is associated with a lower cancer incidence [17]. These findings led to the hypothesis that anticoagulants possess, in addition to their antithrombotic effect, an antitumor effect.

The potential antitumoral effect of anticoagulants has led researchers to investigate the effect of anticoagulation on survival of patients with cancer who otherwise have no indication for anticoagulation. In the early 1980s, a large clinical trial suggested that warfarin, as a single anticoagulant agent, may favorably modify the course of some types cancers such as small cell lung cancer (SCLC) [18]. Similarly, a number of randomized controlled trials (RCTs) have suggested that heparin might improve the survival of patients with cancer [19,20].

Relative benefits and harms of anticoagulants are required for judgments regarding the appropriate anticoagulation in patients with cancer. In this paper we summarize a series of Cochrane Systematic Reviews that we conducted to evaluate the benefits and harms of different anticoagulants for prophylactic and therapeutic indications in patients with cancer.

PATIENTS AND METHODS

We summarize the results of 6 systematic Cochrane reviews assessing the benefits and harms of anticoagulation in patients with cancer for the following patient populations: central venous catheters thromboprophylaxis [21,22], perioperative thromboprophylaxis [23], treatment of venous thromboembolism [24,25], and prolonging survival [26-29] (Tab. 1).

The reviews had a common search strategy that included a search of 4 electronic databases (MEDLINE, CENTRAL, EMBASE, and ISI the Web of Science) in January 2007, a hand search of 2 conference proceedings (American Society of Clinical Oncology and the American Society of Hematology), a review of reference lists, and the use of the "related article" feature in PubMed. The reviewers conducted title and abstract screening, full text screening, methodological quality assessment and data abstraction in duplicate. The reviewers included only RCTs and pooled their results using standard meta-analytic techniques.

For the evaluation of the methodological quality for the outcomes evaluated in the reviews we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [30]. The GRADE approach specifies four levels of quality of high, moderate, low, and very low quality evidence. We produced Summary of Findings (SoF) tables using GRADEpro (version 3.1.1) software as described by the Cochrane Collaboration [31]. SoF tables present the main findings of a review in a transparent and simple tabular format. A SoF table provides key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all important outcomes.

RESULTS

Central venous catheters thromboprophylaxis

The systematic review evaluating the efficacy and safety of anticoagulation for reducing VTE events in patients with cancer and CVC included 9 RCTs [21]. One RCT was in pediatric patients and none of the RCTs tested fondaparinux or ximelagatran. Data was not available for 3 eligible RCTs published as abstracts and 1 eligible study in which patients with cancer constituted a subgroup (Tab. 2 and 3, see apendix). The quality of evidence was moderate for death, symptomatic DVT and thrombocytopenia and low for major bleeding.

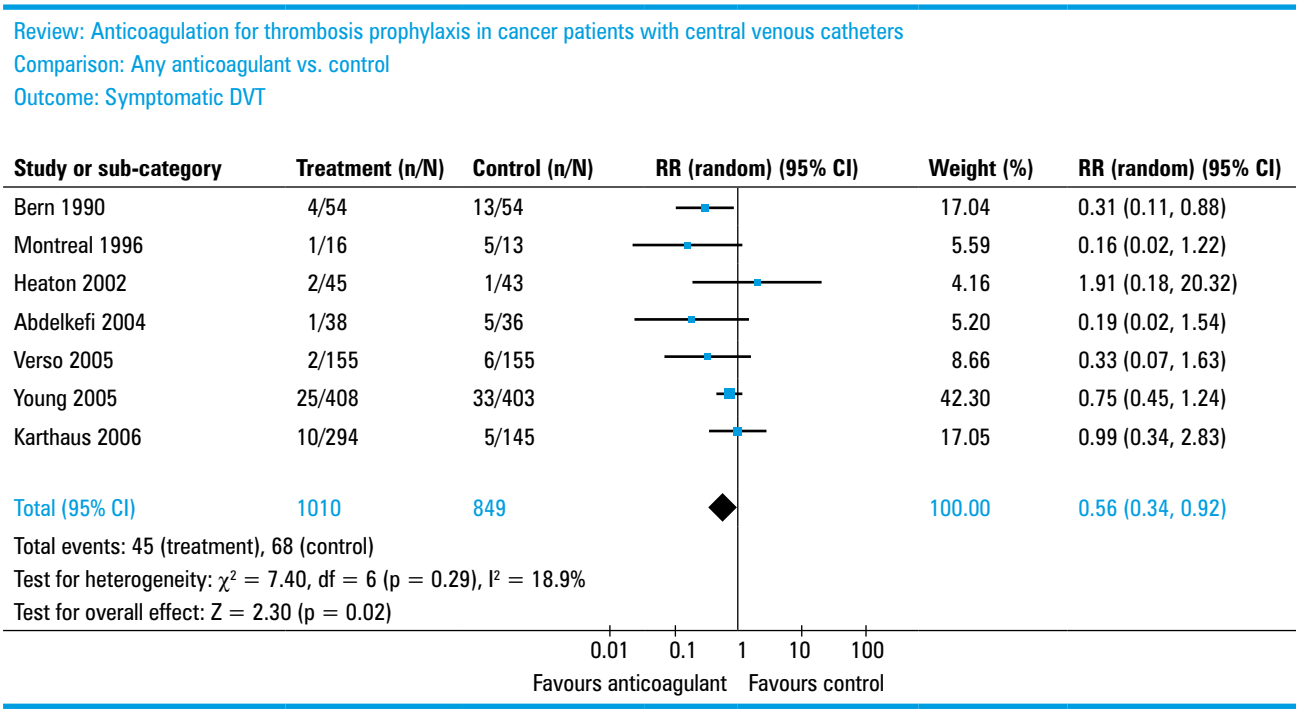

Fig. 1. Symptomatic deep venous thrombosis in cancer patients with central venous catheters and with low-molecular-weight heparin, unfractionated heparin and warfarin. DVT – deep vein thrombosis

The use of heparin in cancer patients with CVC was associated with a trend towards a reduction in symptomatic DVT (relative risk [RR] 0.43, 95% CI 0.18–1.06), but the data did not show any statistically significant effect on mortality (RR 0.74, 95% CI 0.40–1.36), infection (RR 0.91, 95% CI 0.36–2.28), major bleeding (RR 0.68, 95% CI 0.10–4.78) or thrombocytopenia (RR 0.85, 95% CI 0.49–1.46). The effect of warfarin on symptomatic DVT was not statistically significant (RR 0.62, 95% CI 0.30–1.27).

In a *post hoc* analysis pooling studies assessing different types of anticoagulants, symptomatic DVT rates were significantly reduced (RR 0.56, 95% CI 0.34–0.92) (Fig. 1). One additional observation was that the baseline risk of symptomatic DVT decreased by year of publication.

Perioperative thromboprophylaxis

The systematic review comparing the relative efficacy and safety of LMWH and UFH for perioperative thromboprophylaxis in patients with cancer included 14 RCTs, all using preoperative prophylactic anticoagulation [23]. Data was not available for 12 eligible trials that included cancer patients as subgroups (Tab. 4, see apendix). The quality of evidence was moderate for death, DVT, pulmonary embolism major bleeding, and wound hematoma and, was low for postoperative transfusion and thrombocytopenia, and was very low for minor bleeding.

The meta-analysis showed no difference between patients receiving LMWH or UFH in mortality (RR 0.89, 95% CI 0.61–1.28), clinically suspected DVT (RR 0.73, 95% CI 0.23–2.28), pulmonary embolism (RR 0.60, 95% CI 0.22–1.64), major bleeding (RR 0.95, 95% CI 0.51–1.77), minor bleeding (RR 0.88, 95% CI 0.47–1.66), or thrombocytopenia (RR 1.18, 95% CI 0.49–2.81).

In a *post hoc* analysis including all studies assessing DVT, irrespectively of the diagnostic strategy used, LMWH was superior to UFH (RR 0.72, 95% CI 0.55–0.94) (Fig. 2). The benefit was significant in the subgroup of trials comparing LMWH to UFH administered twice a day (RR 0.66, 95% CI 0.44–0.99) but not in the subgroup of trials comparing LMWH to UFH administered three times a day (RR 0. 78, 95% CI 0.53–1.15, I^2 0%). The difference between the RRs for the 2 subgroups was not statistically significant (p = 0.278)

Initial treatment of venous thromboembolism

The systematic review comparing the efficacy and safety of LMWH, unfractionated UFH, and fondaparinux for the initial treatment of VTE in patients with cancer included 15 RCTs: 13 studies compared LMWH to UFH, 1 study compared fondaparinux to UFH and 1 study compared dalteparin to tinzaparin. Data was not available for 10 eligible trials that included cancer patients as subgroups. The inverted funnel plot suggested the possibility of publication bias in favor

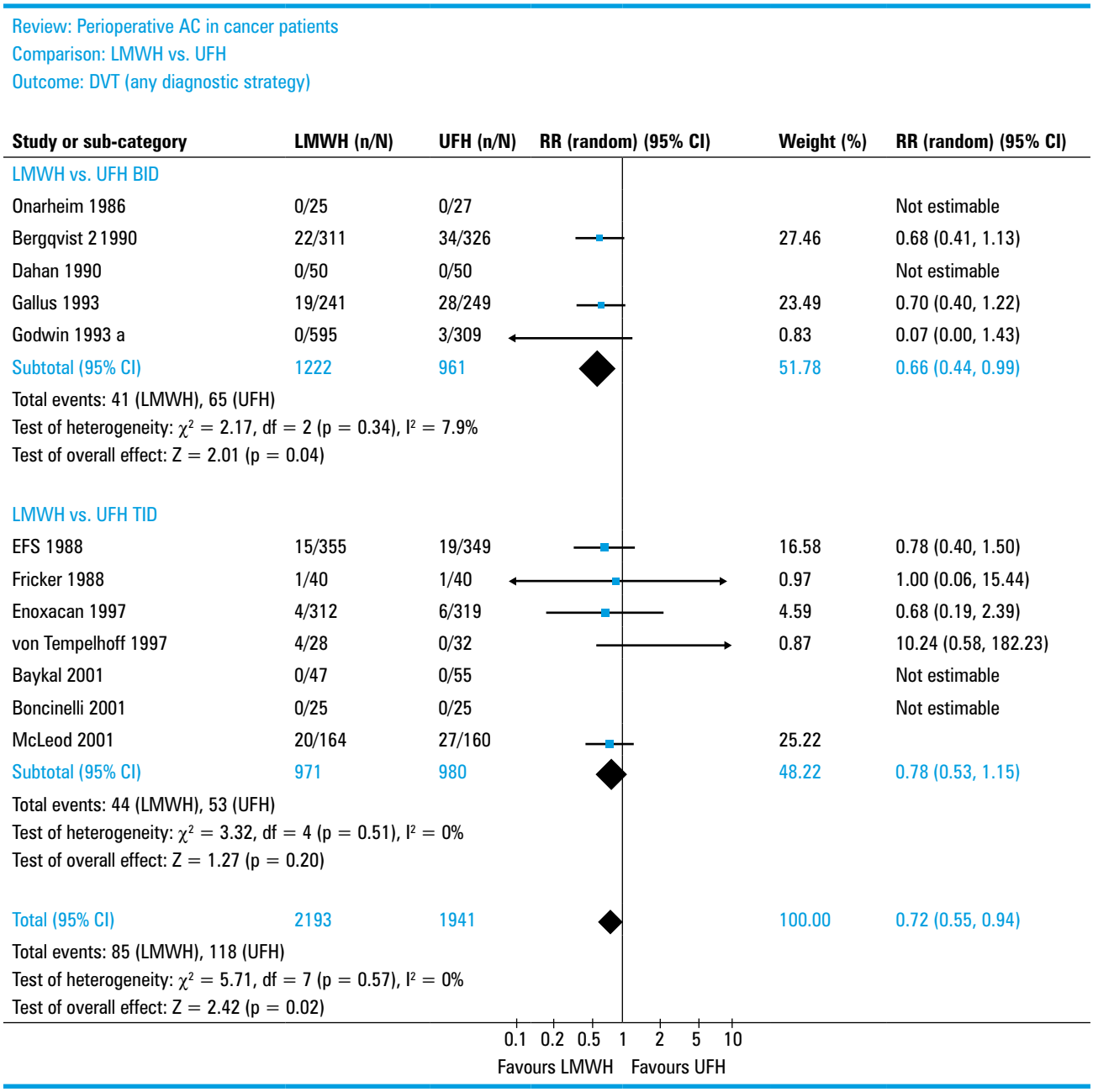

Fig. 2. Deep venous thrombosis (any diagnostic strategy) in patients with cancer receiving perioperative thromboprophylaxis with low molecular weight heparin (LMWH) vs. unfractionated heparin (UFH)

of LMWH (Tab. 5, see apendix). The quality of evidence was moderate for death and very low for recurrent VTE.

There was a statistically significant mortality reduction at 3 months in patients treated with LMWH compared with those treated with UFH (RR 0.71, 95% CI 0.52–0.98) (Fig. 3). There was little change in the results after excluding studies of lower methodological quality (RR 0.72, 95% CI 0.52–1.00). A meta-analysis of three studies comparing LMWH with UFH in reducing recurrent VTE showed no statistically significant difference (RR 0.78, 95% CI 0.29–2.08). No data was available for bleeding outcomes, thrombocytopenia or postphlebitic syndrome. Compared-UFH, fondaparinux showed a non-statistically significant benefit for the outcome of death (RR 0.52, 95% CI 0.26–1.05). The one study comparing dalteparin-tinzaparin showed a non-statistically significant mortality reduction with dalteparin (RR 0.86, 95% CI 0.43–1.73).

Review: Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer
Comparison: LMWH vs. UFH
Outcome: Death al 3 months

Study or sub-category	LMWH (n/N)	UFH (n/N)	RR (random) (95% CI)	Weight (%)	RR (random) (95% CI)
Duroux 1991	0/6	2/12		1.23	0.37 (0.02, 6.71)
Hull 1992	7/46	14/49		15.59	0.53 (0.24, 1.20)
Lopaciuk 1992	0/7	0/2		Not estimable	
Prandoni 1992	1/15	6/18		2.57	0.20 (0.03, 1.48)
Simmoneau 1993	2/7	1/2		3.13	0.57 (0.09, 3.51)
Lindmaker 1994	2/7	2/9		3.60	1.29 (0.24, 6.99)
Koopman 1996	3/34	3/36		4.40	1.06 (0.23, 4.89)
Levine 1996	11/46	14/57		21.81	0.97 (0.49, 1.94)
Columbus 1997	20/119	27/113		38.45	0.70 (0.42, 1.18)
Simmoneau 1997	2/26	4/34		3.93	0.65 (0.13, 3.30)
Galilei 2004	3/76	5/80		5.29	0.63 (0.16, 2.55)
Total (95% CI)	389	412		100.00	0.71 (0.52, 0.98)

Total events: 51 (LMWH), 78 (UFH)
Test for heterogeneity: $\chi^2 = 3.88$, df = 9 (p = 0.92), $I^2 = 0\%$
Test for overall effect: Z = 2.07 (p = 0.04)

Fig. 3. Death at 3months in patients with cancer receiving low molecular weight heparin (LMWH) vs. unfractionated heparin (UFH)as the initial anticoagulation for a thromboembolic event

Long-term treatment of VTE

The systematic comparing the efficacy and safety of LMWH and oral anticoagulants (vitamin K antagonist [VKA] and ximelagatran) for the long-term treatment of venous thromboembolism in patients with cancer included 8 RCTs. Data was not available for 11 eligible trials that included cancer patients as subgroups (Tab. 6, see apendix). The quality of evidence was low for death and moderate for recurrent VTE.

Meta-analysis of 6 RCTs showed that LMWH, compared-VKA provided no statistically significant survival benefit (hazard ratio [HR] 0.96, 95% CI 0.81–1.14) but a statistically significant reduction in venous thromboembolism (HR 0.47, 95% CI 0.32–0.71) (Fig. 4). There was no statistically significant difference between LMWH and VKA in bleeding outcomes (RR 0.91, 95% CI 0.64–1.31) or thrombocytopenia (RR 1.02, 95% CI 0.60–1.74). One RCT compared tinzaparin and dalteparin and showed no differences in the outcomes of interest. One RCT compared a 6 months extension of anticoagulation with 18 months ximelagatran 24 mg twice a day vs. placebo. It showed a reduction in venous thromboembolism (HR 0.16, 95% CI 0.09–0.30) with no apparent effect on survival or bleeding.

Oral anticoagulation for prolonging survival

The systematic review evaluating the efficacy and safety of oral anticoagulation (including VKA and ximelagatran) for improving the survival of patients with cancer included 5 RCTs [26,28]. Warfarin was the oral anticoagulant in all of these RCTs and it was compared – either placebo or no intervention (Tab. 7, see apendix). The quality of evidence was moderate for death and minor bleeding, and high for major bleeding.

The effect of warfarin on reduction in mortality was not statistically significant at 6 months RR 0.96, 95% CI 0.80–1.16), at 1 year (RR 0.94, 95% CI 0.87–1.03) (Fig. 5) at 2 years (RR 0.97, 95% CI 0.87–1.08) or at 5 years (RR 0.91, 95% CI 0.83–1.01). In the subgroup of patients with small cell lung cancer (SCLC), warfarin reduced mortality at 6 months (RR 0.69, 95% CI 0.50–0.96) (Fig. 6) but not at 1 year (RR 0.88, 95% CI 0.77–1.01).

One study assessed the effect of warfarin on venous thromboembolism and showed a RR reduction of 85% (p = 0.031). Warfarin increased both major bleeding (RR 4.24, 95% CI 1.85–9.68) and minor bleeding (RR 3.34, 95% CI 1.66–6.74).

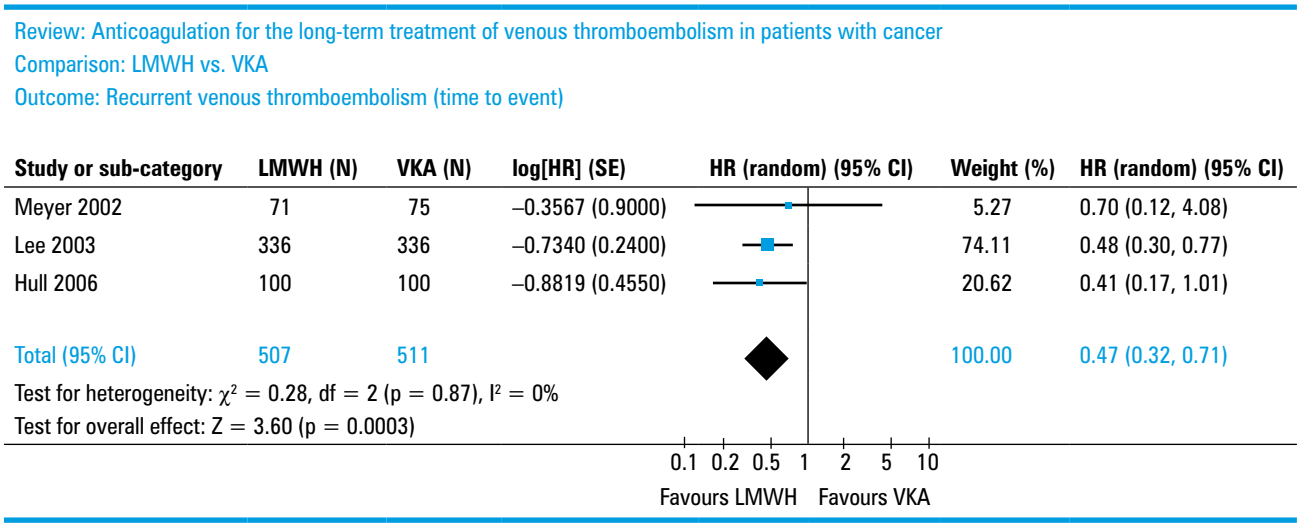

Fig. 4. Recurrent venous thromboembolism in patients with cancer receiving low molecular weight heparin (LMWH) vs. unfractionated heparin (UFH) as the long-term anticoagulation for a thromboembolic event. VKA – vitamin K antagonists

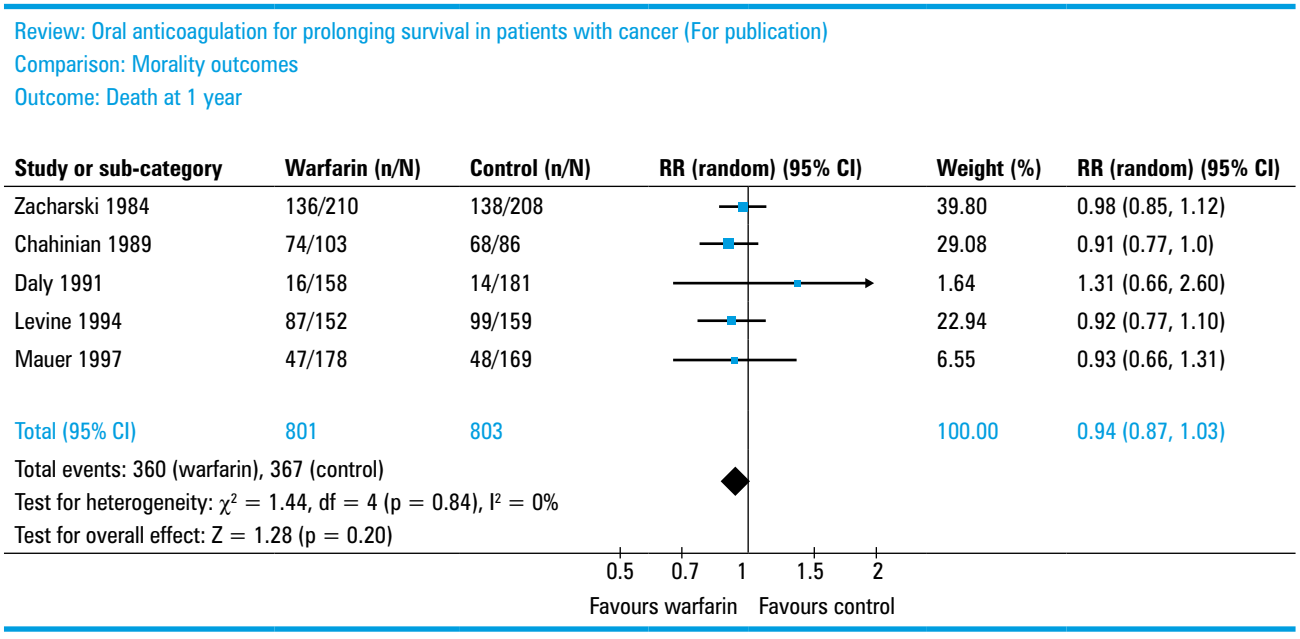

Fig. 5. All cause mortality at 1 year in patients with cancer on warfarin compared with control

Parenteral anticoagulation for prolonging survival

The systematic review evaluating the efficacy and safety of parenteral anticoagulation for improving the survival of patients with cancer included 5 RCTs [27]. In all included RCTs the intervention consisted of heparin (either UFH or LMWH) and no study evaluated fondaparinux. Six eligible studies published as abstracts were not included because the needed data were not available (Tab. 8, see apendix). The quality of evidence was high for survival, low for major and minor bleeding, and very low for DVT.

Heparin therapy was associated with a statistically and clinically significant survival benefit (HR 0.77, 95% CI 0.65–0.91) (Fig. 7). In subgroup analyses, patients with limited SCLC experienced a clear survival benefit (HR 0.56, 95% CI 0.38–0.83). The survival benefit was not statistically significant for patients with extensive small cell lung cancer (HR 0.80, 95% CI 0.60–1.06) or for patients with advanced cancer (HR 0.84, 95% CI 0.68–1.03). The increased

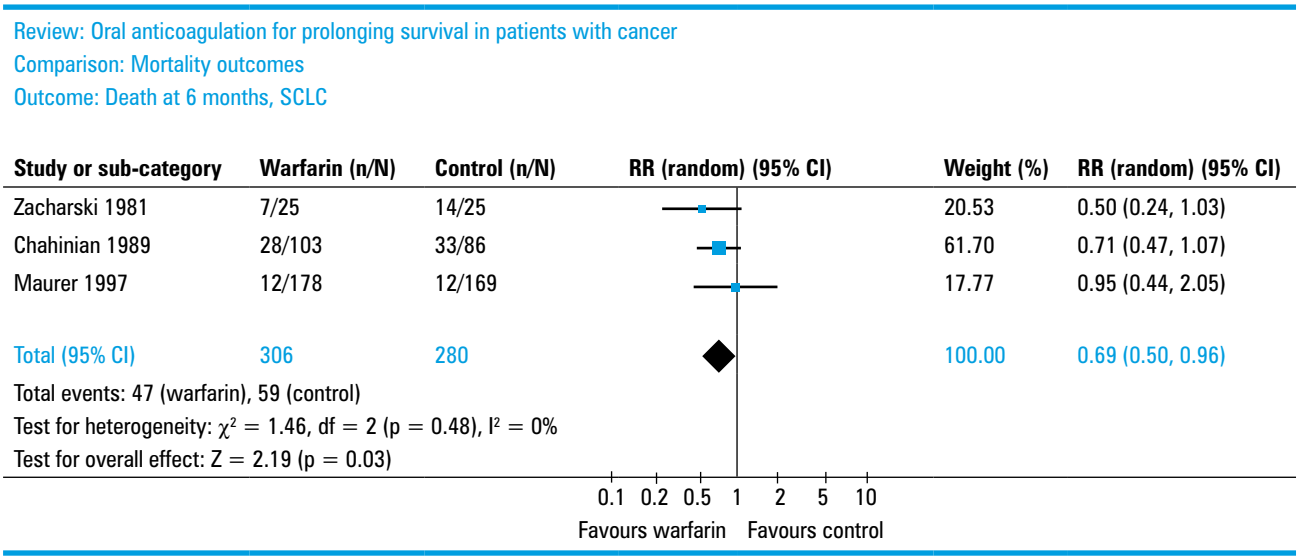

Fig. 6. All cause mortality at 6 months in patients with extensive small cell lung cancer (SCLC) on warfarin compared with control

risk of bleeding with heparin was not statistically significant (RR 1.78, 95% CI 0.73–4.38).

DISCUSSION

In summary, central venous catheters thromboprophylaxis with either heparin or warfarin do not reduce the incidence of symptomatic DVT. For perioperative thromboprophylaxis, LMWH and UFH have similar effects on mortality and morbidity outcomes, but the evidence suggests that one of these agents should be used pre-operatively. For the initial treatment of VTE, LMWH compared with VKA probably reduces mortality at 3 months. For the long-term treatment of VTE, LMWH compared with VKA reduces VTE recurrence but not mortality. As interventions to improve survival, warfarin suggests a survival benefit at 6 months in the subgroup of SCLC while heparin suggests a survival benefit in patients with cancer in general and in those with limited SCLC in particular.

This overview is based on 6 Cochrane systematic reviews with a number of strengths. Their common search strategy is comprehensive, had no language restrictions, and was relatively recent (2007). The validity of the reviews' results is enhanced by the use of the rigorous systematic review methods, e.g., duplicate screening, duplicate and rigorous methodological quality assessment, and duplicate data extraction.

A major and common limitation to these systematic reviews is the inability to obtain data for the subgroups of patients with cancer included in a number of eligible trials. On one hand, missing data might bias the reviews results if the treatment effect estimated from those data were different from the true effects. On the other hand, missing data decreases the power to detect true differences. Indeed, while the absence of statistically significant difference for many of the comparisons might reflect a true absence of effect, it could also be related to the lack of power to detect important differences. Another common limitation is that trials varied in the types of malignancies, dosing of anticoagulant medications, follow-up periods and the measurements of the outcomes. The relatively small number of trials included in some reviews did not allow the exploration of whether these variables modify the relative effects of the anticoagulants under study.

In terms of CVC thromboprophylaxis, an earlier systematic review suggested that low-dose warfarin and LMWH significantly reduce the incidence of catheter related thrombosis [32]. The discrepancy with the results of the review discussed above could be related to the smaller number of participants, the smaller number of events, and the lower methodological quality (i.e., stoppage early for benefit [33], assessing screening-detected asymptomatic cases) of the earlier studies driving the results of that earlier systematic review. On the other hand, the decrease in the baseline risk of symptomatic DVT by year of publication noted above could reflect technological advances in CVC material and design, better CVC management strategies (e.g., port flushing) and advances in clinical care in general (e.g., early mobilization of patients). These factors could interact with the efficacy of anticoagulation and reduce the relative effect of these agents. Overall the findings suggest that clinicians do not routinely use thromboprophylaxis in patients with cancer and CVC.

In terms of perioperative thromboprophylaxis, the results of the systematic review are consistent with 2 other systematic review in colorectal surgery [34] and gynecologic surgery [35] suggesting no statistically significant difference between LMWH and UFH on DVT. It is important to note that all included studies comparing LMWH to UFH started antico-

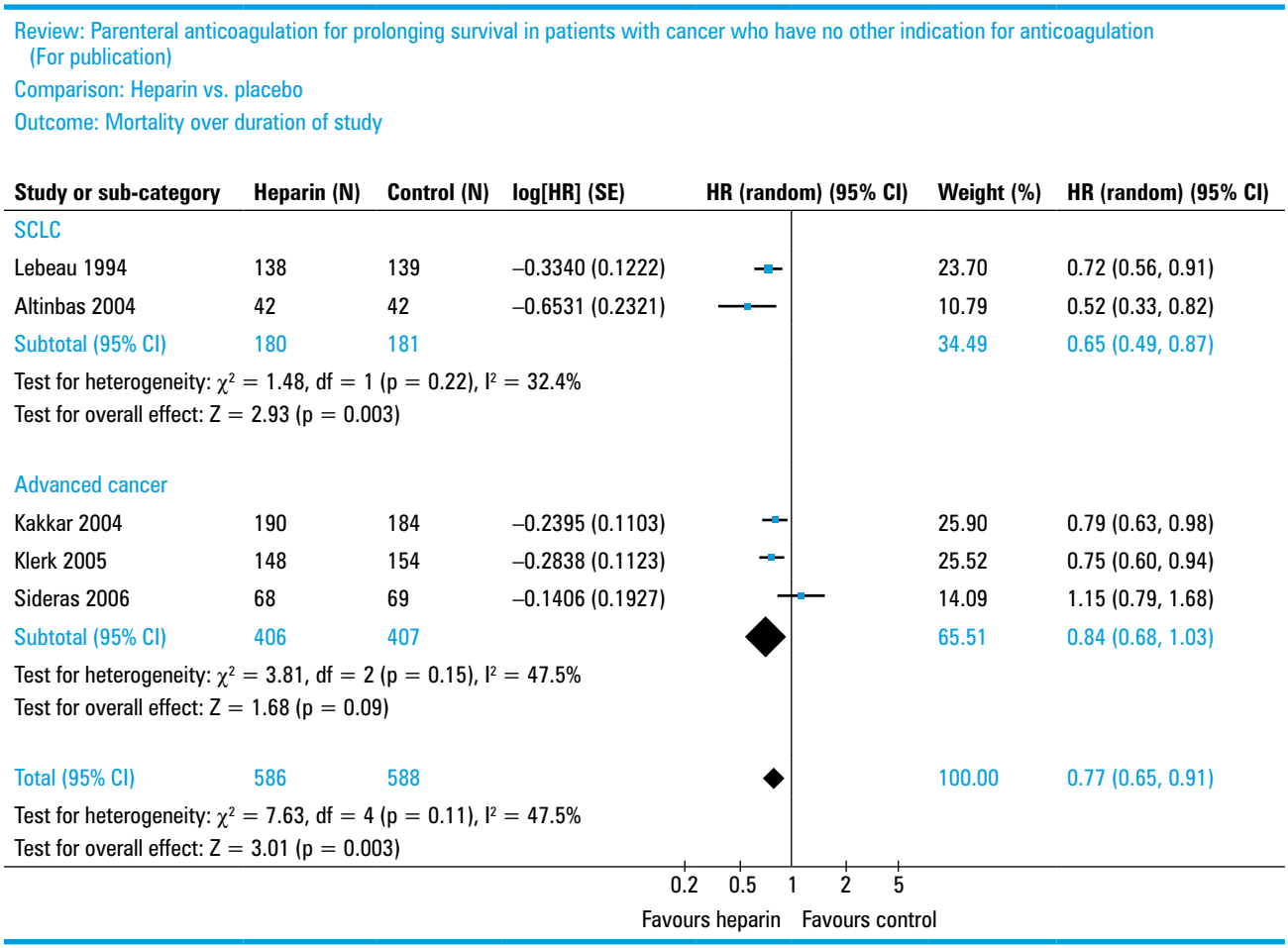

Fig. 7. Survival in patients with cancer on heparin compared with control

agulant treatment preoperatively. Thus, it is not certain how the results apply to settings in which anticoagulant treatment is started postoperatively. Support for preoperative use comes from studies that did not find statistically significant differences in the amount of blood loss when patients were randomized to a first dose of enoxaparin 12 hours before surgery versus postoperatively [32]. The results of the subgroup analysis suggesting lower rates of DVT in trials comparing LMWH to UFH administered twice a day rather than three times a day should be interpreted cautiously as the analysis does not meet all criteria for a credible subgroup difference [30]. Overall the findings suggest that LMWH and UFH are equivalent for perioperative thromboprophylaxis, keeping in mind the possibility that thrice daily UFH dosing may be more effective than twice daily dosing. In choosing one or the other agent, patients and physicians should consider factors such as cost, ease of administration and patient preferences.

In terms of initial treatment of VTE, LMWH is probably superior to UFH but publication bias may have exaggerated the observed effects. The results of the systematic review are overall consistent with those of 3 previous systematic reviews [15,36,37] finding statistically significant survival benefit of LMWH over UFH in patients with cancer. Existing evidence suggests that the survival benefit of LMWH over UFH might be restricted to patients with cancer [38]. Overall the findings suggest that LMWH is probably superior to UFH. In choosing one or the other agent, patients and physicians should consider factors such as cost, ease of administration, possibility of outpatient treatment, and patient preferences.

In terms of long-term treatment of VTE, LMWH compared to VKA reduces venous thromboembolic events but not death. One previous review showed that in patients with cancer there was no statistically significant difference in mortality between LMWH and VKA. Overall the findings suggest that LMWH is superior to warfarin in reducing VTE but not death. In choosing one or the other agent, patients and physicians should consider factors such as cost, ease of administration, need for monitoring, and patient preferences.

In terms of oral anticoagulation for survival benefit, the systematic review did not provide sufficient evidence for a survival benefit from oral anticoagulation in cancer patients in gen-

eral; it suggested however a potential benefit at 6 months in patients with SCLC. The decision to start warfarin for survival benefit in patients with SCLC should consider the benefits the downsides, including the risk of bleeding and the burden of warfarin treatment, and, most importantly, patient values and preferences for the outcomes and interventions.

In terms of parenteral anticoagulation, the result of the systematic review are consistent with those of another systematic review addressing the same question and showing a survival benefit with heparin [39]. The statistically significant survival benefit of heparin in the subgroup of patients with limited SCLC and in the subgroup of patients with life expectancy greater than 6 months in one of the included trials [20] suggests that the less ill patients get greater benefit from heparin. Similarly to warfarin, the decision to start heparin therapy for survival benefit should balance the benefits and downsides, including the risk of bleeding and the burden of subcutaneous injection, and integrate the patient's values and preferences.

Future studies of anticoagulation in patients with cancer should explore the hypotheses raised by the subgroup and the *post hoc* analyses discussed above. These studies should further explore the effects of anticoagulants, including the newer ones such as fondaparinux and ximelagatran, in cancer patients. The studies should also adhere to rigorous methodological criteria and be powered to assess patient-important outcomes including adverse events such as bleeding.

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APPENDIX

Table 2. SoF Table for heparin for thromboprophylaxis in patients with cancer and central venous catheters

Patient or population: patients with cancer and a central venous line for thromboprophylaxis

Settings: outpatient

Intervention: heparin

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Heparin				
Death	Low risk population		RR 0.74 (0.4–1.36)	913 (3)	⊕⊕⊕O moderate[2]	
	10 per 1000	7 per 1000 (4–14)				
	High risk population					
	100 per 1000	74 per 1000 (40–136)				
Symptomatic DVT	Low risk population		RR 0.43 (0.18–1.06)	852 (4)	⊕⊕⊕O moderate[2]	
	30 per 1000	13 per 1000 (5–32)				
	High risk population					
	400 per 1000	172 per 1000 (72–424)				
Major bleeding	Low risk population		RR 0.68 (0.1–4.78)	499 (2)	⊕⊕OO low[2,3]	
	10 per 1000	7 per 1000 (1–48)				
	High risk population					
	30 per 1000	20 per 1000 (3–143)				
Thrombocytopenia	Low risk population		RR 0.85 (0.49–4.46)	836 (3)	⊕⊕⊕O moderate[2]	
	50 per 1000	42 per 1000 (25–223)				
	High risk population					
	150 per 1000	128 per 1000 (74–669)				

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[2] The 95% CI includes both negligible effect and appreciable benefit or appreciable harm.

[3] Out of 4 included studies, only 2 report major bleeding events.

Abbreviations: RR – risk ratio

Table 3. SoF Table for vitamin K antagonists for thromboprophylaxis in patients with cancer and central venous catheters

Patient or population: patients with cancer and a central venous line for thromboprophylaxis
Settings: Outpatient
Intervention: vitamin K antagonists

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	vitamin K antagonists				
Symptomatic DVT	Low risk population		RR 0.62 (0.3–1.27)	1007 (3)	⊕⊕⊕O moderate[2]	
	20 per 1000	12 per 1000 (6–25)				
	High risk population					
	240 per 1000	149 per 1000 (72–305)				

GRADE Working Group grades of evidence – see Table 2

[1] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[2] The 95% CI includes both negligible effect and appreciable benefit or appreciable harm.

Abbreviations – see Table 2

Table 4. SoF Table for low-molecular-weight heparin (LMWH) versus unfractionated heparin (UFH) for perioperative thromboprophylaxis in patients with cancer

Patient or population: patients with cancer for perioperative thromboprophylaxis
Settings: perioperative
Intervention: LMWH
Comparison: UFH

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	UFH	LMWH				
Death (follow-up: median 2 weeks)	Low risk population		RR 0.89 (0.61–1.28)	3008 (7)	⊕⊕⊕O moderate[2]	7 trials assessed PE but 2 of them reported no events
	10 per 1000	9 per 1000 (6–13)				
	High risk population					
	250 per 1000	222 per 1000 (153–320)				
Deep venous thrombosis diagnostic work up triggered by clinical suspicion (follow-up: median 1 weeks)	Low risk population		RR 0.73 (0.23–2.28)	1015 (12)	⊕⊕⊕O moderate	12 trials assessed PE but 4 of them reported no events
	10 per 1000	7 per 1000 (2–23)				
	High risk population					
	20 per 1000	15 per 1000 (5–46)				
Pulmonary embolism (follow-up: median 1 weeks)	Low risk population		RR 0.60 (0.22–1.64)	4549 (12)	⊕⊕⊕O moderate[2]	12 trials assessed PE but 5 of them reported no events
	10 per 1000	6 per 1000 (2–16)				
	High risk population					
	100 per 1000	60 per 1000 (22–164)				
Major bleeding (follow-up: median 1 weeks)	Low risk population		RR 0.95 (0.51–1.77)	2090 (6)	⊕⊕⊕O moderate[2]	
	10 per 1000	9 per 1000 (5 to 18)				
	High risk population					
	300 per 1000	285 per 1000 (153–531)				
Minor bleeding (follow-up: median 1 weeks)	Low risk population		RR 0.88 (0.47–1.66)	1888 (3)	⊕OOO very low[2,3,4]	
	50 per 1000	44 per 1000 (23–83)				
	High risk population					
	150 per 1000	132 per 1000 (70–249)				
Postoperative transfusion (follow-up: median 3 days)	See comment. The mean postoperative transfusion in the control groups was 155.6 cc	See comment		81 (1)	⊕⊕OO low[2,5]	SMD 0.26; 95% CI –0.18–0.70

Wound hematoma (follow-up: median 1 weeks)	Low risk population		RR 0	426 (3)	⊕⊕⊕O moderate[1]	
	50 per 1000	0 per 1000				
	High risk population					
	300 per 1000	0 per 1000				
Heparin induced thrombocytopenia	See comment	See comment	Not estimable	0	See comment	None of the studies assessed this outcome
Thrombocytopenia	Low risk population		RR 1.18 (0.49–2.81)	1280 (3)	⊕⊕OO low[2,6]	3 trials assessed PE but 1 of them reported no events
	10 per 1000	12 per 1000 (5 to 28)				
	High risk population					
	30 per 1000	35 per 1000 (15 to 84)				

GRADE Working Group grades of evidence – see Table 2

[1] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[2] The 95% CI includes both negligible effect and appreciable benefit or appreciable harm.

[3] Heterogeneity was severe (I^2 75%).

[4] Only 3 out of 14 studies included in the systematic review reported minor bleeding.

[5] Only 1 of the 14 studies included in the systematic review reported this outcome.

[6] Only 3 of 14 studies included in the systematic review assessed thrombocytopenia.

Abbreviations – see Table 2

Table 5. SoF Table for low-molecular-weight heparin (LMWH) compared to unfractionated heparin (UFH) for patients with cancer requiring initial anticoagulation for venous thromboembolism (VTE)

Patient or population: patients with cancer requiring initial anticoagulation for venous thromboembolism

Settings: Inpatient or outpatient

Intervention: LMWH

Comparison: UFH

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	UFH	LMWH				
Death (follow-up: median 3 months)	Low risk population		RR 0.71 (0.51–0.97)	801 (11)	⊕⊕⊕O moderate[2]	
	50 per 1000	35 per 1000 (25–49)				
	High risk population					
	500 per 1000	355 per 1000 (255–485)				
Recurrent VTE (follow-up: median 3 months)	Low risk population		RR 0.78 (0.29–2.08)	371 (3)	⊕OOO very low[2,3,4]	
	50 per 1000	39 per 1000 (14–104)				
	High risk population					
	200 per 1000	156 per 1000 (58–416)				

GRADE Working Group grades of evidence – see Table 2

[1] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[2] Although the funnel plot does not suggest publication bias, cancer subgroup data was not available for 11 trials.

[3] Breddin 2001 with the largest effect estimate: not clear whether randomization was concealed or whether ITT principle adhered to, 89% follow-up rate.

[4] The 95% CI around the RR includes both appreciable benefit and appreciable harm.

Abbreviations – see Table 2

Table 6. SoF Table for low-molecular-weight heparin (LMWH) compared to vitamin K antagonists (VKA) for patients with cancer requiring long term anticoagulation for venous thromboembolism (VTE)

Patient or population: patients with cancer requiring long term anticoagulation for VTE

Settings: outpatient

Intervention: LMWH

Comparison: VKA

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	VKA	LMWH				
Mortality (follow-up: 3–6 months)	Population		RR 0.95 (0.81–1.11)	1346 (4)	⊕⊕OO low[2,3]	
	310 per 1000	294 per 1000 (251–344)				
	Low risk population					
	30 per 1000	28 per 1000 (24–33)				
	High risk population					
	1000 per 1000	950 per 1000 (810–1110)				
Recurrent VTE (binary) (follow-up: 3–12 months)	Population		RR 0.51 (0.35–0.74)	1109 (4)	⊕⊕⊕O moderate[3]	
	139 per 1000	71 per 1000 (49–103)				
	Low risk population					
	40 per 1000	20 per 1000 (14–30)				
	High risk population					
	160 per 1000	82 per 1000 (56–118)				
Major bleeding (follow-up: 3–6 months)	Low risk population		RR 1.05 (0.53–2.1)	1120 (4)	⊕⊕OO low[3,4]	
	30 per 1000	31 per 1000 (16–63)				
	High risk population					
	160 per 1000	168 per 1000 (85–336)				
Minor bleeding (follow-up: 3–6 months)	Low risk population		RR 0.85 (0.53–1.35)	1120 (4)	⊕OOO very low[3,5]	
	120 per 1000	102 per 1000 (64–162)				
	High risk population					
	500 per 1000	425 per 1000 (265–675)				

GRADE Working Group grades of evidence – see Table 2

[1] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[2] There is a possibility for important benefit and harm considering the importance of this outcome.

[3] We could not obtain data for subgroups of patients with cancer in 11 RCTs.

[4] RR 1.05, 95% CI 0.53–2.10

[5] Inconsistency was severe (I^2 65%).

Abbreviations – see Table 2

Table 7. SoF Table for oral anticoagulation for prolonging survival in patients with cancer

Patient or population: prolonging survival in patients with cancer

Settings: outpatient

Intervention: oral anticoagulation

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Oral anticoagulation				
Death (follow-up: median 1 years)	Low risk population		RR 0.94 (0.87–1.03)	1604 (4)	⊕⊕⊕O moderate[2]	
	50 per 1000	47 per 1000 (44–51)				
	High risk population					
	650 per 1000	611 per 1000 (566–669)				
Major bleeding (follow-up: median 1 years)	Low risk population		RR 4.24 (1.85–9.68)	1282 (4)	⊕⊕⊕⊕ high	
	0 per 1000	0 per 1000				
	High risk population					
	40 per 1000	170 per 1000 (74–387)				
Minor bleeding	Low risk population		RR 3.34 (1.66–6.74)	851 (3)	⊕⊕⊕O moderate[3]	
	20 per 1000	67 per 1000 (33–135)				
	High risk population					
	400 per 1000	1336 per 1000 (664–2696)				

GRADE Working Group grades of evidence – see Table 2

[1] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[2] The 95% CI includes both negligible effects as well as appreciable benefit or appreciable harm.

[3] Only 3 of the 5 included studies reported minor bleeding events.

Abbreviations – see Table 2