Review Article

Thromboprophylaxis in cancer patients with central venous catheters

A systematic review and meta-analysis

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Summary

It was the aim of the review to determine the risks and benefits of primary thromboprophylaxis with anticoagulants in cancer patients with central venous devices. Medline, Central and Google Scholar databases were searched for randomized controlled trials (RCTs) in June 2006. Two reviewers extracted data and appraised the quality of RCTs. Results were expressed as relative risk (RR) with 95% confidence intervals (CI) using random effects model for the outcomes of catheter-related thrombosis, bleeding and thrombocytopenia. Eight RCTs (1,428 patients) were included. There was no statistically significant difference in the risk of catheter-related thrombosis for the use of warfarin versus placebo (3 trials, 425 patients, RR 0.75, 95% CI 0.24–2.35, p=0.63), heparin versus placebo (4 trials, 886 patients, RR 0.46 95% CI 0.18–1.20, p=0.06) or warfarin, unfractionated heparin or low-molecular-weight heparin versus placebo (7 trials, 1,311 patients, RR 0.59, 95% CI 0.31–1.13, p=0.11). Substantial statistical heterogeneity was noted among these trials (I^2>50%). The use of anticoagulants showed no statistically significant difference in the risk of overall bleeding (5 trials, 1,193 patients, RR 1.24, 95% CI 0.84–1.82, p=0.28), and thrombocytopenia for heparin versus placebo (4 trials, 958 patients, RR 0.85, 95% CI 0.49, 1.46, p=0.55) without any statistical heterogeneity (I^2=0%). In cancer patients with central venous devices, thromboprophylaxis has no significant effect on the risk of catheter related thrombosis or bleeding. The use of primary thromboprophylaxis in cancer patients with central venous catheters while not causing any harm provides no benefit.

Keywords

Cancer, thromboprophylaxis, catheter-related thrombosis

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Introduction

Central venous catheters (CVCs) in the form of surgically tunneled catheters, or totally implanted venous access devices, are increasingly being used for long duration infusion chemotherapy (1, 2). Although these devices have revolutionized the clinical management of cancer patients, they are associated with several complications, including infection, catheter thrombosis and pulmonary embolism (PE). Catheter-related venous thrombosis can lead to considerable morbidity, occasional mortality, and the loss of catheters (1, 3). The incidence of venous thrombosis in the general population is reported to be 1.97 per 1,000 person-years (4), most of which is seen in the lower extremities. However, the diagnosis of upper extremity deep venous thrombosis (UEDVT) is increasing. UEDVT constitutes about 18% of all DVTs. About 7–9 % of patients with UEDVT have been reported to develop acute PE (3).

The reported incidence of catheter-related thrombosis varies considerably ranging from 12–60% in various studies (1, 5). The wide variability in incidence of catheter-related thrombosis is due in part to the differences in catheter type, position, duration of insertion, type of malignancy and use of different chemotherapeutic agents (1). Catheter-related thrombosis is frequently under-diagnosed, as most patients are asymptomatic or have non-specific symptoms. Since the catheters are deep in the mediastinum, thrombosis or catheter infection may be clinically occult until late in its course, and when discovered can be potentially lethal (2, 6, 7).

The high rate of thrombosis in cancer patients with CVCs has led to the use of several methods to prevent this complication. These include routine flushing of the catheter ports with unfractionated heparin (UFH), saline or other agents (8, 9). The main effort to reduce CVC thrombosis, however, has been the use of

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systemic anticoagulant therapy (warfarin, UFH or low-molecular-weight heparin [LMWH]) (4). Several studies conducted to analyze the role of systemic anticoagulation in preventing catheter-related thrombosis have shown conflicting results. In 2001, the sixth American College of Chest Physicians (ACCP) guidelines stated that 1 mg of warfarin or LMWH daily is a valid prophylactic option for CVC thrombosis (1). However, the seventh ACCP guidelines (2004) reversed its earlier recommendation and advised against the routine use of anticoagulation in cancer patients with central venous lines (9, 10).

Given the conflicting recommendations regarding the role of anticoagulant prophylaxis in cancer patients with CVCs and the uncertainty about their risk and benefits, we undertook a systematic review of all randomized control trials (RCTs) comparing the efficacy of systemic anticoagulation (low-dose warfarin, UFH, and LMWH) in preventing catheter-related thrombosis in cancer patients with CVCs. We also analyzed secondary outcomes such as bleeding complications and thrombocytopenia with these strategies.

Methods

Inclusion criteria

All RCTs analyzing the efficacy of primary thromboprophylaxis (low-dose warfarin [1 mg/day], UFH or LMWH) as compared to placebo or no treatment in preventing catheter related thrombosis and systemic embolization in cancer patients (haematological or solid tumors) with central venous devices were considered for inclusion. Studies comparing the efficacy of two different thromboprophylaxis regimens in preventing catheter-related thrombosis were also included. The first period of randomized crossover studies were included.

Exclusion criteria

Animal studies, non-RCTs, RCTs of interventions not relevant to this systematic review and studies analyzing the efficacy of heparin flushes or heparin-bonded catheters alone in preventing catheter-related thrombosis were excluded.

Search strategy for identification of studies

Medline (1966 to June 2006), Cochrane Central Register of RCTs (June 2006) and Google Scholar (June 2006) were searched for relevant articles using appropriate MESH terms: *warfarin, coumadin, heparin, anticoagulants, anticoagulation, low molecular weight heparin, direct thrombin inhibitors, thromboprophylaxis, anticoagulant prophylaxis cancer, malignancy, central venous catheters, indwelling catheters, totally implanted venous access devices, catheterization, tunneled catheters, mediport, totally implanted catheters, randomized controlled trials*. References of the included studies were searched for additional studies. There was no language restriction. Abstracts of the search results were screened according to the inclusion criteria.

Data analysis

Two authors (PC, AN) independently assessed each trial and extracted data on the characteristics of participants, interventions, comparisons, and the following outcomes: catheter-associated venous thrombosis, all cause bleeding, major bleeding episodes, minor bleeding episodes, and thrombocytopenia using a standardized data extraction form. The quality of RCTs was assessed by standard methods including allocation concealment, blinding of participants, investigators, outcome assessors, use of intention-to-treat principle, and completeness to follow up (11). Any discrepancies were resolved by discussion with an arbitrator (SDN). In the RCTs data were reported either as the number of events per catheter or as number of events per patients. However, we included data as number of events per patients in this review. Dichotomous data (catheter related thrombosis, all cause bleeding, major bleeding, minor bleeding, and thrombocytopenia) were analyzed using the relative risk (RR) measure and its 95% confidence interval (CI).

Risks estimated from individual trials were pooled using the DerSimonian-laird random effects model. Heterogeneity across the included studies was analyzed using heterogeneity chi-square (Cochrane Q) statistic and I^2 test. An I^2 of greater than 50% was evidence of substantial statistical heterogeneity. All p-values are reported as two sides. Sensitivity analysis and meta-regression analysis were not performed secondary to the small number of studies. We conducted a separate analysis to analyze the effect of different types of thromboprophylactic regimens in preventing thrombosis. All analyses were undertaken in RevMan 4.2.8.

Results

Search results

The combined search of Medline, Cochrane Central Register of RCTs and Google Scholar identified 569 articles of which 547 were excluded (Fig. 1). The main reason for exclusion at this stage was that the studies were either non-randomized or evaluated interventions irrelevant to this review. Full text assessment

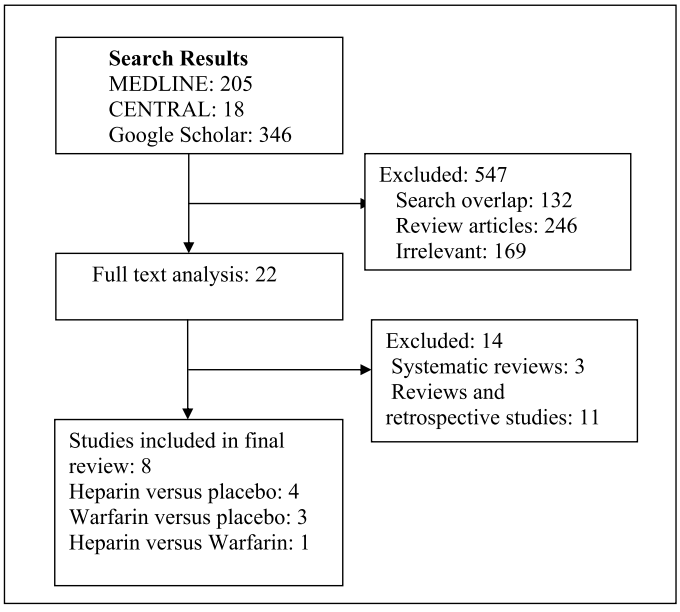

Figure 1: Flowchart showing number of citations retrieved by individual searches and number of included studies.

Table 1: Characteristics of study methods, participants, interventions and outcomes analyzed in the included studies.

Study/ year	Type of study	Type of catheter	Type of malignancy	Intervention	Thrombosis assessment method	Duration of treatment	Follow up (weeks)	n/N	Endpoint assessment
Heaton et al. 2002 (14)	RCT, non-blinded, no ITT	Double lumen catheters	Hematological	Warfarin 1 mg vs. no treatment	Venography in symptomatic patients	13 weeks	NA	45 / 43	Catheter thrombosis, bleeding,
Couban et al. 2005 (13)	RCT, blinded, ITT	Tunneled and implanted	Solid and hematological	Warfarin 1 mg vs. placebo	Venography in symptomatic patients	Until CVC was removed or patient had thrombosis	3 months	130 / 125	Catheter thrombosis, bleeding
Bern et al. 1990 (12)	RCT, non-blinded, no ITT	Port-a-cath	Solid and hematological	Warfarin 1 mg vs. no treatment	Venography in symptomatic patients, end of treatment	13 weeks	NA	42 / 40	Catheter thrombosis, mortality
Verso et al. 2005 (17)	RCT blinded, ITT	Polyurethane or silicone	Solid and hematological	Enoxaparin 40 mg sc vs. placebo	Venography in symptomatic patients, end of treatment	6 weeks	3 months	189 / 193	Catheter thrombosis, bleeding, thrombocytopenia
Monreal et al. 1996 (2)	RT, non-blinded, no ITT	Port-a-cath	Solid tumors	Dalteparin 2,500 IU sc vs. no treatment	Venography in symptomatic patients, end of treatment	13 weeks	NA	16 / 13	Catheter thrombosis, bleeding, thrombocytopenia
Abdelkefi et al. 2004 (16)	RCT, blinded, no ITT	Non-tunneled, double lumen catheter	Hematological	Unfractionated heparin 100 IU/kg iv vs. placebo	Ultrasound in symptomatic patients, end of treatment	Until patient was discharged from the hospital	8 weeks after catheter removal	55 / 53	Catheter thrombosis, bleeding, thrombocytopenia
Karthaus et al. 2005 (15)	RCT, blinded, ITT	Unclear	Solid and hematological	Dalteparin sc vs. placebo	Venography or ultrasound in symptomatic patients and end of treatment	16 weeks	NA	294 / 145	Catheter thrombosis, Bleeding, thrombocytopenia
Mismetti et al. (18)	RCT, no ITT	Totally implanted port system	Solid tumors	Nadroparin 2,850 SC vs. warfarin 1 mg	Venography in symptomatic patients and end of treatment	13 weeks	6 months	21 / 24 *	Catheter thrombosis

RT- randomized trial, RCT –randomized controlled trial, SC- subcutaneous, IV-intravenous, N: number of patients in control arm, n: number of patients in treatment arm, ITT: intention to treat, CVC: central venous catheters, NA: not applicable.* In the trial by Mismetti et al N stands for number of patients in nadroparin group and n for the number of patients in warfarin group.

of 22 potentially relevant articles resulted in identification of eight eligible trials. Trials excluded were either review articles or meta-analysis that did not include cancer patients alone or did not meet the inclusion criteria.

Trial characteristics

Characteristics of the participants and the interventions of the included trials are detailed in Table1. The number of participants ranged from 29 to 439. Most studies used superior vena cava catheters. However, the type of catheter used in each study was variable and unknown in the trial by Karthaus et al. (15) (Table 1). None of the studies reported using heparin-bonded catheters. Four studies used heparin flushes during the study as per the hospital protocol (2, 12, 14, 15). Catheter thrombosis was diagnosed with contrast venography in nearly all studies, except by Abdelkefi et al. in which ultrasonography was used (16). It was unclear why Karthaus et al. used two different methods for detection of catheter thrombosis. More than half of the patients underwent venography, while the remaining patients underwent compression ultrasound for the diagnosis of UEDVT (15). Most studies looked for catheter thrombosis in symptomatic patients as well as at the end of treatment period. However, two studies looked for catheter thrombosis in symptomatic patients alone but not at the end of the treatment period (13, 14).

Trial quality

By current methodological standards, trial quality was variable. Allocation concealment was unclear in all the trials. Blinding was complete in four studies (13, 15–17). Only three trials were analyzed on intention to treat basis (13, 15, 17). Two trials were not placebo controlled (2, 12). Loss to follow- up was not reported in the included studies.

Trial results

Catheter-related thrombosis

Thromboprophylaxis versus placebo or no treatment (Fig. 2): Anticoagulation as compared to placebo or no treatment had no

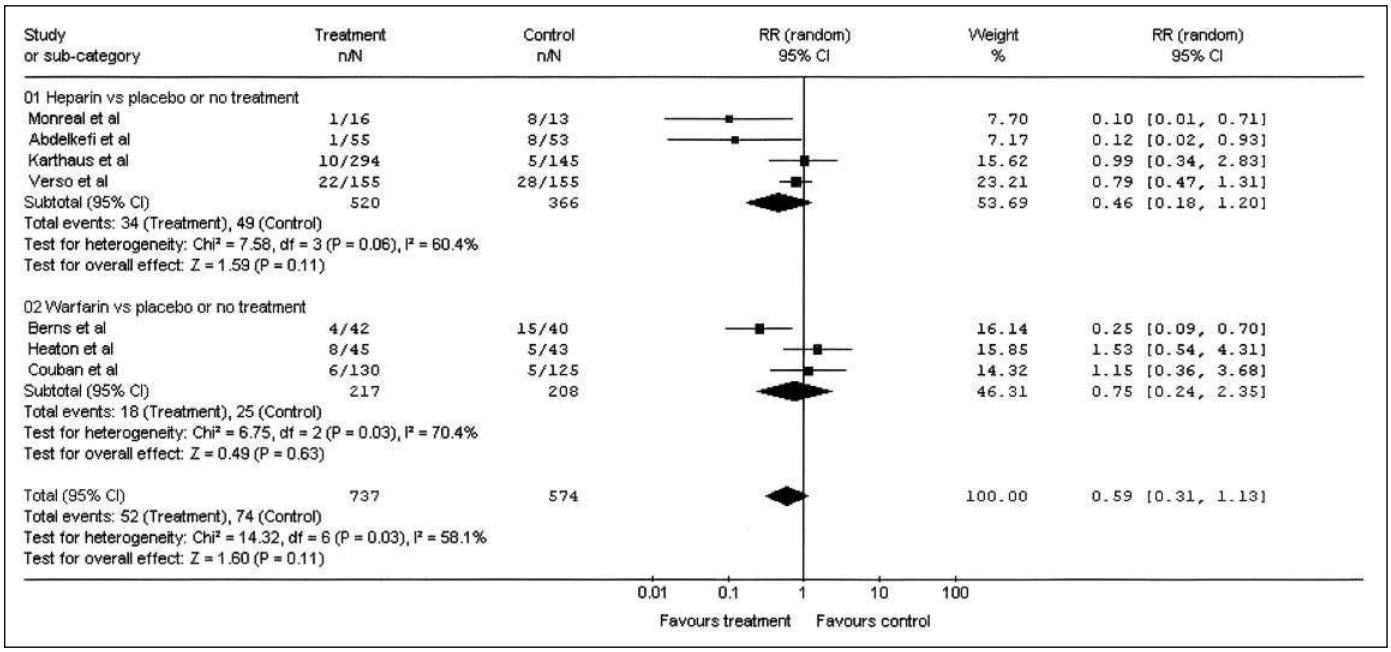

Figure 2: Effect of anticoagulation of the incidence of catheter-related thrombosis in cancer patients.

impact on the risk of catheter-related thrombosis (7 trials, 1311 patients, RR 0.59, 95% CI 0.31, 1.13, p=0.11) (2, 12–17). There was substantial statistical heterogeneity among the included studies (heterogeneity Chi^2=14.32, I^2 = 58.1%). Heterogeneity could be attributed to the differences in the type of anticoagulants used, sample size, type of catheters, and use of heparin flushes in some studies.

Low-dose warfarin versus placebo or no treatment: Warfarin in comparison to placebo or no treatment showed no statistically significant difference in the risk of catheter related thrombosis (3 studies, 425 patients, RR 0.75, 95% CI 0.24, 2.35, p=0.63). There was substantial statistical heterogeneity among the included studies (Chi^2= 6.75, I^2= 70.4%). Heterogeneity could be attributed to the difference in the sample size, and duration of treatment.

Heparin (UFH or LMWH) versus placebo or no treatment: Heparin as compared to placebo or no treatment showed no statistically significant difference in the risk of catheter-related venous thrombosis (4 studies, 886 patients, RR 0.46, 95% CI 0.18, 1.20, p=0.06) (2, 15–17). There was substantial statistical heterogeneity among the included studies (Chi^2=7.58, I^2=60.4%). Heterogeneity could be attributed to the differences in type of catheters, and use of heparin flushes in some studies.

LMWH versus low-dose warfarin: Only one trial was included in this group (18). This study showed no statistically significant difference in the incidence of catheter thrombosis between the two treatment groups (45 patients, RR 1.71, 95% CI 0.56, 5.26).

Bleeding episodes

Thromboprophylaxis versus placebo or no treatment (Overall) (Fig. 3): Use of anticoagulants showed no statistically significant difference in the risk of overall bleeding in comparison to placebo (5 trials, 1,193 patients, RR 1.24, 95% CI 0.84, 1.82, p=0.28) (2, 13–15, 17). There was no substantial statistical heterogeneity among the included studies (Chi^2=1.60, I^2=0%). Similarly, the risk of major bleeding (6 trials, 1,301 patients, RR 0.44, 95% CI 0.12, 1.67, p=0.28) or minor bleeding did not differ between the two groups (5 trials, 1,193 patients, RR 1.36, 95% CI 0.91, 2.03, p=0.12).

Low-dose warfarin versus placebo or no treatment: There was no statistically significant difference in the risk of overall bleeding with the use of warfarin in comparison to placebo (2 studies, 343 patients, RR 0.93, 95% CI 0.31, 2.77, p=0.19), without any statistical heterogeneity among the studies (Chi^2=0.55, I^2 =0%, p=0.45) (13, 14). The occurrence of major bleeding (2 trials, 343 patients, RR 0.14, 95% CI 0.01, 2.63, p=0.49) or minor bleeding did not differ between the two groups (2 trials, 343 patients, RR 1.76, 95% CI 0.49, 6.40, p=0.39) (13, 14).

Heparin (UFH or LMWH) versus placebo or no treatment: There was no increase in the risk of bleeding episodes in patients taking heparin than in patients with no treatment or placebo (3 trials, 850 patients, RR 1.29, 95% CI 0.85, 1.95, p=0.23) (2, 15, 17), without any statistical heterogeneity among the included studies (Chi^2 =0.76, I^2 =0%, p=0.69). The risk of major bleeding (4 trials, 958 patients, RR 0.41, 95% CI 0.05, 3.30, p=0.49) or minor bleeding did not differ between the two groups (3 trials, 850 patients, RR 1.31, 95% CI 0.86, 2.00, p=0.23).

Thrombocytopenia

Heparin versus placebo or no treatment: The risk of thrombocytopenia did not increase with the use of heparin in comparison to placebo (4 trials, 958 patients, RR 0.85, 95% CI 0.49, 1.46, p=0.55) without any statistical heterogeneity among the included studies (Chi^2 =0.0.11, I^2 =0%).

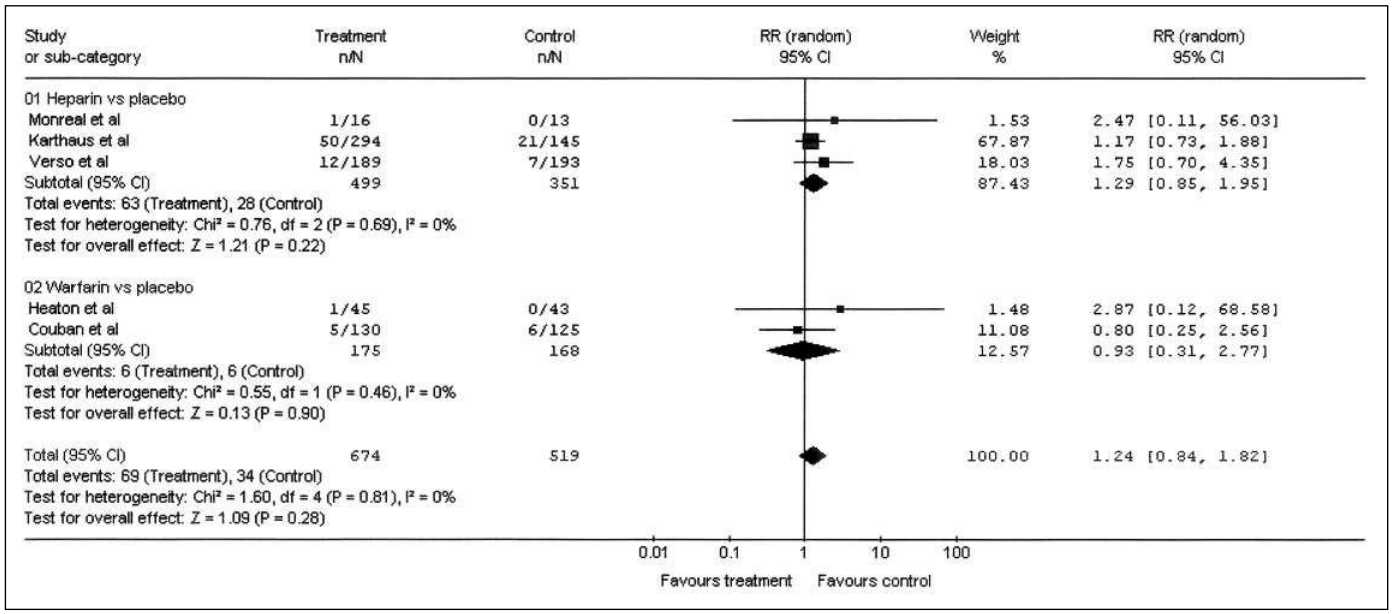

Figure 3: Effect of anticoagulation of the incidence of overall bleeding in cancer patients.

Discussion

Our meta-analysis showed no statistically significant benefit with the use of primary thromboprophylaxis in the form of warfarin, UFH or LMWH in preventing catheter-related thrombosis in cancer patients. The risk of thrombocytopenia and bleeding episodes (all-cause bleeding, major bleeding, minor bleeding) was comparable between patients receiving anticoagulation and placebo. To our knowledge, this is the first metaanalysis of RCTs, which analyzed the efficacy of various thromboprophylactic regimens in preventing venous thrombosis exclusively in cancer patients with CVCs.

Our results differ from previous reviews in the literature. A meta-analysis of RCTs by Randolph et al. (19) comparing all heparin regimens (heparin infusion, flushes and heparin-bonded catheters) in patients with venous access devices showed a reduction in catheter-related thrombosis (RR 0.66, 95% CI 0.42, 1.05). However, this study included patients without malignancies and did not conduct a separate analysis for cancer patients. A recent systematic review by Klerk et al. compared many subgroups of patients with CVCs (20). A subgroup analysis of cancer patients, which included two studies (Berns et al., Monreal et al.) showed some benefit in decreasing catheter-related thrombosis in patients with systemic anticoagulation. A meta-analysis was not done in this review secondary to the limited number of studies. Another review by Cunningham et al., which did not include a meta-analysis, observed a reduction in absolute baseline of thrombotic events in newer studies as compared to older studies (3). But, newer studies included in this review show no benefit from thromboprophylaxis in preventing catheter thrombosis (13, 15, 17). All the three newer studies were double blind trials (13, 15, 17) and hence provided higher quality evidence than the earlier published randomized trials, which were not blinded. The authors speculated that the reason for this decline in the catheter-related events could be due to better catheter care, use of newer, less thrombogenic catheters, use of heparin-bonded catheters and the routine use of heparin or saline flushes.

There are several limitations to our review. The RCTs lacked a clear consensus definition of catheter-related thrombosis, and different diagnostic modalities (venography vs. ultrasound) were used to diagnose catheter-related thrombosis. RCTs included patients with varying malignancies (haematological malignancies in some [14, 16] or solid tumors in others), who also received different modes of chemotherapy. The trials were usually short-term and inadequately powered to estimate long-term mortality differences or differences in the rate of subsequent PE. The combination of small cohort sizes, discrepant study population, differences in study design, and the use of different thromboprophylaxis agents for varying duration accounts for the significant statistical heterogeneity. The wide CI (RR 0.31 to 1.13) around the point estimates cannot rule out the possibility of a 69% reduction in the catheter thrombosis, as well as the possibility of a 13% increase in this risk. In light of the overall estimates of RR (0.59) with CI estimates very close to 1 along with heterogeneity in the study designs, the possibility of some potential benefit from anticoagulation not detected by the current study designs cannot be ruled out.

A recent systematic review concluded that anticoagulants, particularly LMWH, significantly improved overall survival in cancer patients without venous thrombosis (RR-0.90) while increasing the risk for bleeding complications (27). This review also noted that the benefit was noted in some cancer types and not in all cancer patients. Several anticoagulants are available for the treatment and prophylaxis in cancer patients without prior history of thrombosis (28, 29). The use of anticoagulants has been known to cause several serious adverse events including the risk of bleeding (29, 30). However, given the limitations of available data, the universal use of anticoagulants as antineoplastic therapy or anticoagulation in all cancer patients cannot be recommended until additional RCTs confirm that the benefits of anticoagulation outweigh their risks.

Future RCTs of thromboprophylaxis with CVCs need to be adequately powered to detect differences in both short-term and long-term outcomes (such as PE, bleeding, hospitalization rates, mortality rates) in cancer patients. They need to be of better methodological quality, with an adequate duration of follow up to discern differences between symptomatic versus asymptomatic CVC thrombosis. Separate trials need to be conducted for hematological or solid tumors. More importantly, these trials should have a consensual definition of catheter-related thrombosis.

Our findings have potential clinical implications. Physicians and patients should weigh the risk and benefit of anticoagulation in cancer patients with central venous devices. Until we have more solid evidence to the contrary, the use of thromboprophylaxis in cancer patients with CVCs while not causing any harm provides no benefit.

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