REVIEWS

A Systematic Review of Venous Thromboembolism Prophylaxis Strategies in Patients With Renal Insufficiency, Obesity, or on Antiplatelet Agents

Sosena Kebede, MD, MPH[1]*, Kalpana R. Prakasa, MBBS, MS[1], Kenneth Shermock, PharmD, PhD[1,2], Hasan M. Shihab, MBChB, MPH[2], Daniel J. Brotman, MD[1], Ritu Sharma, BSc[2], Yohalakshmi Chelladurai, MBBS, MPH[2], Elliott R. Haut, MD[3], Sonal Singh, MD, MPH[1,2], Jodi B. Segal, MD, MPH[1,2]

[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [3]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland.

BACKGROUND: There is uncertainty about optimal strategies for venous thromboembolism (VTE) prophylaxis among select populations such as patients with renal insufficiency, obesity, or patients taking antiplatelet drugs including aspirin. Their physiologies make prophylaxis particularly challenging.

PURPOSE: We performed a comparative effectiveness review of the literature on efficacy and safety of VTE prophylaxis in these populations.

DATA SOURCES: We searched MEDLINE, EMBASE, SCOPUS, CINAHL, International Pharmaceutical Abstracts, clinicaltrial.gov, and the Cochrane Library through August 2012. Eligible studies included controlled trials and observational studies.

DATA EXTRACTION: Two reviewers evaluated studies for eligibility, serially abstracted data, and independently evaluated the risk of bias and strength of evidence supporting interventions to prevent VTE in these populations.

RESULTS: After a review of 30,902 citations, we identified 9 controlled studies, 5 of which were trials, and the other 4 were observational studies. Five articles addressed prophylaxis of patients with renal insufficiency, 2 addressed obese patients, and 2 addressed patients on antiplatelet agents. No study tested prophylaxis in underweight patients or those with liver disease. The majority of observational studies had a high risk of bias. The strength of evidence ranged from low to insufficient regarding the comparative effectiveness and safety of VTE prophylaxis among these patients.

CONCLUSION: The current evidence is insufficient regarding optimal VTE prophylaxis for patients with renal insufficiency, obesity, or those who are on antiplatelet drugs including aspirin. High-quality studies are needed to inform clinicians about the best VTE prophylaxis for these patients. *Journal of Hospital Medicine* 2013;8:394–401. © 2013 Society of Hospital Medicine

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is estimated to affect 900,000 Americans each year and is a cause of significant morbidity and mortality with associated high healthcare costs.[1] Accordingly, the comparative effectiveness and safety of interventions for the prevention and treatment of VTE are among the national priorities for comparative effectiveness research.[2] Whereas we have evidence-based guidelines for the prophylaxis of VTE in the general population, there are no guidelines informing the care of select patient populations. Select populations are those patients in whom there is decisional uncertainty about the optimal choice, timing, and dose of VTE prophylaxis. Not only do these patients have an increased risk of DVT and PE, but most are also at high risk of bleeding, the most important complication of VTE prophylaxis.[3–6]

The objectives of this systematic review were to define the comparative effectiveness and safety of pharmacologic and mechanical strategies for VTE prevention in some of these select medical populations including obese patients, patients on concomitant antiplatelet therapy, patients with renal insufficiency, patients who are underweight, and patients with coagulopathy due to liver disease.

METHODS

The methods for this comparative effectiveness review (CER) follow the guidelines suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[7] The protocol was publically posted.[8]

Search Strategy

We searched MEDLINE, EMBASE, and SCOPUS through August 2011, CINAHL, International Pharmaceutical Abstracts, clinicaltrial.gov, and the Cochrane Library through August 2012. We developed a search strategy based on medical subject headings (MeSH) terms and text words of key articles that

we identified a priori[9] (see the Appendix for search strategy details).

Study Selection

We reviewed titles followed by abstracts to identify randomized controlled trials (RCTs) or observational studies with comparison groups reporting on the effectiveness or safety of VTE prevention in our populations. Two investigators independently reviewed abstracts, and we excluded the abstracts if both investigators agreed that the article met 1 or more of the exclusion criteria. We included only English-language articles that evaluated the effectiveness of pharmacological or mechanical interventions that have been approved for clinical use in the United States. To be eligible, the studies must have addressed relevant key questions in the population of our interest. We resolved disagreements by consensus. We used DistillerSR (Evidence Partners Inc., Ottawa, Ontario, Canada), a Web-based database management program to manage the review process. Two investigators assessed the risk of bias in each study independently, using the Downs and Black instrument for observational studies and trials.[10]

Data Synthesis

For each select population, we created detailed evidence tables containing the information abstracted from the eligible studies. After synthesizing the evidence, we graded the quantity, quality, and consistency of the best available evidence for each select population by adapting an evidence-grading scheme recommended in the Methods Guide for Conducting Comparative Effectiveness Reviews.[7]

RESULTS

We identified 30,902 unique citations and included 9 studies (Figure 1). There were 5 RCTs with relevant subgroups and 4 observational studies (Table 1). Two studies reported on the risk of bleeding in patients given pharmacologic prophylaxis while they are concomitantly taking nonsteroidal anti-inflammatory drugs (NSAIDS) or antiplatelet agents/aspirin, 1 RCT and 1 prospective observational study reported on obese patients, and 5 studies described outcomes of patients with renal insufficiency (see Supporting Information, Table 1, in the online version of this article). No study tested prophylaxis in underweight patients or those with liver disease.

Obese Patients

We found 1 subgroup analysis of an RCT (total 3706 patients, 2563 nonobese and 1118 obese patients) that reported on the comparative effectiveness and safety of fixed low-dose dalteparin 5000 IU/day compared to placebo among 1118 hospitalized medically ill patients with body mass indices (BMI) greater than 30 kg/m^2.[11] Neither group received additional concurrent prophylactic therapies. The 3 most prevalent medical diagnoses prompting hospitalization were congestive heart failure, respiratory failure, and infectious diseases. Compression ultrasound was performed in all patients by day 21 of hospitalization. The primary end point was the composite of VTE, fatal PE, and sudden death, and secondary end points included DVT, bleeding, and thrombocytopenia by day 21 (Table 1). In obese patients, the primary end point occurred in 2.8% (95% confidence interval [CI]: 1.3–4.3) of the dalteparin group and in 4.3% (95% CI: 2.5–6.2) of the placebo group (relative risk [RR]: 0.64; 95% CI: 0.32-1.28). In nonobese patients, the primary end point occurred in 2.8% (95% CI: 1.8-3.8) and 5.2% (95% CI: 3.9-6.6) of the dalteparin and placebo groups, respectively (RR: 0.53; 95% CI: 0.34-0.82). When weight was modeled as a continuous variable, no statistically significant interaction between weight and dalteparin efficacy was observed ($P = 0.97$). The authors calculated the RR in predefined BMI subgroups and found that dalteparin was effective in reducing VTE in patients with BMIs up to 40, with RRs of <1.0 for all (approximate range, 0.2–0.8). However, a fixed dose of dalteparin 5000 IU/day was not better than placebo for individuals with BMI >40 kg/m^2. There was no significant difference in mortality or major hemorrhage by day 21 between treatment and placebo groups.

Freeman and colleagues prospectively assigned 31 medically ill patients with extreme obesity (BMI >40 kg/m^2) to 1 of 3 dosing regimens of enoxaparin: a fixed dose of 40 mg daily enoxaparin (control group, n = 11), enoxaparin at 0.4 mg/kg (n = 9), or enoxaparin at 0.5 mg/kg (n = 11).[12] The average BMI of the entire cohort was 62.1 kg/m^2 (range, 40.5–82.4). All patients had anti-factor Xa levels drawn on the day of enrollment and daily for 3 days (Table 2). The relationship between anti-factor Xa levels and clinical efficacy of low-molecular weight heparin (LMWH) in VTE prophylaxis is still unclear; however, an anti-factor Xa level of 0.2 to 0.5 IU/mL, measured 4 hours after the fourth dose of LMWH, is the target level recommended for VTE prophylaxis.[13] Patients who received weight-based enoxaparin at 0.5 mg/kg achieved target anti-factor Xa level 86% of the time compared to 32% of the time in those receiving 0.4 mg/kg and 19% of the time for those in the fixed-dose group ($P < 0.001$). No clinical outcomes were reported in this study.

Patients on Antiplatelet Drugs

We did not find studies that directly looked at the comparative effectiveness of VTE prophylaxis in patients who were on antiplatelet drugs including aspirin. However, there were 2 studies that looked at the risk of bleeding in patients who received VTE pharmacologic prophylaxis while concurrently taking antiplatelet agents including aspirin. Both studies used pooled data from large phase III trials.
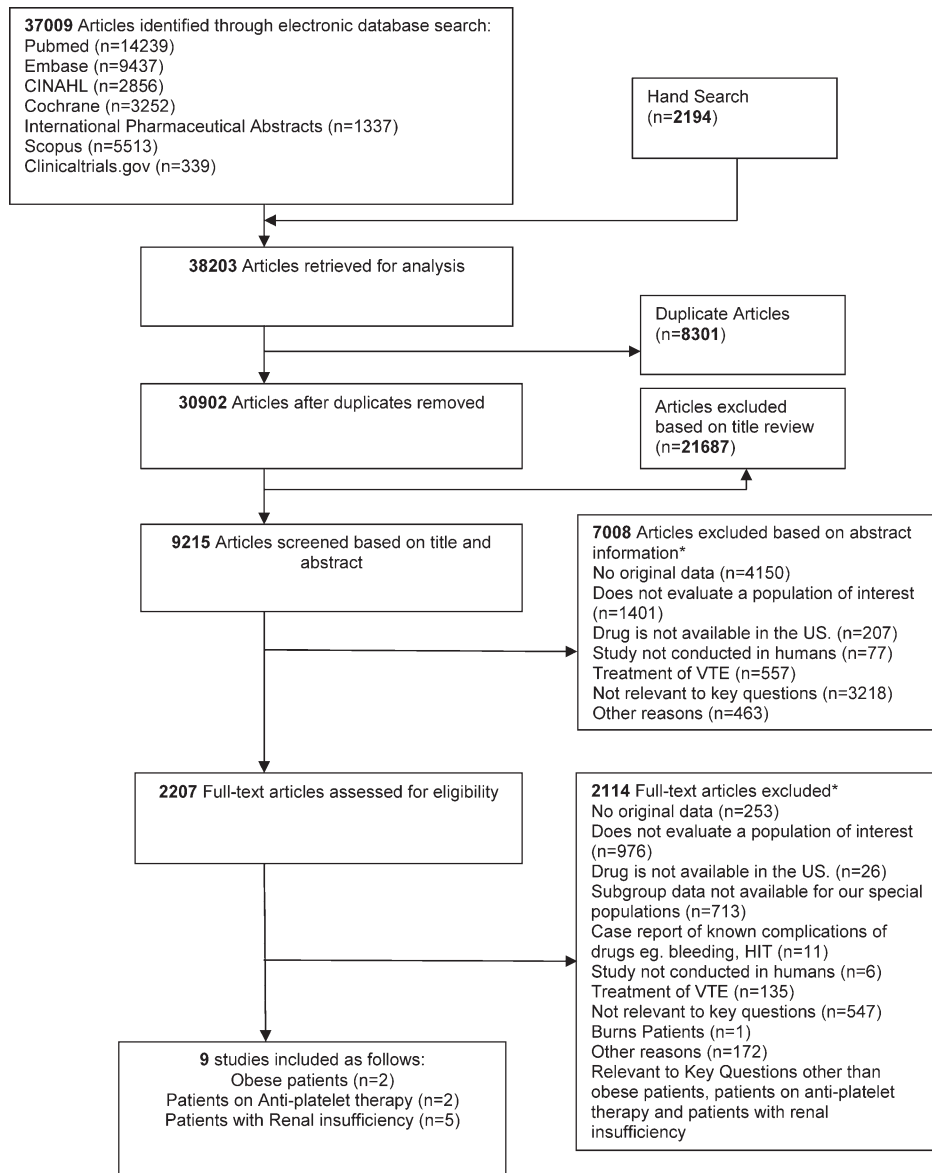
FIG. 1. Flow diagram of studies included in the systematic review. *Total exceeds the number in the exclusion box because reviewers were allowed to mark more than 1 reason for exclusion. Abbreviations: HIT, heparin-induced thrombocytopenia; VTE, venous thromboembolism.

The study by Eriksson et al. used data from the RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) trial where over 12,000 patients undergoing elective total knee or hip replacement were randomized to receive VTE prophylaxis with oral rivaroxaban or subcutaneous enoxaparin.[14] Nine percent of participants in each arm (563 in rivaroxaban and 526 in enoxaparin/placebo) were concomitantly using antiplatelet agents or aspirin at least once during the at risk period, defined as starting at day 1 of surgery up to 2 days after the last intake of the study drug. The only end point evaluated was bleeding, and the authors found no statistically significant bleeding difference among the 2 arms (Table 1). Any

bleeding event in the rivaroxaban with antiplatelets or aspirin arm was found in 20 (3.6%) patients, whereas in those on enoxaparin/placebo with antiplatelets or aspirin arm it was 17 (3.2%). The relative rate of bleeding among users versus nonusers of antiplatelet drugs or aspirin was 1.32 (95% CI: 0.85-2.05) in the rivaroxaban group and 1.40 (95% CI: 0.87-2.25) in the enoxaparin arm (Table 1).

Friedman et al. used pooled data from the RE-MODEL, RENOVATE, and REMOBILIZE trials, where patients who were undergoing hip or knee arthroplasty were randomized to 220 mg of dabigatran once daily, 150 mg of dabigatran once daily (we focused on this lower dosage as this is the only available dose used in the US), 40 mg of enoxaparin once

TABLE 1. Study Outcomes for Patients With Renal Insufficiency, Obesity, or on Antiplatelet Agents

Study	Arm, n	Total VTE (DVT and PE)	Bleeding	Other Outcomes
Obese patients				
Kucher et al., 2005[11]	Arm 1 (dalteparin), 558	2.8% (95% CI: 1.3–4.3)	0%	Mortality at 21 days: 4.6%
	Arm 2 (placebo), 560	4.3% (95% CI: 2.5–6.2)	0.7%	Mortality at 21 days: 2.7%
Freeman et al., 2012[12]	Arm 1 (fixed-dose enoxaparin), 11	NR	NR	Peak anti-factor Xa level ~19 %
	Arm 2 (lower-dose enoxaparin), 9	NR	NR	Peak anti-factor Xa level ~32 %
	Arm 3 (higher-dose enoxaparin), 11	NR	NR	Peak anti-factor Xa level ~86 %
Patients on antiplatelet agents				
Eriksson et al., 2012[14]	Arm 1 (rivaroxaban), 563	NR	20 (3.6%), rate ratio for use vs nonuse: 1.32 (95% CI: 0.85-2.05)	NR
	Arm 2 (enoxaparin/placebo), 526	NR	17 (3.2%), rate ratio for use vs nonuse: 1.40 (95% CI: 0.87-2.25)	NR
Friedman et al., 2012[15]	Arm 2 (150 mg dabigatran, no ASA), 1149	NR	11 (1.0%)*	NR
	Arm 5 (150 mg dabigatran + ASA), 128	NR	2 (1.6%)*	NR
	Arm 3 (enoxaparin, no ASA), 1167	NR	14 (1.2%)*	NR
	Arm 6 (enoxaparin + ASA), 132	NR	4 (3.0%)†	NR
	150 mg dabigatran compared with enoxaparin No concomitant ASA therapy	NR	RR: 0.82 (95% CI: 0.37-1.84)	NR
	150 mg dabigatran compared with enoxaparin With concomitant ASA therapy	NR	RR: 0.55 (95% CI: 0.11-2.78)	NR
Patients with renal insufficiency				
Bauersachs et al., 2011[16]	Arm 2 (GFR <30), 92	Total DVT: 11.11%; Total PE: 0%	Major bleeding: 4/92 (4.35%), minor bleeding: 9/92 (9.78%)	Mortality: 5.81%
Mahé et al., 2007[17]	Arm 2 (tinzaparin), 27	NR	Major bleeding: 2/27 (7.4%), minor bleeding: 3/27 (11.1%)	Factor Xa level: AF: CmaxD8/ Cmax D1 = 1.05
	Arm 3 (enoxaparin), 28	NR	Major bleeding: 1/28 (3.6%), minor bleeding: 3/28 (10.7%)	Factor Xa level: AF: CmaxD8/ Cmax D1 = 1.22
Dahl et al., 2012[18]	Arm 1 (enoxaparin), 332	Major VTE: 8 (9.0%)	Major bleeding: 6 (4.7%)	Infections and infestations: 25 (7.5%), Wound infection: 4 (1.2%)
	Arm 2 (dabigatran), 300	Major VTE: 3 (4.3%)	Major bleeding: 0 (0%)	Infections and infestations: 21 (7.0%), Wound Infection: 3 (1.0%)
Shorr et al., 2012[19]	Arm 1 (enoxaparin, CrCL ≥60 mL/min), 353	Total VTE: 17/275 (6.2%)	Major bleeding: 0/351 (0%)	NR
	Arm 2 (desirudin, CrCL ≥60 mL/min), 353	Total VTE: 13/284 (4.3%)	Major bleeding: 2/349 (0.27%)	NR
	Arm 3 (enoxaparin, CrCL 45–59 mL/min), 369	Total VTE: 18/282 (6.2%)	Major bleeding: 1/365 (0.27%)	NR
	Arm 4 (desirudin, CrCL 45–59 mL/min), 395	Total VTE: 17/303 (5.6%)	Major bleeding: 1/393 (0.25%)	NR
	Arm 5 (enoxaparin, CrCL <45 mL/min), 298	Total VTE: 24/216 (11.1%)	Major bleeding: 1/294 (0.34%)	NR
	Arm 6 (desirudin, CrCL <45 mL/min), 279	Total VTE: 7/205 (3.4%)	Major bleeding: 5/275 (1.82%)	NR
Elsaid et al., 2012[20]	Arm 1 (enoxaparin, CrCL ≥60 mL/min), 17	NR	Major bleeding: 2 (11.8%)	NR
	Arm 2 (enoxaparin, CrCL 30–59 mL/min), 86	NR	Major bleeding: 9 (10.5%)	NR
	Arm 3 (enoxaparin, CrCL ≤30 mL/min), 53	NR	Major bleeding: 10 (18.9%)	NR
	Arm 4 (UFH, CrCL ≥60 mL/min), 19	NR	Major bleeding: 2 (10.5%)	NR
	Arm 5 (UFH, CrCL 30–59 mL/min), 99	NR	Major bleeding: 3 (3%)	NR
	Arm 6 (UFH, CrCL ≤30 mL/min), 49	NR	Major bleeding: 2 (4.1%)	NR

NOTE: **Abbreviations:** AF, anti-Xa accumulation factor; ASA, aspirin; CI, confidence interval; CrCl, creatinine clearance; CrCl, creatinine clearance; DVT, deep venous thrombosis; GFR, glomerular filtration rate; IVC, inferior vena cava; NR, not reported; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism; UFH, unfractionated heparin.

* Odds ratio comparing Arm 2 and Arm 5 : 1.64 (95% CI: 0.36-7.49), P = 0.523. †Odds ratio comparing Arm 3 and Arm 6: 2.57 (95% CI: 0.83-7.94), P = 0.101.

daily, or 30 mg of enoxaparin twice a day.[15] Of the 8135 patients, 4.7% were on concomitant aspirin. The baseline characteristics of those on aspirin were similar to the other enrollees. The primary outcome was major bleeding events requiring transfusion, symptomatic internal bleeding, or bleeding requiring surgery. Among patients receiving 150 mg of dabigatran, bleeding events with and without concomitant aspirin occurred in 1.6% and 1.0%, respectively (odds ratio [OR]: 1.64; 95% CI: 0.36-7.49; P = 0.523). The percentages of participants with bleeding who received enoxaparin, with and without aspirin, were 3.0% and 1.2%, respectively (OR: 2.57; 95% CI: 0.83-7.94; P = 0.101). The RR of bleeding on dabigatran compared to enoxaparin with and without

aspirin therapy was 0.55 (95% CI: 0.11-2.78) and 0.82 (95% CI: 0.37-1.84), respectively (Table 1).

Patients With Renal Insufficiency

We found 5 studies that evaluated the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE in patients with acute kidney injury, moderate renal insufficiency, severe renal insufficiency not undergoing dialysis, or patients receiving dialysis. Four studies were RCTs,[16–19] and 1 used a cohort design assessing separate cohorts before and after a quality improvement intervention.[20] Bauersachs and colleagues conducted an RCT comparing unfractionated heparin at 5000 IU, 3 times daily to certoparin, which is not approved in the United States and

TABLE 2. Strength of Evidence and Magnitude of Effect for Obese Patients, Patients on Antiplatelet Agents, and Patients With Renal Insufficiency

Intervention	Outcome	Risk of Bias	Evidence Statement and Magnitude of Effect
Patients on antiplatelet agents			
Rivaroxaban vs enoxaparin	Major bleeding	Low	Insufficient to support no difference in rates of major bleeding with prophylactic rivaroxaban or enoxaparin in patients concomitantly treated with antiplatelet agents; 3.6% vs 3.25%
Dabigatran vs enoxaparin	Major bleeding	Low	Insufficient to support no difference in rates of major bleeding with prophylactic dabigatran or enoxaparin in patients concomitantly treated with aspirin; 1.6% vs 3.0%
Obese patients			
Dalteparin vs placebo	VTE	Moderate	Insufficient evidence for effectiveness of dalteparin vs placebo in reducing total VTE in obese patients; 2.8% vs 4.3%, RR: 0.64, 95% CI: 0.32-1.28
Dalteparin vs placebo	Mortality	Moderate	Insufficient evidence for effectiveness of dalteparin vs placebo in reducing mortality in obese patients; 9.9% vs 8.6%, $P = 0.36$
Dalteparin vs placebo	Major bleeding	Moderate	Insufficient evidence for safety of dalteparin vs placebo in reducing major bleeding in obese patients; 0% vs 0.7%, $P > 0.99$
Enoxaparin 40 mg daily vs 0.4 mg/kg	Percentage of patients achieving target anti-factor Xa level	Moderate	Insufficient evidence for effectiveness of enoxaparin 40 mg daily versus 0.4 mg/kg in achieving peak anti-factor Xa level in obese patients; 19% vs 32%, $P = $ NR
Enoxaparin 40 mg daily vs 0.5 mg/kg	Percentage of patients achieving target anti-factor Xa level	Moderate	Insufficient evidence for effectiveness of enoxaparin 40 mg daily versus 0.5 mg/kg in achieving peak anti-factor Xa level in obese patients; 19% vs 86%, $P < 0.001$
Enoxaparin 0.4 mg/kg vs 0.5 mg/kg	Percentage of patients achieving target anti-factor Xa level	Moderate	Insufficient evidence for effectiveness of enoxaparin 0.4 mg/kg versus 0.5 mg/kg in achieving peak anti-factor Xa level in obese patients; 32% vs 86%, $P = $ NR
Patients with renal insufficiency			
Tinzaparin vs enoxaparin	VTE	High	Insufficient evidence about superiority of either drug for preventing VTE in patients with renal insufficiency, 0/27 vs 0/28*
Tinzaparin vs enoxaparin	Bleeding	High	Insufficient evidence about safety of either drug in patients with renal insufficiency; 5/27 vs 4/28, $P = 0.67$
Dabigatran vs enoxaparin	VTE	Moderate	Insufficient evidence for effectiveness of dabigatran in reducing VTE in severe renal compromise patients vs enoxaparin; 4.3% vs 9%, OR: 0.48, 95% CI: 0.13-1.73, $P = 0.271$
Dabigatran vs enoxaparin	Bleeding	Moderate	Insufficient evidence for safety of dabigatran vs enoxaparin in patients with renal impairment; 0 vs 4.7%, $P = 0.039$
Desirudin vs enoxaparin	VTE	Moderate	Insufficient evidence for effectiveness of desirudin vs enoxaparin in reducing VTE in patients with renal impairment; 4.9% vs 7.6%, $P = 0.019$
Desirudin vs enoxaparin	Bleeding	Moderate	Insufficient evidence for safety of desirudin vs enoxaparin in patients with renal impairment; 0.8% vs 0.2%, $P = 0.109$
Enoxaparin vs UFH	Bleeding	High	Insufficient evidence for increased risk of bleeding with enoxaparin vs unfractionated heparin in patients with all levels of renal impairment, 13.5% vs 4.2%, RR: 3.2, 95% CI: 1.4–7.3; and for the subgroup of patients with creatinine clearance <30 mL/min; 18.9% vs 4.1%, RR: 4.68, 95% CI: 1.1–20.6
UFH in severe renal compromise vs all other renal status (undifferentiated)	VTE	Moderate	Insufficient evidence regarding differential benefit of unfractionated heparin by renal function; 2.6% of patients had a VTE event
UFH in severe renal compromise vs all other renal status (undifferentiated)	Bleeding	Moderate	Insufficient evidence for differential harm from unfractionated heparin by renal function; 13 events in 92 patients

NOTE: **Abbreviations:** NR, not reported; OR, odds ratio; RR, relative risk; UFH, unfractionated heparin; VTE, venous thromboembolism. *: VTE rates were not reported.

is not further discussed here.[16] The rate of DVT among patients treated with unfractionated heparin in patients with a glomerular filtration rate >30 mL/min was marginally lower than those with severe renal dysfunction (10.3 vs 11.1%) (Table 1).

Patients with severe renal dysfunction who received 5000 IU of unfractionated heparin 3 times a day were at increased risk of all bleeds (RR: 3.4; 95% CI: 2.0–5.9), major bleeds (RR: 7.3; 95% CI: 3.3–16), and minor bleeds (RR: 2.6; 95% CI: 1.4-4.9) compared to patients treated with unfractionated heparin without severe renal dysfunction.[16]

A randomized trial by Mahé and colleagues compared drug accumulation and anti-Xa activity in elderly patients with renal dysfunction (defined as a glomerular filtration rate of 20 to 50 mL/min) who received either tinzaparin at 4500 IU once daily or enoxaparin at 4000 IU once daily.[17] Enoxaparin accumulated to a greater extent from day 1 to day 8 than did tinzaparin; the ratio of maximum concentration on day 8 compared to day 1 was 1.22 for enoxaparin and 1.05 for tinzaparin ($P = 0.016$). No VTE events were reported in patients who received tinzaparin or enoxaparin. There was no statistical difference in the incidence of bleeding events between patients receiving tinzaparin (5, including 2 major events) and enoxaparin (4, including 3 major events, $P = 0.67$) (Table 1).

The trial by Dahl and colleagues randomly assigned patients who were over 75 years of age and/or who had moderate renal dysfunction (defined as creatinine clearance between 30 and 49 mL/min) to receive enoxaparin 40 mg daily or dabigatran 150 mg daily.[18] There was no significant difference in the rate of major VTE events between patients receiving dabigatran (4.3%) and enoxaparin (9%) (OR: 0.48; 95% CI: 0.13-1.73; $P = 0.271$) (Table 1). The rate of major bleeding was significantly higher among patients

randomly assigned to receive enoxaparin (4.7%) versus dabigatran (0%) ($P = 0.039$).[18]

Shorr and colleagues published a post hoc subgroup analysis of a multicenter trial in which orthopedic patients were randomly assigned to receive desirudin 15 mg twice daily or enoxaparin 40 mg once daily.[19] Evaluable patients (1565 of the 2079 patients randomized in the trial) receiving desirudin experienced a significantly lower rate of major VTE compared with patients receiving enoxaparin (4.9% vs 7.6%, $P = 0.019$). This relationship was particularly pronounced for evaluable patients whose creatinine clearance was between 30 and 44 mL/min. In evaluable patients with this degree of renal dysfunction, 11% of patients taking enoxaparin compared to 3.4% of those taking desirudin had a major VTE (OR: 3.52; 95% CI: 1.48-8.4; $P = 0.004$). There was no significant difference in the rates of major bleeding among a subset of patients assessed for safety outcomes (2078 of the 2079 patients randomized in the trial) who received desirudin (0.8%) or enoxaparin (0.2%) (Table 1).

Elsaid and Collins assessed VTE and bleeding events associated with the use of unfractionated heparin 5000U either 2 or 3 times daily and enoxaparin 30 mg once or twice daily across patients stratified by renal function (creatinine clearance <30, 30–59, and ≥60 mL/min). The investigators made assessments before and after a quality improvement intervention that was designed to eliminate the use of enoxaparin in patients whose creatinine clearance was <30 mL/min. No VTE events were reported. Patients receiving enoxaparin were significantly more likely to experience a major bleeding episode compared with patients receiving unfractionated heparin (overall rates for all levels of renal function: 13.5% vs 4. 2%; RR: 3.2; 95% CI: 1.4–7.3) (Table 2). This association was largely driven by the subgroup of patients with a creatinine clearance <30 mL/min. For this subgroup with severe renal insufficiency, patients receiving enoxaparin were significantly more likely to have a bleed compared with patients receiving unfractionated heparin (18.9% vs 4.1%; RR: 4.68; 95% CI: 1.1–20.6) (Tables 1 and 2). There was no difference in the bleeding rates for patients whose creatinine clearances were >60 mL/min.[20]

Strength of Evidence
Obese Patients
Overall, we found that the strength of evidence was insufficient regarding the composite end point of DVT, PE, and sudden death, and the outcomes of mortality and bleeding (Table 2). This was based on a paucity of available data, and a moderate risk of bias in the reviewed studies. Additionally, 92% of the enrolled patients in the studies were white, limiting the generalizability of the results to other ethnic groups.

Patients on Antiplatelets
The strength of evidence was insufficient in the studies reviewed here to conclude that there is no difference in rates of bleeding in patients who are concomitantly taking antiplatelet drugs while getting VTE prophylaxis with rivaroxaban, dabigatran, or enoxaparin. We based this rating because of the imprecision of results and unknown consistencies across multiple studies.

Patients With Renal Insufficiency
One RCT had a high risk of bias for our key question because data from only 1 study arm were useful for our review.[16] The other RCTs were judged to have a moderate risk of bias. The analyses led by Dahl and Shorr[18,19] were based on post hoc (ie, not prespecified) analysis of data from RCTs. Additionally, outcomes in the Shorr et al. trial were reported for evaluable subpopulations of the cohort that was initially randomized in the clinical trial.

We rated the strength of evidence as insufficient to know the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal insufficiency, severe renal insufficiency not undergoing dialysis, and patients receiving dialysis. We based this rating on the risk of bias associated with published studies and a lack of consistent evidence regarding associations that were reported. Similarly, we rated the strength of evidence as insufficient that 5000 U of unfractionated heparin 3 times daily increases the risk of major and minor bleeding events in patients with severely compromised renal function compared to this dose in patients without severely compromised renal function. We based this rating on a high risk of bias of included studies and inconsistent evidence. Likewise, we rated the strength of evidence as insufficient that enoxaparin significantly increases the risk of major bleeding compared with unfractionated heparin in patients with severe renal insufficiency. We based this rating on a high risk of bias and inconsistent published evidence.

We similarly found insufficient evidence to guide treatment decisions for patients with renal insufficiency. Our findings are consistent with other recent reviews. The American College of Chest Physicians (ACCP) practice guidelines[21] make dosing recommendations for the therapeutic use of enoxaparin. However, their assessment is that the data are insufficient to make direct recommendations about prophylaxis. Their assessment of the indirect evidence regarding bioaccumulation and increased anti-factor Xa levels are consistent with ours. The ACCP guidelines also suggest that decreased clearance of enoxaparin has been associated with increased risk of bleeding events for patients with severe renal insufficiency. However, the cited study[20] compares patients with and without severe renal dysfunction who received the same

therapy. Therefore, it is not possible to determine the additional risk conveyed by enoxaparin therapy, that is, above the baseline increased risk of bleeding among patients with renal insufficiency, particularly those receiving an alternate pharmacologic VTE prevention strategy, such as unfractionated heparin.

DISCUSSION

We found that the evidence was very limited about prevention of VTE in these select and yet prevalent patient populations. Despite the fact that there is an increasing number of obese patients and patients who are on antiplatelet therapies, most clinical practice guidelines do not address the care of these populations, which may be entirely appropriate given the state of the evidence.

The ACCP practice guidelines[21] suggest using a higher dose of enoxaparin for the prevention of VTE in obese patients. The subgroup analysis by Kucher et al.[11] showed effect attenuation of dalteparin when given at a fixed dose of 5000 IU/mL to patients with a BMI of >40 kg/m^2. The Freeman study[12] showed that extremely obese patients (average BMI >62.1 kg/m^2) who are given a fixed dose of enoxaparin achieved target anti-factor Xa levels significantly less often than those who received a higher dose of enoxaparin. The 2 separate findings, although not conclusive, lend some credence to the current ACCP guidelines.[21]

The studies we reviewed on VTE prophylaxis in patients who are concomitantly on antiplatelets including aspirin reported no major increased risk of bleeding; however, in the Friedman et al. study,[15] 3.0% of patients who were put on enoxaparin while still on aspirin had a bleeding event compared to 1.2% of those on enoxaparin alone. This difference is not statistically significant but is a trend possibly worth noting, especially when one looks at the lower RR of bleeding at 0.55 compared to 0.82 when dabigatran is compared with enoxaparin with and without concomitant aspirin therapy, respectively (Table 1). The highest dose of aspirin used in either of the studies was 160 mg/day, and neither study addressed other potent antiplatelets such as clopidogrel or ticlopidine separately, which limits the generalizability of the finding to all antiplatelets. Current ACCP guidelines do not recommend aspirin as a sole option for the prevention of VTE in orthopedic surgery patients.[22] Concerns remain among clinicians that antiplatelets, including aspirin, on their own are unlikely to be fully effective to thwart venous thrombotic processes for most patients, and yet the risk of bleeding is not fully known when these agents are combined with other anticoagulants for VTE prophylaxis.

Our review has several limitations, including the possibility that we may have missed some observational studies, as the identification of relevant observational studies in electronic searches is more challenging than that of RCTs. The few studies made it impossible to quantitatively pool results. These results, however, have important implications, namely that additional research on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE is needed for the optimal care of these patient subgroups. This might be achieved with trials dedicated to enrolling these patients or prespecified subgroup analyses within larger trials. Observational data may be appropriate as long as attention is paid to confounding.

APPENDIX

MEDLINE Search Strategy

(("pulmonary embolism"[mh] OR PE[tiab] OR "Pulmonary embolism"[tiab] OR thromboembolism [mh] OR thromboembolism[tiab] OR thromboembolisms[tiab] OR Thrombosis[mh] OR thrombosis[tiab] OR DVT[tiab] OR VTE[tiab] OR clot[tiab]) AND (Anticoagulants[mh] OR Anticoagulants[tiab] OR Anticoagulant[tiab] OR "thrombin inhibitors"[tiab] OR Aspirin[mh] or aspirin[tiab] OR aspirins[tiab] or clopidogrel[nm] OR clopidogrel[tiab] OR Plavix[tiab] or ticlopidine[mh] or ticlopidine[tiab]OR ticlid[tiab] OR prasugrel[nm]Or prasugrel[tiab]OR effient[tiab]OR ticagrelor[NM] OR ticagrelor[tiab]OR Brilinta [tiab] OR cilostazol[NM] OR cilostazol[tiab]OR pletal[tiab] OR warfarin[mh]OR warfarin[tiab]OR coumadin[tiab] OR coumadine[tiab] OR Dipyridamole[mh]OR dipyridamole[tiab]OR persantine[tiab] OR dicoumarol[MH] OR dicoumarol[tiab] OR dicumarol[tiab] OR Dextran sulfate[mh] OR dextran sulfate[tiab] OR"thrombin inhibitors"[tiab] OR "thrombin inhibitor"[tiab] OR heparin[mh] OR Heparin[tiab] OR Heparins[tiab] OR LMWH[tiab] OR LDUH[tiab] OR Enoxaparin[mh] OR Enoxaparin [tiab] OR Lovenox[tiab] OR Dalteparin[tiab] OR

Fragmin[tiab] OR Tinzaparin[tiab] OR innohep[tiab] OR Nadroparin[tiab] OR Fondaparinux[nm] OR Fondaparinux[tiab] OR Arixtra[tiab] OR Idraparinux[nm] OR Idraparinux[tiab] OR Rivaroxaban[nm] OR Rivaroxaban[tiab] OR novastan[tiab] OR Desirudin [nm] OR Desirudin[tiab] OR Iprivask[tiab]OR "direct thrombin inhibitor"[tiab] OR Argatroban[nm] OR Argatroban[tiab] OR Acova[tiab] OR Bivalirudin[nm] OR Bivalirudin[tiab] OR Angiomax[tiab] OR Lepirudin[nm] OR Lepirudin[tiab] OR Refludan[tiab] OR Dabigatran[nm] OR Dabigatran[tiab] OR Pradaxa [tiab] OR "factor xa"[mh] OR "factor Xa"[tiab] OR vena cava filters[mh] OR filters[tiab] OR filter [tiab] OR compression stockings[mh] OR intermittent pneumatic compression devices[mh] OR compression [tiab] OR "Venous foot pump"[tiab])) AND(prevent* [tiab] OR prophyla*[tiab] OR prevention and control [subheading]) NOT (animals[mh] NOT humans[mh]) NOT (editorial[pt] OR comment[pt]) NOT ((infant [mh] OR infant[tiab] OR child[mh] OR child[tiab] OR children[tiab] OR adolescent[mh] OR adolescent [tiab] OR "teen-age"[tiab] OR pediatric[tiab] OR perinatal[tiab]) NOT (adult[tiab] OR adults[tiab] OR adult[mh])) NOT ("mechanical valve"[tiab] OR "heart valve"[tiab] OR "atrial fibrillation"[mh] OR "atrial fibrillation"[tiab] OR thrombophilia[mh] OR thrombophilia[tiab] OR pregnancy[mh])

References

1. Heit J, Cohen A, Anderson A. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US. *Blood*. 2005;106:910.
2. Institute of Medicine. Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. Washington, DC: National Academies Press; 2009.
3. Lovenox (enoxaparin sodium injection for subcutaneous and intravenous use: prescribing information). Bridgewater, NJ: SanofiAventis; 2011. Available at: http://products.sanofi.us/lovenox/lovenox.html. Accessed October 17, 2012.
4. Innohep (tinzaparin sodium injection). Ballerup, Denmark: LEO Pharmaceutical Products; 2008. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020484s011lbl.pdf. Accessed October 17, 2012.
5. Leizorovicz A. Tinzaparin compared to unfractionated heparin for initial treatment of deep vein thrombosis in very elderly patients with renal insufficiency- the IRIS trial. [50th ASH Annual Meeting and Exposition abstract 434]. *Blood*. 2008;11:112.
6. Fragmin (dalteparin sodium injection). New York, NY: Pfizer Inc.; 2007. Available at: http://www.pfizer.com/files/products/uspi_fragmin.pdf. Accessed October 17, 2012.
7. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality; August 2011. AHRQ publication No. 10 (11)-EHC063-EF. Available at: http://www.effectivehealthcare.ahrq.gov. Accessed October 17, 2012.
8. Comparative effectiveness of pharmacologic and mechanical prophylaxis of venous thromboembolism among special populations. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/341/928/VTE-Special-Populations_Protocol_20120112.pdf. Accessed April 17, 2012.
9. Singh S, Haut E, Brotman D, et al. Comparative effectiveness of pharmacologic and mechanical prophylaxis of venous thromboembolism among special populations. Evidence Report/Technology Assessment (AHRQ). Available at: http://effectivehealthcare.ahrq.gov/ehc/products/341/1501/venous-thromboembolism-special-populations-report-130529.pdf. 2013.
10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377–384.
11. Kucher N, Leizorovicz A, Vaitkus PT, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. *Arch Intern Med*. 2005;165(3):341–345.
12. Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. *Am J Hematol*. 2012;87(7):740–743.
13. Simoneau MD, Vachon A, Picard F. Effect of prophylactic dalteparin on anti-factor xa levels in morbidly obese patients after bariatric surgery. *Obes Surg*. 2010;20(4):487–491.
14. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. *Thromb Res*. 2012;130(2):147–151.
15. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: No increased risk of bleeding. *Thromb Haemost*. 2012;108(1):183–190.
16. Bauersachs R, Schellong SM, Haas S, et al. CERTIFY: prophylaxis of venous thromboembolism in patients with severe renal insufficiency. *Thromb Haemost*. 2011;105(6):981–988.
17. Mahe I, Aghassarian M, Drouet L, et al. Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function: a comparative pharmacokinetic study. *Thromb Haemost*. 2007;97(4):581–586.
18. Dahl OE, Kurth AA, Rosencher N, Noack H, Clemens A, Eriksson BI. Thromboprophylaxis in patients older than 75 years or with moderate renal impairment undergoing knee or hip replacement surgery [published correction appears in *Int Orthop*. 2012;36(5):1113]. *Int Orthop*. 2012;36(4):741–748.
19. Shorr AF, Eriksson BI, Jaffer AK, Smith J. Impact of stage 3B chronic kidney disease on thrombosis and bleeding outcomes after orthopedic surgery in patients treated with desirudin or enoxaparin: insights from a randomized trial. *J Thromb Haemost*. 2012;10(8):1515–1520.
20. Elsaid KA, Collins CM. Initiative to improve thromboprophylactic enoxaparin exposure in hospitalized patients with renal impairment. *Am J Health Syst Pharm*. 2012;69(5):390–396.
21. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):7S–47S.
22. Stewart DW, Freshour JE. Aspirin for the prophylaxis of venous thromboembolic events in orthopedic surgery patients: a comparison of the AAOS and ACCP guidelines with review of the evidence. *Ann Pharmacother*. 2013;47(1):63–74.