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Kahale LA, Tsolakian IG, Hakoum MB, Matar CF, Barba M, Yosuico VED, Terrenato I, Sperati F, Schünemann H, Akl EA

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[Intervention Review]

Anticoagulation for people with cancer and central venous catheters

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ABSTRACT

Background

Central venous catheter (CVC) placement increases the risk of thrombosis in people with cancer. Thrombosis often necessitates the removal of the CVC, resulting in treatment delays and thrombosis-related morbidity and mortality. This is an update of the Cochrane Review published in 2014.

Objectives

To evaluate the efficacy and safety of anticoagulation for thromboprophylaxis in people with cancer with a CVC.

Search methods

We conducted a comprehensive literature search in May 2018 that included a major electronic search of Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), and Embase (Ovid); handsearching of conference proceedings; checking of references of included studies; searching for ongoing studies; and using the 'related citation' feature in PubMed. This update of the systematic review was based on the findings of a literature search conducted on 14 May 2018.

Selection criteria

Randomized controlled trials (RCTs) assessing the benefits and harms of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), vitamin K antagonists (VKA), or fondaparinux or comparing the effects of two of these anticoagulants in people with cancer and a CVC.

Data collection and analysis

Using a standardized form, we extracted data and assessed risk of bias. Outcomes included all-cause mortality, symptomatic catheter-related venous thromboembolism (VTE), pulmonary embolism (PE), major bleeding, minor bleeding, catheter-related infection, thrombocytopenia, and health-related quality of life (HRQoL). We assessed the certainty of evidence for each outcome using the GRADE approach (Balshem 2011).

Main results

Thirteen RCTs (23 papers) fulfilled the inclusion criteria. These trials enrolled 3420 participants. Seven RCTs compared LMWH to no LMWH (six in adults and one in children), six RCTs compared VKA to no VKA (five in adults and one in children), and three RCTs compared LMWH to VKA in adults.

LMWH versus no LMWH

Six RCTs (1537 participants) compared LMWH to no LMWH in adults. The meta-analyses showed that LMWH probably decreased the incidence of symptomatic catheter-related VTE up to three months of follow-up compared to no LMWH (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.22 to 0.81; risk difference (RD) 38 fewer per 1000, 95% CI 13 fewer to 52 fewer; moderate-certainty evidence). However, the analysis did not confirm or exclude a beneficial or detrimental effect of LMWH on mortality at three months of follow-up (RR 0.82, 95% CI 0.53 to 1.26; RD 14 fewer per 1000, 95% CI 36 fewer to 20 more; low-certainty evidence), major bleeding (RR 1.49, 95% CI 0.06 to 36.28; RD 0 more per 1000, 95% CI 1 fewer to 35 more; very low-certainty evidence), minor bleeding (RR 1.35, 95% CI 0.62 to 2.92; RD 14 more per 1000, 95% CI 16 fewer to 79 more; low-certainty evidence), and thrombocytopenia (RR 1.03, 95% CI 0.80 to 1.33; RD 5 more per 1000, 95% CI 35 fewer to 58 more; low-certainty evidence).

VKA versus no VKA

Five RCTs (1599 participants) compared low-dose VKA to no VKA in adults. The meta-analyses did not confirm or exclude a beneficial or detrimental effect of low-dose VKA compared to no VKA on mortality (RR 0.99, 95% CI 0.64 to 1.55; RD 1 fewer per 1000, 95% CI 34 fewer to 52 more; low-certainty evidence), symptomatic catheter-related VTE (RR 0.61, 95% CI 0.23 to 1.64; RD 31 fewer per 1000, 95% CI 62 fewer to 51 more; low-certainty evidence), major bleeding (RR 7.14, 95% CI 0.88 to 57.78; RD 12 more per 1000, 95% CI 0 fewer to 110 more; low-certainty evidence), minor bleeding (RR 0.69, 95% CI 0.38 to 1.26; RD 15 fewer per 1000, 95% CI 30 fewer to 13 more; low-certainty evidence), premature catheter removal (RR 0.82, 95% CI 0.30 to 2.24; RD 29 fewer per 1000, 95% CI 114 fewer to 202 more; low-certainty evidence), and catheter-related infection (RR 1.17, 95% CI 0.74 to 1.85; RD 71 more per 1000, 95% CI 109 fewer to 356; low-certainty evidence).

LMWH versus VKA

Three RCTs (641 participants) compared LMWH to VKA in adults. The available evidence did not confirm or exclude a beneficial or detrimental effect of LMWH relative to VKA on mortality (RR 0.94, 95% CI 0.56 to 1.59; RD 6 fewer per 1000, 95% CI 41 fewer to 56 more; low-certainty evidence), symptomatic catheter-related VTE (RR 1.83, 95% CI 0.44 to 7.61; RD 15 more per 1000, 95% CI 10 fewer to 122 more; very low-certainty evidence), PE (RR 1.70, 95% CI 0.74 to 3.92; RD 35 more per 1000, 95% CI 13 fewer to 144 more; low-certainty evidence), major bleeding (RR 3.11, 95% CI 0.13 to 73.11; RD 2 more per 1000, 95% CI 1 fewer to 72 more; very low-certainty evidence), or minor bleeding (RR 0.95, 95% CI 0.20 to 4.61; RD 1 fewer per 1000, 95% CI 21 fewer to 95 more; very low-certainty evidence). The meta-analyses showed that LMWH probably increased the risk of thrombocytopenia compared to VKA at three months of follow-up (RR 1.69, 95% CI 1.20 to 2.39; RD 149 more per 1000, 95% CI 43 fewer to 300 more; moderate-certainty evidence).

Authors' conclusions

The evidence was not conclusive for the effect of LMWH on mortality, the effect of VKA on mortality and catheter-related VTE, and the effect of LMWH compared to VKA on mortality and catheter-related VTE. We found moderate-certainty evidence that LMWH reduces catheter-related VTE compared to no LMWH. People with cancer with CVCs considering anticoagulation should balance the possible benefit of reduced thromboembolic complications with the possible harms and burden of anticoagulants.

PLAIN LANGUAGE SUMMARY

Blood thinners to prevent blood clots in people with cancer and central venous catheters

Background

A central venous catheter (CVC) is a tube that is inserted into a large vein to give fluids or medicines. CVC placement increases the risk of blood clots in people with cancer. This review evaluated the effectiveness and safety of blood thinning agents (anticoagulants) in people with cancer and a CVC.

Study characteristics

We searched the scientific literature for studies of anticoagulants in people with cancer and a CVC. The evidence is current to 14 May 2018.

Key results

We included 13 trials enrolling 3420 people with cancer and a CVC. Most trials included people with various types and stages of cancer. Seven studies compared injectable blood thinners to no anticoagulation, six studies compared blood thinner pills to no anticoagulation, and three studies compared injectable blood thinners to blood thinner pills. When considering people with cancer and a CVC, injectable blood thinners probably reduced the risk of CVC-related blood clots compared to no anticoagulation and probably increased the risk of thrombocytopenia (low levels of platelets in the blood, which causes bleeding into the tissues) compared to blood thinner pills.

Certainty of the evidence

When comparing injectable blood thinners to no anticoagulation, we judged the certainty of the evidence to be moderate for blood clot at the catheter site, low for mortality, infection at the catheter site and minor bleeding, and very low for major bleeding.

When comparing blood thinner pills to no anticoagulation, we judged the certainty of the evidence to be low for mortality major and minor bleeding, premature catheter removal and catheter-related infection low, and very low for blood clot at the catheter site.

When comparing injectable blood thinners to blood thinner pills, we judged the certainty of the evidence to be low for mortality and blood clots in the limbs and very low for blood clot at the catheter site, major and minor bleeding.

Summary of findings for the main comparison. Low-molecular-weight heparin (LMWH) compared to no LMWH for people with cancer and central venous catheters

Low-molecular-weight heparin (LMWH) compared to no LMWH for people with cancer and central venous catheters

Patient or population: people with cancer with thrombosis prophylaxis and central venous catheters

Settings: outpatient or inpatient

Intervention: LMWH

Comparison: no LMWH

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no LMWH	Risk difference with LMWH
All-cause mortality (up to 3 months)	1236 (5 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	**RR 0.82** (0.53 to 1.26)	Study population	
				77 per 1000	14 fewer per 1000 (36 fewer to 20 more)
Symptomatic catheter-related thrombosis (up to 3 months)	1089 (5 RCTs)	⊕⊕⊕⊖ **Moderate**[c]	**RR 0.43** (0.22 to 0.81)	Study population	
				67 per 1000	38 fewer per 1000 (52 fewer to 13 fewer)
Symptomatic catheter-related thrombosis measured as asymptomatic catheter-related thrombosis (up to 3 months)	1089 (5 RCTs)	⊕⊖⊖⊖ **Very low**[d,e,f]	**RR 0.95** (0.62 to 1.46)	Study population	
				96 per 1000	5 fewer per 1000 (36 fewer to 44 more)
Major bleeding (up to 3 months)	1018 (4 RCTs)	⊕⊖⊖⊖ **Very low**[g,h]	**RR 1.49** (0.06 to 36.28)	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
				Low	
				1 per 1000	0 fewer per 1000

					(1 fewer to 35 more)
Minor bleeding (up to 3 months)	544 (2 RCTs)	⊕⊕⊖⊖ **Low**[i,j]	**RR 1.35** (0.62 to 2.92)	Study population	
				41 per 1000	14 more per 1000 (16 fewer to 79 more)
Catheter-related infection (up to 3 months)	474 (2 RCTs)	⊕⊕⊖⊖ **Low**[k,l]	**RR 0.97** (0.52 to 1.79)	Study population	
				92 per 1000	3 fewer per 1000 (44 fewer to 73 more)
Thrombocytopenia (up to 3 months)	1002 (4 RCTs)	⊕⊕⊖⊖ **Low**[m,n]	**RR 1.03** (0.80 to 1.33)	Study population	
				176 per 1000	5 more per 1000 (35 fewer to 58 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **LMWH:** low-molecular-weight heparin; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level due to serious risk of bias; lack of blinding in participants and personnel in three studies, incomplete outcome data not addressed in three studies, and unclear or no allocation concealment in four out of five studies.
[b]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (36 per 1000 absolute reduction) and the possibility of important harm (20 per 1000 absolute increase), including 79 events in total.
[c]Downgraded by one level due to serious risk of bias; lack of blinding in participants and personnel in two studies; incomplete outcome data not addressed in three studies; and unclear or no allocation concealment in four out of five studies.
[d]Downgraded by one level due to concern about inconsistency, outcome measured as surrogate outcome.
[e]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (36 per 1000 absolute reduction) and the possibility of important harm (40 per 1000 absolute increase), including 94 events in total.
[f]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; incomplete outcome data not addressed in three studies; and unclear or no allocation concealment in four out of five studies.
[g]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in one study; incomplete outcome data not addressed in four studies; and unclear or no allocation concealment in three out of four studies.
[h]Downgraded by two levels due to concern about imprecision; 95% CI was consistent with the possibility for benefit (1 per 1000 absolute reduction) and the possibility of important harm (35 per 1000 absolute increase), including five events in total. Given the observed baseline risk of 0% we used 0.1% to generate an absolute effect and a confidence interval.

[i]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in one study; incomplete outcome data not addressed in two studies; and unclear or no allocation concealment in two out of two studies.
[j]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (16 per 1000 absolute reduction) and the possibility of important harm (79 per 1000 absolute increase), including 26 events in total.
[k]Downgraded by one level due to concern about risk of bias; incomplete outcome data not addressed in two studies; and unclear or no allocation concealment in one out of two studies.
[l]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (35 per 1000 absolute reduction) and the possibility of important harm (58 per 1000 absolute increase), including 36 events in total.
[m]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; incomplete outcome data not addressed in two studies; and unclear or no allocation concealment in three out of four studies.
[n]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (35 per 1000 absolute reduction) and the possibility of important harm (58 per 1000 absolute increase) including 163 events in total.

Summary of findings 2. Vitamin K antagonist (VKA) compared to no VKA for people with cancer and central venous catheters

Vitamin K antagonist (VKA) compared to no VKA for people with cancer and central venous catheters

Patient or population: people with cancer with thrombosis prophylaxis and central venous catheters

Settings: outpatient or inpatient

Intervention: VKA

Comparison: no VKA

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no VKA	Risk difference with VKA
All-cause mortality (up to 3 months)	701 (4 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	**RR 0.99** (0.64 to 1.55)[c]	Study population	
				95 per 1000	1 fewer per 1000 (34 fewer to 52 more)
Symptomatic catheter-related thrombosis (up to 3 months)	1271 (4 RCTs)	⊕⊕⊖⊖ **Low**[d,e,f]	**RR 0.61** (0.23 to 1.64)	Study population	
				80 per 1000	31 fewer per 1000 (62 fewer to 51 more)
Symptomatic catheter-related thrombosis measured as asymptomatic catheter-related thrombosis (up to 3 months)	384 (2 RCTs)	⊕⊖⊖⊖ **Very low**[g,h,i]	**RR 0.61** (0.27 to 1.40)	Study population	
				73 per 1000	29 fewer per 1000 (54 fewer to 29 more)

Major bleeding (up to 3 months)	1026 (2 RCTs)	⊕⊕⊖⊖ **Low**[j,k]	**RR 7.14** (0.88 to 57.78)	Study population	
				2 per 1000	12 more per 1000 (0 fewer to 110 more)
Minor bleeding (up to 3 months)	1026 (2 RCTs)	⊕⊕⊖⊖ **Low**[l,m]	**RR 0.69** (0.38 to 1.26)	Study population	
				48 per 1000	15 fewer per 1000 (30 fewer to 13 more)
Catheter-related infection (3 months)	88 (1 RCT)	⊕⊕⊖⊖ **Low**[n,o]	**RR 1.17** (0.74 to 1.85)	Study population	
				419 per 1000	71 more per 1000 (109 fewer to 356 more)
Premature CVC removal (3 months)	88 (1 RCT)	⊕⊕⊖⊖ **Low**[n,p]	**RR 0.82** (0.30 to 2.24)	Study population	
				163 per 1000	29 fewer per 1000 (114 fewer to 202 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CVC:** central venous catheter; **RCT:** randomized controlled trial; **RR:** risk ratio; **VKA:** vitamin K antagonist.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in four studies and unclear or no allocation concealment in two out of four studies.

[b]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (34 per 1000 absolute reduction) and the possibility of important harm (52 per 1000 absolute increase), including 67 events in total.

[c]The trial WARP showed no overall survival advantage in participants taking warfarin compared with participants in the no-warfarin group (hazard ratio 0.98, 95% CI 0.77 to 1.25; P = 0.26) (Young 2009).

[d]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in four studies and no clear information concerning allocation concealment in one out of four studies).

[e]Downgraded by one level due to unexplained inconsistency (I^2 = 70%). Imprecision was partially driven by the inconsistency between the studies and was taken into consideration when downgrading by two levels for serious risk of bias and serious inconsistency.

[f]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (63 per 1000 absolute reduction) and the possibility of important harm (57 per 1000 absolute increase), including 87 events in total.

[g]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies and no clear information about allocation concealment in one out of two studies.
[h]Downgraded by one level due to concern about inconsistency, outcome measured as surrogate outcome.
[i]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (54 per 1000 absolute reduction) and the possibility of important harm (29 per 1000 absolute increase), including 22 events in total.
[j]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies and no clear information about allocation concealment in one out of two studies.
[k]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for no effect (0 per 1000 absolute reduction) and the possibility of important harm (120 per 1000 absolute increase), including eight events in total.
[l]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in three studies; and unclear or no allocation concealment in two out of three studies.
[m]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (30 per 1000 absolute reduction) and the possibility of important harm (16 per 1000 absolute increase), including 42 events in total.
[n]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in the included study).
[o]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (109 per 1000 absolute reduction) and the possibility of important harm (356 per 1000 absolute increase), including 40 events in total.
[p]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (114 per 1000 absolute reduction) and the possibility of important harm (202 per 1000 absolute increase), including 13 events in total.

Summary of findings 3. Low-molecular-weight heparin (LMWH) compared to vitamin K antagonist (VKA) for people with cancer and central venous catheters

Low-molecular-weight heparin (LMWH) compared to vitamin K antagonist (VKA) for people with cancer and central venous catheters

Patient or population: people with cancer with thrombosis prophylaxis and central venous catheters

Settings: outpatient or inpatient

Intervention: LMWH

Comparison: VKA

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with VKA	Risk difference with LMWH
All-cause mortality (up to 3 months)	561 (3 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	**RR 0.94** (0.56 to 1.59)	Study population	
				94 per 1000	6 fewer per 1000 (41 fewer to 56 more)
Symptomatic catheter-related thrombosis (up to 3 months)	327 (2 RCTs)	⊕⊖⊖⊖ **Very low**[c,d]	**RR 1.83** (0.44 to 7.61)	Study population	
				19 per 1000	15 more per 1000

					(10 fewer to 122 more)
Symptomatic catheter-related thrombosis measured as asymptomatic catheter-related thrombosis (up to 3 months)	317 (2 RCTs)	⊕⊖⊖⊖ **Very low**[e,f,g]	**RR 1.61** (0.75 to 3.46)	Study population	
				63 per 1000	39 more per 1000 (16 fewer to 156 more)
Pulmonary embolism (up to 3 months)	327 (2 RCTs)	⊕⊕⊖⊖ **Low**[h,i]	RR 1.70 (0.74 to 3.92)	Study population	
				49 per 1000	35 more per 1000 (13 fewer to 144 more)
Major bleeding (up to 3 months)	289 (2 RCTs)	⊕⊖⊖⊖ **Very low**[j,k]	**RR 3.11** (0.13 to 73.11)	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
				Low	
				1 per 1000	2 more per 1000 (1 fewer to 72 more)
Minor bleeding (up to 3 months)	234 (1 RCT)	⊕⊖⊖⊖ **Very low**[l,m]	**RR 0.95** (0.20 to 4.61)	Study population	
				26 per 1000	1 fewer per 1000 (21 fewer to 95 more)
Thrombocytopenia (up to 3 months)[n]	327 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[o]	**RR 1.69** (1.20 to 2.39)	Study population	
				216 per 1000	149 more per 1000 (43 more to 300 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **LMWH:** low-molecular-weight heparin; **RCT:** randomized controlled trial; **RR:** risk ratio; **VKA:** vitamin K antagonist.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimat4%e of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in three studies; and unclear allocation concealment in two out of three studies.

[b]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (41 per 1000 absolute reduction) and the possibility of important harm (56 per 1000 absolute increase), including 51 events in total.

[c]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies and unclear allocation concealment in one out of two studies.

[d]Downgraded by two levels due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (10 per 1000 absolute reduction) and the possibility of important harm (122 per 1000 absolute increase), including nine events in total.

[e]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; and unclear allocation concealment in one out of two studies.

[f]Downgraded by one level due to concern about inconsistency, outcome measured as surrogate outcome.

[g]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (16 per 1000 absolute reduction) and the possibility of important harm (156 per 1000 absolute increase), including 26 events in total.

[h]Downgraded by one level due to concern both risk of bias; lack of blinding in participants and personnel in two studies; and allocation concealment not clear in one out of two studies.

[i]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (13 per 1000 absolute reduction) and the possibility of important harm (144 per 1000 absolute increase), including 22 events in total.

[j]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; and allocation concealment not clear in one out of two studies.

[k]Downgraded by two levels due to concern about imprecision; 95% CI was consistent with the possibility for benefit (1 per 1000 absolute reduction) and the possibility of important harm (51 per 1000 absolute increase), including one event in total. Given the observed baseline risk of 0% we used 0.1% to generate an absolute effect and a confidence interval.

[l]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in the study and unclear allocation concealment).

[m]Downgraded by two levels due to concern about imprecision (95% CI was consistent with the possibility for benefit (21 per 1000 absolute reduction) and the possibility of important harm (95 per 1000 absolute increase), including six events in total.

[n]The study by Lavau-Denes and colleagues included all grades of thrombocytopenia (even mild cases) (Lavau-Denes 2013).

[o]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; and allocation concealment not clear in one out of two studies.

BACKGROUND

See the glossary for the definitions of technical terms (Table 1).

Description of the condition

People with cancer often require long-term central venous access to receive chemotherapy, transfusions, parenteral nutrition, and antibiotics. However, central venous catheter (CVC) placement increases the risk of thrombosis in people with cancer (Agnelli 2005a). Even in the absence of a CVC, people with cancer have a four- to six-fold increased risk of thrombosis compared with the general population (Blom 2005; Blom 2006; Sutherland 2003). Moreover, cancer treatments, including surgery, radiotherapy (Guy 2017), and systemic therapy, also increase the risk of thrombosis (Agnelli 2005a). As a result, the incidence of clinically overt CVC-related deep venous thrombosis (DVT) in people with cancer ranges from 0.3% to 28.3% (Verso 2003). The incidence of clinically overt pulmonary embolism (PE) with CVC-related DVT varies between 15% and 25% (Verso 2003).

Both thrombosis and infection often necessitate the removal of the CVC, resulting in treatment delays as well as the clinical consequences of thrombosis and infections themselves (Kuter 2004). More importantly, these complications can lead to significant morbidity and mortality (Kreuziger 2015). Indeed, people with cancer with venous thromboembolism (VTE), compared with people with cancer without VTE, have a significantly reduced survival with an estimated mortality ratio of 2.2 (Sorensen 2000). In addition, people with cancer treated for VTE have higher thrombosis recurrence rates and more hemorrhagic complications compared with people without cancer treated for VTE (Hutten 2000; Prandoni 2002). For example, among people with venous thrombosis on anticoagulation, bleeding was related to cancer status and cancer severity but could not be explained by subtherapeutic or supratherapeutic levels of anticoagulation (Prandoni 2002).

Description of the intervention

Parenteral anticoagulants such as unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), and fondaparinux do not have intrinsic anticoagulant activity but potentiate the activity of antithrombin III in inhibiting activated coagulation factors. Heparin and its low-molecular-weight derivatives are not absorbed orally and must be administered parenterally by intravenous infusion or subcutaneous injections (Motlekar 2006).

Oral anticoagulants such as vitamin K antagonists (VKA) have been the mainstay of oral anticoagulant therapy since the 1950s. Well-designed clinical trials have shown their effectiveness for the primary and secondary prevention of several venous and arterial thrombotic diseases (Ansell 2008).

How the intervention might work

Researchers have hypothesized that, because of the risk of thromboembolic events related to a CVC, anticoagulants may improve outcomes by reducing the incidence of these events. Moreover, researchers have hypothesized that anticoagulants may improve outcomes in people with cancer through an antitumor effect in addition to its antithrombotic effect (Smorenburg 2001; Thodiyil 2002). In addition, anticoagulation has the potential to reduce infections by preventing thrombus formation, a suspected risk factor for catheter-related infection (Lordick 2003). However, anticoagulants increase the risk for bleeding. In fact, in people with venous thrombosis on anticoagulation the risk of bleeding was higher if people had cancer and correlated with the extent of cancer (Prandoni 2002). Heparins are also known to cause thrombocytopenia and heparin-induced thrombocytopenia (HIT) syndrome (Girolami 2006).

Why it is important to do this review

Several studies have evaluated the efficacy of thromboprophylaxis with anticoagulants in people with cancer with CVC. One 2003 systematic review of thrombosis prophylaxis in people with CVC identified two randomized controlled trials (RCTs) conducted in people with cancer (Klerk 2003). Our systematic review conducted in 2014 identified 12 trials reporting follow-up data on 2823 participants (Bern 1990; De Cicco 2009; Heaton 2002; Karthaus 2006; Lavau-Denes 2013; Massicotte 2003; Mismetti 2003; Monreal 1996; Niers 2007; Ruud 2006; Verso 2008; Young 2009). The included trials provided evidence of reduction in catheter-related thrombosis when comparing LMWH to no LMWH, of a decrease in asymptomatic catheter-related thrombosis when comparing VKA to no VKA, and an increase in thrombocytopenia when comparing LMWH to VKA. Since then, we are aware of two new reports of a previously included study addressing this question (Verso 2008).

OBJECTIVES

To evaluate the efficacy and safety of anticoagulation for thromboprophylaxis in people with cancer and a CVC.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People of any age with cancer and a CVC, with either solid or hematologic cancer, at any stage of their cancer, and irrespective of the type of cancer therapy received. Participants had to have no clinical evidence of VTE at enrolment.

Types of interventions

Intervention:

- parenteral anticoagulants (including UFH, LMWH, and fondaparinux) irrespective of the dose;
- VKA irrespective of the dose;
- direct oral anticoagulant (DOACs) irrespective of the dose.

Control:

- placebo or no intervention;
- any of the anticoagulants listed under intervention.

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

- Catheter-related thrombosis. The diagnosis of CVC thrombosis could have resulted either from screening with the described screening methods or from clinical suspicion with subsequent confirmation by one of the described tests.
- Non-catheter-related thrombosis. DVT events diagnosed using an objective diagnostic test such as: venography, ^{125}I-fibrinogen-uptake test, impedance plethysmography, or compression ultrasound.
- PE events diagnosed using an objective diagnostic test such as: pulmonary perfusion/ventilation scan, computed tomography, pulmonary angiography, or autopsy.
- Major bleeding: authors' definitions of major bleeding.
- Minor bleeding: authors' definitions of minor bleeding.
- Catheter-related infection: author's definition of catheter-related infection.
- Thrombocytopenia: authors' definitions of thrombocytopenia.
- Health-related quality of life (HRQoL): measured using a validated tool.
- Premature CVC removal.
- HIT.
- Heparin-induced thrombocytopenia with thrombosis (HITT).

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in people with cancer. We did not use language restrictions. We conducted comprehensive searches on 14 May 2018, following the original electronic searches in January 2007, February 2010, February 2013, and February 2016 (last major search). We electronically searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid; starting 1966), and Embase (Ovid; starting 1980). For each database, the search strategies combined terms for anticoagulants, terms for cancer, and a search filter for RCTs. We used no language restrictions. We list the full search strategies for each of the electronic databases in Appendix 1; Appendix 2; and Appendix 3.

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO, starting with its first volume, 1982 up to May 2018) and of the American Society of Hematology (ASH, starting with its 2003 issue up to May 2018). We also searched ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform for ongoing studies. We reviewed the reference lists of papers included in this review and of other relevant systematic reviews. We used the 'related citation' feature in PubMed to identify additional articles and 'citation tracking' of included studies in Web of Science Core Collection. In addition, we contacted experts in the field for information about unpublished and ongoing trials.

Data collection and analysis

Selection of studies

Two review authors independently screened the title and abstract of identified article citations for potential eligibility. We retrieved the full text of articles judged potentially eligible by at least one review author. Two review authors then independently screened the full-text article for eligibility using a standardized form with explicit inclusion and exclusion criteria (as detailed in the Criteria for considering studies for this review section) and resolved their disagreements by discussion or by consulting a third review author.

Data extraction and management

Two review authors independently extracted data from each included study and resolved any disagreements by discussion. We collected data related to the following.

Participants

- Number of participants randomized to each study arm.
- Number of participants followed up in each study arm.
- Number of participants who discontinued the intervention in each arm.
- Population characteristics (e.g. age, gender, co morbidities, co interventions).
- Type of cancer.
- Stage of cancer.
- Time since cancer diagnosis.
- CVC characteristics: type (e.g. port, external, tunneled versus non-tunneled, coated versus not coated), site (e.g. subclavian, internal jugular, external jugular, femoral), placement side, type of medication/fluids infused, specialty of physician placing the CVC (e.g. surgeon, radiologist, physician-in-training), aseptic insertion technique, and antibiotic coverage during placement.

Interventions

- Type of anticoagulant studied: LMWH, UFH, VKA, fondaparinux.
- Type and dosage of LMWH (therapeutic versus prophylactic). We classified the dosage of LMWH as either prophylactic or therapeutic using a standardized chart (Table 2).
- Dosage of UFH.
- Intensity of VKA therapy (international normalized ratio (INR) target or dose).
- Initiation of treatment relative to time of CVC insertion.
- Duration of treatment.
- Cointerventions including radiation therapy or systemic therapy (type and duration).
- Control: placebo or no intervention.

Outcomes

We attempted to extract both time-to-event data (for survival outcome) and categorical data (for all outcomes). However, none of the studies reported time-to-event data for participants with cancer.

For dichotomous data, we extracted data necessary to conduct complete-case analysis as the primary analysis. We aimed to abstract data for all-cause mortality at three and six months (time point defined a priori in the protocol).

We attempted to contact study authors for incompletely reported data. We decided a priori to consider abstracts in the main analysis only if authors supplied us with full reports of their methods and results; otherwise abstracts were included only in the sensitivity analysis.

Other

We extracted from each included trial any information on the following points.

- Source of funding.
- Ethical approval.
- Conflict of interest.

Assessment of risk of bias in included studies

We assessed risk of bias at the study level using Cochrane's 'Risk of bias' tool (Higgins 2011). Two review authors independently assessed the methodologic quality of each included study and resolved their disagreements by discussion. 'Risk of bias' criteria included the following:

- adequate sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- percentage of follow-up, and whether incomplete outcome data were addressed;
- whether the study was free of selective reporting;
- whether the study was stopped early for benefit.

See Dealing with missing data section for information on assessing risk of bias associated with participants with missing data per outcome and across studies.

Measures of treatment effect

We collected and analyzed risk ratios (RRs) with 95% confidence intervals (CI) for dichotomous data. None of the outcomes of interest was meta-analyzed as a continuous variable.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Determining participants with missing data

It was unclear whether certain participant categories (e.g. those described as 'withdrew consent' or 'experienced adverse events') were followed up by the trial authors (versus had missing participant data) (Akl 2016). To deal with this issue, we made the following considerations:

- 'ineligible participants' and 'did not receive the first dose' participant categories, which were defined prior to the initiation of the study intervention, most likely had missing participant data;
- 'withdrew consent,' 'lost to follow-up' (LTFU), and 'outcome not assessable' participant categories and any other category explicitly reported as not being followed up, which were defined after the initiation of the study intervention, most likely had missing participant data;
- 'dead,' 'experienced adverse events,' 'non-compliant,' and 'discontinued prematurely' (and similarly described) participant categories, less likely to have had missing participant data.

Dealing with participants with missing data in the primary meta-analysis

In the primary meta-analysis, we used a complete-case analysis approach, that is, we excluded participants considered to have missing data (Guyatt 2017).

For categorical data, we used the following calculations for each study arm:

- denominator: (number of participants randomized) – (number of participants most likely with missing data, both pre- and postintervention initiation);
- numerator: number of participants with observed events (i.e. participants who had at least one event for the outcome of interest during their available follow-up time).

For continuous data, we planned to use for each study arm, the reported mean and standard deviation (SD) for participants followed up by the trial authors.

Assessing the risk of bias associated with participants with missing data

When the primary meta-analysis of a specific outcome found a statistically significant effect, we conducted sensitivity meta-analyses to assess the risk of bias associated with missing participant data. Those sensitivity meta-analyses used a priori plausible assumptions about the outcomes of participants considered to have missing data. The assumptions we used in the sensitivity meta-analyses were increasingly stringent to challenge the statistical significance of the results of the primary analysis progressively (Akl 2013; Ebrahim 2013).

For categorical data, and for RR showing a reduction in effect (RR less than 1), we used the following increasingly stringent but plausible assumptions (Akl 2013).

- For the control arm, relative incidence (RI) among participants with missing data (LTFU) compared to participants with available data (followed up, FU) in the same arm ($RI_{LTFU/FU}$) = 1; for the intervention arm, $RI_{LTFU/FU}$ = 1.5.
- For the control arm, $RI_{LTFU/FU}$ = 1; for the intervention arm, $RI_{LTFU/FU}$ = 2.
- For the control arm, $RI_{LTFU/FU}$ = 1; for the intervention arm, $RI_{LTFU/FU}$ = 3.
- For the control arm, $RI_{LTFU/FU}$ = 1; for the intervention arm, $RI_{LTFU/FU}$ = 5.

For RR showing an increase in effect (RR greater than 1), we switched the above assumptions between the control and interventions arms (i.e. used $RI_{LTFU/FU}$ = 1 for the intervention arm).

Specifically, we used the following calculations for each study arm:

- denominator: (number of participants randomized) – (number of participants most likely with missing data, pre intervention initiation);
- numerator: (number of participants with observed events) + (number of participants most likely with missing data postintervention initiation, with assumed events).

Assumed events were calculated by applying the a priori plausible assumptions to the participants considered most likely with missing data postintervention initiation.

For continuous data, we planned to use the four strategies suggested by Ebrahim and colleagues (Ebrahim 2013). The strategies imputed the means for participants with missing data based on the means of participants followed up in individual trials included in the systematic review. To impute SD, we used the median SD from the control arms of all included trials (Ebrahim 2013).

Assessment of heterogeneity

We assessed heterogeneity between trials by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (I^2 test; Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we attempted to investigate the possible reasons for this (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We assessed selective outcome reporting bias by trying to identify whether the study was included in a trial registry, whether a protocol was available, and whether the methods section provided a list of outcomes. We compared the list of outcomes from those sources to the outcomes reported in the published paper. We planned to create funnel plots for outcomes including 10 or more trials.

Data synthesis

For dichotomous data, we calculated the RR separately for each study (DerSimonian 1986; RevMan 2014). When analyzing data related to participants who were reported as not compliant, we attempted to adhere to the principles of intention-to-treat (ITT) analysis. We approached the issue of non-compliance independently from that of missing data (Alshurafa 2012). We then pooled the results of the different studies using a random-effects model. We assessed the certainty of evidence at the outcome level using the GRADE approach (Balshem 2011).

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses based on characteristics of participants but did not conduct them as the data were not available.

Sensitivity analysis

We planned for sensitivity meta-analyses to assess the risk of bias associated with missing participant data when the primary meta-analysis of a specific outcome found a statistically significant effect.

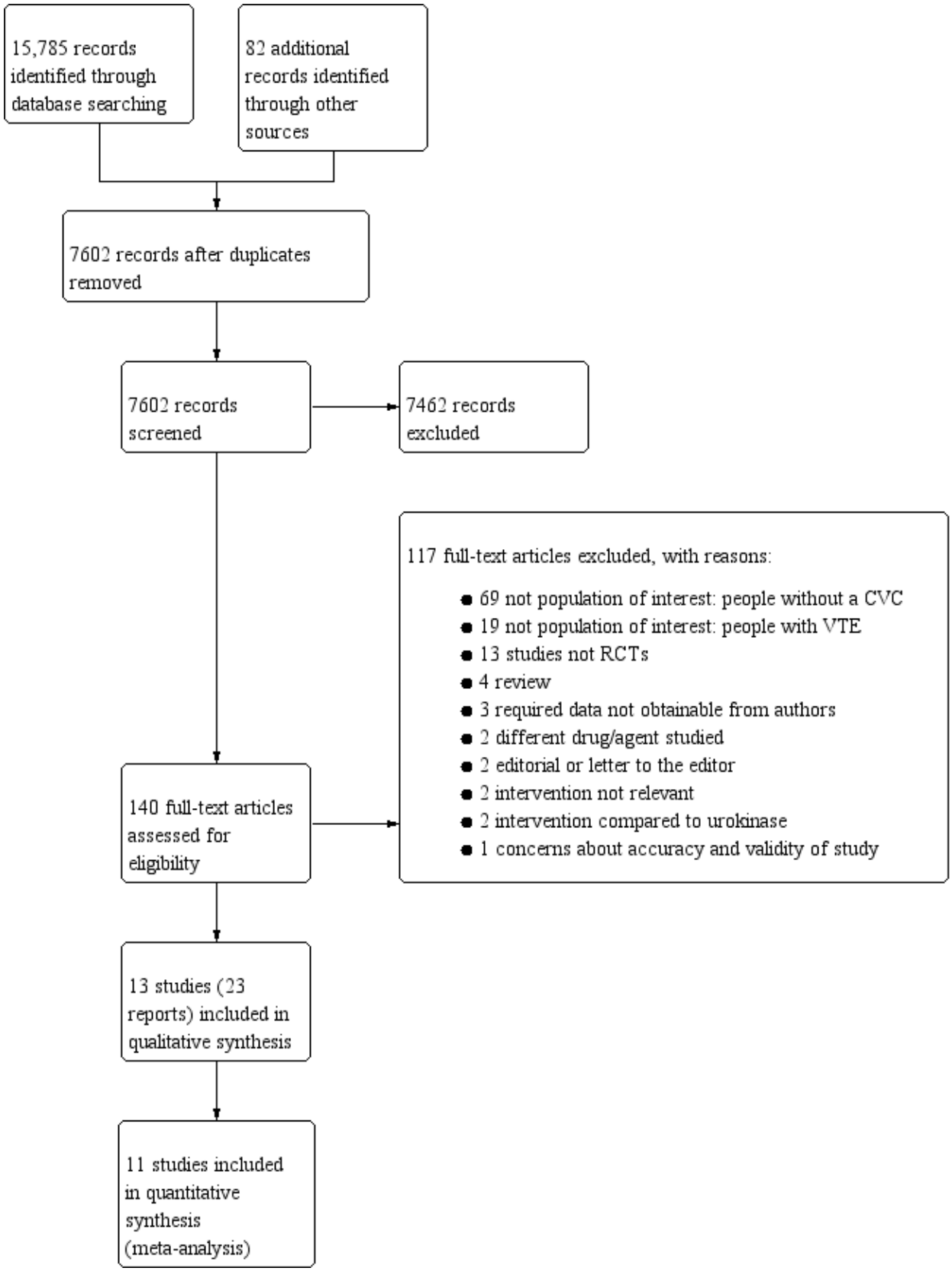
RESULTS

Description of studies

Results of the search

Figure 1 shows the study flow diagram. As of May 2018, the search strategy identified 7602 unique citations after removal of duplicates. The title and abstract screening identified 140 potentially eligible citations. The full-text screening identified 13 eligible RCTs published as full reports (Bern 1990; Couban 2005; De Cicco 2009; Heaton 2002; Karthaus 2006; Lavau-Denes 2013; Massicotte 2003; Mismetti 2003; Monreal 1996; Niers 2007; Ruud 2006; Verso 2008; Young 2009). In the previous version of this review, we excluded the study by Couban and colleagues due to different follow-up times between the study arms (Couban 2005). For the current update, we update to include it in the systematic review but not in the meta-analysis. The February 2016 search identified two new reports for each of two previously included trials (Couban 2005; Verso 2008).

Figure 1. Study flow diagram.



Agreement between review authors for study eligibility was excellent (kappa = 0.94).

Included studies

The 13 included RCTs enrolled 3420 participants. They examined either prophylactic-dose heparin (UFH or LMWH) or low-dose VKA (either fixed low dose or target INR less than 2). Two of the RCTs conducted a three-way comparison (LMWH versus VKA versus no anticoagulation) (De Cicco 2009; Lavau-Denes 2013). Most studies administered treatments for the specified fixed period or until CVC removal or thrombosis diagnosis. The studies varied in the thromboembolic outcomes they assessed (e.g. whether thrombosis was symptomatic or not, at the site of the catheter or not, CVC-related or not) and the definitions of CVC-related infection. The study by Couban and colleagues followed up participants for three months after catheter removal (which was different for the two study groups) and was not included in the meta-analysis due to a differential follow-up relative to randomization (63 days for the warfarin group and 84 days for the placebo group) (Couban 2005). This study was excluded from the previous version of this review (Akl 2014), but we decided to include it in the current version, only in the narrative section without including it in the meta-analysis.

Bern 1990 recruited 121 adults with solid or hematologic cancer and CVC with a minimum life expectancy of three months. Participants were randomized to receive warfarin (1 mg/day for 90 days starting three days prior to catheter placement) or no intervention. Surgeons placed subclavian ports with no antibiotic prophylaxis and flushed with heparin. Assessed outcomes were CVC-associated thrombosis and death. Participants were followed up for three months. The authors reported 96% follow-up.

Couban 2005 recruited 255 participants with cancer and CVC. Participants were randomized to receive fixed-dose warfarin 1 mg daily or placebo until the study endpoint or CVC removal. Assessed outcomes were CVC-related thrombosis, bleeding, or death. Participants were followed up for three months after removal of CVC or until reaching a study endpoint. The study authors reported complete follow-up.

De Cicco 2009 recruited 450 participants with cancer and CVC aged at least 18 years, and a minimum life expectancy of three months. Participants were randomized to receive acenocumarine (1 mg/day for three days before and eight days after CVC insertion) or dalteparin (two hours before and daily for eight days after CVC insertion) or no anticoagulation. Assessed outcomes were death, CVC-related thrombosis, major bleeding, and minor bleeding. Participants were followed up for three months. The study authors reported 78% follow-up.

Heaton 2002 recruited 88 hematologic participants with cancer and one or more CVCs. Participants were randomized to receive warfarin (1 mg/day for 90 days) or no intervention. Radiologists placed external, tunneled subclavian catheters with no antibiotic prophylaxis and flushed with heparin or saline. Seventy-seven participants had one catheter, eight had two catheters, and three had three catheters. Assessed outcomes were CVC-related thrombosis, CVC-related infection, and premature removal of CVC. Participants were followed up for 90 days. The study authors report complete follow-up.

Karthaus 2006 recruited 425 participants with solid or hematologic cancers and CVC aged at least 18 and a minimum life expectancy of 16 weeks. Participants were randomized to dalteparin (prophylactic dose for 16 weeks starting seven days prior to catheter placement) or placebo. Participants had mostly ports that were placed either proximal or distal to the axilla and flushed with normal saline or heparin. Assessed outcomes were catheter-associated thrombosis and death. Participants were followed up for 16 weeks. The study authors reported 91% follow-up.

Lavau-Denes 2013 recruited 420 participants with solid invasive cancer, locally advanced or metastatic, and a minimum life expectancy of three months. Participants were randomized to LMWH (dalteparin, nadroparin, or enoxaparin) once daily, or warfarin (1 mg/day), or no anticoagulation. Participants had a subclavian CVC inserted for fewer than seven days. Assessed outcomes were catheter-associated thrombosis and death. Participants were followed up for 90 days. The study authors reported 97% follow-up.

Massicotte 2003 recruited 94 participants with cancer and a CVC, aged 0 to 18 years. Overall, the study recruited 186 participants. Participants were randomized to twice daily reviparin sodium or no treatment. Assessed outcomes were death, CVC-related thrombosis, and bleeding. Participants were followed up for 30 days. The study authors reported complete follow-up.

Mismetti 2003 recruited 59 participants with solid cancer and CVC aged at least 18 years, and a minimum life expectancy of three months. Participants were randomized to nadroparin (prophylactic dose for 90 days started two hours prior to CVC placement) or warfarin (1 mg/day for 90 days started three days prior to CVC placement) or no treatment. Assessed outcomes were upper extremity thrombosis, bleeding, and death. Participants were followed up for six months. The study authors reported 98% follow-up.

Monreal 1996 recruited 32 participants with solid tumors and a minimum life expectancy of three months. Participants were randomized to dalteparin (prophylactic dose for 90 days starting two hours prior to catheter placement) or no intervention. Surgeons placed subclavian ports with no antibiotic prophylaxis and flushed with heparin (Monreal 1996). Assessed outcomes were catheter-related DVT, death, and thrombocytopenia. Participants were followed up for 90 days. Study was stopped early for benefit. The study authors reported complete follow-up.

Niers 2007 recruited 113 participants with hematologic malignancies aged at least 18 years. Participants were randomized to daily prophylactic-dose nadroparin or placebo injections. The study medication was started two hours before insertion of the CVC, and was continued for three weeks or until the day of CVC removal, whichever came first. The CVC was inserted according to a standard protocol under sterile conditions (Niers 2007). Assessed outcomes were catheter-related thrombosis, bleeding, and infection. Participants were followed up for 21 days. The authors reported 77% follow-up.

Ruud 2006 recruited 73 children with solid or hematologic cancers and CVC with mean age of 6.8 years (Ruud 2006). Participants were randomized to receive warfarin starting from the day of CVC insertion (target INR 1.3 to 1.9) or no intervention. Participants had jugular external tunneled catheters or ports. Assessed outcomes

were VTE, bleeding, infection, and removal of CVC. Participants were followed up for six months (Ruud 2006). The authors reported 84% follow-up.

Verso 2008 recruited 385 participants with solid or hematologic cancers aged at least 18 years and a minimum life expectancy of three months (Verso 2008). Participants were randomized to enoxaparin (prophylactic dose for six weeks starting two hours prior to catheter placement) or placebo. Participants had either jugular or subclavian second-generation catheters. Assessed outcomes were CVC-related thrombosis, bleeding, and death. Participants were followed up for three months. The authors reported 81% follow-up.

Young 2009 randomized 812 participants with solid or hematologic cancers aged at least 16 years who were receiving chemotherapy through CVC to no warfarin, fixed-dose warfarin (1 mg/day), or dose-adjusted warfarin to maintain INR between 1.5 and 2.0 (Young 2009). The study pooled data from fixed-dose VKA and adjusted dose VKA arms. Assessed outcomes were catheter-related thrombosis, bleeding, and death. Participants were followed up for a median of 45 months (range 26 to 88 months). Study authors reported 99% follow-up.

Excluded studies

We excluded 117 studies from the review for the following reasons: not population of interest: people without a CVC (69 studies), people with VTE (19 studies); not design of interest: not an RCT (13 studies), review (four studies), editorial or letter to the editor (two studies), not intervention of interest: intervention used was not relevant (four studies), intervention was compared with urokinase (two studies), required data not obtainable from authors (three studies), concerns about accuracy and validity of study (one study) (see Characteristics of excluded studies table).

Risk of bias in included studies

The judgments for the risk of bias are summarized in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

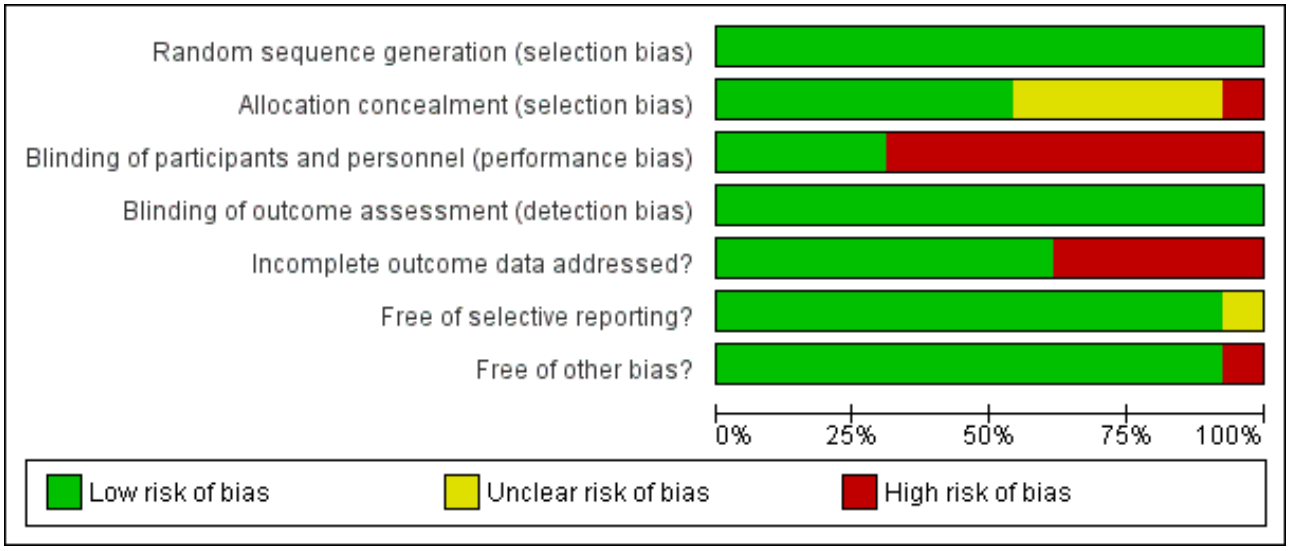
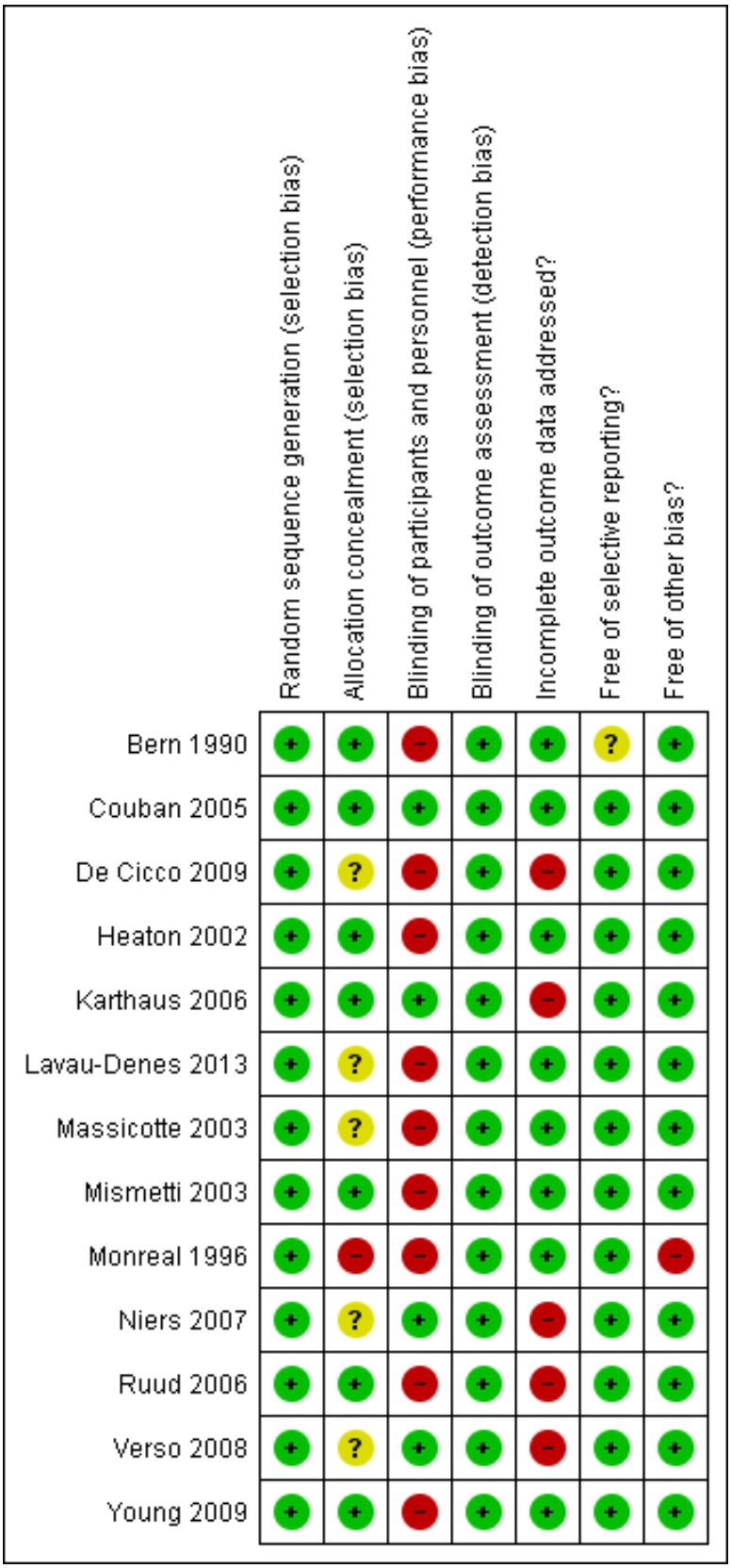


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

The method of sequence generation was clear for all studies (low risk of bias).

Allocation was adequately concealed in seven studies (low risk of bias; Bern 1990; Couban 2005; Heaton 2002; Karthaus 2006; Mismetti 2003; Ruud 2006; Young 2009), allocation concealment was not reported in five studies (unclear risk of bias; De Cicco 2009; Lavau-Denes 2013; Massicotte 2003; Niers 2007; Verso 2008), and allocation was not concealed in one study (high risk of bias; Monreal 1996).

Blinding

Blinding of participants and personnel (performance bias)

We judged participants and personnel to be definitely blinded in four studies (low risk of bias; Couban 2005; Karthaus 2006; Niers 2007; Verso 2008), and definitely not blinded in nine studies (high risk of bias; Bern 1990; De Cicco 2009; Heaton 2002; Lavau-Denes 2013; Massicotte 2003; Mismetti 2003; Monreal 1996; Ruud 2006; Young 2009).

Blinding of outcome assessment (detection bias)

We judged outcome assessors to be definitely blinded in 11 studies (low risk of bias; Bern 1990; Couban 2005; De Cicco 2009; Karthaus 2006; Massicotte 2003; Mismetti 2003; Monreal 1996; Niers 2007; Ruud 2006; Verso 2008; Young 2009), and probably not blinded in two studies (Heaton 2002; Lavau-Denes 2013).

Incomplete outcome data

Four studies reported complete follow-up (low risk of bias; Couban 2005; Heaton 2002; Massicotte 2003; Monreal 1996).

Bern 1990 reported 96% overall follow-up, Lavau-Denes 2013 reported 97% follow-up, Mismetti 2003 reported 98% follow-up, and Young 2009 reported 99% follow-up (all low risk of bias).

De Cicco 2009 reported 78% overall follow-up, Karthaus 2006 reported 91% follow-up, Niers 2007 reported 77% follow-up, Ruud 2006 reported 84% follow-up, and Verso 2008 reported 81% follow-up (all high risk of bias).

Selective reporting

Only two studies were registered and all outcomes listed in the registry were reported (Lavau-Denes 2013; Young 2009). None of the other studies had a published protocol. All studies reported on the outcomes listed in their methods section except Bern 1990, who did not provide a list of outcomes in the methods section.

Other potential sources of bias

Two studies were stopped early: one for insufficient accrual (Massicotte 2003), and one for benefit (Monreal 1996). Nine studies used the ITT principle (Couban 2005; De Cicco 2009; Heaton 2002; Karthaus 2006; Lavau-Denes 2013; Massicotte 2003; Mismetti 2003; Verso 2008; Young 2009), two studies were unclear about the use of the ITT principle (Bern 1990; Niers 2007), and two studies did not use the ITT principle (Monreal 1996; Ruud 2006).

The study by Young and colleagues pooled data from the fixed-dose VKA and adjusted-dose VKA arms (Young 2009).

Effects of interventions

See: **Summary of findings for the main comparison** Low-molecular-weight heparin (LMWH) compared to no LMWH for people with cancer and central venous catheters; **Summary of findings 2** Vitamin K antagonist (VKA) compared to no VKA for people with cancer and central venous catheters; **Summary of findings 3** Low-molecular-weight heparin (LMWH) compared to vitamin K antagonist (VKA) for people with cancer and central venous catheters

Low-molecular-weight heparin versus no low-molecular-weight heparin

We did not include the study by Massicotte and colleagues with the trials in the same meta-analysis given it focused on children (Massicotte 2003), so we report its results here separately. The trial did not confirm or exclude a beneficial or detrimental effect of LMWH compared with no intervention on VTE (odds ratio (OR) 1.15, 95% CI 0.42 to 3.23) or infection (OR 0.59, 95% CI 0.32 to 1.10). The paper reported no statistically significant differences between groups in incidences of minor bleeding (48/90 with heparin versus 41/94 with no heparin; P = 0.24), major bleeding (0/90 with heparin versus 1/94 with no heparin; P = 1.0), and mortality (0/92 with heparin versus 2/94 with no heparin; P = 1.0).

We present below the meta-analysis of the remaining five studies that were conducted in adults.

All-cause mortality

Meta-analysis of the five RCTs including 1236 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on mortality at three months compared to no LMWH (RR 0.82, 95% CI 0.53 to 1.26; RD 14 fewer per 1000, 95% CI 36 fewer to 20 more; Analysis 1.1) (De Cicco 2009; Karthaus 2006; Lavau-Denes 2013; Monreal 1996; Verso 2008). There was no heterogeneity (I^2 = 0%). We did not create funnel plots due to the low number of included trials for the outcome of mortality. The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings for the main comparison).

Symptomatic catheter-related thrombosis

Meta-analysis of five RCTs including 1089 participants showed that LMWH probably decreased the risk of symptomatic catheter-related thrombosis compared to no LMWH (RR 0.43, 95% CI 0.22 to 0.81; RD 38 fewer per 1000, 95% CI 52 fewer to 13 fewer; moderate-certainty evidence; Analysis 1.2) (Karthaus 2006; Lavau-Denes 2013; Monreal 1996; Niers 2007; Verso 2008). There was low heterogeneity (I^2 = 2%). Data from De Cicco 2009 was not included because the study authors did not specify the number of symptomatic versus non-symptomatic events. Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing participant data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the Methods section. The effect estimate remained statistically significant for at least four stringent plausible assumptions. However, it lost significance with the most stringent plausible assumptions (see Appendix 7). The certainty of evidence was moderate due to serious risk of bias (Summary of findings for the main comparison).

Meta-analysis of five RCTs including 1089 participants did not show or exclude a beneficial or detrimental effect of LMWH on asymptomatic catheter-related thrombosis (RR 0.95, 95% CI 0.62 to 1.46; RD 5 fewer per 1000, 95% CI 36 fewer to 44 more; very low-certainty evidence) (Karthaus 2006; Lavau-Denes 2013; Monreal 1996; Niers 2007; Verso 2008). There was low heterogeneity (I^2 = 9%).

Pulmonary embolism

None of the studies reported PE.

Major bleeding

Meta-analysis of four RCTs including 1018 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on major bleeding compared to no LMWH (RR 1.49, 95% CI 0.06 to 36.28; RD 0 fewer per 1000, 95% CI 1 fewer to 35 more; Analysis 1.4) (De Cicco 2009; Karthaus 2006; Niers 2007; Verso 2008). There was no heterogeneity (I^2 = 0%). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings for the main comparison).

Minor bleeding

Meta-analysis of two RCTs including 544 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on minor bleeding compared to no LMWH (RR 1.35, 95% CI 0.62 to 2.92; RD 14 more per 1000, 95% CI 16 fewer to 79 more; Analysis 1.5) (De Cicco 2009; Verso 2008). There was no heterogeneity (I^2 = 0%). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings for the main comparison).

Catheter-related infection

Meta-analysis of two RCTs including 474 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on catheter-related infection compared to no LMWH (RR 0.97, 95% CI 0.52 to 1.79; RD 3 fewer per 1000, 95% CI 44 fewer to 73 more; Analysis 1.6) (Karthaus 2006; Niers 2007). There was no heterogeneity (I^2 = 0%). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings for the main comparison).

Thrombocytopenia

Meta-analysis of four RCTs including 1002 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on thrombocytopenia compared to no LMWH (RR 1.03, 95% CI 0.80 to 1.33; RD 5 more per 1000, 95% CI 35 fewer to 58 more; Analysis 1.7) (Karthaus 2006; Lavau-Denes 2013; Monreal 1996; Verso 2008). There was no heterogeneity (I^2 = 0%). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings for the main comparison).

Health-related quality of life

None of the included studies assessed HRQoL.

Premature central venous catheter removal

None of the included studies assessed premature CVC removal.

Heparin-induced thrombocytopenia

None of the included studies assessed HIT.

Heparin-induced thrombocytopenia with thrombosis

None of the included studies assessed HITT.

Low-dose vitamin K antagonist versus no vitamin K antagonist

We did not include the study by Ruud and colleagues with the trials in the same meta-analysis given its focus on children (Ruud 2006), so we report its results here separately. The study was stopped early because of a higher incidence of ultrasound-detected VTE in the warfarin group (15/31 with warfarin versus 17/42 with no warfarin; P = 0.36). There was only one symptomatic VTE event in each group.

We present below the meta-analysis of the remaining five studies that were conducted in adults.

All-cause mortality

Meta-analysis of the four RCTs including 701 participants did not confirm or exclude a beneficial or detrimental effect of low-dose VKA on mortality at three months compared to no VKA (RR 0.99, 95% CI 0.64 to 1.55; RD 1 fewer per 1000, 95% CI 34 fewer to 52 more; Analysis 2.1) (Bern 1990; De Cicco 2009; Heaton 2002; Lavau-Denes 2013). There was no heterogeneity (I^2 = 0%). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings 2).

Symptomatic catheter-related thrombosis

Meta-analysis of the four RCTs including 1271 participants did not include or exclude a beneficial or detrimental effect of low-dose VKA on symptomatic catheter-related thrombosis compared to no VKA (RR 0.61, 95% CI 0.23 to 1.64; RD 31 fewer per 1000, 95% CI 62 fewer to 51 more; Analysis 2.2) (Bern 1990; Heaton 2002; Lavau-Denes 2013; Young 2009). There was moderate heterogeneity (I^2 = 70%). The certainty of evidence was low due to serious risk of bias and serious heterogeneity (Summary of findings 2).

Meta-analysis of two studies including 384 participants did not confirm or exclude a beneficial or detrimental effect of low-dose VKA on asymptomatic catheter-related thrombosis compared to no VKA (RR 0.61, 95% CI 0.27 to 1.40; RD 29 fewer per 1000, 95% CI 54 fewer to 29 more) (Bern 1990; Lavau-Denes 2013). There was no heterogeneity (I^2 = 0%). The certainty of evidence was very low due to serious risk of bias, serious imprecision, and serious indirectness (Summary of findings 2).

Pulmonary embolism

None of the studies reported PE.

Major bleeding

One of the two studies assessing major bleeding reported no events (De Cicco 2009). The other study including 751 participants did not show or exclude a beneficial or detrimental effect of low-dose VKA on major bleeding compared to no VKA (RR 7.14, 95% CI 0.88 to 57.78; RD 12 more per 1000, 95% CI 0 fewer to 110 more; Analysis 2.4) (Young 2009). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings 2).

Minor bleeding

Two studies assessing minor bleeding including 1026 participants did not confirm or exclude a beneficial or detrimental effect of low-dose VKA on minor bleeding compared to no VKA (RR 0.69,

95% CI 0.38 to 1.26; RD 15 fewer per 1000, 95% CI 30 fewer to 13 more; Analysis 2.5) (De Cicco 2009; Young 2009). There was no heterogeneity (I^2 = 0%). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings 2).

Catheter-related infection

One study including 88 participants did not confirm or exclude a beneficial or detrimental effect of low-dose VKA on catheter-related infection compared to no VKA (RR 1.17, 95% CI 0.74 to 1.85; RD 71 more per 1000, 95% CI 109 fewer to 356 more) (Heaton 2002). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings 2).

Thrombocytopenia

None of the included studies assessed thrombocytopenia.

Health-related quality of life

None of the included studies assessed HRQoL.

Premature central venous catheter removal

One study did not confirm or exclude a beneficial or detrimental effect of low-dose VKA on premature CVC removal compared to no VKA (RR 0.82, 95% CI 0.30 to 2.24; RD 29 fewer per 1000, 95% CI 114 fewer to 202 more) (Heaton 2002). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings 2).

Heparin-induced thrombocytopenia

None of the included studies assessed HIT.

Heparin-induced thrombocytopenia with thrombosis

None of the included studies assessed HITT.

Low-molecular-weight heparin versus low-dose vitamin K antagonist

All-cause mortality

Meta-analysis of three RCTs including 561 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on mortality compared to VKA (RR 0.94, 95% CI 0.56 to 1.59; RD 6 fewer per 1000, 95% CI 41 fewer to 56 more; Analysis 3.1) (De Cicco 2009; Lavau-Denes 2013; Mismetti 2003). There was no heterogeneity (I^2 = 0%). The certainty of evidence was low due to serious risk of bias and serious imprecision (Summary of findings 3).

Symptomatic catheter-related thrombosis

Meta-analysis of two RCTs including 327 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on symptomatic catheter-related thrombosis compared to VKA (RR 1.83, 95% CI 0.44 to 7.61; RD 15 more per 1000, 95% CI 10 fewer to 122 more; Analysis 3.2) (Lavau-Denes 2013; Mismetti 2003). There was no heterogeneity (I^2 = 0%). The certainty of evidence was very low due to serious risk of bias and very serious imprecision (Summary of findings 3).

Meta-analysis of two RCTs including 327 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on asymptomatic catheter-related thrombosis compared to VKA (RR 1.61, 95% CI 0.75 to 3.46; RD 39 more per 1000, 95% CI 16 fewer to 156 more) (Bern 1990; Lavau-Denes 2013). There was no heterogeneity (I^2 = 0%). The certainty of evidence was very low due to serious risk of bias, serious imprecision, and serious indirectness (Summary of findings 3).

Pulmonary embolism

Two studies including 327 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on the risk of PE compared to VKA (RR 1.70, 95% CI 0.74 to 3.92; RD 35 more per 1000, 95% CI 13 fewer to 144 more; Analysis 3.4) (Lavau-Denes 2013; Mismetti 2003). The certainty of evidence was low due to serious risk of bias and serious imprecision.

Major bleeding

One of two studies assessing major bleeding reported no events (De Cicco 2009). The other study including 60 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on major bleeding compared to VKA (RR 3.11, 95% CI 0.13 to 73.11; RD 2 more per 1000, 95% CI 1 fewer to 72 more; Analysis 3.5) (Mismetti 2003). The certainty of evidence was very low due to serious risk of bias and very serious imprecision (Summary of findings 3).

Minor bleeding

One study including 234 participants did not confirm or exclude a beneficial or detrimental effect of LMWH on minor bleeding compared to VKA (RR 0.95, 95% CI 0.20 to 4.61; RD 1 fewer per 1000, 95% CI 21 fewer to 95 more; Analysis 3.6) (De Cicco 2009). The certainty of evidence was very low due to serious risk of bias and very serious imprecision (Summary of findings 3).

Catheter-related infection

None of the included studies assessed catheter-related infection.

Thrombocytopenia

Lavau-Denes and colleagues included all grades of thrombocytopenia in their study (including mild cases). Meta-analysis of two RCTs including 327 participants showed that LMWH increased thrombocytopenia compared to VKA at three months of follow-up (RR 1.69, 95% CI 1.20 to 2.39; RD 149 more per 1000, 95% CI 43 fewer to 300 more; moderate-certainty evidence; Analysis 3.7) (Lavau-Denes 2013; Mismetti 2003). There was no heterogeneity (I^2 = 0%). Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing participant data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the Methods section. The effect estimate remained statistically significant for the all plausible assumptions. The certainty of evidence was moderate due to serious risk of bias (Summary of findings 3).

Health-related quality of life

None of the included studies assessed HRQoL.

Premature central venous catheter removal

None of the included studies assessed premature CVC removal.

Heparin-induced thrombocytopenia

None of the included studies assessed HIT.

Heparin-induced thrombocytopenia with thrombosis

None of the included studies assessed HITT.

DISCUSSION

Summary of main results

The evidence was not conclusive for the effect of LMWH compared to no LMWH on mortality, the effect of VKA compared to no VKA on mortality and catheter-related thrombosis, and the effect of LMWH compared to VKA on mortality and catheter-related thrombosis. We found moderate-certainty evidence that LMWH reduced catheter-related thrombosis compared to no LMWH. In considering anticoagulation, people with cancer with CVCs should balance the possible benefit of reduced thromboembolic complications with the possible harms and burden of anticoagulants.

We noted an interesting decrease in the baseline risk of symptomatic DVT by year of publication. This decline could reflect technologic advances in CVC materials and designs, better CVC management strategies (e.g. shorter insertion times), and advances in clinical care in general (e.g. early mobilization of participants). There was also a progressive decrease in the effect size of anticoagulation on thrombosis in people with cancer with CVC by year of publication, particularly in studies testing heparin therapy. A similar decrease in effect size of specific interventions has been shown in studies of mental health as more data have become available (Trikalinos 2004). The smaller size of earlier studies (Bern 1990: 121 participants; Monreal 1996: 32 participants) provides a possible explanation for this phenomenon in our review, as small trials have been shown to exaggerate intervention effects compared with larger trials (Kjaergard 2001). Another potentially contributing explanation is the early stopping of the study by Monreal and colleagues for benefit (Monreal 1996); Montori have shown that RCTs stopped early for benefit show implausibly large treatment effects (Montori 2005).

Overall completeness and applicability of evidence

The included studies recruited participants with a variety of cancer types and stages, which should increase the applicability of the results. The results apply best to LMWH given that only one study evaluated UFH. Unfortunately, we found no data to evaluate the impact of the intervention on HRQoL. This outcome is important given the potential burden of both oral and subcutaneous anticoagulants.

Quality of the evidence

When comparing LMWH to no LMWH, we judged the certainty of evidence to be moderate for symptomatic catheter-related thrombosis due to serious risk of bias; low for mortality, minor bleeding, and catheter-related infection due to serious risk of bias and serious imprecision; very low for asymptomatic catheter-related thrombosis due to serious risk of bias, serious indirectness, and serious imprecision; and very low for major bleeding due to serious risk of bias and very serious imprecision.

When comparing VKA to no VKA, we judged the certainty of evidence to be low for mortality, major bleeding, minor bleeding, premature catheter removal, and catheter-related infection due to serious risk of bias and serious imprecision, low for symptomatic catheter-related thrombosis due to serious risk of bias and serious indirectness, very low for asymptomatic catheter-related thrombosis due to serious risk of bias, serious indirectness, and serious imprecision; and

When comparing LMWH to VKA, we judged the certainty of evidence to be moderate for thrombocytopenia due to serious risk of bias; low for mortality and PE due to serious risk of bias and serious imprecision; very low for symptomatic catheter-related thrombosis, major bleeding, and minor bleeding due to serious risk of bias and very serious imprecision; very low for asymptomatic catheter-related thrombosis due to serious risk of bias, serious indirectness, and serious imprecision.

Potential biases in the review process

Our systematic approach to searching, study selection, and data extraction should have minimized the likelihood of missing relevant studies or relevant data.

Additional strengths of the review include the high agreement between review authors and the low likelihood of publication bias. One limitation of this review is that the 'no difference' findings may be related to the relatively small number of RCTs, small number of participants and events, and the absence of a true effect. Another limitation related to the small number of RCTs was our inability to conduct subgroup analyses exploring the impact on the treatment effect of the characteristics of participants (adult versus children, solid versus hematologic cancer, type of catheter), outcomes (symptomatic versus screening-detected DVT, early versus late DVTs), and methodologic quality criteria (allocation concealment and blinding).

Agreements and disagreements with other studies or reviews

Chaukiyal and colleagues conducted a systematic review to assess primary thromboprophylaxis in people with cancer with CVCs, and included eight RCTs with 1428 participants (Chaukiyal 2008). While we included six of these trials. We excluded Couban and colleagues because of unequal follow-up of the two study groups (Couban 2005). We excluded Abdelkefi and colleagues because the publishing journal published an "Expression of Concern," reportedly, concerns about the accuracy and validity of the trial findings were raised by readers, and when asked by the editors "to provide evidence that the study was conducted, the authors were unable to provide this evidence" (Abdelkefi 2004). Chaukiyal and colleagues found no statistically significant difference in catheter-related thrombosis for the use of warfarin versus placebo; heparin versus placebo; or warfarin, UFH, or LMWH versus placebo. Moreover, the results did not confirm a detrimental effect of thromboprophylaxis on the risk of overall bleeding and thrombocytopenia.

A more recently published systematic review focused on children with cancer with CVC (Schoot 2013). The authors could not confirm or exclude any effect of preventive systemic treatments (including LMWH, antithrombin supplementation, low-dose warfarin, and cryoprecipitate/fresh frozen plasma) compared with no intervention on VTE (symptomatic and asymptomatic), major bleeding, or minor bleeding.

AUTHORS' CONCLUSIONS

Implications for practice

People with cancer with central venous catheters (CVCs) considering anticoagulation should balance the possible benefit of reduced incidence of thromboembolic complications with the harms and burden of taking anticoagulants. People may opt against prophylactic anticoagulation because they are bleeding averse, because anticoagulants (e.g. daily subcutaneous injections) would be a burden for them, or they are uncomfortable with the uncertainty of benefit. Other people may opt for prophylactic anticoagulation because they have low aversion to bleeding, because they do not consider anticoagulation as a burden, and they have a high preference for avoidance of thrombosis (and the associated increased risk of a pulmonary embolism, premature CVC removal, and the need to start a relatively long therapeutic anticoagulation).

Implications for research

More data from randomized controlled trials (RCT) are needed to answer the question about the role of anticoagulants for thromboprophylaxis in people with cancer and CVC confidently. Studies should adhere to high methodologic quality and be adequately powered to assess participant-important outcomes such as mortality, premature CVC removal, symptomatic thrombosis, and bleeding. Studies should also aim to use standardized definitions for major and minor bleeding and for catheter-related infections. Research should demonstrate a definite benefit of anticoagulation before conducting additional studies comparing the effects of different anticoagulants. Researchers should consider making the raw data of RCTs available for individual participant data meta-analysis. In addition, as recognized by Cochrane, addressing all important outcomes including harm is of great importance in making evidence-based healthcare decisions.

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For our update of these reviews, we followed Cochrane methods using the same eligibility criteria and outcomes used previously. The ASH guidelines group used slightly different methods that generated slightly different results. For example, the ASH guideline panel agreed to prioritize different outcomes; include unpublished data; include abstracts; use different definitions for duration of treatment; and rate certainty of evidence slightly differently for some outcomes, for instance because of imprecision or indirectness. These differences are not described in this publication. Instead, they will be described in the ASH guideline publication.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bern 1990

Methods	Randomized controlled trial
Participants	121 participants with solid or hematologic (or both) cancers Mean age: 56 years for warfarin; 60.6 years for no warfarin Minimum life expectancy: 3 months
Interventions	Intervention: warfarin 1 mg/day; 3 days prior to CVC placement and continued for 90 days Control: no intervention
Outcomes	Follow-up: 90 days • Mortality • Asymptomatic CRT • Symptomatic CRT **Screening test for CRT:** venography **Diagnostic test for CRT:** venography
Notes	• CVC characteristics: port; subclavian; placed by surgeons; flushed with heparin; no antibiotic prophylaxis • Ethical approval: not mentioned • Conflict of interest: not mentioned • Funding: Pharmacia-NuTech, Inc. and E.I. DuPont • ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Assignment to receive or not receive the drug was made according to a previously established yes or no code."
Allocation concealment (selection bias)	Low risk	Communication with author: "yes or no code held in sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The radiologists who interpreted the venograms were blinded to the patients' randomization status."

Bern 1990 *(Continued)*

		Comment: definitely blinded
Incomplete outcome data addressed?	Low risk	Comment: judgment based on comparison between MPD rate (VKA: 0%; no VKA: 5/61 = 8.2%) and event rate (mortality: VKA: 12/60 = 20%; no VKA: 14/56 = 25%)
Free of selective reporting?	Unclear risk	Study not registered. No published protocol. No complete list of outcomes provided in the methods section. Deaths mentioned to be equal between the 2 groups but not reported numerically.
Free of other bias?	Low risk	Study not stopped early for benefit

Couban 2005

Methods	Randomized double-blind placebo-controlled study
Participants	255 participants from 3 centers with biopsy-confirmed cancer and with an indwelling CVC for ≥ 7 days. 152 men and 103 women, median age 52 years 166 participants had solid tumors and 89 participants had leukemia or the CVC was inserted prior to high-dose therapy and transplant. There were 138 Hickman type, 67 PICC-type, 46 Portacath-type and 4 Passport-type CVCs. No differences in the participant or CVC characteristics between the 2 treatment groups.
Interventions	Intervention: warfarin 1 mg/day orally started within 72 hours of CVC insertion Control: identical placebo
Outcomes	Follow-up: 90 days • Symptomatic CVC-associated thrombosis • Bleeding • Death Diagnosis of symptomatic CVC-associated thrombosis: compression ultrasonography, venogram
Notes	• As per the investigators, a major limitation of the study was the last number of participants (191/255 = 75%) in whom treatment was interrupted usually because of thrombocytopenia. • Funding: not reported • Ethical approval: quote: "The trial was approved by the local institutional review board at each center, and all patients gave informed consent before randomization." • Conflict of interest: for a detailed description of these categories, or for more information about ASCO's conflict of interest policy, refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue. • ITT: quote: "all analyses were according to the intent-to-treat principle."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients at each center were randomized centrally in permuted blocks of up to six patients."

Couban 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Patients at each center were randomized centrally in permuted blocks of up to six patients."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study design noted as double-blind placebo controlled. Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All suspected primary outcome events, bleeding episodes, and deaths were adjudicated centrally by two individuals blinded to the treatment assignments." Comment: definitely blinded
Incomplete outcome data addressed?	Low risk	Study reported complete follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. Outcomes listed in the methods section were reported on in the results sections.
Free of other bias?	Low risk	Study not stopped early for benefit

De Cicco 2009

Methods	Randomized controlled trial
Participants	450 participants aged ≥ 18 years with solid or hematologic (or both) cancers Mean age: 55.5 years for acenocumarine group; 55.3 years for dalteparin group; 55.1 years for no anticoagulant group Expected life expectancy ≥ 3 months Discontinued treatment: "The primary efficacy population was 77.3% (348 of 450 patients): 76% in group A [dalteparin], 80% in group D [acenocumarine] and 76% in group NT [no treatment]."
Interventions	Intervention 1: dalteparin prophylactic dose; started 2 hours before and daily for 8 days after CVC insertion Intervention 2: acenocumarine 1 mg/day for 3 days before and 8 days after CVC insertion Intervention 3: no anticoagulant treatment
Outcomes	Follow-up: 2 months for 3 visits after initial 30 days, therefore, 7 months total • CVC-related thrombosis • Clinically overt PE • Compulsory catheter removal • Major bleeding (retroperitoneal and intracranial bleeding and any other hemorrhage requiring surgical intervention were also considered as major. Any other bleeding was considered as minor). • Mortality **Screening test for CRT:** venography on days 8 and 30 after insertion and then every 2 months for three times or earlier if there was a clinical suspicion **Screening test for PE:** high-probability V/Q lung scanning or by multislice CT
Notes	• Funding: not reported

De Cicco 2009 *(Continued)*

- Ethical approval: quote: "The study protocol was approved by the local ethical committee and patients gave written informed consent before randomization."
- Conflict of interest: not reported
- ITT: "Data analysis was carried out on an intent-to-treat basis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was carried out ‡4 days before CVC insertion. Permuted blocks of four were used for treatment allocation."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Venograms were evaluated independently by two radiologists who were unaware of the patients' clinical status and the assigned treatment, immediately after venography had been carried out." Comment: definitely blinded
Incomplete outcome data addressed?	High risk	Comment: judgment based on comparison between MPD rate (acenocumarine: 24%; dalteparin: 20%; no anticoagulant: 24%) and event rate (CVC-related DVT: acenocumarine: 21.9%, dalteparin: 40%; no anticoagulant: 52.6%)
Free of selective reporting?	Low risk	Study not registered. No published protocol
Free of other bias?	Low risk	Study not stopped early for benefit

Heaton 2002

Methods	Randomized controlled trial
Participants	88 participants with hematologic cancers Mean age: 43 years
Interventions	Intervention: warfarin 1 mg/day with CVC placement Control: no intervention
Outcomes	Follow-up: 90 days • CRT • Premature removal of the catheter for any reason before day 90 • Catheter-related infection • CVC occlusion **Diagnostic test for CRT:** venography

Heaton 2002 *(Continued)*

Notes	• CVC characteristics: external, tunneled; subclavian; place by radiologists; flushed with heparin or saline; no antibiotic prophylaxis • Funding: not funded • Ethical approval: approval of the Canterbury Ethics Committee • Conflict of interest: not mentioned • ITT: quote: "All patients randomized were included in the analysis." • Comment: probably yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Communication with the author: "Randomisation was from computer generated sequentially numbered sealed opaque envelope."
Allocation concealment (selection bias)	Low risk	Communication with the author: "Randomisation was from computer generated sequentially numbered sealed opaque envelope."
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Comment: probably not blinded; knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data addressed?	Low risk	Complete follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section reported on Comment: probably yes
Free of other bias?	Low risk	Study not stopped early for benefit

Karthaus 2006

Methods	Multinational, double-blind randomized controlled trial (phase III)
Participants	425 participants with solid or hematologic (or both) cancers Mean age 56.3 years; minimum age 18 years Minimum life expectancy: 16 weeks
Interventions	Intervention: dalteparin prophylactic dose; started 5-7 days prior to CVC placement; once daily for 16 weeks Control: placebo

Karthaus 2006 *(Continued)*

	Cointervention: chemotherapy for ≥ 12 weeks, administered to both groups
Outcomes	Follow-up: 16 weeks • CRT that was symptomatic or that required anticoagulation treatment or infusion of fibrinolytic agent with or without catheter removal • Catheter-related clinically relevant PE with or without catheter removal • Catheter obstruction requiring catheter removal • Asymptomatic CRT • Incidence of CRC per day of exposure to the study drug • Time to the first clinically relevant CRC • Time to catheter removal • Catheter-related infection or positive catheter tip culture, or both • Use of bolus injections of fibrinolytic agents for CRT or catheter obstruction • Clinically relevant and objectively verified non-catheter-related venous or arterial TEE • Clinical and laboratory adverse events (major bleeding, thrombocytopenia) **Diagnostic test for CRT:** screening by venography or Doppler or CT scan (16 weeks); diagnosis by venography or Doppler or CT scan **Diagnostic test for PE:** V/Q scan or spiral CT
Notes	• CVC characteristics: mostly ports; proximal or distal to axilla; flushed with heparin and saline • Funding: Pfizer, Inc • Ethical approval: positive local ethics votes obtained from all participating centers. All participants gave written informed consent to inclusion in the study. • Conflict of interest: not mentioned • ITT: quote: "Intention-to-treat and as treated study populations were evaluated."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients with documented cancer were randomly assigned to receive dalteparin or placebo." Comment: probably generated sequence randomly
Allocation concealment (selection bias)	Low risk	Quote: "...centralized interactive voice processing system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as double-blind, placebo-controlled study Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a central adjudication committee reviewed all tests (venograms, CTs, US [ultrasound], etc.) obtained for a suspected CRC and made final judgement, blinded to patient treatment assignment." Comment: definitely blinded
Incomplete outcome data addressed?	High risk	Comment: judgment based on comparison between MPD rate (dalteparin: 26/285 = 9.1%; placebo: 12/140 = 8.5%) and event rate (CRC: dalteparin: 7%; placebo: 3.4%)

Karthaus 2006 *(Continued)*

Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Lavau-Denes 2013

Methods	Open-label, randomized controlled trial (phase III)
Participants	420 participants with histologic evidence of solid invasive cancer, locally advanced or metastatic status Subclavian CVC inserted for < 7 days Receiving first-line chemotherapy Median age: 61 years, 75% males, 46% had a metastatic extension Life expectancy: > 3 months Setting: Centre Hospitalier Universitaire de Limoges
Interventions	Duration of treatment: first 6 days after central venous access device implantation and prescribed for 90 days Intervention 1: LMWH 2500 U anti-XA/day (subcutaneous: dalteparin, nadroparin, or enoxaparin, once daily) Intervention 2: warfarin oral 1 mg/day Intervention 3: no anticoagulant Cointervention: chemotherapy, administered to all groups
Outcomes	Duration of follow-up: 3 months • Symptomatic and asymptomatic CRT of the ipsilateral upper limbs and cervical veins • Superior vena cava, subclavian vein, jugular, and humeral vein thrombosis • PE **Diagnostic test for CRT:** Doppler ultrasound and venographies
Notes	Funding: not reported in the manuscript; however, in ClinicalTrial.gov "sponsors and collaborators: University Hospital, Limoges" (clinicaltrials.gov/show/NCT00199602) Ethical approval: quote: "The study protocol was approved by the local ethical committee." Conflict of interest: none ITT: quote: "The intention to treat population was evaluated and was defined as all randomized patients."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization list was generated by an independent statistician who used a standard method of permuted block of variable size without stratification."

Lavau-Denes 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Comment: probably not blinded; knowledge of the assigned intervention may not impact the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data addressed?	Low risk	Comment: judgment based on comparison between MPD rate (13/420 = 3%) and event rate (catheter-related DVT: no anticoagulant: 20/135 = 14.8%; LMWH: 14/138 = 10.1%)
Free of selective reporting?	Low risk	Study registered in ClinicalTrials.gov (clinicaltrials.gov/show/NCT00199602) Some outcomes of interest were poorly reported (e.g. survival)
Free of other bias?	Low risk	Study not stopped early for benefit

Massicotte 2003

Methods	Open-label, multicenter, international randomized controlled trial
Participants	186 participants aged 0 to 18 years 51% had cancer
Interventions	Intervention: reviparin prophylactic dose, started within 12 hours of randomization (randomization could occur up to 5 days after insertion of the CVC) Control: no intervention
Outcomes	Follow-up: 30 days but varied depending on the time of CVC removal • Symptomatic CRT venogram on day 30 or at time of CVC removal • Asymptomatic CRT • Mortality; catheter-related • Major bleeding • Minor bleeding **Diagnostic test for CRT:** venography on day 30 or at time of CVC removal
Notes	• CVC characteristics: different types (subcutaneous, exteriorized, percutaneous inserted central catheter); flushed with heparin • Funding: Medical Research Council of Canada, Pharmaceutical Manufacturers Association of Canada Health Program, and Knoll AG • ITT: quote: "The analysis included all patients randomized who had evaluable outcome assessments and was based on the intention-to-treat principle."

Massicotte 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...randomly assigned by a computer derived protocol" Comment: definitely yes
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded central outcome adjudication Comment: definitely yes
Incomplete outcome data addressed?	Low risk	Study reported complete follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on Comment: probably yes
Free of other bias?	Low risk	Study stopped early for insufficient accrual but not for benefit

Mismetti 2003

Methods	Multicenter, open, parallel-group randomized controlled study
Participants	60 participants with solid (non-hematologic) cancers Minimum age: 18 years; mean age: 58.7 years Minimum life expectancy: 3 months
Interventions	Intervention: prophylactic dose; nadroparin 2850 IU subcutaneously, once daily started 2 hours prior to CVC placement; for 90 days Control: warfarin 1 mg/day; starting 3 days prior to CVC placement; 90 days
Outcomes	Follow-up: 6 months • Mortality (90 days, 6 months) • CVC premature removal • Symptomatic CRT • Asymptomatic CRT • Non-catheter-site DVT • Catheter-related infection • Major bleed

Mismetti 2003 *(Continued)*

	• HIT **Diagnostic test for DVT:** venography of the extremities, Doppler or venography of lower limbs (or both) **Diagnostic test for PE:** V/Q scan, pulmonary angiogram, helical CT
Notes	• CVC characteristics: port; subclavian; placed by surgeons; flushed with heparin and saline; no antibiotic prophylaxis • Funding: Sanofi-Synthélabo, Inc. • Ethical approval: approved by the local Ethics Committee • Conflict of interest: none • ITT: efficacy and safety analyses were by ITT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer derived treatment schedules were used to assign treatment regimens. To obtain a continuing balance of treatments, the randomized list was divided into consecutive blocks."
Allocation concealment (selection bias)	Low risk	Quote: "...concealment of randomization was achieved through centralized distant randomization."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial Comment: probably not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All venograms were reviewed by an independent reading committee, the members of which were unaware of the patients' treatment allocation." Comment: probably not blinded
Incomplete outcome data addressed?	Low risk	Comment: judgment based on comparison between MPD rate (1/60 = 1.7%) and event rate (upper extremity thrombosis: nadroparin: 6/21 = 28.6%; warfarin: 4/24 = 16.6%)
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on Comment: probably yes
Free of other bias?	Low risk	Study not stopped early for benefit

Monreal 1996

Methods	Open randomized controlled trial
Participants	32 participants with solid tumors Mean age: 54 years Minimum life expectancy: 3 months

Monreal 1996 *(Continued)*

	29 participants completed the study (study was stopped prematurely)
Interventions	Intervention: dalteparin (Fragmin; LMWH) 2500 IU subcutaneously; 2 hours prior to CVC placement; 90 days Control: no intervention
Outcomes	Follow-up: 90 days • Mortality • Symptomatic CRT • Asymptomatic CRT • Infection • Major bleeding **Diagnostic test for CRT:** venography
Notes	• CVC characteristics: port; subclavian; placed by surgeons; flushed with heparin; no antibiotic prophylaxis • Funding: not funded • Ethical approval: quote: "The study was approved by the Ethics Committee of the hospital." • Conflict of interest: not reported • ITT: only participants who completed the study were included in the analysis (comment: probably not used).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...prescribed randomized arrangement to receive or not 2500 IU (subcutaneous) of a low molecular weight heparin."
Allocation concealment (selection bias)	High risk	According to the following communication with the author: "We used an open list of random numbers to randomize patients." Comment: there was no allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Interpretation of venograms was done independently by two expert radiologists who were unaware of patients' status and therapy." Comment: definitely blinded
Incomplete outcome data addressed?	Low risk	Complete follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	High risk	Quote: "Patient recruitment was terminated earlier than planned, after inclusion of 32 patients, because of an excess of thrombotic events in patients without prophylaxis."

Monreal 1996 *(Continued)*

	Study stopped early for benefit

Niers 2007

Methods	Single-center, randomized, placebo-controlled, double-blind study
Participants	113 participants with hematologic malignancies Aged: > 18 years; mean age: 56.5 years (nadroparin: 58 years; placebo: 55 years)
Interventions	Intervention: once-daily nadroparin (LMWH) 2850 IU subcutaneously prophylactic dose; started 2 hours before CVC insertion; for 3 weeks or until the day of CVC removal Control: placebo injections subcutaneously
Outcomes	Follow-up: 3 weeks • CRT • Major, clinically relevant non-major, or minor bleeding • Catheter colonization • Catheter-related sepsis **Diagnostic test for DVT:** venography
Notes	• Funding: quote: "The study drug was obtained commercially, and there was financial support for the study." • Ethical approval: quote: "The study protocol was approved by the local ethics committee." • Conflict of interest: quote: "The authors state that they have no conflict of interest." • ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...prospective, randomized, placebo controlled double-blinded study" Comment: probably generated sequence randomly
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo controlled double-blinded study" Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All venograms were independently adjudicated by an expert radiologist using prior criteria without knowledge of treatment allocation." Comment: definitely blinded
Incomplete outcome data addressed?	High risk	Comment: judgment based on comparison between MPD rate (nadroparin: 15/56 = 26.7%; placebo: 15.8%) and event rate (thrombosis rate: nadroparin: 17%; placebo: 9%)
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on

Niers 2007 *(Continued)*

		Comment: probably yes
Free of other bias?	Low risk	Study not stopped early for benefit

Ruud 2006

Methods	Randomized controlled study
Participants	73 children with solid or hematologic (or both) cancers Mean age: 6.8 years Setting: 2 university hospitals in Oslo, Norway
Interventions	Intervention: warfarin 0.1 mg/kg starting the day of insertion of CVC (target INR 1.3-1.9), duration not reported Control: no intervention
Outcomes	Follow-up: 6 months • Symptomatic CRT • Asymptomatic CRT • Major bleeding • Presence of infections (positive blood cultures) • Removal of CVC due to CVC-related infection CVC characteristics: external tunneled catheters and ports; jugular DVT assessment: screening (1, 3, and 6 months): ultrasound
Notes	Funding: Norwegian Cancer Society ITT: quote: "Only children who completed the study satisfactorily (n=62) from the basis of our descriptive statistics and analyses." Comment: ITT not used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Children were randomized to receive low-dose warfarin or to a control group." Comment: probably generated sequence randomly
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was practically organized by the primary investigator by drawing closed envelopes from boxes." "We did not use block randomization, but (...) we used stratified randomization (according to whether patient is also receiving asparaginase, a hypothesized significant pro thrombotic factor)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The children in the standard arm did not receive placebo." Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).

Ruud 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The radiologists who performed the ultrasonography were blinded to the treatment assignment." Comment: definitely yes
Incomplete outcome data addressed?	High risk	Comment: judgment based on comparison between MPD rate (11/73 = 16%) and event rate (CRT: warfarin: 3/30 = 10%; no intervention: 3/33 = 9%)
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on Comment: probably yes
Free of other bias?	Low risk	Study stopped early for harm but not for benefit

Verso 2008

Methods	Multicenter (11 Italian centers), double-blind randomized controlled trial
Participants	385 participants with solid or hematologic (or both) cancers Minimum age: 18 years; mean age: 59.3 years Minimum life expectancy: 3 months
Interventions	Intervention: enoxaparin 40 mg/day subcutaneously prophylactic dose; started 2 hours prior to CVC placement; for 6 weeks Control: placebo (preloaded syringes)
Outcomes	Follow-up: 3 months • Mortality (6 weeks, 4.5 months) • Symptomatic CRT • Asymptomatic CRT • VTE (4.5 months) • Major bleeding • Minor bleeding • Thrombocytopenia **Diagnostic test for DVT:** screening by venography (6 weeks); diagnosis by venography **Diagnostic test for PE:** V/Q scan, CT, pulmonary angiogram, autopsy
Notes	• CVC characteristics: second-generation CVC; jugular or subclavian • Funding: grant-in-aid from Aventis, Inc. • Ethical approval: protocol approved by ethical committees of the participating centers • Conflict of interest: quote: "The authors indicated no potential conflicts of interest." • ITT: quote: "The intent-to-treat population was defined as..."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to receive drug or placebo permuted blocks of 4 were used for treatment allocation."

Verso 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind study" Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Venographies were evaluated by a central adjudication committee consisting of three radiologists who were unaware of the patients' clinical status." Comment: definitely blinded
Incomplete outcome data addressed?	High risk	Comment: judgment based on comparison between MPD rate (enoxaparin: 36/191 = 18.9%; placebo: 39/194 = 20%) and event rate (thrombosis rate: enoxaparin: 14.1%; placebo: 18%)
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Young 2009

Methods	Open-label, multicenter, randomized controlled trial Setting: 68 clinical centers in the UK
Participants	590 participants with solid or hematologic (or both) cancers Minimum age: 16 years; median age: 60.5 years (warfarin: 60 years; no intervention: 61 years)
Interventions	Intervention: warfarin: fixed dose 1 mg/day or dose adjusted to maintain INR 1.5-2 Control: no intervention
Outcomes	Follow-up: median 45 months (range 26 to 88 months) • Mortality • VTE symptomatic (CVC-related local thrombosis or PE in participants who had catheter complications) • Non-catheter-related thrombotic events • Catheter patency • Major bleeding • Minor bleeding • Catheter-related infection **Diagnostic test for CRT:** venography
Notes	All types of CVC allowed Funding: Medical Research Council and Cancer Research UK Ethical approval: quote: "The clinical centres received ethical approval from the West Midlands multicentre research ethics committee." Conflict of interest: quote: "We declare that we have no conflict of interest."

Young 2009 *(Continued)*

ITT: quote: "Analysis was by intention-to-treat basis"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomly assigned patients using computerised block algorithm"
Allocation concealment (selection bias)	Low risk	Personal communication with the author: "Randomisation was executed via a computerised block algorithm and performed by randomisation officers at the central randomisation office in the departmental trials unit, accessed by telephone and fax."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All thromboses were radiologically confirmed by two investigators, unaware of treatment allocation" Comment: definitely blinded; knowledge of the assigned intervention may not impact the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.)
Incomplete outcome data addressed?	Low risk	Comment: judgment based on comparison between MPD rate (warfarin: 13/408 = 3%; no intervention: 1/404 = 0.2%) and event rate (thrombotic event rate: warfarin: 3%; no intervention: 6%; major bleeding rate: warfarin: < 1%; no intervention: 3%)
Free of selective reporting?	Low risk	Study registered as ISRCTN50312145. All outcomes listed in the registry were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

ASCO: American Society of Clinical Oncology; CT: computed tomography; CRC: catheter-related complication; CRT: catheter-related thrombosis; CVC: central venous catheter; HIT: heparin-induced thrombocytopenia; INR: international normalized ratio; ITT: intention to treat; IU: international unit; LMWH: low-molecular-weight heparin; MPD: missing participant data; PE: pulmonary embolism; TEE: thromboembolic event; U: unit; V/Q: ventilation/perfusion.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdelkefi 2004	Concerns about the accuracy and validity of the data reported, and the practical aspects of the published protocol. When asked by the review authors, the authors were unable to provide evidence that the study had been conducted.
Agnelli 1998	Not the population of interest (participants without CVC)
Agnelli 2005b	Not the population of interest (participants without CVC)
Agnelli 2015 (AMPLIFY)	Not the population of interest (participants with cancer with VTE); includes 2 reports

Study	Reason for exclusion
Alikhan 2003 (MEDENOX)	Not the population of interest (participants without CVC); includes 2 reports
Anderson 1987	Not an RCT; no control group
Anderson 1989	Not an RCT; observational study
Attal 1992	Not population of interest (participants did not previously have CVC, it was rather inserted for intervention)
Auer 2011	Not the population of interest (participants without CVC)
Barman 2005	Not an RCT; observational study
Bigg 1992	Not the population of interest (participants without CVC)
Boraks 1998	Not an RCT; historic control
Cahan 2000	Not the population of interest (participants without CVC)
Ciftci 2012	Not the population of interest (participants without CVC)
Clarke-Pearson 1993	Not the population of interest (participants without CVC)
Cohen 1997	Not the population of interest (participants without CVC)
Cohen 2006	Not the population of interest (participants without CVC)
Cohen 2007 (PREVENT)	Not the population of interest (participants without CVC); included 3 reports
Conte 2003	No obtainable needed data from study authors
Curigliano 2004	Not an RCT; retrospective study
Dickinson 1998	Not the population of interest (participants without CVC)
Dillon 2004	Inadequate control groups; intervention compared with urokinase
Freytes 2003	Review
Goldhaber 2002	Not the population of interest (participants without CVC)
Gould 1996	No obtainable needed data from study authors
Haas 2011	Not the population of interest (participants without CVC); included 3 reports
Handrup 2012	Not intervention of interest (locking solution)
Harenberg 1996	Not the population of interest (participants without CVC); included 2 reports
Hata 2016	Not the population of interest (participants without CVC)
Henrickson 2000	Different drug/agent studied
Hoffman 2001	Different drug/agent studied

Study	Reason for exclusion
Horne 2006	Not intervention of interest (flushing solution)
Huisman 2006	Review
Iniesta 2003	Not an RCT; observational study
Jansson 2005	Review
Kakkar 2010 (CANBESURE)	Not the population of interest (participants without CVC); included 2 reports
Kakkar 2014 (SAVE-ABDO)	Not the population of interest (participants without CVC); included 2 reports
Khorana 2017 (PHACS)	Not the population of interest (participants without CVC); included 2 reports
Klerk 2003	Review
Klerk 2004	Letter to the editor
Koppenhagen 1992	Not the population of interest (participants without CVC)
Larocca 2012	Not the population of interest (participants without CVC)
Lee 2015 (CATCH)	Not the population of interest (participants with cancer with VTE); included 9 reports
Lersch 2002	Not an RCT; observational study
Levine 2005	Editorial
Macbeth 2016 (FRAGMATIC)	Not the population of interest (participants without CVC); included 4 reports
Magagnoli 2004	Not an RCT; retrospective study
Magagnoli 2005	Not an RCT; no control group
Maxwell 2001	Not the population of interest (participants without CVC)
Mazilu 2014 (OVIDIUS)	Not the population of interest (participants with cancer with VTE)
Murakami 2002	Not the population of interest (participants without CVC)
Nagata 2015	Not the population of interest (participants without CVC)
Nurmohamed 1996	Not the population of interest (participants without CVC)
Palumbo 2011	Not the population of interest (participants without CVC)
Park 1999	No obtainable needed data from the authors
Pelzer 2015 (CONKO-004)	Not the population of interest (participants without CVC); included 10 reports
Prins 2014 (EINSTEIN)	Not the population of interest (participants with cancer with VTE); included 2 reports
Raskob 2016 (HOKUSAI)	Not the population of interest (participants with cancer with VTE); included 3 reports
Ratcliffe 1999	Not an RCT

Study	Reason for exclusion
Romano 2005	Not an RCT
Sakon 2010	Not the population of interest (participants without CVC)
Schulman 2003	Not the population of interest (participants with cancer with VTE)
Schulman 2013 (RE-MEDY)	Not the population of interest (participants with cancer with VTE)
Schulman 2015 (RECOVER)	Not the population of interest (participants with cancer with VTE)
Solomon 2001	Inadequate control groups; intervention compared with urokinase
Song 2014	Not the population of interest (participants with cancer with VTE)
Tesselaar 2001	Not an RCT; retrospective study
Thürlmann 1992	Not population of interest (peripheral venous catheter and not CVC)
Vadhan-Raj 2013	Not the population of interest (participants with cancer with VTE)
van Rooden 2003	Not an RCT; observational study
Vedovati 2014	Not the population of interest (participants with cancer with VTE)
Ward 1998	Not the population of interest (participants with cancer with VTE)
Wester 1996	Not the population of interest (participants with cancer with VTE); included 2 reports
Zheng 2014	Not the population of interest (participants with cancer with VTE)
Zwicker 2013 (MICRO TEC)	Not the population of interest (participants with cancer with VTE); included 2 reports

CVC: central venous catheter; RCT: randomized controlled trial; VTE: venous thromboembolism.

DATA AND ANALYSES

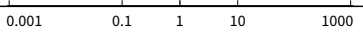
Comparison 1. Low-molecular-weight heparin (LMWH) versus no LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (up to 3 months)	5	1236	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.53, 1.26]
2 Symptomatic catheter-related thrombosis (up to 3 months)	5	1089	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.22, 0.81]
3 Asymptomatic catheter-related thrombosis (up to 3 months)	5	1089	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.62, 1.46]
4 Major bleeding (up to 3 months)	4	1018	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.06, 36.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Minor bleeding (up to 3 months)	2	544	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.62, 2.92]
6 Catheter-related infection (up to 3 months)	2	474	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.52, 1.79]
7 Thrombocytopenia (up to 3 months)	4	1002	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.80, 1.33]

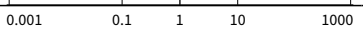
Analysis 1.1. Comparison 1 Low-molecular-weight heparin (LMWH) versus no LMWH, Outcome 1 All-cause mortality (up to 3 months).

Study or subgroup	LMWH n/N	No LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
De Cicco 2009	12/120	11/114		30.86%	1.04[0.48,2.25]
Karthaus 2006	4/259	1/128		3.92%	1.98[0.22,17.51]
Lavau-Denes 2013	7/138	8/135		19.15%	0.86[0.32,2.29]
Monreal 1996	1/17	2/15		3.53%	0.44[0.04,4.39]
Verso 2008	13/155	20/155		42.54%	0.65[0.34,1.26]
Total (95% CI)	**689**	**547**		**100%**	**0.82[0.53,1.26]**
Total events: 37 (LMWH), 42 (No LMWH)					
Heterogeneity: Tau^2=0; Chi^2=1.74, df=4(P=0.78); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					



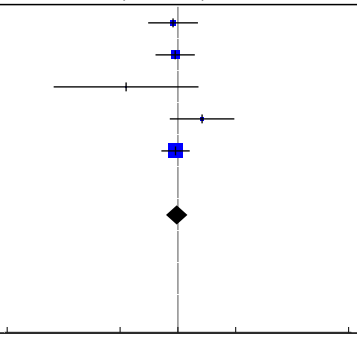
Analysis 1.2. Comparison 1 Low-molecular-weight heparin (LMWH) versus no LMWH, Outcome 2 Symptomatic catheter-related thrombosis (up to 3 months).

Study or subgroup	LMWH n/N	No LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Karthaus 2006	10/259	5/128		35.67%	0.99[0.35,2.83]
Lavau-Denes 2013	4/138	15/135		34.13%	0.26[0.09,0.77]
Monreal 1996	1/17	5/15		9.93%	0.18[0.02,1.35]
Niers 2007	0/41	1/46		4.1%	0.37[0.02,8.91]
Verso 2008	2/155	6/155		16.17%	0.33[0.07,1.63]
Total (95% CI)	**610**	**479**		**100%**	**0.43[0.22,0.81]**
Total events: 17 (LMWH), 32 (No LMWH)					
Heterogeneity: Tau^2=0.01; Chi^2=4.1, df=4(P=0.39); I^2=2.49%					
Test for overall effect: Z=2.59(P=0.01)					



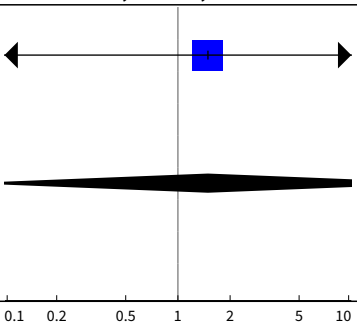
Analysis 1.3. Comparison 1 Low-molecular-weight heparin (LMWH) versus no LMWH, Outcome 3 Asymptomatic catheter-related thrombosis (up to 3 months).

Study or subgroup	LMWH n/N	No LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Karthaus 2006	10/259	6/128		16.97%	0.82[0.31,2.22]
Lavau-Denes 2013	11/138	12/135		25.82%	0.9[0.41,1.96]
Monreal 1996	0/17	3/15		2.15%	0.13[0.01,2.27]
Niers 2007	7/41	3/46		10.41%	2.62[0.72,9.47]
Verso 2008	20/155	22/155		44.64%	0.91[0.52,1.6]
Total (95% CI)	**610**	**479**		**100%**	**0.95[0.62,1.46]**
Total events: 48 (LMWH), 46 (No LMWH)					
Heterogeneity: Tau^2=0.02; Chi^2=4.39, df=4(P=0.36); I^2=8.89%					
Test for overall effect: Z=0.22(P=0.83)					



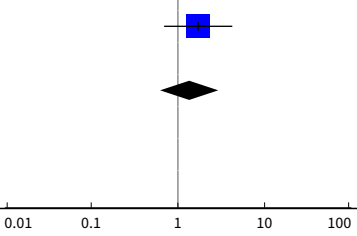
Analysis 1.4. Comparison 1 Low-molecular-weight heparin (LMWH) versus no LMWH, Outcome 4 Major bleeding (up to 3 months).

Study or subgroup	LMWH n/N	No LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
De Cicco 2009	0/120	0/114			Not estimable
Karthaus 2006	1/259	0/128		100%	1.49[0.06,36.28]
Niers 2007	0/41	0/46			Not estimable
Verso 2008	0/155	0/155			Not estimable
Total (95% CI)	**575**	**443**		**100%**	**1.49[0.06,36.28]**
Total events: 1 (LMWH), 0 (No LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					



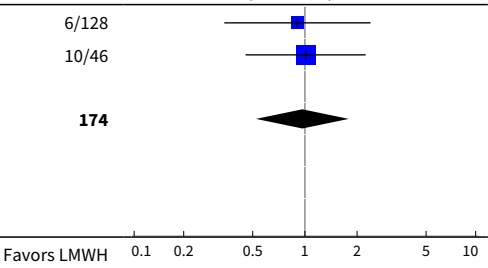
Analysis 1.5. Comparison 1 Low-molecular-weight heparin (LMWH) versus no LMWH, Outcome 5 Minor bleeding (up to 3 months).

Study or subgroup	LMWH n/N	No LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
De Cicco 2009	3/120	4/114		27.36%	0.71[0.16,3.11]
Verso 2008	12/155	7/155		72.64%	1.71[0.69,4.24]
Total (95% CI)	**275**	**269**		**100%**	**1.35[0.62,2.92]**
Total events: 15 (LMWH), 11 (No LMWH)					
Heterogeneity: Tau^2=0; Chi^2=0.99, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=0.76(P=0.45)					



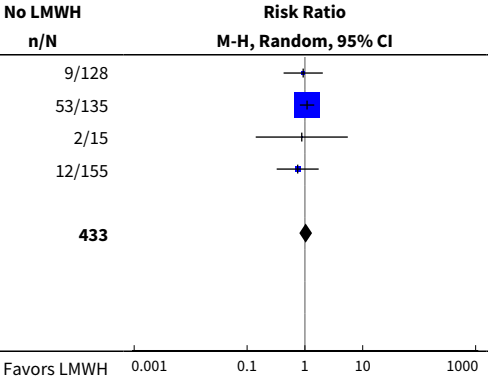
Analysis 1.6. Comparison 1 Low-molecular-weight heparin (LMWH) versus no LMWH, Outcome 6 Catheter-related infection (up to 3 months).

Study or subgroup	LMWH n/N	No LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Karthaus 2006	11/259	6/128		40.15%	0.91[0.34,2.39]
Niers 2007	9/41	10/46		59.85%	1.01[0.46,2.24]
Total (95% CI)	**300**	**174**		**100%**	**0.97[0.52,1.79]**
Total events: 20 (LMWH), 16 (No LMWH)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					



Analysis 1.7. Comparison 1 Low-molecular-weight heparin (LMWH) versus no LMWH, Outcome 7 Thrombocytopenia (up to 3 months).

Study or subgroup	LMWH n/N	No LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Karthaus 2006	17/259	9/128		10.49%	0.93[0.43,2.04]
Lavau-Denes 2013	59/138	53/135		78.46%	1.09[0.82,1.45]
Monreal 1996	2/17	2/15		1.9%	0.88[0.14,5.52]
Verso 2008	9/155	12/155		9.15%	0.75[0.33,1.73]
Total (95% CI)	**569**	**433**		**100%**	**1.03[0.8,1.33]**
Total events: 87 (LMWH), 76 (No LMWH)					
Heterogeneity: Tau^2=0; Chi^2=0.82, df=3(P=0.85); I^2=0%					
Test for overall effect: Z=0.24(P=0.81)					

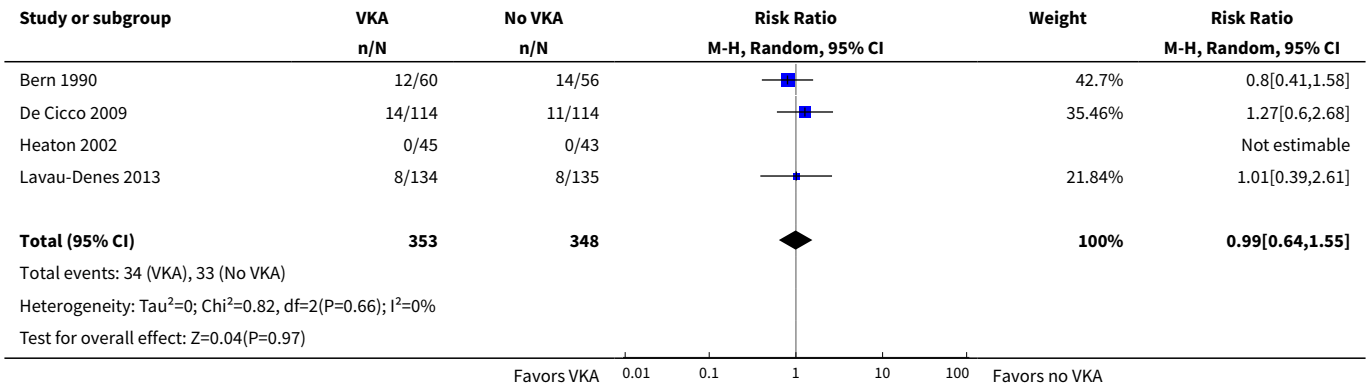


Comparison 2. Vitamin K antagonist (VKA) versus no VKA

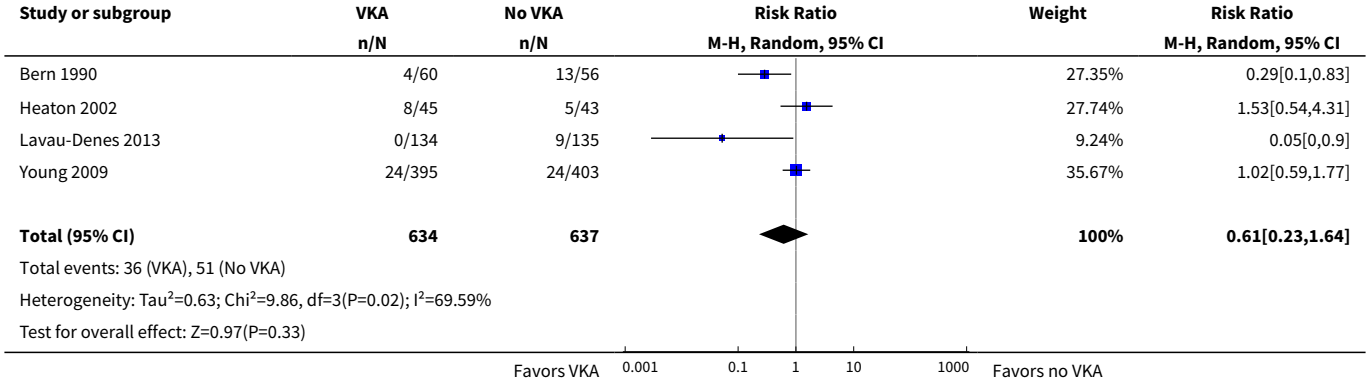
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (up to 3 months)	4	701	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.64, 1.55]
2 Symptomatic catheter-related thrombosis (up to 3 months)	4	1271	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.23, 1.64]
3 Asymptomatic catheter-related thrombosis	2	384	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.27, 1.40]
4 Major bleeding (up to 3 months)	2	1026	Risk Ratio (M-H, Random, 95% CI)	7.14 [0.88, 57.78]
5 Minor bleeding (up to 3 months)	2	1026	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.38, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Catheter-related infection	1	88	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.74, 1.85]
7 Premature central venous catheter removal	1	88	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.30, 2.24]

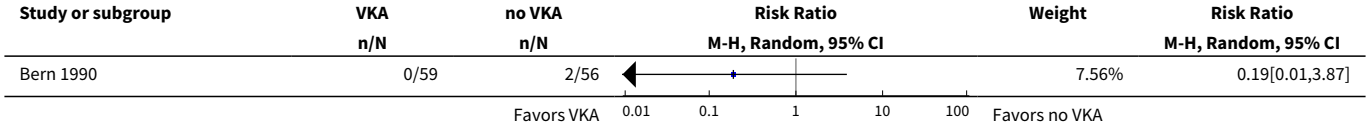
Analysis 2.1. Comparison 2 Vitamin K antagonist (VKA) versus no VKA, Outcome 1 All-cause mortality (up to 3 months).

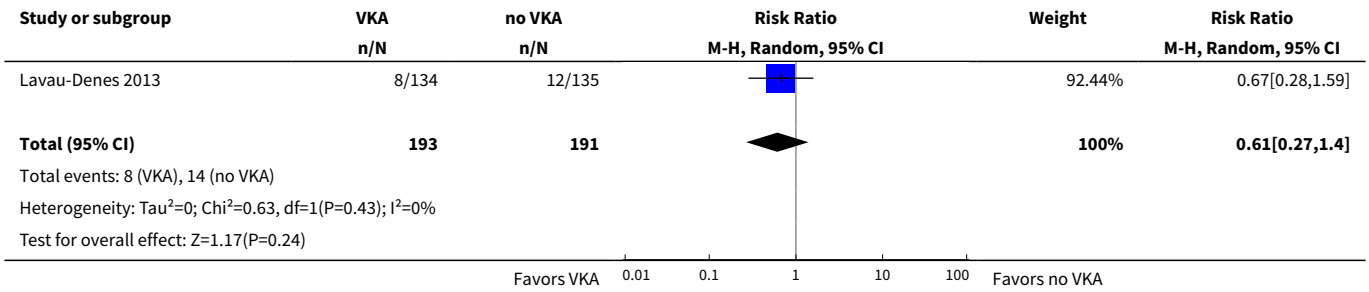


Analysis 2.2. Comparison 2 Vitamin K antagonist (VKA) versus no VKA, Outcome 2 Symptomatic catheter-related thrombosis (up to 3 months).

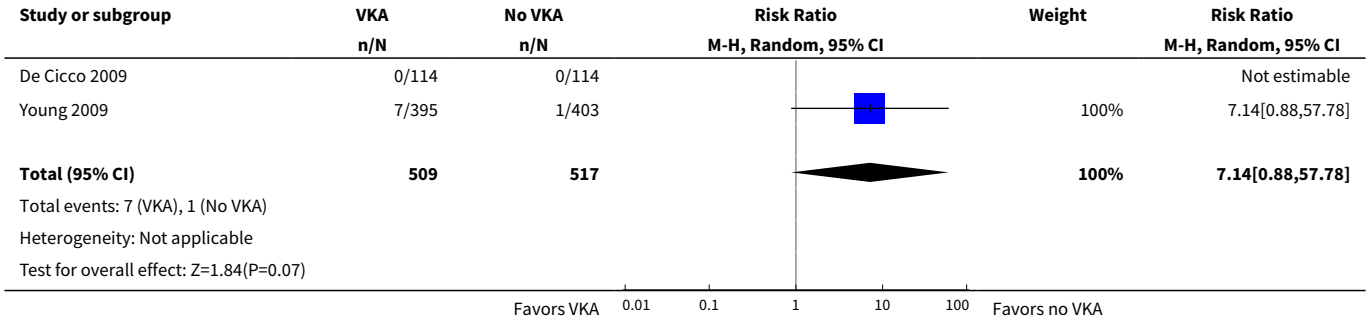


Analysis 2.3. Comparison 2 Vitamin K antagonist (VKA) versus no VKA, Outcome 3 Asymptomatic catheter-related thrombosis.

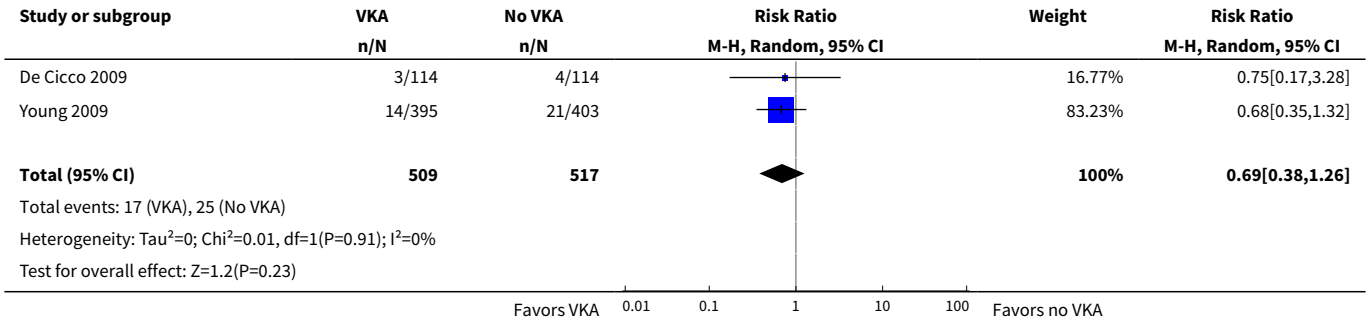




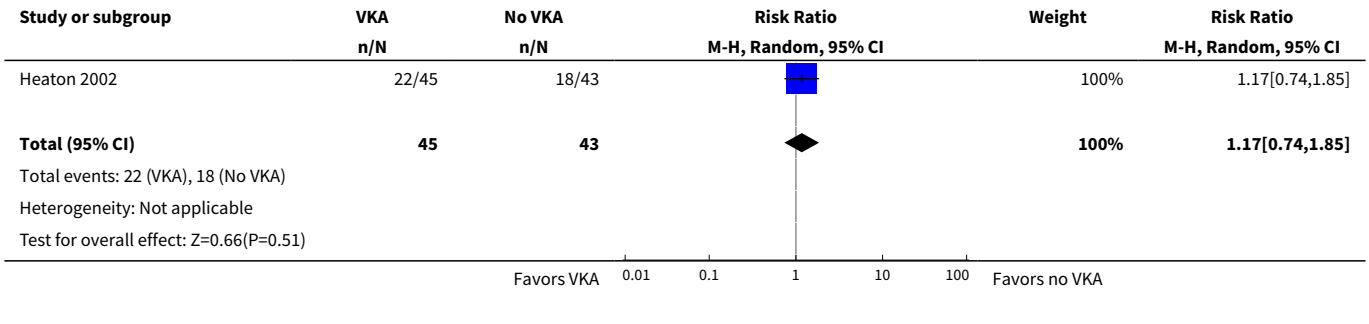
Analysis 2.4. Comparison 2 Vitamin K antagonist (VKA) versus no VKA, Outcome 4 Major bleeding (up to 3 months).



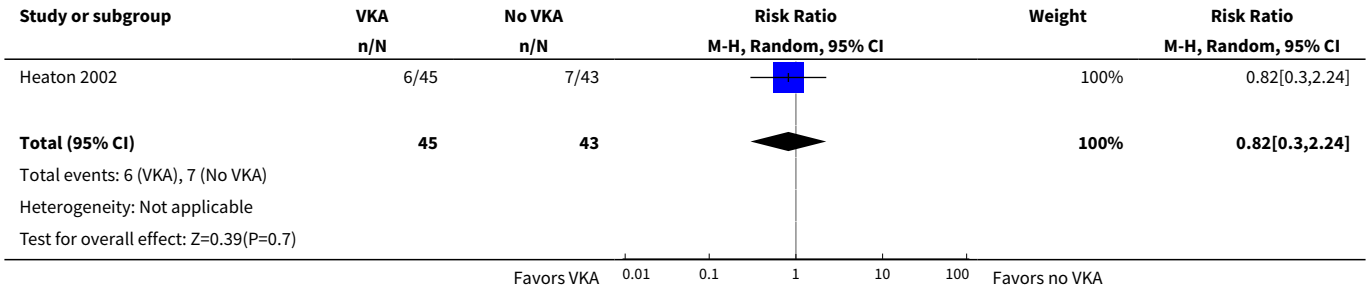
Analysis 2.5. Comparison 2 Vitamin K antagonist (VKA) versus no VKA, Outcome 5 Minor bleeding (up to 3 months).



Analysis 2.6. Comparison 2 Vitamin K antagonist (VKA) versus no VKA, Outcome 6 Catheter-related infection.



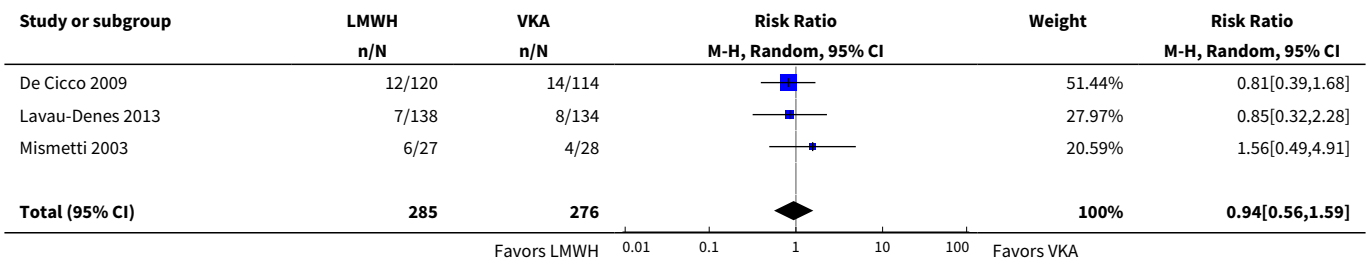
Analysis 2.7. Comparison 2 Vitamin K antagonist (VKA) versus no VKA, Outcome 7 Premature central venous catheter removal.

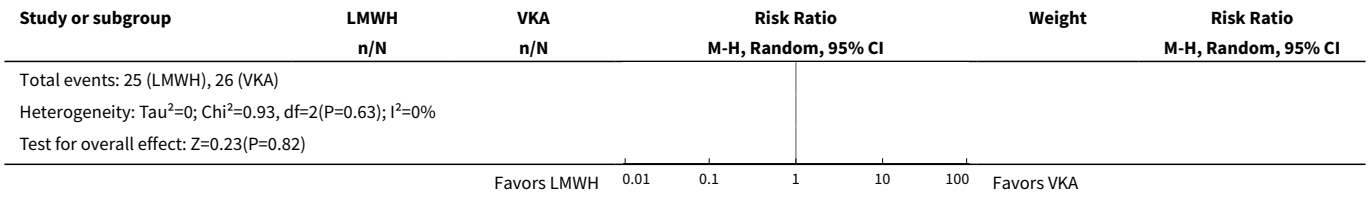


Comparison 3. Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA)

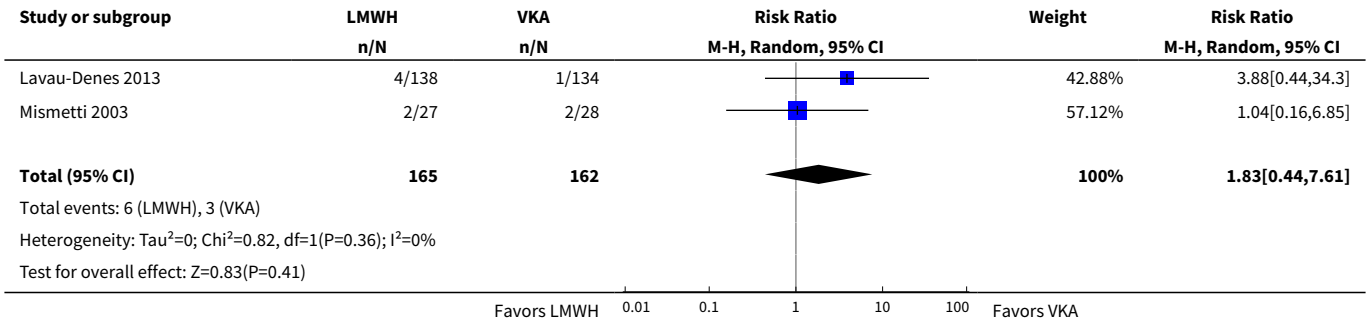
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (up to 3 months)	3	561	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.56, 1.59]
2 Symptomatic catheter-related thrombosis (up to 3 months)	2	327	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.44, 7.61]
3 Asymptomatic catheter-related thrombosis	2	317	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.75, 3.46]
4 Pulmonary embolism (up to 3 months)	2	327	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.74, 3.92]
5 Major bleeding (up to 3 months)	2	289	Risk Ratio (M-H, Random, 95% CI)	3.11 [0.13, 73.11]
6 Minor bleeding (up to 3 months)	1	234	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.20, 4.61]
7 Thrombocytopenia (up to 3 months)	2	327	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.20, 2.39]

Analysis 3.1. Comparison 3 Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 1 All-cause mortality (up to 3 months).

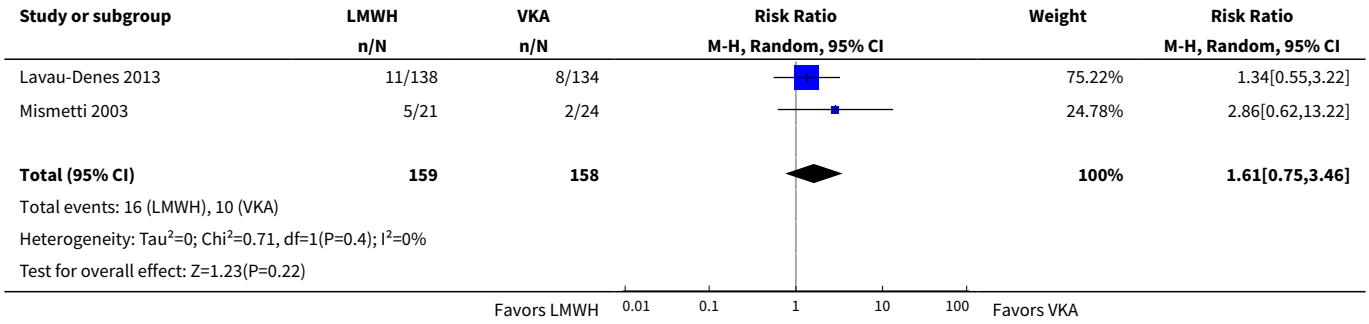




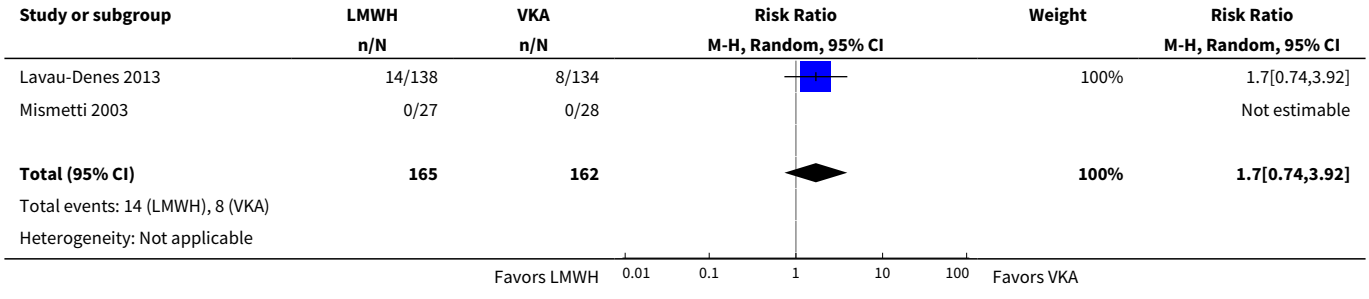
Analysis 3.2. Comparison 3 Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 2 Symptomatic catheter-related thrombosis (up to 3 months).

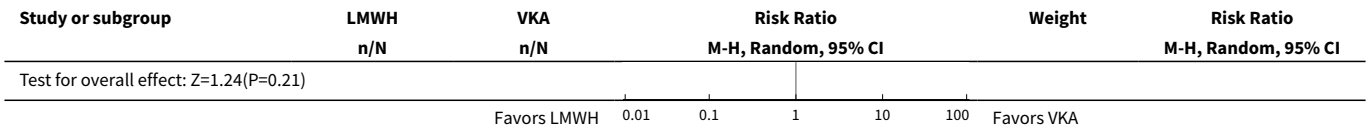


Analysis 3.3. Comparison 3 Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 3 Asymptomatic catheter-related thrombosis.

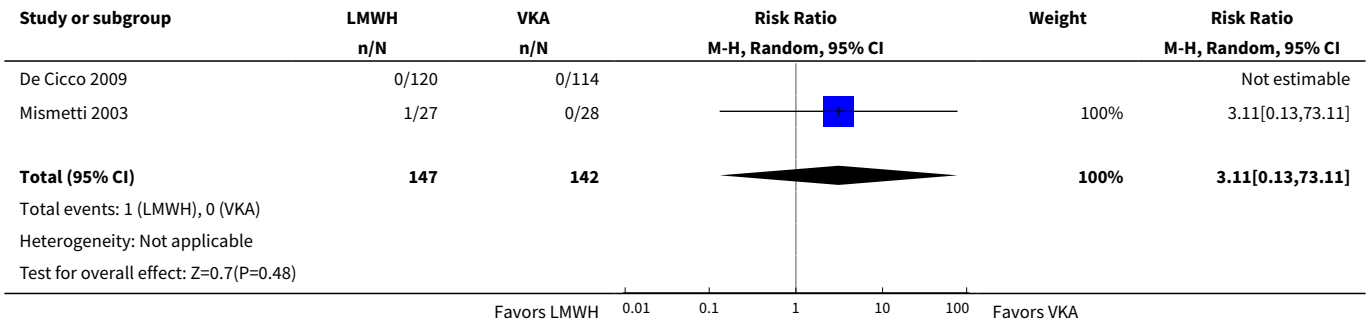


Analysis 3.4. Comparison 3 Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 4 Pulmonary embolism (up to 3 months).

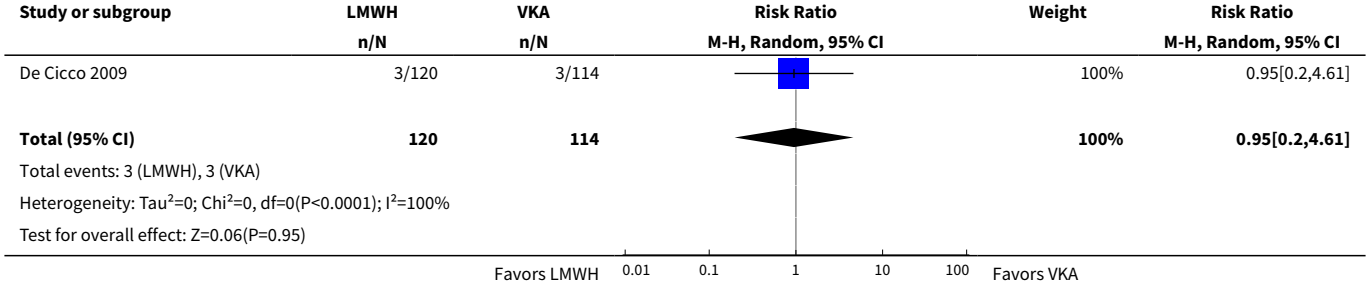




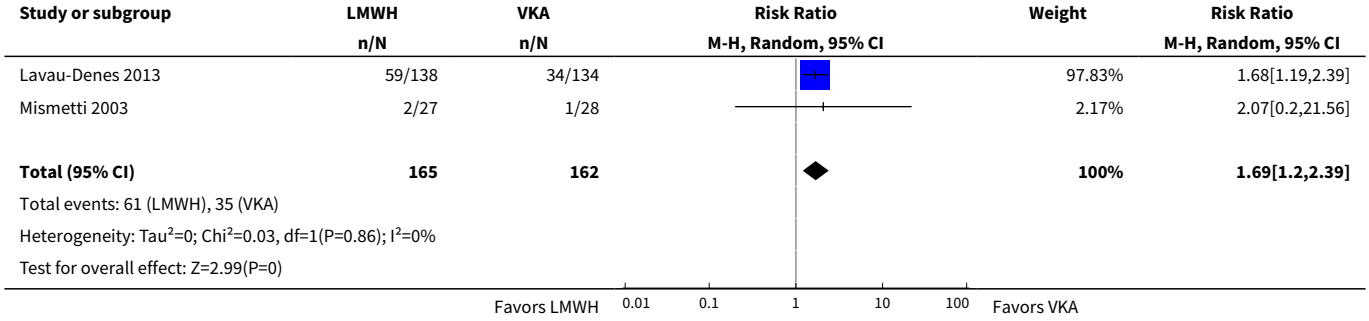
Analysis 3.5. Comparison 3 Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 5 Major bleeding (up to 3 months).



Analysis 3.6. Comparison 3 Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 6 Minor bleeding (up to 3 months).



Analysis 3.7. Comparison 3 Low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 7 Thrombocytopenia (up to 3 months).



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Adjuvant therapy	Assisting in the amelioration, or cure of disease
Anticoagulation	Process of hindering the clotting of blood especially by treatment with an anticoagulant.
Antithrombotic	Used against or tending to prevent thrombosis (clotting)
Bacteremia	Presence of bacteria in the blood
Central venous line	Synthetic tube that is inserted into a central (large) vein to provide temporary intravenous access for the administration of fluid, medication, or nutrients.
Coagulation	Clotting
Deep venous (vein) thrombosis (DVT)	Condition marked by the formation of a thrombus within a deep vein (as of the leg or pelvis) that may be asymptomatic or be accompanied by symptoms (as swelling and pain) and that is potentially life threatening if dislodgment of the thrombus results in pulmonary embolism
Fibrin	White insoluble fibrous protein formed from fibrinogen by the action of thrombin especially in the clotting of blood
Fondaparinux	Anticoagulant medication
Hemostatic system	System that shortens the clotting time of blood and stops bleeding
Heparin	Enzyme occurring especially in the liver and lungs that prolongs the clotting time of blood by preventing the formation of fibrin. 2 forms of heparin that are used as anticoagulant medications are: unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH)
Impedance plethysmography	Technique that measures the change in blood volume (venous blood volume as well as the pulsation of the arteries) for a specific body segment
Kappa statistics	Measure of degree of non-random agreement between observers or measurements of a specific categorical variable or both
Metastasis	Spread of cancer cells from the initial or primary site of disease to another part of the body
Oncogene	Gene having the potential to cause a normal cell to become cancerous
Osteoporosis	Condition that affects especially older women and is characterized by decrease in bone mass with decreased density and enlargement of bone spaces producing porosity and brittleness
Parenteral nutrition	Practice of feeding a person intravenously, circumventing the gastrointestinal tract
Pulmonary embolism (PE)	Embolism of a pulmonary artery or 1 of its branches that is produced by foreign matter and most often a blood clot originating in a vein of the leg or pelvis and that is marked by labored breathing, chest pain, fainting, rapid heart rate, cyanosis, shock, and sometimes death.
Stroma	Supporting framework of an organ typically consisting of connective tissue
Thrombin	Proteolytic enzyme formed from prothrombin that facilitates the clotting of blood by catalyzing conversion of fibrinogen to fibrin

Table 1. Glossary *(Continued)*

Thrombocytopenia	Persistent decrease in the number of blood platelets that is often associated with hemorrhagic conditions
Thrombosis	Formation or presence of a blood clot within a blood vessel
Vitamin K antagonists (VKA)	Anticoagulant medications that are used for anticoagulation. Warfarin is a vitamin K antagonist
Warfarin	Anticoagulant medication that is a vitamin K antagonist that is used for anticoagulation
Ximelagatran	Anticoagulant medication

Table 2. Low-molecular-weight heparin definitions of prophylactic and therapeutic dosages

LMWH	Generic name	Prophylactic dose	Therapeutic dose
Lovenox	Enoxaparin	40 mg once daily	1 mg/kg twice daily
Fragmin	Dalteparin	2500-5000 U once daily	200 U/kg once daily or 100 U/kg twice daily
Innohep	Tinzaparin, logiparin	4500 U once daily	90 U/kg twice daily
Fraxiparine	Nadroparin	35-75 anti-Xa IU/kg/day	175 anti-Xa IU/kg/day
Certoparin	Sandoparin	3000 anti-Xa IU once daily	–
Reviparin	Reviparin	1750-4200 anti-Xa IU	7000-12,600 anti-Xa IU

IU: international units; U: units; Xa: factor Xa.

APPENDICES

Appendix 1. Full search strategies for the electronic databases - update 2010

Database	Strategy
Cochrane Central Register of Controlled Trials (CENTRAL)	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumor OR tumor #8 6 AND 7
MEDLINE	#1 Heparin/

(Continued)

	#2 Heparin.tw #3 Heparin, Low-Molecular-Weight/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 (fondaparinux OR Arixtra).tw #11 (ximelagatran OR Exanta).tw #12 (Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban).tw. #13 5 OR 9 OR 10 OR 11 OR 12 #14 Neoplasms/ #15 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumor OR tumor).tw #16 14 OR 15 #17 clinical trial.pt. OR random:.tw. OR tu.xs. #18 animals/ NOT human/ #19 17 NOT 18 #20 13 AND 16 AND 19
Embase	#1 Heparin/ #2 heparin.tw #3 Low Molecular Weight Heparin/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarin derivative/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 fondaparinux/ #11 (fondaparinux OR Arixtra).tw #12 ximelagatran/ #13 (ximelagatran OR Exanta).tw #14 (Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban).tw. #15 5 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 #16 Neoplasm/ #17 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumor OR tumor).tw #18 16 OR 17 #19 Random:.tw. OR clinical trial:.mp. OR exp health care quality #20 animals/ NOT human/ #21 19 NOT 20 #22 15 AND 18 AND 21
ISI (International Scientific Information) the Web of Science	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta

(Continued)

	# 5 Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumor OR tumor #8 random$ OR placebo$ OR versus OR vs OR double-blind OR double-blind OR compar$ OR controlled #9 6 AND 7 AND 8

Appendix 2. Full search strategies for the electronic databases - update 2013

Database	Strategy
Cochrane Central Register of Controlled Trials (CENTRAL)	#1 MeSH descriptor: [Heparin] explode all trees #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum) #3 MeSH descriptor: [Coumarins] explode all trees #4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA) #5 (fondaparinux or arixtra) #6 (ximelagatran or exanta) #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Neoplasms] explode all trees #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*) #11 #9 or #10 #12 #8 and #10
MEDLINE	#1 exp Heparin/ #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw. #3 exp Coumarins/ #4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw. #5 (fondaparinux or arixtra).tw. #6 (ximelagatran or exanta).tw. #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw. #8 1 or 2 or 3 or 4 or 5 or 6 or 7

(Continued)

	#9 exp Neoplasms/ #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw. #11 9 or 10 #12 8 and 11 #13 randomised controlled trial.pt. #14 controlled clinical trial.pt. #15 randomized.ab. #16 placebo.ab. #17 drug therapy.fs. #18 randomly.ab. #19 trial.ab. #20 groups.ab. #21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 #22 12 and 21 #23 exp animals/ not humans.sh. #24 22 not 23
Embase	#1 heparin/ #2 exp low molecular weight heparin/ #3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw. #4 exp coumarin derivative/ #5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw. #6 (fondaparinux or arixtra).tw. #7 (ximelagatran or exanta).tw. #8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw. #9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 #10 exp neoplasm/ #11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw. #12 10 or 11 #13 9 and 12 #14 crossover procedure/

(Continued)

	#15 double-blind procedure/
	#16 randomised controlled trial/
	#17 single-blind procedure/
	#18 random*.mp.
	#19 factorial*.mp.
	#20 (crossover* or cross over* or cross-over*).mp.
	#21 placebo*.mp.
	#22 (double* adj blind*).mp.
	#23 (singl* adj blind*).mp.
	#24 assign*.mp.
	#25 allocat*.mp.
	#26 volunteer*.mp.
	#27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
	#28 13 and 27
	#29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
	#30 28 not 29

Appendix 3. Full search strategies for the electronic databases - update 2018

Database	Strategy
MEDLINE	**RCT search strategy**:
	1. exp Anticoagulants/
	2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.
	3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
	4. exp Coumarins/
	5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp.

(Continued)

6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

7. (thrombin adj inhibitor*).mp.

8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp Neoplasms/

13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

14. 12 or 13

15. 11 and 14

16. randomized controlled trial.pt.

17. controlled clinical trial.pt.

18. randomized.ab.

19. placebo.ab.

20. clinical trials as topic.sh.

21. randomly.ab.

22. trial.ti.

23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. (animals not (humans and animals)).sh.

25. 23 not 24

26. 15 and 25

Systematic Review search strategy:

1. exp Anticoagulants/

2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.

(Continued)

4. exp Coumarins/

5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp.

6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

7. (thrombin adj inhibitor*).mp.

8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp Neoplasms/

13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

14. 12 or 13

15. 11 and 14

16. (review or review,tutorial or review, academic).pt.

17. (medline or medlars or embase or pubmed or cochrane).tw,sh.

18. (scisearch or psychinfo or psycinfo).tw,sh.

19. (psychlit or psyclit).tw,sh.

20. cinahl.tw,sh.

21. ((hand adj2 search*) or (manual* adj2 search*)).tw,sh.

22. (electronic database* or bibliographic database* or computeri?ed database* or online database*).tw,sh.

23. (pooling or pooled or mantel haenszel).tw,sh.

24. (peto or dersimonian or der simonian or fixed effect).tw,sh.

25. (retraction of publication or retracted publication).pt.

26. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. 16 and 26

28. meta-analysis.pt.

29. meta-analysis.sh.

30. (meta-analys* or meta analys* or metaanalys*).tw,sh.

31. (systematic* adj5 review*).tw,sh.

(Continued)

	32. (systematic* adj5 overview*).tw,sh. 33. (quantitativ* adj5 review*).tw,sh. 34. (quantitativ* adj5 overview*).tw,sh. 35. (methodologic* adj5 review*).tw,sh. 36. (methodologic* adj5 overview*).tw,sh. 37. (integrative research review* or research integration).tw. 38. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 39. 27 or 38 41. 15 and 39
Embase	**RCT search strategy:** 1. exp anticoagulant agent/ 2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp. 3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp. 4. exp coumarin derivative/ 5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp. 6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp. 7. (thrombin adj inhibitor*).mp. 8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp. 9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp. 10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw. 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12. exp neoplasm/ 13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

(Continued)

14. 12 or 13

15. 11 and 14

16. crossover procedure/

17. double-blind procedure/

18. randomized controlled trial/

19. single-blind procedure/

20. random*.mp.

21. factorial*.mp.

22. (crossover* or cross over* or cross-over*).mp.

23. placebo*.mp.

24. (double* adj blind*).mp.

25. (singl* adj blind*).mp.

26. assign*.mp.

27. allocat*.mp.

28. volunteer*.mp.

29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30. 15 and 29

Systematic Review search strategy:

1. exp anticoagulant agent/

2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.

4. exp coumarin derivative/

5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp.

6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

7. (thrombin adj inhibitor*).mp.

8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

(Continued)

	9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp. 10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw. 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12. exp neoplasm/ 13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw. 14. 12 or 13 15. 11 and 14 16. exp review/ 17. (literature adj3 review*).ti,ab. 18. exp meta analysis/ 19. exp "Systematic Review"/ 20. 16 or 17 or 18 or 19 21. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab. 22. RETRACTED ARTICLE/ 23. 21 or 22 24. 20 and 23 25. (systematic* adj2 (review* or overview)).ti,ab. 26. (meta?anal* or meta anal* or meta-anal* or metaanal* or metanal*).ti,ab. 27. 24 or 25 or 26 28. 15 and 27
CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Anticoagulants] explode all trees #2 (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock) #3 FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216 #4 MeSH descriptor: [Coumarins] explode all trees

(Continued)

#5 (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-bis-coumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl)

#6 (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix)

#7 thrombin near inhibitor*

#8 factor Xa inhibitor* or antithrombin* or anticoagul*

#9 rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b

#10 TSOAC* or NOAC* or DOAC*

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

#12 MeSH descriptor: [Neoplasms] explode all trees

#13 malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*

#14 #13 or #14

#15 #11 and #14

Appendix 4. GRADE evidence profile: low-molecular-weight heparin (LMWH) versus no LMWH

Certainty assessment							№ of participants		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**No LMWH**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (up to 3 months)												
5	RCTs	Serious[a]	Not serious	Not serious	Serious[b]	None	37/689 (5.4%)	42/547 (7.7%)	**RR 0.82** (0.53 to 1.26)	**14 fewer per 1000** (from 20 more to 36 fewer)	⊕⊕⊖⊖ Low	Critical
Symptomatic catheter-related thrombosis (up to 3 months)												
5	RCTs	Serious[c]	Not serious	Not serious	Not serious	None	17/610 (2.8%)	32/479 (6.7%)	**RR 0.43** (0.22 to 0.81)	**38 fewer per 1000** (from 13 fewer to 52 fewer)	⊕⊕⊕⊖ Moderate	Critical
Symptomatic catheter-related thrombosis measured as asymptomatic catheter-related thrombosis (up to 3 months)												
5	RCTs	Serious[d]	Not serious	Serious[e]	Serious[f]	None	48/610 (7.9%)	46/479 (9.6%)	**RR 0.95** (0.62 to 1.46)	**5 fewer per 1000** (from 36 fewer to 44 more)	⊕⊖⊖⊖ Very low	Critical
Major bleeding (up to 3 months)												
4	RCTs	Serious[g]	Not serious	Not serious	Very serious[h]	None	1/575 (0.2%)	0/443 (0.0%) 0.1%	**RR 1.49** (0.06 to 36.28)	**0 fewer per 1000** (from 0 fewer to 0 fewer) **0 fewer per 1000** (from 1 fewer to 35 more)	⊕⊖⊖⊖ Very low	Critical
Minor bleeding (up to 3 months)												
2	RCTs	Serious[i]	Not serious	Not serious	Serious[j]	None	15/275 (5.5%)	11/269 (4.1%)	**RR 1.35** (0.62 to 2.92)	**14 more per 1000** (from 16 fewer to 79 more)	⊕⊕⊖⊖ Low	Critical
Catheter-related infection (up to 3 months)												

(Continued)

2	RCTs	Serious[k]	Not serious	Not serious	Serious[l]	None	20/300 (6.7%)	16/174 (9.2%)	**RR 0.97** (0.52 to 1.79)	**3 fewer per 1000** (from 44 fewer to 73 more)	⊕⊕⊖⊖ Low	Critical
Thrombocytopenia (up to 3 months)												
4	RCTs	Serious[m]	Not serious	Not serious	Serious[n]	None	87/569 (15.3%)	76/433 (17.6%)	**RR 1.03** (0.80 to 1.33)	**5 more per 1000** (from 35 fewer to 58 more)	⊕⊕⊖⊖ Low	Critical

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

Explanations

[a]Downgraded by one level due to serious risk of bias; lack of blinding in participants and personnel in three studies; incomplete outcome data not addressed in three studies; and unclear or no allocation concealment in four out of five studies.

[b]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (36 per 1000 absolute reduction) and the possibility of important harm (20 per 1000 absolute increase), including 79 events in total.

[c]Downgraded by one level due to serious risk of bias; lack of blinding in participants and personnel in two studies; incomplete outcome data not addressed in three studies; and unclear or no allocation concealment in four out of five studies.

[d]Downgraded by one level due to concern about inconsistency, outcome measured as surrogate outcome.

[e]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (36 per 1000 absolute reduction) and the possibility of important harm (40 per 1000 absolute increase), including 94 events in total.

[f]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; incomplete outcome data not addressed in three studies; and unclear or no allocation concealment in four out of five studies.

[g]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in one study; incomplete outcome data not addressed in four studies; and unclear or no allocation concealment in three out of four studies.

[h]Downgraded by two levels due to concern about imprecision; 95% CI was consistent with the possibility for benefit (1 per 1000 absolute reduction) and the possibility of important harm (35 per 1000 absolute increase), including five events in total. Given the observed baseline risk of 0% we used 0.1% to generate an absolute effect and a confidence interval.

[i]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in one study; incomplete outcome data not addressed in two studies; and unclear or no allocation concealment in two out of two studies.

[j]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (16 per 1000 absolute reduction) and the possibility of important harm (79 per 1000 absolute increase), including 26 events in total.

[k]Downgraded by one level due to concern about risk of bias; incomplete outcome data not addressed in two studies; and unclear or no allocation concealment in one out of two studies.

[l]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (35 per 1000 absolute reduction) and the possibility of important harm (58 per 1000 absolute increase), including 36 events in total.

[m]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; incomplete outcome data not addressed in two studies; and unclear or no allocation concealment in three out of four studies.

[n]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (35 per 1000 absolute reduction) and the possibility of important harm (58 per 1000 absolute increase), including 163 events in total.

Appendix 5. GRADE evidence profile: vitamin K antagonist (VKA) versus no VKA

Certainty assessment							№ of participants		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VKA**	**No VKA**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (up to 3 months)												
4	RCTs	Serious[a]	Not serious	Not serious	Serious[b]	None	34/353 (9.6%)	33/348 (9.5%)	**RR 0.99** (0.64 to 1.55)[c]	**1 fewer per 1000** (from 34 fewer to 52 more)	⊕⊕⊖⊖ Low	Critical
Symptomatic catheter-related thrombosis (up to 3 months)												
4	RCTs	Serious[d]	Serious[e]	Not serious	Not serious[f]	None	36/634 (5.7%)	51/637 (8.0%)	**RR 0.61** (0.23 to 1.64)	**31 fewer per 1000** (from 51 more to 62 fewer)	⊕⊕⊖⊖ Low	Critical
Symptomatic catheter-related thrombosis measured as asymptomatic catheter-related thrombosis (up to 3 months)												
2	RCTs	Serious[g]	Not serious	Serious[h]	Serious[i]	None	8/193 (4.1%)	14/191 (7.3%)	**RR 0.61** (0.27 to 1.40)	**29 fewer per 1000** (from 29 more to 54 fewer)	⊕⊖⊖⊖ Very low	Critical
Major bleeding (up to 3 months)												
2	RCTs	Serious[j]	Not serious	Not serious	Serious[k]	None	7/509 (1.4%)	1/517 (0.2%)	**RR 7.14** (0.88 to 57.78)	**12 more per 1000** (from 0 fewer to 110 more)	⊕⊕⊖⊖ Low	Critical
Minor bleeding (up to 3 months)												
2	RCTs	Serious[l]	Not serious	Not serious	Serious[m]	None	17/509 (3.3%)	25/517 (4.8%)	**RR 0.69** (0.38 to 1.26)	**15 fewer per 1000** (from 13 more to 30 fewer)	⊕⊕⊖⊖ Low	Critical
Catheter-related infection (follow-up: 3 months)												
1	RCT	Serious[n]	Not serious	Not serious	Serious[o]	None	22/45 (48.9%)	18/43 (41.9%)	**RR 1.17** (0.74 to 1.85)	**71 more per 1000** (from 109 fewer to 356 more)	⊕⊕⊖⊖ Low	Critical

(Continued)

Premature catheter removal (follow-up: 3 months)

1	RCT	Serious[n]	Not serious	Not serious	Serious[p]	None	6/45 (13.3%)	7/43 (16.3%)	**RR 0.82** (0.30 to 2.24)	**29 fewer per 1000** (from 114 fewer to 202 more)	⊕⊕⊖⊖ Low	Critical

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

Explanations

[a]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in four studies and unclear or no allocation concealment in two out of four studies.

[b]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (34 per 1000 absolute reduction) and the possibility of important harm (52 per 1000 absolute increase), including 67 events in total.

[c]The trial WARP showed no overall survival advantage in participants taking warfarin compared with participants in the no-warfarin group (hazard ratio 0.98, 95% CI 0.77 to 1.25; P = 0.26) (Young 2009)

[d]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in four studies and no clear information concerning allocation concealment in one out of four studies).

[e]Downgraded by one level due to unexplained inconsistency (I^2 = 70%). Imprecision was partially driven by the inconsistency between the studies and was taken into consideration when downgrading by two levels for serious risk of bias and serious inconsistency.

[f]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (63 per 1000 absolute reduction) and the possibility of important harm (57 per 1000 absolute increase), including 87 events in total.

[g]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies and no clear information about allocation concealment in one out of two studies.

[h]Downgraded by one level due to concern about inconsistency, outcome measured as surrogate outcome.

[i]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (54 per 1000 absolute reduction) and the possibility of important harm (29 per 1000 absolute increase), including 22 events in total.

[j]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies and no clear information about allocation concealment in one out of two studies.

[k]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for no effect (0 per 1000 absolute reduction) and the possibility of important harm (120 per 1000 absolute increase), including eight events in total.

[l]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in three studies; and unclear or no allocation concealment in two out of three studies.

[m]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (30 per 1000 absolute reduction) and the possibility of important harm (16 per 1000 absolute increase), including 42 events in total.

[n]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in the included study).

[o]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (109 per 1000 absolute reduction) and the possibility of important harm (356 per 1000 absolute increase), including 40 events in total.

pDowngraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (114 per 1000 absolute reduction) and the possibility of important harm (202 per 1000 absolute increase), including 13 events in total.

Appendix 6. GRADE evidence profile: low-molecular-weight heparin (LMWH) versus vitamin K antagonist (VKA)

Certainty assessment							№ of participants		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH**	**VKA**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (up to 3 months)												
3	RCTs	Serious[a]	Not serious	Not serious	Serious[b]	None	25/285 (8.8%)	26/276 (9.4%)	**RR 0.94** (0.56 to 1.59)	**6 fewer per 1000** (from 41 fewer to 56 more)	⊕⊕⊖⊖ Low	Critical
Symptomatic catheter-related thrombosis (up to 3 months)												
2	RCTs	Serious[c]	Not serious	Not serious	Very serious[d]	None	6/165 (3.6%)	3/162 (1.9%)	**RR 1.83** (0.44 to 7.61)	**15 more per 1000** (from 10 fewer to 122 more)	⊕⊖⊖⊖ Very low	Critical
Symptomatic catheter-related thrombosis measured as asymptomatic catheter-related thrombosis (up to 3 months)												
2	RCTs	Serious[e]	Not serious	Serious[f]	Serious[g]	None	16/159 (10.1%)	10/158 (6.3%)	**RR 1.61** (0.75 to 3.46)	**39 more per 1000** (from 16 fewer to 156 more)	⊕⊖⊖⊖ Very low	Critical
Pulmonary embolism (up to 3 months)												
2	RCTs	Serious[h]	Not serious	Not serious	Serious[i]	None	14/165 (8.5%)	8/162 (4.9%)	**RR 1.70** (0.74 to 3.92)	**35 more per 1000** (from 13 fewer to 144 more)	⊕⊕⊖⊖ Low	Critical
Major bleeding (up to 3 months)												
2	RCTs	Serious[j]	Not serious	Not serious	Very serious[k]	None	1/147 (0.7%)	0/142 (0.0%)	**RR 3.11** (0.13 to 73.11)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ Very low	Critical
								0.1%		**2 more per 1000** (from 1 fewer to 72 more)		
Minor bleeding (up to 3 months)												

(Continued)

1	RCTs	Serious[l]	Not serious	Not serious	Very serious[m]	None	3/120 (2.5%)	3/114 (2.6%)	**RR 0.95** (0.20 to 4.61)	**1 fewer per 1000** (from 21 fewer to 95 more)	⊕⊖⊖⊖ Very low	Critical
Thrombocytopenia (up to 3 months)[n]												
2	RCTs	Serious[o]	Not serious	Not serious	Not serious	None	61/165 (37.0%)	35/162 (21.6%)	**RR 1.69** (1.20 to 2.39)	**149 more per 1000** (from 43 more to 300 more)	⊕⊕⊕⊖ Moderate	Critical

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

Explanations

[a]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in three studies; and unclear allocation concealment in two out of three studies.

[b]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (41 per 1000 absolute reduction) and the possibility of important harm (56 per 1000 absolute increase), including 51 events in total.

[c]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies and unclear allocation concealment in one out of two studies.

[d]Downgraded by two levels due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (10 per 1000 absolute reduction) and the possibility of important harm (122 per 1000 absolute increase), including nine events in total.

[e]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; and unclear allocation concealment in one out of two studies.

[f]Downgraded by one level due to concern about inconsistency, outcome measured as surrogate outcome.

[g]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (16 per 1000 absolute reduction) and the possibility of important harm (156 per 1000 absolute increase), including 26 events in total.

[h]Downgraded by one level due to concern both risk of bias; lack of blinding in participants and personnel in two studies; and allocation concealment not clear in one out of two studies.

[i]Downgraded by one level due to concern about imprecision; 95% CI was consistent with the possibility for important benefit (13 per 1000 absolute reduction) and the possibility of important harm (144 per 1000 absolute increase), including 22 events in total.

[j]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; and allocation concealment not clear in one out of two studies.

[k]Downgraded by two level due to concern about imprecision; 95% CI was consistent with the possibility for benefit (1 per 1000 absolute reduction) and the possibility of important harm (51 per 1000 absolute increase), including one event in total. Given the observed baseline risk of 0% we used 0.1% to generate an absolute effect and a confidence interval.

[l]Downgraded by one level due to concern about risk of bias (lack of blinding in participants and personnel in the study and unclear allocation concealment).

[m]Downgraded by two levels due to concern about imprecision (95% CI was consistent with the possibility for benefit (21 per 1000 absolute reduction) and the possibility of important harm (95 per 1000 absolute increase), including six events in total.

[n]The study by Lavau-Denes and colleagues included all grades of thrombocytopenia (even mild cases) (Lavau-Denes 2013).

[o]Downgraded by one level due to concern about risk of bias; lack of blinding in participants and personnel in two studies; and allocation concealment not clear in one out of two studies.

Appendix 7. Detailed results of sensitivity analysis

Systematic review	CVC
Comparison	LMWH vs no LMWH
Outcome	Symptomatic catheter-related thrombosis
CCA effect estimate	RR 0.43, 95% CI 0.22 to 0.81
Sensitivity analysis	
All participants with MPD had the event	RR 0.80, 95% CI 0.52 to 1.22

(Continued)

None of participants with MPD had the event	RR 0.42, 95% CI 0.22 to 0.80
Best-case scenario (intervention: none; control: all)	RR 0.15, 95% CI 0.07 to 0.32
Worst-case scenario (intervention: all; control: none)	RR 2.06, 95% CI 0.53 to 7.64
RI 1 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 0.42, 95% CI 0.22 to 0.81
RI 1.5 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 0.44, 95% CI 0.22 to 0.85
RI 2 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 0.45, 95% CI 0.23 to 0.89
RI 3 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 0.48, 95% CI 0.23 to 0.97
RI 5 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 0.52, 95% CI 0.24 to 1.12

Systematic review	CVC
Comparison	LMWH vs VKA
Outcome	Thrombocytopenia
CCA effect estimate	RR 1.69, 95% CI 1.20 to 2.39
Sensitivity analysis	
All participants with MPD had the event	RR 1.61, 95% CI 1.17 to 2.22
None of participants with MPD had the event	RR 1.69, 95% CI 1.19 to 2.39
Best-case scenario (intervention: none; control: all)	RR 1.85, 95% CI 1.31 to 2.60
Worst-case scenario (intervention: all; control: none)	RR 1.46, 95% CI 1.05 to 2.03
RI 1 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 1.69, 95% CI 1.19 to 2.39
RI 1.5 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 1.67, 95% CI 1.18 to 2.36
RI 2 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 1.66, 95% CI 1.18 to 2.34
RI 3 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 1.64, 95% CI 1.16 to 2.31
RI 5 $_{\text{intervention}}^{1}$ $_{\text{control}}$	RR 1.61, 95% CI 1.15 to 2.27

CCA: complete-case analysis; CI: confidence interval; CVC: central venous catheter; DVT: deep venous thrombosis; LMWH: low-molecular-weight heparin; MPD: missing participant data; RR: risk ratio; VKA: vitamin K antagonist.

WHAT'S NEW

Date	Event	Description
25 February 2019	Amended	Additional text added to Acknowledgements.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 3, 2007

Date	Event	Description
11 July 2018	Amended	Minor correction to text.
9 July 2018	Amended	Minor correction to text.
28 June 2018	Amended	Declaration of interest updated.
23 May 2018	New citation required but conclusions have not changed	Search updated 14 May 2018 (one new study found, conclusions not changed).
23 May 2018	New search has been performed	Author list updated.
7 February 2010	New citation required but conclusions have not changed	Updated search (February 2010) and included two new studies
4 August 2008	Amended	Converted to new review format.
11 November 2007	New search has been performed	Minor update. We added DeCicco 2006 as an excluded study. We updated the interpretation of heterogeneity based on I^2 as follows: 0 to 30 = low; 30 to 60 = moderate and worthy of investigation; 60 to 90 = severe and worthy of understanding; 90 to100 = allowing aggregation only with major caution We explained the implications for practice by providing two examples. We expanded on the limitations of the review particularly in relation to the small number of included studies and to the 3 abstracts for which we could not obtain. We have updated the funding and conflict of interest sections.
12 April 2007	New citation required and conclusions have changed	Substantive amendment

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LAK: searching for trials, full-text retrieval, screening, data extraction, data analysis, data interpretation, manuscript drafting, review co-ordination.
IGT: screening, full-text retrieval, data extraction, manuscript drafting.
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CM: screening, full-text retrieval, data extraction.
MB: screening, full-text retrieval, data extraction.
VY: screening, full-text retrieval, data extraction.
IT: screening, full-text retrieval, data extraction.
FS: screening, full-text retrieval, data extraction.
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DECLARATIONS OF INTEREST

LAK: declares no conflicts of interests.
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INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects] [*therapeutic use]; Catheter-Related Infections [epidemiology]; Catheterization, Central Venous [*adverse effects]; Heparin [adverse effects] [therapeutic use]; Heparin, Low-Molecular-Weight [adverse effects] [therapeutic use]; Neoplasms [mortality] [*therapy]; Randomized Controlled Trials as Topic; Secondary Prevention [methods]; Thrombocytopenia [chemically induced]; Venous Thrombosis [etiology] [mortality] [*prevention & control]; Vitamin K [antagonists & inhibitors]

MeSH check words

Adult; Child; Humans