Comparative Effectiveness Review
Number 116

Effective Health Care Program

Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations

Executive Summary

Introduction

Background

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are collectively known as venous thromboembolism (VTE). VTE affects an estimated 900,000 Americans every year, resulting in significant morbidity and mortality.[1,2] Although the average annual incidence of DVT currently ranges from 48 to 122 per 100,000 in the United States,[1,2] rates will rise with the aging population. There are significant adverse consequences of DVT and PE,[1] including an estimated 300,000 fatalities annually and hundreds of thousands of hospitalizations in nonfatal cases.[1,2] In addition, a diagnosis of DVT or of PE in the hospital increases the costs of the hospitalization by roughly $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

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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in "special populations." Special populations are those patients for whom the benefit and risk of VTE prophylaxis are uncertain, or patients for 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] Some of these patient groups have a 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 for patients with altered clearance of medications.[26-30]

Therapies of Interest

In this review, we describe the evidence for drugs and devices that are currently available in the United States, and are either FDA approved for VTE prophylaxis or are used off label by clinicians for this indication. We included studies of unfractionated heparin (UFH) and low molecular weight heparins (LMWH) delivered subcutaneously,[26-29] as well as fondaparinux, a synthetic pentasaccharide. Similarly, we included antiplatelet agents 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 dabigatran for the prevention of stroke in patients with atrial fibrillation, but it also has the potential for off-label use for prophylaxis of VTE. Rivaroxaban was included; it 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.[4]

Key Questions

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

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

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

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

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

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

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

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

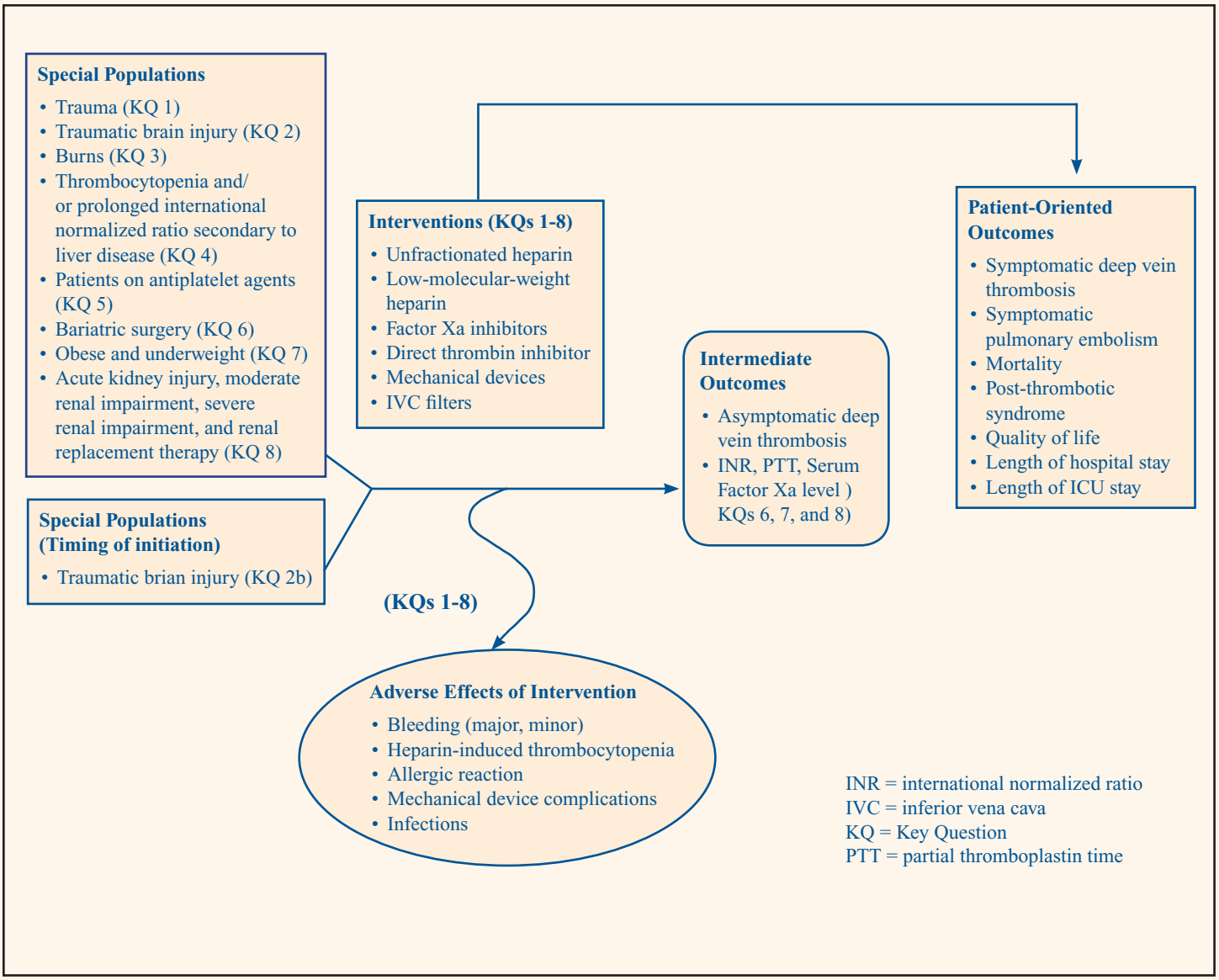
KQ 7. What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?

KQ 8. What are 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, therapies, and intermediate and clinical outcomes we reviewed, as well as the adverse consequences associated with these prophylactic regimens.

Figure A. Analytic framework: Pharmacologic and mechanical prophylaxis of venous thromboembolism among special populations



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" (www.effectivehealthcare.ahrq.gov/methods guide.cfm).

Search Strategy

We searched the following databases for primary studies through July 2012: MEDLINE®, Embase®, SCOPUS, CINAHL®, International Pharmaceutical Abstracts, clinicaltrials.gov, and the Cochrane Library. 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 may have been missed in the original search. In addition, we requested and reviewed Scientific Information Packets (SIPs) 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; we excluded abstracts only if both investigators agreed that the article met one or more of the exclusion criteria. We resolved disagreements by consensus. The inclusion and exclusion criteria are shown in Table A. The population, intervention, comparator, outcome, timing, and setting are shown in Table B.

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.

Assessment of Methodological Quality of Individual Studies

We conducted the risk of bias assessment 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 did not consider any study without randomization to have a low risk of bias.

Data Synthesis and Analysis

For each KQ, we created a detailed set of evidence tables containing all information abstracted from eligible studies, and grouped the information by comparison interventions and qualitatively synthesize the results. For studies amenable to pooling quantitatively, we conducted meta-analysis using relative risks by using a DerSimonian and Laird random effects model.[32] Since most of the outcomes were rare and several studies had zero events, we used the treatment arm continuity correction to estimate the relative risk.[33] We conducted sensitivity analysis using alternative continuity corrections (0.5, 0.1), as well as no continuity correction (Peto Odds Ratio).[33] All analyses were conducted using Stats Direct and Stata version 11.0. When there was substantial statistical and clinical heterogeneity we did not report pooled results but displayed the relative risks with 95% confidence intervals for the individual studies. For KQ 1, we calculated 95% exact binomial confidence intervals surrounding the proportions of patients experiencing events in each of the observational studies. These were plotted ordered by the year of the study, with the size of the box representing the number of individuals in the denominator.

Grading the Evidence for Each KQ

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 Comparative Effectiveness Reviews."[34] In assigning evidence grades, we considered the four recommended domains: 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)

4. Insufficient grade (evidence is unavailable). A single high risk or moderate risk of bias study was considered to be insufficient evidence.

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."[34] We evaluated whether the included 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 individual studies that 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 co-interventions (early ambulation), and the choice and dosing of comparators.

Peer Review and Public Comment

A full draft report was reviewed by experts and posted for public commentary from August 2, 2012, through August 30, 2012. Comments received from either invited reviewers or through the public comment Web site were compiled and addressed. A disposition of comments will be posted on the Effective Health Care Program Web site 3 months after the release of the evidence report.

Table A. Study inclusion and exclusion criteria

PICOTS	Inclusion	Exclusion
Populations	• Human subjects (only) • Adults in special patient populations, including: ◆ Trauma ◆ Traumatic brain injury ◆ Burns ◆ Liver disease ◆ Antiplatelet therapy ◆ Bariatric surgery ◆ Obese and underweight ◆ Acute kidney injury, moderate renal impairment, severe renal impairment, renal replacement therapy	• Animal studies/models • Children • Pediatric • Adolescent • Adults in the following patient populations: ◆ Treatment of VTE ◆ Secondary prophylaxis ◆ Catheter thrombosis ◆ Antiphospholipid antibodies/other autoimmune diseases ◆ Cancer (malignancy, chemotherapy, radiotherapy) ◆ Cardiovascular (coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty) patients on full-dose anticoagulation ◆ Pregnancy ◆ Disseminated intravascular coagulation ◆ Heparin-induced thrombocytopenia ◆ Congenital platelet disorders ◆ VTE prophylaxis for long distance travel ◆ Abdominal surgery ◆ Vascular surgery ◆ Urological surgery ◆ Gynecological surgery
Intervention	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

Table A. Study inclusion and exclusion criteria (continued)		
PICOTS	**Inclusion**	**Exclusion**
Outcomes	• 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 6, 7 and 8)	No data on relevant outcomes of interest
Type of Study	We included the following study designs • Randomized controlled trials • Prospective cohort studies • Retrospective cohort studies • Case-control studies • Uncontrolled case-series for devices • Case reports of device complications in the relevant special populations • 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

ICU = intensive care unit; INR = international normalized ratio; PTT = partial thromboplastin time; VTE = venous thromboembolism

Table B. PICOTS (population, intervention, comparator, outcome, timing, and setting) for each Key Question

PICOTS	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

Table B. PICOTS (population, intervention, comparator, outcome, timing, and setting) for each Key Question (continued)

PICOTS	KQ 1	KQ 2	KQ 3–KQ 5	KQ 6	KQ 7–KQ 8
Outcomes measures	• Symptomatic DVT • Symptomatic PE • Asymptomatic • DVT • Bleeding • Mortality • Post-thrombotic syndrome • Quality of life • Length of stay • Allergic reaction • Mechanical device complications Infections	• Symptomatic DVT • Symptomatic PE • Asymptomatic • DVT • Bleeding • Mortality • Post-thrombotic syndrome • Quality of life • Length of stay • Length of ICU stay Heparin-induced thrombocytopenia • Allergic reaction Mechanical device complications Infections	• Symptomatic DVT • Symptomatic PE • Asymptomatic • DVT • Bleeding • Mortality • Post-thrombotic syndrome • Quality of life • Length of stay • Heparin-induced thrombocytopenia • Allergic reaction • Mechanical device complications • Infections	• Symptomatic DVT • Symptomatic PE • Asymptomatic • DVT • Bleeding • Mortality • Post-thrombotic syndrome • Quality of life • Length of stay • Heparin-induced thrombocytopenia • Allergic reaction • Mechanical device complications • Infections	• Symptomatic DVT • Symptomatic PE • Asymptomatic • DVT • Bleeding • Mortality • INR, PTT, Factor Xa level (KQs 7and 8) • Post-thrombotic syndrome • Quality of life • Length of stay • Bleeding (major, minor) • Heparin-induced thrombocytopenia • Allergic reaction • Mechanical device complications • Infections
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; INR = international normalized ratio; IVC = inferior vena cava; KQ = Key Question; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PTT = partial thromboplastin time; SCD = sequential circumferential compression device; UFH = unfractionated heparin

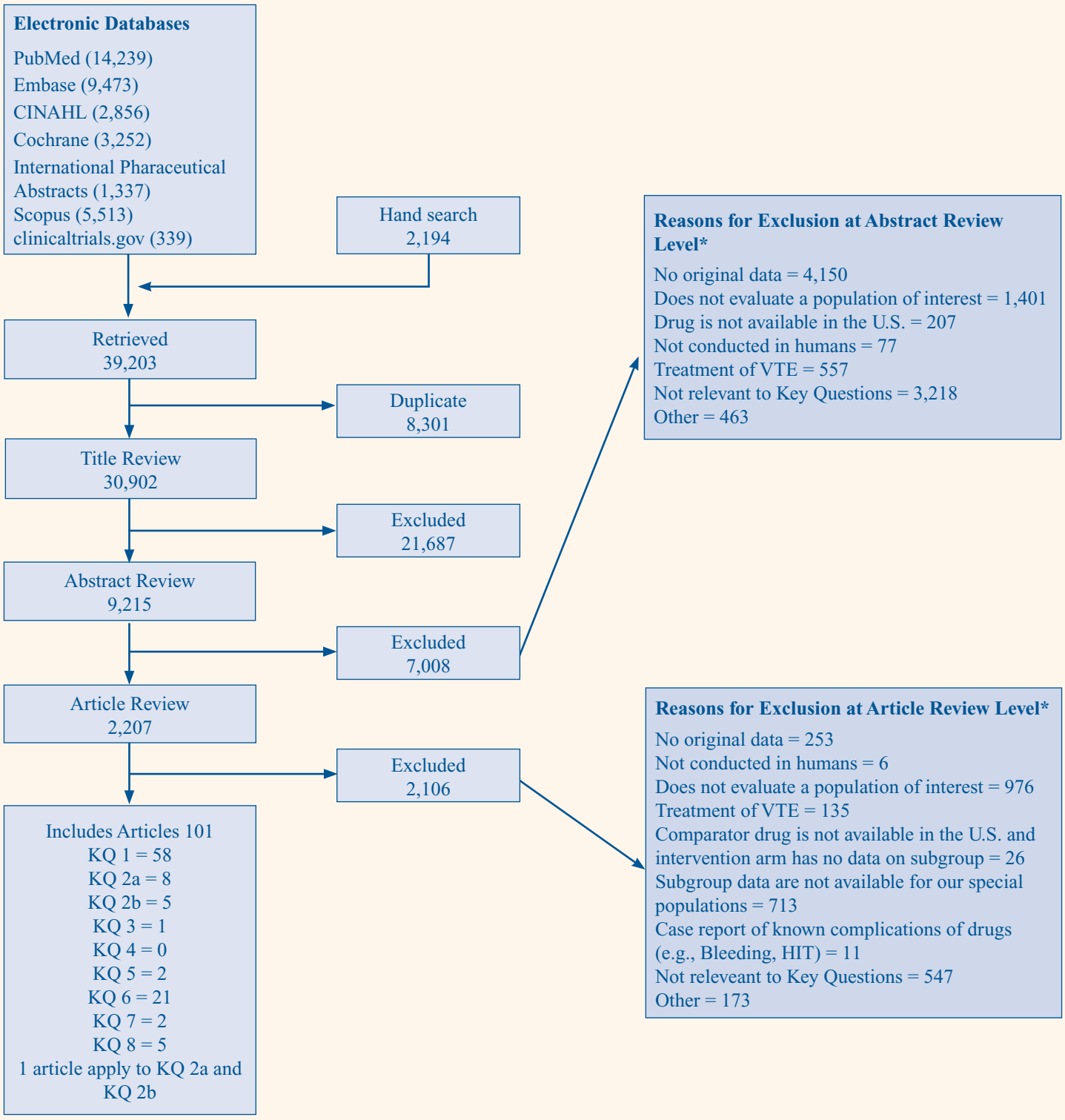
Results

Search Results

Figure B summarizes the search results. The literature search identified 30,902 unique citations. We excluded 21,687 of these citations during title screening, and 7,008 during abstract screening. An additional 2,106 articles were excluded at the article screening level because they did not meet one or more of the inclusion criteria (Table A).

One hundred and one articles were included in the review. Only six were randomized controlled trials. Of the included studies, 58 studies compared the effects of IVC filter use in patients with trauma, 12 studies compared the effects of pharmacoprophylaxis in patients with traumatic brain injury, and one study reported on patients with burns. We did not identify any studies among patients with liver failure. Twenty-one studies reported on patients with obesity surgery, two reported on antiplatelet therapy, and five reported on patients with renal failure.

Figure B. Summary of the literature search



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

Results by Population

KQ 1. Patient With Trauma

Fifty-eight studies addressed this KQ. Most studies had a high risk of bias except five observational studies that had a moderate risk of bias (Table C).

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

KQ 2a. Patients With Traumatic Brain Injury

There were eight studies that evaluated the effectiveness and safety of pharmacological and mechanical strategies in patients with traumatic brain injury. Most studies had a high risk of bias (Table C). The insufficient strength of evidence rating was based on either inconsistency in the body of evidence, our inability to assess consistency (consistency unknown), imprecision in the outcomes reported, or a high risk of bias in the included studies.

- The strength of evidence is low that enoxaparin reduces the rates of DVT compared with no pharmacoprophylaxis.
- The strength of evidence is low that UFH reduces total mortality compared with no pharmacoprophylaxis.
- The strength of evidence is insufficient to comment on the comparative effectiveness and safety of any other pharmacological and mechanical strategies on VTE outcome and bleeding.

KQ 2b. Patients With Traumatic Brain Injury

Five studies evaluated the effectiveness and safety of early (<72 hrs) versus late pharmacoprophylaxis (>72 hrs) in patients with traumatic brain injury (Table C). All studies were rated to be at high risk of bias. Estimates were often imprecise and inconsistent 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 VTE, DVT, PE, fatal PE, total mortality, major and minor bleeding.

KQ 3. Patients With Burns

- There was just one study for 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. 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.

KQ 4. Patients With Liver Disease

We found no studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies for VTE prevention in patients with liver disease.

KQ 5. Patients Receiving Antiplatelet Therapy

We found two studies addressing this question.

- The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic rivaroxaban with enoxaparin in patients concomitantly treated with antiplatelet agents.
- The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic dabigatran with enoxaparin in patients concomitantly treated with aspirin.

KQ 6. Patient Having Bariatric Surgery

There were 21 observational studies on this question. Most studies had a high risk of bias, with either inconsistent or unknown consistency of findings across studies (Table C).

In hospitalized patients having bariatric surgery:

- The strength of evidence is low that prophylactic IVC filters do not decrease the risk of PE relative to no filter use, in patients also receiving noninvasive mechanical measures.
- The strength of evidence is low that prophylactic inferior vena cava filters increase the risk of all-cause death relative to no filter use, in patients also receiving noninvasive mechanical measures.
- The strength of evidence is insufficient that prophylactic inferior vena cava filters increase the risk of post-operative DVT relative to no filter use, in patients also receiving noninvasive mechanical measures and pharmacological prophylaxis.

- The strength of evidence is insufficient that prophylactic inferior vena cava filters decrease the risk of fatal PE relative to no filter use, in patients also receiving noninvasive mechanical measures.
- The strength of evidence is insufficient to support the comparative effectiveness and safety of any pharmacological strategies.

KQ 7. Hospitalized Patients Who Are Obese or Underweight

We included two studies on this Key Question. We rated the strength of evidence as insufficient for all outcomes because of unknown consistency and imprecision.

- The strength of evidence is insufficient to comment on the effectiveness of prophylaxis with fixed-dose dalteparin over placebo in reducing VTE in hospitalized obese patients.
- The strength of evidence is insufficient to comment on the effectiveness of prophylaxis with fixed-dose dalteparin over placebo in reducing major bleeding and mortality in hospitalized obese patients.
- The strength of evidence is insufficient to comment on whether fixed-dose enoxaparin at 40 mg dose compared with various weight-based dosing regimens (0.4 mg/kg or 0.5 mg/kg of enoxaparin) differ in achieving target anti-factor Xa level in obese hospitalized patients.
- There were no studies that specifically evaluated underweight patients.

KQ 8. Patients With Renal Insufficiency or Failure

We included five studies on this Key Question (Table C).

- The strength of evidence is insufficient to know the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis. We found no studies that directly assessed this question.

Table C. Summary of the strength of evidence by Key Question								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 1								
IVC filter vs. no filter	PE	6	966	High	Direct	Precise	Consistent	Low that IVC filter placement is associated with a lower incidence of PE in hospitalized patients with trauma compared with no IVC filter placement RR 0.20 (95% CI = 0.06 to 0.70; I2=0%)
	Fatal PE	3	570	High	Direct	Precise	Consistent	Low that IVC filter placement is associated with a lower incidence of fatal PE in hospitalized patients with trauma compared with no IVC filter placement RR 0.09 (0.01 to 0.81; I2= 0%)
	Mortality	3	478	High	Direct	Imprecise	Inconsistent	Insufficient that IVC filter placement is associated with less mortality in hospitalized patients with trauma compared with no IVC filter placement RR 0.70 (0.40 to 1.23; 12=6.7%)
	DVT	3	266	High	Direct	Imprecise	Inconsistent	Insufficient that IVC filter placement is associated with a higher incidence of DVT compared with no IVC filter placement RR 1.76 (95% CI = 0.49 to 6.18; I2= 56.8%): p=0.38
	Filter related thrombosis	1	324	High	Direct	Imprecise	Unknown	Insufficient to support that IVC filter placement is associated with a higher incidence of filter related thrombosis compared with no IVC filter placement 1.8 % vs 0 %

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 2a								
Enoxaparin vs. dalteparin	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
	Progression of ICH	1	287	Moderate	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs dalteparin in reducing progression of ICH in TBI patients
Enoxaparin vs. UFH	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%
	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
	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
	Progression of ICH	1	329	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs UFH in reducing progression of ICH in TBI patients; 5% vs. 12%; p<0.05

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 2a (continued)								
Enoxaparin vs. IPC/control	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
	DVT	3	397	Moderate	Direct	Imprecise	Consistent	Low grade evidence to suggest that enoxaparin reduces DVT in TBI patients when compared with IPC/control
	PE	3	397	Moderate	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
	Mortality	2	182	Moderate	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing total mortality in TBI patients
	Progression of ICH	2	182	Moderate	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin vs IPC/control/placebo in reducing Exacerbation of epidural hematoma in TBI patients

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 2a (continued)								
UFH vs. control	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
	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%*
	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%*
	Mortality	2	1040	High	Direct	Precise	Consistent	Low grade evidence to suggest that UFH reduces mortality in TBI compared with controls
Dalteparin vs. control	VTE	1	122	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs control in reducing Total VTE in TBI patients 0% vs 0%*
	Progression of ICH	1	122	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs control in reducing progression of ICH in TBI patients 0% vs 0%*
IPC vs. control	VTE	1	32	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of IPC vs. control in reducing total VTE in TBI patients 8.6% vs. 22.2%: p=0.7
	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%*

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 2b								
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
	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% *
	Progression of ICH	2	924	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
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
	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

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 5								
Rivaroxaban vs. enoxaparin	Major bleeding	1	1089	Low	Direct	Imprecise	Unknown	Insufficient evidence to comment on difference in rates of major bleeding with prophylactic rivaroxaban or enoxaparin in patients concomitantly treated with antiplatelet agents 3.6% vs. 3.25%*
Dabigatran vs. enoxaparin	Major bleeding	1	258	Low	Direct	Imprecise	Unknown	Insufficient evidence to comment on difference in rates of major bleeding with prophylactic dabigatran or enoxaparin in patients concomitantly treated with aspirin 1.6% vs. 3.0%, risk ratio 0.68 (95% C.I. 0.22 to 2.1)*
KQ 6								
Enoxaparin vs. 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
	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%*

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 6 (continued)								
Enoxaparin vs. 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
	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
	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

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 6 (continued)								
Enoxaparin at standard dosing vs. 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	PE	4	99960	High	Direct	Precise	Consistent	Low grade evidence to support that prophylactic IVCFs do not reduce PE in patients undergoing bariatric surgery compared with controls RR = 0.91 (95% CI = 0.32 to 2.57;p=0.858; 12=16.3%)
	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	4	99960	High	Direct	Imrecise	Consistent	Insufficient evidence to support that IVCFs increase DVT in patients undergoing bariatric surgery compared with controls RR = 2.77 (95% CI=0.87 to 8.85; p=0.086; 12=62.6%)

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 6 (continued)								
Filter vs. no filter	Mortality	4	106006	High	Direct	Precise	Consistent	Low grade evidence to support that IVCFs are associated with increased mortality in patients undergoing bariatric surgery RR =3.63 (95% CI=1.99 to 6.61;p=<0.05; 12=0.0%)
KQ 7								
Dalteparin vs. Placebo	VTE	1	1118	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs placebo in reducing total VTE in obese patients; 2.8% vs 4.3%; (RR, 0.64; 95% CI 0.32-1.28)
	Mortality	1	1118	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs placebo in reducing mortality in obese patients; 9.9% vs 8.6%, p=0.36
	Major bleeding	1	1118	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on safety of dalteparin vs placebo in reducing major bleeding in obese patients; 0% vs 0.7%, p>0.99
Enoxaparin 40 mg daily vs. 0.4 mg/kg	Percentage of patients achieving target anti-Factor Xa level	1	20	Moderate	Indirect	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin 40 mg daily versus 0.4 mg/kg in achieving peak anti-Factor Xa level in obese patients; 19% vs 32%, p=NR
Enoxaparin 40 mg daily vs. 0.5 mg/kg	Percentage of patients achieving target anti-Factor Xa level	1	22	Moderate	Indirect	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin 40 mg daily versus 0.5 mg/kg in achieving peak anti-Factor Xa level in obese patients; 19% vs 86%,, p<0.001

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 7 (continued)								
Enoxaparin 0.4 mg/kg vs. 0.5 mg/kg	Percentage of patients achieving target anti-Factor Xa level	1	20	Moderate	Indirect	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin 0.4 mg/kg versus 0.5 mg/kg in achieving peak anti-Factor Xa level in obese patients; 32% vs. 86%, p=NR
KQ 8								
Tinzaparin vs. enoxaparin	VTE	1	55	High	Direct	Imprecise	Unknown	Insufficient on reducing VTE in patients with renal insufficiency 0/27 vs. 0/28*
	Bleeding	1	55	High	Direct	Imprecise	Unknown	Insufficient on bleeding in patients with renal insufficiency 5 /27 vs. 4/28 (p=0.67)
Dabigatran vs. enoxaparin	VTE	1	632	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of dabigatran in reducing VTE in severe renal compromise patients vs. enoxaparin (4.3% vs. 6.4%, OR: 0.68, 95% CI: 0.31-1.48, p=0.334)
	Bleeding	1	632	Moderate	Direct	Precise	Unknown	Insufficient evidence to comment on the safety of dabigatran vs. enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise 0 vs. 4.7%, p=0.039
Desirudin vs. enoxaparin	VTE	1	2047	Moderate	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of desirudin in reducing VTE in severe renal compromise patients vs. enoxaparin 4.9% vs. 7.6%, p=0.019
	Bleeding	1	2047	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on the safety of desirudin vs. enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise 0.8% vs 0.2%, p=0.109

Table C. Summary of the strength of evidence by Key Question (continued)								
Intervention	**Outcome**	**Studies N**	**Enrolled Participants**	**Risk of Bias**	**Directness**	**Summary Precision**	**Consistency**	**Strength of Evidence, Evidence Statement, and Magnitude of Effect**
KQ 8 (continued)								
Enoxaparin vs. unfractionated heparin	Bleeding	1	323	High	Direct	Precise	Unknown	Insufficient evidence to comment on the safety of unfractionated heparin vs. enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise 13.5% vs. 4.1%, RR: 0.31, 95% CI: 0.14 to 0.71
UHF in severe renal compromise vs. all other renal status (undifferentiated)	VTE	1	2615	Moderate	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	1	2615	Moderate	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

*P-values or tests of statistical significance not reported

CI = confidence interval; DVT=deep vein thrombosis; ICH=intracranial hemorrhage; IPC=intermittent pneumatic compression; IVCF=inferior vena cava filters; PE=pulmonary embolism; RR = ; TBI=traumatic brain injury, UFH=unfractionated heparin; 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.

Summary of Studies

Patients With Trauma

The strength of evidence is low that prophylactic IVC filter placement when compared with no filter use is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma. We also found insufficient evidence that prophylactic IVC filter placement is associated with an increased incidence of DVT in hospitalized patients with trauma when compared with no use of filters. We found insufficient evidence to comment on mortality associated with prophylactic IVC filter placement in hospitalized 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 versus 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 that 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 followup. 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.[41] This variation could lead to selection bias for any observational studies of IVCFs.

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.[35] The authors concluded 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 the evidence on optional IVC filters was not sufficient to support evidence-based recommendations.[36]

There are conflicting guidelines on this topic. The practice guideline from the Eastern Association for the Surgery of Trauma states that insertion of a prophylactic IVC filters should be considered in very high-risk trauma patients.[37] 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.[38] 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 recommend against IVC filters for primary VTE prevention in patients with trauma (Grade 2C).[38]

Patients With Traumatic Brain Injury

We identified two RCTs 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 high-quality studies having minimal risk of bias, 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, we found low-grade evidence to support the idea that enoxaparin reduces the rates of DVT compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury. We also found low-grade evidence to support the idea that UFH reduces the rates of total mortality compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury.

Five retrospective cohort studies evaluated the timing of pharmacologic prophylaxis in patients with traumatic brain injury. The lack of high-quality studies precludes 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.[37] Additionally, the ACCP guidelines do not specifically address DVT prophylaxis in these patients.[38]

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.[39] The ACCP 2012 guidelines do not provide specific recommendations for preventing VTE in patients with burns.[40]

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 identified two studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies among hospitalized patients receiving antiplatelet therapy. We found insufficient evidence about difference in rates of major bleeding with prophylactic rivaroxaban or enoxaparin in patients concomitantly treated with antiplatelet agents. We also found insufficient evidence to support differences in rates of major bleeding with prophylactic dabigatran or enoxaparin in patients concomitantly treated with aspirin.

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. Regardless, the process of selecting patients for filters based on real or perceived VTE risk may bias toward a lack of filter efficacy, or the appearance of harm.[42] In each of the studies that we included that specifically noted retrieval rates, physicians ultimately removed more than two-thirds of the retrievable filters placed.

In the absence of high-quality studies, 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 preoperative initiation of pharmacologic prophylaxis and perioperative bleeding, or between postoperative initiation of pharmacologic prophylaxis and thrombosis. A study of extended prophylaxis versus inpatient prophylaxis suggested that continuing enoxaparin therapy for 10 days after discharge may be associated with a lower risk of VTE, when compared with shorter therapy.[43] The rate of fatal PE 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.[44,45]

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.[46] They concluded that the incidence of symptomatic postoperative VTE appeared to be less than 1 percent with either prophylactic strategy, but that with screening for events, 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 identified two studies that reported on this Key Question. One subgroup analysis of an RCT 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. The strength of evidence was insufficient to comment

on the effectiveness of prophylaxis with fixed dose dalteparin over placebo in reducing VTE in hospitalized obese patients. The strength of evidence was insufficient to comment on the effectiveness of prophylaxis with fixed dose dalteparin over placebo in reducing major bleeding and mortality in hospitalized obese patients. We also found that strength of evidence was insufficient to comment on whether fixed dose enoxaparin at 40 mg dose compared with various weight-based dosing regimens (0.4 mg/kg or 0.5 mg/kg of enoxaparin) differed in achieving target anti-factor Xa level in obese hospitalized patients. 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

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.[30,47-50] Although 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.[51,52] 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 were small and had methodological limitations. The majority of observational studies had 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 definitions of VTE and bleeding outcomes. 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. Although we included study designs other than randomized controlled trials in our review, the identification and indexing of observational studies is far more challenging than that of randomized controlled trials. It is possible we may have missed a few observational studies. The potential impact of this on the strength of our inference is unknown. We were unable to assess the possibility of publication bias or selective outcomes reporting and its impact on our findings, and it is difficult to determine the impact of unpublished data on the findings of the systematic review.

Future Research

Our report highlights the need for additional research on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE among these special populations. For many of the questions, multicenter clinical trials may be prohibitively expensive or impossible. We describe here options for observational research as well as trials.

There remains a significant research gap regarding the efficacy and safety for IVC filters for PE prophylaxis in trauma patients. The American Venous Forum and the Society of Interventional Radiology Multidisciplinary Consensus Conference have placed a high priority on studies of filters in trauma.[36] If feasible, a large, multicenter RCT could definitively answer the question on the efficacy and safety of IVC filters in patients with trauma including patients with traumatic brain injury.[36] We recognize that this may be prohibitively complex and expensive; therefore, answering this question with well-designed observational research may be optimal. These observational studies could be prospective cohort studies with the exposed group defined as individuals with trauma receiving filters and with a carefully matched comparison group of individuals—having comparable injuries and comorbid conditions—who do not receive filters. Additionally, observational research could be facilitated with use of registry data, such as from the National Trauma Data Bank.[55] Although presently there is insufficient

detail about filter placement in this registry, this could be rectified. This would then allow cohort studies to be nested within this registry. The information that would need to be captured would be filter-related information including timing, indication, type of filter, as well as complications from placement. Retrospective cohort studies may also be valuable for this question but there needs to be much better control for confounding by indication than was done in the studies included in this review. With careful risk adjustment through regression or the use of other methods such as propensity score matching or instrumental variable analyses, valid inferences can be drawn from retrospective studies. Future studies should also attempt to determine the reasons for low filter retrieval rates.

Additional studies among patients with traumatic brain injury may include trials, including trials about the timing of initiation of prophylaxis. The level of detail about timing of dosing in observational data may be limited. Studies should also determine how to better risk stratify patients to inform decisions about pharmacologic prophylaxis. This could be addressed with observational studies describing outcomes of patients in different strata of risk.

For this systematic review, we searched for studies that measured the effect of pharmacologic strategies on anti-Xa concentration, which is a reasonable surrogate for bleeding risk, for the Key Questions addressing patients with renal insufficiency and obesity and underweight. Pharmacokinetic studies are needed in other patient populations to determine whether 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.[53] More broadly, additional research is needed to better understand what raises VTE risk in patients with burns. Electronic health record data should provide sufficient information about exposures to pharmacologic and mechanical interventions in burned patients, as well as the patients' outcomes; and would allow for the control of confounding by indication with information about comorbid conditions, burn severity and surface area affected. Given that there are likely important institutional differences in practice patterns regarding prophylaxis of burns, the use of the institution as an instrumental variable is conceivable (assuming that the patient mix is comparable across institutions).

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 characterize the relative risks of bleeding and thrombosis across stages of liver disease, which will require clinical information such as from electronic health records.

The question of elevated risk of bleeding with dual therapy with prophylactic anticoagulation and aspirin therapy remains unanswered. Rare events such as bleeding from prophylactic doses of anticoagulant are difficult to answer in trials; this question too will require high-quality observational studies that control for confounding by indication with the use of propensity score methods or possibly instrumental variables.

Trials of IVC filters in patients undergoing bariatric surgery might not be warranted. There is established value of pharmacologic prophylaxis in this patient population, so that RCTs that do not allow pharmacological treatment might be considered to be unethical. Similarly, because the rates of events are so low in patients with pharmacological treatment, exposing individuals to filter placement in an RCT may expose them to complication risk while there is little opportunity to demonstrate improvement in PE rates over the existing low rates. Such trials should include only those patients deemed to be at highest risk for VTE complications, such as those with prior VTE. RCTs might 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. We suggest that weight-based dosing compared with fixed-dosing, rather than BMI-based dosing compared with fixed-dosing, is the more relevant scientific question.

RCTs should evaluate the comparative effectiveness and safety of LMWHs in obese 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. RCTs of VTE prevention will ideally report data on subgroups of obese and overweight patients, as well as subgroups of patients defined by renal impairment status. Future trials should seek to enroll a subpopulation of patients with renal insufficiency to add to this body of evidence. Observational analyses may be useful for this question as well. We propose that large trials that have been completed should report subgroup results, including subgroups that were not specified at the start of the trial, so that this information is available to researchers doing meta-analysis.[54] Whereas the results in these subgroups might be considered exploratory in the context of the parent trial, when pooled across studies, the added power may allow for stronger, yet cautious, conclusions.

Even with evidence for the above, it still may not be clear what is the best practice as this may depend on patients' preferences for the possible outcomes. An individual's tolerance of risk without an intervention may exceed his tolerance of a different risk with an intervention, and this has importance for decisionmaking. These questions are best answered with qualitative methods or possibly with quantitative methods designed for learning patients' preferences. These can then be used in decision-analytic models that may be informative to clinicians and patients.

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 RCTs typically exclude or do not report on these special populations.

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Full Report

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