ORIGINAL RESEARCH

# Incidence of Venous Thromboembolism and Benefits and Risks of Thromboprophylaxis After Cardiac Surgery: A Systematic Review and Meta-Analysis

Kwok M. Ho, MPH, PhD, FRCP; Ebrahim Bham, MBBS; Warren Pavey, MBBS

***Background*—**Optimal thromboprophylaxis after cardiac surgery is uncertain. This systematic review aimed to define the incidence and risk factors for deep vein thrombosis (DVT), fatal and nonfatal pulmonary embolism (PE), and assess whether venous thromboembolism (VTE) prophylaxis was effective in reducing VTE without complications after cardiac surgery.

***Methods and Results*—**Two reviewers independently searched and assessed the quality and outcomes of randomized, controlled trials (RCTs) and observational studies on VTE after cardiac surgery in the MEDLINE, EMBASE, and Cochrane controlled trial register (1966 to December 2014). Sixty-eight studies provided data on VTE outcomes or complications related to thromboprophylaxis after cardiac surgery. The majority of the studies were observational studies (n=49), 16 studies were RCTs, and 3 were meta-analyses. VTE prophylaxis was associated with a reduced risk of PE (relative risk [RR], 0.45; 95% confidence interval [CI], 0.28–0.72; *P*=0.0008) or symptomatic VTE (RR, 0.44; 95% CI, 0.28–0.71; *P*=0.0006) compared to the control without significant heterogeneity. Median incidence (interquartile range) of symptomatic DVT, PE, and fatal PE were 3.2% (0.6–8.1), 0.6% (0.3–2.9), and 0.3% (0.08–1.7), respectively. Previous history of VTE, obesity, left or right ventricular failure, and prolonged bed rest, mechanical ventilation, or use of a central venous catheter were common risk factors for VTE. Bleeding or cardiac tamponade requiring reoperation owing to pharmacological VTE prophylaxis alone, without systemic anticoagulation, was not observed.

***Conclusions*—**Unless proven otherwise by adequately powered RCTs, initiating pharmacological VTE prophylaxis as soon as possible after cardiac surgery for patients who have no active bleeding is highly recommended. **(*J Am Heart Assoc*. 2015;4: e002652 doi: 10.1161/JAHA.115.002652)**

**Key Words:** deep vein thrombosis • heart surgery • prevention • pulmonary embolism

Hospitalization is a major risk factor for venous thromboembolism (VTE). According to the latest Centers for Disease Control and Prevention (CDC) analysis, approximately 547 596 hospitalizations were complicated by VTE each year among those age ≥18 years in the United States.[1] Deep vein thrombosis (DVT) occurred in 348 558 hospitalizations, pulmonary embolism (PE) occurred in 277 549 hospitalizations, and concomitant DVT and PE occurred in 78 511 hospitalizations each year. The total cost of VTE per person including loss of productivity and well-being was estimated to be over A$1 470 000 in the year 2008, and it was estimated that the total cost of VTE for Australia in 2008 was A3.9 billion, more than the costs of all other diseases including cancers.[2]

The practice of VTE prophylaxis after cardiac surgery is controversial. According to the European Association for Cardiothoracic Surgery (EACTS) guidelines, prophylactic anticoagulation for VTE should be commenced from the first postoperative day.[3] However, an increased risk of bleeding and cardiac tamponade resulting from pharmacological thromboprophylaxis remains a major concern for patients who have undergone cardiac surgery.[4] Indeed, the latest American College of Chest Physicians evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis have also stressed that patients after cardiac surgery are at high risk of major bleeding complications with only moderate risk for VTE (Grade-2C), and suggested that

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pharmacological VTE prophylaxis is only needed for those with prolonged hospitalization postsurgery.[5] These Grade-2C recommendations were mainly based on consensus among experts or weak evidence.

Recent evidence suggested that a prothrombotic state owing to multiple mechanisms, including increased fibrinogen concentrations, thrombin generation, tissue factor activation, reduced fibrinolysis, return of normal platelet aggregation, and aspirin resistance,[6–13] is common after cardiac surgery from postoperative day 1, reaches a peak prothrombotic state between day 3 and day 5 after surgery,[6–9] and can last up to 30 days postsurgery.[6] Therefore, patients after cardiac surgery are not necessarily protected from VTE from day 1 postoperatively, despite their tendency for bleeding during the intraoperative and immediate postoperative period. Whether the benefits of VTE prophylaxis would outweigh its possible harms in patients after cardiac surgery remains contentious. In this systematic review, we aimed to define the incidence of DVT, fatal and nonfatal PE, risk factors for VTE, and also to assess whether VTE prophylaxis was indeed effective in reducing VTE without increasing risk of complications after cardiac surgery.

## Methods

### Data Sources and Study Selection

Two reviewers searched the Cochrane controlled trial register (2014, issue 4) and the EMBASE (January 1988 to December 12, 2014) and MEDLINE databases (1966 to December 12, 2014) independently. During the electronic database search, the following exploded Medical Subject Heading (MeSH) terms were used: “heart surgery” or “cardiac surgery” or “coronary artery bypass” or “valve surgery” or “valvular surgery” AND “venous thromboembolism” or “pulmonary embolism” or “deep vein thrombosis”. The search included all forms of publications, including case series, cohort or case control studies, clinical trials, letters, editorials, reviews, meta-analysis, or randomized, controlled trials (RCTs) without any age or language restrictions. Animal studies, studies without involving cardiac surgery, or isolated case reports were excluded from this review. The reference lists of related editorials, reviews, and original articles identified were searched for relevant studies. Finally, the websites of the International Network of Agencies of Health Technology Assessment in Health Care were searched to ensure all suitable trials were included.

Two reviewers independently examined all identified studies to confirm they fulfilled the inclusion criteria and VTE outcomes were reported. For RCTs, the quality of the trial, such as allocation concealment, randomization method, and blinding of treatment and assessment of outcome, was assessed. The grading of allocation was based on the Cochrane approach, that is, adequate, inadequate, or uncertain. When the reported methodology and results of the included trials were unclear, the corresponding authors of the trials were contacted to clarify the data (n=2, but 1 did not respond to our study inquiries). Any disagreements between the 2 independent reviewers were resolved by consensus.

### Data Reporting and Statistical Analysis

VTE was the primary outcome of this review, and, whenever possible, we reported the incidence of symptomatic and asymptomatic VTE separately. In trying to identify the risk factors for VTE and complications after the use of VTE prophylaxis, only risk factors that were significant in the multivariate analyses were reported in this review. We also assessed whether the incidence of DVT was different between the leg with and without the great saphenous vein harvested for coronary artery bypass grafting (CABG) surgery.

The other outcomes assessed included the risk factors for bleeding complications or cardiac tamponade. In trying to identify whether VTE prophylaxis, in general, would be effective in reducing VTE after cardiac surgery, all interventions aimed to VTE were analyzed together against no comparative VTE prophylaxis. Outcomes were reported as relative risk (RR) with 95% confidence interval (CI), using a random-effects model (with the Mantel–Haenszel method, which estimates the amount of between-study variation by comparing each study’s result with a Mantel–Haenszel fixed-effect meta-analysis result). The presence of heterogeneity between trials was assessed by the chi-square statistics and the extent of inconsistency was assessed using $I^2$ statistics.[14] An $I^2$>40% was considered as significant heterogeneity in this study, and when heterogeneity was present, the data were further examined to explore for reasons for the heterogeneity by metaregression. Data were analyzed by the Review Manager (version 4.2.6 for Windows; Oxford, UK: The Cochrane Collaboration, 2003) and metaregression was conducted by Comprehensive Meta-analysis (version 2.2.034, 2006, USA). A *P* value of less than 0.05 was taken as significant in this systematic review.

### Sensitivity Analysis

In assessing the incidence of VTE, we did a sensitivity analysis by restricting the analysis to higher-quality studies (RCTs and prospective cohort studies). We also assessed whether the incidence of VTE was related to the sample size of the studies and how recent the study was conducted. In assessing effectiveness of VTE prophylaxis, we did a sensitivity analysis by restricting our analysis to studies that had adequate allocation concealment. In assessing whether the leg with the great saphenous vein harvested was associated with a higher

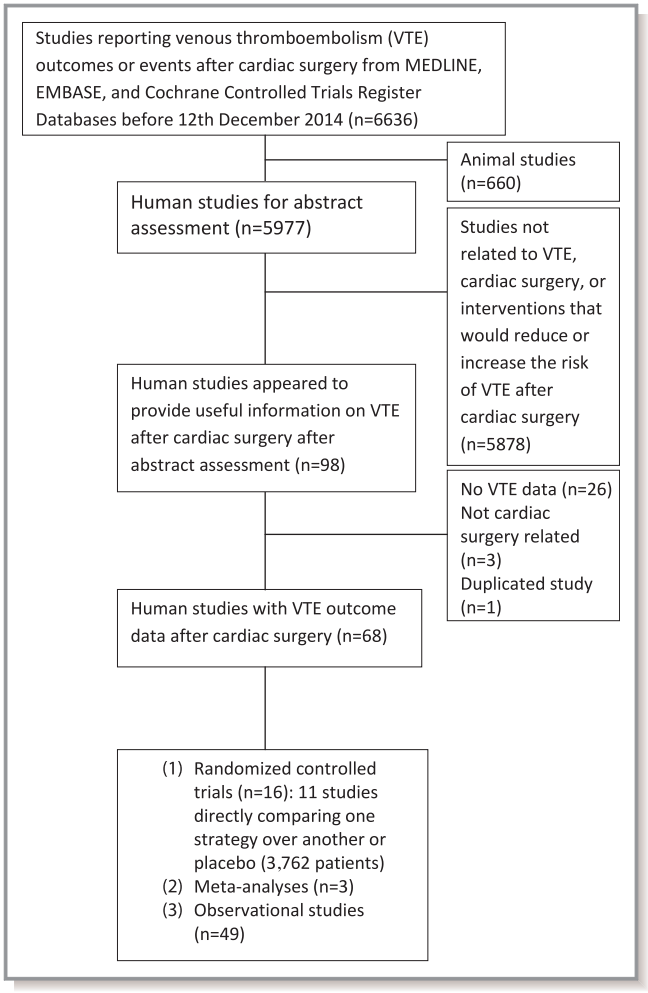


**Figure 1.** Flowchart showing the inclusion and exclusion of studies for this systematic review.

risk of DVT, we restricted our analysis to studies that utilized routine ultrasound scans on both legs regardless of whether the patients had symptoms of DVT.

# Results

## Study Characteristics

Of the 6636 studies identified in the literatures search, a total of 68 studies provided data on VTE outcomes or complications related to VTE prophylaxis after cardiac surgery (Figure 1). The majority of the studies were observational studies (n=49), 16 studies were RCTs, and 3 were meta-analyses (Tables 1 and 2).[15–84] Of the 16 RCTs identified,* only 9 studies had allocation concealment and 6 used some form of blinding (Table 1). Seven RCTs assessed 1 method of VTE prophylaxis against a placebo or control group, and 5 studies compared 1 pharmacological agent against another (eg, 3 studies on warfarin vs. aspirin, 2 studies on unfractionated heparin [UFH] vs. low-molecular-weight heparin [LMWH] or hirudin). Six RCTs compared interventions primarily not aiming at reducing VTE, but VTE data were reported (eg, activated factor VIIa, off-pump CABG vs. on-pump CABG, placebo vs. cyclooxygenase 2 inhibitors, and different types of autograft/prosthesis or cell saver devices) (Table 1). The 3 meta-analyses identified were related to use of factor VIIa or tranexamic acid for adult cardiac surgery and warfarin versus antiplatelet agents after Fontan surgery for congenital heart diseases.[62,63,74]

Of the 49 observational studies included in this study, only 9 (18%) were prospective studies and 13 reported risk factors for VTE events or complications from VTE prophylaxis after adjusting for known risk factors for VTE or complications with a multivariate analysis, respectively (Table 2).

## VTE Events After Cardiac Surgery With Prophylaxis Versus Control/Placebo

Pooling all forms of VTE prophylaxis after cardiac surgery together, VTE prophylaxis was associated with a reduced risk of PE (RR, 0.45; 95% CI, 0.28–0.72; $P$=0.0008; $I^2$=0%) and symptomatic VTE (RR, 0.44; 95% CI, 0.28–0.71; $P$=0.0006; $I^2$=0%) (Figures 2 and 3) compared to the control group without significant heterogeneity. After restricting our analyses to only studies that had adequate allocation concealment,** the benefits of VTE prophylaxis on risks of PE (RR, 0.38; 95% CI, 0.23–0.63; $I^2$=0%) and symptomatic VTE (RR, 0.38; 95% CI, 0.23–0.62; $I^2$=0%) remained unchanged (Figures 4 and 5, respectively). Similarly, restricting the analysis to adult cardiac surgical patients only, the benefits of VTE prophylaxis on risks of PE (RR, 0.45; 95% CI, 0.28–0.72; $I^2$=0%) and symptomatic VTE also remained unchanged (RR, 0.44; 95% CI, 0.28–0.67; $I^2$=0%). Using VTE as an outcome measure, the funnel plot did not suggest presence of a significant publication bias (Figure 6).

## VTE Events After 2 Different VTE Pharmacological Prophylaxis Agents

Only a small number of patients (n=276) had been enrolled in 3 RCTs comparing warfarin against high-dose aspirin (>300 mg/day for adults, 5 mg/kg per day for children), and the risk of VTE was not different (RR, 0.97; 95% CI, 0.50–1.89; $P$=0.94; $I^2$=0%). One meta-analysis comparing aspirin with warfarin after Fontan surgery also did not show a significant difference in symptomatic VTE.[63] Similarly, only a very small number of patients (n=59) had been enrolled in a direct comparison between UFH and LMWH or hirudin, and the risk of VTE was also not different between the 2 groups

*References 16, 17, 33, 36, 39, 42, 45, 52, 55, 56, 64, 66, 68–70, 78.

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**Table 1.** Characteristics of the Included RCT and Meta-Analysis Comparing Different Interventions With Outcome Data on VTE

| Study (Year of Publication, First Author, [Reference Number]) | Type of Surgery and Sample Size | Mean Age, y (or No. of Studies in Meta-Analysis) | Interventions | Outcomes Including Complications | Bias Assessment |
|---|---|---|---|---|---|
| 1996, Ramos et al. [16] | Mixed (n=2551) | 64 | IPC stockings till fully ambulatory, both groups received UFH | Symptomatic PE (4% control vs. 1.5% IPC), complications not reported | Allocation concealment adequate, no blinding, loss to follow-up (0%) |
| 2013, Mirhosseini et al. [17] | Off-pump CABG (n=120) | 62 | UFH alone vs UFH+aspirin (80 mg daily) for the first 7 to 10 days | Asymptomatic lower-limb DVT (16.6% UFH alone vs 3.3% UFH+aspirin). Postoperative bleeding (1.7% UFH alone vs. 6.7% UFH+aspirin, no multivariate analysis was reported) | Allocation concealment adequate, patients and research nurses blinded to the intervention, loss to follow-up (0%) |
| 2013, Ayatollahzade-Isfahani et al. [36] | CABG (n=185) | 60 | Leg elevation during surgery vs. supine position, no UFH was used for both groups | Asymptomatic lower-limb DVT (18.4% supine group vs. 8.6% leg elevation group; ipsilateral leg 21/185 vs. contralateral leg 4/185) | Allocation concealment adequate, no blinding, loss to follow-up (0%) |
| 2005, Nussmeier et al. [39] | On-pump CABG (n=1636) | 62 | Placebo vs. valdecoxib or valdecoxib+parecoxib. All patients received aspirin and standard VTE prophylaxis for all 3 groups | Symptomatic PE (0.2% placebo vs. 0.4% for both valdecoxib and valdecoxib+parecoxib groups) | Allocation concealment adequate, double-blinded, loss to follow-up (2%) |
| 2009, Gill et al. [42] | Mixed (n=172) | 64 | Placebo vs. activated factor VIIa (40 μg/kg) vs. activate factor VIIa (80 ug/kg) | Symptomatic PE (0% for all 3 groups) | Allocation concealment adequate, double-blinded, loss to follow-up (3.9%) |
| 2013, McCrindle et al. [45] | Fontan procedure (n=111) | 5 | Aspirin vs. warfarin | Symptomatic VTE (7% aspirin vs. 5.8% warfarin) and asymptomatic VTE (14% aspirin vs. 19% warfarin) | Allocation concealment adequate, single-blinded, loss to follow-up (2.7%) |
| 2011, Doss et al. [52] | Aortic valve replacement (n=60) | 62 | Pulmonary autograft vs. mechanical valve, stentless bioprothesis vs. mechanical valve, or stentless vs. stented bioprothesis | Symptomatic PE (5% in the stented bioprothesis group, 0% for the all those 5 groups) | Allocation concealment uncertain, no blinding, loss to follow-up (0%) |
| 2003, Lee et al. [55] | CABG (n=60) | 66 | Off-pump vs on-pump CABG | Symptomatic PE (3.3% in the off-pump group vs. 0% in the on-pump group) | Allocation concealment adequate, single-blinded, loss to follow-up (0%) |
| 2007, Riess et al. [56] | CABG (n=20) | 58 | IV lepirudin vs. IV heparin on bypass and first 2 days after surgery | Symptomatic PE (10% in the lepirudin group vs. 0% for the IV heparin group) | Allocation concealment unclear, no blinding, loss to follow-up (0%) |
| 2011, Adler Ma et al. [62] | Off-pump CABG (n=544) | 8 studies | IV tranexamic acid for patients undergoing off-pump CABG | Symptomatic VTE (0.7% tranexamic acid vs. 1.5% control group) | Allocation concealment unclear in 25% and also no blinding in 25% of the studies. No significant heterogeneity on VTE data between studies |
| 2011, Marrone et al. [63] | Fontan surgery (n=1075) | 20 studies | Warfarin vs. antiplatelet agents | Symptomatic VTE (5% anticoagulation vs. 4.5% antiplatelet agents) | 95% were observational studies. No significant heterogeneity on VTE data between studies |

Continued

**Table 1.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Surgery and Sample Size | Mean Age, y (or No. of Studies in Meta-Analysis) | Interventions | Outcomes Including Complications | Bias Assessment |
|---|---|---|---|---|---|
| 1993, Beghi et al. [64] | Mixed (n=39) | 60 | LMWH-Fluxum 3200 anti-Xa units daily vs. calcium heparin 5000 IU 3 times daily | Symptomatic VTE (0 vs. 0%) by USS | Allocation concealment unclear, no blinding, loss to follow-up (0%) |
| 1995, Goldhaber et al. [66] | CABG (n=344) | 64 | IPC with graduated compression stockings vs. graduated compression stockings alone. All patients received aspirin | Asymptomatic DVT before discharge (19% in IPC vs. 22% in control group). Symptomatic PE (1.2% in IPC vs. 0.6% in control group) | Allocation concealment unclear, no blinding, loss to follow-up (4%) |
| 1979, Pantely et al. [68] | CABG (n=65) | 54 | Warfarin vs control vs. high-dose antiplatelet agent group (aspirin 325 mg+dipyridamole 75 mg both 3 times per day) | Symptomatic PE (6.7% in control, 0% in antiplatelet agent group and warfarin group). Symptomatic DVT (3.3% in control, 0% in antiplatelet agent and warfarin group) | Allocation concealment adequate, no blinding, loss to follow-up to VTE outcomes (0%) |
| 2010, Schroeder et al. [69] | Congenital heart diseases (n=90) | 4 months | IV heparin (10 U/kg per hour vs. 5% dextrose) for 14 days or until central venous catheter removed | Asymptomatic central venous catheter related thrombosis (15% heparin vs. 16% placebo group) | Allocation concealment adequate, double-blinded, loss to follow-up (0%) |
| 2013, Weltert et al. [70] | Mixed (n=1049) | 67 | CardioPAT intra- and postoperative cell saver system vs. standard intraoperative cell saver system (hemonetics) without using postoperative cell saver | Symptomatic DVT (1.9% CardioPAT vs. 2.7% hemonetics system) | Allocation concealment unclear, no blinding, loss to follow-up (0%) |
| 2011, Ponschab et al. [74] | Mixed (n=470) | 6 studies including the study by Gill [28] | Recombinant activated factor VII vs. placebo | Outcomes on symptomatic VTE extracted from the studies included in this meta-analysis (0.4% factor VIIa vs. 0% control) | Only 2 studies were double-blinded RCTs with adequate allocation concealment, no significant heterogeneity between studies on VTE outcomes |
| 1982, McEnany et al. [78] | CABG (n=216) | 50 | Placebo vs. aspirin (300 mg bd) vs. warfarin (prothrombin time 1.5 to 2.0 of control) | Symptomatic PE (1.3% placebo vs. 2.8% aspirin vs. 1.5% warfarin) | Allocation concealment unclear, partial blinding on warfarin group and double-blinded for aspirin group, loss to follow-up (0%) |
| 2006, Lahtinen et al. [33] | Off-pump CABG, no UFH unless in atrial fibrillation (12.5% of the included patients) (n=24) | 67 | Secondary analysis of an RCT comparing a new proximal aortic anastomotic device to a conventional hand-sewn technique | Routine CTPA 1 week after surgery (all asymptomatic, PE 25% in each treatment arm) | Allocation concealment unclear, unblinded, loss to follow-up (0%) (but the study was terminated prematurely owing to unavailability of the anastomotic devices) |

Mixed surgery includes CABG, heart valve, and other types of cardiac surgery. CABG indicates coronary artery bypass grafting; CTPA, computed tomographic pulmonary angiogram; DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; RCT, randomized, controlled trials; UFH, unfractionated heparin; USS, ultrasound scan; VTE, venous thromboembolism.

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**Table 2.** Characteristics of Original Studies Reporting on Incidence and Risk Factors for VTE After Cardiac Surgery

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 1995, Ramos et al. [15], likely same cohort of patients as in [16] | Cohort, UFH 5000 U bd | Mixed (n=2551) | 30 days | PE (2.7%) by pulmonary angiography or high-probability V/Q scan, fatal PE (0.08%) by postmortem | Not reported | VTE:<br>1. Prior history of VTE (OR, 3.1).<br>2. Obesity (OR, 2.6).<br>3. Preoperative LVEF <40% (OR, 6.8).<br>4. Previous right heart catheterization (OR, 2.9).<br>5. IPPV >3 days (OR, 2.5).<br>6. HITS (OR, 2.5).<br>7. Postoperative CHF (OR, 4.1) | Retrospective, no blinding |
| 2013, Mirhosseini et al. [17] | RCT, UFH 5000 U tds | Off-pump CABG (n=120) | Uncertain | PE (0%), unclear modality | DVT (10%) by USS | No multivariate analysis was conducted, bleeding of uncertain severity occurred in 4 patients (6.7%) after UFH with aspirin against 1 patient (1.7%) with heparin alone ($P$=0.34). | Prospective, double-blinded |
| 1999, Pouplard et al. [18] | Cohort, UFH 120 U/kg per day followed by 200 U/kg per day after valve surgery, LMWH after CABG | Valve (n=157)+CABG (n=150) | 10 days | Fatal PE (0.3%) (in a patient with HIT) | Not reported | No multivariate analysis was conducted. | Prospective, no blinding |
| 2012, Kulik et al. [19] | Cohort, 5 different VTE prophylaxis (1) mechanical only (2) LMWH or UFH (3) fondaparinux (4) mechanical+LMWH or UFH (5) no prophylaxis, all these strategies were measured at 48 hours after surgery | Either off (19%) or on-pump (91%) CABG (n=92 699) | 6 weeks | VTE (0.74%) by USS or venography, or CTPA or V/Q scan | Not reported | VTE:<br>No difference between the 5 strategies of VTE prophylaxis (HR, 1.07 to 1.16 compared to no VTE prophylaxis)<br>Bleeding:<br>No difference between the 5 strategies of VTE prophylaxis (HR, 0.9 to 1.01 compared to no VTE prophylaxis: 1.5%, 1.7%, 3.4%, 1.5%, 1.4%, respectively) | Retrospective, no blinding |

Continued

**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 2004, Ambrosetti et al. [20,27] | Cohort, UFH not used in 37% or used <3 days in 38%, bilateral GCS used only in 7% | CABG (n=270) | 4 to 19 days after surgery (on admission to rehabilitation center) | Fatal PE (0.4%) and PE (0.7%) by V/Q scan | DVT (17.4%): 23/47 on the leg without the great saphenous vein harvested vs. 24/47 on the leg with the vein harvested; 21% for those without UFH by routine USS screening | VTE: Age, female, postoperative complications, and no UFH before discharge from the surgery unit were predictive of DVT on admission to rehabilitation unit (all $P<0.001$, but ORs not reported). Cardiac tamponade: Routine echocardiography (n=235) at time of USS and then 2 and 4 weeks later: no differences in incidence of tamponade between those with and without systemic anticoagulation | Prospective, no blinding |
| 2008, Frizzelli et al. [21] | Cohort, UFH 200 U/kg per day after removal of drains for 48 to 72 hours after CABG, LMWH followed by warfarin after prosthetic valve surgery or in atrial fibrillation after CABG | Mixed (n=815) | 5 to 7 days after surgery (on admission to rehabilitation center) | PE (0.7%) by CTPA: 3.5% for those on aspirin+UFH vs. 0% for those on warfarin+UFH | Central venous catheter related DVT (48%) routine USS | No multivariate analysis was conducted. | Prospective, no blinding |
| 1991, DeLaria and Hunter [22] | Cohort, no routine UFH was used after CABG, warfarin after valve surgery | Mixed (75% CABG) (n=10 638) | Uncertain | DVT (0.7%) (20/36 on the leg without the great saphenous vein harvested vs. 18/36 on the leg with great saphenous vein harvested) by USS or venography, PE (0.4%) by high probability V/Q scan or pulmonary angiography, fatal PE (0.09%) | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 2013, Ho et al. [23] | Cohort, routine UFH for all patients | Mixed (n=2131) | 30 months | VTE (1.6%), fatal PE (0.2%), diagnosis by ICD-10 codes | Not reported | VTE: 1. Body mass index (OR, 1.2 per index increment). 2. Charlson comorbidity index (OR, 1.20 per index increment) | Retrospective, no blinding |

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**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 1982, Hanson and Levine [24] | Cohort, no routine UFH and antiplatelet agents | CABG (n=5000) | Uncertain | PE (0.5%) by high probability V/Q scan or pulmonary angiography, fatal PE (0.06%) | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 2010, Schwann et al. [25] | Cohort, routine dual antiplatelet agents after CABG, aspirin+warfarin for combined valve-CABG, warfarin for valve alone, all patients also received enoxaparin 40 mg/day (if <100 kg)+bilateral intermittent pneumatic compression+daily ambulation | Mixed (n=1070) | Day 3 to 4 first USS and then weekly until hospital discharge | PE (0.09%) | DVT (13%) (62/139 on the leg without the great saphenous vein harvested vs. 114/139 on the leg with the great saphenous vein harvested) by routine USS on day 3 to 4 and then day 6 to 7 and then weekly | VTE:<br>1. Age (OR, 1.2 per 10 year increment).<br>2. Reintubation (OR, 2.57).<br>3. Transfusion (OR, 2.24).<br>4. Ventilation (OR, 1.02 per 10 hours)<br>Bleeding requiring re-exploration was not different between those with DVT treated with systemic anticoagulation and those without DVT. | Prospective, no blinding |
| 2013, Saranteas et al. [26] | Cohort, pharmacological and mechanical VTE prophylaxis | Mixed (n=315) | 24 hours after surgery | DVT (0.6%) by unclear modality, fatal PE (0.3%) | Inferior vena cava thrombus (2.5%) by echocardiography | No multivariate analysis was conducted. | Retrospective, no blinding |
| 1975, Rao et al. [28] | Cohort, GCS and ambulation only, no UFH | CABG (n=231) | Uncertain | PE (9.5%) by high probability V/Q scan or pulmonary angiography, fatal PE (1.7%) | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 1993, Josa et al. [29] | Cohort, warfarin from day 3 after heart valve surgery, no UFH postoperatively | Mixed (valve: n=120; CABG: 819; CABG+valve: n=94) (total 1033) | Uncertain (but PE was reported up to 2 weeks) | PE (overall 3.2%, 3.9% after CABG, 0% after valve, 1% after combined CABG+valve) by high probability V/Q scan or pulmonary angiography, fatal PE (0.6%) by postmortem, DVT (0.7%) (1/819 on the contralateral to harvest side vs. 5/819 on the harvest side) was investigated only after PE was diagnosed | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |

Continued

**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 1992, Gillinov et al. [30] | Case-control, warfarin after valve surgery, aspirin and dipyridamole after CABG | Mixed (n=64) | Uncertain | PE (0.6%) by high probability V/Q scan or CTPA, fatal PE (0.2%) by postmortem | Not reported | VTE:<br>1. Preoperative bed rest (OR, 6).<br>2. >Hospital day preoperatively (OR, 6).<br>3. <15 day between coronary catheterization and surgery (OR, 5).<br>4. Postoperative congestive heart failure (OR, 8).<br>5. Postoperative bed rest >3 days (OR, 5) | Retrospective, no blinding |
| 1991, Reis et al. [31] | Cohort (nonconsecutive), GCS and aspirin only, no UFH | CABG (n=29) | Until hospital discharge | Not reported | DVT (48%): (10/29 on the leg without the great saphenous vein harvested vs. 10/29 on the leg with the vein harvested), routinely on both legs for all patients | No multivariate analysis was conducted. | Prospective, no blinding |
| 2009, Egawa et al. [32] | Two cohort: (1) No VTE guidelines, (2) GCS for all, intermittent pneumatic compression for moderate to high-risk patients, anticoagulation for high-risk patients | Mixed (1st group: 1467, 2nd group: 1389) | Until hospital discharge (mean 22 to 25 days) | Group 1: PE (0.4%), Group 2: PE (0%), CTPA | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 2006, Lahtinen et al. [33] | Secondary analysis of a RCT comparing a new proximal aortic anastomotic device to a conventional hand-sewn technique, no UFH unless in atrial fibrillation (12.5% of the included patients) | Off-pump CABG (n=24) | 1 week after surgery | PE (0%) | PE (25%) by routine CTPA | No multivariate analysis was conducted. | Prospective, no blinding |

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**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 2010, Mitra et al. [34] | Two cohorts (1st group: received activated factor VIIa, 2nd group: cardiothoracic registry), VTE prophylaxis strategies uncertain | Mixed (1st group: n=705, 2nd group: n=6554) | Uncertain | PE (1st group: 0.4%, 2nd group: 7%), unclear modality | Not reported | VTE:<br>1. Urgent surgery (OR, 2.8).<br>2. Massive transfusion (OR, 2.8).<br>3. Activated factor VIIa (OR, 0.02) | Retrospective, no blinding |
| 1992, Canver and Fiedler [35] | Cohort, no UFH | Mixed (n=4393) | Until hospital discharge | PE (0.1%), fatal PE (0.02%), DVT (0.2%), venous Doppler, contrast venography, lung isotope scan or pulmonary angiography | Not reported | No multivariate analysis was conducted, 1 patient developed HIT and retroperitoneal hematoma after initiating systemic UFH with DVT | Retrospective, no blinding |
| 2013, Ayatollahzade-Isfahani et al. [36] | RCT, no UFH | CABG (n=185) | Until 5 to 7 days after surgery | DVT (0.5%) by USS | DVT (13.5%) by routine USS | No multivariate analysis result was reported. | Prospective, no blinding |
| 2007, Gandhi et al. [37] | Cohort, VTE prophylaxis strategies uncertain | Ventricular assist device or orthotopic heart transplant requiring activated factor VIIa (n=15) | Until hospital discharge | DVT (6.7%), unclear modality | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 2007, Mueller et al. [38] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=259) | 5 days after surgery | Not reported | PE (1.9%) by CTPA | No multivariate analysis was conducted. | Prospective, no blinding |
| 2005, Nussmeier et al. [39] | RCT, aspirin for all patients and standard VTE prophylaxis strategy permitted | On-pump CABG (n=1636) | 30 days after surgery | PE (0.3%), DVT (0.06%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Prospective, double-blinded |
| 2009, Belczak et al. [40] | Cohort (nonconsecutive), VTE prophylaxis strategies uncertain | CABG (n=44) | 90 days after surgery | DVT (2.3%) on the leg with long-saphenous vein harvested, USS modality | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 2011, ElBardissi et al. [41] | Cohort, VTE prophylaxis strategies uncertain | Transcatheter aortic valve implantation (n=249) | 30 days | PE (0.4%), unclear modality | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |

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**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 2009, Gill et al. [42] | RCT, VTE prophylaxis strategies uncertain | Mixed (n=172) | 30 days | PE (0%), clinical signs with postmortem or V/Q scan, DVT by venography or duplex USS | Not reported | No multivariate analysis was conducted. | Prospective, double-blinded |
| 2014, Alfirevic et al. [43] | Case-control, VTE prophylaxis strategies uncertain | Mixed (n=503) | Until hospital discharge | VTE (9.5%), unclear modality | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 2003, White et al. [44] | Cohort, VTE prophylaxis strategies uncertain | Mixed. Group 1: without malignancy (valve: n=16 036, CABG: n=66 180). Group 2: with malignancy+ CABG (n=2243) | 90 days | Without malignancy: VTE (heart valve 0.5% [0.2% after hospital discharge], CABG 1.1% [0.7% after hospital discharge]). With malignancy: VTE (CABG 1.5% with 0.8% after discharge), VTE by ICD-9 codes, unclear modality | Not reported | No multivariate analysis was conducted. | Retrospective, no blinding |
| 2013, McCrindle et al. [45] | RCT, aspirin (5 mg/kg per day) vs. warfarin (INR 2 to 3) as VTE prophylaxis | Fontan surgery (n=111) | 2.5 years | VTE (17%), TEE or echocardiography | VTE (6.5%), routine TEE or echocardiography | VTE:<br>1. Uncontrolled warfarin, INR between 2 and 3 <30% time (OR, 3.5).<br>2. Central venous catheter >10 days or at ICU discharge (OR, 17.8).<br>3. Pulmonary atresia with intact ventricular septum (OR, 3.6).<br>4. Lower preoperative bilirubin (OR, 0.8) | Prospective, single-blinded |
| 2013, Zahn et al. [46] | Cohort, VTE prophylaxis strategies uncertain | Transcatheter aortic valve implantation (n=1318) | 12 months | PE (1.6%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 2012, Iribarne et al. [47] | Cohort, VTE prophylaxis strategies uncertain | Isolated mitral valve surgery (n=6297) | Until hospital discharge | VTE (0.8%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |

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**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 2010, Thielmann et al. [48] | Cohort, VTE prophylaxis strategies uncertain | Mixed (n=153), including patients who had a low platelet count and an HIT test was initiated | Until hospital discharge | PE (3.3%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 1995, Rosenthal et al. [49] | Cohort, no UFH, aspirin or warfarin | Fontan surgery (n=70) | 1.9 to 5.5 years | VTE (20%), TEE or CTPA | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 1999, Michalopoulos et al. [50] | Case-control, VTE prophylaxis strategies uncertain | CABG (n=2014) | Until hospital discharge | Fatal PE (0.05%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 1996, Briffa and Large [51] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=1400) | Until hospital discharge | PE (overall 0.5%) (urgent bed rest before surgery cases 2.2%, nonurgent cases 0.2%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 2011, Doss et al. [52] | RCT, warfarin for 3 months after bioprothesis, lifelong warfarin after mechanical valve, and no anticoagulation with autografts | Aortic valve replacement (n=120) | 12 months | PE (0.8%) | Not reported | No multivariate analysis on VTE was conducted, 3 patients (2.5%) treated with warfarin had bleeding requiring reoperation. | Prospective, no blinding |
| 2011, Bucci et al. [53] | Cohort, UFH (SC for aortic mechanical or tissue valve or mitral tissue valve; IV UFH for mechanical mitral value) or LMWH (double dose for mechanical mitral compared to tissue mitral or all types of aortic) until INR within targets | Valve (n=203) | Until hospital discharge | PE (0%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. Major bleeding (6.4%): Systemic anticoagulation with concomitant aspirin and/or clopidogrel (OR, 7.4), 6 patients (3%) had international normalized ratio >5 postoperatively. | Retrospective, no blinding |
| 2000, Montalescot et al. [54] | Cohort, systemic anticoagulation IV UFH or SC LMWH from day 6 after surgery | Single or double mechanical valve surgery (n=208) | Until hospital discharge | PE (0%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. Bleeding occurred in 4 patients (1.9%) (2 after UFH and 2 after LMWH) with 1 patient with UFH being systemically overanticoagulated | Retrospective, no blinding |

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**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 2003, Lee et al. [55] | RCT, on-pump vs. off-pump, VTE prophylaxis strategies uncertain | CABG (n=60) | Until hospital discharge | Fatal PE (1.7%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Prospective, single-blinded |
| 2007, Riess et al. [56] | RCT, IV lepirudin vs. IV heparin on bypass and first 2 days after surgery | CABG (n=20) | Until day 3 after surgery | PE (5%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Prospective, no blinding |
| 2005, Rastan et al. [57] | Cohort (autopsy study), VTE prophylaxis strategies uncertain | Mixed (n=468) | Mean survival time 14 days after surgery | Fatal PE (total 6.6%, 3.8% not diagnosed before postmortem accounting for 11.4% of the unexplained deaths) | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 1997, Zehr et al. [58] | Cohort (autopsy study), VTE prophylaxis strategies uncertain | Mixed (n=147) | Mean survival time 22 days after surgery | Fatal PE (total 4.1%, 1.4% not diagnosed before postmortem accounting for 20% of the unexplained deaths) | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 1976, Heard [59] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=80) | 13 months | Fatal PE (2.5%), diagnosed by postmortem | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 2014, Song et al. [60] | Cohort, VTE prophylaxis strategies uncertain | Mixed (n=25) who received prothrombin complex concentrates for coagulopathy | Until hospital discharge | Central venous catheter related DVT (4%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 1994, Sanchez and Haft [61] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=224) | 30 days | PE (0.5%) by V/Q scan, DVT (4%) by clinical criteria with a negative V/Q scan | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 2013, Clark et al. [65] | Cohort, VTE prophylaxis strategies uncertain | Mixed (n=11) and received factor IX complex for bleeding | Until hospital discharge | PE (9.1%) | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 2012, Thibodeau et al. [67] | Cohort, VTE prophylaxis strategies uncertain | Cardiac transplantation (n=201) | Mean 1.8 to 3.6 years | Symptomatic DVT (12% in sirolimus treated vs 7% in nonsirolimus treated), PE (sirolimus 3% vs. nonsirolimus 0.7%), unclear modality | Not reported | VTE: Sirolimus treatment remained associated with an increased risk of VTE after adjusting for body mass index. | Retrospective, no blinding |

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DOI: 10.1161/JAHA.115.002652

**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 2014, Urbanski et al. [71] | Cohort, VTE prophylaxis strategies uncertain | Bentall procedure with either tissue or mechanical valve (n=29) | 4.5 years | Symptomatic fatal PE (3.5%) | Not reported | No multivariate analysis on VTE was conducted. | Retrospective, no blinding |
| 2011, Manlhiot et al. [72] | Cohort, heparinization of arterial and central venous catheters, antithrombotic therapy for aortopulmonary shunt or mechanical valve | Congenital heart disease requiring surgery (n=1542) | Until hospital discharge | Symptomatic DVT (7.9%), PE (0.3%), fatal PE (0.06%) by either US, CTPA, MRI, echocardiography, surgery, or postmortem | Not reported | VTE:<br>1. Younger than 31 days (OR, 2.0).<br>2. Oxygen saturation <85% (OR, 2.0).<br>3. Previous thrombosis (OR, 2.6).<br>4. Heart transplantation (OR, 4.1).<br>5. Deep hypothermic circulatory arrest (OR, 1.9).<br>6. Central venous catheter >5 days (OR 1.2).<br>7. Postoperative use of ventricular assist device or extracorporeal membrane oxygenation (OR, 5.2) | Retrospective, no blinding |
| 2012, Manlhiot et al. [73] | Cohort, either without VTE, aspirin, or warfarin prophylaxis | SCPC (n=139) or Fontan (n=162) | Until Oct 2009 (since 2000–2009 after Fontan and since 2003–2008 for single ventricle cardiac lesions) | Symptomatic DVT after Fontan (21%) and after SCPC (34%) by radiology, surgery, catheterization findings, or postmortem, thrombotic complication as a cause of death (3.6%) | Not reported | VTE:<br>1. Use of thromboprophylaxis (HR, 0.2 after SCPC and HR, 0.27 warfarin vs. aspirin or 0.18 warfarin vs. none after Fontan) | Retrospective, no blinding |
| 1995, Goldhaber et al. [66] | RCT, IPC with graduated compression stockings vs. graduated compression stockings alone. All patients received aspirin | CABG (n=344) | Until hospital discharge | Symptomatic PE (0.9%) by high probability V/Q scan, fatal PE (0.3%) | Asymptomatic DVT (21%) by routine USS | No multivariate analysis on VTE was conducted. | Prospective, no blinding |

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**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 1979, Pantely et al. [68] | RCT, Warfarin vs. control vs. high-dose antiplatelet agent group (aspirin 325 mg+dipyridamole 75 mg both 3 times per day) | CABG (n=65) | Until hospital discharge | Symptomatic PE (3%), DVT (1.5%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Prospective, no blinding |
| 2010, Schroeder et al. [69] | RCT, IV heparin (10 U/kg per hour vs. 5% dextrose) for 14 days or until central venous catheter removed | Congenital heart diseases (n=90) | Until day 14 or removal of central venous catheter | Not reported | Asymptomatic central venous catheter related thrombosis (16%) by echocardiography or USS | VTE:<br>1. Central venous catheter 7 days or longer (OR, 4.3).<br>2. Central venous catheter malfunction (OR, 11.2)<br>Bleeding requiring interruption of study drug in 1 patient in the placebo group | Prospective, double blinded |
| 2013, Weltert et al. [70] | RCT, VTE prophylaxis strategies uncertain | Mixed (n=1049) | Until hospital discharge | Symptomatic DVT (2.4%), unclear modality | Not reported | No multivariate analysis on VTE was conducted. | Prospective, no blinding |
| 2013, Rahman et al. [75] | Cohort, enoxaparin 20 or 40 mg/day | Aortic surgery (n=189) | 12 months after surgery | Not reported | Not reported | Incidence of pericardial effusion (21% after 40 mg enoxaparin vs. 19% after 20 mg enoxaparin). No multivariate analysis on pericardial effusion was conducted. | Retrospective, no blinding |
| 1988, Ikäheimo et al. [76] | Cohort, warfarin from postoperative day 2 (valve surgery group 1), aspirin+dipyridamole on day of surgery (CABG group 2), or warfarin started 2 weeks before surgery (CABG group 3) | Mixed (n=150) | 2 weeks after surgery | Not reported | Not reported | Incidence of pericardial effusion (68% group 1 vs. 80% group 2 vs. 84% group 3). No multivariate analysis on pericardial effusion was conducted. | Prospective, no blinding |
| 2013, Alassar et al. [77] | Cohort, VTE prophylaxis strategies uncertain | Transcatheter aortic valve implantation (n=119) | 4 years after surgery | Fatal PE (0.8%) | Not reported | No multivariate analysis on VTE outcome was conducted. | Retrospective, no blinding |

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**Table 2.** Continued

| Study (Year of Publication, First Author, [Reference Number]) | Type of Study and Use of LMWH, UFH, or Other Forms of VTE Prophylaxis | Type of Surgery and Sample Size | Duration of Follow-up | Incidence of Symptomatic DVT and PE, Diagnostic Modality | Incidence of Asymptomatic DVT and PE (%), Diagnostic Modality | Significant Adjusted Risk Factors for VTE and Complications | Bias Assessment |
|---|---|---|---|---|---|---|---|
| 1982, McEnany et al. [78] | RCT, no UFH. Placebo vs aspirin 300 mg bd) vs. warfarin (INR, 1.5 to 2.0) starting on day 3 or 4 after surgery | CABG (n=216) | 12 months after surgery | Symptomatic PE (1.9%) | Not reported | No multivariate analysis on VTE outcome was conducted, bleeding only occurred in 3 patients (4.4%) on warfarin. | Prospective, partial blinding for warfarin, double-blinded for aspirin group |
| 2010, Garvin et al. [79] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=1403) | Hospital discharge | Symptomatic PE (0.57%) by high probability V/Q scan or CTPA | Not reported | No multivariate analysis on VTE outcome was conducted. | Prospective, no blinding |
| 2007, Jensen and Yang [80] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=315) | Hospital discharge | Symptomatic PE (0.32%), unclear modality | Not reported | No multivariate analysis on VTE outcome was conducted. | Retrospective, no blinding |
| 1975, Wisoff et al. [81] | Cohort, UFH for all patients | CABG (n=200) | Hospital discharge | Symptomatic PE (3.5%), unclear modality | Not reported | No multivariate analysis on VTE outcome was conducted. | Retrospective, no blinding |
| 1994, Parenti [82] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=120) | Hospital discharge | Symptomatic PE (4.1%) | Not reported | No multivariate analysis on VTE outcome was conducted. | Retrospective, no blinding |
| 1991, Saito et al. [83] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=8100) | Hospital discharge | Symptomatic PE (0.074%) | Not reported | No multivariate analysis on VTE outcome was conducted. | Retrospective, no blinding |
| 1987, Dorros et al. [84] | Cohort, VTE prophylaxis strategies uncertain | CABG (n=674) >70 years old | 1 year follow-up | Symptomatic PE (2.1%), unclear modality | Not reported | No multivariate analysis on VTE, bleeding requiring reoperation in 24 patients (3.6%), but uncertain whether bleeding was related to VTE prophylaxis as the latter information was not described. | Retrospective, no blinding |

bd indicates twice a day; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CTPA, computed tomographic pulmonary angiogram; DVT, deep vein thrombosis; GCS, graduate compression stockings; HIT, heparin-induced thrombocytopenia; HR, hazard ratio; ICD, International Classification of Diseases; IV, intravenous; INR, international normalized ratio; IPPV, invasive mechanical ventilation; LMWH, low-molecular-weight heparin; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; OR, odds ratio; PE, pulmonary embolism; RCT, randomized, controlled trial; SC, subcutaneous; SCPC, superior cavopulmonary connection; tds, three times a day; TEE, transesophageal echocardiography; UFH, unfractionated heparin; USS, ultrasound scan; VTE, venous thromboembolism.

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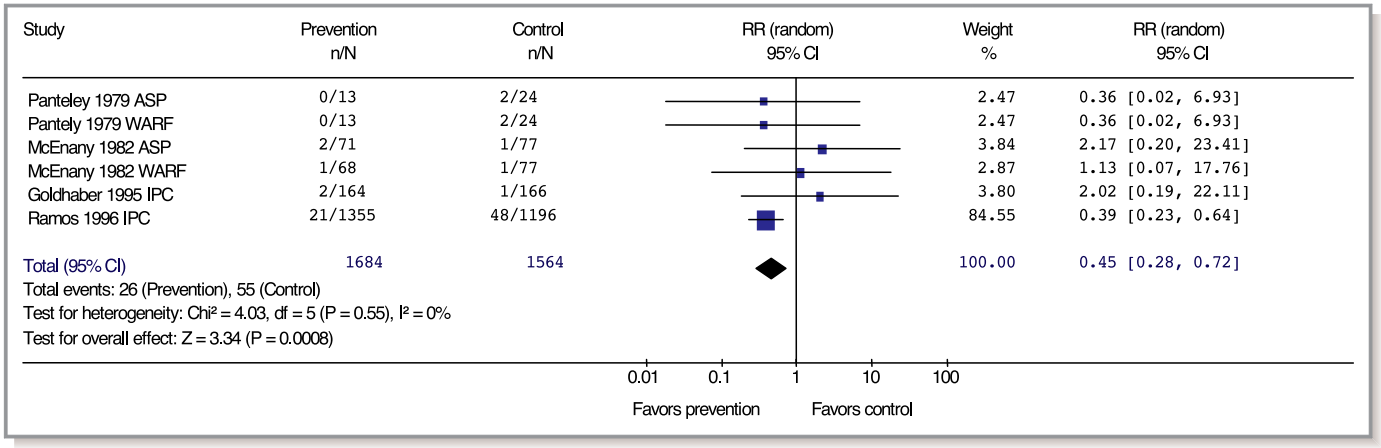


**Figure 2.** Forest plots showing the difference in risks of symptomatic or asymptomatic PE with and without using some forms of venous thromboembolism prophylaxis. ASP indicates aspirin; CI, confidence interval; IPC, intermittent pneumatic compression to the lower limbs; PE, pulmonary embolism; RR, relative risk; WARF, warfarin.

(RR, 3.0; 95% CI, 0.14–66; *P*=0.49). There were no RCTs directly comparing UFH or LMWH against aspirin alone for VTE prophylaxis after cardiac surgery.

## Incidences and Risk Factors for Symptomatic and Asymptomatic VTE

The median incidence (interquartile range; IQR) of asymptomatic DVT and PE reported in the included studies were 14.8% (10.8–40.4) and 1.9% (0.4–25), respectively. The median incidence (IQR) of symptomatic DVT, PE, and fatal PE were 3.2% (0.6–8.1), 0.6% (0.3–2.9), and 0.3% (0.08–1.7), respectively. After restricting our analysis to only prospective cohort studies or RCTs, the median incidence of symptomatic PE (0.7%; IQR, 0.1–1.7) and fatal PE (0.4%; IQR, 0.3–1.4) were similar to when all studies were considered. The incidence of symptomatic PE and fatal PE were not associated with the sample size of the included studies (*P*=0.606 and 0.142, respectively) or how recent the study was conducted (*P*=0.207 and 0.802, respectively). Incidence of VTE and modality used to diagnose DVT and PE for each RCT as well as observational study are described in Table 2. For prospective

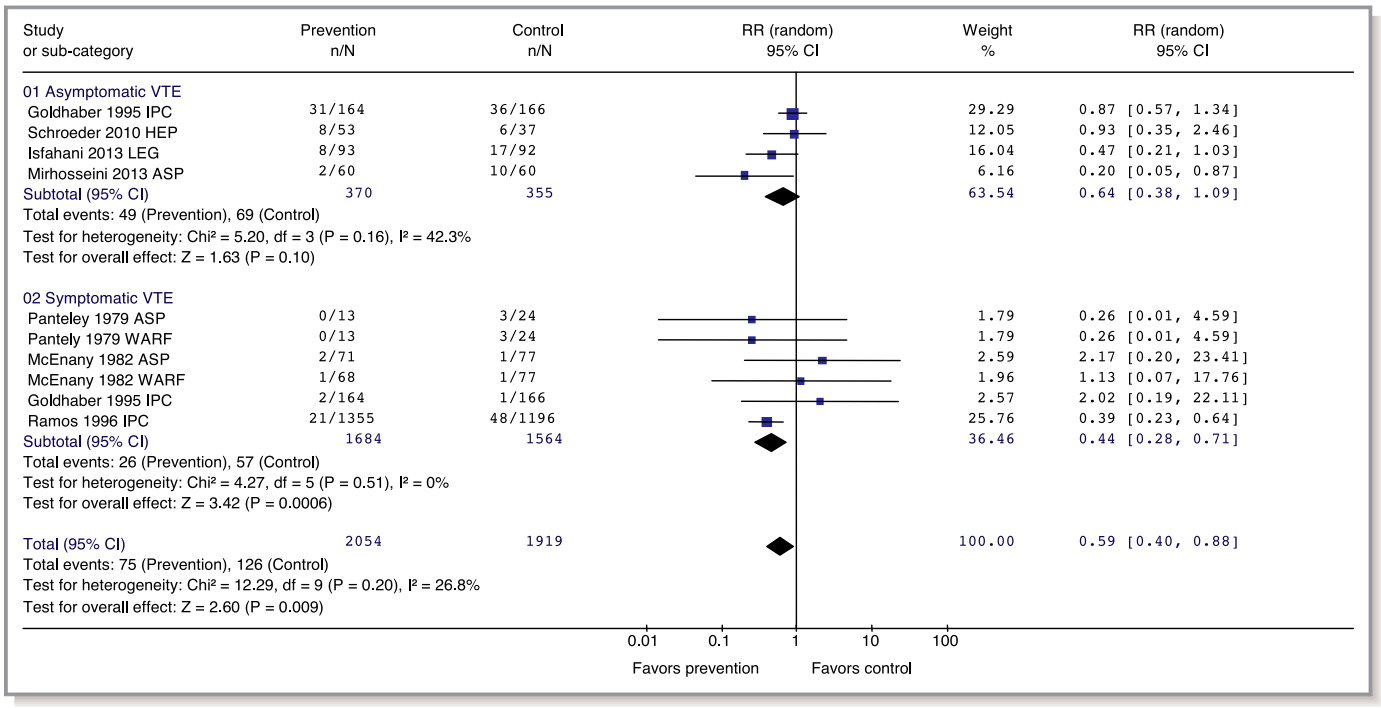


**Figure 3.** Forest plots showing the difference in the risks of symptomatic and asymptomatic VTE with and without using VTE prophylaxis. ASP indicates aspirin; CI, confidence interval; HEP, unfractionated heparin; IPC intermittent pneumatic compression to the lower limbs; LEG, leg elevation; RR, relative risk; VTE, venous thromboembolism; WARF, warfarin.

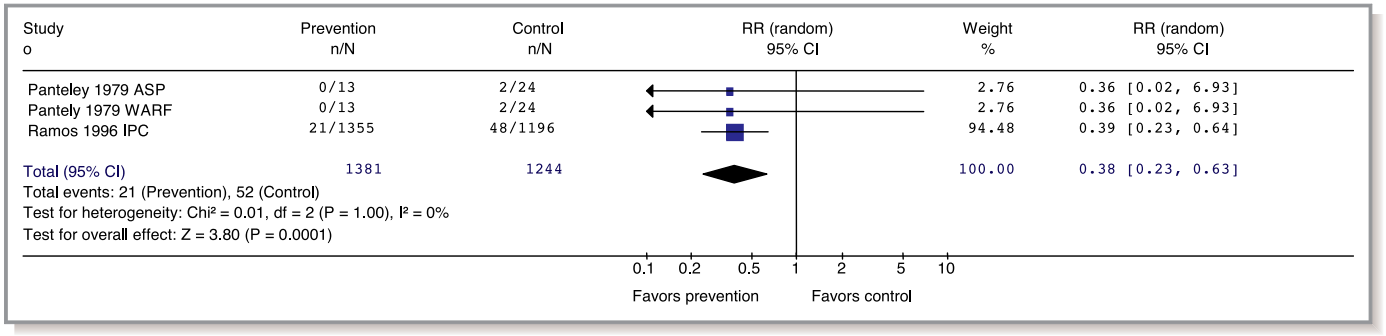


**Figure 4.** Benefits of VTE prophylaxis on risks of PE after excluding studies without adequate allocation concealment. ASP indicates aspirin; CI, confidence interval; IPC intermittent pneumatic compression to the lower limbs; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism; WARF, warfarin.

studies, all patients with clinical signs of DVT were expected to have an ultrasound scan (USS) as part of the studies, but the percentage of patients who had USS when clinical signs of DVT were present in the retrospective studies was not available.

We identified 2 large postmortem studies, and, in these 2 studies, fatal PE accounted for 11% to 20% of the unexplained deaths after cardiac surgery.[57,58] Diagnosis of PE was suspected or diagnosed clinically by a CT pulmonary angiogram before death only in 33% to 42% of the patients.[57,58] Many patients who died from fatal PE were misdiagnosed clinically as having acute heart failure, acute myocardial infarction, pneumonia, or sudden cardiac death.[57] Fatal PE was reported within 24 hours of cardiac surgery in at least 1 observational study.[26]

The risk factors for VTE after cardiac surgery that remained significant after adjustment by a multivariate analysis are summarized in Table 3. Previous history of VTE, increasing age, obesity, left or right ventricular failure, prolonged bed rest/mechanical ventilation/use of a central venous catheter, and omission of all forms of anticoagulation or -platelet agents were the most consistent risk factors for VTE after cardiac surgery. Results of 2 meta-analyses on use of activated factor VIIa or tranexamic acid could not confirm these drugs as a significant risk factor for VTE after cardiac surgery.[62,74] There was a suggestion that the leg with the great saphenous vein harvested could have a higher risk of DVT compared to the contralateral leg (RR, 1.48; 95% CI, 0.96–2.26; $P$=0.07; $I^2$=71%), but this result did not reach statistical significance and had substantial heterogeneity

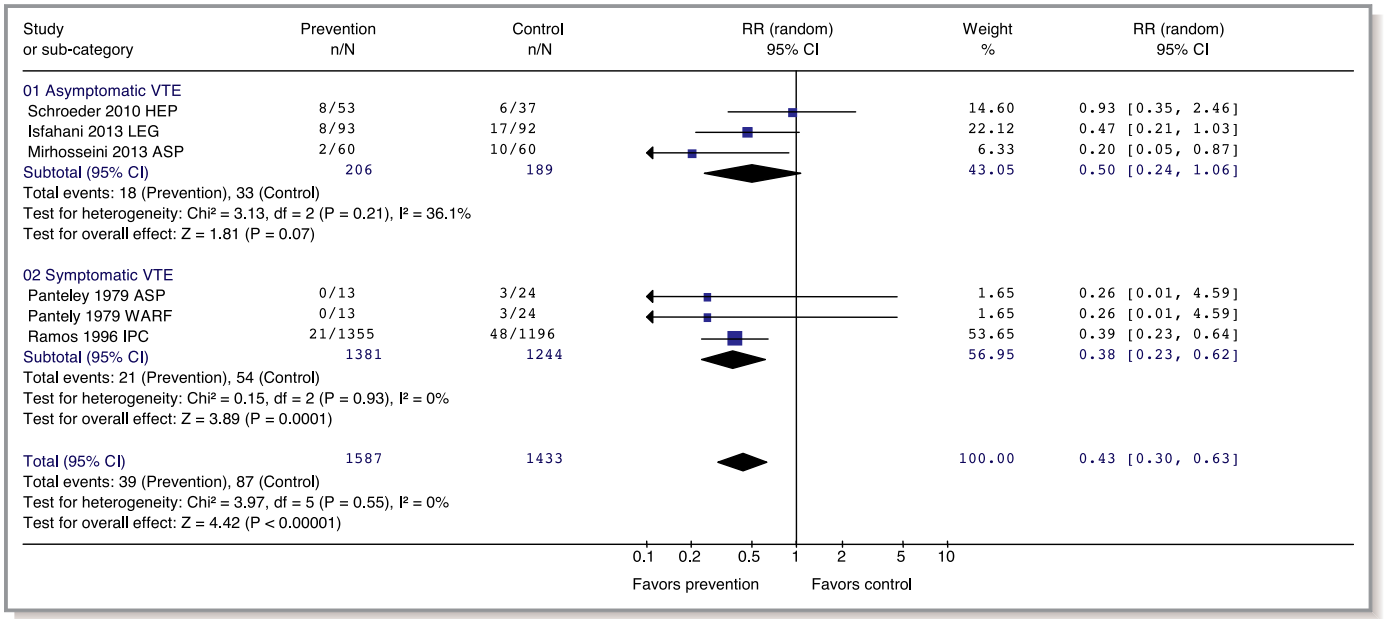


**Figure 5.** Benefits of VTE prophylaxis on risks of symptomatic VTE by excluding studies without adequate allocation concealment. ASP indicates aspirin; CI, confidence interval; HEP, unfractionated heparin; IPC, intermittent pneumatic compression to the lower limbs; LEG, leg elevation; RR, relative risk; VTE, venous thromboembolism; WARF, warfarin.

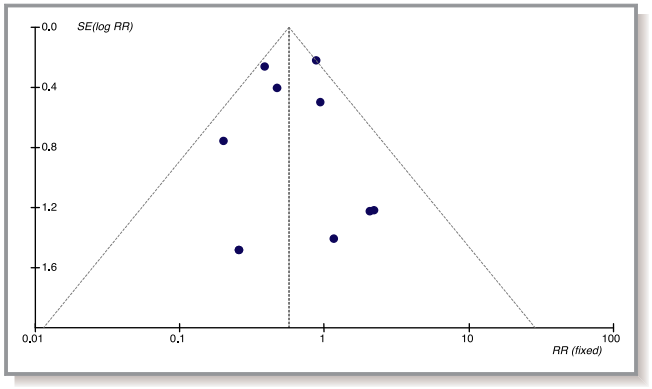


**Figure 6.** Funnel plot showing a lack of publication bias, using all forms of venous thromboembolic events as an outcome. RR indicates relative risk.

(Figure 7). Restricting the analysis to studies that used routine USS for both legs[20,25,31,36] did not change the results significantly (RR, 1.58; 95% CI, 0.96–2.61; $P$=0.07; $I^2$=77%). Metaregression suggested that sample size was likely the main reason behind this heterogeneity (slope=0.004; 95% CI, 0.002–0.006; $P$=0.001; Figure 8), with large sample size studies more likely to show an increased risk of DVT in the leg with the great saphenous vein harvested than smaller studies.

## Incidences and Risk Factors for Complications From VTE Prophylaxis

Eight studies reported incidence of bleeding after cardiac surgery,[17,19,25,53,54,78,84] but only 1 study reported risk factors for bleeding after multivariate analysis, with concurrent use of aspirin with systemic anticoagulation as the only significant risk factor in causing bleeding after valvular surgery, with some of these bleeding patients with an international normalized ratio (INR) >5.[53]

Although pericardial effusion was common after cardiac surgery (up to 84%),[76] using different doses of enoxaparin (20 vs. 40 mg/day) for VTE prophylaxis after proximal aortic surgery did not affect the incidence of pericardial effusion (19% vs. 21%, respectively) nor the risk of cardiac tamponade requiring surgical interventions.[75] Similarly, initiation of systemic anticoagulation for confirmed VTE also did not increase the risk of pericardial effusion in patients who took aspirin after CABG surgery.[27] Similar to bleeding after cardiac surgery, therapeutic systemic anticoagulation (INR >2.5) was the only reported risk factor for cardiac tamponade after valvular surgery in another observational study not included in this review.[85] No multivariate analysis on risk factors for cardiac tamponade or pericardial effusion was, however, presented in these studies.[27,75,76,85]

## Discussion

Cardiac surgery is increasingly offered to older patients with coexisting comorbidities,[86] and it is certain that the incidence of VTE after cardiac surgery will be increasing. Although VTE is an important preventable cause of morbidity and mortality in hospitalized patients, both the quality and amount of evidence to guide VTE prophylaxis after cardiac surgery were relatively sparse. With the evidence available, we confirmed that VTE prophylaxis could reduce the risk of PE and symptomatic VTE after cardiac surgery without increasing risk of bleeding and cardiac tamponade, unless the patients were systemically anticoagulated. Although some risk factors for VTE were specifically related to cardiac surgery, many important risk factors for VTE after cardiac surgery were indeed similar to risk factors for VTE in other patient populations. These results are clinically relevant and require further discussion.

First, although we demonstrated that some form of VTE prophylaxis was effective in reducing PE and symptomatic VTE, we could not identify whether 1 form of VTE prophylaxis was more effective than another, nor whether 1 particular pharmacological agent was superior to the others. Recent studies showed that platelets play a significant role in the pathogenesis of VTE and antiplatelet agents can have a protective effect against the first episode of VTE in patients with hip fracture or undergoing hip arthroplasty (n=13 356) and recurrent VTE after treatment with systemic anticoagulation.[87–91] Our results showed that aspirin appears to be effective in reducing VTE after cardiac surgery in the pediatric population (using 5 mg/kg/day)[45] or when a higher dose of aspirin is used in adults (>300 mg/day).[68] Evidence suggests that aspirin resistance is common within the first week after cardiac surgery and the standard low-dose aspirin (100 mg/day) would not be adequate to exert its full antiplatelet effects in many patients.[11–13] Because cardiac surgical patients are also prothrombotic postsurgery (up to 30 days),[6–9] use of low-dose antiplatelet agents alone would not be sufficient in preventing VTE during this high-risk period if the patients have multiple risk factors for VTE (Table 3). We noted that fatal PE after cardiac surgery still occurred within the last decade despite advances in cardiac surgical care, including routine use of low-dose aspirin post-CABG.[23,26,71,73,77] Fatal PE accounted for approximately 11% to 20% of all unexplained deaths after cardiac surgery, with at least 50% not diagnosed before death.[57,58] Median incidence of fatal PE (0.3%) reported in this review was consistent with the data from these 2 postmortem reports if the overall mortality after cardiac surgery was approximately 3%, and this may, in part, explain why omission of early VTE prophylaxis is associated with an increased mortality in the critically ill.[92] Initiating UFH or LMWH, which offers additional VTE protection above intermittent pneumatic lower-limb compression,[93,94] should

**Table 3.** Risk Factors for VTE and Bleeding After Cardiac Surgery That Remained Significant After Adjustment by Multivariate Analysis in the Included Studies

| | Reported Odds Ratio |
|---|---|
| Preoperative risk or protective factors for VTE | |
| Prior history of VTE | 2.6, 3.1 |
| Obesity | 2.6 (or 1.2 per body mass index increment) |
| Charlson comorbidity index | 1.2 (per index increment) |
| Increasing age | 1.2 per 10 years increment |
| Female | NR |
| Previous right heart catheterization (or right heart failure) | 2.9 |
| Preoperative bed rest, acute surgery within 15 days of coronary angiography | 2.8, 5.0, 6.0 |
| Preoperative left ventricular failure (eg, ejection fraction <40%) | 6.8 |
| Pulmonary atresia with intact ventricular septum before Fontan surgery | 3.6 |
| Low bilirubin (suggestive of low right-sided filling pressure) before Fontan surgery | 0.8 |
| Cyanotic heart disease (oxygen saturation <85%) | 2.0 |
| Intraoperative risk factors for VTE | |
| Deep hypothermic circulatory arrest | 1.9 |
| Heart transplantation | 4.1 |
| Postoperative risk factors for VTE | |
| Left ventricular failure | 4.1, 8.0 |
| Bed rest >3 days | 5.0 |
| Mechanical ventilation >3 days | 2.5 (or 1.02 per 10 hours ventilation) |
| Failed extubation requiring reintubation | 2.6 |
| Central venous catheter >7 to 10 days | 4.3, 17.8 |
| Presence of a malfunctioning central venous catheter | 11.2 |
| Transfusion | 2.2, 2.8 |
| Use of ventricular assist device or ECMO after congenital heart surgery | 5.2 |
| No heparin prophylaxis before discharge from surgical unit | NR |
| Subtherapeutic warfarin | 3.5 |
| No aspirin or warfarin after Fontan surgery | 5.6 |
| Use of sirolimus after cardiac transplantation | NR |
| Risk factors for bleeding | |
| Concomitant use of aspirin and systemic anticoagulation | 7.4 |

ECMO indicates extracorporeal membrane oxygenation; NR, not reported; VTE, venous thromboembolism.

be seriously considered for all cardiac surgical patients as soon as possible, or on postoperative day 1, if the patients have no active bleeding, especially for those with multiple risk factors for VTE.

Second, we could not identify sufficient data to support the notion that use of low-dose UFH or LMWH would increase the risks of bleeding (eg, mediastinal, intracranial, or gastrointestinal hemorrhage), pericardial effusion, and cardiac tamponade.[4] Though these complications are not rare after surgery,[76,95,96] whether low-dose UFH or LMWH would substantially increase such risks remains scientifically unproven. In one large, retrospective cohort study, use of UFH or LMWH at 48 hours post-CABG was not associated with an increased risk of bleeding compared to no VTE prophylaxis.[19] Using different doses of enoxaparin (20 vs. 40 mg/day) for VTE prophylaxis after proximal aortic surgery also did not appear to affect incidence of pericardial effusion nor risk of cardiac tamponade requiring surgical interventions.[75] In fact, most studies reported that bleeding after cardiac surgery only occurred in the presence of systemic

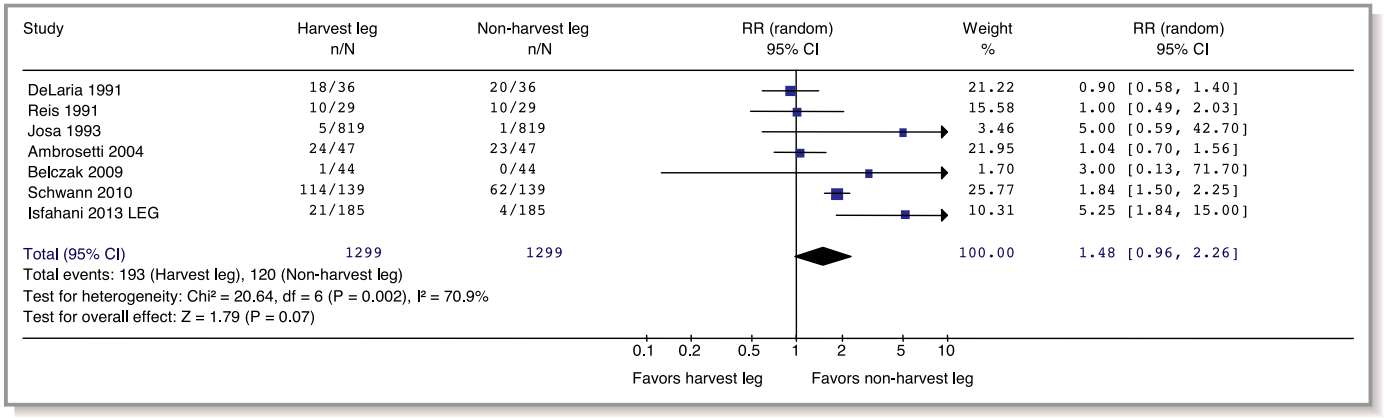


**Figure 7.** Forest plot showing the incidence of deep vein thrombosis in the leg with great saphenous vein harvested against the leg without the great saphenous vein harvested for coronary artery bypass graft surgery. CI indicates confidence interval; LEG, leg elevation; RR, relative risk.

anticoagulation,[35,52–54,78] especially when patients were overanticoagulated.[53,54] Of all the studies included in this review, only 1 study reported risk factors for bleeding after using multivariate analysis, and it showed that only concurrent use of systemic anticoagulation with an antiplatelet agent was associated with an increased risk of bleeding.[53] Nevertheless, most reported studies are underpowered to detect small increases in rare side effects; clinicians should still be mindful about the rare, but serious, effect of pericardial hematoma before initiating anticoagulants. Perhaps, a lower than usual threshold to cease the bridging UFH (subcutaneously or intravenously) or LMWH would reduce a patient's risk of bleeding and cardiac tamponade, while the patient is taking concurrent aspirin and warfarin (eg, when INR >1.5).[85]

The last consideration is the limitations of this systematic review. Although we have searched extensively for the evidence on risks and benefits of VTE prophylaxis after cardiac surgery, there is an obvious evidence gap, suggesting that an adequately powered RCT is needed to confirm whether initiating low-dose UFH or LMWH from postoperative day 1 after cardiac surgery would be more cost-effective than using low- or high-dose aspirin, warfarin, or intermittent lower-limb pneumatic compression alone in reducing morbidity and mortality of VTE. Our results suggested that DVT could be more common in the leg with the great saphenous vein harvested for CABG. This finding is not surprising because the lower-limb venous system has been disrupted after the great saphenous vein is harvested. Whether this increased risk was also contributed by wound pain causing immobilization, intolerance to graduate compression stockings, or intermittent pneumatic compression remains uncertain. Finally, we noted that many studies have a relatively short follow-up period in detecting VTE. With those studies with an extended follow-up period beyond the acute hospital stay,[23,44–46,49,59,71] symptomatic VTE continued to occur. Hence, future cohort studies and RCTs on VTE after cardiac surgery should consider VTE events well beyond the immediate postoperative period.

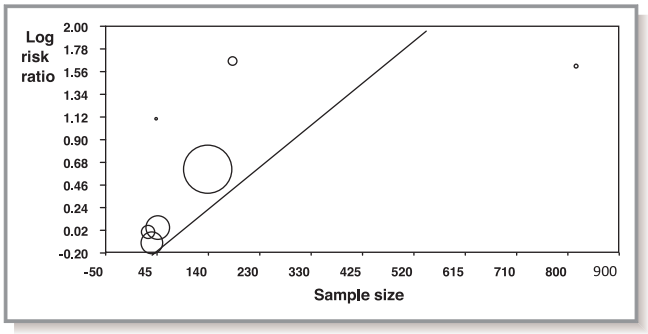


**Figure 8.** Meta-regression showing an association between sample size and differences in relative risk of having deep vein thrombosis in the leg with and without great saphenous veins harvested for coronary artery bypass surgery.

In conclusion, PE and symptomatic VTE are not rare after cardiac surgery and these events can be reduced with VTE prophylaxis. Data on whether one form of VTE prophylaxis is superior to another are sparse. Although VTE rates appeared to be similar between patients taking high-dose aspirin (>300 mg/day for adults and 5 mg/kg/day for children) and warfarin, low-dose aspirin (100 mg/day) used to keep the bypass graft patent is unlikely to be adequate in preventing VTE post-CABG, especially for patients with multiple risk factors for VTE. We found no evidence to support the notion that use of low-dose UFH or LMWH for VTE prophylaxis would increase risk of cardiac tamponade or bleeding after cardiac surgery. Bleeding after cardiac surgery is mainly related to systemic overanticoagulation or concurrent use of systemic anticoagulation and -platelet agents. Unless proven otherwise by adequately powered RCTs, initiating low-dose UFH or LMWH as soon as possible or on postoperative day 1 after cardiac surgery for patients who have no active bleeding is highly recommended, especially if they have multiple risk factors for VTE.

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