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Comparative Effectiveness of Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Structured Abstract

Background: Venous thromboembolism is a leading cause of morbidity and mortality. Patients hospitalized with trauma, traumatic brain injury, burns, or liver disease; patients on antiplatelet therapy, obese or underweight patients, those having obesity surgery, or with acute or chronic renal failure may be at a higher risk of thrombosis. Most are also at high risk of bleeding.

Objectives: To systematically review the comparative effectiveness and safety of pharmacological and mechanical methods of prophylaxis of VTE in these special populations.

Data Sources: MEDLINE®, EMBASE®, SCOPUS, CINAHL®, www.clinicaltrials.gov, International Pharmaceutical Abstracts (IPA), and the Cochrane Library were searched in August 2011. This was complemented by hand searches from the reference lists and unpublished studies provided by sponsors.

Review Methods: We included randomized controlled studies and controlled observational studies of pharmacologic agents. We also included uncontrolled observational studies and case series describing inferior vena caval filters**.** Two reviewers evaluated studies for eligibility, serially abstracted data using standardized forms, and independently evaluated the risk of bias of included studies. We qualitatively synthesized the evidence.

Results: After a review of 28,526 citations, we included 95 studies. The majority of observational studies included in this review were at high risk of bias. We found insufficient strength of evidence for several comparisons of pharmacologic and mechanical strategies on VTE and bleeding outcomes among patients hospitalized with trauma, traumatic brain injury and those having obesity surgery due to the risk of bias of included studies and inconsistencies in the body of evidence. The strength of evidence was insufficient to assess the comparative effectiveness and safety among patients with burns, liver disease, patients on antiplatelet therapy, obese or underweight or those with acute or chronic renal failure.

Conclusions: Our systematic review demonstrates a paucity of evidence from robust studies to inform these key questions. Future research using high quality observational studies that control for confounding by indication, such as provider and practice patterns, and confounding by disease severity may be needed as randomized controlled trials typically exclude, or do not report on these special populations.

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Executive Summary

Introduction

Background

Pulmonary embolism (PE) resulting from deep vein thrombosis (DVT), collectively known as venous thromboembolism (VTE), affects an estimated 900,000 Americans each year and results in significant morbidity and mortality.[1 2] The average annual incidence of DVT in the United States (U.S.) ranges from 48 to 122 per 100,000. [1 2] With the ageing U.S. population, the number of cases of VTE is likely to rise. There are significant adverse consequences of DVT and PE.[1] Two-thirds of all VTE cases are nonfatal and yet result in hundreds of thousands of hospitalizations, whereas approximately one-third of these cases are fatal causing an estimated 300,000 deaths each year.[1 2] A new diagnosis of DVT or PE in the hospital increases the costs of the index hospitalization by approximately $10,000 and $20,000, respectively.[3] Thus VTE is an important patient safety issue with significant morbidity, mortality, and health care costs.[4] Accordingly, the comparative effectiveness and safety of interventions for the prevention and treatment of VTE are among the national priorities for comparative effectiveness research.[5]

In this review, we describe the evidence about prevention of DVT in "special populations". Special populations are those patients in whom the benefit or risk of VTE prophylaxis is uncertain, or patients in whom there is decisional uncertainty about the optimal choice, timing, and dose of VTE prophylaxis or significant practice variation. The burden of VTE is higher among some patient populations including patients who have experienced recent trauma,[6-11] traumatic brain injury or burns,[12-14]patients undergoing bariatric surgery,[15-21]and patients with acute renal failure, chronic renal failure, or end-stage renal disease. [22-25]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. Therefore, the risk-benefit ratio of prophylactic medications in these populations is uncertain and is similarly unclear in populations of patients with altered clearance of medications.[26-30]

Therapies of Interest

In this review, we describe the evidence for drugs and devices that currently are available in the U.S. and that are either FDA-approved for VTE prophylaxis or that clinician's use off-label for this indication. The pharmacologic agents of interest included unfractionated heparin (UFH) and low molecular weight heparins (LMWH) delivered subcutaneously.[26-29] Fondaparinux, a synthetic pentasaccharide, is also included in this review. Similarly, we included antiplatelet agents, such as aspirin and clopidogrel, as well as the anticoagulant warfarin, which clinicians may use off-label for this indication. We also included dabigatran, a recently approved oral anticoagulant that directly inhibits thrombin; the FDA approved it for the prevention of stroke in patients with atrial fibrillation, but it has the potential for off-label use for prophylaxis of VTE. Rivaroxaban is an oral factor Xa inhibitor that the FDA approved in July 2011 for VTE prophylaxis for patients undergoing elective hip and knee arthroplasty; this drug also has the potential for off-label use in other patient populations. We also included sequential compression devices, venous foot pumps, and various types of IVC filters in this review.[4]

Key Questions

This report includes our review of the evidence about the efficacy, effectiveness, and safety of pharmacological and mechanical methods of prophylaxis in our defined special populations. The KQs we explored are as follows:

Key Question 1. What is the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?

Key Question 2a. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with traumatic brain injury?

Key Question 2b. What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent VTE in hospitalized patients with traumatic brain injury?

Key Question 3. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns?

Key Question 4. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

Key Question 5. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

Key Question 6. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in patients having bariatric surgery?

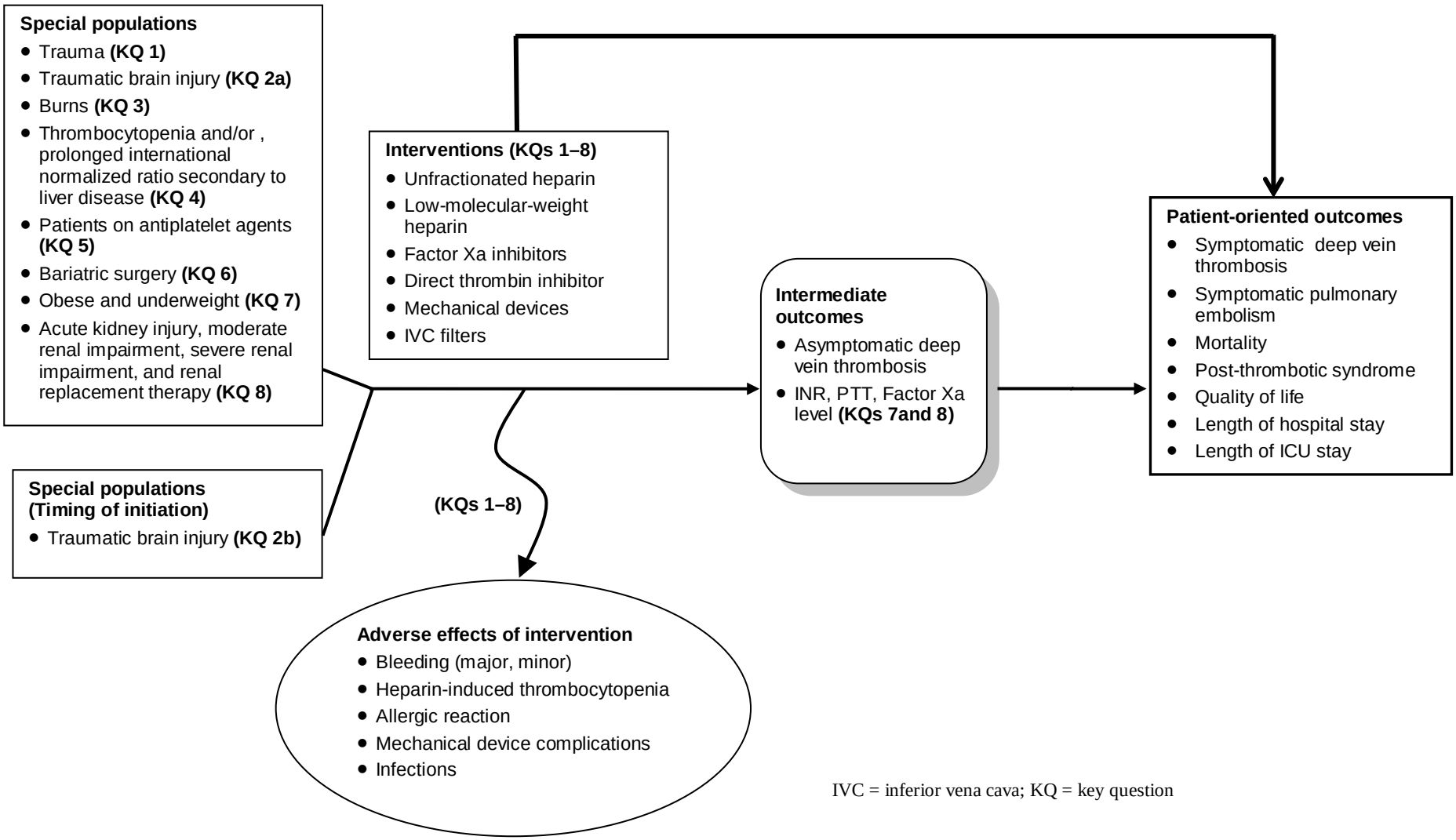
Key Question 7. What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?

Key Question 8. What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

Framework

Our conceptual model for the systematic review is presented in Figure A. The figure illustrates the special populations of interest, the therapies, and the intermediate and clinical outcomes that we reviewed, as well as the adverse consequences associated with these prophylactic regimens.

Figure A. Analytic Framework: Comparative Effectiveness of Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations



IVC = inferior vena cava; KQ = key question

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at: http://www.effectivehealthcare.ahrq.gov/methods guide.cfm)

Search Strategy

We searched the following databases for primary studies: MEDLINE® through August 2011, EMBASE® through August 2011 SCOPUS through August 2011, CINAHL® through August 2011, International Pharmaceutical Abstracts through August 2011, clinicaltrial.gov through August 2011, and the Cochrane Library through August 2011. We developed a search strategy for MEDLINE, accessed via PubMed®, based on medical subject headings (MeSH®) terms and text words of key articles that we identified a priori. (Appendix B) We reviewed the reference lists of all included articles, relevant review articles, and related systematic reviews to identify articles that the database searches might have missed. In addition, we requested and reviewed Scientific Information Packets provided by the pharmaceutical manufacturers.

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 venous thromboembolism prevention in our populations. Two investigators independently reviewed abstracts and we excluded the abstracts if both investigators agreed that the article met one or more of the exclusion criteria. We resolved disagreements by consensus.

Data Abstraction and Data Management

We used DistillerSR (Evidence Partners, 2010) to manage the screening and review process. DistillerSR is a Web-based database management program that manages all levels of the review process. We uploaded to the system all applicable citations identified by the search strategies.

Assessment of Methodological Quality of Individual Studies

We conducted the risk of bias independently and in duplicate using the Downs and Black instrument for observational studies and trials.[31] We found that 10 items were most relevant to this review and we prioritized them in our assessment of risk of bias. We could not consider any study without randomization to have a low risk of bias. Such studies could be at moderate or high risk of bias. Low risk of bias studies had the least bias and the results were considered valid. Moderate risks of bias studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies. High risk of bias studies had significant flaws that might have invalidated the results.

Data Synthesis and Analysis

For each KQ, we created a detailed set of evidence tables containing all information abstracted from eligible studies. We grouped the information for each KQ by comparison interventions. The studies were sufficiently heterogeneous precluding any pooling in a meta-

analysis. Given the substantial statistical and clinical heterogeneity we did not report pooled results but displayed the individual relative risks with 95% confidence intervals for the individual studies. All analyses were conducted using Stats Direct.

Grading the Evidence for Each Key Question

After synthesizing the evidence, we graded the quantity, quality, and consistency of the best available evidence addressing KQs 1 to 8 by adapting an evidence grading scheme recommended in the Methods Guide for Conducting Comparative Effectiveness Reviews.[32] In assigning evidence grades, we considered the four recommended domains, including risk of bias in the included studies, directness of the evidence, consistency across studies, and precision of the pooled estimate or the individual study estimates. We found that few of the studies reported precision, although we were able to calculate confidence intervals for some of the outcomes. We classified evidence pertaining to KQs 1 to 8 into four categories: 1) "high" grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient" grade (evidence is unavailable). Single high risk of bias studies were rated to be insufficient

Assessing Applicability

We assessed applicability of the evidence separately for the outcomes of benefit (reduction in VTE) and harm (increased risk of bleeding) as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions.[32] We evaluated whether the include populations in these studies were representative of participants in the real world. We assessed whether the concomitant interventions administered in these studies were also representative of real world management strategies for these special populations. We assessed whether there were features of the individuals studies which limited the applicability of the study's findings including whether studies excluded patients with comorbidities, whether studies allowed or disallowed the concomitant use of nonmedical cointerventions (early ambulation), and the choice and dosing of comparators.

Table A: Study Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Human subjects (only)	• Animal studies/models
• Adults in special patient populations, including: o Trauma o Traumatic brain injury o Burns o Liver disease o Antiplatelet therapy o Bariatric surgery o Obese and underweight o Acute kidney injury, moderate renal impairment, severe renal impairment, renal replacement therapy	• Children • Pediatric • Adolescent • Adults in the following patient populations: o Treatment of VTE o Secondary prophylaxis o Catheter thrombosis o Antiphospholipid antibodies/other autoimmune diseases o Cancer (malignancy, chemotherapy, radiotherapy) o Cardiovascular (coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty) patients on full-dose anticoagulation o Pregnancy o Disseminated intravascular coagulation o Heparin-induced thrombocytopenia o Congenital platelet disorders o VTE prophylaxis for long distance travel o Abdominal surgery o Vascular surgery o Urological surgery o Gynecological surgery
We included the following study designs* o Randomized controlled trials o Prospective cohort studies o Retrospective cohort studies o Case-control studies o Uncontrolled case-series for devices o Case reports of device complications in the relevant special populations o Case reports of pharmacologic therapies other than the known complications of bleeding and heparin-induced thrombocytopenia	• Case reports of efficacy • Case reports of bleeding or heparin-induced thrombocytopenia associated with pharmacologic strategies • In vitro studies • Animal studies • Cost-effectiveness studies • Modeling studies • Risk assessment studies • Registries without descriptions of interventions • Diagnostic studies • Ecologic study designs • Time-series designs • No original data, commentary, or editorial • Systematic reviews and meta-analysis
Studies that evaluate interventions or mechanical devices	Studies of agents that have not been approved for thromboprophylaxis in the United States or interventions not available in the United States will not be evaluated
• Symptomatic deep vein thrombosis • Symptomatic pulmonary embolism • Mortality • Post-thrombotic syndrome • Quality of life • Length of hospital stay • Length of ICU stay • Bleeding (major, minor) • Heparin-induced thrombocytopenia • Allergic reaction • Mechanical device complications • Infections • Asymptomatic deep vein thrombosis • INR, PTT, factor Xa level **(KQs 7 and 8)**	• No data on relevant outcomes of interest

Table B. PICOTS for each Key Question

	KQ 1	KQ 2	KQ 3–KQ 5	KQ 6	KQ 7–KQ 8
Population(s)	• Trauma	• Traumatic brain injury	• Burns (KQ 3) • Liver disease (KQ 4) • Antiplatelet therapy (KQ 5)	• Bariatric surgery	• Obese and underweight patients (KQ 7) • Patients with acute kidney injury or moderate or severe renal impairment (KQ 8) • Patients receiving dialysis (KQ 8)
Interventions	• IVC filters	• Mechanical devices • Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • IVC filters	• Mechanical devices • Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)	• Pharmacologic (UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • Mechanical devices • IVC filters	• Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • Mechanical devices
Comparators	• No IVC filters. (Studies that included usual care or those that did not use IVC filters as active controls including mechanical prophylaxis (e.g., SCDs, compression stockings) and pharmacologic controls	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, studies that used active controls, and uncontrolled studies.	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, studies that used active controls, and uncontrolled studies.	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, or studies that used active controls, and uncontrolled studies.	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, studies that used active controls, and uncontrolled studies.
Outcomes measures	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• INR, PTT, Factor Xa level • Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality
Adverse effects of intervention(s) and treatment burden	• Major bleeding defined as including: fatal bleeding; clinically overt bleeding causing a fall in hemoglobin of ≥2 g/dL or leading to transfusion of two or more units of packed cells or whole blood; or bleeding into critical organs (retroperitoneal or intracranial) • In surgical patients: an assessment of the amount of blood loss, minor bleeding, surgical site bleeding, and complications from mechanical IVC filters (e.g., device migration, perforation, fractures, filter thrombosis, infections, prolonged hospitalization, mortality)				
Timings	• Studies with all durations of followup				
Settings	• Hospital setting	• Hospital Setting	• Hospital setting	• Hospital setting	• Hospital setting

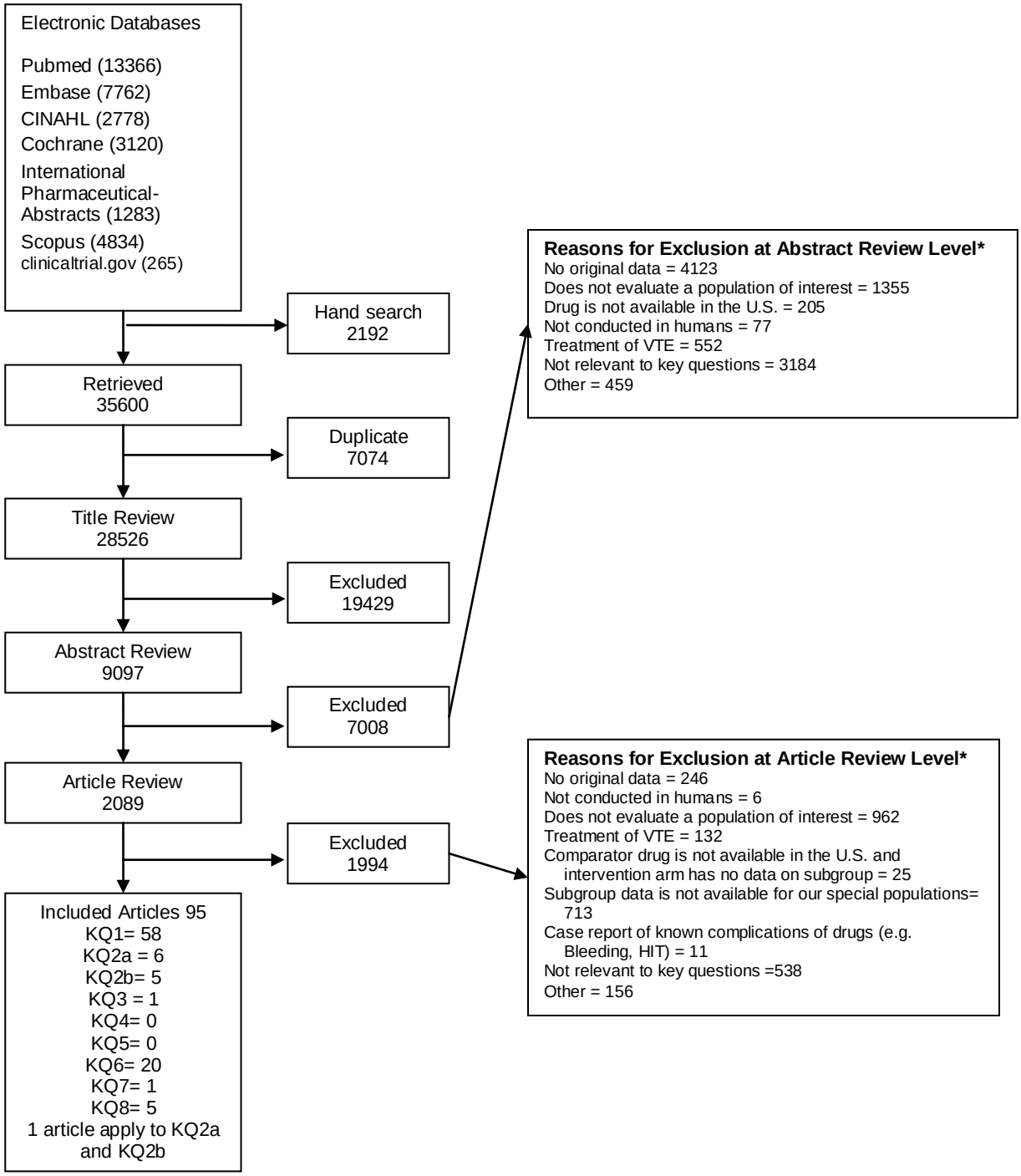
DVT = deep vein thrombosis; IVC = inferior vena cava; KQ = key question; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SCD = sequential circumferential compression device; UFH = unfractionated heparin

Results

Results of the Search Results

Figure 2 summarizes the search results. The literature search identified 28, 526, unique citations. During the title screening, we excluded 19,429 citations. During the abstract screening, we excluded 7,008 citations. During article screening, we excluded an additional 1,994 articles that did not meet one or more of the inclusion criteria (Table A). Ninety-five articles were included in the review. Of the included studies, 58 studies compared the effects of IVC filter use in patients with trauma, 10 studies compared the effects of IVC filters in patients with traumatic brain jury. One study reported on patients with burns. We did not identify any studies among patients with liver failure, or on antiplatelet therapy. We found one randomized controlled trial among obese patients. Twenty studies reported on patients with obesity surgery and five studies reported on patients with renal failure.

Figure B. Results of Search



* Total exceeds the # in the exclusion box because reviewers were allowed to mark more than 1 reason for exclusion, KQ=Key Question, HIT=heparin induced thrombocytopenia, VTE=venous thromboembolism

Results by Population

KQ1. Patient with Trauma

There were 58 studies on this KQ as shown in body of evidence tables. Most studies were rated at high risk of bias except 5 observational studies were at moderate risk of bias.(Table C)

- The strength of evidence is insufficient to support that IVC filter placement is associated with a lower incidence of PE or fatal PE in hospitalized patients with trauma compared to no IVC filter placement. We based this rating on the high risk of bias, imprecision and inconsistency of findings across studies.
- The strength of evidence is insufficient to support that IVC filter placement is associated with a higher incidence of DVT in hospitalized patients with trauma compared to no IVC filter placement. We based this rating on the high risk of bias and inconsistency in the findings across studies.The strength of evidence is insufficient to support that IVC filter placement is associated with a higher mortality in hospitalized patients with trauma compared to no IVC filter placement. We based this rating on the high risk of bias, imprecision and inconsistency in the findings across studies.
- The strength of evidence is low to support that IVC filter placement is associated with filter related thrombosis in hospitalized patients with trauma compared to no IVC filter placement. The risk of bias was high. However the findings were direct, precise and consistent.

KQ2a. Patients with Traumatic Brain Injury

There were 6 studies on this KQ as shown in body of evidence tables. Most studies were rated at high risk of bias except 1 observational study was at moderate risk of bias. (Table C) The insufficient strength of evidence rating was based on either inconsistencies in the body of evidence, or our inability to assess consistency (consistency unknown) in a single study.

- The strength of evidence is insufficient to support the effectiveness of prophylaxis with enoxaparin over dalteparin in reducing the incidence of VTE in hospitalized patients with traumatic brain injury.
- The strength of evidence is insufficient to support the effectiveness of prophylaxis with enoxaparin over UFH in reducing the incidence of DVT, incidence of PE and mortality in hospitalized patients with traumatic brain injury.
- The strength of evidence is insufficient to support the effectiveness of prophylaxis with enoxaparin over no pharmacoprophylaxis/ intermittent pneumatic compression in reducing the incidence of VTE, incidence of DVT, incidence of PE and rates of mortality in hospitalized patients with traumatic brain injury.
- The strength of evidence is insufficient to support the effectiveness of prophylaxis with UFH over no pharmacoprophylaxis in reducing the incidence of VTE, incidence of DVT and incidence of PE in hospitalized patients with traumatic brain injury.
- The strength of evidence is low to support that UFH reduced the rates of total mortality compared to no pharmacoprophylaxis in hospitalized patients with traumatic brain injury. We based this rating on consistent, direct and precise evidence from two studies.

- The strength of evidence is insufficient to support the effectiveness of prophylaxis with intermittent pneumatic compression over no prophylaxis in reducing the incidence of VTE and PE events in hospitalized patients with traumatic brain injury.

KQ2b. Patients with Traumatic Brain Injury

There were 5 studies on this KQ as shown in body of evidence tables. All studies were rated at high risk of bias. (Table C) Estimates were often imprecise and consistency of effect was unknown leading to conclusions of insufficient strength of evidence.

- The strength of evidence was insufficient to comment on the effectiveness of early (< 72 hours) versus late (> 72 hours) pharmacoprophylaxis with enoxaparin, UFH or any heparin on the outcomes of venous thromboembolic events, DVT, PE, fatal PE, total mortality, major and minor bleeding.

KQ3. Patients with Burns

There was one study on this key question which received a high risk of bias rating due to methodologic limitations in design and reporting, sample size, and the absence of a control group to allow any meaningful conclusions.

- The strength of evidence is insufficient to comment on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns.

KQ4. Patients with Liver Disease

We found no studies that directly address the comparative effectiveness and safety of pharmacologic strategies among patients with liver disease.

KQ5. Patients Receiving Antiplatelet Therapy

We found no studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies among hospitalized patients receiving antiplatelet therapy

KQ6. Patient having Bariatric Surgery

There were 20 included observational studies on this question. Most studies were at high risk of bias, except 1 study was at moderate risk of bias with either inconsistent or unknown consistency of findings. (Table C)

In hospitalized patients having bariatric surgery:

- The strength of evidence is low supporting that prophylactic inferior vena cava filters increase the risk of post-operative DVT relative to no filters, in patients also receiving non-invasive mechanical measures and pharmacological prophylaxis. We based this rating on consistent and precise estimate of increased risk of DVT with filters compared to no filters (RR = 2.28, 95% CI=1.06 to 4.94).
- The strength of evidence is insufficient supporting that prophylactic inferior vena cava filters decrease the risk of PE or fatal PE relative to no filters, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient that prophylactic inferior vena cava filters increase the risk of all-cause death relative to no filters, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient supporting that enoxaparin 40 mg twice daily or higher decreases the risk of DVT or fatal PE compared to lower doses of enoxaparin or unfractionated heparin 5000 units subcutaneously three times daily, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient supporting that enoxaparin 40 mg twice daily or higher increases the risk of bleeding compared to lower doses of enoxaparin or unfractionated heparin 5000 units subcutaneously three times daily, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient to support the comparative effectiveness and safety of any pharmacological strategies other than enoxaparin and unfractionated heparin for prevention of VTE in this population.

KQ7. Hospitalized Patients who are Obese or Underweight

There was one RCT among patients who were obese which was rated at moderate risk of bias. We did not find any studies that evaluated patients who were underweight. We rated the strength of evidence as insufficient for all outcomes because of unknown consistency and imprecision.

- The strength of evidence is insufficient that fixed low dose dalteparin reduces the risk of VTE or fatal PE compared to placebo during hospitalization of obese patients.
- The strength of evidence is insufficient that fixed low dose dalteparin increases the risk of major bleeding compared to placebo during hospitalization of obese patients.
- The strength of evidence is insufficient to conclude that fixed low dose dalteparin reduces the risk of fatal PE compared to placebo during hospitalization of obese patients.

KQ8. Patients with Renal Insufficiency or Failure

We included 5 studies on this key question. (Table C) We based our strength of evidence rating on a lack of evidence that directly addressed our question (or evidence that was so inconsistent and at high risk of bias that it did not permit a conclusion).

- The strength of evidence is insufficient to assess the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients

with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis.

Table C: Summary of the strength of evidence by KQ

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Evidence Statement and Magnitude of Effect
KQ1								
IVC filter vs. no Filter	PE	8	4626	High	Direct	Imprecise	Inconsistent	Insufficient to support reduction in PE in trauma RR0.55 (95% CI = 0.10 to 2.96);p=0.48;
	Fatal PE	5	3226	High	Direct	Imprecise	Inconsistent	Insufficient to support reduction in fatal PE in trauma RR 0.36 (95% CI = 0.015496 to 8.161554): p=0.54
	Mortality	5	4040	High	Direct	Imprecise	Inconsistent	Insufficient to support higher mortality in trauma; RR1.33 (95% CI = 0.53 to 3.32);p=0.54
	DVT	3	300	High	Direct	Imprecise	Inconsistent	Insufficient to support higher DVT in trauma RR 1.76 (95% CI = 0.49 to 6.18):p=0.38
	Filter related thrombosis	3	3972	High	Direct	Precise	Consistent	Low to support higher incidence of filter related thrombosis in trauma; RR 51.4 (95% CI = 7.43 to 355):p<0.0001
KQ2a								
Enoxaparin vs. dalteparin	Total VTE	1	287	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin vs. Dalteparin in reducing Total VTE in TBI patients 7% vs 7.5%;p=0.868
Enoxaparin vs. UFH	Total DVT	1	329	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin vs. UFH in reducing Total DVT in TBI patients 1% vs 1%*
	Total PE	1	329	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin vs. UFH in reducing Total PE in TBI patients 0% vs 4% ; p<0.05
	Total mortality	1	329	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin vs. UFH in reducing Total mortality in TBI patients 5% vs 15.8%;p<0.05

Table C: Summary of the strength of evidence by KQ continued

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Evidence Statement and Magnitude of Effect
Enoxaparin vs. IPC/control	Total VTE	1	480	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin vs. IPC/control in reducing Total VTE in TBI patients. 3.9% vs 2.2%;p=0.29
	Total DVT	2	335	High	Direct	Imprecise	Consistent	Insufficient evidence to comment on effectiveness of Enoxaparin vs. IPC/control in reducing Total DVT in TBI patients
	Total PE	2	335	High	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of Enoxaparin vs. IPC/control in reducing Total PE in TBI patients
	Fatal PE	1	120	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin vs. IPC/control in reducing Fatal PE in TBI patients 6.6% vs 3.3%:p=0.04
	Total mortality	2	335	High	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of Enoxaparin vs. IPC/control in reducing Total mortality in TBI patients
	Exacerbation of epidural hematoma	1	120	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin vs. IPC/control in reducing Exacerbation of epidural hematoma in TBI patients 1.6% vs 1.6%*
UFH vs. control	Total VTE	1	812	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing Total VTE in TBI patients 1% vs 3%;p=0.019
	Total DVT	1	228	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing Total DVT in TBI patients 1% vs 2% *
	Total PE	1	228	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing Total PE in TBI patients 4% vs 2%*
	Total mortality	2	1040	High	Direct	Precise	Consistent	Low grade evidence to suggest that UFH reduces mortality in TBI compared to controls

Table C: Summary of the strength of evidence by KQ continued

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Evidence Statement and Magnitude of Effect
IPC vs. control	Total VTE	1	32	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of IPC vs. control in reducing Total VTE in TBI patients 28.6% vs 22.2%: p=0.7
	Total PE	1	32	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of IPC vs. control in reducing Total PE in TBI patients 28.6% vs 11.1%*
KQ2b								
Enoxaparin <72 hrs. vs. >72 hrs.	VTE	1	255	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs. vs. >72 hrs. in reducing VTE in TBI patients 5.6% vs 2.7%;p=0.26
	Proximal DVT	1	669	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs. vs. >72 hrs. in reducing proximal DVT in TBI patients 1.5% vs 3.5%;p= 0.12
	PE	1	669	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs. vs. >72 hrs. in reducing PE in TBI patients 1.5% vs 2.2%; p=0.49
	Fatal PE	1	669	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs. vs. >72 hrs. in reducing fatal PE in TBI patients 0% vs 0.3% *
	Mortality due to bleeding	1	669	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs. vs. >72 hrs. in reducing mortality due to bleeding in TBI patients 0% vs 0% *
UFH <72 hrs. vs. >72 hrs.	DVT	1	64	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs. vs. >72 hrs. in reducing DVT in TBI patients 4.3% vs 5.9%;p=1.00
	PE	1	64	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs. vs. >72 hrs. in reducing PE in TBI patients 4.3% vs 0%; p=0.96

Table C: Summary of the strength of evidence by KQ continued

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Evidence Statement and Magnitude of Effect
	Total mortality	1	64	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs. vs. >72 hrs. in reducing total mortality in TBI patients 8.5% vs 5.9% ; p=1.00
KQ6								
Enoxaparin versus Unfractionated Heparin	PE	1	476	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing PE in patients undergoing bariatric surgery 0% vs 0.4%; p=0.99
	DVT	1	476	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing DVT in patients undergoing bariatric surgery 0% vs 0%*
	Major bleeding	1	476	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing major bleeding in patients undergoing bariatric surgery 5.9% vs 1.3%; p=0.011
	Total mortality	1	476	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing mortality in patients undergoing bariatric surgery 0% vs 0%
Enoxaparin versus extended duration of Enoxaparin	PE	1	308	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing PE in patients undergoing bariatric surgery 2.3 % vs 0% *
	VTE	1	308	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing VTE in patients undergoing bariatric surgery 4.6% vs 0% ;P=0.006

Table C: Summary of the strength of evidence by KQ continued

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Evidence Statement and Magnitude of Effect
	DVT	1	308	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing DVT in patients undergoing bariatric surgery 2.3% vs 0%
	Major bleeding	1	308	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing major bleeding in patients undergoing bariatric surgery 4.5% vs 0% ;p= 0.06
	Total Mortality	1	308	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing mortality in patients undergoing bariatric surgery 0% vs 0%; p = NS
Enoxaparin at standard dosing versus Augmented dosing	PE	3	1319	High	Direct	Unknown	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing PE in patients undergoing bariatric surgery
	DVT	3	1319	High	Direct	Unknown	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing DVT in patients undergoing bariatric surgery
	VTE	1	481	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing VTE in patients undergoing bariatric surgery 5.4% vs 0.6% ; p <0.01
	Bleeding	3	1319	High	Direct	Unknown	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing bleeding in patients undergoing bariatric surgery
Filter vs. no filter	Total VTE	1	6376	Medium	Direct	Precise	Unknown	Insufficient to comment on effectiveness of IVC in reducing PE in bariatric surgery 2.0% vs 0.5%; p<0.0001

Table C: Summary of the strength of evidence by KQ continued

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Evidence Statement and Magnitude of Effect
	PE	3	2832	High	Direct	Imprecise	Inconsistent	Insufficient to comment on effectiveness of IVCF in reducing PE in bariatric surgery RR = 0.54 (95% CI = 0.11 to 2.72;P = 0.46; 1^2=30%)
	Fatal PE	1	409	High	Direct	Imprecise	Unknown	Insufficient to comment on effectiveness of IVCF in reducing fatal PE in bariatric surgery 0% vs 11.1%
	DVT	3	2832	High	Direct	Precise	Consistent	Low grade evidence to support that IVCFs increase DVT in patients undergoing bariatric surgery compared to controls RR = 2.28 (95% CI=1.06 to 4.94; p=0.03;1^2=53%)
	Total mortality	3	8878	High	Direct	Precise	Inconsistent	Insufficient to comment on effectiveness of IVCF in increasing mortality in bariatric surgery RR =3.44 (95% CI=1.79 to 6.58; p=0.0002; 1^2=0%)
KQ8								
Tinzaparin vs. enoxaparin	Total VTE Events	1	55	High	Direct	Imprecise	Unknown	Insufficient on reducing VTE in patients with renal insufficiency 0 events in 27 patients (tinzaparin) vs 0 events in 28 patients (enoxaparin)
	Cmax	1	55	High	Direct	Precise	Unknown	Insufficient on Cmax in patients with renal insufficiency The ratio of Cmax on day eight to day one was 1.05 for tinzaparin and 1.22 for enoxaparin (p=0.016).
	bleeding events	1	55	High	Direct	Imprecise	Unknown	Insufficient on bleeding in patients with renal insufficiency 5 /27 vs 4/28 (p=0.67)
UHF in severe renal compromise vs. all other renal status (undifferentiated)	Total VTE Events	1	92	High	Direct	Imprecise	Unknown	Insufficient on reducing VTE in severe renal compromise patients vs. all other renal patients 2.6% of patients had a VTE event
	Bleeding Events	1	92	High	Direct	Imprecise	unknown	Insufficient evidence to comment on effectiveness of UFH in increasing bleeding in severe renal compromise patients vs. all other renal patients Insufficient evidence; 13 events in 92 patients

Table C: Summary of the strength of evidence by KQ continued

* P-values or tests of statistical significance not reported
¶* Two studies with the outcome “filter complications” list only filter as the intervention
DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism;

Discussion

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high quality studies to inform several of these key questions for these special populations.

Patients with Trauma

We identified only a single RCT addressing prophylaxis in this population and it had significant methodological limitations. This pilot trial randomized patients to usual care plus IVC filters vs. usual care but was underpowered for all outcomes. Most studies in our database were assessed as having a high risk of bias except five observational studies which were assessed as having a moderate risk of bias. There was significant heterogeneity among the included studies in design and eligibility, and inconsistency in efficacy and safety outcome assessment methods. Although many of the studies reported on the VTE outcomes, most did not provide details about anatomic locations of the DVTs or PEs. There were also differences in reporting and duration of follow-up. The included studies lacked adequate details about enrolled patient characteristics, such as race and gender, and details of the extent and severity of the trauma limiting our ability to generalize findings from these studies to other ethnic groups or age categories.

Several uncontrolled observational studies provided information on the rare occurrences of filter complications such as strut fracture, insertion site thrombosis, arterial-venous fistulas, filter misplacement, filter tilt, filter migration and IVC thrombosis. The low rates of such complications, the significant risks of bias in the included studies, and the lack of control groups precluded any definitive assessment of the comparative safety of different filter types in patients with trauma.

Our current findings should be interpreted in the context of other systematic reviews on this topic. A recent review conducted a qualitative synthesis of data from 24 studies and found increasing use of retrievable filters and low rates of filter related complications.[33] The authors concluded that there was a lack of high quality data, and therefore the true efficacy of prophylactic IVC filters for prevention of PE in trauma patients remains unclear. A review from 2006, endorsed by the American Venous Forum, found that the evidence on optional IVC filters was not sufficient to support evidence-based recommendations.[34]

There are conflicting guidelines on this topic. The practice guideline from the Eastern Association for the Surgery of Trauma recommends that insertion of a prophylactic IVC filters *should be considered* in very high risk trauma patients.[35] A recent American College of Chest Physicians (ACCP) review suggested that that placement of an IVC filter probably reduces the risk of PE over the short term, but notes that the complications are “frequent” and long term outcomes are unclear. [36] This group noted that removable filters may mitigate the long-term complication rate, but also noted that they are often not removed. Thus the ACCP guidelines *recommends against* IVC filters for primary VTE prevention in patients with trauma (Grade 2C).[36]

Patients with Traumatic Brain Injury

We found only one RCT that addressed DVT prophylaxis in patients with traumatic brain injury. The remaining studies were single-center cohort studies, the majority of which were retrospective. The majority of the cohort studies were assessed as having a high risk of bias. Due to lack of large RCTs we were unable to comment on the comparative effectiveness of

pharmacological and mechanical prophylaxis of venous thromboembolism in hospitalized patients with traumatic brain injury. However, low grade evidence supported that rates of mortality were lower with use of UFH as opposed to no pharmacoprophylaxis in these patients.

Five retrospective cohort studies evaluated the timing of pharmacologic prophylaxis in patients with traumatic brain injury. The lack of large RCTs precludes any definitive conclusions about the timing and initiation of prophylaxis in patients with brain trauma.

The two organizations, EAST and the Traumatic Brain Foundation, that provide guidelines for the care of the patients with trauma and patients with traumatic brain injury, respectively, do not make specific recommendations about DVT prophylaxis in patients with traumatic brain injury due to the paucity of evidence.[35]Additionally, the ACCP guidelines do not specifically address DVT prophylaxis in these patients.[36]

Patients with Burns

We did not find any studies that evaluated the comparative effectiveness and safety of pharmacologic strategies in the prevention of VTE among patients with burns. The only included cohort study of IVC filter placement had a high risk of bias with significant methodological limitations. It included just 20 patients and did not have a control group. The very high mortality rate in this study (9 out of 20 participants) was likely related to multi-organ failure.[37] The ACCP 2012 guidelines do not provide specific recommendations for preventing VTE in patients with burns. [38]

Patients with Liver Disease

We found no studies that directly address the comparative effectiveness and safety of pharmacologic strategies among patients with liver disease.

Patients on Antiplatelet Therapy

We found no studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies among hospitalized patients receiving antiplatelet therapy

Patients having Bariatric Surgery

There was marked practice variation in filter use for VTE prophylaxis among hospitalized patients undergoing bariatric surgery, beyond what could be explained by differences in the patient populations. Birkmeyer et al observed an attenuation of the unadjusted association between the use of IVC filters and adverse clinical outcomes after propensity score adjustment. This suggests that the process of selecting patients for filters based on VTE risk may bias toward a lack of filter efficacy, or the appearance of harm.[39] In each of the studies that we included, physicians ultimately removed more than two-thirds of the retrievable filters placed.

In the absence of RCTs, we were unable to determine the comparative effectiveness and safety, or the optimal timing and duration, of prophylactic pharmacotherapy. The observational studies did not provide a clear association between the use of pre-operative initiation of pharmacologic prophylaxis and perioperative bleeding, or between post-operative initiation of pharmacologic prophylaxis and thrombosis. A study of extended prophylaxis versus inpatient prophylaxis suggested that continuing enoxaparin therapy for 10 days discharge may be associated with a lower risk of VTE, when compared to shorter therapy.[40] The rate of fatal pulmonary emboli appears to be low in patients receiving pharmacologic prophylaxis. Consistent with current practice, the majority of the studies emphasized the use of compression devices,

compression stockings, and early ambulation. Additionally, the studies that focused on IVC filters generally included patients receiving concurrent pharmacologic prophylaxis.

Pharmacokinetic data from two studies suggest that "subtherapeutic" anti-Xa levels are common when patients receive standard prophylactic doses of enoxaparin, particularly 30 mg twice daily, and that "supratherapeutic" levels are common when patients receive doses of 60 mg twice daily. However, the extent to which anti-Xa levels predict bleeding in obese patients undergoing bariatric surgery is unknown.

In contrast to our comparative effectiveness review, which evaluated only comparative studies of pharmacologic regimens, Becattini et al. also included uncontrolled single-arm studies of pharmacologic prophylaxis.[41] They concluded that the incidence of symptomatic postoperative VTE appeared to be less than 1 percent with either prophylactic strategy, but that with screening, the rate was approximately 2 percent. Using a standardized definition of bleeding, bleeding rates were approximately 1 percent for standard-dose regimens, and 1.6 percent for weight-adjusted (augmented) pharmacological prophylaxis. The authors concluded that there might be a higher rate of bleeding with augmented dosing regimens with no evidence of increased efficacy, similar to our findings.

Obese or Underweight Hospitalized Patients

We found only one subgroup analysis of an RCT that reported on the comparative effectiveness and safety of fixed low-dose dalteparin 5000 IU/day versus placebo among hospitalized obese patients with a BMI less than 40kg/m2. However the strength of evidence was insufficient on the composite endpoint of DVT, PE and sudden death; and the outcomes of mortality and bleeding. We did not find any evidence about the role of other pharmacologic or mechanical strategies among hospitalized obese patients. There were no studies among patients who are underweight.

Patients with Renal Insufficiency or Failure

Despite that patients with compromised renal function who require pharmacologic VTE prophylaxis are common; we found insufficient evidence to guide treatment decisions. Our findings are consistent with other recently published reviews. The ACCP guidelines make dosing recommendations for the *therapeutic* use of LMWH.[42 43]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-Xa levels are consistent with ours. The ACCP guidelines also suggest that decreased clearance of LMWHs has been associated with increased risk of bleeding events for patients with severe renal insufficiency. However, the cited study 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 LMWH therapy, that is, above the baseline increased risk of bleeding among patients with renal insufficiency.

Limitations

Our systematic review identified important weaknesses in the literature. We did not identify high quality RCTs on any of these KQs. The RCTs identified for some of these KQs were small and had methodological limitations. The majorities of observational studies included in this review were either at high or moderate risk of bias and did not report on several quality items of interest. The greatest risk to their validity was confounding by indication in that the sicker

patients received more intense prophylaxis than the less sick patients, with no or inadequate adjustment for differences between treatment groups. The studies were heterogeneous in definition of VTE and bleeding outcomes precluding any meaningful pooling in a meta-analysis. We also did not find data on several pharmacologic comparisons of interest or details about appropriate dosing strategies in these special populations.

Our systematic review has several limitations. Although our search strategy was comprehensive, we may have missed studies. We were unable to assess the possibility of publication bias or selective outcomes reporting and its impact on our findings.

Future Research

Our report highlights the need for several areas of research on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE among these special populations. There remains a significant research gap regarding the efficacy and safety for IVC filters for PE prophylaxis in trauma patients. Such a study would ideally include sufficient participants with traumatic brain injury, an important subgroup of trauma patients. A large, multi-center RCT is required to definitively answer the question on the efficacy and safety of IVC filters in trauma and patients with traumatic brain injury.[34] A carefully matched cohort may also be informative on this KQ. Studies should also determine the role of appropriate classification and severity of traumatic brain injury when deciding to administer pharmacologic prophylaxis.

Among patients with burns, studies are needed to clarify the relationship between the burned surface area and thrombotic complications. Studies are also needed to determine whether the altered pharmacokinetics of enoxaparin may result in inadequate dosing in burn patients, and whether dose-adjustment of enoxaparin based on serum anti-Xa monitoring is warranted.[44] Future research should include high-quality observational studies to determine the comparative effectiveness and safety of various pharmacological and mechanical strategies among patients with liver disease. Trials of pharmacoprophylaxis should consider reporting rates of VTE and bleeding among subgroups of patients receiving antiplatelet therapy. High quality observational studies that control for confounding by indication, such as provider and practice patterns, and confounding by disease severity may be more realistic to answer some questions on these special populations. Observational designs using propensity scores or instrumental variables may also provide useful information.

RCTs may be useful to evaluate the efficacy and safety of IVC filters in high-risk bariatric surgery patients. Such trials should include only those patients deemed to be at highest risk for VTE complications, such as those with prior VTE. Randomized trials should also address whether standard doses of prophylaxis that have been proven safe and effective in other types of surgery (such as 5,000 units of subcutaneous unfractionated heparin three times daily, enoxaparin 30 mg twice daily, or enoxaparin 40 mg once daily) are adequate for patients undergoing bariatric surgery. Clinical trials should consider weight-based dosing compared to fixed-dosing, rather than comparing BMI-based dosing compared to fixed-dosing. Such trials need to ensure that those at both extremes of weight the underweight (BMI < 18 kg/m2) and severely obese (BMI > 40 kg/m2) are adequately represented.

These trials should also consider adequately reporting data on subgroups of obese and overweight patients. There may be sufficient numbers of subjects with renal impairment in completed trials whose analysis by subgroups may yield useful information. Future trials should seek to enroll a subpopulation of patients with renal insufficiency.

Conclusions

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high quality studies to inform these key questions for these special populations. Our systematic review identified important weaknesses in the literature. Future research using high quality observational studies that control for confounding by indication, such as provider and practice patterns, and confounding by disease severity may be needed as randomized controlled trials typically exclude or do not report on these special populations.

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Introduction

Background

Pulmonary embolism (PE) resulting from deep vein thrombosis (DVT), collectively known as venous thromboembolism (VTE), affects an estimated 900,000 Americans each year and results in significant morbidity and mortality.[1-2] The average annual incidence of DVT in the United States (U.S.) ranges from 48 to 122 per 100,000. [1 2] With the ageing U.S. population, the number of cases of VTE is likely to rise. There are significant adverse consequences of DVT and PE.[1] Two-thirds of all VTE cases are nonfatal and yet result in hundreds of thousands of hospitalizations, whereas approximately one-third of these cases are fatal causing an estimated 300,000 deaths each year.[1-2] A diagnosis of DVT or PE in the hospital increases the costs of the index hospitalization by approximately $10,000 and $20,000, respectively.[3] Thus VTE is an important patient safety issue with significant morbidity, mortality, and health care costs.[4] Accordingly, the comparative effectiveness and safety of interventions for the prevention and treatment of VTE are among the national priorities for comparative effectiveness research. [5]

In this review, we describe the evidence about prevention of DVT in "special populations", which we define below. For most of these populations, there are no guidelines that provide recommendations regarding their care. Additionally, for most, there is considerable decisional uncertainty about the best option for thromboprophylaxis for these patients. The results of this comparative effectiveness review will inform those developing guidelines for the care of these special patient populations. This report should also be useful to clinicians and patients who are making decisions about the best approach to prophylaxis.

Special populations are those patients in whom the benefit or risk of VTE prophylaxis is uncertain, or patients in whom there is decisional uncertainty about the optimal choice, timing, and dose of VTE prophylaxis or significant practice variation. The burden of VTE is higher among some patient populations including patients who have experienced recent trauma[6-11] or burns;[12-14] patients undergoing bariatric surgery;[15-21] and patients with acute renal failure, chronic renal failure, or end-stage renal disease. [22-25] 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. Therefore, the risk-benefit ratio of prophylactic medications in these populations is uncertain, and is similarly unclear in populations of patients with altered clearance of medications.[26-30]

Special Populations

General Traumatic Injury

Trauma is known to be a major risk factor for VTE. A prospective study reported rates of DVT as high as 58 percent among those who experience severe trauma (injury severity score >9) without thromboprophylaxis.[6] Among hospitalized trauma patients, PE occurs in one of every 25 patients and studies have linked PE with considerable mortality.[6] Some patients with special types of trauma, such as those with spinal trauma, are at the highest risk of DVT, with rates approximating 80 percent.[4] There appear to be significant practice variation and clinical uncertainty around the role of pharmacologic versus mechanical prophylaxis among patients

with trauma. Although clinicians commonly recommend pharmacologic prophylaxis, some may consider it to be contraindicated in certain trauma patients, such as those with: solid organ injury (i.e., liver, spleen, or kidney); pelvic or retroperitoneal hematoma; ocular injury with hemorrhage; or thrombocytopenia (platelet count <50,000). In these cases, there is debate about the placement of prophylactic inferior vena cava (IVC) filters to prevent PE. Some authors suggest that using this intervention among patients at very high risk may prevent the most dramatic and life-threatening cases of PE, although evidence for this is uncertain. Other studies associate IVC filters with significant complications,[45 46] such as the occurrence of DVT,[47] and recommend that clinicians not use them for this reason. Other studies show that placement of IVC filters does not lower the rate of PE and may not be of benefit in the trauma setting[48] or among other patient populations.[48] Ongoing uncertainty exists about whether clinicians should use prophylactic IVC filters in trauma patients for whom anticoagulation is relatively contraindicated. The concept of temporary (also known as "retrievable" or "optional") IVC filters is appealing, yet further complicates the picture. Current guidelines from the American College of Chest Physicians (ACCP) recommend against the use of IVC filters for primary prevention in patients without proven VTE.[4] The Eastern Association for the Surgery of Trauma guidelines suggest that clinicians can consider using prophylactic IVC filters in patients who have certain significant injury patterns, are at very high risk for VTE, and cannot receive pharmacologic prophylaxis.[35]

Patients with Traumatic Brain Injury

There is also considerable practice variation and clinical uncertainty about the choice of a prophylaxis modality (pharmacologic or mechanical) and about the optimal pharmacologic agent, dose, timing of initiation, and duration among patients with traumatic brain injury.[49] This population is at increased risk for VTE due to a combination of factors (i.e., the brain injury itself, other injuries, intensive care unit admission, immobilization, major surgery, etc.). This risk should prompt routine thromboprophylaxis; however, the associated elevated risk of bleeding in patients with traumatic brain injury often leads physicians to withhold anticoagulant thromboprophylaxis. The concern about anticoagulant thromboprophylaxis in this population is progression of intracranial bleeding that may result in clinical deterioration and possibly worse long-term outcomes. There is ongoing clinical uncertainty and wide variations in practice regarding the appropriate time to initiate pharmacologic prophylaxis. In this comparative effectiveness review (CER) we assess the role of pharmacologic versus mechanical prophylaxis, and the optimal time to initiate pharmacologic prophylaxis in hospitalized patients with traumatic brain injury.

Patients with Burns

Patients hospitalized with burns are at an increased risk for VTE, but there is no consensus about the most appropriate prophylactic strategy for treating bleeding in these patients.[50] DVT has a reported incidence of 1 to 23 percent in a series of burn patients.[14]The ACCP guidelines recommend thromboprophylaxis if possible for burn patients who have additional risk factors for VTE such as advanced age, morbid obesity, extensive burns, burns to the lower extremities, concomitant trauma to the lower extremities, use of a femoral venous catheter, and/or prolonged immobility (Grade 1C). [4] However, concerns about the potential risk of heparin-associated bleeding may have resulted in very low rates of heparin use and considerable uncertainty about the optimal choice of therapy among burn centers.[13] There is considerable uncertainty around

specific drugs, dosing regimens, and the risk-benefit trade-off for these particular subpopulations of patients.

Patient with Liver Disease

Patients with liver diseases such as cirrhosis may be simultaneously at increased risk for both bleeding and thrombosis, thus complicating the decisions related to VTE prevention.[51] Patients with thrombocytopenia, platelet dysfunction, and a prolonged international normalized ratio (INR), secondary to liver disease, are at increased risk for both minor and major bleeding secondary to altered hemostasis.[52] However, patients with these specific conditions often remain at risk for venous thromboembolism, particularly since many of the illnesses that lead to defects in hemostasis—such as cirrhosis—can directly precipitate thrombosis as a result of activated hemostasis and may also precipitate thrombosis indirectly through complications such as infection. There is clinical uncertainty about the optimal choice of VTE prophylaxis in this patient population and about the optimal threshold of thrombocytopenia and the prolonged INR value at which bleeding increases with anticoagulant thromboprophylaxis. There are no specific reviews or guidance documents that clarify the role of thromboprophylaxis in these patients.

Individuals Receiving Antiplatelet Therapy

Patients receiving antiplatelet therapy with acetylsalicylic acid or thienopyridines, such as clopidogrel, ticlopidine, and prasugrel, are at increased risk for bleeding. These patients constitute a large proportion of patients hospitalized for various medical conditions.[51] There is clinical uncertainty about the optimal choice of VTE prophylaxis in this patient population, as some physicians may consider antiplatelets to be sufficient for VTE prophylaxis. There are no specific guidance documents that clarify the role of thromboprophylaxis in this subgroup of patients.

Individuals Having Bariatric Surgery

Another population in which there is uncertainty about venous thromboprophylaxis is patients who undergo bariatric surgery. In an analysis of a large cohort in the Bariatric Outcomes Longitudinal Database,[20] the incidence of VTE after bariatric surgery was 0.42 percent within 90 days after surgery. Although these obese patients were at risk of VTE, their hospitalizations were short, and they were able to ambulate early. The risk of VTE was greater in the patients who underwent gastric bypass than in those who underwent adjustable gastric banding (0.55 vs. 0.16 percent). The risk of VTE was also greater in patients who had an IVC filter placed (hazard ratio 7.7; 95 percent confidence interval 4.5–13). The ACCP guidelines recommend low dose unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) or fondaparinux at higher than usual doses for patients undergoing bariatric surgery.[4] A recent survey of bariatric surgeons noted their overall preference for using prophylactic medications. Nearly 60 percent of bariatric surgeons preferred LMWH for prophylaxis, but many were uncertain about the best choice of therapy and about the timing and duration of VTE prophylaxis.[15] Therefore, there is much practice variation, ranging from no prophylaxis to multimodality thromboprophylaxis that might also include preoperative placement of an IVC filter.

Obese or Underweight Hospitalized Patients

Studies associate obesity, including severe obesity, with an increased risk of VTE.[53] It is uncertain if fixed doses of pharmacologic agents such as UFH, LMWH, and factor Xa inhibitors

provide optimal prophylaxis in this special population. The pharmacokinetics of several agents may be different among obese patients requiring dose adjustments.[54] Although LMWH and other pharmacologic agents that clinicians use to treat patients at the extremes of weight may require dosage adjustments, the optimal dosing strategy (including duration of therapy) for these patients is not clear. Similarly, the optimal choice and dosing regimens for patients who are underweight (body mass index <18.5 kg/m^2) is unclear. This CER evaluates the comparative effectiveness and safety of pharmacologic prophylaxis among patients at the extremes of weight and assesses the optimal drugs, dosages, dose frequency, and duration of pharmacologic prophylaxis during hospitalization of obese and underweight patients.

Patients with Acute or Chronic Renal Failure

In a prospective community-based cohort, patients with stage 3 or 4 chronic kidney disease (CKD) had a higher risk of VTE than those with normal kidney function.[22] The rates of VTE among patients with end-stage renal disease were also high. Generally, the burden of VTE among patients with CKD also falls disproportionately on Hispanics and African Americans.[55] Patients with advanced CKD also have a tendency to bleed because of platelet dysfunction.[56] Fondaparinux and LMWHs are primarily eliminated via the renal pathway and may accumulate in patients with renal failure. This accumulation is dependent in part on the chain lengths of the LMWHs and their subsequent renal clearance, thereby resulting in different pharmacokinetic and pharmacodynamic effects.[30] Consequently, patients with diminished renal function may be at an increased risk for adverse events, particularly bleeding. Although there appear to be differences between the LMWHs with regard to accumulation risk, the relationship between their use and the incidence of bleeding is not well established. ACCP guidelines recommend that clinicians should dose adjust, monitor, or simple avoid anticoagulant medications that bioaccumulate (Grade 1C). Cook et al.[25] argued that LMWHs may be the optimal choice, given the lower incidence of thrombocytopenia in patients with CKD. The optimal treatment choice and dosing strategy for thromboprophylaxis for patients with CKD remains uncertain. There are similar concerns about the optimal strategies for VTE prophylaxis among patients with acute kidney injury. Apart from evaluating the comparative effectiveness and safety of pharmacologic prophylaxis, in our CER we assess the optimal drugs, dosages, dose frequency, and duration of pharmacologic prophylaxis during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment without dialysis, and patients receiving dialysis.

Therapies of Interest

The U.S. Food and Drug Administration (FDA) has approved a number of antithrombotic drugs and antithrombotic mechanical devices. It approved some for primary prevention (or prophylaxis) of VTE, but clinicians use other devices without an indication ("off-label") for this purpose. (Table 2) In this review, we describe the evidence for drugs and devices that currently are available in the U.S. and that are either FDA approved for VTE prophylaxis or that clinicians use off-label for this indication. The pharmacologic agents of interest include UFH and LMWH delivered subcutaneously.[26-29] Fondaparinux, a synthetic pentasaccharide, is also available as an option for thromboprophylaxis, and thus we included it in this review. Similarly, we included antiplatelet agents, such as aspirin and clopidogrel, as well as the anticoagulant warfarin, which clinicians may use off-label for this indication.

We also included dabigatran, a recently approved oral anticoagulant that directly inhibits thrombin; the FDA approved it for the prevention of stroke in patients with atrial fibrillation, but

it has the potential for off-label use for prophylaxis of VTE. Rivaroxaban is an oral factor Xa inhibitor that the FDA approved in July 2011 for VTE prophylaxis for patients undergoing elective hip and knee arthroplasty; this drug also has the potential for off-label use in other patient populations.

We also included sequential compression devices, venous foot pumps, and various types of IVC filters, in this review.[4] They are all devices that clinicians use for VTE prophylaxis.

Key Questions

This report includes our review of the evidence about the efficacy, effectiveness, and safety of pharmacological and mechanical methods of prophylaxis in our defined special populations. The KQs we explore are as follows:

Key Question 1. What is the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?

Key Question 2. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with traumatic brain injury? What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent VTE in hospitalized patients with traumatic brain injury?

Key Question 3. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns?

Key Question 4. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

Key Question 5. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

Key Question 6. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in patients having bariatric surgery?

Key Question 7. What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?

Key Question 8. What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of

patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

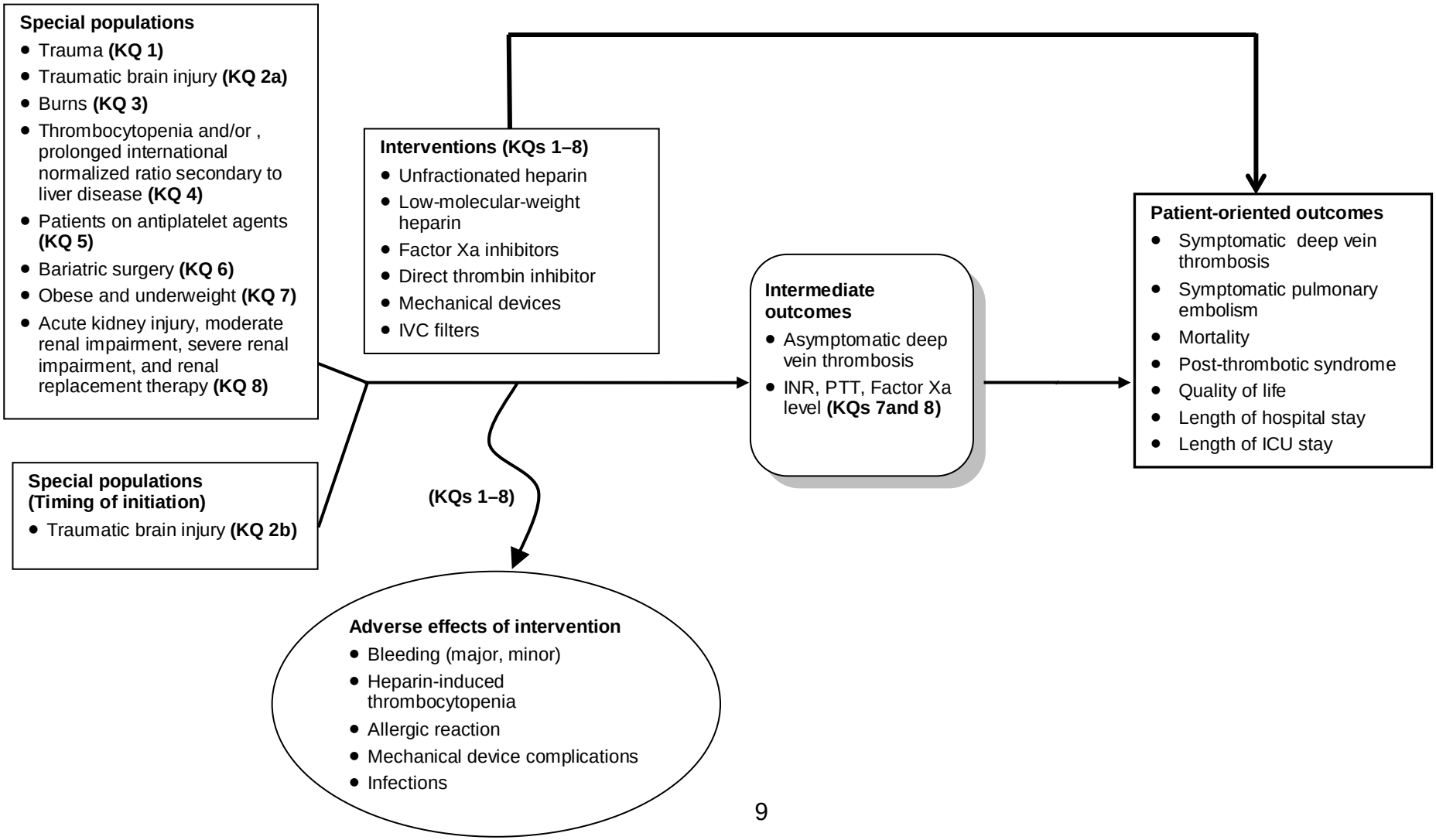
Table 1: Study Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Human subjects (only)	• Animal studies/models
• Adults in special patient populations, including: o Trauma o Traumatic brain injury o Burns o Liver disease o Antiplatelet therapy o Bariatric surgery o Obese and underweight o Acute kidney injury, moderate renal impairment, severe renal impairment, renal replacement therapy	• Children • Pediatric • Adolescent • Adults in the following patient populations: o Treatment of VTE o Secondary prophylaxis o Catheter thrombosis o Antiphospholipid antibodies/other autoimmune diseases o Cancer (malignancy, chemotherapy, radiotherapy) o Cardiovascular (coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty) patients on full-dose anticoagulation o Pregnancy o Disseminated intravascular coagulation o Heparin-induced thrombocytopenia o Congenital platelet disorders o VTE prophylaxis for long distance travel o Abdominal surgery o Vascular surgery o Urological surgery o Gynecological surgery
We included the following study designs* o Randomized controlled trials o Prospective cohort studies o Retrospective cohort studies o Case-control studies o Uncontrolled case-series for devices o Case reports of device complications in the relevant special populations o Case reports of pharmacologic therapies other than the known complications of bleeding and heparin-induced thrombocytopenia	• Case reports of efficacy • Case reports of bleeding or heparin-induced thrombocytopenia associated with pharmacologic strategies • In vitro studies • Animal studies • Cost-effectiveness studies • Modeling studies • Risk assessment studies • Registries without descriptions of interventions • Diagnostic studies • Ecologic study designs • Time-series designs • No original data, commentary, or editorial • Systematic reviews and meta-analysis
Studies that evaluate interventions or mechanical devices –Table 2	Studies of agents that have not been approved for thromboprophylaxis in the United States or interventions not available in the United States will not be evaluated
• Symptomatic deep vein thrombosis • Symptomatic pulmonary embolism • Mortality • Post-thrombotic syndrome • Quality of life • Length of hospital stay • Length of ICU stay • Bleeding (major, minor) • Heparin-induced thrombocytopenia • Allergic reaction • Mechanical device complications • Infections • Asymptomatic deep vein thrombosis • INR, PTT, factor Xa level **(KQs 7 and 8)**	• No data on relevant outcomes of interest

Framework

Our conceptual model for the systematic review is presented in Figure 1. This figure depicts the KQs we address. The figure illustrates the special populations of interest, the therapies, and the intermediate and clinical outcomes that we sought to review, as well as the adverse consequences associated with these prophylactic regimens.

Figure 1. Analytic Framework: Comparative Effectiveness of Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations



Abbreviations: IVC = inferior vena cava; KQ = key question

Table 2: Pharmacologic agents and medical devices approved in the United States for some indication and that may be considered for VTE prophylaxis

Pharmacologic Agents					
Intervention	Route	Dose	Manufacturer	U.S. Availability	Comments
Antiplatelets					
Aspirin	Oral	Various	Various	Yes	NA
Clopidogrel (Plavix®)	Oral	75 or 300 mg base	Sanofi Aventis/ Bristol-Myers Squibb	Yes	NA
Ticlopidine (Ticlid®)	Oral	125 or 250 mg	Hoffman-La Roche Inc.		NA
Prasugrel (Effient®)	Oral	EQ 5 or 10 mg base	Roche Palo	Yes	NA
Ticagrelor (Brilinta®)	Oral	90 mg	AstraZeneca LP	Yes	NA
Dipyridamole (Persantine®)	Oral	25, 50, or 75 mg	Boehringer Ingelheim	Yes	NA
Cilostazol (Pletal®)	Oral	50 or 100 mg	Otsuka	Yes	NA
Dextran sulphate				Yes	NA
Vitamin K Antagonists					
Warfarin (Coumadin®)	Oral	1–10 mg	Various generics; Bristol-Myers Squibb	Yes	NA
Dicumarol	Oral	Various			
Low-Dose Unfractionated Heparins					
Heparin	Subcutaneous	5,000 Units BID or TID	Several	Yes	NA
Low-Molecular-Weight Heparins					
Enoxaparin sodium (Lovenox®)	Subcutaneous	40 mg QD or 30 mg BID (30 mg for renal impairment)	Sanofi-Aventis; generic from Sandoz (2010)	1993	Dosing indication for abdominal surgery and acutely ill medical patients
Dalteparin sodium (Fragmin®)	Subcutaneous	5,000 IU QD	Eisai/Pfizer	1994	Indicated for surgery prophylaxis
Tinzaparin sodium (Innohep®)	Subcutaneous	3,500 IU QD to 4500 IU SC daily	LEO Pharma/Celgene	2000	Indicated for surgery prophylaxis
Factor Xa Inhibitors					
Fondaparinux (Arixtra®)	Subcutaneous	2.5 mg QD	GSK	2001	Indicated for abdominal surgery prophylaxis
Rivaroxaban (Xarelto®)	Oral	10 mg QD	Johnson and Johnson	2011	Indicated for elective hip/knee arthroplasty
Direct Thrombin Inhibitors					
Argatroban (Argatroban®)	Intravenous Infusion	100 mg/mL	Pfizer	2000	Prophylaxis with active HIT
Dabigatran (Pradaxa®)	Oral	75 and 150 mg	Boehringer Ingelheim	2010	Prevent stroke and systemic embolism in AF
Bivalirudin (Angiomax®)	Intravenous	250 mg/Vial	The Medicines Company	2000	
Lepirudin (Refludin®)	Intravenous Infusion	50 mg/Vial	Bayer	1998	Anticoagulation with HIT to prevent further thromboembolic complications

Table 2: Pharmacologic agents and medical devices approved in the United States for some indication and that may be considered for VTE prophylaxis continued

Mechanical Devices			
Intervention	**Name**	**Manufacturer**	**Comments**
Intermittent Pneumatic compression	Aircast VenaFlow	DJO	Apply intermittent application of pressure to a patient's calf, thigh or foot for the purpose of assisting blood flow in the veins.
	SCD Express	Tyco/Kendall	DVT prophylaxis
Graduated compression stockings	Jobst T.E.D.® Others	Jobst	To prevent pooling of blood in legs
Venous Foot Pumps	A-V Impulse System Venodyne	Novamedix	DVT prophylaxis
Inferior Vena Caval Filters			
Name	**Type**	**Manufacturer**	**Comments**
Greenfield Stainless Steel®	Permanent	Boston Scientific	Prevention of PE with venous thrombosis or pulmonary thromboembolism when anticoagulants are contraindicated
Simon Nitinol®	Permanent	Bard Peripheral Vascular	Preventing PE from migrating to the pulmonary arteries
TRAPEASE®	Permanent	Cordis	Prevention of recurrent PE when anticoagulants are contraindicated
Greenfield Titanium®	Permanent	Boston Scientific	No information available
Vena Tech LP®	Permanent	B. Braun	Partial interruption of IVC to prevent PE when anticoagulants are contraindicated
Gianturco-Roehm Bird's Nest®	Permanent	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
Celect®	Retrievable	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
Gunther Tulip®	Retrievable	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
G2®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE
G2x®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE when anticoagulants are contraindicated
Eclipse®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE when anticoagulants are contraindicated
VenaTech LGM®	No longer sold	B. Braun	Partial interruption of IVC to prevent PE when anticoagulants are contraindicated
Tempofilter®	Retrievable	B. Braun	NA
ALN IVC®	Retrievable	ALN Implants	Prevention of recurrent PE when anticoagulants are contraindicated
Option IVC®	Retrievable	Rex/Angio Tech	Prevention of recurrent PE when anticoagulants are contraindicated
Safeflo®	Permanent	Rafael Medical	Prevention of recurrent PE when anticoagulants are contraindicated
OPTEASE®	Retrievable	Cordis Corp	Prevention of recurrent PE when anticoagulants are contraindicated

AF= atrial fibrillation; BID = twice a day; DVT = deep vein thrombosis; EQ = equivalent; HIT = heparin-induced thrombocytopenia; IU = international unit; IVC = inferior vena cava; PE = pulmonary embolism; QD = once a day; SC = subcutaneous; TID = three times a day

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative effectiveness Reviews (available at: http://www.effectivehealthcare.ahrq.gov/methods guide.cfm) The main sections of this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA checklist. This systematic review was carried out according to a prespecified protocol registered at the AHRQ website.[57]

Our Evidence-based Practice Center (EPC) established a team and a work plan to develop this evidence report. The project involved recruiting key informants and technical experts, formulating and refining the questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review and public comment.

Topic Refinement

We chose the topic for this report using a public process. At the beginning of the project, we recruited a panel of key informants to give input on key steps including the selection and refinement of the questions to be examined. The panel included local experts with expertise in bariatric and external informants including expertise in burns, hematology, trauma, payer, and patient representatives.

With the input of a key informant panel, and staff of AHRQ and the Scientific Resources Center, we developed the Key Questions (KQs). Our draft key questions were posted on Effective Health Care Program Web site for public comment on August 16th, 2011. We then refined the KQs based on the feedback received.

The final KQs focus on the comparisons of the methods for prevention of venous thromboembolism in special population. We recruited a panel of technical experts, which included experts in the prevention of venous thrombosis, on burn care, on trauma management, on bariatric surgery perioperative care, and hematologists. The TEP provide input to the EPCs throughout the evidence review process, particularly relevant to the protocol for conducting the review. With input from the technical expert panel and representatives from AHRQ, we finalized the protocol. The protocol was posted on the Effective Health Care Program Web site on January 12th, 2012

Search Strategy

We searched the following databases for primary studies: MEDLINE® through August 2011, EMBASE® through August 2011, SCOPUS through Augutst 2011, CINAHL® through August 2011,www.clinicaltrials.gov through August 2011 International Pharmaceutical Abstracts through August 2011, and the Cochrane Library through August 2011. We did not have any restrictions on the start dates which were analogous to the inception of the databases. We developed a search strategy for MEDLINE®, accessed via PubMed®, based on medical subject headings (MeSH®) terms and text words of key articles that we identified a priori. (Appendix B) We reviewed the reference lists of all included articles, relevant review articles, and related systematic reviews to identify articles that the database searches might have missed. In addition, we requested and reviewed Scientific Information Packets provided by the pharmaceutical

manufacturers. Our search did not have any language restrictions. We included non-English articles for in our review but did not find any non-English article applicable to our project.

Study Selection

We reviewed titles followed by abstracts to identify randomized controlled trials (RCTs) or observational studies and case reports reporting on the effectiveness or safety of venous thromboembolism prevention in our selected populations.

Two investigators independently reviewed abstracts and we excluded the abstracts if both investigators agreed that the article met one or more of the exclusion criteria. We resolved disagreements by consensus. We recognized that much of the evidence about use of IVC filters would be from observational studies without comparison groups; therefore in our review of titles and abstracts we were inclusive of any design, including uncontrolled observational studies, case series and case reports, which described unanticipated harms from use of these devices.

For inclusion in this review, we required that studies enrolled or reported on patients who were members of our special populations. This included patients with traumatic brain injury, with burns requiring burn unit care, individuals with liver disease, patients receiving antiplatelet therapy, patients undergoing bariatric surgery, obese and underweight hospitalized medical patients, and patients with any degree of renal impairment. If the studies included a mixed population that included one of our special populations, the study either needed to report results separately for our population, or our population needed to comprise 80 percent or more of the total population. We excluded studies that were predominantly describing outcomes for children, adolescents, or pregnant women. We also excluded studies specifically evaluating any of our excluded patient populations: patients with antiphospholipid antibodies, cancer, disseminated intravascular coagulation, treatment of heparin-induced thrombocytopenia, or congenital platelet disorders. We excluded studies that used pharmacotherapy for treatment of venous thrombosis or that were evaluating secondary prevention of venous thrombosis outside of our stated patient populations.

We included trials if the comparators were pharmacotherapies for prevention of venous thrombosis available in the United States (U.S.), vena cava filters available in the U.S., or mechanical devices or usual care practices. We did not require that observational studies about vena cava filters have comparison groups. We resolved differences regarding article inclusion through consensus adjudication, and a third reviewer audited a random sample to ensure consistency in the reviewing process.

At the point of full article review, we excluded studies that did not report on at least one of our outcomes of interest. These were: symptomatic or asymptomatic deep vein thrombosis or pulmonary embolism, fatal pulmonary embolism, mortality, post-thrombotic syndrome, quality of life, length of hospital stay or intensive care unit stay, bleeding, heparin-induced thrombocytopenia, allergic reactions, mechanical device complications, infections, international normalized ratio, prothromin time, or factor Xa levels (for KQ 7 or 8, only).

Data Abstraction and Data Management

We used DistillerSR (Evidence Partners, 2010) to manage the screening and review process. DistillerSR is a Web-based database management program that manages all levels of the review process. We uploaded to the system all applicable citations identified by the search strategies.

Two independent reviewers conducted title scans. For a title to be eliminated at this level, both reviewers had to indicate that the study was ineligible. If the reviewers disagreed, we

advanced the article to the next level, abstract review. Two investigators reviewed abstracts and we excluded the abstracts if both investigators agreed that the article meets one or more of the exclusion criteria. We tracked and resolved differences between investigators regarding abstract inclusion or exclusion through consensus adjudication. Articles promoted on the basis of abstract review had an independent parallel review to determine if they should be included in review. We resolved the differences by consensus adjudication.

We created standardized forms for data extraction. (Appendix C) We pilot tested the forms prior to the beginning the process of data extraction. Each article had double review by study investigators for data abstraction. The second reviewer confirmed the first reviewer's data abstraction for completeness and accuracy. Reviewer pairs included personnel with both clinical and methodological expertise. We tracked and resolved differences between investigators regarding data through consensus adjudication. A third reviewer audited a random sample of articles selected by the first two reviewers to ensure consistency in the abstraction of data from the articles. We did not mask reviewers from the authors, institution, or journal for each article.

Reviewers extracted information on general study characteristics, study participants, eligibility criteria, interventions, outcome measures, the method of ascertainment, and the outcomes, including measures of variability where available. We entered all information from the article review process into the DistillerSR database. We used the DistillerSR database maintain the data, which we then exported into Excel for the preparation of evidence tables.

Assessment of Methodological Quality of Individual Studies

We conducted the risk of bias independently and in duplicate. Although the original protocol planned to use different tools for trials and observational studies in the protocol, we chose a single instrument the Downs and Black instrument (Appendix E).[31] The need to standardize the rating of risk of bias across heterogenous study designs including case reports, case-series, uncontrolled cohort studies, case-control studies, prospective and retrospective cohort studies and randomized trials prompted this change. We categorized the trials as having low risk of bias, moderate risk of bias, or high risk of bias and observational studies as having moderate risk of bias and high risk of bias.

We found that 10 items were most relevant to this review and we prioritized them in our assessment of risk of bias. We considered studies to have a low risk of bias if all of the following were true: the article completely described the hypothesis, the outcomes (in the introduction or methods section), the characteristics of the included subjects, the distribution of the potential confounders in each group, the interventions and comparisons (if relevant), the main findings, adverse events, and characteristics of the subjects lost to followup. Additionally, we judged studies to be at low risk of bias if they randomized subjects to the intervention and concealed the assignment until requirement was complete, and if they attempted to blind the study participants and to blind those who measured the main outcomes. By this system, we could not consider any study without randomization to have a low risk of bias. Such non-randomized studies could only be at moderate or high risk of bias. We rated studies as having a moderate risk of bias if one of those items was not true, even if all of the others were true, or if the reporting on the distribution of potential confounders in each group was at least partially done. If we found two of the elements were not true, we considered the study to have a high risk of bias

Low risk of bias studies had the least bias and the results were considered valid. Moderate risk of bias studies was susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some

deficiencies. High risk of bias studies had significant flaws that might have invalidated the results.

Data Synthesis and Analysis

For each KQ, we created a detailed set of evidence tables containing all information abstracted from eligible studies. We grouped the information for each KQ by comparison interventions. We conducted narrative synthesis of the evidence since the population, intervention and outcome characteristics across studies were heterogenous. For studies amenable to pooling with meta-analysis we conducted meta-analysis using relative risks by using a DerSimonian and Laird Random effects model. We identified substantial statistical heterogeneity in the trials as an I-squared statistic with a value greater than 50 %. Since most of the outcomes were rare and several studies had zero events, with an imbalance in treatment arms we used the treatment arm continuity correction approach to estimate the relative risk.[57] We conducted sensitivity analysis to examine the influence of outliers that could explain the underlying statistical heterogeneity by excluding one study at a time. All analyses were conducted using Stats Direct.

Grading the Evidence for Each Key Question

After synthesizing the evidence, two reviewers graded the quantity, quality, and consistency of the best available evidence addressing KQs 1 to 8 by adapting an evidence grading scheme recommended in the Methods Guide for Conducting Comparative Effectiveness Reviews.[32] In assigning evidence grades, we considered the four recommended domains, including risk of bias in the included studies, directness of the evidence, consistency across studies, and precision of the pooled estimate or the individual study estimates. We were unable to assess for publication bias or selective outcomes reporting because the tests for publication bias were underpowered when the number of studies is low (<10).

The risk of bias for an individual study was derived from the algorithm described above. We assessed the aggregate risk of bias of studies and integrated these assessments into a qualitative assessment of the summary risk of bias score. Since the majority of studies in our evidence based were at high risk of bias, most aggregate scores resulted in a high risk of bias rating.

Precision of individual studies was assessed by evaluating the statistical significance of a comparison. We found that few of the studies reported effect sizes and 95% confidence intervals. We estimated the confidence intervals for some of the outcomes, and also visually examined the Forest plots to assess precision for certain outcomes. We also examined the summary estimates to assess precision for certain outcomes when meta-analysis was possible. If all studies in an evidence base were precise then the evidence base was rated to be precise. Studies whose effect size overlapped with the line of no difference were designated as imprecise. When studies did not report measures of dispersion or variability we rated the precision as unknown.

We rated the evidence as being direct if the intervention was directly linked to the patient oriented outcomes of interest in our analytic framework. We rated the evidence as indirect for intermediate outcomes (anti-Xa) when direct evidence linking the intervention to the ultimate health outcome of bleeding was lacking.

We used an algorithm for assigning consistency based on the number of studies with similar directions of effect. If all the studies in an evidence base showed a similar direction of effect, we rated the evidence base as consistent. Single studies were rated as consistency unknown.

To incorporate multiple domains into an overall grade to the strength of the body of evidence we used the estimate of the summary risk of bias score, directness, and consistency along with precision to provide support for an intervention. We used a qualitative approach to incorporating these multiple domains into an overall grade. Since the majority of studies were at high risk of bias, we initially assigned a low strength of evidence for all outcomes. Consistent, precise and direct evidence from such high risk of bias studies was rated as low strength of evidence. The strength of evidence was downgraded to insufficent when consistency was unknown (i.e. single study) or inconsistent. The strength of evidence was downgraded to insufficent when evidence was indirect. Imprecision or unknown precision also led to a downgrade in the strength of evidence from low to insufficient.

We classified evidence pertaining to KQs 1 to 8 into four categories: 1) "high" grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient" grade (evidence is unavailable).

Assessing Applicability

Two reviewers assessed applicability separately for the outcomes of benefit (reduction in VTE) and harm (increased risk of bleeding) for the entire body of evidence guided by the PICOTS framework as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions.[32] We evaluated whether the include populations in thes studies were representative of participants in the real world. We assessed whether the concomitant interventions administered in these studies were also representative of real world management strategies for these special populations. We assessed whether there were features of the individuals studies which limited the applicability of the study's findings including whether studies excluded patients with comorbidities, whether studies allowed or disallowed the concomitant use of nonmedical cointerventions (early ambulation), and the choice and dosing of comparators. We assessed whether findings were applicable to various ethnic groups.

Table 3. PICOTS for each Key Question

	KQ 1	KQ 2	KQ 3–KQ 5	KQ 6	KQ 7–KQ 8
Population(s)	• Trauma	• Traumatic brain injury	• Burns (KQ 3) • Liver disease (KQ 4) • Antiplatelet therapy (KQ 5)	• Bariatric surgery	• Obese and underweight patients (KQ 7) • Patients with acute kidney injury or moderate or severe renal impairment (KQ 8) • Patients receiving dialysis (KQ 8)
Interventions	• IVC filters	• Mechanical devices • Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • IVC filters	• Mechanical devices • Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)	• Pharmacologic (UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • Mechanical devices • IVC filters	• Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • Mechanical devices
Comparators	• No IVC filters (Could include active controls including mechanical prophylaxis (e.g., SCDs, compression stockings), placebo-controlled studies or pharmacologic controls) • Uncontrolled studies.	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, studies that used active controls, and uncontrolled studies.	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, studies that used active controls, and uncontrolled studies.	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, or studies that used active controls, and uncontrolled studies.	• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • Placebo- controlled studies, studies that used active controls, and uncontrolled studies.
Outcomes measures	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality
Adverse effects of intervention(s) and treatment burden	• Major bleeding defined as including: fatal bleeding; clinically overt bleeding causing a fall in hemoglobin of ≥2 g/dL or leading to transfusion of two or more units of packed cells or whole blood; or bleeding into critical organs (retroperitoneal or intracranial) • In surgical patients: an assessment of the amount of blood loss, minor bleeding, surgical site bleeding, and complications from mechanical IVC filters (e.g., device migration, perforation, fractures, filter thrombosis, infections, prolonged hospitalization, mortality)				
Timings	• Studies with all durations of followup				
Settings	• Hospital setting	• Hospital Setting	• Hospital setting	• Hospital setting	• Hospital setting

DVT = deep vein thrombosis; IVC = inferior vena cava; KQ = key question; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SCD = sequential circumferential compression device; UFH = unfractionated heparin

Results

Results of the Search

Figure 2 summarizes the search results. The literature search identified 28,526 unique citations. During the title screening, we excluded 19,429 citations. During the abstract screening, we excluded 7,008 citations that met at least one of the exclusion criteria. During article screening, we excluded an additional 1,994 articles that did not meet one or more of the inclusion criteria. (Appendix D) Ninety-five articles were included in the review.

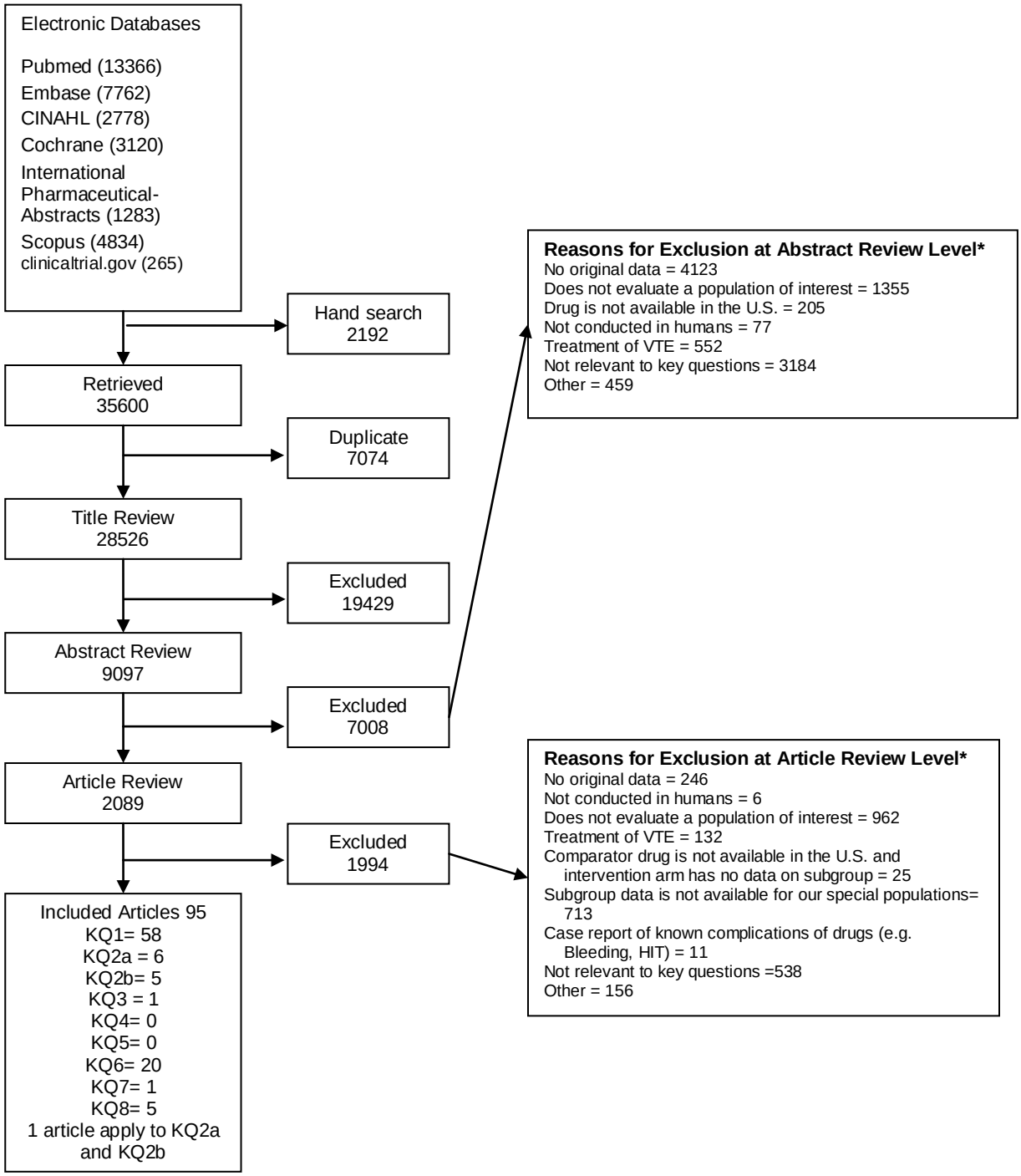
Description of Types of Studies Retrieved

Of the included studies, 58 studies addressed Key Question 1(Patients with trauma), 6 studies addresses Key Question 2a (Patients with traumatic brain injury), 5 studies addressed Key Question 2a (Patients with traumatic brain injury–timing of initiation and duration of pharmacological prophylaxis), 1 study address Key Question 3 (Patients with burns), 20 studies address Key Question 6 (Patients having bariatric surgery), 1 study address Key Question 7 (Obese and underweight patients), and 5 studies addressed Key Question 8 (Patients with acute kidney injury and renal impairment). There were no studies identified that addressed Key Questions 4(Patients with liver failure) and 5(Patients receiving antiplatelet therapy).

Scientific information packets (SIP)

As part of the gray literature search, pharmaceutical companies with drugs or devices included in this review were asked to provide information about pertinent studies conducted with their products (published, unpublished, and clinical trials). Three companies responded with letters indicating that no relevant studies had been conducted. Four companies provided comprehensive scientific information packets (SIP), which identified potentially relevant studies; these citations were carefully crosschecked against our existing reference database (to avoid redundancy), yielding six new references, none of which were applicable to this review. One additional SIP was submitted by the American Association of Neurological Surgeons, however, this was a chemoprophylaxis protocol and therefore did not meet the eligibility criteria for this review.(Appendix F)

Figure 2. Summary of the Literature Search



* Total exceeds the # in the exclusion box because reviewers were allowed to mark more than 1 reason for exclusion, KQ=Key Question, HIT=heparin induced thrombocytopenia, VTE=venous thromboembolism

Key Question 1. What is the comparative effectiveness and safety of inferior vena cava filters to prevent pulmonary embolisms in hospitalized patients with trauma?

Key Points and Evidence Grades

In hospitalized patients with trauma:

- The strength of evidence is low to support that IVC filter placement is associated with filter related thrombosis in hospitalized patients with trauma compared to no IVC filter placement.
- The strength of evidence is insufficient to support that IVC filter placement is associated with a lower incidence of PE compared to no IVC filter placement.
- The strength of evidence is insufficient to support that IVC filter placement is associated with a lower incidence of fatal PE in hospitalized patients with trauma compared to no IVC filter placement.
- The strength of evidence is insufficient to support that IVC filter placement is associated with a higher incidence of DVT compared to no IVC filter placement.
- The strength of evidence is insufficient to support that IVC filter placement is associated with a higher mortality in hospitalized patients with trauma compared to no IVC filter placement.
- The strength of evidence is insufficient to support that IVC filter placement is associated with filter tilt/migration in hospitalized patients with trauma compared to no IVC filter placement.

Study Characteristics

Randomized Controlled Trials and Controlled Observational Studies

Eight controlled studies evaluated the effect of IVC filters versus no filters on VTE events in adult trauma patients. [58-65] (Table 3) Two controlled studies also compared IVC filters to IVC filters.[66, 67] (Table 4)

All studies were within single institutions in North America. Only one study reported the funding source, which was industry. One was an RCT,[58] three were prospective cohort studies with concurrent comparison groups,[59- 61 62] four were retrospective cohort studies, [63 65-67]and two were prospective cohort studies with historical controls.[60- 64] The duration of followup was 6 months in the RCT.

Uncontrolled Studies

Forty-eight uncontrolled studies evaluated the use of IVC filters in hospitalized patients with trauma.[48 68-114] They were conducted in North America,[48 68-70 72 73 76-78 81-86 88-114] Europe[79 80 87], Asia[75], and Australia[71 74]. Of these 48 studies, there were 34 cohort studies, ,[48 68 70 71 73 75-78 80-90 93 97 100-103 105-109 112-114]. There were 12 prospective cohort studies, and the remaining were retrospective cohorts. There was one combined retrospective review and prospective study.[110] There were six case series,[72 74 79 96 98 104] six case reports,[69 91 92 94 99 111] These studies enrolled a median of 99 patients (range, 3 to 310) in the cohort studies, 30 patients (range, 8 to 249) in the case series, and one patient (range, 1 to 2) in the case reports. Four studies enrolled men only,[91 92]

[99 109] and two studies enrolled women only.[111 115] The majority followed participants during the period of hospitalization until discharge, with only a few cohorts following patients beyond discharge. (Table 5)

Participant Characteristics

Randomized Controlled Trials and Controlled Observational Studies

The mean age of participants in the RCT was 53.7 years and 41.2 years in the control and IVC filter groups, respectively.[58] Of the enrolled patients, 62.5 and 72.2 percent were men, respectively. The patients in the controlled observational studies were largely aged 35 to 50 years old, with men comprising roughly 60 to 75 percent of the studied population.

Only two studies reported exclusion criteria. The trial excluded pregnant patients, patients with previously placed IVC filters, those with a contraindication to filter placement, and patients that were terminally ill or not expected to survive for more than 24 hours.[58] A second study excluded elderly patients with isolated rib fractures.[60] The remaining studies did not report exclusion criteria. Most studies did not describe the race of the patients.

Uncontrolled Studies

The mean age of patients in the uncontrolled studies was roughly 40 years. The majority of studies enrolled both men and women with a preponderance of men in each study population. The mean injury severity scores were variable and ranged from 23.1[101] to 38[80] across studies, reflecting varying degrees of trauma severity. The inclusion and exclusion criteria varied widely. (Table 5)

Intervention Characteristics

Randomized Controlled Trials and Controlled Observational Studies

Eight studies evaluated the comparative effectiveness of IVC filters versus no IVC filters in trauma patients.[58-65] All studies analyzed patients in two groups. One group of patients received "standard" therapy alone, and the other group received IVC filters in addition to "standard" therapy. The definitions of standard therapy varied. The most common standard therapy was a combination of venous compression devices with subcutaneous LMWH.[58 61-64] Two studies defined standard therapy as venous compression devices alone.[59 60] One study provided various VTE prophylaxis regimens (some venous compression devices and others LMWH).[65]

Two retrospective cohort studies compared the effectiveness of different kinds of IVC filters on the prevention of VTE in hospitalized patients with trauma.[66 67] One study compared the Gunther Tulip filter versus the Celect filter. [66] Both of these filters are temporary and clinicians placed them bedside in the ICU. The second study compared the Gunther Tulip filter versus the Optease filter.[67] Both of these filters are temporary and interventional radiologists placed them in angiography suites.

Uncontrolled Studies

The uncontrolled IVC filter studies varied in the protocol used for VTE prophylaxis. Thirty-three studies used IVC filters only[48 68 71-73 75-79 82-85 89-92 94-97 99 102-104 107-109 111-114] and 15 studies involved the use of concurrent therapy with a pharmacological agent, ,[69 70 87 105] a mechanical

agent,[110] or a combination of a pharmacological agent and a mechanical agent.[74 80 81 86 88 93 98 100 101 106] The brand of filters varied and included Bard Recovery, Celect®, Cook Bird's nest, G2®, Gianturco-Roehm Bird's Nest®, Greenfield Stainless Steel®, Greenfield Titanium®, Gunther Tulip®, OPTEASE®, Poliser, Recovery, Simon Nitinol®, TRAPEASE®, VenaTech LGM®, and Vena Tech LP® types. One retrospective, single-center, uncontrolled study compared outcomes by the specific filter type, which included both permanent (Greenfield, VenaTech, TrapEase) and retrievable (Gunther Tulip, and Recovery IVC) filters.[114] The multi-center study compared three retrievable IVC filters (Gunter-Tulip, Recovery, and Optease).[113] The type of filter was retrievable in 16 studies, [70 71 73-77 79 81-83 85 88 94 109 113] permanent in three studies,[72 101 111], and both permanent and retrievable in five studies.[48 80 87 112 114]Twenty-four studies did not specify the type of filters used.[68 69 78 84 86 89-93 95-100 102-108 110] Two uncontrolled studies also reported data on outcomes by different types of IVC devices.[113 114]

Ascertainment

Randomized Controlled Trials and Controlled Observational Studies

Most studies relied on duplex ultrasonography for diagnosis of DVT, although some older studies used outdated modalities such as impedance plethysmography (IPG).[59 61] For the diagnosis of PE, most studies used computed tomography angiography. Some studies used angiography for the diagnosis of PE. Infrequently, studies used ventilation/perfusion scans for PE diagnosis.

Uncontrolled Studies

Most of the uncontrolled studies used objective measures typically applied in clinical practice to document the occurrence of these events (duplex ultrasonography of DVT, computed tomography angiography, ventilation-perfusion for PE), while only few reports used other measures, such as plethysomography, venography, and autopsy, when possible.

Outcomes

Our results for the relative risk meta-analysis on the outcome of PE, fatal PE, mortality, DVT and filter related thrombosis among filters vs no filters in patients with trauma in controlled studies are shown in **Figure 3- 7.** Our results for the propoation and 95% Confidence intervals on the outcome of PE, mortality and DVT and filter related thrombosis among filters vs no filters in patients with trauma are shown in **Figure 8-10.**

Pulmonary Embolism

Inferior Vena Cava Filter versus No Inferior Vena Cava Filter

Eight controlled studies reported on PE outcomes.[58-65] Figure 3 shows the relative risk meta-analysis on the outcome of PE (RR, 0.55,95% CI = 0.10 to 2.96;p=0.48). This demonstrate the substantial statistical heterogeneity and imprecision among the included studies with an I^2=61. 6%.

The results of sensitivity analysis to examine the statistical heterogeneity are shown in **Apppendix G**. Rogers et al 1997 contributed substantially to the statistical heterogeneity for the outcome of PE, with statistical heterogeneity droping to 30% after removing the Rogers study.[59]

This study may have contained overlapping participants with another study by the same authors.[60] Although most of our studies in our evidence base were at high risk of bias, these two studies had severe methodologic deficiencies such as the poor choice of controls (historical controls) and severe imbalance in injury severity scores results.[59 60] Sensitivity analysis after exclusion of both the studies showed a precise and consistent evidence of reduction in PE with IVC filters compared to no IVC filters without any evidence of statistical heterogeneity (RR, 0.20, 95% CI , 0.06-0.70; I^2=0%.)

In the RCT, there was no statistical difference in the incidence of PE between the two groups.[58] There were no PEs in the IVC filter group and one PE among patients without filters. Five of the seven observational studies reported lower PE rates with IVC filter placement;[60-62 64 65] four of these were statistically significant findings. Two studies reported higher PE rates with IVC filter use.[59 63] However, one had a non-significant finding with a single PE in each group (but many more patients in its control arm).[59] One study of spinal cord injury patients found a single patient who had a PE diagnosed after a clinician placed an IVC filter.[63](Table 6)

Inferior Vena Cava Filter versus Inferior Vena Cava Filter

Two studies reported on the outcome of PE between Gunther Tulip vs Celect filters[66] and Gunther Tulip vs Optease filters.[67] There were no statistically significant differences in the incidence of PE in the studies although the incidence of PE was higher in the Gunther Tulip arm compared to the Optease arm.[67] Another uncontrolled study which also reported on differences between filter types found no difference in "breakthrough" PE rates between filters.[113](Table 7)

Uncontrolled Studies of Inferior Vena Cava Filters

Thirty-five studies reported the occurrence of PE, with percentages ranging from 0 to 5.8 percent, with the vast majority reporting PE proportions of 2 percent or less.[48 69 71-74 79-90 93 95-103 105-110 114] Figure 9 describes the proportion and 95 % CI of patients with PE in uncontrolled studies of of IVC filters among patients with trauma.

Most of these studies had limited followup. The longest study reported followup of 7 years for 97 patients, with a PE proportion of 2.1 percent.[72] One study reported only the total PE as the primary outcomes, with a prevalence of 3.5 percent among 226 patients.[114](Table 8)

Fatal Pulmonary Embolism

Randomized Controlled Trials and Controlled Observational Studies

Five studies reported on this outcome. Figure 5 shows the relative risk meta-analysis on the outcome of fatal PE(RR 0.36,95% CI = 0.015 to 8.16; p=0.54). This also demonstrate the substantial statistical heterogeneity among the included studies with an I^2=70.4 %.

The results of sensitivity analysis to examine the statistical heterogeneity are shown in **Apppendix G**. Rogers et al 1995 contributed to substantial statistical heterogeneity. Sensitivity analysis after exclusion of this study showed a precise and consistent evidence of reduction in fatal PE with IVC filters compared to no IVC filters, without any evidence of statistical heterogeneity (RR, 0.09,95% CI 0.01 to 0.81; I^2=0%)

There was no VTE related deaths in the trial.[58 60 61 64 65] A prospective cohort study with historical controls identified a statistically significant increase in the incidence of fatal PE in patients that did not receive IVC filters (4 percent versus zero percent. p-value < 0.0.3).[64] There

were no differences in fatal PE in two prospective cohort studies that compared IVC filters to compression devices.[59 60]

Uncontrolled Studies

Among the uncontrolled studies that reported on prophylactic IVC filters in hospitalized patients with trauma, five studies reported on the outcome of fatal PE. [80 86 98 101 103] Four studies reported no deaths due to PE.

Mortality

Randomized Controlled Trials and Controlled Observational Studies

Inferior Vena Cava Filters versus No Inferior Vena Cava Filters

Five studies reported on mortality.[58-60 64 65] Figure 6 shows the relative risk meta-analysis on the outcome of fatal PE (RR1.33, 95% CI = 0.53 to 3.32;p=0.54). This figure demonstrate the substantial statistical heterogeneity among the included studies with an I^2=69.8 %. The results of sensitivity analysis to examine the statistical heterogeneity are shown in **Apppendix G**. We were unable to explain the statistical heterogeneity as there was no appreciable change in the estimates after removing each study.

There were no differences observed in the trial with regards to VTE and non-VTE mortality between groups.[58] In another prospective cohort study, all-cause mortality was higher in the IVC filters group as compared to the compression device only group (11.4 percent versus 5.1 percent).[59] Similarly, in another study, total mortality was higher in the IVC filter group than the compression device only group,[60] while higher mortality was reported in the control group compared to IVC filter in another study.[64]

Inferior Vena Cava Filters versus Inferior Vena Cava Filters

The study by Rosenthal et al. defined a secondary outcome as total mortality unrelated to VTE. In this study, the mortality was higher in the Gunther tulip group than in the Celect group (29 percent versus 11 percent).[66]

Uncontrolled Studies

Thirty studies reported on mortality in hospitalized patients with trauma. Figure 10 describes the proportion and 95 % CI of patients with mortality in uncontrolled studies of of IVC filters among patients with trauma. The mortality rates were variable and ranged from 0 percent to as high as 31 percent.[88 98]

Deep Vein Thrombosis

Randomized Controlled Trials and Controlled Observational Studies

Inferior Vena Cava Filters versus No Inferior Vena Cava Filters

Three studies reported on DVT outcomes.[58 63 65] Figure 6 shows the relative risk meta-analysis on the outcome of DVT(RR 1.76, 95% CI = 0.49 to 6.18:p=0.38). This demonstrate the substantial statistical heterogeneity among the included studies with an I^2=56.8 %.

In the RCT, there were no significant differences in the incidence of DVT between the two groups. There was one DVT in the IVC filter group and none in the control group.[58] One

retrospective cohort study reported a statistically significant increase in the incidence of DVT in the IVC filter group (20.4 percent versus 5.2 percent, p value <0.021).[63] One additional study found a non-significant difference in DVT incidence, which was lower in the IVC filter group (15 percent versus 19 percent).[65]

Inferior Vena Cava Filters versus Inferior Vena Cava Filters

Two studies reported on the outcome of DVT between Gunther Tulip vs Celect filters[66] and Gunther Tulip vs Optease filters.[67] Although, the data were sparse both studies reported a higher incidence of DVT in the Gunther Tulip arm. There were no statistically significant differences in the incidence of DVT.

Uncontrolled Studies

Twenty-three studies reported the total DVT events, with proportions ranging from 0 to 47 percent, with a total sample size ranging between one to 248 patients.[48 68 69 80 83 84 86 87 89 93 95-98 100 101 103-106 108 110 113] Figure 11 describes the proportion and 95 % CI of patients with DVT in uncontrolled studies of of IVC filters among patients with trauma.

The study that reported the highest proportion of DVT (affecting 47 percent of patients) included only 30 patients and had a long followup period (42 months) compared to most other reports.[106] Aside from this study, DVTs occurred in 27 percent or fewer patients.

Nine studies reported lower extremity DVT events with sample sizes of one to 122 patients.[70 71 75 76 78 81 85 99 113] The followup was limited to a hospital stay or up to 2 months, except for one study that had a one-year followup.[76] The event rates ranged between 0 and 7.8 percent. Only two studies reported upper extremity DVT events.[74 82] Those two studies had 17 and 83 patients, respectively, and one upper extremity DVT occurred in either group, corresponding to rates of 5.8 and 1.2 percent, respectively.

Filter Complications

Randomized Controlled Trials and Controlled Observational Studies

Inferior Vena Cava Filters versus No Inferior Vena Cava Filters

Four comparative studies reported data on filter complications[59 60 64 65] The majority of the adverse events were related to filter complications, such as tilting,[59] migration,[116] IVC thrombosis and insertion-site thrombosis.[60] Of these, insertion-site thrombosis was the most common, occurring in 5.7 percent of patients in one study.[59] Other filter complications such as tilting and migration occurred less frequently, occurring in 1 to 2 percent of patients in most studies.

Inferior Vena Cava Filters versus Inferior Vena Cava Filters

Two studies examined the comparative effectiveness of different kinds of filters and reported adverse events.[66 67] In the study by Rosenthal et al., four patients developed groin hematomas and six patients in the Gunther Tulip group had filter misplacement at insertion.[66] In the Celect arm, one patient developed a groin hematoma and another patient had filter migration. In the study by Keller et al., one patient developed filter migration, and 7 percent of the patients

developed acute caval occlusion in the Gunther Tulip arm.[67] In the Optease arm, 3 percent of the patients developed acute caval occlusion. No filter migrations occurred in the Optease arm.

Uncontrolled Studies

Strut Fracture

Six uncontrolled studies reported on the outcome of strut fracture with IVC filters. [48 71 72 76 82 85] These rates were uniformly low and affected fewer than 1.5 percent of filter recipients.(Table 10)

Filter Migration

Seventeen uncontrolled studies reported on the rare occurrence of filter migration which was very infrequent.[72 77-80 88 90 92 93 96 97 105 106 108 109 117](Table 10)

Filter Tilt

Seven uncontrolled studies reported on the complication of filter tilt which was rare. [48 77 95 103 105 108 118] One study of 132 patients with 5-year followup data reported substantial filter tilt (> 14 degrees) among 5.5 % of participants. The same study also reported strut malposition proportions as high as 38 percent.[103] Another small study of 13 patients, assessing the retrievability of Bard filters at 180 days, reported a mild filter tilt (3 to 25 degrees) in eight cases (61.5%), and more severe filter tilt (greater than 10 percent) in two patients (15%).[77] (Table 10)

Filter Thrombosis

Seventeen uncontrolled studies reported on the complication of filter related thrombosis. .[71 75 80 81 83 85 86 88 90 93 96 102 106 108-110] These included the complications of insertion-site thrombosis or occlusion.[88] The rates were uniformly low. The rates of insertion related thrombosis was zero in several studies [77 88 102 108]and 3.1 percent at 5 years in the long term study.[103] (Table 10)

Arterial-Venous Fistulas

Two uncontrolled studies reported on the outcome of arterial-venous fistulas[85 100] with IVC filters. The percentage of patients developing fistulas ranged from 0[85] to 0.5 percent.[100] (Table 10)

Filter Misplacement

Ten uncontrolled studies reported on the outcome of filter misplacement.[83 85 90 95 98 100-102 106] The percentage of patients having filter misplacement ranged from as low as 0 percent to as high as 3.2 percent.[85 102] The overall proportions were uniformly low to allow any meaningful analysis.(Table 10)

Filter Penetration or Perforation

Ten uncontrolled studies reported on the complication of filter perforation or penetration. [69 71 73 83 85 88 91 95 96 102] Four studies reported no filter perforation in any patients.[85 88 96 102] The overall rates were uniformly low to allow any meaningful analysis. One small study reported small (<1 cm) IVC defects without contrast extravasations in three patients among 44 patients who underwent uneventful filter retrieval.[83](Table 10)

Inferior Vena Cava Thrombosis or Occlusion

Thirteen uncontrolled studies reported on the complication of IVC thrombosis or occlusion.[76 79 86 90 95 97 101 104-106 108 109 114] The overall proportions were uniformly low. Two studies reported no IVC thrombosis or occlusion.[86 109] (Table 10)

Bleeding

Fifteen uncontrolled studies reported on bleeding complications. [68 68 83 83 85 90 91 95 96 98 100-103 106 106 109] The type of bleeding included minor bleeding, groin hematomas, and non-serious bleeding. The percentages ranged from no episodes of bleeding in several studies to rates as high as 3 percent of filter recipients.[103] The overall proportions were uniformly low. Major bleeding from the IVC occurred in one study.[91 98 101 102 106] (Table 10)

Infections

Four uncontrolled studies reported on infections. .[85 89 93 95] Two studies reported no infections during the studies. Another study reported that 2.5 percent of patients had sepsis,[89] while another study reported rates as high as 3.8 percent.[95] None of these studies could distinguish whether these complications were filter related or due to the underlying risks of the severely injured trauma population. (Table 10)

Other Adverse Events

Other complications reported in a single patient included technical failure to remove IVC filter in one study,[68] incorrect deployment of the IVC filter in a single patient in the operating room in another study,[103] and supraventricular tachycardia in a patient during insertion in another study.[78]

Proportion of Filters Retrieved

Randomized Controlled Trials and Controlled Observational Studies

An increasing number of temporary filters are being placed in patients with trauma to prevent PE. However there are concerns that several of these temporary filters are not retrieved in the long term placing patients at higher risk of filter related complications. Among 16 filters that were retrievable in the RCT only 2 were retrieved at 6 months.[58] Retrieval rates were not consistently reported in the controlled observational studies.

Inferior Vena Cava Filters versus Inferior Vena Cava Filters

In the study by Rosenthal et al., the filter retrieval rate was higher in the Celect filter arm (84 percent versus 54 percent) compared to the Gunther Tulip filter.[66] The study by Keller et al. reported the filter retrieval rate as a secondary outcome. The filter retrieval rate was higher in the Optease filter group than the Gunther Tulip filter (70 percent versus 49 percent).[67]

Uncontrolled Studies

Seventeen uncontrolled studies reported on the proportion of filters retrieved after prophylactic IVC filter placement among patients with trauma.[48 68 70 71 73-77 79-85 112] There was great variability in these proportions. Although, one small cohort study of 13 patients reported clinicians retrieved all of the filters they inserted, the usual recovery rates in other cohorts were

lower.[77] These ranged from clinicians removing as few as one-third of the filters they inserted. Most other studies reported filter retrieval proportions that were higher.

Post-thrombotic Syndrome

One uncontrolled study reported on the outcome of post-thrombotic syndrome in patients having prophylactic IVC filter placement. Among 30 patients with IVC filters, post-thrombotic syndrome occurred in 14 patients.[106]

Length of Stay in the Hospital and Intensive Care Unit

Only six uncontrolled studies reported on length of stay in the hospital. [80 82 89 96 97 119] The mean length of stay in the hospital ranged from 26 days (range 6-159) to 38.5 days (range 6-118).[80 96] Among these six studies, two studies also reported on the length of stay in the intensive care unit. The mean length of stay in days in the ICU ranged from 11 to 14.1 days.[96]

Risk of Bias

We rated the only small RCT on this question as having a high risk of bias[58] Among the observational studies, we rated only five studies as having a moderate risk of bias and the remainder as having a high risk of bias. [63 73 85 96 113] (Appendix E). Although the majority of observational studies were at high risk of bias, two included studies had severe methodological flaws including substantial differences in injury severity score and inadequate adjustment for injury severity score. [59 60]

Strength of evidence

All included studies which assessed the comparative effectiveness and safety of IVC Filter vs no filters were at high risk of bias, except one study at moderate risk of bias. [63] We rated the strength of evidence as insufficient to support reduction in PE and fatal PE in trauma with IVC filters.

We based this rating on the high risk of bias, imprecision and inconsistency of findings across studies. (**Figure 3 and Figure 4**) Our sensitivity analysis showed that removal of the two studies with major methodologic deficiencies would allow us to conclude that there is low grade evidence of benefit of IVC filters on the outcome of PE. [59 60] Similarly, removal of the one of the studies with major methodologic deficiencies, [60] would allow us to conclude that there is low grade evidence of benefit of IVC filters on the outcome of fatal PE.

We rated the strength of evidence as insufficient to support an increase in mortality in trauma with IVC filters. We based this rating on the high risk of bias, imprecision and inconsistency in the findings across studies. **(Figure 5)** We rated the strength of evidence as insufficient to support an increase in DVT in trauma with IVC filters. We based this rating on the high risk of bias and inconsistency in the findings across studies. (**Figure 6**) We rated the strength of evidence as low to support an increase in filter related thrombosis in trauma with IVC filters. **(Figure 7)** We based this rating on the high risk of bias, precision, directness and consistency in the findings across studies.

Applicability

Most of these studies occurred in trauma centers and their findings would apply to severely injured trauma patients. Although most studies occurred at level 1 trauma centers, the findings might also apply to injured patients cared for in other settings with access to IVC filters. The patients in these studies were mostly severely injured as noted in their high mean/median ISS scores. The applicability of these findings to patients with less severe trauma is unknown. The proportion of men was typically higher than women, as expected in any trauma study, which may impact the generalizabilty of these results to female trauma patients. The studies are most directly applicable to the middle-aged adult patient population as that was the population most frequently studied, although most studies did not have any older age range cutoff. Information on racial composition was unavailable from several studies to comment on whether these findings are applicable to non-whites patients. The definitions of standard therapy varied across studies making it difficult to determine applicability to settings where the standard therapy may be different.

Table 4: Study characteristics for controlled studies IVCF vs control for KQ1

Author, year	Study design	Arm	Sample Size (N)	Mean Age, Years	% Male	Mean ISS scores
*Rajasekhar A, 2011[58]	RCT	IVCF	18	41.2	72.2	26.6
		Control	16	53.7	62.5	24.1
Rogers FB, 1997[59]	PC	IVCF	35	58.4	NR	22.8
		Control	905	38.9	NR	9.83
Gosin JS, 1997[62]	PC	IVCF	99	42.6	71.7	23.4
		Control	151	NR	NR	NR
Rogers FB, 1995[60]	Historical comparison	IVCF	63	38.9	73.0	31.5
		Controls	2525	NR	NR	NR
Wilson JT, 1994[61]	Historical comparison	PGF	15	31.4	NR	30.0
		Control	111	30.0	NR	29.0
Gorman PH, 2009[63]	RC	IVCF	54	37.1	96.0	NR
		Control	58	48.1	69.0	NR
Rodriguez JL, 1996[65]	PC	IVCF	40	44.0	58.0	31 .0
		Control	80	41.0	68.0	29.0
Khansarinia S, 1995[64]	Historical comparison	PGF	108	35.9	76.0	28.0
		Control	216	38.3	75.5	25.4

*Study did not report characteristics by treatment group; IVCF=Inferior Vena Cava Filter; PGF=Prophylactic Greenfield Filter

RCT= RCT, PC= Prospective Cohort; RC= Retrospective Cohort

Table 5: Study characteristics for controlled studies inferior vena cava filter (IVCF) vs IVCF

Author, year	Study design	Filter Type	Sample size (N)	Mean Age	% Male	Mean ISS	Filter Retrieval Rate %
*Rosenthal D, 2009[66]	RC	Gunther Tulip	97	44	58.2	28.5	54
		Celect Retrievable	90	44	58.2	28.5	84
Keller IS, 2007[67]	RC	Gunther Tulip	92	45.6	69.6	NR	49
		OptEase	80	47.8	58.8	NR	70

*Study did not report characteristics by treatment group
† Retrievable and non-retrievable filters
RC= Retrospective Cohort

Table 6: Study characteristics for uncontrolled studies of IVC Filters in Trauma

Author, year	Study type	Sample size (N)	Mean age, Years	% Male	Filter retrieval rate n, (%)
O'Keefe T, 2011[68]	RC	91		70	(47)
Shang EK, 2011[69]	Case report	1	46	0	NR
Smooth RL, 2010[114]	RC	226	49	61.1	NR
Roberts A, 2010[70]	RC	45	39.7	82.2	17 (37)
Doody O, 2009[71]	RC	115	47.97	63.4	57 (49.6)
Phelan HA, 2009[72]	Series	82	34.1	63.4	NR
Cherry RA, 2008[48]	PC	244	43.8	63.5	82/140 (58.6)
Hermsen JL, 2008[73]	RC	74	38.4	68	30/39 (77)
Lo CH, 2008[74]	Series	17	37	70.6	13/16
Mahier A, 2008[75]	RC	80	38.5	66	29 (36)
Zakhary EM, 2008[76]	RC	122	38.5	70.1	47/116 (40.5)
Karmy-Jones R, 2007[113]	RC	310	NR	NR	NR
Rosenthal D, 2007[112]	RC	105	NR	NR	91/105 (86.7)
Binkert CA, 2006[77]	RC	13	46.2	46.2	13
Gonzalez RP, 2006[78]	PC	134	38.6	NR	NR
Meier C, 2006[79]	Series	37	35	62	32 (86)
Meier C, 2006[80]	RC	95	38	70.5	65/67 (97)
Rosenthal D, 2006[81]	RC	127	42	60.6	66 (60)
Stefanidis D, 2006[82]	PC	83	43	71	47 (57)
Rosenthal D, 2005[83]	PC	103	40	62.1	44
Hoff WS, 2004[84]	PC	35	NR	71.4	18 (51.4)
Rosenthal D, 2004[85]	RC	94	38	60.6	31
Duperier T, 2003[86]	RC	133	NR	NR	NR
Kurtoglu M, 2003[87]	PC	11	NR	NR	NR
Offner PJ, 2003[88]	PC	44	37	55	NR
Carlin AM, 2002[89]	RC	NR	NR	NR	NR
Conners MS, 2002[90]	RC	284	41	71	NR
Bochicchio GV, 2001[91]	Case report	1	48	100	NR
Rogers F, 2001[92]	Case report	1	48	100	NR
Sekharan J, 2001[93]	RC	33	38.1	75.8	NR
Sing RF, 2001[94]	Case report	2	54	50	NR
Sing RF, 2001[95]	PC	158	42.2	71.5	NR

Table 6: Study characteristics for uncontrolled studies of IVC Filters in Trauma Continued

Author, year	Study type	Sample size (N)	Mean age, Years	% Male	Filter retrieval rate n, (%)
Greenfield LJ, 2000[96]	Series	249	43	61.8	NR
Wojcik R, 2000[97]	RC	105	54.8	71.4	NR
Benjamin ME, 1999[98]	Series	23	46	86.95	NR
Hughes GC, 1999[99]	Case report	2	32.5	100	NR
Langan EM, 1999[100]	PC	NR	NR	NR	NR
McMurtry AL, 1999[101]	RC	248	33.7	68.1	NR
Tola JC, 1999[102]	RC	NR	NR	NR	NR
Rogers FB, 1997[103]	PC	132	39.1	73	NR
Sing RF,1997[104]	Series	8		87.5	NR
Nunn CR, 1997[105]	PC	49	31	-	NR
Patton JH Jr, 1996[106]	RC	110	47.2	61.8	NR
Zolfaghari D, 1995[107]	RC	45		51.1	NR
Leach TA, 1994[108]	PC	201	NR	73	NR
Millward SF, 1994[109]	PC	3	36	100	NR
Rogers FB, 1993[110]	PC/RC	34	41.6	NR	NR
Bach JR, 1990[111]	Case report	1	NR	0	NR

* Retrievable and non-retrievable filters
N = Number, ISS = Injury Severity Score, IVC = Inferior vena cava, PC = Prospective cohort, RC= Retrospective cohort

Table 7: Outcomes Data for Controlled Studies (Inferior Vena Cava Filter (IVCF) vs Control)

Study, year	Arm	Sample size (N for analysis)	Total DVT n	Total Mortality n	Fatal PE n	PE n
Rajasekhar A, 2011[58]	IVCF	18	1	1*	0	0
	Control	16	0	0	0	1
Rogers FB, 1997[59]	IVCF	35	NR	4	NR	1
	Control	905	NR	46	NR	1
Gosin JS, 1997[62]	IVCF	99	NR	NR	NR	0
	Arm: Other DVT Prophylaxis	151	NR	NR	NR	4
	Control No IVCF and No DVT Prophylaxis	249	NR	NR	NR	12
Rogers FB, 1995[60]	IVCF	63	19	3	1	1
	Historical Controls	2525	NR	28	7	25†
Wilson JT, 1994[61]	IVCF	15	0	NR	0	0
	Control	111	NR	NR	3	8‡
Gorman PH, 2009[63]	IVCF	54	11	NR	NR	1
	Control	58	3	NR	NR	0
Rodriguez JL, 1996[65]	IVCF	40	6	2	0	1
	Control	80	15	13	8	14
Khansarinia S, 1995[64]	PGF§	108	NR	18	0	0
	Control	216	NR	47	9 **	13Ω

*Non VTE related death
†25-total PEs in historical control group, of these 7 were fatal PEs; ‡8- total PEs, of these 3 were fatal PEs; §PGF (Prophylactic Greenfield Filter)
**Statistically significant difference in fatal PE, P = 0.03; Ω13-total PEs, of these 9 were fatal PEs

Table 8: VTE Outcomes and complications for comparison of different types of IVC filters

Source	Filter Type	Sample size (N for analysis)	Filter Retrieval Rate (%)	Total DVT (n)	Total Mortality (%)	PE (n)
Rosenthal D, 2009[66] #	Gunther Tulip	97	54	2	29 *	1
	Celect Retrievable	90	84	NR	11 *	1
Keller IS, ## 2007[67]	Gunther Tulip Filter	92	49	1	NR	2
	OptEase Filter	80	70	NR	NR	1

* Non VTE related death

Rosenthal et also reported on complications for Gunther Tulip compared to Celect filters: groin hematomas 4.1 % vs 1.1% and Filter misplacement/migration: 6.2% vs 1.1%

Keller et al also reported on complications for Gunther Tulip compared to Optease: Filter migration: 1.1% vs 0% Caval occlusion: 7 % vs 3%

Table 9: Outcomes data for uncontrolled studies of IVC filters

Author, year	Total DVT n (%)	Total Mortality n (%)	Pulmonary Embolism n (%)
O'keefe T, 2011[68]	10 (15)	NR	NR
Smooth RL, 2010[114]	NR	NR	8 (4)
Roberts A, 2010[70]	0 (0)	NR	NR
Doody O, 2009[71]	NR	NR	1 (0.9)
Phelan HA, 2009[72]	NR	15 (15.5)	2 (2.1)
Cherry RA, 2008[48]	22 (9)	NR	4 (1.6)
Hermsen JL, 2008[73]	NR	4 (4.3)	3 (3.2)
Lo CH, 2008[74]	NR	1 (5.9)	1 (5.9)
Mahier A, 2008[75]	NR	NR	NR
Zakhary EM, 2008[76]	NR	NR	NR
Karmy-Jones R, 2007[113]	18 (20)	NR	NR
Gonzalez RP, 2006[78]	0 (0)	NR	NR
Meier C, 2006[79]	- NR	1 (2.7)	1 (2.7)
Meier C, 2006[80]	2 (2.1)	7 (7.4)	1 (1.1)
Rosenthal D, 2006[81]	NR	39 (30.7)	1 (0.8)
Stefanidis D, 2006[82]	NR	3 (4)	0 (0)
Rosenthal D, 2005[83]	2 (1.9)	24 (23.3)	1 (1)
Hoff WS, 2004[84]	3 (8.6)	NR	0 (0)
Rosenthal D, 2004[85]	NR	19 (20.2)	1 (1.1)
Duperier T, 2003[86]	31 (23.3)	0 (0)	1 (0.8)
Kurtoglu M, 2003[87]	0 (0)	NR	0 (0)
Offner PJ, 2003[88]	NR	0 (0)	0 (0)
Carlin AM, 2002[89]	5 (6.4)	2 (4)	0 (0)
Conners MS, 2002[90]	NR	36 (12.7)	1 (0.4)
Sekharan J, 2001[93]	2 (6.1)	18 (17)	0 (0)
Sing RF, 2001[95]	8 (5.1)	18 (11.4)	1 (0.6)
Greenfield LJ, 2000[96]	16 (10.8)	39 (15.6)	3 (1.5)
Wojcik R, 2000[97]	NR	13 (6.8)	0 (0)
Benjamin ME, 1999[98]	0 (0)	3 (13)	0 (0)
Langan EM, 1999[100]	24 (12.8)	27 (14.4)	1 (0.5)
McMurtry AL, 1999[101]	6 (2.4)	31 (13)	4 (1.6)
Tola JC, 1999[102]	NR	4 (0.2)	0 (0)
Rogers FB, 1997[103]	12 (9.1)	6 (4.4)	3 (2.3)
Sing RF,1997[104]	1 (12.5)	1 (12.5)	NR
Nunn CR, 1997[105]	1 (2.0)	NR	0 (0)
Patton JH Jr, 1996[106]	7 (6.4)	22 (20)	0 (0)
Zolfaghari D, 1995[107]	- NR	1 (1.2)	0 (0)
Leach TA, 1994[108]	1 (0.5)	1 (0.5)	0 (0)
Millward SF, 1994[109]	NR	0 (0)	0 (0)
Rogers FB 1993[110]	6 (17.6)	2 (5.9)	0 (0)

* Total VTE, †Length of ICU stay, 1 UE DVT was reported, ICU = Intensive Care Unit, DVT = Deep Vein Thrombosis, PE = Pulmonary Embolism

Table 10: Adverse events for controlled studies inferior vena cava filter (IVCF) vs control)

Author, year	Arm	Sample size (n)	Filter Related Complications			
			Filter tilt (%)	Filter migration (%)	Filter thrombosis (%)	IVC thrombosis/ occlusion (%)
Rogers FB, 1997[59]	IVCF	35	1	NR	2	NR
	Control	905	NR	NR	NR	NR
Rogers FB, 1995[60]	IVCF	63	NR	NR	2	2
	Control	3088	NR	NR	NR	NR
Rodriguez JL, 1996[65]*	IVCF	40	NR	NR	NR	NR
	Control	80	NR	NR	NR	NR
Khansarinia S, 1995[64]‡	PGF	108	NR	1	1†	NR
	Control	216	NR	NR	NR	NR

*gastrointestinal bleeding requiring blood transfusion:4 patients
†Internal Jugular vein thrombosis due to the Prophylactic Greenfield Filter (PGF) insertion.
‡Authors reported on infection as a complication, but none of the groups developed this complication.
None of the studies reported these filter related adverse events: strut fracture, misplacement, perforation and bleeding.

Table 11: Adverse events for uncontrolled studies of IVC filters

Author, year	Filter complications							Bleeding events, N
	Strut fracture, n (%)	Filter tilt, n (%)	Filter migration, n (%)	Filter thrombosis, n (%)	Misplacement, n (%)	Perforation, n(%)	IVC thrombosis/ Occlusion, n (%)	
Smooth RL, 2010[114]	NR	NR	NR	NR	NR	NR	15 (6.6)	NR
Doody O, 2009[71]	1 (1.6)	NR	NR	15 (24.6)	NR	2 (3.3)	1 (1.6)	NR
Phelan HA, 2009[72]	1 (1.5)	NR	0 (0)	NR NR	NR	NR	NR	NR
Cherry RA, 2008[48]	2 (0.8)	1 (0.4)	NR	NR	NR	NR	3 (1.2)	NR
Hermsen JL, 2008[73]	NR	NR	NR	NR	NR	1 (1.1)	NR	NR
Mahier A, 2008[75]	NR	NR	NR	8 (25)	NR	NR	NR	NR
Zakhary EM, 2008[76]	1 (0.6)	NR	NR	NR	NR	NR	4 (3.4)	NR
Binkert CA, 2006[77]	NR	8 (61.5)*	0 (0)	0 (0)	NR	NR	NR	NR
Gonzalez RP, 2006[78]	NR	NR	2 (1.5)	NR	NR	NR	NR	NR
Meier C, 2006[79]	NR	NR	1 (2.7)	NR	NR	NR	5 (13.5)	NR
Meier C, 2006[80]	NR	†2 (3)	1 (1.1)	5 (5.3)	NR	NR	NR	NR
Rosenthal D, 2006[81]	NR	NR	NR	3 (2.4)	NR	NR	NR	NR
Stefanidis D, 2006[82]	1 (1.2)	NR	NR	NR	NR	NR	NR	NR
Rosenthal D, 2005[83]§	NR	NR	NR	§3 (6.8)	3 (2.9)	§3 (6.8)	NR	3 (2.9)
Rosenthal D, 2004[85]	§0 (0)	NR	NR	3 (3.2)	3 (3.2)	§0 (0)	NR	2 (2.1)
Duperier T, 2003[86]	NR	NR	NR	1 (0.8)	NR	NR	0 (0)	NR
Kurtoglu M, 2003[87]§	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Offner PJ, 2003[88]§	NR		0 (0)	0 (0)	NR	0 (0)		

Table 11: Adverse events for uncontrolled studies of IVC filters continued

Author, year	Filter complications							Bleeding events, N
	Strut fracture, n (%)	Filter tilt, n (%)	Filter migration, n (%)	Filter thrombosis, n (%)	Misplacement, n (%)	Perforation, n(%)	IVC thrombosis/ Occlusion, n (%)	
Conners MS, 2002[90]	NR	NR	1 (0.4)	1 (0.4)	6 (2)	NR	3 (1)	1 (0.4)
Sekharan J, 2001[93]	NR	NR	0 (0)	Δ1 (0.9)	NR	NR	NR	NR
Sing RF, 2001[95]	NR	2 (1.3)			1 (0.63)	1 (0.6)	1 (0.6)	2 (1.3)
Greenfield LJ, 2000[96]§	NR	NR	1 (1.4)	5 (3.5)	NR	0 (0)	NR	‡2 (0.8)
Wojcik R, 2000[97]	NR	NR	1 (1)	NR	NR	NR	1 (0.95)	NR
Benjamin ME, 1999[98]	NR	NR	NR	NR	1 (4.3)	NR	NR	0
Langan EM, 1999[100]	NR	NR	NR	NR	1 (0.5)	NR	NR	2 (1.1)
McMurtry AL, 1999[101]	NR	NR	NR		2 (0.8)		3 (1.2)	0
Tola JC, 1999[102]	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)
Rogers FB, 1997[103]	NR	7 (5.5)	NR	NR	NR	NR	NR	4 (3.0)
Sing RF[104]	NR	NR	NR	NR	NR	NR	1 (12.5)	NR
Nunn CR, 1997[105]	NR	1 (2.0)	1 (2.0)	NR	NR		1 (2.0)	NR
Patton JH Jr, 1996[106]	NR	NR	1 (0.9)	3 (2.7)	3 (2.7)	NR	1 (0.9)	0 (0)
Leach TA, 1994[108]	NR	1 (0.5)	1 (0.5)	NR	NR	NR	0 (0)	NR
Millward SF, 1994[109]	NR	NR	0 (0)	1 (33.3)	NR	NR	0 (0)	0 (0)
Rogers FB, 1993[110]	NR	NR	NR	1 (2.9)	NR	NR	NR	NR

*Mild Filter tilt in eight cases (61.5%) and more severe tilt in 2 cases 15%
† Data for subset of patients who underwent filter retrieval
‡ Data for overall baseline population
§These studies also reported on insertion-vein thrombosis and rates ranged from 0% in (5230), 2% in (4231), 2% in (6522), 9% in (5199),
N = Number, IVC = Inferior vena N N = Number, IVC = Inferior vena cava

Table 12: Body of evidence for placement of IVC filter vs no filter in the prevention of VTE in hospitalized patients with trauma

Author, Year	Outcome	Risk of Bias	Directness	Precision#	Consistency	Strength of evidence and magnitude of effect
	PE	**High**	**Direct**	**Imprecise**	**Inconsistent**	**Insufficient to support that IVC filter placement is associated with a lower incidence of PE in hospitalized patients with trauma compared to no IVC filter placement.** RR0.55 (95% CI = 0.10 to 2.96);p=0.48;
Rajesekhar, A 2011[58 ##]		High	Direct	imprecise	Inconsistent ;I^2=62%	0 % vs 6.2 %
Wilson JT, 1994[61]		High	Direct	imprecise		0 % vs 7.2 %
Gosin JS, 1997[62]		High	Direct	Precise		0 % vs 4.8 %
Gorman PH, 2009[63]		Moderate	Direct	imprecise		1.8 % vs 0 %
Khansarinia, S 1995[64]		High	Direct	Precise		0 % vs 6.0 %
Rogers, FB, 1997[59]		High	Direct	Precise		2.8 % vs 0.1 %
Rogers, FB, 1995[60]		High	Direct	Imprecise		1.6 % vs 0.9 %
Rodriguez JL, 1996[65]		High	Direct	precise		2.5 % vs 17.5 %
	Fatal PE	**High**	**Direct**	**Imprecise**	**Inconsistent**	**Insufficient to support that IVC filter placement is associated with a lower incidence of fatal PE in hospitalized patients with trauma compared to no IVC filter placement.** RR 0.36 (95% CI = 0.015496 to 8.161554): p=0.54
*Rajesekhar, A 2011[58]		High	Direct	Imprecise	Inconsistent; I^2= 70.4%	0 % vs 0 %
Wilson JT, 1994[61]		High	Direct	Imprecise		0 % vs 2.7 %
Khansarinia, S 1995[64]		High	Direct	Precise		0 % vs 5.5 %
Rogers, FB, 1995[60]		High	Direct	imprecise		1.6 % vs 0.3 %
Rodriguez JL, 1996[65]		High	Direct	imprecise		0 % vs 10.0 %
	Mortality	**High**	**Direct**	**Imprecise**	**Inconsistent**	**Insufficient to support that IVC filter placement is associated with a higher mortality in hospitalized patients with trauma compared to no IVC filter placement** RR1.33 (95% CI = 0.53 to 3.32);p=0.54

Table 12: Body of evidence for placement of IVC filter vs no filter in the prevention of VTE in hospitalized patients with trauma continued

Author, Year	Outcome	Risk of Bias	Directness	Precision#	Consistency	Strength of evidence and magnitude of effect
*Rajesekhar, A 2011[58]		High	Direct	Imprecise	Inconsistent; = 1^2=69.8 %	5.5 % vs 0%
Khansarinia, S 1995[64]		High	Direct	Imprecise		16.6 % vs 21.7 %
Rogers, FB, 1997[59]		High	Direct	Imprecise		11.4 % vs 5.1 %
Rogers, FB, 1995[60]		High	Direct	Imprecise		4.7 % vs 1.1 %
Rodriguez JL, 1996[65]		High	Direct	imprecise		5.0 % vs 16.2 %
	DVT	**High**	**Direct**	**Imprecise**	**Inconsistent**	**Insufficient to support that IVC filter placement is associated with a higher incidence of DVT compared to no IVC filter placement.** RR 1.76 (95% CI = 0.49 to 6.18):p=0.38
Rajesekhar, A 2011[58]		High	Direct	imprecise	Inconsistent; Statistical heterogeneity I^2= 56.8 %	5.5 % vs 0 %
Rodriguez JL, 1996[65]		High	Direct	imprecise		15.0 % vs 18.7 %
Gorman PH, 2009[63]		Moderate	Direct	Precise		20.4 % vs 5.2 %
	Filter related thrombosis **	**High**	**Direct**	**Precise**	**Consistent**	**low to support that IVC filter placement is associated with a higher incidence of filter related thrombosis compared to no IVC filter placement.** RR 51.4 (95% CI = 7.43 to 355):p<0.0001
Khansarinia, S 1995[64]		High	Direct	Precise	Consistent; Statistical heterogeneity I^2= 49.4%	1.8 % vs 0 %
Rogers, FB, 1997[59]		High	Direct	Precise		8.6 % vs 0 %
Rogers, FB, 1995[60]		High	Direct	Precise		6.3 % vs 0 %

** Graded on Filter related thrombosis. Data were too sparse on other complications such as filter tilt and migration to provide meaningful SOE grades on these specific complications
*No VTE-related deaths in the RCT
See Figures 3,4,5,6 and & for ratings on precision
Only RCT on this KQ

Figure 3 Meta-analysis of IVC Filter vs No Filter with IVC on PE in trauma

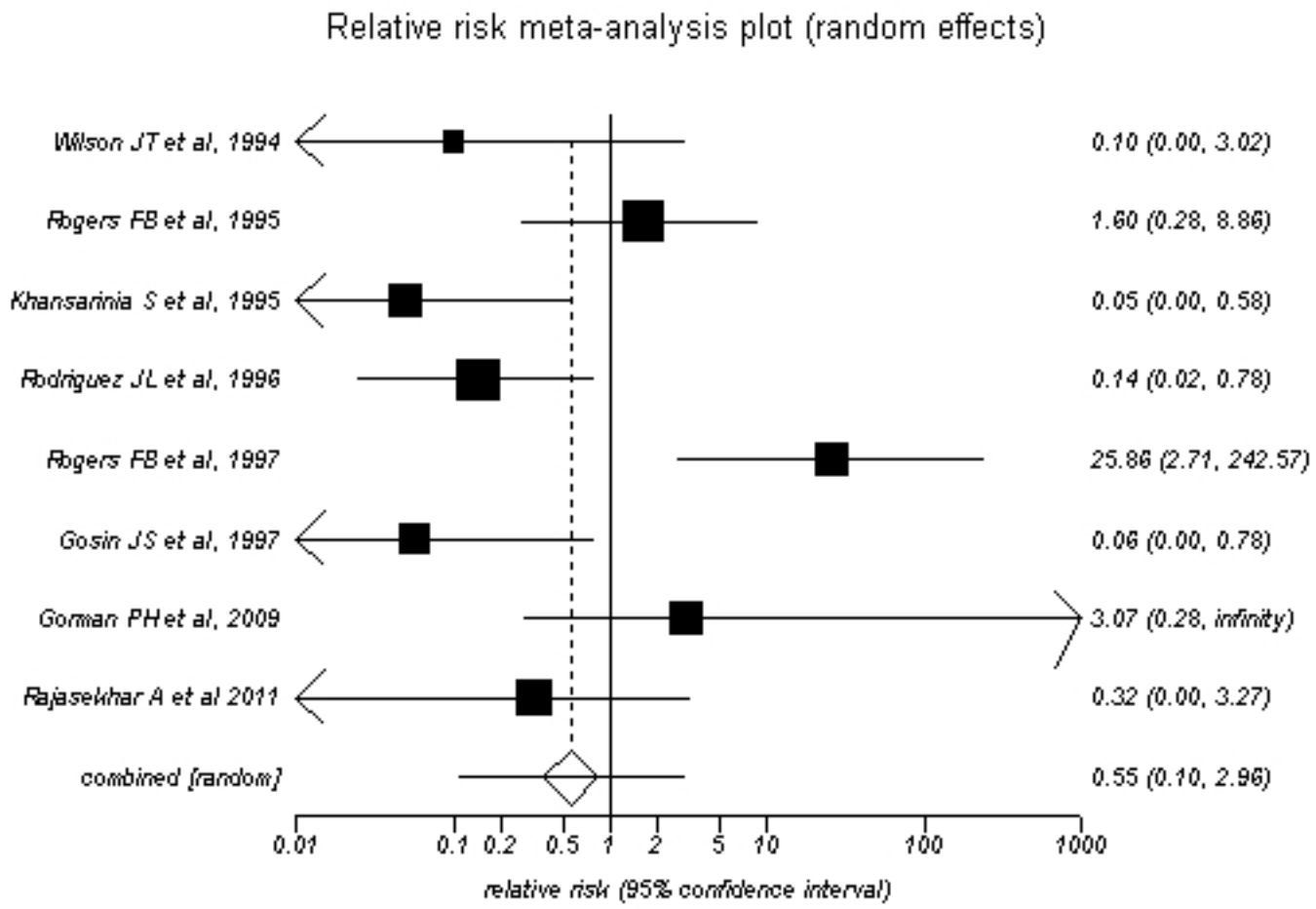


Figure 4. Relative Risk Forest plot (random effects) of IVC filters vs no filters in trauma on fatal PE

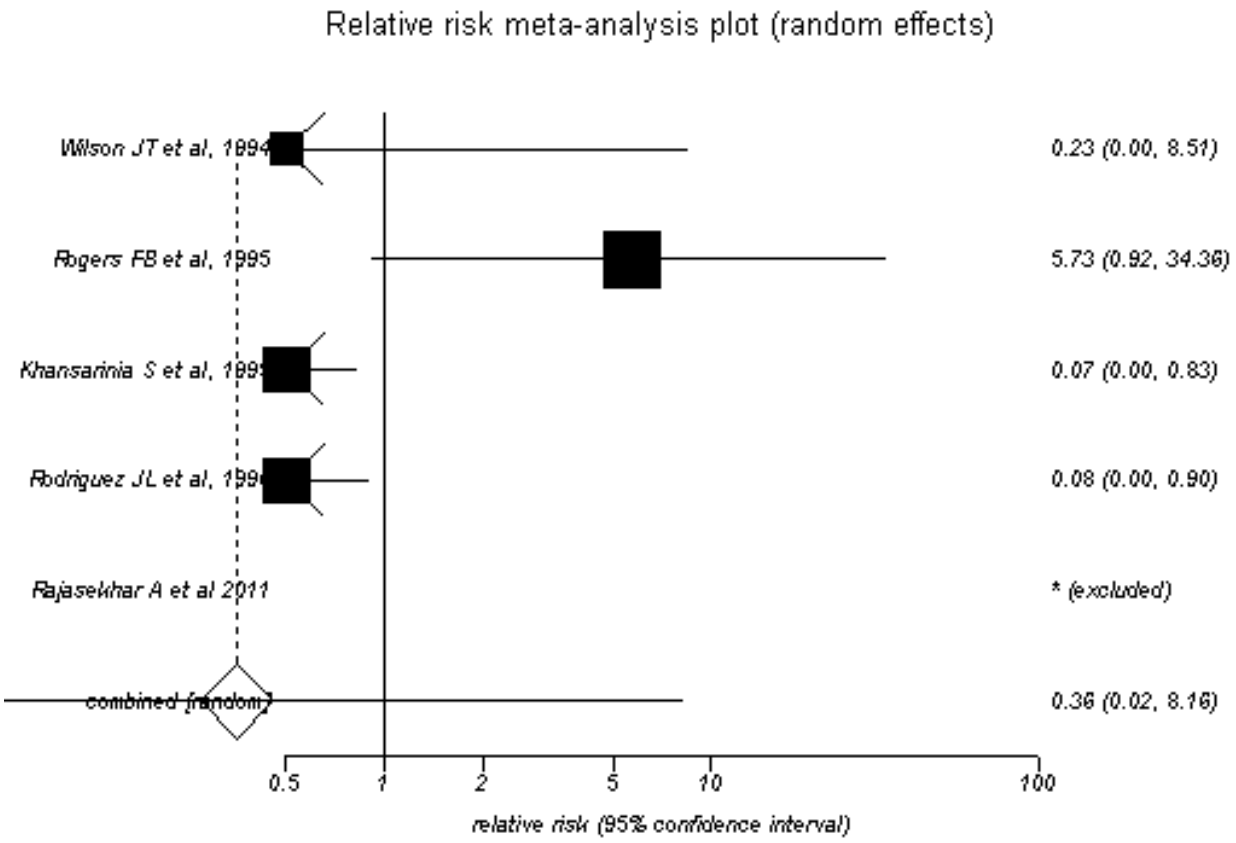


Figure 5. Relative risk Forest plot (random effects) IVC filters vs nofilters in trauma on mortality

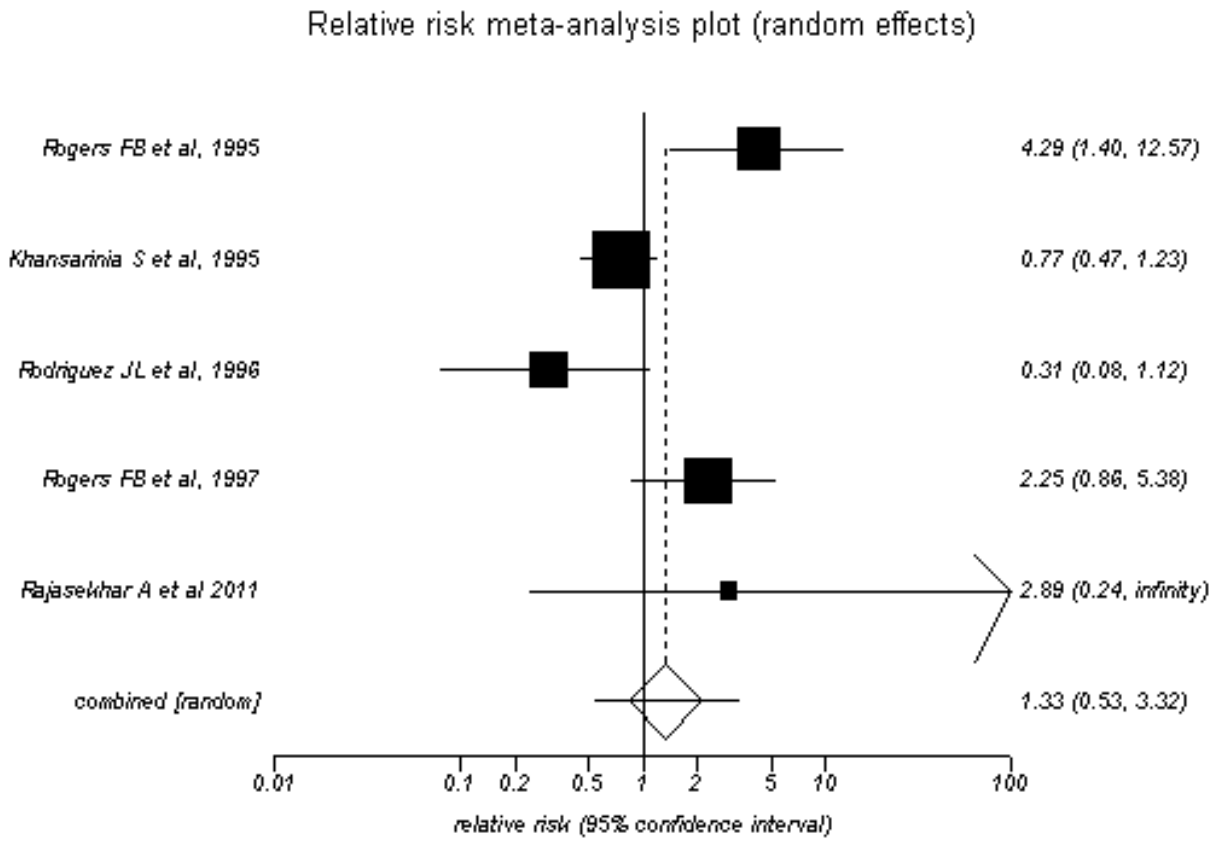


Figure 6. Relative risk Forest Plot (random effects) IVC filters vs nofilters in trauma on DVT

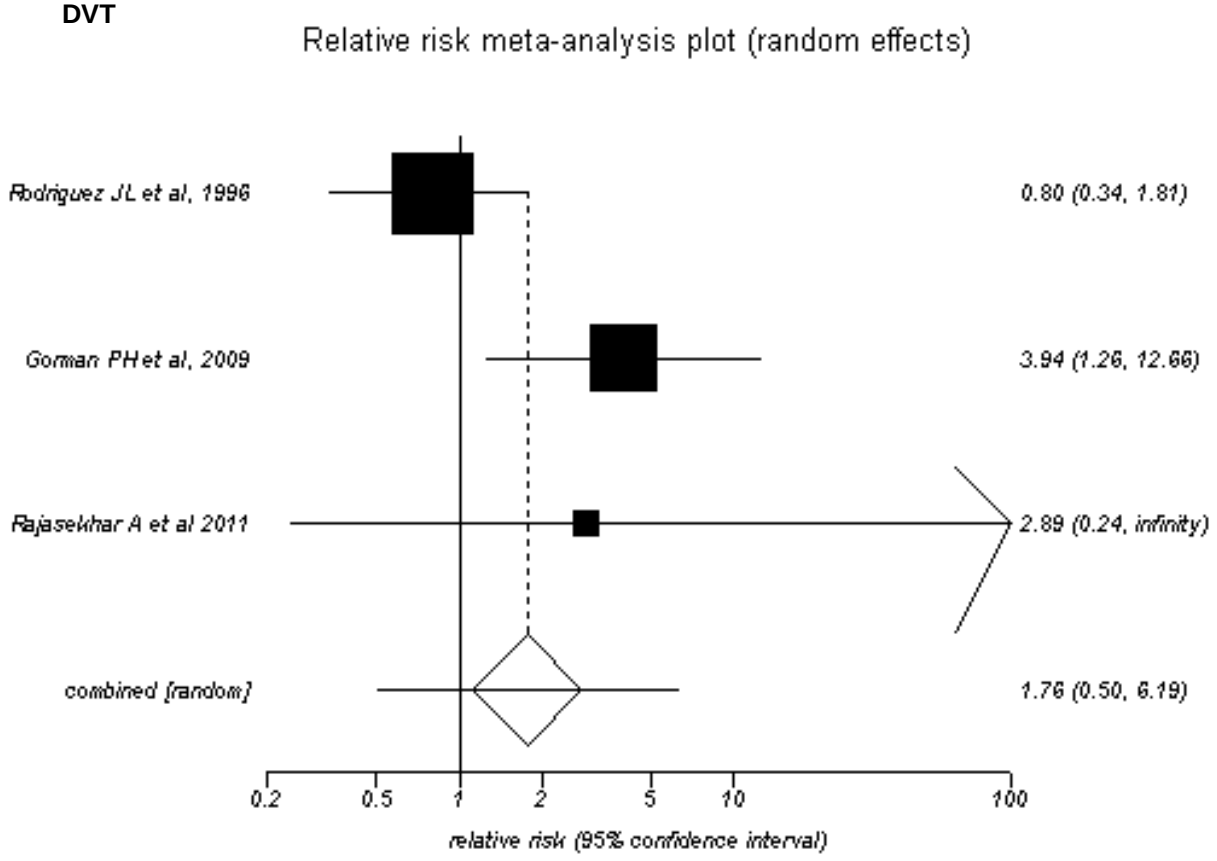


Figure 7. Relative risk Forest Plot (random effects) IVC filters vs nofilters in trauma on Filter related thrombosis

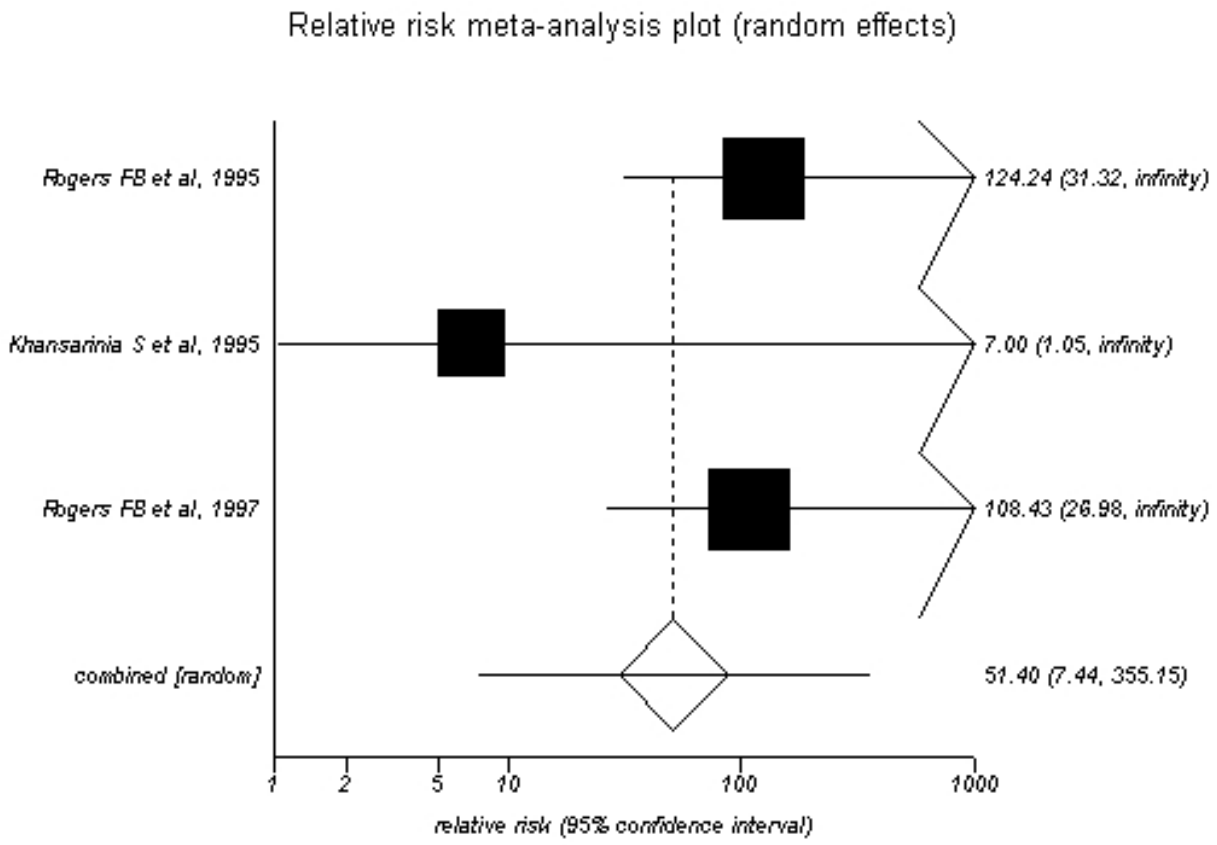


Figure 8. Proportion plot for PE in uncontrolled studies of IVC filters [random effects]

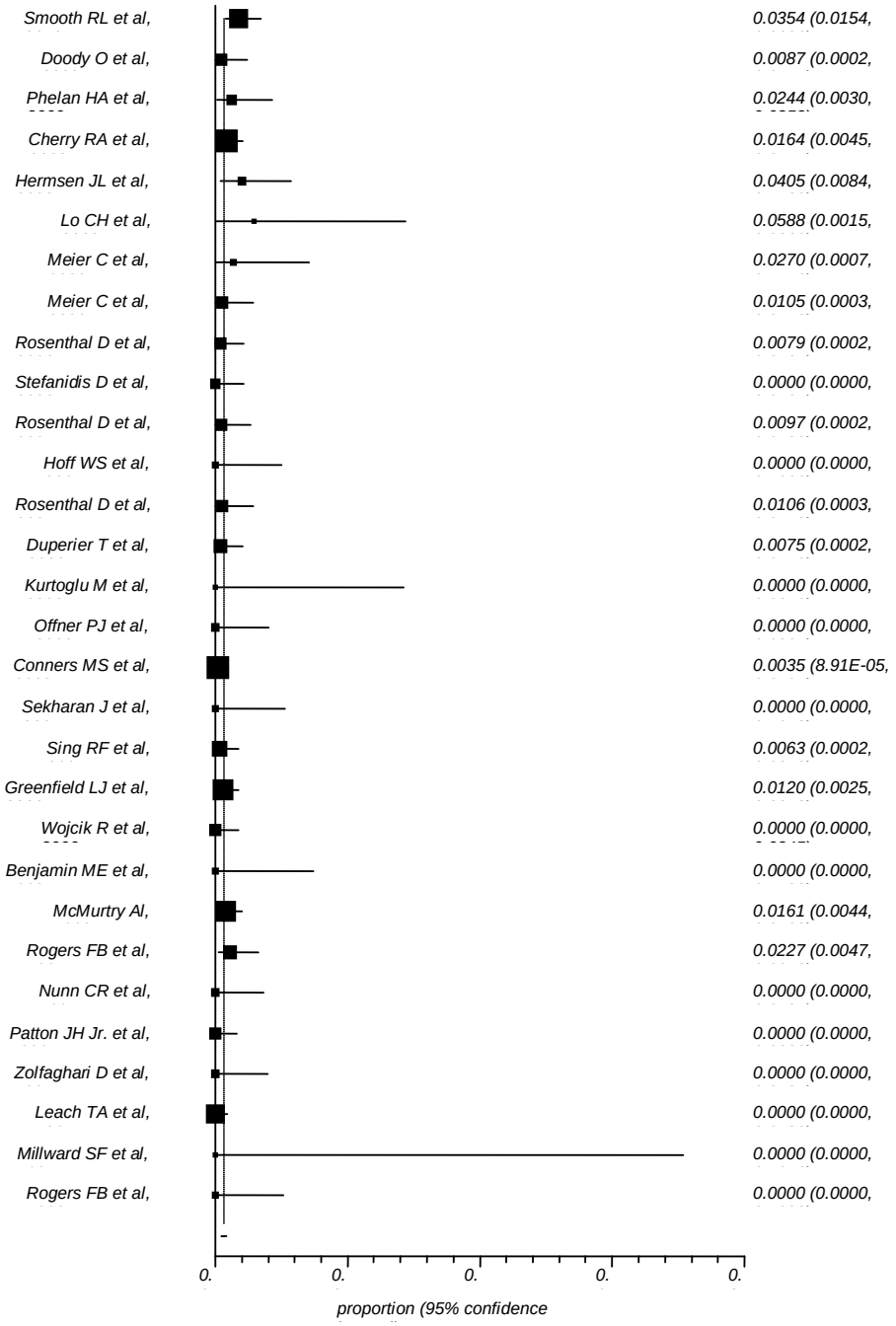


Figure 9. Proportion plot of mortality in Uncontrolled Filter Studies [random effects]

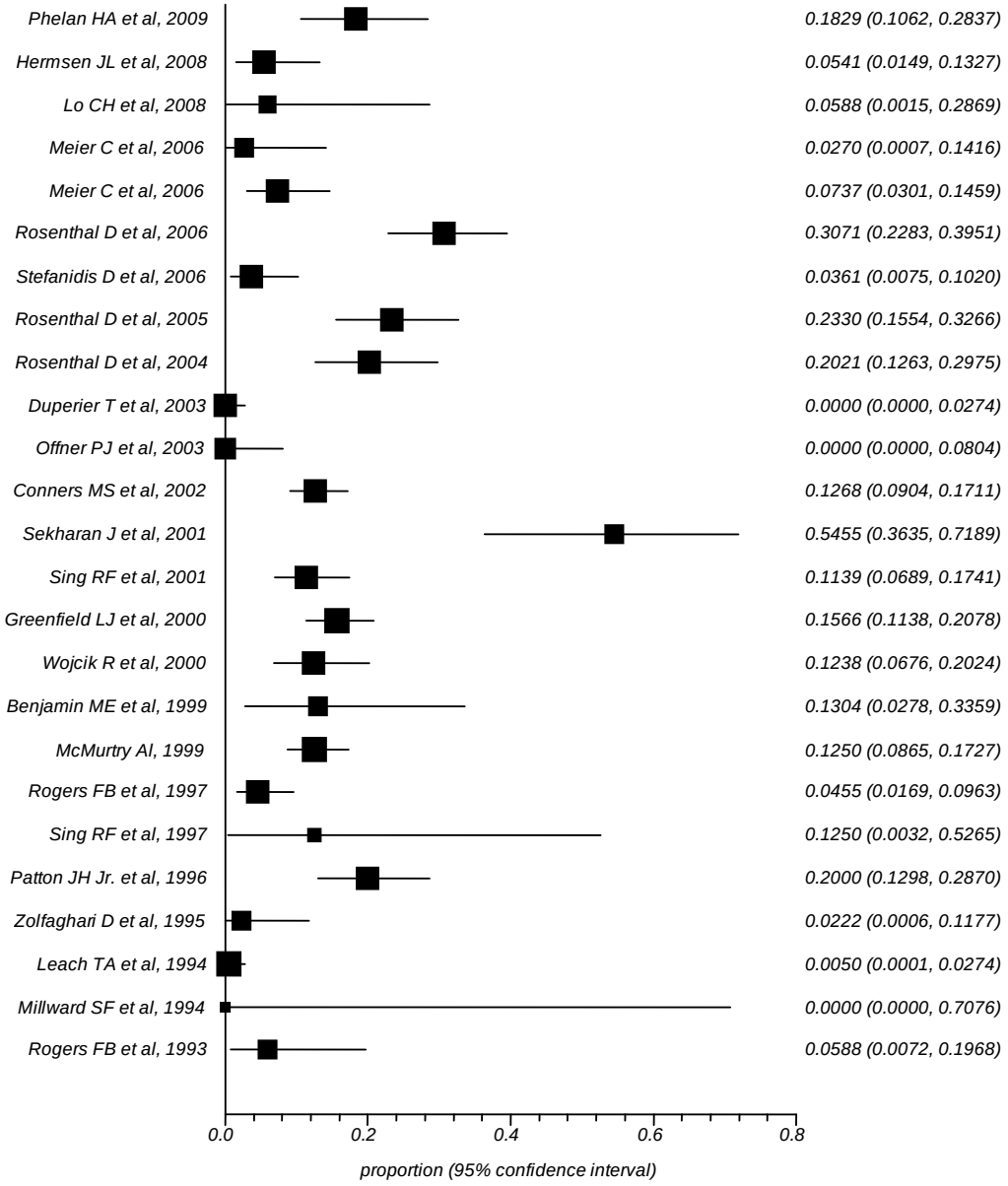
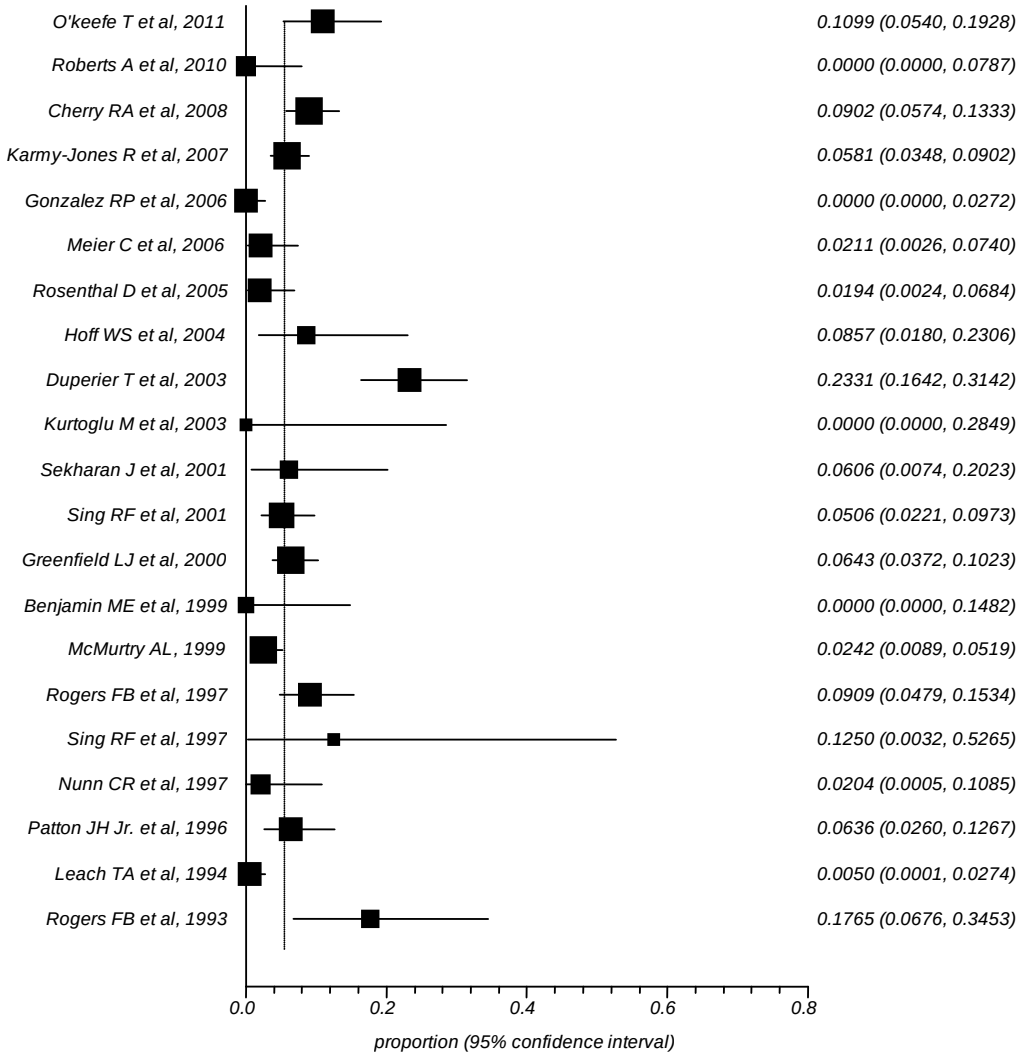


Figure 10. Proportion of DVT in uncontrolled studies of IVC filters



KQ2a: What is the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in hospitalized patients with traumatic brain injury?

Key Findings and Evidence Grades

- The strength of evidence was insufficient to comment on the effectiveness of prophylaxis with enoxaparin, dalteparin, UFH or mechnaical strategies in reducing the rates of venous thromboembolic events, DVT, PE, fatal PE, major and minor bleeding.
- The strength of evidence is low to support that UFH reduced the rates of total mortality compared to no pharmacoprophylaxis in hospitalized patients with traumatic brain injury

Study Characteristics

Six studies evaluated the effectiveness of pharmacological and mechanical strategies to prevent VTE in hospitalized patients with TBI.[120-125] Most studies took place in North America.[120 121 123-125] Only one study reported the source of funding.[125]

Of the six studies, one was a RCT[122], four were retrospective cohort studies,[120 121 123 124] and one was a prospective cohort study.[125] Most studies recruited from the year 2000 onwards.[120-124]

The retrospective cohort studies described patients admitted to trauma centers,[120 121 123 124] and most were level 1 trauma centers. The prospective cohort study and the trial enrolled patients admitted to intensive care units.[122 125] One study included patients with a Glascow Coma Scale score less than 8[125] and another included TBI patients with a head abbreviated injury score score greater than 1[124]. One cohort excluded patients with contraindications to anticoagulants[120] and the trial excluded patients with history of thromboembolism, liver disease, an INR greater than 1.5, or platelets less than 100,000/uL.[122] One cohort excluded patients requiring craniotomy.[124] (Table 13)

Participant Characteristics

The number of participants in the included studies ranged from 32 to 812. Four studies reported the mean age of the participants which ranged from 36 to 47 years[121 123-125]. The majority of included participants were men (range 69 to 78 percent, respectively).[120 121 124 125] No studies reported the race of participants. All the studies reported the Injury Severity Score of participants on admission; the mean ranged from 16.6 to 33.8.[120-125] Two studies reported the mean Glasgow Coma Scale score of participants; it ranged from 6.8 to 8.[120 125] (Table 13)

Intervention Characteristics

Pharmacological Agent versus Pharmacological Agent

One retrospective cohort study compared the effectiveness of different LMWHs (enoxaparin versus dalteparin) in preventing VTE in brain injury patients.[120] Another compared the effectiveness of enoxaparin versus UFH.[121] The two studies used the following doses:

enoxaparin at 30 mg every 12 hours, dalteparin at 5,000 U daily, or UFH at 5,000 units three times per day. (Table 13)

Pharmacological Agent versus Sequential Compression Devices

The RCT compared the effectiveness of enoxaparin 40 mg daily versus sequential compression devices in preventing VTE events in TBI patients.[122] (Table 13)

Pharmacological Agent versus Control (No Pharmacoprophylaxis)

Two retrospective cohort studies conducted in patients with brain injury evaluated the effectiveness of enoxaparin or UFH in preventing VTE events as compared to no treatment.[123 124] The dosing schedules were 30 mg of enoxaparin or 5,000 IU of UFH administered subcutaneously every 12 hours. Both studies used sequential compression devices concurrently. (Table 13)

Mechanical Agent versus Control

One prospective cohort study of TBI patients compared the effectiveness of sequential compression devices compared to a control group in preventing VTE.[125] (Table 13)

Ascertainment

Most studies did not routinely screen for VTE.[120-122] One study performed weekly surveillance using duplex ultrasound examination or technetium venoscans and ventilation/perfusion scans.[125] One study only routinely screened patients at high risk for VTE.[124]

Outcomes

Venous Thromboembolism

Pharmacological Agent versus Intermittent Pneumatic Compression

The single RCT demonstrated lower rates of DVT in the enoxaparin treated group as compared to the group receiving intermittent pneumatic compression (5 vs. 6.6 percent, respectively, p=0.07), whereas the rates of PE were higher in the enoxaparin group compared to the group receiving intermittent pneumatic compression (6.6 vs. 3.3 percent, respectively, p=0.04). [122](Table 14)

Pharmacological Agent versus Intermittent Pneumatic Compression

The single RCT demonstrated lower rates of DVT in the enoxaparin treated group as compared to the group receiving intermittent pneumatic compression (5 vs. 6.6 percent, respectively, p=0.07), whereas the rates of PE were higher in the enoxaparin group compared to the group receiving intermittent pneumatic compression (6.6 vs. 3.3 percent, respectively, p=0.04). [122](Table 14)

Any Pharmacologic Agent versus Control (No Pharmacoprophylaxis)

One retrospective cohort study showed higher rates of VTE in the control group as opposed to UFH treatment group (3 vs. 1 percent, respectively, p=0.019), [124] while another cohort study

demonstrated the opposite effect; the rates of VTE were higher in enoxaparin treatment group as opposed to no pharmacoprophylaxis.(3.9 vs. 2.2 percent, respectively, p=0.29).[123]

Another study showed that rates of DVT were less for the enoxaparin and UFH treated patients compared to the control group (1 percent versus 1 percent versus 2 percent, respectively, p value not reported).[121] But the same study showed that rates of PE were double in the UFH group compared to control (4 vs. 2 percent, respectively, p value not reported). (Table 14)

Intermittent Pneumatic Compression Device versus Control (No Prophylaxis)

One cohort study showed similar rates of total VTE in the pneumatic compression and control groups (28.6 vs. 22.2 percent, respectively, p= 0.7) but increased rates of PE with IPC as opposed to control (28.6 vs. 11.11 percent, respectively, p value not reported).[125](Table 14)

Fatal Pulmonary Embolism

Enoxaparin versus Intermittent Pneumatic Compression Devices

The RCT showed increased rates of fatal PE in enoxaparin treated patients as opposed to patients treated with pneumatic compression (6.6 vs. 3.3 percent, respectively, p=0.04). [122](Table 14)

Total Mortality

Enoxaparin versus Unfractionated Heparin

One study showed that total mortality was lower in the enoxaparin group as opposed to the unfractionated heparin group (5 percent versus 15.8, respectively, p<0.05).[121](Table 14)

Enoxaparin versus Intermittent Pneumatic Compression

Total mortality was similar in both enoxaparin and pneumatic compression group (13.3 vs. 11.6 percent, respectively, p=0.08).[122](Table 14)

Pharmacological Agent versus Control (No Pharmacoprophylaxis)

One study showed lower rate of mortality in the UFH group relative to the control group (0.75 percent versus 3.6 percent, respectively),[124] and another study showed lower rates of mortality in the enoxaparin and heparin groups relative to the control group (5 percent versus 16 percent versus 47 percent, respectively, p<0.05).[121](Table 14)

Adverse Outcomes

Bleeding Outcomes

Enoxaparin versus Unfractionated Heparin

One cohort study showed that rates of ICH were higher in heparin treated patients in comparison to enoxaparin treated patients.[121] The proportions of patients with of progression of intracranial hemorrhage in the unfractionated heparin and enoxaparin groups were 20 and 13 percent, respectively. The rates of progression of intracranial hemorrhage after initiation of chemoprophylaxis in the two groups were 12 and 5 percent, respectively, (p<0.05). Similarly, the

rates of intracranial hemorrhage that required craniectomy in the two groups were 1 and 0 percent, respectively, ($p<0.05$). Another study reported the rates of intracranial bleeding in patients treated with enoxaparin and dalteparin (0 vs. 0.08 percent, respectively).[120](Table 14)

Pharmacological Agent versus Sequential Compression Devices

One RCT showed that exacerbation of epidural hematoma occurred in 1.6 percent, respectively, in both enoxaparin and intermittent sequential compression groups.[122] The rates of hematuria, injection site hematoma and bleeding from tracheostomy site were 8.3, 3.3, and 1.6 percent, respectively, in the enoxaparin group. The rates for the same in the intermittent sequential compression group were 6.6, 0, and 0 percent, respectively. (Table 14)

Pharmacological Agent versus Control (No Pharmacoprophylaxis)

A cohort study showed that rates of progression of intracranial hemorrhage were lower in the enoxaparin and unfractionated heparin group relative to the control group (13 versus 20 versus 25 percent, respectively).[121](Table 14)

Mean Hospital Stay

Pharmacological Agent versus Control

One cohort study showed that the median hospital stay was longer in the enoxaparin and unfractionated heparin groups than in the control group. (17 versus 4 versus 19 days, respectively, $p<0.05$).[121]

Mean Intensive Care Unit stay

Pharmacological Agent versus Control

The same cohort study also showed that median ICU stay was longer in the enoxaparin and unfractionated heparin groups relative to the control group (11 versus 2 versus 8 days, respectively, $p<0.05$). [121]

Pharmacological Agent versus Sequential Compression Devices

In one RCT the mean intensive care unit stay was similar in both the enoxaparin and intermittent pneumatic compression groups (10.7 versus 10.3 days, respectively, p value not reported). [122]

Mechanical Agent versus Control

In one study the mean ICU stay was 21.2 days in the sequential compression group and 18.4 days in the control group. ($p = 0.5$).[125]

Infections

Pharmacological Agent versus SCDs

The RCT evaluated the rates of infections.[122] The enoxaparin treated patients and patients treated with intermittent pneumatic compression had similar rates of infection (23.3 vs. 20 percent, respectively, $P = 0.07$)

Risk of bias

We rated only one study as having only moderate risk of bias.[120] We rated the remaining studies as high risk of bias.[121-127]. The RCT had biases arising from improper randomization and blinding.[122] The cohort studies generally had incomplete description of the important confounders and lack of adjustment for differences between groups. They also had incomplete accounting of losses to followup. All of these are important confounders and threaten the internal validity of these studies.

Strength of Evidence

Most of the included studies that assessed the comparative effectiveness of pharmacological and mechanical prophylaxis in hospitalized patients with traumatic brain injury were at high risk of bias. We rated the strength of evidence as low to support that UFH reduced the rates of total mortality compared to no pharmacoprophylaxis in hospitalized patients with traumatic brain injury. We based this rating on consistent, direct and precise evidence from two studies. [121,124] The remainder of comparisons on the outcomes of PE, DVT, VTE and exacerbation of intracranial hemorrhage for were all rated as insufficient. We based this rating on either inconsistencies in the body of evidence, or our inability to assess consistency (consistency unknown) in a single study. (Table 15)

Applicability

The participants that these studies recruited were typical of participants admitted to other trauma centers and hence findings are generalizable. We did not have details to assess the applicability of this evidence to older subgroups and other racial groups since the studies inconsistently reported race.

Table13: Study, Participant and Intervention characteristics for KQ2a

Author, year	Study design	Intervention (Dose)	N	Mean Age Years	% Male	Mean ISS	Mean GCS	Mean AIS head
Dudley,R.R., 2010[120]	Retrospective cohort	Enoxaparin (30mg, sc, bd)	128	47.4	77.3	31.1	8	NR
		Dalteparin (5000 U, sc, od)	159	45.9	72.3	35	6.9	NR
Minshall, C.T., 2011[121]	Retrospective cohort	Enoxaparin (30mg, sc, bd)	158	41.2	75	29	NR	3.8
		UFH(5000 U,sc, tid)	171	42	78	33.8	NR	4.1
		Usual care/ No Intervention	57	38.3	69	30.9	NR	4.3
Kurtoglu,M., 2004[122]	Randomized controlled trial	Enoxaparin (40 mg, od)	60	NR	NR	19.5	NR	NR
		IPC	60	NR	NR	18.3	NR	NR
Salottolo, K., 2010[123]	Retrospective cohort	Enoxaparin (30mg, sc, bd)	255	48	NR	NR	NR	NR
		no prophylaxis	225	59.5	NR	NR	NR	NR
Scudday,T., 2010[124]	Retrospective cohort	UFH (NR)	402	45.2	69	23.8	NR	3.4
		no prophylaxis	410	51.5	69	16.6	NR	3.4
Gersin,K., 1992[125]	Prospective cohort	Scd	14	38.3	71.4	30.5	7.1	NR
		no intervention	18	36.1	77.8	32.1	6.8	NR

UFH = Unfractionated heparin; IPC = Intermittent pneumatic compression devices; SCD = Sequential compression devices; NR = Not reported; BMI = Body mass index; ISS = Injury severity score; GCS = Glasgow coma scale; AIS = Abbreviated injury scale; sc = subcutaneous; bd = twice daily; od= once daily;

Table 14: Venous thromboembolic, mortality and major bleeding outcomes in TBI patients receiving pharmacological/mechanical prophylaxis

Refid	Intervention	Surveillance for VTE	N patients	% Total VTE	% Total DVT	% Total PE	% Mortality	% Progression of ICH
Dudley,R.R., 2010[120]	Enoxaparin	No	128	7*	NR	NR	NR	0.08
	Dalteparin	No	159	7.5*	NR	0.6	NR	0
Minshall, C.T., 2011[121]	Enoxaparin	No	158	NR	1	0**	5	5**
	UFH	No	171	NR	1	4**	15.8	12**
	No Intervention	No	57	NR	2	2	47	NR
Kurtoglu,M., 2004[122]	Enoxaparin	No	60	NR	5*	6.6**†	13.3	1.6
	IPC	No	60	NR	6.6*	3.3**†	11.6	1.6
Salottolo, K., 2010[123]	Enoxaparin	No	225	3.92*	NR	NR	NR	NR
	no prophylaxis	No	225	2.2*	NR	NR	NR	8.44
Scudday,T., 2010[124]	UFH	no	402	1**	NR	NR	0.75	NR
	no prophylaxis	Yes	410	3**	NR	NR	3.66	NR
Gersin.K., 1992[125]	Scd	Yes	14	28.6*	0	28.6	NR	NR
	no intervention	Yes	18	22.2*	11.1	11.11	NR	NR

* p value not significant; ** p value significant; † - Of the total PE, 6.6% in the enoxaparin arm and 3.3% in the IPC arm were fatal.

UFH = Unfractionated heparin; IPC = Intermittent pneumatic compression devices; USG = Ultrasonogram; V/Q= ventilation- perfusion; VTE= Venous Thromboembolism; DVT= Deep Vein Thrombosis; PE= Pulmonary Embolism; TBI = Traumatic brain injury; ICH= Intracranial hemorrhage

Table 15: Body of evidence for Pharmacological Prophylaxis for Patients with Traumatic Brain Injury

Author, Year	Outcomes	Patients (N)	Risk of bias	Directness	Precision	Consistency	Magnitude of effect	Strength of evidence
Enoxaparin vs Dalteparin								
Dudley,R.R., 2010[120]	Total VTE	287	Moderate	Direct	Imprecise	Unknown	7% vs 7.5%;p=0.868	**Insufficient evidence to comment on effectiveness of Enoxaparin vs Dalteparin in reducing Total VTE in TBI patients**
Dudley,R.R., 2010[120]	Progression of ICH	287	Moderate	Direct	Unknown	Unknown	0.08% vs 0%*	**Insufficient evidence to comment on effectiveness of Enoxaparin vs Dalteparin in reducing progression of ICH in TBI patients**
Enoxaparin vs. UFH								
Minshall, C.T., 2011[121]	Total DVT	329	High	Direct	Unknown	Unknown	1% vs 1%*	**Insufficient evidence to comment on effectiveness of Enoxaparin vs UFH in reducing Total DVT in TBI patients**
Minshall, C.T., 2011[121]	Total PE	329	High	Direct	Precise	Unknown	0% vs 4% ; p<0.05	**Insufficient evidence to comment on effectiveness of Enoxaparin vs UFH in reducing Total PE in TBI patients**
Minshall, C.T., 2011[121]	Total mortality	329	High	Direct	Precise	Unknown	5% vs 15.8%;p<0.05	**Insufficient evidence to comment on effectiveness of Enoxaparin vs UFH in reducing Total mortality in TBI patients**
Minshall, C.T., 2011[121]	Progression of ICH	329	High	Direct	Precise	Unknown	5% vs 12%; p<0.05	**Insufficient evidence to comment on effectiveness of Enoxaparin vs UFH in reducing progression of ICH in TBI patients**
Enoxaparin vs. Control/IPC								
Salottolo, K., 2010[123]	Total VTE	480	High	Direct	Imprecise	Unknown	3.9% vs 2.2%;p=0.29	**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Total VTE in TBI patients**

Table 15: Body of evidence for Pharmacological Prophylaxis for Patients with Traumatic Brain Injury continued continued

Author, Year	Outcomes	Patients (N)	Risk of bias	Directness	Precision	Consistency	Magnitude of effect	Strength of evidence
	Total DVT	**335**	**High**	**Direct**	**Imprecise**	**Consistent**		**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Total DVT in TBI patients**
Minshall, C.T., 2011[121]	Total DVT	215	High	Direct	Imprecise	Consistent	1% vs 2% *; P= 0.46	**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Total DVT in TBI patients**
Kurtoglu,M., 2004[122]		120	High	Direct	Imprecise		5% vs 6.6%; p=0.07	
	Total PE	335	**High**	**Direct**	**Imprecise**	**Inconsistent**		**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Total PE in TBI patients**
Minshall, C.T., 2011[121]	Total PE	215	High	Direct	Imprecise	Inconsistent	0% vs 2%: #P=0.46	**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Total PE in TBI patients**
Kurtoglu,M., 2004[122]		120	High	Direct	Precise		6.6% vs 3.3%:p=0.04	
Kurtoglu,M., 2004[122]*	Fatal PE	120	High	Direct	Precise	Unknown	6.6% vs 3.3%;p=0.04	**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Fatal PE in TBI patients**
	Total mortality	335	High	Direct	Imprecise	Inconsistent		**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Total mortality in TBI patients**
Kurtoglu,M., 2004[122]*	Total mortality	120	High	Direct	Imprecise	Inconsistent	13.3% vs 11.6%;p=0.08	**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Total mortality in TBI patients**

Table 15: Body of evidence for Pharmacological Prophylaxis for Patients with Traumatic Brain Injury continued continued

Author, Year	Outcomes	Patients (N)	Risk of bias	Directness	Precision	Consistency	Magnitude of effect	Strength of evidence
Kurtoglu,M., 2004[122]	Exacerbation of epidural hematoma	120	High	Direct	Unknown	Unknown	1.6% vs 1.6%*	**Insufficient evidence to comment on effectiveness of Enoxaparin vs IPC/control in reducing Exacerbation of epidural hematoma in TBI patients**
UFH vs. control								
Scudday,T., 2010[124]	Total VTE	812	High	Direct	Precise	Unknown	1% vs 3%;p=0.019	**Insufficient evidence to comment on effectiveness of UFH vs control in reducing Total VTE in TBI patients**
Minshall, C.T., 2011[121]	Total DVT	228	High	Direct	Unknown	Unknown	1% vs 2% *	**Insufficient evidence to comment on effectiveness of UFH vs control in reducing Total DVT in TBI patients**
Minshall, C.T., 2011[121]	Total PE	228	High	Direct	Unknown	Unknown	4% vs 2%*	**Insufficient evidence to comment on effectiveness of UFH vs control in reducing Total PE in TBI patients**
	Total mortality	**1040**	**High**	**Direct**	**Precise**	**Consistent**		**Low grade evidence to suggest that UFH reduces mortality in TBI compared to controls**
Scudday,T., 2010[124]	Total mortality	812	High	Direct	Precise	Consistent	0.75% vs 3.66%; P=0.007 #	**Low grade evidence to suggest that UFH reduces mortality in TBI compared to controls**
Minshall, C.T., 2011[121]		228	High	Direct	Precise		15.8% vs 47%: p<0.05	
IPC vs. control								
Gersin.K., 1992[125]	Total VTE	32	High	Direct	Imprecise	Unknown	28.6% vs 22.2%: p=0.7	**Insufficient evidence to comment on effectiveness of IPC vs control in reducing Total VTE in TBI patients**
Gersin.K., 1992[125]	Total PE	32	High	Direct	Unknown	Unknown	28.6% vs 11.1%*	**Insufficient evidence to comment on effectiveness of IPC vs control in reducing Total PE in TBI patients**

DVT= deep venous thrombosis, ICH=intracranial hemorrhage, IPC=intermittent pneumatic compression, PE= pulmonary embolism, SCD=sequential compression device, UFH=unfractionated heparin, VTE=venous thromboembolism, * Randomized controlled trial, * P-values or tests of statistical significance not reported, # Two sided P-estimated using Fishers exact test.

KQ 2b: What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent venous thromboembolism in hospitalized patients with traumatic brain injury?

Key Findings and Evidence Grades

The strength of evidence was insufficient to comment on the effectiveness of early (< 72 hours) versus late (> 72 hours) pharmacoprophylaxis with enoxaparin, UFH or any heparin on the outcomes of venous thromboembolic events, DVT, PE, fatal PE, total mortality, major and minor bleeding.

Study characteristics

Five retrospective cohort studies assessed the optimal timing of initiation of pharmacologic prophylaxis to prevent venous thromboembolism in patients with traumatic brain injury.[49 123 126-128] All studies were conducted in North America. None of the studies reported their sources of funding. All studies had recruitment dates from the year 2000 onwards. All studies included patients over 18 years of age with traumatic brain injury admitted to trauma centers. One study excluded pregnant women and patients with histories of venous thromboembolism.[49] Two studies excluded patients with low platelet counts[49 129] and one study excluded patients with penetrating head injuries.[127] (Table 16)

Participant characteristics

The numbers of participants in these studies ranged from 64 to 669. The mean age of participants was reported in three studies and ranged from 37to 44 years.[49 126 128] Only two studies reported on sex and the majority of participants were men.[49 126]. The mean Injury Severity Score was reported in two studies at 28.6[49] and 33.2 respectively.[128] One study reported a mean Glascow Coma Scale score of 9.25.[128](Table 16)

Intervention Characteristics

All five studies evaluated the effectiveness of pharmacoprophylaxis, initiated at different times, to prevent venous thromboembolic events in hospitalized patients with traumatic brain injury. [49 123 126-128] In two studies, patients were treated with only enoxaparin[49 123] and in one only with UFH. [128] In the remaining two studies patients were treated with either enoxaparin or UFH; the percentages of each are unknown and this treatment has been termed “any heparin.” Four studies reported the effectiveness of pharmacoprophylaxis in preventing venous thromboembolic events when initiated before 72 hours of hospitalization (early) compared to after 72 hours of hospitalization (late).[49 123 127 128] Another retrospective cohort study with three arms evaluated the effectiveness of initiating pharmacologic prophylaxis before 24 hours, 24 to 48 hours, and after more than 48 hours of hospitalization.[126] In three studies, sequential compression devices were placed concurrently on all patients;[123 126 127] in one, pneumatic compression devices were used.[128] The doses of enoxaparin and UFH used in all studies were 30 mg every 12 hours and 5000 IU daily, respectively. (Table 16)

Ascertainment of Venous Thromboembolism

One study did weekly ultrasound examination in all patients,[128] while in another only high risk patients were screened routinely with weekly duplex ultrasound examinations.[127] Three studies did not screen patients for venous thromboembolic events.[49 123 126]

Outcomes

Total venous thromboembolic events

Early (<72 hrs) vs late (>72 hrs) pharmacoprophylaxis

A single study showed that rate of all venous thromboembolism was greater in patients who were started on enoxaparin before than 72 hrs of hospitalization (early) compared to patients in whom enoxaparin was started after 72 hours (5.56 percent versus 2.72 percent, OR 2.10, p value=0.26).[123] (Table 17)

Deep vein thrombosis

Early (<72 hrs) vs late (72 hrs) pharmacoprophylaxis

In a different study, two out of 47 patients in an early UFH prophylaxis (<72 hours) group developed DVT compared to one out of 17 patients a late UFH prophylaxis (>72 hours) group.[128] The difference was not statistically significant (p=1.00) The effectiveness of prophylaxis with any heparin initiated within 72 hours of admission as compared later than 72 hours was reported in another cohort study, where the percentage of patients developing DVTs in the two groups were 10.4 percent and 14.6 percent respectively (p value not reported).[127] In one cohort study, of the 268 patients receiving enoxaparin within 72 hours of hospitalization, one patient developed upper extremity proximal DVT and three developed lower extremity DVT.[49] Of the 401 patients beginning prophylaxis after 72 hours, five patients developed upper extremity DVT and nine patients developed DVT of the lower extremity. The difference in rates of upper and lower extremity deep venous thromboses between the two groups was not statistically significant (p=0.24 and 0.28 respectively) (Table 17)

Other timings of initiation of prophylaxis

Another cohort study assessed the DVT risk per 100 patients in the 3 arms. The proportion of DVT in patients with any heparin initiated before 24 hours, 24 to 48 hours and after 48 hours were 3.6/100 patients, 4.5/100 patients, 15.4/100 patients respectively. The p values are not reported.[126](Table 17)

Pulmonary embolism

Early (<72 hrs) vs late (72 hrs) pharmacoprophylaxis

In one cohort, 4.3 percent of patients receiving UFH as prophylaxis within 72 hours of hospitalization developed PE as compared to none in the group that received the same prophylaxis after 72 hrs of admission (p=0.96).[128] Similarly, in another cohort, 3.5% of patients receiving any heparin within 72 hours of hospital admission developed PEs while no PEs occurred in the group that received prophylaxis after 72 hours (p value not reported).[127] In a third

cohort, there was a higher rate of pulmonary embolism in the group receiving enoxaparin as prophylaxis within 72 hours of hospital admission compared to after 72 hours (1.5 percent versus 2.2 percent, respectively, p=0.49).[49] (Table 17)

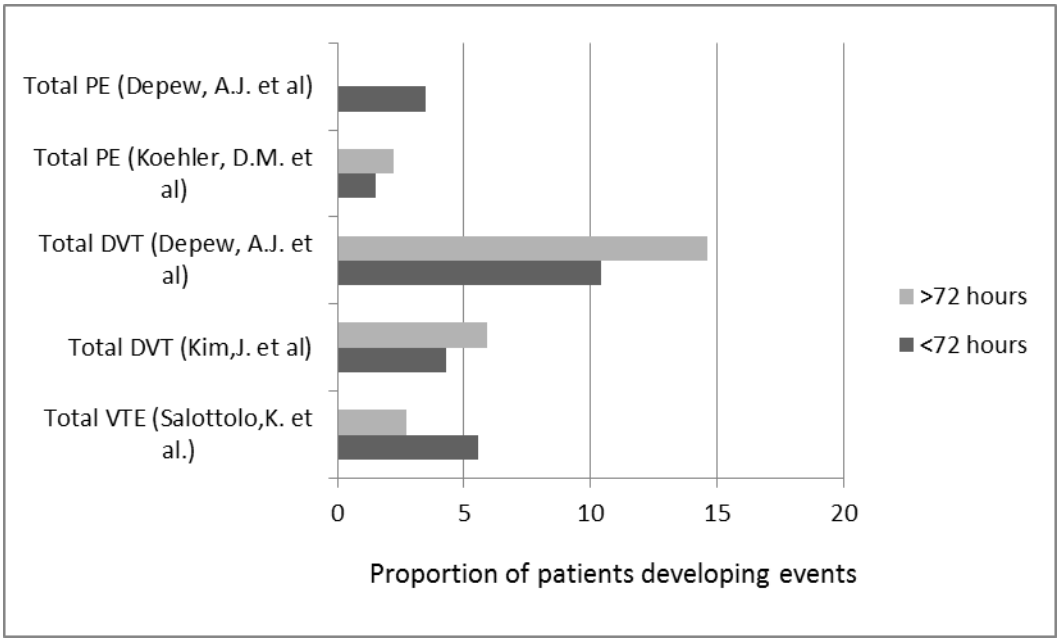


Fig 11: Studies reporting percent of patients developing thromboembolic outcomes in early (<72 hours) and late prophylaxis groups (>72 hours)

Other Outcomes

Fatal PE

Of the 401 patients in one study receiving prophylaxis with enoxaparin later than 72 hrs after hospitalization, 1 patient died due to pulmonary embolism.[49] There were no fatal pulmonary embolic events in the group receiving the same prophylaxis within 72 hours (p value not reported).

Total mortality

One cohort reported four deaths in a group of 47 patients receiving UFH within 72 hours of admission and one in the group of 17 patients receiving prophylaxis after 72 hours (p=1.0).[128] Another cohort reported that there were no deaths due to bleeding in either the early and late prophylaxis groups.[49]

Major bleeding

The rates of radiographic progression of intracranial hemorrhage were reported in three studies[49 123 127]. In one study, the rates were similar in patients treated with enoxaparin within 72 hours of hospital admission and after 72 hours (1.46 percent versus 1.54 percent, respectively (p=0.912).[49] Similar findings were observed in another study (3.5 percent versus 3.8 percent, p value not reported).[127] Only one study showed that rates of progression of intracranial hemorrhage were

lower in the group receiving enoxaparin prophylaxis earlier rather than later (6.48 percent versus 14.3 percent, p=0.92). [123] (Table 17)

Minor bleeding

Two studies reported rates of minor bleeding events. According to one study, the rates of hematuria in patients treated with UFH within 72 hours of hospital admission and after 72 hours were six percent (p=1.00).[128] Another study reported that none of the patients developed any non-cranial bleeding complications from enoxaparin prophylaxis.[49] (Table 17)

Risk of bias

All five included studies were at high risk of bias. The studies had biases arising from incomplete description of principal confounders and their adjustment and improper accounting of losses to follow-up.

Strength of evidence

All of the included studies that assessed the comparative effectiveness of early versus late pharmacoprophylaxis in hospitalized patients with traumatic brain injury were at high risk of bias. We rated the strength of evidence as insufficient for all comparisons and outcomes. We based this rating on either inconsistencies in the body of evidence, or our inability to assess consistency (consistency unknown) in a single study. (Table 18)

Applicability

The studies were generally representative of patients with traumatic brain injury in the United States. Gender was inconsistently reported thus we could not assess the applicability of these findings to females. Some studies excluded patients with previous VTE as well as those at higher risk of bleeding such as those with low platelet counts limiting generalizability to these high risk subgroups.

Table16: Study, Participants and Intervention characteristics for KQ2b

Author, year	Study design	Intervention (Dose)	Timing of first dose	N patients	Mean Age Years	% Male	Mean ISS/GCS/ AIS head
Koehler D.M., 2011,[49]	Retrospective cohort	Enoxaparin (30mg, sc, bd)	<=72 hrs	268	39.8	69	27.8/NR/4
		Enoxaparin (30mg, sc, bd)	>72 hrs	401	40.2	75	29.4/NR/NR
Kim J., 2002,[128]	Retrospective cohort	UFH (5000 U, sc, bd)	<72 hrs	47	37.7	NR	30.7/9.1/NR
		UFH (5000 U, sc, bd)	>72 hrs	17	44	NR	35.7/9.4/NR
Salotto K., 2011,[123]	Retrospective cohort	Enoxaparin (30mg)	<=72 hrs	108	NR	NR	NR
		Enoxaparin (30mg)	>72 hrs	147	NR	NR	NR
Reiff D.A., 2009,[126]	Retrospective cohort	Any heparin	<24 hrs	84	37.2	71.4	NR
		Any heparin (NR)	24 to <48 hrs	177	39.8	62.7	NR
		Any heparin (NR)	>48 hrs	293	43	63.8	NR
Depew A.J., 2008,[127]	Retrospective cohort	Any heparin (30 mg/5000 U, sc, bd)	<72 hrs	29	NR	NR	NR
		Any heparin (30 mg/5000 U, sc, bd)	>72 hrs	41	NR	NR	NR

UFH = Unfractionated heparin; NR = Not reported; BMI = Body mass index; ISS = Injury severity score; GCS = Glasgow coma scale; AIS = Abbreviated injury scale; sc = subcutaneous; bd = twice daily

Table17: Venous thromboembolic, mortality and major bleeding outcomes in TBI patients receiving early and late pharmacological prophylaxis

Author, year	Intervention	Surveillance for VTE	N patients	% Total DVT	% Total PE	% Mortality	% Progression of ICH
Koehler D.M., 2011,[49]	Enoxaparin < 72hrs	No	268	NR	1.5*	NR	1.46*
	Enoxaparin >72 hrs	No	401	NR	2.2*	NR	1.54*
Kim J., 2002,[128]	UFH < 72 hrs	Yes	47	4.3*	4.3*	8.5*	NR
	UFH >72 hrs	Yes	17	5.9*	0*	5.9*	NR
Salotto K., 2011,[123]	Enoxaparin < 72hrs	No	108	NR	NR	NR	6.48*
	Enoxaparin >72 hrs	No	147	NR	NR	NR	14.29*
Reiff D.A., 2009,[126]	Any heparin <24 hrs	No	84	NR	NR	NR	NR
	Any heparin 24-48 hrs	No	177	NR	NR	NR	NR
	Any heparin >48 hrs	No	293	NR	NR	NR	NR
Depew A.J., 2008,[127]	Any heparin <72 hrs	No	29	10.4	3.5	NR	3.5
	Any heparin >72 hrs	no	41	14.6	0	NR	3.8

* p value not significant; UFH = Unfractionated heparin; VTE= Venous Thromboembolism; DVT= Deep Vein Thrombosis; PE= Pulmonary Embolism; TBI = Traumatic brain injury; ICH= Intracranial hemorrhage; NR = Not reported

Table 18: Body of Evidence for Timing of Pharmacological Prophylaxis for Patients with Traumatic Brain Injury

Author, year	Outcomes	Risk of bias	Directness	Precision	Consistency	Magnitude of effect
Enoxaparin <72 hrs vs >72 hrs						
	VTE	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs vs >72 hrs in reducing VTE in TBI patients**
Salotto K., 2011[123]		High	Direct	Imprecise	Unknown	5.6% vs 2.7%;p=0.26
	Proximal DVT	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs vs >72 hrs in reducing proximal DVT in TBI patients**
Koehler D.M., 2011[49]		High	Direct	Imprecise	Unknown	1.5% vs 3.5%;p= 0.12
	PE	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs vs >72 hrs in reducing PE in TBI patients**
Koehler D.M., 2011[49]		High	Direct	Imprecise	Unknown	1.5% vs 2.2%; p=0.49
	Fatal PE	**High**	**Direct**	**Unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs vs >72 hrs in reducing fatal PE in TBI patients**
Koehler D.M., 2011[49]		High	Direct	Unknown	Unknown	0% vs 0.3% *
	Mortality due to bleeding	**High**	**Direct**	**Unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs vs >72 hrs in reducing mortality due to bleeding in TBI patients**
Koehler D.M., 2011[49]		High	Direct	Unknown	Unknown	0% vs 0% *
	Progression of ICH	**High**	**Direct**	**Imprecise**	**Inconsistent**	**Insufficient evidence to comment on effectiveness of Enoxaparin started <72 hrs vs >72 hrs in reducing progression of ICH in TBI patients**
Koehler D.M., 2011[49]		High	Direct	Imprecise	Inconsistent	1.5% vs 1.5%; p=0.912
Salotto K.,2011[123]		High	Direct	Imprecise		6.5% vs 14.3%; p=0.92
UFH <72 hrs vs >72 hrs						
	DVT	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of UFH started <72 hrs vs >72 hrs in reducing DVT in TBI patients**

Table 18: Body of Evidence for Timing of Pharmacological Prophylaxis for Patients with Traumatic Brain Injury continued

Author, year	Outcomes	Risk of bias	Directness	Precision	Consistency	Magnitude of effect
Kim J., 2002[128]		High	Direct	Imprecise	Unknown	4.3% vs 5.9%;p=1.00
	PE	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of UFH started <72 hrs vs >72 hrs in reducing PE in TBI patients**
Kim J., 2002[128]		High	Direct	Imprecise	Unknown	4.3% vs 0%; p=0.96
	Total mortality	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of UFH started <72 hrs vs >72 hrs in reducing total mortality in TBI patients**
Kim J., 2002[128]		High	Direct	Imprecise	Unknown	8.5% vs 5.9% ; p=1.00
Any heparin <72 hrs vs >72 hrs						
	DVT	**High**	**Direct**	**unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of any heparin started <72 hrs vs >72 hrs in reducing DVT in TBI patients**
Depew A.J., 2008[127]		High	Direct	Unknown	Unknown	10.4% vs 14.6% *
	PE	**High**	**Direct**	**unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of any heparin started <72 hrs vs >72 hrs in reducing PE in TBI patients**
Depew A.J.,2008[127]		High	Direct	Unknown	Unknown	3.5% vs 0% *

DVT= Deep venous thrombosis, ICH = Intracranial hemorrhage, PE=Pulmonary Embolism, UFH=Unfractionated heparin,
#There were no randomized controlled trials
* Tests of statistical significance between groups or P values unavailable.

Key Question 3. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent venous thromboembolism in hospitalized patients with burns?

Key Points and Evidence Grades

The strength of evidence was insufficient to comment on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns.

Study Characteristics

We identified only one small cohort study of 20 patients that reported on PE prophylaxis with IVC filters for patients with burns.[37] This was a single center study in an academic medical center's burn unit conducted over a period of 2 years. The study followup was up to 1 year after hospital discharge.

Participant Characteristics

The investigators placed IVC filters in 20 patients with acute burns at high risk for PE. These risk factors included prolonged immobilization due to ventilator dependence, old age, size of burn, site of burns, previous history of VTE, and contraindications against use of anticoagulants. The investigators placed five filters due to preexisting VTE and the remaining 15 filters for PE prophylaxis. The study required Doppler imaging prior to filter placement to exclude DVT. Among the 15 patients who underwent insertion of filters strictly for prophylaxis there were nine men and six women. Of these, the mean age was 38.9 years, with a range of 22 to 69 years. Burn size ranged from 15 to 79 percent total body surface area (mean, 37.8 percent).

Intervention Characteristics

Vascular surgeons placed Venatech titanium birds nest filters; 18 were placed with femoral access and two with right jugular percutaneous access. Filter insertions happened from 1 to 75 days after the burn incident. The patients received no other VTE preventative therapies.

Outcomes

Deep Vein Thrombosis/Pulmonary Embolism

There were no PEs in any patient after filter insertion.

Mortality

Data on mortality among the 15 who received filters for prophylaxis was unavailable. However, nine of the 20 enrolled patients died.

Adverse Events

The study reported no significant bleeding, IVC thromboses, or filter related complications.

Risk of Bias

The study received a high risk of bias rating due to methodologic limitations in design and reporting, sample size, and the absence of a control group to allow any meaningful conclusions.

Strength of Evidence

The strength of evidence was insufficient to comment on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns. We based this rating on the high risk of bias and unknown consistency from a single study.

Applicability

This was a single center study at an academic burn center and the participants were similar to those at other academic burn centers. The study did not report racial composition of participants. However the overall small sample size of the study limits generalizability.

Key Question 4. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

We found no studies that directly address the comparative effectiveness and safety of pharmacologic strategies among patients with liver disease.

Key Question 5. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

We found no studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies among hospitalized patients receiving antiplatelet therapy.

Key Question 6. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent venous thromboembolism in hospitalized patients undergoing bariatric surgery?

Key Points and Evidence Grades

In hospitalized patients having bariatric surgery:

- The strength of evidence is low supporting that prophylactic inferior vena cava filters increase the risk of post-operative DVT relative to no filters, in patients also receiving non-invasive mechanical measures and pharmacological prophylaxis.
- The strength of evidence is insufficient supporting that prophylactic inferior vena cava filters decrease the risk of PE relative to no filters, in patients also receiving non-invasive mechanical measures.

- The strength of evidence is insufficient to support that prophylactic inferior vena cava filters decrease the risk of fatal PE relative to no filters, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient that prophylactic inferior vena cava filters increase the risk of all-cause death relative to no filters, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient supporting that both enoxaparin 40 mg twice daily or higher and lower doses of enoxaparin or unfractionated heparin 5000 units subcutaneously three times daily, decreases the risk of DVT in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient supporting that enoxaparin 40 mg twice daily or higher increases the risk of bleeding compared to lower doses of enoxaparin or unfractionated heparin 5000 units subcutaneously three times daily, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient to support the comparative effectiveness and safety of any pharmacological strategies other than enoxaparin and unfractionated heparin for prevention of VTE in this population.

Study Characteristics

We identified 20 articles that reported on VTE prevention strategies in hospitalized patients undergoing bariatric surgery. There were no RCTs addressing this KQ; all included studies were observational cohort studies. We also identified two case reports (1 patient each) that described filter complications in bariatric surgery patients. Six studies reported prospective data collection,[40,130-132,142,145] and one other reported that a portion of the data was collected prospectively.[133] The remaining studies were retrospective cohorts.[39, 133-141, 143,144] or case reports of filter complications.[146 147] All studies took place in the U.S.; only two enrolled patients from multiple centers.[39 140](Table19 and Table 20)

Participant Characteristics

Patients underwent a variety of different bariatric surgical procedures. Types of surgeries included Roux-en-Y gastric bypass (both open and laparoscopic, but predominantly laparoscopic), adjustable laparoscopic gastric banding, and biliary-pancreatic diversion. Patient characteristics were generally consistent across studies. All studies included both men and women, and the mean age of participants, when reported, ranged from 39.5 to 49.8years. Most studies reported mean Body Mass Index (BMI), it ranged from 45 to 71 kg/m^2. Most studies did not explicitly describe the prevalence of a prior history of VTE. The duration of follow-up was generally 2 to 6 weeks, however one study reported a mean follow-up of 262 days[134] and another study reported follow-up of greater than 2 years.[144]

Among the 11 studies that reported on filters,[39 132-139 146 147] four studies included control groups of patients undergoing bariatric surgery who did not receive filters.[39 133 135 136] One of these was a multicenter, observational study of patients in Michigan who had been included in a large clinical registry.[39] Five studies reported on uncontrolled cohorts of patients who underwent filter placement.[132 134 136 138 139] Studies size ranged from one patient (case reports of filter complications) to 6,376 patients (registry study) of whom 542 had filters.[39] The uncontrolled cohorts ranged in size from nine patients[139] to 59 patients.[132] The smallest of these cohorts

focused on patients undergoing bilateral common iliac vein filter placement (rather than IVC filter placement) in patients with unusually large inferior vena cava diameters.[139] Two studies were case reports of single bariatric surgical patients who had filter-related complications.[146 147] Excluding the two case reports, 1,170 patients received filters. The studies on pharmacologic prophylaxis ranged in size from 40 patients[131] to 668 patients,[140] and included 2,695 patients.

Patient and hospitalization characteristics varied by treatment allocation in studies that compared interventions. For the more intensive prophylaxis, the studies appeared to target patients at higher risk of thrombosis. In the study by Birkmeyer et al.,[39] patients with filters tended to be older, have lower baseline mobility, be male, and have a prior history of VTE. In the study by Kardys et al.,[134] clinicians preferentially placed filters in patients with a history of prior VTE, a known hypercoagulable state or a history of profound immobility, or who were morbidly obese (having a mean BMI of 71.2 kg/m2). Overby et al. offered filters to patients with elevated levels of coagulation markers, impaired mobility, severe sleep apnea or hypoventilation, prior VTE, and more severe obesity.[136] Obeid et al. also preferentially placed filters in the most obese patients, and those with prior VTE; they also placed significantly more filters in men than in women.[135]

Similarly, clinicians appeared to use different pharmacological regimens depending on the severity of obesity, or according to practice patterns at the study center. Consequently, different prophylactic regimens tended to be associated with the type of surgery (laparoscopic vs. open), the duration of surgery, or the length of hospital stay. Of the four studies of pharmacological prophylaxis that used enoxaparin doses of 60 mg twice daily,[40 131 141 144] two did so only in the most obese patients (with BMIs of >59 kg/m2, average BMI of 65[144] or >50 kg/m2, average BMI of 57.4).[40] In the study by Gargiulo et al.,[133] all patients received weight-adjusted subcutaneous heparin (50 units per kg) and pneumatic compression; however, investigators preferentially placed filters in patients with BMI greater than 55 kg/m^2. In the one study that compared unfractionated heparin to enoxaparin,[130] BMI was slightly but significantly higher in enoxaparin-treated patients (48.7 vs. 47 kg/m^2, $p = 0.04$), and mean operative time was more than 30 minutes longer in the unfractionated heparin-treated patients (130 vs. 160 minutes, $p< 0.001$). In the single study of prolonged pharmacological prophylaxis versus inpatient prophylaxis alone, the 132 patients who underwent surgery between 2003 and 2005 received 30 mg twice daily of enoxaparin subcutaneously starting 1 hour prior to surgery and continued through hospitalization, which averaged 3.0 days in duration. A second group of 176 patients who underwent surgery in 2006 and 2007, received enoxaparin starting 12 hours postoperatively, and continued throughout hospitalization (averaging 2.2 days in duration) and for a 10-day period following discharge. In addition to the significantly shorter length-of-stay in the second group, patients in this group had fewer open procedures (0 versus 4 patients) and fewer conversions to open procedures after failed laparoscopic interventions (0 versus 5 patients).[142]

Intervention Characteristics

Inferior Vena Cava Filters

Ten studies evaluated IVC filters,[39 132-138 146 147] one studied bilateral common iliac vein filters,[139] and nine examined pharmacological approaches.[40 130 131 140-145] The types of filters varied according to physician practice and preference. Filters included the retrievable Gunther Tulip®, Bard Recovery®, OptEase®, Cook Celect®, Bard G2®; as well as filters that are not generally intended for retrieval including Greenfield stainless steel, Simon Nitinol®, and Cordis

TRAPEASE® filters. The large registry study by Birkmeyer et al. did not report on the specific filters.[39] Seven studies of filter prophylaxis described concurrent use of both mechanical prophylaxis with sequential compression devices and pharmacotherapy (enoxaparin, heparin, or warfarin).[132 134-136 139 146] Two described the use of filters with concurrent heparin or low molecular weight heparin prophylaxis only.[138 147] Only one of the controlled studies reported filter retrieval rates,[136] however all four of the uncontrolled cohort studies that used retrievable filters reported filter retrieval rates,[132 137-139] which ranged from 68 to 100 percent.
There were no studies comparing different types of IVC filters head-to-head, but some studies used multiple filter types.[133 136 138 139]

Pharmacologic Prophylaxis

Studies of pharmacologic prophylaxis involved patients receiving at least two different regimens; enoxaparin and unfractionated heparin were the only drugs studied. Two studies used weight-based enoxaparin dosing.[40 144] All studies used active drug therapy in all patients, rather than comparisons to placebo or no prophylaxis. UFH and enoxaparin were the only two agents these studies used. Seven studies employed varying doses of enoxaparin,[40 131 140 141 143-145] In the one study that included patients receiving either enoxaparin or unfractionated heparin,[130] one group of patients received enoxaparin 40 mg subcutaneously twice daily and group received unfractionated heparin 5,000 units subcutaneously every 8 hours. In one study, all patients received enoxaparin 30 mg subcutaneously twice daily, but the timing of initiation and duration of prophylaxis differed between the two comparison groups.[142] The dosing regimens of enoxaparin were: 30 mg once daily[140] or twice daily,[142-145], 40 mg once daily[140] or twice daily,[40 130 131 140 141 143 144] 50 mg twice daily,[144] and 60 mg twice daily.[40 131 141 144]

Dose of Pharmacotherapy

We categorized doses as “standard” prophylactic dosing (enoxaparin 30 mg twice daily or 40 mg once daily and heparin 5000u q8hrs) or “augmented” dosing, including enoxaparin 40 mg, 50 mg, and 60 mg twice daily. According to this classification, four studies included groups of patients receiving standard versus augmented dosing,[140 143-145] and three studies compared two or more augmented dosing regimens.[40 141 144] One of these studies also included patients who received reduced dosing (30 mg once daily).[140] Each of the four studies that included two or more augmented dosing regimens included a group receiving 40 mg twice daily and a group receiving 60 mg twice daily.[40 131 141 144]

Timing of Pharmacotherapy

Four studies initiated pharmacotherapy prior to surgery,[130 142-144] and four studies initiated pharmacotherapy after surgery;[40 131 141 145] the timing was variable in the five-center study by Hamad et al.[140] The planned duration of pharmacotherapy was for the hospital stay in three studies;[130 131 142] until “fully ambulatory” or hospital discharge in one study;[143] for 2 weeks post-operatively in one study;[141] for 10 days following discharge in one study;[40] was not clearly specified in one study;[144] and varied by center in the multicenter study by Hamad et al., ranging from 2 to 10 days.[140] In the pharmacokinetic study by Rowan et al. that compared two different doses of enoxaparin, the study assessed anti-Xa level after the first and third doses of the drug, so the total duration of prophylaxis was neither relevant to the results, nor reported.[145] Some studies described concurrent mechanical prophylactic interventions, including pneumatic compression devices in six studies[40 130 142-145] and early ambulation in five.[40 143-145] None of the included

studies indicated that other prophylactic measures were delivered to only one treatment arm and not the other.

Ascertainment of Thrombotic Outcomes

Most studies relied on clinically diagnosed (symptomatic) thrombosis, and did not employ routine surveillance for VTE prior to hospital discharge. However, three studies reported using ultrasound and/or computed tomographic venography prior to filter removal.[132 136 139] and one study reported performing bilateral lower extremity ultrasound prior to hospital discharge.[142]

Outcomes

Pulmonary Embolism

Inferior Vena Cava Filter versus No Inferior Vena Cava Filter

In the study by Gargiulo et al.,[133] no perioperative PEs occurred in the 58 patients with filters (0 percent), whereas the nine of the 351 patients without filters suffered from PE (2.6 percent), of whom five died (1.4 percent). There were no multivariable adjustments for differences between groups. Obeid et al. compared 1,847 patients who did not get filters to 246 patients who did.[135] Perioperative PE occurred in 11 of those who did not get filters (0.59 percent) and two of those with filters (0.8 percent). In a study by Overby et al.,[136] there were five PEs identified in the 170 patients who did not receive filters (2.9 percent), and one in the 160 patients who did (0.63 percent).

Uncontrolled Studies of Inferior Vena Cava Filters

In the uncontrolled cohort studies, perioperative PE rates ranged from 0 to 6.5 percent.[134]

Enoxaparin versus Unfractionated Heparin

In the study that compared enoxaparin 40 mg subcutaneously twice daily to unfractionated heparin 5,000 units every 8 hours, a single PE occurred in the heparin-treated patients (0.42 percent), with no thrombotic events in the enoxaparin-treated patients within 30 days of surgery.[130]

VTE Outcomes

Enoxaparin versus Extended-duration Enoxaparin

Thrombotic events occurred in six of the 132 patients in the short-term prophylaxis group (4.5 percent) and none of the 176 in the extended-prophylaxis group (p= 0.006).[142] Three of the thrombotic events were DVTs and three were PEs. This difference remained statistically significant after excluding from the analysis patients who required conversion to open procedures (p = 0.03).(Table 23)

Enoxaparin at Standard versus Augmented Dosing

Three studies reported on VTE outcomes in patients receiving standard versus augmented enoxaparin dosing.[140 143 144] In the study by Scholten et al., among 92 patients receiving enoxaparin 30 mg twice daily (standard dosing) there were five thrombotic events (5.4 percent), including four PEs (4.3 percent) and one DVT (1.1 percent).[143] In this same study, among 389

patients who received 40 mg twice daily (augmented) there were two thrombotic events (0.5 percent), both DVTs. In the study by Singh et al.,[144] none of the 11 patients receiving standard dose enoxaparin (30 mg twice daily) had thrombotic events. Similarly, none of the 159 patients who received augmented dosing (ranging from 40 mg to 60 mg every 12 hours according to weight) had thrombotic events. Hamad et al. found one patient of 264 (0.4 percent) with a PE with standard dosing of 40 mg twice daily, and one patient of 180 (0.6 percent) with a PE in the augmented treatment group dosed with 40mg twice daily.[140] There were no DVTs described in either arm. (Table 23)

Enoxaparin at Standard versus Reduced Dosing

In the five-center study by Hamad et al., two of the centers used enoxaparin at 30 mg once daily (reduced dosing, 224 patients), and two other centers used 40 mg once daily (standard dosing, 264 patients).[140] The study reported thrombotic events in five patients (2.2 percent) receiving 30 mg once daily (4 PEs [1.8 percent] and 1 DVT [0.4 percent]). There was one PE in a patient receiving 40 mg once daily (0.4 percent). (Table 23)

Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily versus 50 or 60 mg Twice Daily

In the study by Borkgren-Okonen et al., among the 124 patients receiving 40 mg twice daily, there were two thrombotic events (1.6 percent) (1 PE [0.8 percent] and 1 DVT [0.8 percent]).[40] Among the 99 patients receiving 60 mg twice daily, there were no thrombotic events. Singh et al.[144] reported no thrombotic events among the 145 patients receiving 40 mg twice daily and no events among the five patients receiving 60 mg twice daily. Additionally, no patients of nine receiving 50 mg twice daily none developed thrombosis. Ojo et al.[14] and Simone et al.[19] did not report on thrombotic outcomes. (Table 23)

Deep Vein Thrombosis

Inferior Vena Cava Filter versus No Inferior Vena Cava Filter

Obeid et al. reported perioperative DVT in 12 (0.65 percent) patients not receiving filters and three (1.2 percent) of those who did.[135] Overby et al. reported DVT in four patients without filters (2.4 percent) and five patients with filters (3.1 percent).[136]

Uncontrolled Studies of Inferior Vena Cava Filters

In the uncontrolled cohort studies of IVC filters, perioperative DVT rates ranged from 0 percent [132 138 139] to 25 percent (6 of 24 patients).[137]

Mortality

Inferior Vena Cava Filter versus No Inferior Vena Cava Filter

Obeid et al. reported two patients with filters died (0.81 percent) and four patients who did not receive filters died (0.22 percent).[135] In the study by Gargiulo et al. there with no fatalities in the 58 patients with filters and five fatal PEs among the 351 patients who did not receive filters (1.4 percent).[133](Table 21)

Uncontrolled Studies of Inferior Vena Cava Filters

Three of these uncontrolled cohorts reported all-cause perioperative mortality rates of 0 percent,[132] 2.4 percent,[138] and 6.5 percent.[134] (Table 21)

Enoxaparin versus Unfractionated Heparin

There were no deaths in either group in this study.[130](Table 24)

Enoxaparin versus Extended-duration Enoxaparin

There were no perioperative deaths in this study.[130](Table 24)

Enoxaparin at Standard versus Augmented Dosing

None of the three studies reported any perioperative deaths among patients receiving standard or augmented enoxaparin dosing.[140 143 144] (Table 24)

Enoxaparin at Standard versus Reduced Dosing

Two of the patients receiving reduced dosing of enoxaparin died (0.9 percent) compared with none of those receiving standard dosing in a single study.[140](Table 24)

Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily versus 50 or 60 mg Twice Daily

Only one study reported on mortality. Borkgren-Okonek et al. reported one death in a patient receiving 60 mg twice daily (0.4 percent) and no deaths among the patients receiving 40 mg twice daily. The study attributed the fatality to respiratory failure and prolonged post-operative mechanical ventilation in a patient with a BMI of 82 and did not attribute it to VTE or bleeding.[40] (Table 24)

Composite Outcomes

Inferior Vena Cava Filter versus No Inferior Vena Cava Filter

In the study by Birkmeyer et al.,[39] the odds ratio for death or permanent disability associated with filter placement was 2.4 (95% C.I. 0.99 to 6.3) after adjustment for the likelihood of receiving a filter. In the same study, after adjustment for differences between groups, IVC filter use was not statistically significantly associated with VTE or major complications.[39] However there was a trend toward more “serious complications” (including reoperation, renal failure, and other complications associated with risk of death or disability) in patients receiving filters [OR: 1.4 (95 percent confidence interval, 0.91 to 2.2)]. These authors also found that patients treated at hospitals that used filters in over 10 percent of their bariatric surgery patients had a significantly higher risk of perioperative VTE (PE and DVT combined) than patients treated at hospitals with less liberal use of filters [OR 1.6 (95 % C.I. 1.2 to 2.0).] The data did not allow for assessment of individual endpoints such as PE or mortality. (Table 21)

Filter Complications

The cohort studies (both controlled and uncontrolled) reported adverse events including: filter migration to the heart (1 patient),[39] nonfatal IVC thrombosis (1 patient),[137] fatal IVC thrombosis (1 patient),[39] errant placement of the filter into the common iliac vein (1 patient),[138] wrong positioning of the filter (2 patients),[134] pneumothorax (1 patient),[136] hemopericardium (1

patient),[136] and the inability to perform a transvenous ablation of a cardiac accessory pathway due to the filter (1 patient).[136]

Among the case reports of unexpected filter complications, in one case the filter migrated to the right ventricle and was successfully removed percutaneously via a transjugular approach.[147] The second report attributed a patient death to an occlusive thrombus at the site of the IVC filter occurring 2 weeks postoperatively.[146] Additional autopsy findings included a small rent in the IVC with a small retroperitoneal hematoma, thought to be not large enough to have caused the patient's death. The authors postulated that an acute decrease in cardiac filling due to acute IVC occlusion was responsible for this patient's hemodynamic collapse. (Table 22)

Bleeding

Enoxaparin versus Unfractionated Heparin

Bleeding events requiring transfusion occurred in 14 patients (5.9 percent) treated with enoxaparin and three patients (1.3 percent) receiving heparin (p= 0.01).[130] Reoperation for bleeding was required in four patients in the enoxaparin group (1.7 percent) and none in the heparin group. (Table 24)

Enoxaparin versus Extended-duration Enoxaparin

Bleeding events requiring reoperation occurred in one patient in the short-term prophylaxis group (0.75 percent) and one patient in the extended prophylaxis group (0.56 percent).[15] There was no significant difference between the two groups in the mean drop in hemoglobin during surgery. (Table 24)

Enoxaparin at Standard versus Augmented Dosing

In the study by Scholten et al.,[143] among 92 patients receiving enoxaparin 30 mg twice daily (standard dosing), there was one bleeding event that required transfusion (1.1 percent). Among the 389 patients who received 40 mg twice daily (augmented), there was a single bleeding event requiring re-operation. Singh et al. reported no bleeding events reported among the 11 patients receiving standard dose enoxaparin (30 mg twice daily), while among the 159 patients who received augmented dosing, there were five bleeding episodes requiring transfusion (3.1 percent), one of which required reoperation (0.6 percent).[144] Hamad et al., reported three bleeding events requiring transfusion among the 264 patients receiving standard dosing (1.1 percent), and three bleeding events requiring transfusion in 180 patients receiving augmented dosing (1.7 percent). [140] (Table 24)

Enoxaparin at Standard versus Reduced Dosing

Bleeding requiring transfusion was reported in one patient receiving reduced dosing enoxaparin (0.4 percent) and in three patients receiving standard dosing (1.1 percent).[140](Table 24)

Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily versus 50 or 60 mg Twice Daily

Borkgren-Okonek et al. reported major bleeding events in four (3.2 percent) of the 124 patients receiving 40 mg twice daily, one of whom required reoperation (0.8 percent). One patient who received 60 mg twice daily developed major bleeding (1.0 percent), but did not

require reoperation.[40] Singh et al. reported four bleeding events (2.8 percent) among the 145 patients receiving 40 mg twice daily, one of which one required reoperation (0.7 percent). There was one major bleeding event (20.0 percent) among the five patients receiving 60 mg twice daily; the patient did not require reoperation.[144] Ojo et al.reported no bleeding events in either group.[141] Simone et al. reported one bleeding episode (4.2 percent), which required transfusion among the 24 patients receiving 40 mg twice daily, and no bleeding events among the 16 patients receiving 60 mg twice daily.[146] (Table 24)

Anti-Xa levels

Two studies reported on this outcome.[145, 131]

Enoxaparin at Standard versus Augmented Dosing

One of the studies that included patients receiving either standard dose enoxaparin (30 mg twice daily) or augmented dosing (40 mg twice daily), and studied only pharmacokinetic endpoints, specifically anti-Xa levels drawn after the first and third doses of the drug, measured 4 hours after the dose.[145] The study defined appropriate prophylactic levels as 0.18-0.44 units/mL. Nineteen patients (mean weight 141.6 kg) received the 30 mg twice-daily dose, and 33 patients (mean weight 135.6 kg) received the 40 mg twice-daily dose. Patients receiving 30 mg twice daily had mean anti-Xa levels of 0.06 units/mL after the first dose, and 0.8 units/mL after the third dose. Levels were 0.14 and 0.15 units/mL, respectively, in patients receiving 40 mg doses. None of the patients receiving 30 mg doses had therapeutic levels after the first dose, and only 9 percent had therapeutic levels after the third dose. In those receiving 40 mg, 31 and 42 percent were therapeutic after the first and third doses, respectively.

Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily versus 50 or 60 mg Twice Daily

In the study by Simone et al., 24 patients (mean weight 135 kg) received 40 mg twice daily and 16 patients (mean weight 127 kg) received 60 mg twice daily.[131] The study measured anti-Xa levels 4 hours after the first and third doses of drug and defined appropriate prophylactic levels as 0.18-0.44 units/mL. Mean anti-Xa levels were 0.173 units/mL in the 40 mg group and 0.261 units/mL in the 60-mg group, after the first dose. After the third dose, levels were 0.21 and 0.43 units/mL respectively. None of the patients receiving the 60 mg dose remained subtherapeutic after three doses, in contrast to 44 percent of those receiving 40 mg. However, there were no supratherapeutic levels in the patients receiving 40 mg, in contrast to 57 percent of the levels in patients receiving 60 mg doses.

Risk of Bias

All studies were observational in design and at high risk of bias, except one which had moderate risk of bias.[39] The studies were rated to have a high risk of bias due to severe methodological limitations in design and analysis. The preference of the surgical team or the protocol employed at the center during a particular timeframe usually defined the prophylactic strategy. Some authors described allocating interventions based on real or perceived risk factors for post-operative VTE, such as prior history of VTE, age, degree of immobility, or severity of obesity; or varied the dose of pharmacotherapy based on patient weight in an effort to ensure that patients received an adequate prophylactic blood level of the drug. This targeted prophylactic approach would tend to bias these studies toward poorer efficacy with more aggressive

prophylactic strategies employed in riskier patients. In keeping with the low numbers of patients and events, none of the studies performed multivariable adjustments to account for patient differences according to intervention allocation, except one that sought to define the efficacy of IVC filters by comparing those who got filters to those who did not by propensity score stratification.[39] None of the studies focusing on pharmacologic prophylaxis used multivariate adjustment to account for differences between patients who received different prophylactic strategies.

Strength of Evidence

We rated most included studies on this KQ as being at high risk of bias. We considered most of the evidence direct except for the surrogate outcome of anti-Xa levels.

In the studies that evaluated IVC filters, we rated the strength of evidence as low that IVC filters increased the rates of DVT compared to no IVC filters in patients undergoing bariatric surgery. We based this rating on consistent and precise estimate of increased risk of DVT with filters compared to no filters (RR = 2.28, 95% CI=1.06 to 4.94) (Figure 13 B). We rated the strength of evidence as insufficient that prophylactic IVC filters reduced PE, fatal PE, VTE or mortality compared to no IVC filters in patients undergoing bariatric surgery. We based this rating on either inconsistencies in the body of evidence, or our inability to assess consistency (consistency unknown) in a single study. (Table 25) (Figure 12, Fiure 14). The -analysis forest plot for IVC filter vs no filter on the outcome of PE, mortality and DVT are shown in Figure 12-14.

We rated the strength of evidence as insufficient for all outcomes and comparisons in studies that evaluated pharmacologic interventions. We based this rating on either inconsistencies in the body of evidence, or our inability to assess consistency (consistency unknown) in a single study. (Table 26)

Applicability

Patient characteristics were consistent with those expected in the bariatric surgery population, including obese middle-aged patients of both sexes. Types of surgeries included the types of bariatric procedures frequently employed in the U.S. (including roux-en-Y gastric bypass and adjustable gastric banding); most surgeries were laparoscopic, consistent with current practice. Most studies did not report race in general, so we cannot make firm conclusions related to potential interactions between race and prophylactic strategy. Although many studies reported single center experiences, patient characteristics and surgery types appear relatively consistent across study centers. The single-center nature of these studies, by itself, is not a major factor limiting generalizability since the characteristics of patients recruited were similar to those in other centers. However, several of these studies targeted specific pharmacologic strategies and IVC filters for patients with more severe obesity such as BMI> 55 kg/m2. Thus the applicability of these findings to those with lower levels of BMI is uncertain.

Table 19. Characteristics of Studies of IVC Filters among patients undergoing bariatric surgery

Author, year	Design	Arm	N	Mean Ag, years	Male, %	Body Mass Index, kg/m^2
Controlled observational studies						
Gargiulo, N.J., 2006[133]	Retrospective-Prospective	Filter	58	NR	41.3	NR
		No filter	351	NR		44-58
Birkmeyer, N. J., 2010[39]	Retrospective Cohort,	Filter	542	NR	30	>50 in 72%
		No filter	5834	NR	19	>50 in 34%
Obeid, F. N., 2007[135]	Retrospective Cohort	Filter	246	46.6	23.6	60
		No filter	1847	44.7	14	48.8
Overby, D. W., 2009[136]	Retrospective Cohort	Filter	160	NR	14.55	51.42
		No filter	170	NR		
Uncontrolled observational studies						
Piano, G., Ketteler, 2007[132]	Prospective Cohort	Filter	59	43	17	61
Vaziri, K., 2010[138]	Retrospective Cohort	Filter	41	48	29	58.4
Schuster, R., 2007[137]	Retrospective Cohort	Filter	24	49.8	58.3	>50 in 88%
Kardys, C. M. 2008[134]	Retrospective Cohort	Filter	31	42	NR	71.2
Van H, T. G., 2011[139]	Retrospective Cohort	Filter	9	45	60	>50
Case reports of filter complications						
Schweitzer, M., 2006[146]	Case report	Filter	1	63	NR	45
Veerapong J., 2008[147]	Case report	Filter	1	31	NR	74[1]

BMI=Body Mass Index; NR=Not Reported

Table 20. Characteristics of Studies of Pharmacologic comparisons among patients undergoing bariatric surgery

Author, year	Design	Intervention and comparator	N patients	Mean Age Years	%Male	BMI(kg/m^2)
Kothari, S. 2007[130]	Prospective Cohort	Enoxaparin 40mg sq q12 and SCD, ambulation (A)	238	42	NR	48.7
		Heparin sq 5000iu q8hrs and SCD, ambulation (S)	238	44	NR	47
Simone, E. 2008[131]	Prospective Cohort	Enoxaparin 40mg sq q12 (A)	24	40	12.5	48.8
		Enoxaparin 60mg sq q12(A)	16	41	6.3	47.3
Borkgren-Okonek, M. 2008[40]	Prospective Cohort	Enoxaparin 40mg sq q12, SCD, ambulation and preop heparin sq, BMI ≤50 and qd for 10 days post discharge (A)	124	44.7	22.6	44.9
		Enoxaparin 60mg sq q12, SCD, ambulation and preop heparin sq, BMI >50 and qd for 10 days post discharge (A)	99	44.3	27.3	57.4
Raftopoulos, I., 2008[142]	Prospective Cohort	Enoxaparin 30mg sq q12 extended for 10days post d/c (S)	176	44.1	18.75	46.1
		Enoxaparin 30mg sq q12 during hospital stay, SCD (S)	132	42.6	15.2	47.8
Scholten, D. J., 2002[143]	Retrospective Cohort	Enoxaparin 40mg sq q12, SCD and ambulation (A)	389	44.3	15.8	50.4
		Enoxaparin 30mg sq q12 and SCD, ambulation (S)	92	43.7	20.2	51.7
Singh, K., 2011[144]	Retrospective Cohort	Enoxaparin 40mg sq q12, ambulation for BMI 41-49 (A)	145	43	53	48
		Enoxaparin 50mg sq q12, ambulation for BMI 50-59 (A)	9			51
		Enoxaparin 60mg sq q12, ambulation for BMI > 60 (A)	5			65
		Enoxaparin 30mg sq q12, ambulation for BMI < 40 (S)	11			39
Hamad, G.G., 2005[140]	Retrospective Cohort	Enoxaparin 40mg sq q12 (A)	180	39.7	3	46
		Enoxaparin 40mg sq qd (S)- post op for 12-120 hours	84	47.5	29	56.8
		Enoxaparin 40mg sq qd (S)-post op for 12-24 hours	180	41.9	10	49.9
		Enoxaparin 30mg sq qd (R)-pre op	100	39.5	25	47
		Enoxaparin 30mg sq qd (R)-post discharge	124	42.1	18	51.5
Ojo, P., 2008[141]	Retrospective Cohort	Enoxaparin 40mg sq q12 (S)	59	48	33.9	57
		Enoxaparin 60mg sq q12 (A)	68	46	61.8	58
Rowan, BO., 2008[145*]	Prospective Cohort	Enoxaparin 40mg sq q12, SCD and ambulation (A)	33	40.8	18	48.5
		Enoxaparin 30mg sq q12, SCD and ambulation (S)	19	41.7	26	48.4

Table 20. Characteristics of Studies of Pharmacologic comparisons among patients undergoing bariatric surgery Continued

Simone, E. 2008[131] *	Prospective Cohort	Enoxaparin 40mg sq q12 (A)	24	40	12.5	48.8
		Enoxaparin 60mg sq q12(A)	16	41	6.3	47.3

iu= International Units; sq= Subcutaneous; qd= Once daily; q12= Once every 12 hours; BMI= Body Mass Index; SCD= Sequential Compression Devices; NR= Not Reported
A= Augmented dose, R= reduced dose, S= Standard dose given for VTE prophylaxis

- *Studies measured Serum Factor Xa- levels

Table 21. VTE Outcomes among patients undergoing bariatric surgery who received IVC filters

Study	Design	Arm	N patients	Device type	VTE Diagnosis	Pulmonary Embolism, n(%)	DVT (including device related DVT), n(%)	Total Mortality, n(%)
IVC Filter versus no IVC Filter								
Birkmeyer, N. J., 2010[39]	Retrospective Cohort	Filter	542	NR	NR	11(2.03)	NR	10(1.85)
		No filter	5834	No filter	NR	31(0.53)	NR	30(0.51)
Obeid, F. N., 2007[135]	Retrospective Cohort	Filter	246	NR	NR	2 (0.8)	3(1.2)	2(0.81)
		No filter	1847	No filter	NR	11 (0.59)	12 (0.65)	4(0.22)
Overby, D. W., 2009[136]	Retrospective Cohort	Filter	160	Celect, Gunther Tulip, Bard Recovery, Optease, Venatech, Bard G2	CT Venography or Doppler US	1(0.63)	5(3.13)	3(0.9)
		No filter	170	No filter	CT Venography or Doppler US	5(2.94)	4(2.35)	
Gargiulo, N.J., 2006[133]	Retrospective-Prospective	Filter, BMI >55	58	Trapease, Simon-Nitinol, Greenfield, Bard Recovery	NR	0(0)	3(9)	0(0)
		No filter, BMI 44-58	351	No filter	NR	9(2.56)	0(0)	5(1.42)
Uncontrolled studies of IVC Filter								
Piano, G., Ketteler, 2007[132]	Prospective Cohort	Filter	59	Gunther Tulip®	Doppler US	1 (1.69)	0 (0)	0(0)
Vaziri, K., 2010[138]	Retrospective Cohort	Filter	41	Gunther Tulip®, G2® filters	NR	1(2.4)	2 (4.9)	1(2.4)
Schuster, R., 2007[137]	Retrospective Cohort	Filter	24	Gunther Tulip®	NR	0(0)	6(25)	0(0)
Kardys, C. M. 2008[134]	Retrospective Cohort	Filter	31	Greenfield Stainless Steel®	NR	2 (6.5)	1(3.2)	2(6.5)
Van H, T. G., 2011[139]	Retrospective Cohort	Filter (Iliac vein)	10	Gunther Tulip, Celect	Doppler US, Venogram	0(0)	0(0)	NR

NR= not reported

Table 22. Filter retrieval rates and device complications in Bariatric surgery patients who received IVC filters

Author, year	Arm	N patients	Device type	Filter Retrieval rate n(%)	Device Complications, other n (%)
Controlled observational studies					
Birkmeyer, N. J., 2010[39]	Filter	542	NR	NR	2*
	No filter	5834	no filter	NR	NA
Obeid, F. N., 2007[135]	Filter	246	NR	NR	NR
	No filter	1847	no filter	NR	NA
Overby, D. W., 2009[136]	Filter	160	Multiple	147(91.88%)	4(2.47)§
	No filter	170	no filter	NR	NA
Gargiulo, N.J., 2006[133]	Filter	58	Multiple	NR	3(5.17)Ω
	No filter	351	no filter	NA	NA
Uncontrolled observational studies					
Piano, G., Ketteler, 2007[132]	Filter	59	Gunther Tulip®	52(88)	NR
Vaziri, K., 2010[138]	Filter	41	Gunther Tulip®, G2® filters	28(68)	2(4.87)α
Schuster, R., 2007[137]	Filter	24	Gunther Tulip®	20(80)	NR
Kardys, C. M. 2008[134]	Filter	31	Greenfield Stainless Steel®	NR	2(6.4)β
Van H, T. G., 2011[139]	Filter (Iliac vein)	10	Gunther Tulip, Celect	10(100)	NR
Case reports					
Schweitzer, M., 2006[146]	Case report	1	Optease	NA	1(100)#
Veerapong J., 2008[147]	Case report	1	Gunther-Tulip	1(100	1(100)δ

NR=not reported; NA=not applicable

* The complications included fatal IVC thrombosis and IVC filter migration to the heart.

§ The complications were due to insertion (pneumothorax), early removal (hemopericardium, pulmonary embolism) and delayed removal (unable to perform transvenous accessory pathway ablation) of the IVC filter.

Ω 1 postoperative IVC thrombosis occurred 4 months after Trapease IVC filter placement while 2 postoperative localized, insertion-site DVTs occurred 3 months after filter placement.

α 1 patient had self-limiting pain at the insertion site of the IVC filter for 5 days while the other patient had a filter deployed in the right common iliac vein.

β The complication was malposition of the IVC filter in the 2 patients.

The IVC filter was completely occluded by a thrombus in this patient.

δ The IVC filter migrated to the right ventricle in this patient.

Table 23: VTE Outcomes among Bariatric Surgery patients undergoing pharmacological prophylaxis

Author, year	Design	Arm	N patients	VTE Diagnosis	Peri Operative Pulmonary Embolism, n(%)	Peri Operative DVT, n(%)
Kothari, S. 2007[130]	Prospective Cohort	Enoxaparin 40mg sq q12 and SCD, ambulation	238	NR	0(0)	0(0)
		heparin sq 5000u q8hrs and SCD, ambulation	238	NR	1(0.42)	0 (0)
Raftopoulos, I., 2008[142] *	Prospective Cohort	enoxaparin 30mg sq q12, SCD extended for 10days post d/c	176	Doppler US prior to d/c, chest CT	0(0)	0(0)
		enoxaparin 30mg sq q12, SCD during hospital stay, SCD	132	Doppler US prior to d/c, chest CT	3(2.3)	3(2.3)
Scholten, D. J., 2002[143]	Retrospective Cohort	enoxaparin 40mg sq q12, SCD and ambulation (A)	389	NR	0(0)	2(0.5)
		enoxaparin 30mg sq q12 and SCD, ambulation (S)	92	NR	4 (4.3)	1 (1.1)
Singh, K., 2011[144]	Retrospective Cohort	enoxaparin 40mg sq q12, SCD, ambulation for BMI 41-49(A)	145	Doppler US, CT Angio	0 (0) (	0 (0)
		enoxaparin 50mg sq q12, SCD, ambulation for BMI 50-59 (A)	9	Doppler US, CT Angio	0 (0)	0 (0)
		enoxaparin 60mg sq q12, SCD, ambulation for BMI > 60 (A)	5	Doppler US, CT Angio	0 (0)	0 (0)
		enoxaparin 30mg sq q12, SCD, ambulation for BMI < 40 (S)	11	Doppler US, CT Angio	0 (0)	0 (0)
Hamad, G.G., 2005[140]	Retrospective Cohort	enoxaparin 40mg sq q12(A)	180	NR	1(0.6)	0(0)
		enoxaparin 40mg sq qd (S) post op for 12-120 hours	84	NR	1(1)	0(0)
		enoxaparin 40mg sq qd(S) post op for 12-24 hours	180	NR	0(0)	0(0)
		enoxaparin 30mg sq qd(R)pre op	100	NR	2(2)	0(0)
		enoxaparin 30mg sq qd(R)post discharge	124	NR	2(1.6)	1(0.8)
Borkgren-Okonek, M. 2008[40]	Prospective Cohort	enoxaparin 40mg sq q12, SCD, ambulation and preop heparin sq, BMI ≤50 and qd for 10 days post discharge	124	US, CTA, VQ scan	NR	NR

Table 23: VTE Outcomes among Bariatric Surgery patients undergoing pharmacological prophylaxis continued

Author, year	Design	Arm	N patients	VTE Diagnosis	Peri Operative Pulmonary Embolism, n(%)	Peri Operative DVT, n(%)
		enoxaparin 60mg sq q12, SCD, ambulation and preop heparin sq, BMI >50 and qd for 10 days post discharge	99	US, CTA, VQ scan	NR	NR
Singh, K., 2011[144]	Retrospective Cohort	enoxaparin 40mg sq q12, SCD, ambulation for BMI 41-49(A)	145	Doppler US, CT Angio	0 (0)	0 (0)
		enoxaparin 50mg sq q12, SCD, ambulation for BMI 50-59 (A)	9	Doppler US, CT Angio	0 (0)	0 (0)
		enoxaparin 60mg sq q12, SCD, ambulation for BMI > 60 (A)	5	Doppler US, CT Angio	0 (0)	0 (0)
		enoxaparin 30mg sq q12, SCD, ambulation for BMI < 40 (S)	11	Doppler US, CT Angio	0 (0)	0 (0)
Simone, E. 2008[131]	Prospective Cohort	enoxaparin 40mg sq q12	24	NR	NR	NR
		enoxaparin 60mg sq q12	16	NR	NR	NR
Ojo, P., 2008[141]	Retrospective Cohort	enoxaparin 40mg sq q12	59	NR	NR	NR
		enoxaparin 60mg sq q12	68	NR	NR	NR

Raftopoulos, I., 2008[142] also reported statistically significant difference on VTE outcomes between extended duration vs enoxaparin group, 6 vs 0 or 4.5% vs 0 %; P=0.006
Scholten, D. J., 2002[143] also reported on statistically significant difference on VTE outcomes between Standard dose and Auggment dose, 5 vs 2 or 5.4% vs 0.6%, P<0.01
A= Augmented dose, R= reduced dose, S= Standard dose given for VTE prophylaxis NR= not reported; sq= subcutaneous; qd=once daily; q12=once every 12 hours

Table 24: Safety Profile of Pharmacological Interventions to Prevent VTE in Bariatric Surgical Patients

Author, year	Arm	N patients	Bleeding requiring PRBC, n(%)	Bleeding requiring surgery, n(%)	Minor Bleeding, n (%)	Total Peri Operative mortality, n(%)
Enoxaparin versus Unfractionated Heparin						
Kothari, S. 2007[130]	enoxaparin 40mg sq q12 and SCD, ambulation	238	14(5.9)	4(1.7)	NR	0(0)
	heparin sq 5000u q8hrs and SCD, ambulation	238	3(1.3)	0(0)	NR	0(0)
Enoxaparin versus Extended- duration Enoxaparin						
Raftopoulos, I., 2008[142]	enoxaparin 30mg sq q12 extended for 10days post d/c	176	0(0)	1(0.56)	NR	0(0)
	enoxaparin 30mg sq q12 during hospital stay, SCD	132	6(4.5)	1(0.75)	NR	0(0)
Enoxaparin at Standard versus Augmented dosing						
Scholten, D. J., 2002[143]	enoxaparin 40mg sq q12, SCD and ambulation(A)	389	NR	1(0.26)	NR	NR
	enoxaparin 30mg sq q12 and SCD, ambulation(S)	92	1(1.1)	NR	NR	NR
Singh, K., 2011[144]	enoxaparin 40mg sq q12, ambulation for BMI 41-49(A)	145	4(2.8)	1(0.7)	NR	NR
	enoxaparin 50mg sq q12, ambulation for BMI 50-59(A)	9	0(0)	0(0)	NR	NR
	enoxaparin 60mg sq q12, ambulation for BMI > 60(A)	5	1(20)	0(0)	NR	NR
	enoxaparin 30mg sq q12, ambulation for BMI < 40(S)	11	0(0)	0(0)	NR	NR
Hamad, G.G., 2005[140] p-values not reported	enoxaparin 40mg sq q12(A)	180	3(1.7)	NR	NR	NR
	enoxaparin 40mg sq qd(S) post op for 12-120 hours	84	0(0)	NR	NR	NR
	enoxaparin 40mg sq qd(S) post op for 12-24 hours	180	3(1.7)	NR	NR	NR
	enoxaparin 30mg sq qd(R) pre op	100	0(0)	NR	NR	NR
	enoxaparin 30mg sq qd(R) post discharge	124	1(0.8)	NR	NR	2(1.6)
Differing Augmented Enoxaparin Dosing Regimens						
Borkgren-Okonek, M. 2008[40]	enoxaparin 40mg sq q12, SCD, ambulation and preop heparin sq, BMI ≤50 and qd for 10 days post discharge	124	4(3.2)	1(0.8)	NR	0(0)
	enoxaparin 60mg sq q12, SCD, ambulation and preop heparin sq, BMI >50 and qd for 10 days post discharge	99	1(1)	0(0)	NR	1(1)

Table 24: Safety Profile of Pharmacological Interventions to Prevent VTE in Bariatric Surgical Patients continued

Author, year	Arm	N patients	Bleeding requiring PRBC, n(%)	Bleeding requiring surgery, n(%)	Minor Bleeding, n (%)	Total Peri Operative mortality, n(%)
Singh, K., 2011[144]	enoxaparin 40mg sq q12, ambulation for BMI 41-49(A)	145	4(2.8	1(0.7)	NR	NR
	enoxaparin 50mg sq q12, ambulation for BMI 50-59(A)	9	0(0)	0(0)	NR	NR
	enoxaparin 60mg sq q12, ambulation for BMI > 60(A)	5	1(20)	0(0)	NR	NR
	enoxaparin 30mg sq q12, ambulation for BMI < 40(S)	11	0(0)	0(0)	NR	NR
Simone, E. 2008[131]	enoxaparin 40mg sq q12	24	1(4.3)	NR	NR	NR
	enoxaparin 60mg sq q12	16	0(0)	NR	NR	NR
Ojo, P., 2008[141]	enoxaparin 40mg sq q12	59	0(0)	NR	NR	NR
	enoxaparin 60mg sq q12	68	0(0)	NR	NR	NR

A= Augmented dose, R= reduced dose, S= Standard dose given for VTE prophylaxis

Table 25. Body of Evidence for Inferior Vena Cava Filter vs Controls for the Prevention of Pulmonary Embolism in Patients Undergoing Bariatric Surgery

Author, Year	Outcomes	Risk of bias	Directness	Precision #	Consistency	Magnitude of effect
Filter vs no filter						
	PE	**High**	**Direct**	**Imprecise**	**Inconsistent**	**Insufficient evidence to comment on effectiveness of IVCF vs controls in reducing PE in patients undergoing bariatric surgery** RR = 0.54 (95% CI = 0.11 to 2.72;P = 0.46; 1^2=30%)
Obeid, F. N., 2007[135]		High	Direct	Imprecise	Inconsistent;	0.8 vs 0.6%; p=0.69
Overby, D. W., 2009[136]		High	Direct	Imprecise		0.6% vs 2.9%; p=0.216
Gargiulo, N.J., 2006[133]		High	Direct	Precise		0% vs 2.6%
	Fatal PE	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of IVCF vs controls in reducing fatal PE in patients undergoing bariatric surgery**
Gargiulo, N.J., 2006[133]		High	Direct	Imprecise	Unknown	0% vs 11.1%
	DVT	**High**	**Direct**	**Precise**	**Consistent**	**Low grade evidence to support that IVCFs increase DVT in patients undergoing bariatric surgery compared to controls RR = 2.28 (95% CI=1.06 to 4.94; p=0.03;1^2=53%)**
Obeid, F. N., 2007[135]		High	Direct	Imprecise	Consistent	1.2% vs 4.9%; p=0.56
Overby, D. W., 2009[136]		High	Direct	Imprecise		3.1 % vs 2.4% p=0.744
Gargiulo, N.J., 2006[133]		High	Direct	Precise		5.2% vs 0%
	VTE	**Medium**	**Direct**	**Precise**	**Unknown**	**Insufficient evidence to comment on effectiveness of IVCF vs controls in reducing VTE in patients undergoing bariatric surgery**
Birkmeyer, N. J., 2010[39]		Medium	Direct	Precise	Unknown	2.0% vs 0.5%; p<0.0001
	Mortality**	**High**	**Direct**	**Precise**	**Inconsistent**	**Insufficient evidence to comment on effectiveness of IVCF vs controls in reducing mortality in patients undergoing bariatric surgery RR =3.44 (95% CI=1.79 to 6.58; p=0.0002; 1^2=0%)**
Birkmeyer, N. J., 2010[39#]		Medium	Direct	Precise	*Inconsistent;	1.9 % vs 0.5% p<0.0001
Obeid, F. N., 2007[135]		High	Direct	Imprecise		0.8% vs 0.2%; P=0.37
Gargiulo, N.J., 2006[133]		High	Direct	Imprecise		0% vs 1.4%

Table 25. Body of Evidence for Inferior Vena Cava Filter vs Controls for the Prevention of Pulmonary Embolism in Patients Undergoing Bariatric Surgery continued

DVT=deep venous thrombosis, PE=pulmonary embolism, VTE= venous thromboembolism,
* There were no randomized controlled trials; Reported on mortality and permanent disability;
**Mortality rated as insufficient despite the absence of statistical heterogeneity (I^2=0%) because of clinical heterogeneity with filters being channeled to high risk patients.
See Figure 12- 14 for ratings on precision

Table 26: Body of Evidence for Pharmacological Prophylaxis for the Prevention of Venous Thromboembolism in Patients Undergoing Bariatric Surgery

Author, Year	Outcomes	Risk of bias	Directness	Precision	Consistency	Magnitude of effect
Enoxaparin versus Unfractionated Heparin						
	PE	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs unfractionated heparin in reducing PE in patients undergoing bariatric surgery**
Kothari, S. 2007[130]		High	Direct	Imprecise	Unknown	0% vs 0.4%; p=0.99
	DVT	**High**	**Direct**	**Unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs unfractionated heparin in reducing DVT in patients undergoing bariatric surgery**
Kothari, S. 2007[130]		High	Direct	Unknown	Unknown	0% vs 0%
	Major bleeding#	**High**	**Direct**	**Precise**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs unfractionated heparin in reducing major bleeding in patients undergoing bariatric surgery**
Kothari, S. 2007[130]		High	Direct	Precise	Unknown	5.9% vs 1.3%; p=0.011
	Mortality	**High**	**Direct**	**Unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs unfractionated heparin in reducing mortality in patients undergoing bariatric surgery**
Kothari, S. 2007[130]		High	Direct	Unknown	Unknown	0% vs 0%
Enoxaparin versus extended duration of Enoxaparin						
	PE	**High**	**Direct**	**Unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing PE in patients undergoing bariatric surgery**
Raftopoulos, I., 2008[142]		High	Direct	Unknown	Unknown	2.3% vs 0%

Table 26: Body of Evidence for Pharmacological Prophylaxis for the Prevention of Venous Thromboembolism in Patients Undergoing Bariatric Surgery continued

Author, Year	Outcomes	Risk of bias	Directness	Precision	Consistency	Magnitude of effect
	VTE	**High**	**Direct**	**Precise**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing VTE in patients undergoing bariatric surgery**
Raftopoulos, I., 2008[142]		High	Direct	Precise	Unknown	4.6% vs 0% ;P=0.006
	DVT	**High**	**Direct**	**Unknown**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing DVT in patients undergoing bariatric surgery**
Raftopoulos, I., 2008[142]		High	Direct	Unknown	Unknown	2.3% vs 0%
	Major bleeding#	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing major bleeding in patients undergoing bariatric surgery**
Raftopoulos, I., 2008[142]		High	Direct	Imprecise	Unknown	4.5% vs 0% ;p= 0.06
	Mortality	**High**	**Direct**	**Imprecise**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin vs extended duration enoxaparin in reducing mortality in patients undergoing bariatric surgery**
Raftopoulos, I., 2008[142]		High	Direct	Imprecise	Unknown	0% vs 0%; p = NS
Enoxaparin at standard dosing versus augmented dosing						
	PE	**High**	**Direct**	**Unknown**	**Inconsistent**	**Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing PE in patients undergoing bariatric surgery**

Table 26: Body of Evidence for Pharmacological Prophylaxis for the Prevention of Venous Thromboembolism in Patients Undergoing Bariatric Surgery continued

Author, Year	Outcomes	Risk of bias	Directness	Precision	Consistency	Magnitude of effect
Scholten, D. J., 2002[143]		High	Direct	Unknown	Inconsistent	4.4% vs 0%
Singh, K., 2011[144]		High	Direct	Unknown		0% vs 0%
Hamad, G.G., 2005[140]		High	Direct	Unknown		0. 1% vs 0.6%
	DVT	**High**	**Direct**	**Unknown**	**Inconsistent**	**Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing DVT in patients undergoing bariatric surgery**
Scholten, D. J., 2002[143]		High	Direct	Imprecise	Inconsistent	1.1% vs 0.5%
Singh, K., 2011[144]		High	Direct	Unknown		0% vs 0%
Hamad, G.G., 2005[140]		High	Direct	Unknown		0% vs 0%
	VTE	**High**	**Direct**	**Precise**	**Unknown**	**Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing VTE in patients undergoing bariatric surgery**
Scholten, D. J., 2002[143]		High	Direct	Precise	Unknown	5.4% vs 0.6% ; p <0.01
	Bleeding	**High**	**Direct**	**Unknown**	**Inconsistent**	**Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs augmented dosing in reducing bleeding in patients undergoing bariatric surgery**
Singh, K., 2011[144]		High	Direct	Unknown	Inconsistent	0% vs 2.8%
Hamad, G.G., 2005[140]		High	Direct	Unknown		0% vs 1.7%
Scholten, D. J., 2002[143]		High	Direct	Imprecise		1.1% vs 0.26%; p=NS

Table 26: Body of Evidence for Pharmacological Prophylaxis for the Prevention of Venous Thromboembolism in Patients Undergoing Bariatric Surgery continued

DVT=deep venous thrombosis, PE=pulmonary embolism, VTE= venous thromboembolism, # Requiring transfusion, * There were no randomized controlled trials, NR= Not reported; NS= Not significant

Figure 12 Relative Risk Meta-analysis of IVC Filter vs no filter on PE in bariatric surgery

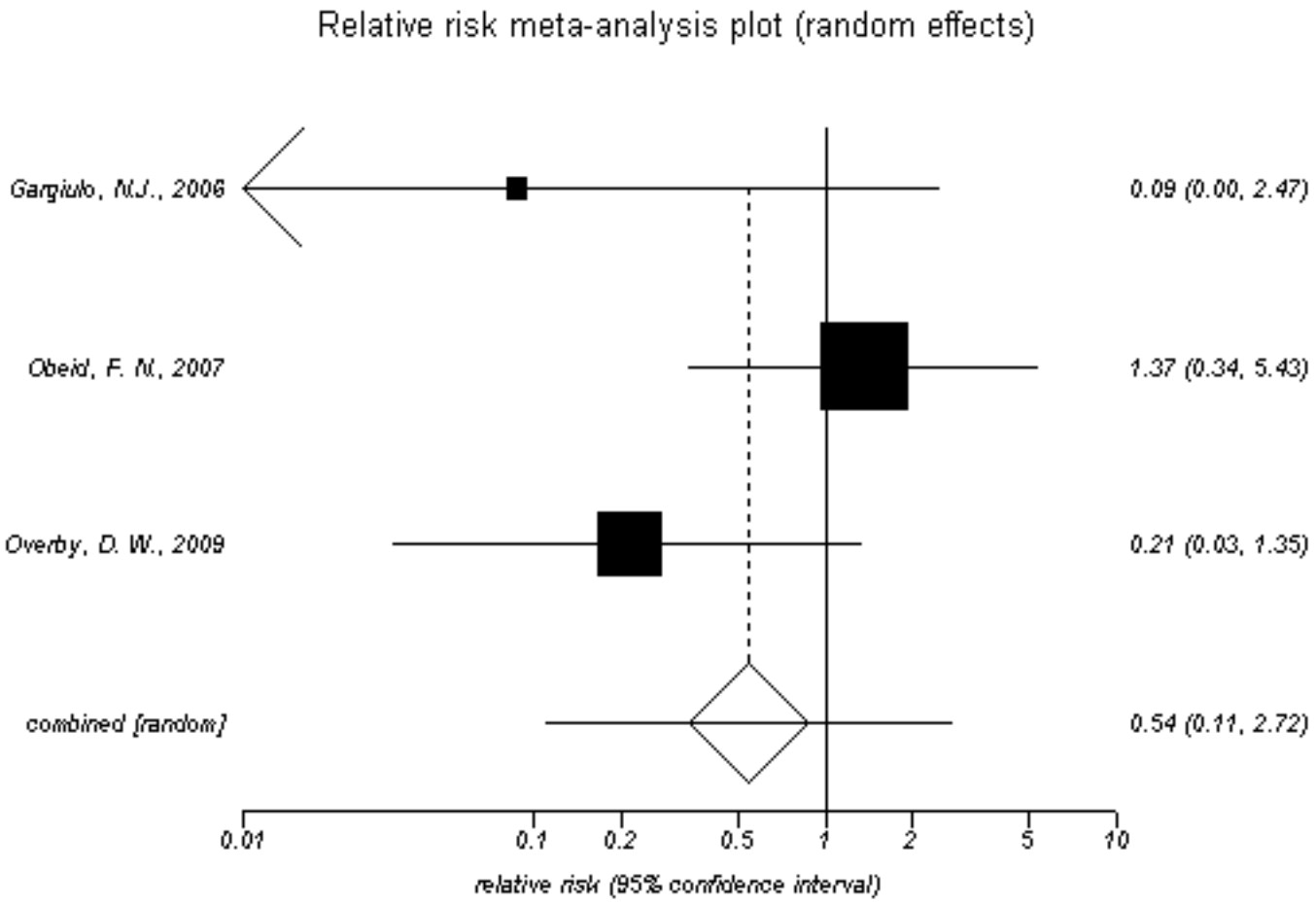


Figure 13A Relative Risk Meta-analysis of IVC Filter vs no filter on DVT in bariatric surgery-Random

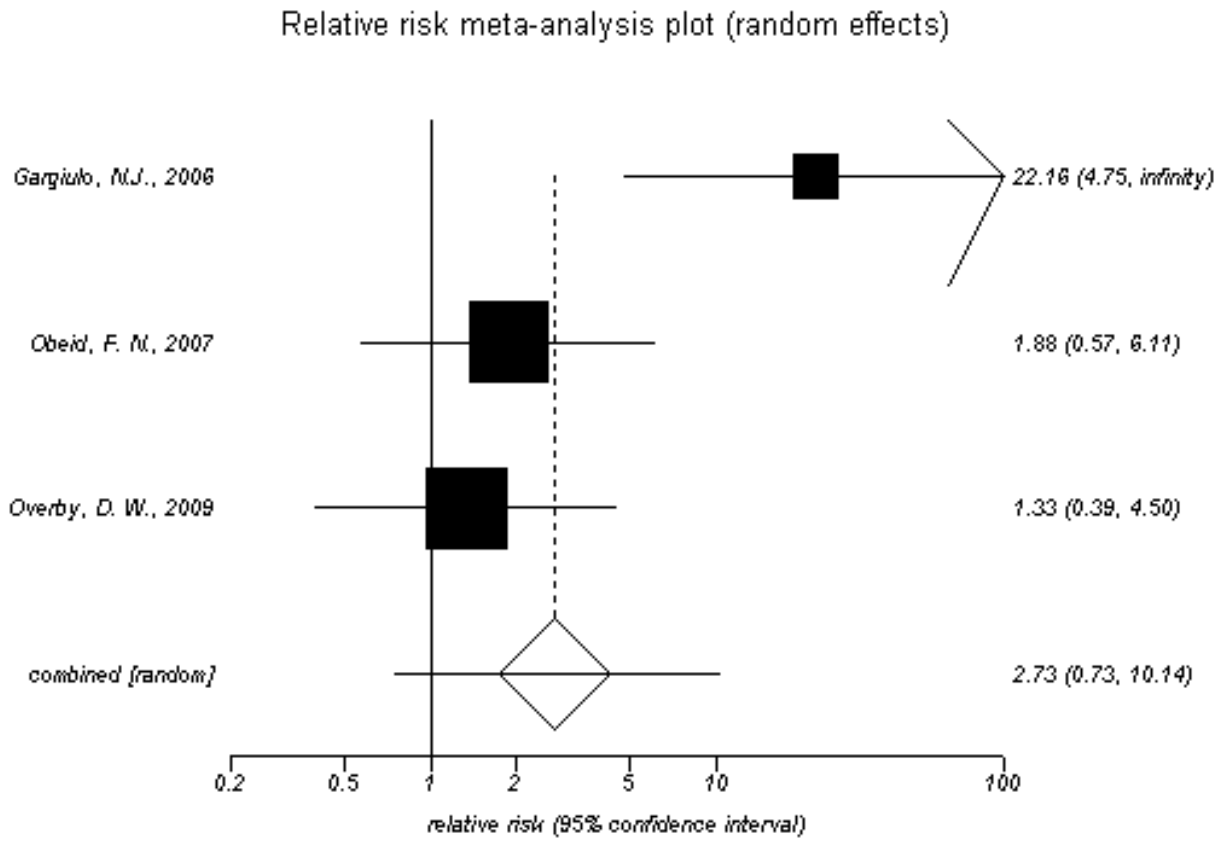


Figure 13B Relative Risk Meta-analysis of IVC Filter vs no filter on DVT in bariatric surgery- Fixed Effect

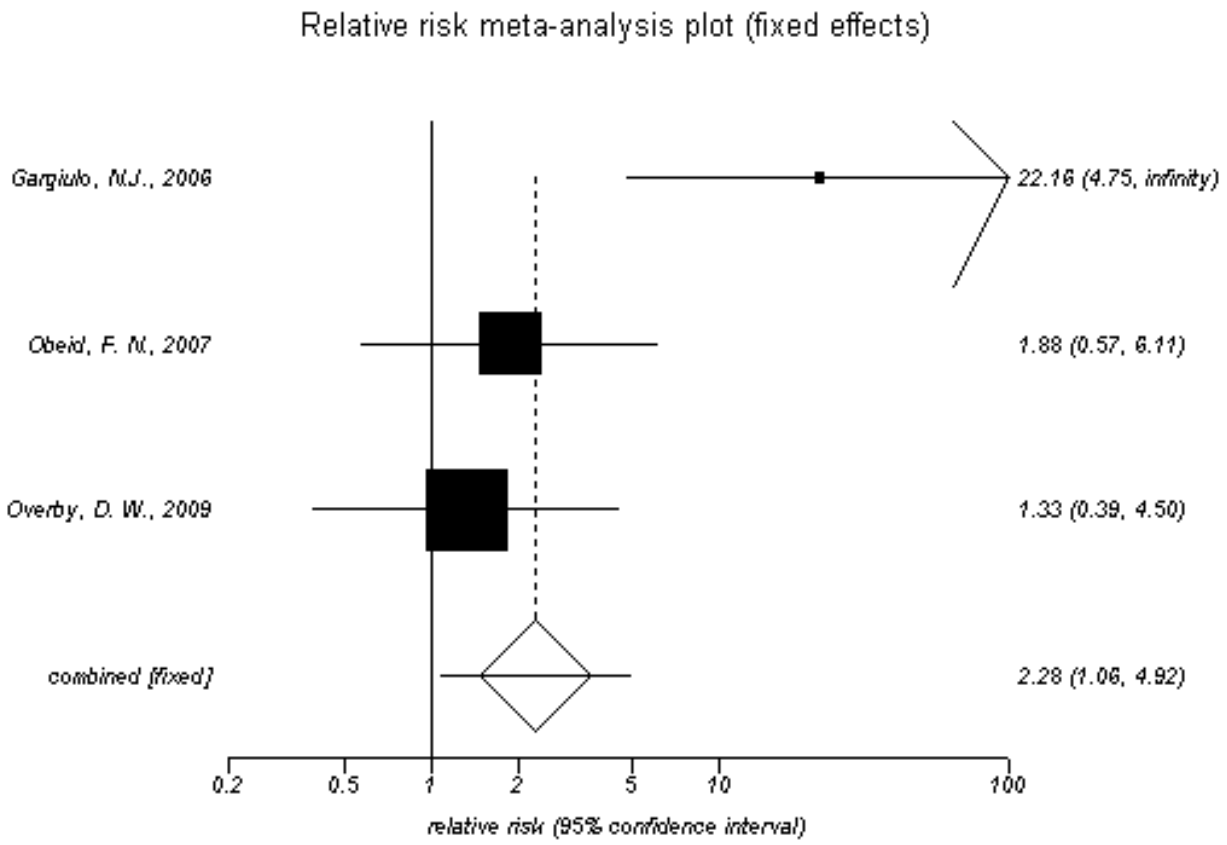
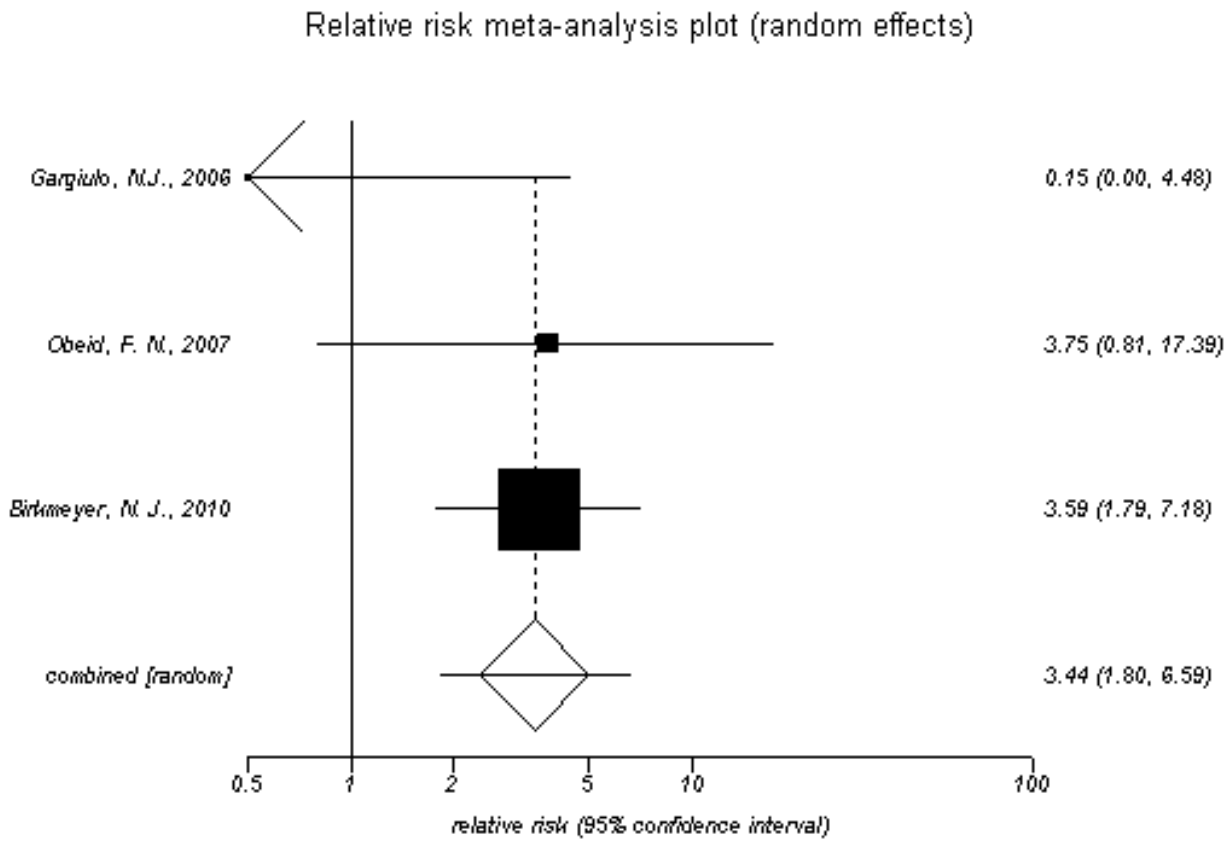


Figure 14 Relative Risk Meta-analysis of IVC Filter vs no filter on Mortality in bariatric surgery



Key Question 7: What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of venous thromboembolism during hospitalization of obese and underweight patients?

Key Points and Evidence Grades

- The strength of evidence is insufficient that fixed low dose dalteparin reduces the risk of VTE compared to placebo during hospitalization of obese patients.
- The strength of evidence is insufficient that fixed low dose dalteparin increase the risk of major bleeding compared to placebo during hospitalization of obese patients.
- The strength of evidence is insufficient to conclude that fixed low dose dalteparin reduces the risk of fatal PE compared to placebo during hospitalization of obese patients.
- The strength of evidence is insufficient to conclude that fixed low dose dalteparin increases the risk of mortality compared to placebo during hospitalization of obese patients.
- There were no studies that specifically evaluated underweight patients

Study Characteristics

A single retrospective subgroup analysis of obese patients (BMI>30 in men, and BMI>28.6 in women) from the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) reported on the comparative effectiveness and safety of medications for the prevention of VTE in obese patients.[148] The PREVENT trial was a multicenter RCT conducted in multiple hospitals in North America and Europe that enrolled 3,706 medically ill patients and randomized them to receive either a daily dose of 5,000 U of dalteparin or placebo. The inclusion criteria were acute congestive heart failure (New York Heart Association III and IV), acute respiratory failure, infectious disease, acute rheumatic disease, or inflammatory bowel disease. In patients with infectious, rheumatic, or inflammatory bowel diseases, at least one additional VTE risk factor had to be present: chronic congestive heart failure, age of 75 years or above, obesity, varicose veins, chronic oxygen requirement, cancer, history of VTE, hormone therapy, or a myeloproliferative syndrome. The exclusion criteria included coagulopathies, advanced liver and kidney disease, as well as recent major surgery.

Participant Characteristics

Of the 1,118 obese patients, 396 were men and 722 were women; 91 percent were Caucasians, and the median BMI was 32.9 kg/m^2. The top three primary medical diagnoses were New York Heart Association class III or IV heart failure, acute respiratory failure, and acute infectious diseases.

Intervention Characteristics

The study randomized patients to the dalteparin arm where they received 5,000 U subcutaneously daily or a placebo. Neither group received any additional concurrent prophylactic therapy.

Outcomes

Dalteparin versus Placebo

The primary endpoint was a composite of symptomatic VTE, fatal PE, sudden death, and asymptomatic proximal DVT detected by compression ultrasound administered to all patients by day 21, the results of which were adjudicated by a core ultrasound laboratory blinded to group assignment. Secondary endpoints were proximal symptomatic and asymptomatic DVT, major and minor bleeding, and thrombocytopenia by day 21; as well as all-cause mortality by days 21 and 90.

Primary Outcome

Primary outcomes were symptomatic VTE, fatal PE, sudden death, and asymptomatic proximal DVT. Among obese patients, the primary end point occurred in 2.8 percent of the dalteparin group (95% C.I. 1.3 to 4.3 percent), and in 4.3 percent of the placebo group (95% C.I. 2.5 to 6.2 percent), (RR, 0.64; 95% C.I. 0.32-1.28). Logistic regression analysis, modeling the probability of the primary endpoint, identified no interaction between dalteparin efficacy and the presence or absence of obesity (P = 0.63). The efficacy of dalteparin in the prevention of primary end points was attenuated in obese patients with a BMI of 40 or greater.

Fatal Pulmonary Embolisms

There were no fatal PEs in the obese patients.

Mortality

Among obese patients, dalteparin was associated with a statistically non-significant increase in mortality by day 21 (4.6 vs. 2.7 percent, P=0.14) and day 90 (9.9 vs. 8.6 percent P=0.36) compared to placebo.

Major Bleeding

Dalteparin in obese patients was not associated with an increase in major hemorrhage by day 21 (0 vs. 0.7 percent placebo; P>0.99) compared to placebo.

Other Adverse Events

Minor hemorrhage by day 21 and thrombocytopenia were not statistically significantly different between the patients with obesity randomized to dalteparin and to placebo.

Risk of Bias

The study was rated as moderate risk of bias due to methodologic limitations in design and reporting.

Strength of Evidence

We rated the strength of evidence as insufficient for all outcomes because of unknown consistency and imprecision.

Applicability

The findings of this study might be generalized to obese elderly hospitalized patients . These findings should not be generalized to patients with coagulopathies, advanced liver and kidney disease as well as recent major surgery. The majority of participants (92%) were white limiting generalizability to other ethnic groups.

Key Question 8: What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of venous thromboembolism during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

Key Points and Evidence Grades

- The strength of evidence is insufficient to assess the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis. We found no studies that directly assessed our KQ.
- The strength of evidence is insufficient that UFH at 5,000 U three times daily increases the risk of major and minor bleeding events in patients with severely compromised renal function (i.e., glomerular filtration rate (GFR) <= 30 ml/min) compared to this dose in patients without severely compromised renal function.

Study Characteristics

Five studies evaluated the effectiveness and safety of pharmacologic prophylaxis for prevention of VTE in patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis or patients receiving dialysis.[30, 149-152] However, none of these studies provided direct evidence relevant to our KQ.Two studies used a randomized, controlled, parallel arm design[30 149] and three were prospective cohort studies.[150-152] The studies used several definitions of renal impairment. Three studies used a GFR or creatinine clearance of less than 30 ml/min to designate severe renal impairment and 30-60 ml/min to signify moderate renal impairment; this was the most common definition.[149 150 152] Two of these same studies also included a group with mild renal impairment, defined as a GFR between 60-90 ml/min.[150 152] Other definitions of renal impairment were a creatinine clearance (CrCl) between 20-50 ml/min,[30] and patients treated with peritoneal dialysis.[151] The studies were international; two from Switzerland,[150 151] one from Germany,[149] one from France,[30] and one from Italy.[152] The studies included six to 189 patients.

Participant Characteristics

The studies did not uniformly report the age of the study participants. Among those that reported average age of the enrolled patients, it ranged from 61 to 88 years;[30 149] and for those that reported median age, it ranged from 53 to 80 years.[150 151] The study populations were between 17 to 100 percent male.[149-151 153 154] Only one study reported race and was one hundred

percent Caucasian.[150] One study reported that the median BMI ranged from 23 to 25 kg/m^2 across the study arms.[150]

Intervention Characteristics

The studies included diverse regimens with virtually no overlap. Therefore, we summarize the pharmacologic regimens for each study below.

Randomized, Controlled Trials

Participants in the study by Bauersachs et al. received UFH at 5,000 IU three times daily This trial also used certoparin, which is not approved in the U.S., therefore, we limited our summary to the UFH arm.[149]

In a study by Mahé et al., participants with a GFR of 20 to 50 ml/min received tinzaparin at 4,500 IU once daily or enoxaparin at 4,000 IU once daily.[30]

Prospective Cohort Studies

Schmid et al. compared dalteparin at 5,000 U per day in patients on peritoneal dialysis to dalteparin at 5,000 U per day in patients with normal renal function.[151]

Schmid et al. studied a regimen of dalteparin at 2,500 U per day for patients with body weight less than 50 kg, 5,000 U per day for patients with a body weight between 50 and 100 kg, and 7,500 U for patients with body weight greater than 100 kg, across each of the three renal function arms (GFR<30, GFR 30-60, and GFR >= 60 ml/minute).[150]

Tincani et al. gave dalteparin at 5,000 U daily for each of the three renal function arms (GFR<30, GFR 30-60, and GFR>=60 ml/minute).[152]

Outcomes

DVT/PE Outcomes

Randomized, Controlled Trial: Tinzaparin versus Enoxaparin

The trial which had a main endpoint of anti-Xa of drug did not record any VTE events in patients who received tinzaparin or enoxaparin.[30]

Randomized, Controlled Trial: Certoparin versus Unfractionated Heparin

As stated, one RCT compared the effectiveness of certoparin to unfractionated heparin. Since certoparin is not approved in the U.S., we could not use this trial to assess our KQ. However, the study stratified the results by renal function (GFR≤30 mL/min versus GFR>30 mL/min), allowing us to assess a question related to our KQ. The rate of DVT among patients treated with unfractionated heparin in patients with GFR greater than 30 mL/min was marginally lower than those with severe renal dysfunction (10.3 vs. 11.1 percent).

Single-arm, Prospective Cohort Studies: Dalteparin

A prospective cohort study of patients undergoing peritoneal dialysis who received 5,000 U of dalteparin did not report any VTE events.[151] Similarly, a prospective cohort studies of patients with renal insufficiency who received either 2,500 U, 5,000 U, or 7,500 U of dalteparin did not report any VTE events.[150 152]

Serum Anti-Xa Levels

In one RCT, enoxaparin accumulated to a greater extent from day one to day eight in elderly patients with renal impairment than did tinzaparin.[30] The ratio of maximum concentration on day eight to day one was 1.22 for enoxaparin and 1.05 for tinzaparin (p=0.016). The ratio of drug concentration area under the curve from day eight to day one yielded similar inferences, 1.26 for enoxaparin and 1.12 for tinzaparin. In a prospective cohort study, patients undergoing peritoneal dialysis experienced a non-significant increase in anti-Xa activity from day one to day four while receiving daily doses of dalteparin (p=0.06).[151] In a separate prospective cohort study by the same group, there was no evidence of significant accumulation of dalteparin over a 10-day period, even among patients with significant renal dysfunction.[150] In a third prospective cohort study, there was no evidence of bioaccumulation after six days of therapy with dalteparin in patients with renal dysfunction.[152]

Bleeding

In the relevant RCT, five bleeding events occurred in patients receiving tinzaparin versus four such events in patients receiving enoxaparin (p=0.67).[30] Three of these were major bleeds, two in the tinzaparin group and one in the enoxaparin group (p=0.61).

Patients with severe renal dysfunction who received 5,000 IU of UFH three times a day had an increased risk for all bleeds (relative risk (RR): 3.4, 95 percent CI: 2.0-5.9), major bleeds (RR: 7.3, 95 percent CI: 3.3-16), and minor bleeds (RR: 2.6 (95 percent CI: 1.4-4.9) compared to patients treated with UFH without severe renal dysfunction.[149]

In a prospective cohort study of patients with renal insufficiency receiving dalteparin prophylaxis, there were no major bleeding events and three minor bleeding events; creatinine clearance was between 30-60 mL/min in all the patients.[152]

Risk of Bias

We rated all observational studies related to this KQ as being at high risk of bias because of limitations in design. These studies were generally very small and researchers designed them for pharmacokinetic and bioaccumulation endpoints. We were unable to assess the level of surveillance for VTE events or the adequacy of adjustment for potential confounders between the groups. One RCT had a high risk of bias for our KQ because data from only one study arm was useful for our review.[149] (Appendix E)

Strength of Evidence

We rated the strength of evidence as insufficient to assess the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis. We based this rating on a lack of evidence that directly addressed our question (or evidence that was so inconsistent and at high risk of bias that it did not permit a conclusion).

We rated the strength of evidence as insufficient that 5,000 U of unfractionated heparin three times daily increases the risk of major and minor bleeding events in patients with severely compromised renal function (i.e., GFR <= 30 ml/min) 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. (Table 27)

Applicability

The design, analytic goals, patient populations and studied regimens were very diverse among these studies. No studies took place in the U.S. Additionally; no study squarely addressed our KQ, which pertained to the comparative effectiveness of pharmacologic prophylaxis agents in patients with varying degrees of renal dysfunction.

Table 27: Body of Evidence for Pharmacological Prophylaxis of Venous Thromboembolism in Patients with Renal Insufficiency

Author, year	Outcomes	Risk of bias	Directness	Precision	Consistency	Strength of evidence and magnitude of effect
Tinzaparin vs. enoxaparin						
	VTE	**High**	**direct**	**imprecise**	**unknown**	**Insufficient evidence to comment on effectiveness of tinzaparin vs enoxaparin in reducing VTE in patients with renal insufficiency**
Mahe, 2007[30]		High	direct	imprecise	unknown	0 events in 27 patients (tinzaparin) vs 0 events in 28 patients (enoxaparin)
	Bleeding	**High**	**direct**	**imprecise**	**unknown**	**Insufficient evidence to comment on the comparative safety of tinzaparin vs enoxaparin on bleeding in patients with renal insufficiency**
Mahe, 2007[30]		High	direct	imprecise	unknown	5 events/27 vs 4/28 (p=0.67)
	Cmax	**High**	**indirect**	**precise**	**unknown**	**Insufficient evidence to comment on Cmax of tinzaparin vs enoxaparin in patients with renal insufficiency**
Mahe, 2007[30]		High	indirect	precise	unknown	The ratio of Cmax on day eight to day one was 1.05 for tinzaparin and 1.22 for enoxaparin (p=0.016).
UHF in severe renal compromise vs all other renal status						
	VTE	**High**	**direct**	**imprecise**	**unknown**	**Insufficient evidence to comment on effectiveness of UFH in reducing VTE in severe renal compromise patients vs all other renal patients**
Bauersachs, 2011[149]		High	direct	imprecise	unknown	Insufficient evidence; 2.6% of patients had a VTE event
	Bleeding	**High**	**direct**	**imprecise**	**unknown**	**Insufficient evidence to comment on effectiveness of UFH in increasing bleeding in severe renal compromise patients vs all other renal patients**
Bauersachs, 2011[149]		High	direct	imprecise	unknown	Insufficient evidence; 13 events in 92 patients

VTE=venous thromboembolism, UFH=unfractionated heparin

Discussion

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high quality studies to inform these key questions for these special populations.

Evidence

Key Question 1. What is the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?

The strength of evidence is insufficient that prophylactic IVC filter placement when compared to no filter use is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma. We also found low grade evidence that prophylactic IVC filter placement is associated with an increased incidence of DVT in hospitalized patients with trauma when compared to no use of filters. We found insufficient evidence to comment on mortality associated with prophylactic IVC filter placement in hospitalized patients with trauma.

We noted the different filter brands may be associated with different complications but we did not have enough comparisons among different filter subtypes to evaluate the comparative effectiveness and safety of various filter subtypes.

We found low strength of evidence from the comparative observational studies that rates of filter- associated thrombosis were higher when prophylactic filters were placed compared to not in this patient population. The evidence was insufficient about rates of other filter complications. Several uncontrolled observational studies provided information on the rare occurrences of filter complications such as strut fracture, insertion site thrombosis, arterial-venous fistulas, filter misplacement, filter tilt, filter migration and IVC thrombosis. The low rates of such complications, the significant risks of bias in the included studies, and the lack of control groups precluded any definitive assessment of the comparative safety of different filter types in patients with trauma. Our review did not evaluate the safety of IVC filters in patients when used for treatment or prevention of recurrent PE where complication rates may be different.

We identified only a single RCT addressing this KQ and it had significant methodological limitations. This pilot trial randomized patients to usual care plus IVC filters vs. usual care but was underpowered for all outcomes. Most studies in our database were assessed as having a high risk of bias except five observational studies which were assessed as having a moderate risk of bias. There was significant heterogeneity among the included studies in design and eligibility, and inconsistency in efficacy and safety outcome assessment methods. Although many of the studies reported on the VTE outcomes, most did not provide details about anatomic locations of the DVTs or PEs. Some studies did not distinguish between DVT and PE. However prophylactic IVC filters may have opposing effects on DVTs and PEs, increasing the rates of DVTs and potentially reducing the risk of PE. There were also differences in reporting and duration of follow-up. The included studies lacked adequate details about enrolled patient characteristics, such as race and gender, and details of the extent and severity of the trauma limiting our ability to generalize findings from these studies to other ethnic groups or age categories. There has been a wide variation in the use of IVCFs in trauma centers which cannot be explained by patient

characteristics.[155] This variation could lead to selection bias for any observational studies of IVCFs.

Our current finding should be interpreted in the context of other systematic reviews on this topic. A recent review conducted a qualitative synthesis of data from 24 studies and found increasing use of retrievable filters and low rates of filter related complications.[33] The authors concluded that there was a lack of high quality data, and therefore the true efficacy of prophylactic IVC filters for prevention of PE in trauma patients remains unclear. They reported that data from case series suggested a reduction in PE and fatal PE in high-risk poly-trauma patients who may have contraindications to DVT prophylaxis. A review from 2006, endorsed by the American Venous Forum, found that the evidence on optional IVC filters was not sufficient to support evidence-based recommendations.[34] Similarly, we only found low grade evidence that IVC filter placement compared to no IVC filter placement is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma, and low grade evidence that prophylactic IVC filters placement is associated with an increased incidence of DVT in hospitalized patients with trauma.

There are conflicting guidelines on this topic. The practice guideline from the Eastern Association for the Surgery of Trauma recommends that insertion of a prophylactic IVC filters *should be considered* in very high risk trauma patients. [35]These include patients who cannot receive anticoagulation because of increased bleeding risk and have severe closed head injury (GCS < 8), incomplete spinal cord injury with part or quadriplegia, complex pelvic fractures with associated long-bone fractures, or multiple long-bone fractures (Level 3 recommendation). However, this guideline is 10 years old and was based primarily on data using permanent IVCFs. A recent American College of Chest Physicians (ACCP) review suggested that that placement of an IVC filter probably reduces the risk of PE over the short term, but notes that the complications are "frequent" and long term outcomes are unclear. [36] This group noted that removable filters may mitigate the long-term complication rate, but also noted that they are often not removed. Thus the ACCP guidelines *recommends against* IVC filters for primary VTE prevention in patients with trauma (Grade 2C).[36]

Key Question 2a. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with traumatic brain injury?

Key Question 2b. What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent VTE in hospitalized patients with traumatic brain injury?

Six studies evaluated pharmacologic and mechanical strategies in hospitalized patients with traumatic brain injury. There was insufficient evidence to support that enoxaparin is more effective than unfractionated heparin in preventing PE and lowering mortality in hospitalized patients with traumatic brain injury. We also found insufficient evidence to support that enoxaparin when compared to heparin led to fewer bleeding complications. We found insufficient evidence to support that enoxaparin is more effective than intermittent pneumonic compression in preventing DVTs. We found insufficient evidence to support that intermittent pneumatic compression devices are more effective than enoxaparin in preventing PEs. We found

low grade evidence that UFH reduced the rates of total mortality compared to no pharmacoprophylaxis in hospitalized patients with traumatic brain injury

We found only one RCT that addressed DVT prophylaxis in patients with traumatic brain injury. The remaining studies were single-center cohort studies, the majority of which were retrospective. Although the studies in this review asked similar questions (i.e., enoxaparin vs. heparin, pharmacologic prophylaxis vs. IPCs) and had similar patient populations, the scarcity of RCTs prevents definitive conclusions. The majority of the cohort studies were assessed as having a high risk of bias.

When looking at progression of ICH, we found insufficient evidence favoring enoxaparin when compared to unfractionated heparin or no use of chemoprophylaxis. When compared to intermittent pneumatic compression, there was insufficient evidence to support that enoxaparin reduces the risk of ICH exacerbation.

Five retrospective cohort studies evaluated the timing of pharmacologic prophylaxis in patients with traumatic brain injury. We found insufficient evidence to support that early (< 72 hours) compared to late administration of enoxaparin (> 72 hours) led to differences in progressions of ICH. The lack of large RCTs precludes any definitive conclusions about the timing and initiation of prophylaxis in patients with brain trauma.

Our results should be interpreted in the context of other systematic reviews and existing guidelines. We did not identify any existing systematic reviews about the role of DVT prophylaxis, and its optimal timing and initiation in patients with traumatic brain injury. The two organizations, EAST and the Traumatic Brain Foundation, that provide guidelines for the care of the patients with trauma and patients with traumatic brain injury, respectively, do not make specific recommendations about DVT prophylaxis in these patients. The Eastern Association for the Surgery of Trauma (EAST) practice guidelines address DVT prophylaxis in the general trauma patient but do not make specific recommendations about patients with brain trauma. In 2007, the Brain Foundation Guidelines for the Management of Severe Traumatic Brain Injury found no good quality data to support the use of DVT prophylaxis in TBI patients. They found level III evidence for IPC and chemoprophylaxis, while stating that "there is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis." Additionally, the ACCP guidelines do not specifically address DVT prophylaxis in these patients.

Key Question 3. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns?

The strength of evidence was insufficient about the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns. The only included cohort study of IVC filter placement was at high risk of bias with significant methodological limitations. It included just 20 patients and did not have a control group. The very high mortality rate in this study (9 out of 20 participants) was likely related to multi-organ failure. Thus, we could not draw any meaningful conclusions[37] on the comparative effectiveness and safety of IVC filters. We did not find any studies that evaluated the comparative effectiveness and safety of pharmacologic strategies in the prevention of VTE among patients with burns.

There are several unanswered clinical questions for patients with burns. These patients are at elevated risk of both VTE and bleeding and the optimal prophylaxis remains unknown. Although the study we reviewed reported that the burned body surface area was not associated with thrombotic complications,[156] this remains unclear.

Clinicians, policymakers, and other decision makers should interpret our findings in the context of existing recommendations for VTE prevention among hospitalized patients with burns. The ACCP 2012 guidelines do not provide specific recommendations for preventing VTE in patients with burns.[38] The 2008 ACCP guidelines recommend routine thromboprophylaxis for burn patients having additional risk factors for VTE (Grade 1A).[157] The guidelines also recommend either low-dose unfractionated heparin or low molecular weight heparin as soon as it is safe (Grade 1C). For patients at risk of bleeding, the guidelines recommend mechanical thromboprophylaxis with graduate compression stockings and or intermittent pneumatic compression until the bleeding risk decreases (Grade 1A). [157]

Key Question 4. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

We found no studies that directly address the comparative effectiveness and safety of pharmacologic strategies among patients with liver disease. Previous studies have estimated that 0.5 to 6.3 percent of patients with chronic liver disease experience VTE. These studies characterize chronic liver disease as a condition complicated by thrombocytopenia and by prevalent portal vein thrombosis.[158] The correlation between international normalized ratio values and VTE risk remains unclear.[159]

There are no specific recommendations for prophylaxis in patients with chronic liver disease. The specific reasons for the lack of evidence on hospitalized patients with liver disease are unclear, but may include exclusion of such high-risk patients from trials.

Key Question 5. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

We found no studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies among hospitalized patients receiving antiplatelet therapy. Similarly, we know of no specific recommendations for prophylaxis in hospitalized patients receiving antiplatelet therapy. The specific reasons for the lack of evidence on hospitalized patients receiving antiplatelet therapy are unclear, but may include exclusion of such patients at an elevated risk of bleeding from trials. Alternatively, trials may have included such patients, but did not adequately report subgroup data.

Key Question 6. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in patients having bariatric surgery?

We found low grade evidence that the placement of IVC filters is associated with an increased risk of DVT in the bariatric surgery population. Other complications of filter

placement occasionally occur, some of which may be fatal.[146] In each of the studies that we included, physicians ultimately removed more than two-thirds of the retrievable filters placed. Because bariatric surgery requires close followup and medical compliance, there may be relatively high rates of filter retrieval in this patient population and a lesser likelihood of long-term filter-related complications. There was marked practice variation in filter use for VTE prophylaxis among hospitalized patients undergoing bariatric surgery, beyond what could be explained by differences in the patient populations. Birkmeyer et al observed an attenuation of the unadjusted association between the use of IVC filters and adverse clinical outcomes after propensity score adjustment. This suggests that the process of selecting patients for filters based on VTE risk may bias toward a lack of filter efficacy, or the appearance of harm.[39]

In the absence of RCTs, we were unable to determine the comparative effectiveness and safety, or the optimal timing and duration of prophylactic pharmacotherapy. The observational studies did not provide a clear association between the use of pre-operative initiation of pharmacologic prophylaxis and perioperative bleeding, or between post-operative initiation of pharmacologic prophylaxis and thrombosis. A study of extended prophylaxis versus inpatient prophylaxis suggested that continuing enoxaparin therapy for 10 days discharge may be associated with a lower risk of VTE, when compared to shorter therapy.[40] However, since this cohort study adopted longer-term treatment during its later years, there were other changes that may have impacted VTE rates favorably, such as shorter surgery durations, fewer open procedures, and shorter lengths of stay, which precludes any definitive conclusions. The rate of fatal pulmonary emboli appears to be low in patients receiving pharmacologic prophylaxis.

Pharmacokinetic data from two studies suggest that “subtherapeutic” anti-Xa levels are common when patients receive standard prophylactic doses of enoxaparin, particularly 30 mg twice daily, and that “supratherapeutic” levels are common when patients receive doses of 60 mg twice daily. However, the extent to which anti-Xa levels predict bleeding in obese patients undergoing bariatric surgery is unknown. Consistent with current practice, the majority of the studies emphasized the use of IPC devices, compression stockings, and early ambulation. Additionally, the studies that focused on IVC filters generally included patients receiving concurrent pharmacologic prophylaxis. The efficacy and safety of these modalities of prophylaxis remains unclear. One study, not included in our review, reported low rates of adverse outcomes in patients undergoing bariatric surgery who did not receive either IVC filters or pharmacologic prophylaxis.[160] This study excluded patients with prior VTE. The study used a prophylactic strategy that included calf-length pneumatic compression devices and early ambulation, and the authors sought to maintain short operative times (averaging 106 minutes). This study, which included 957 patients, reported rates of DVT at 0.31 percent, PE at 0.10 percent, and major bleeding at 0.73 percent. Notable in this study, as well as other studies we included, is that ambulation is often possible within 24 hours of bariatric surgery. The relatively short operative times, laparoscopic approach, and early ambulation may attenuate the VTE risk of laparoscopic bariatric surgeries, despite the large body habitus of those patients undergoing bariatric surgery.

Our results suggest that there may be a higher rate of bleeding with augmented dosing regimens, with no evidence of increased efficacy. These results are generally consistent with the findings from a previous systematic review and meta-analysis conducted by Becattini et al.[41] In contrast to our comparative effectiveness review, which evaluated only comparative studies of pharmacologic regimens, Becattini et al. also included uncontrolled single-arm studies of pharmacologic prophylaxis. They concluded that the incidence of symptomatic postoperative

VTE appeared to be less than 1 percent with either prophylactic strategy, but that with screening, the rate was approximately 2 percent. Because definitions of major bleeding varied, the authors applied, where possible, the International Society of Thrombosis and Haemostasis definition of major bleeding in an effort to standardize the bleeding rates across studies.[161] Using this standardized definition, bleeding rates were approximately 1 percent for standard-dose regimens, and 1.6 percent for weight-adjusted (augmented) pharmacological prophylaxis. The authors concluded that there might be a higher rate of bleeding with augmented dosing regimens with no evidence of increased efficacy similar to our findings.

In the absence of RCTs among patients undergoing bariatric surgery, the ACCP evidence-based clinical practice guidelines used data from trials in other populations such as patients undergoing abdominal and pelvic surgery.[162]These guidelines suggest that clinicians follow the manufacturer's recommendations for dosing of pharmacotherapy, but also state that it may be prudent to consult with a pharmacist regarding dosing in bariatric surgery patients and other patients who are obese who may require higher doses of unfractionated heparin or low molecular weight heparin. The guidelines do not make any recommendations regarding the use of filters in bariatric surgery patients.

Key Question 7. What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?

We found only one subgroup analysis of an RCT that reported on the comparative effectiveness and safety of fixed low-dose dalteparin 5000 IU/day versus placebo among hospitalized obese patients with a BMI less than 40kg/m^2. However the strength of evidence was insufficient on the composite endpoint of DVT, PE and sudden death; and the outcomes of mortality and bleeding. We did not find any evidence about the role of other pharmacologic or mechanical strategies among hospitalized obese patients. There were no studies among patients who are underweight. Previous ACCP guidelines recommended a weight based administration of low molecular weight heparins among obese patients.[157] The FDA-approved dosing provides no specific dose adjustment for obese patients.

Key Question 8. What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

Despite that patients with compromised renal function who require pharmacologic VTE prophylaxis are highly common; we found insufficient evidence to guide treatment decisions. Our findings are consistent with two other recently published reviews. The ACCP guidelines make dosing recommendations for the *therapeutic* use of LMWH. [42 43] 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-Xa levels are consistent with ours. The ACCP guidelines also suggest that decreased clearance of LMWHs has been associated with increased risk of bleeding events for patients with severe renal insufficiency. However, the cited study 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 LMWH therapy, that is, above the baseline increased risk of bleeding among patients with renal insufficiency.

The product labeling for the drugs in our review all recommend decreased dosing for VTE prophylaxis in patients with renal insufficiency. However, these recommendations are not backed by cited peer-reviewed literature.

Limitations

Our systematic review identified important weaknesses in the literature. We did not identify high quality RCTs on any of these KQs. The RCTs identified for some of these KQs were small and had methodological limitations. The majority of observational studies included in this review were at high risk of bias and did not report on several quality items of interest. The greatest risk to their validity was confounding by indication in that the sicker patients received more intense prophylaxis than the less sick patients, with no or inadequate adjustment for differences between treatment groups. The studies were heterogeneous in definition of VTE and bleeding outcomes precluding any meaningful pooling in a meta-analysis. We also did not find data on several pharmacologic comparisons of interest or details about appropriate dosing strategies in these special populations.

Our systematic review has several limitations. Although our search strategy was comprehensive, we may have missed studies. We were unable to assess the possibility of publication bias or selective outcomes reporting and its impact on our findings.

Future Research

Our report highlights the need for several areas of research on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE among these special populations. There remains a significant research gap regarding the efficacy and safety for IVC filters for PE prophylaxis in trauma patients. Such a study would ideally include sufficient participants with traumatic brain injury, an important subgroup of trauma patients. A large, multi-center RCT is required to definitively answer the question on the efficacy and safety of IVC filters in trauma and patients with traumatic brain injury.[34]The American Venous Forum and the Society of Interventional Radiology Multidisciplinary Consensus Conference which has placed a high priority on studies of IVCFs in trauma[34] A carefully matched cohort or large trauma registry based study may also be informative on this KQ. Specific filter related information including timing, indication, type, as well as complications, could be incorporated into trauma registries and the National Trauma Data Bank (NTDB) to allow further studies. Future studies should also attempt to determine the reasons for low retrieval rates to decrease the rate of filter related complications through timely removal of IVCFs that are no longer necessary. Future research should also consider whether decision analysis that weighs the benefits of IVC filters to prevent PE outweighs their potential negative impact via short- and long- term adverse outcomes including a potentially higher rate of DVT. Studies among patients with traumatic brain injury are still needed to determine whether pharmacologic DVT prophylaxis should be used for these patients, and the timing of administration. Studies should also determine the role of appropriate classification and severity of traumatic brain injury when deciding to administer pharmacologic prophylaxis.

Among patients with burns, studies are needed to clarify the relationship between the burned surface area and thrombotic complications. Burns may induce pathophysiological changes that

alter the pharmacokinetic parameters of drugs, such as volume of distribution and clearance.[163] Studies are also needed to determine whether the altered pharmacokinetics of enoxaparin may result in inadequate dosing in burn patients, and whether dose-adjustment of enoxaparin based on serum anti-Xa monitoring [44] is warranted. Trials conducted in this population would be ideal but may not be feasible. In the absence of RCTs, robust observational studies with validated measures of exposure to the pharmacologic and mechanical interventions and VTE outcomes may also provide useful information. Such studies need to control for confounding by indication, such as provider and practice patterns, and confounding by disease severity, such as total body surface area burned.

It appears unlikely that researchers will conduct RCTs for patients with liver disease. However, future research should include high-quality observational studies to determine the comparative effectiveness and safety of various pharmacological and mechanical strategies among patients with liver disease. Such studies should also characterize the relative risks of bleeding and thrombosis across stages of liver disease.

Trials of pharmacoprophylaxis should consider reporting rates of VTE and bleeding among subgroups of patients receiving antiplatelet therapy. Future research should include high-quality observational studies to determine the comparative effectiveness and safety of pharmacological and mechanical strategies among hospitalized patients receiving antiplatelet therapy.

RCTs may be useful to evaluate the efficacy and safety of IVC filters in high-risk bariatric surgery patients, although may not be feasible. Such trials should include only those patients deemed to be at highest risk for VTE complications, such as those with prior VTE. Randomized trials should also address whether standard doses of prophylaxis that have been proven safe and effective in other types of surgery (such as 5,000 units of subcutaneous unfractionated heparin three times daily, enoxaparin 30 mg twice daily, or enoxaparin 40 mg once daily) are adequate for patients undergoing bariatric surgery. Clinical trials should consider weight-based dosing compared to fixed-dosing, rather than comparing BMI-based dosing compared to fixed-dosing. This is because low molecular weight heparins, when used for treatment of VTE, are dosed based on actual body weight; at a given BMI, a heavier (and taller) patient would be expected to have lower blood levels of drug than a lighter (and shorter) patient. Although one non-randomized study suggested that VTE rates may be acceptably low without any pharmacologic or filter prophylaxis, pharmacologic VTE prophylaxis in other studies had an acceptable safety profile. Thus, randomized trials that do not utilize active therapy may not be feasible because of the established efficacy and safety of pharmacologic VTE prophylaxis in other surgical settings and the inconsistent and variable use of non-pharmacological prophylactic measures.

RCTs should evaluate the comparative effectiveness and safety of LMWHs in obese and underweight patients. Such trials need to ensure that those at both extremes of weight the underweight (BMI < 18 kg/m2) and severely obese (BMI > 40 kg/m2) are adequately represented in these trials. Randomized controlled trials of VTE prevention should also consider adequately reporting data on subgroups of obese and overweight patients. There may be sufficient numbers of subjects with renal impairment in completed trials whose analysis by subgroups may yield useful information. Future trials should seek to enroll a subpopulation of patients with renal insufficiency. Retrospective or observational studies could also provide useful evidence.

We found that very few observational studies used appropriate statistical techniques to analyse data. We identified very few studies that used propensity score methods.[39] Even the use of multivariate regression techniques was limited. Our report shows that confounding by indication was a major problem in these studies. Future studies should consider the use of appropriate analytic strategies such as instrumental variables which control for unobserved variables if an appropriate instrument can be identified for analysis.

Conclusion

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high quality studies to inform these key questions for these special populations. Our systematic review identified important weaknesses in the literature. Future research using high quality observational studies that control for confounding by indication, such as provider and practice patterns, and confounding by disease severity may be needed as randomized controlled trials typically exclude or do not report on these special populations.

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