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Effectiveness of Intermittent Pneumatic Compression Devices for Venous Thromboembolism Prophylaxis in High-risk Surgical and Medical Patients

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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ABSTRACT

Context: Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious potential complication in hospitalized patients. Thromboprophylaxis regimens include pharmacological and mechanical options such as intermittent pneumatic compression devices (IPCDs). There are a wide variety of IPCDs available, but it is uncertain if they vary in effectiveness or ease of use.

Objective: To systematically review the literature on the comparative effectiveness of IPCDs for selected outcomes (mortality, VTE, symptomatic or asymptomatic DVT, major bleeding, ease of use, and adherence) in post-operative surgical and high-risk medical patients.

Data Sources and Study Selection: We searched MEDLINE (via PubMed), Embase, CINAHL, and Cochrane CENTRAL from January 1, 1995, to October 30, 2014, for peer-reviewed, English-language randomized controlled trials (RCTs). All searches used terms for IPCDs and the conditions of interest, along with validated search terms for RCTs. We also used terms to identify relevant observational studies on ease of use and adherence. Bibliographies of identified articles were further reviewed. To assess for possible publication bias, we searched ClinicalTrials.gov to identify completed but unpublished studies meeting our eligibility criteria.

Data Synthesis: Eighteen RCTs and 3 observational studies were eligible; most were conducted in patients undergoing joint replacement surgery. Our review considered 3 types of evidence: 1) head-to-head comparisons of IPCDs; 2) indirect comparisons of IPCDs to a common comparator (*eg*, foot vs calf devices, each compared to anticoagulation); and 3) data on ease of use or adherence from patients or staff. The methodological quality of the included studies was variable and generally suboptimal. The most commonly studied devices were the Kendall SCD™ and A-V Impulse System™. Only 3 trials compared different IPCDs directly. One showed lower VTE rates for a VenaFlow® compared to the Kendall SCD, but 2 other studies showed no difference between the PlexiPulse® and the Kendall SCD. IPCDs were comparable to anticoagulation for major clinical outcomes (VTE: risk ratio [RR] 1.39; 95% confidence interval [CI], 0.73 to 2.64). Limited data suggest that concurrent use of anticoagulation with IPCD may lower the risk of VTE compared to anticoagulation alone (RR 0.27; 95% CI 0.05 to 1.64) and that IPCD compared to anticoagulation may lower the risk of major bleeding (RR 0.33; 95% CI 0.07 to 1.51). Subgroup analyses did not show significant differences by device location, mode of inflation, or risk of bias elements. Overall, there were no consistent associations between specific brand-name IPCDs or sleeve location and ease of use or adherence. Chief limitations of the literature were the paucity of head-to-head comparisons between IPCDs in surgical and medical patients, and the identification of primarily asymptomatic DVTs of uncertain clinical importance.

Conclusions: IPCDs are appropriate for VTE thromboprophylaxis when used in accordance with current clinical guidelines. The current evidence base to guide selection of a specific device or type of device is limited. When choosing a specific IPCD, focusing on device flexibility, acceptability by nursing staff and patients, and the most frequently studied devices, as well as on cost, can help direct selection of appropriate IPCDs. Comparative effectiveness studies are urgently needed to address current gaps in evidence.

ABBREVIATIONS TABLE

ACCP	American College of Chest Physicians
CECT	Continuous enhanced circulation therapy
CI	Confidence interval
DVT	Deep vein thrombosis
ECRI	Emergency Care Research Institute
ESP	Evidence-based Synthesis Program
HSR&D	Health Services Research & Development
IPCD	Intermittent pneumatic compression device
ISTH	International Society on Thrombosis and Haemostasis
KQ	Key question
LMWH	Low molecular weight heparin
MeSH	Medical Subject Heading
n	Number
PE	Pulmonary embolism
PICOTS	Population, intervention, comparator, outcomes, timing, and setting
PTT	Partial thromboplastin time
QUERI	Quality Enhancement Research Initiative
RIAC	Rapid inflation asymmetrical compression
RCT	Randomized controlled trial
RD	Risk difference
RR	Risk ratio
SCD	Sequential compression device
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
VA	Veterans Affairs
VHA	Veterans Health Administration
VISN	Veterans Integrated Service Networks
VTE	Venous thromboembolism
V/Q	Ventilation/perfusion

TABLE OF CONTENTS

INTRODUCTION **1**
High-Risk Patient Populations 1
Intermittent Pneumatic Compression Devices 1
Objectives of the Report 2

METHODS **3**
Topic Development 3
Search Strategy 3
Study Selection 4
Data Abstraction 5
Quality Assessment 5
Data Synthesis 6
Rating the Body of Evidence 6
Peer Review 7

RESULTS **8**
Literature Flow 8
Key Question 1: In hospitalized surgical patients at high risk for venous thromboembolism (VTE), what is the comparative effectiveness of VTE prophylaxis with intermittent pneumatic compression devices versus VTE prophylaxis with pharmacologic agents for VTE events, VTE-related mortality, and adverse events? 13
Key Question 2: In hospitalized medical patients at high risk for VTE, what is the comparative effectiveness of VTE prophylaxis with IPC devices versus VTE prophylaxis with pharmacological agents for VTE events, VTE-related mortality, and adverse events? 19
Key Question 3: In hospitalized surgical and medical patients at high risk for VTE, what is the comparative effectiveness of different IPC devices when compared to one another for preventing VTE events? 20
Key Question 4: When used for VTE prophylaxis, do different IPC devices differ in ease of use or adherence? 21

SUMMARY AND DISCUSSION **23**
Summary of Evidence by Key Question (KQ) 25
Clinical and Policy Implications 26
Framework for Selecting IPC Devices 27
Limitations 28
Research Gaps/Future Research 28
Conclusions 29

REFERENCES **30**

TABLES
Table 1. Inclusion and Exclusion Criteria 4
Table 2. Devices Evaluated in Included Studies 10
Table 3. Strength of Evidence for ICPD Effectiveness in Reducing VTE Events 23

Table 4. Evidence Gaps and Future Research Needs....29

FIGURES

Figure 1. Literature Flow Chart 9
Figure 2. Numbers of Comparisons between Interventions (RCTs only, n=18) 10
Figure 3. Risk for VTE Events with IPCD versus Anticoagulation Prophylaxis in Joint Replacement Patients 14
Figure 4. Risk for any DVT Events with IPCD versus Anticoagulation Prophylaxis in Joint Replacement Patients 16
Figure 5. Risk for Major Bleeding Events with IPCD versus Anticoagulation Prophylaxis in Joint Replacement Patients 18

APPENDIX A. Search Strategies 36

APPENDIX B. Quality (Risk of Bias) Assessment of RCTs—Criteria Used and Detailed Ratings 39

APPENDIX C. Peer Review Comments/Author Responses 44

APPENDIX D. Study Characteristics 48

APPENDIX E. Technical Features of Named Devices Evaluated in Included Studies 54

EVIDENCE REPORT

INTRODUCTION

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious potential complication in hospitalized patients. In high-risk groups, such as post-operative surgical patients and acutely ill medical patients,[1-5] VTE is a leading cause of morbidity and mortality.[6-8] VTE prophylaxis is recommended for approximately 60% of high-risk surgical patients and for the 40% of hospitalized medical patients at risk for VTE.[9,10]

Clinical practice guidelines generally recommend *either* pharmacological *or* mechanical VTE prophylaxis. Pharmacological options include anticoagulation (*eg*, low molecular weight heparin [LMWH], new oral anticoagulants, or warfarin) and aspirin, but these may increase the risk of bleeding.[11,12] Mechanical prophylaxis with intermittent pneumatic compression devices (IPCDs) is recommended, particularly in populations at high risk of bleeding,[13-16] due to the decreased risk of major bleeding and surgical site bleeding associated with IPCDs.[17-19] Although IPCDs can offer protection against VTE,[20-22] compliance is often suboptimal,[23,24] and efficacy may vary importantly across various devices.

HIGH-RISK PATIENT POPULATIONS

In hospitalized medical patients, risk factors for VTE include trauma, malignancy, stroke, prior VTE, and congestive heart failure.[25] In surgical populations, lower limb joint replacement surgery in particular is associated with an increased risk of VTE.[25] Without prophylaxis, the incidence of 35-day symptomatic VTE events following orthopedic surgeries is high, with an estimated baseline rate of 4.3%.[16] While the risk of symptomatic VTE is highest in the first 6 weeks following surgery, this risk can remain elevated for up to 2 to 3 months following surgery.[26] Given this natural history, it is important to examine the effects of VTE prophylaxis beyond the period of hospitalization.

INTERMITTENT PNEUMATIC COMPRESSION DEVICES

It is hypothesized that IPCDs prevent DVT formation through 2 mechanisms, namely, by decreasing venous stasis and activating fibrinolysis.[27-29] These effects can be achieved by mechanical compression of the foot or calf alone, or by sequential compression of either the foot and calf, or the calf and thigh.

There are a wide variety of IPCDs currently available that differ in anatomical location of the sleeve garment, number and location of air bladders, patterns of compression cycles, and duration of inflation time and deflation time.[30,31] In general, IPCDs can be categorized into either single-chamber or multi-chamber devices, constant pressure or sequential pressure devices, slow-gradual or rapid inflation devices, and portable or non-portable devices. Portable IPCDs offer the potential advantage of continued use during ambulation in the early post-operative period.[32] By contrast, non-portable devices must be removed when the patient ambulates. Some devices also include an hour meter that may facilitate adherence monitoring. Although some clinical guidelines recommend certain device features such as portability,[16] in general, guidelines do not

make recommendations for or against specific IPCDs or device categories. Therefore, it remains unclear which of these approaches works best for specific patient populations. Consequently, clinicians and health systems routinely struggle with the selection of IPCDs.

OBJECTIVES OF THE REPORT

This study was nominated by the Veterans Affairs (VA) National Surgery Office and Office of Nursing with the aim of evaluating IPCDs to inform best practice strategies, policy, and selection of devices for the VA Health System. The objective of this report is to evaluate the comparative effectiveness of IPCDs in post-operative surgical and high-risk medical patients of high interest to the Veterans Health Administration (VHA). There is a major gap in the existing literature on which specific populations will benefit from IPCD prophylaxis, and whether IPCDs vary importantly in VTE outcomes, adherence, and ease of use. This study addresses these gaps with a methodologically sophisticated systematic review.

METHODS

TOPIC DEVELOPMENT

The topic was nominated after a process that included a preliminary review of published peer-reviewed literature and consultation with investigators, Veterans Affairs (VA) and non-VA experts, and key stakeholders (VA National Surgery Office, VA Office of Nursing). The VA Sequential Pressure Device Evaluation Committee nominated this project. The committee is interested in developing policy about the use of intermittent pneumatic compression devices (IPCDs), and specifically was interested in an evaluation to determine the comparative effectiveness of IPCDs.

We followed a standard protocol for this review, and each step was pilot tested to train and calibrate study investigators. The PROSPERO registration number is CRD42014015157. The final key questions (KQs), developed in consultation with stakeholders, are:

- KQ 1: In hospitalized surgical patients at high risk for venous thromboembolism (VTE), what is the comparative effectiveness of VTE prophylaxis with IPCDs versus VTE prophylaxis with pharmacological agents for VTE events, VTE-related mortality, and adverse events?
    a. Does effectiveness vary by surgical procedure?
    b. Does effectiveness vary by type of IPCD?

- KQ 2: In hospitalized medical patients at high risk for VTE, what is the comparative effectiveness of VTE prophylaxis with IPCDs versus VTE prophylaxis with pharmacological agents for VTE events, VTE-related mortality, and adverse events?
    a. Does effectiveness vary by medical condition?
    b. Does effectiveness vary by type of IPCD?

- KQ 3: In hospitalized surgical and medical patients at high risk for VTE, what is the comparative effectiveness of different IPCDs when compared to one another for preventing VTE events?

- KQ 4: When used for VTE prophylaxis, do different IPCDs differ in ease of use or adherence?

SEARCH STRATEGY

In consultation with an expert librarian, we searched MEDLINE (via PubMed), Embase, CINAHL, and Cochrane CENTRAL from January 1, 1995, to October 30, 2014, for peer-reviewed, English-language randomized controlled trials (RCTs). We used Medical Subject Heading (MeSH) terms and selected free-text terms for IPCDs and the conditions of interest, along with validated search terms for RCTs.[33] For KQ 4, we also used terms to identify relevant observational studies. The exact search strategies used are provided in Appendix A. We further reviewed the bibliographies of included trials and systematic reviews[20-22,30,34-40] for missed publications.

To assess for possible publication bias, we searched ClinicalTrials.gov (www.clinicaltrials.gov) to identify completed but unpublished studies meeting our eligibility criteria.

All citations were imported into 2 electronic databases (for referencing, EndNote® Version X5, Thomson Reuters, Philadelphia, PA; for data abstraction, DistillerSR; Evidence Partners Inc., Manotick, ON, Canada).

STUDY SELECTION

Using pre-specified inclusion and exclusion criteria, 2 trained investigators assessed titles and abstracts for relevance to the KQs. Full-text articles identified by either investigator as potentially relevant were retrieved for further review and examined by 2 investigators against the eligibility criteria. Disagreements on inclusion, exclusion, or the major reason for exclusion were resolved by discussion or by a third investigator. The criteria to screen articles for inclusion or exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 1. In addition, trials with 3 or more arms were examined for appropriateness of all arms for inclusion. For example, data from any active arm that did not include an IPCD or eligible anticoagulant were not abstracted for inclusion in the analysis.

Table 1. Inclusion and Exclusion Criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults 18 years or older hospitalized for THA, TKA, hip fracture surgery, back surgery, bariatric surgery with surgical duration >1 hour, robotic-assisted prostatectomy, or robotic-assisted hysterectomy (KQ 1, KQ 3, KQ 4); and hospitalized medical patients with active malignancy, stroke, trauma, critical illness, or high risk of VTE determined by a validated risk model (KQ 2, KQ 3, KQ 4)	Low risk of VTE Mixed samples with fewer than 70% meeting eligibility criteria
Intervention	IPCD used for ≥24 hours, with or without pharmacological prophylaxis	Graduated compression stockings Devices that stimulate venous flow through ankle flexion and extension
Comparator	KQ 1 and KQ 2: Pharmacological prophylaxis with LMWH, FXa inhibitors, direct thrombin inhibitors, adjusted-dose vitamin K antagonists, fondaparinux, or aspirin KQ 3 and KQ 4: An IPCD	Placebo, antiplatelet drugs other than aspirin, graduated compression stockings, electrical calf stimulation devices, foot flexion/extension devices Any comparator where the effect of the electronic aspect of the intervention could not be isolated

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcome	Studies must report effects on at least one of the following relevant outcomes: KQ 1 and KQ 2: VTE events (DVT and/or PE), mortality, and adverse events KQ 3: VTE events (DVT and/or PE) KQ 4: Staff- or patient-reported ease of use or adherence	–
Timing	Outcomes reported at ≥4 weeks from randomization or study enrollment*	Outcomes reported at <4 weeks
Setting	Hospitalized patients in North America, the European Union, Australia, New Zealand, or Japan†	Outpatients or studies conducted in countries not listed as eligible
Design	KQ 1, KQ 2, and KQ 3: RCTs KQ 4: RCTs and quasi-experimental or cohort studies	–
Other	Publication year 1995 or later‡ English-language publication	–

*Rationale was that approximately 15% of DVTs occur post-hospitalization.

†Rationale was to include economically developed countries with sufficient similarities in healthcare system and culture to be applicable to U.S. medical care.

‡Studies prior to 1995 were excluded because surgical procedures and post-operative care have changed substantially since then, and these changes affect the risk of VTE.

Abbreviations: DVT=deep vein thrombosis; FXa=factor Xa; IPCD=intermittent pneumatic compression device; KQ=key question; LMWH=low molecular weight heparin; PE=pulmonary embolism; RCTs=randomized controlled trials; THA=total hip arthroplasty; TKA=total knee arthroplasty; VTE=venous thromboembolism

DATA ABSTRACTION

Data from included articles were abstracted into the final form by a trained investigator and confirmed by a second investigator. Data elements abstracted included patient descriptors; setting, features, and dose of the intervention (including timing and duration for IPCDs); characteristics of the comparator; outcomes; and risk of bias elements. All data abstractions were confirmed by a second investigator. Disagreements were resolved by consensus or by obtaining a third investigator's opinion. When data were incomplete or missing, we contacted authors to request the data.

QUALITY ASSESSMENT

We assessed the quality (risk of bias) of each study and summarized the overall risk of bias for each study as low, moderate, or high. We used the key risk of bias criteria described in the Agency for Healthcare Research and Quality's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[41] adapted to this specific topic (Appendix B). The key criteria for RCTs are: adequacy of randomization and allocation concealment; comparability of groups at baseline; blinding; completeness of follow-up and differential loss to follow-up; whether incomplete data were addressed appropriately; validity of outcome measures; and conflict of interest. Observational studies were evaluated using the following domains: basic study design, selection bias, performance bias, attrition bias, and detection bias.

DATA SYNTHESIS

We grouped studies into those that enrolled participants undergoing joint replacement, other surgery, and medical patients.

When meta-analysis was feasible, we computed summary estimates of effect. We used R (R Foundation for Statistical Computing, Vienna, Austria) with the metafor package[42] to calculate the summary estimates of treatment effect. Dichotomous outcomes were analyzed using summary risk ratios (RRs). We used a random-effects model and due to the relatively small number of studies we utilized the Knapp and Hartung method to adjust the standard errors of the estimated coefficients.[43,44] We evaluated for statistical heterogeneity in treatment effects using Cochran's Q and I^2 statistics. We planned subgroup analyses to explore potential sources of heterogeneity, specifying a priori: foot, calf, or thigh location of the IPCD; concurrent use of anticoagulation; and risk of bias elements. In some instances, planned subgroup analyses could not be performed because subgroups did not meet the pre-specified minimum of 3 studies per subgroup. When there were at least 3 studies at low or moderate risk of bias, we performed sensitivity analyses to compute summary estimates after excluding studies at high risk of bias. Publication bias was assessed using findings from a search of ClinicalTrials.gov. Funnel plots were not used because analyses did not meet the minimum threshold of at least 10 studies for meaningful analysis.[41]

Where quantitative synthesis was not feasible, we analyzed the data qualitatively. We gave more weight to evidence from higher-quality studies. We focused on identifying patterns in the efficacy and safety of the interventions and finding potential reasons for inconsistency in treatment effects.

RATING THE BODY OF EVIDENCE

In addition to rating the quality of individual studies, we evaluated the overall strength of evidence for selected outcomes (mortality, VTE, symptomatic or asymptomatic DVT, and major bleeding) as high, moderate, low, or insufficient using the domains: risk of bias, directness, consistency of treatment effects, precision of treatment effects, and risk of publication bias.[45] These domains were considered qualitatively, and a summary rating of high, moderate, low, or insufficient strength of evidence was assigned after discussion by 2 investigators. The 4-level rating scale consists of the following definitions:

- **High**—We are very confident that the true effect lies close to the estimate of the effect.
- **Moderate**—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low**—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Insufficient**—Evidence on an outcome is absent or too weak, sparse, or inconsistent to estimate an effect.

To evaluate the evidence for specific IPCDs or class of devices (*eg*, calf device), we considered head-to-head comparisons, indirect comparisons of IPCDs to a common comparator (*eg*, foot vs calf devices, each compared to anticoagulation), and observational data about ease of use or patient comfort. We calculated risk differences (RDs) for outcomes with strength of evidence ratings of low or higher. We used the pooled estimate of effect and baseline event rates from the literature (VTE, 4.3%[16]) or from the event rate in the anticoagulation arms of the included studies (DVT).

PEER REVIEW

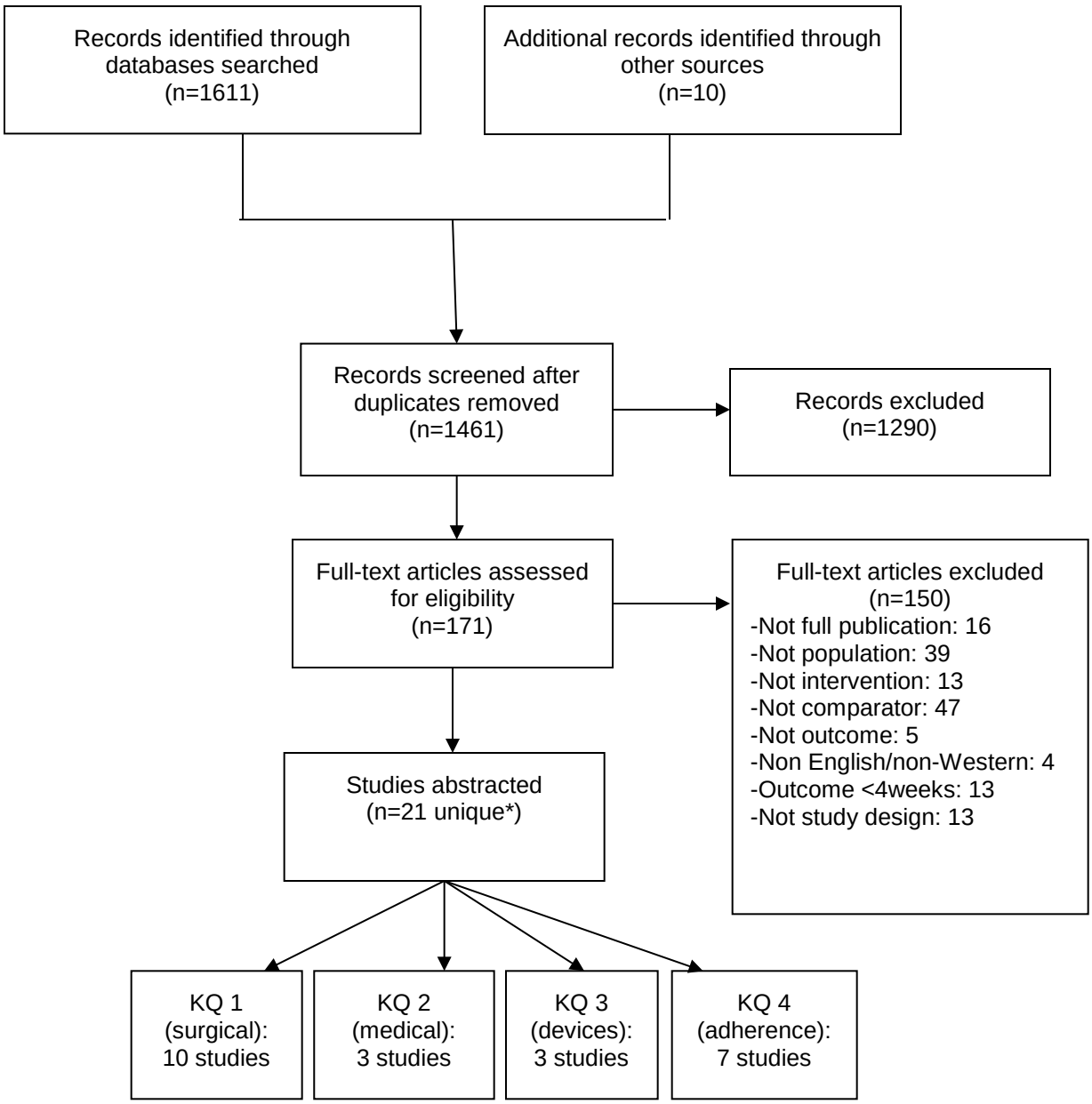
A draft of this report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses is provided in Appendix C.

RESULTS

LITERATURE FLOW

Our literature search (Figure 1) identified 1461 unique citations from a combined search of MEDLINE (n=959), Embase (n=393), CINAHL (n=15), Cochrane CENTRAL (n=84), and the bibliographies of included studies and review articles (n=10). After applying inclusion/exclusion criteria at the title-and-abstract screening level, 171 full texts were retrieved for further review. Of these, 21 unique studies (18 RCTs and 3 observational studies) were retained for data abstraction and grouped by key question (KQ).

Figure 1. Literature Flow Chart



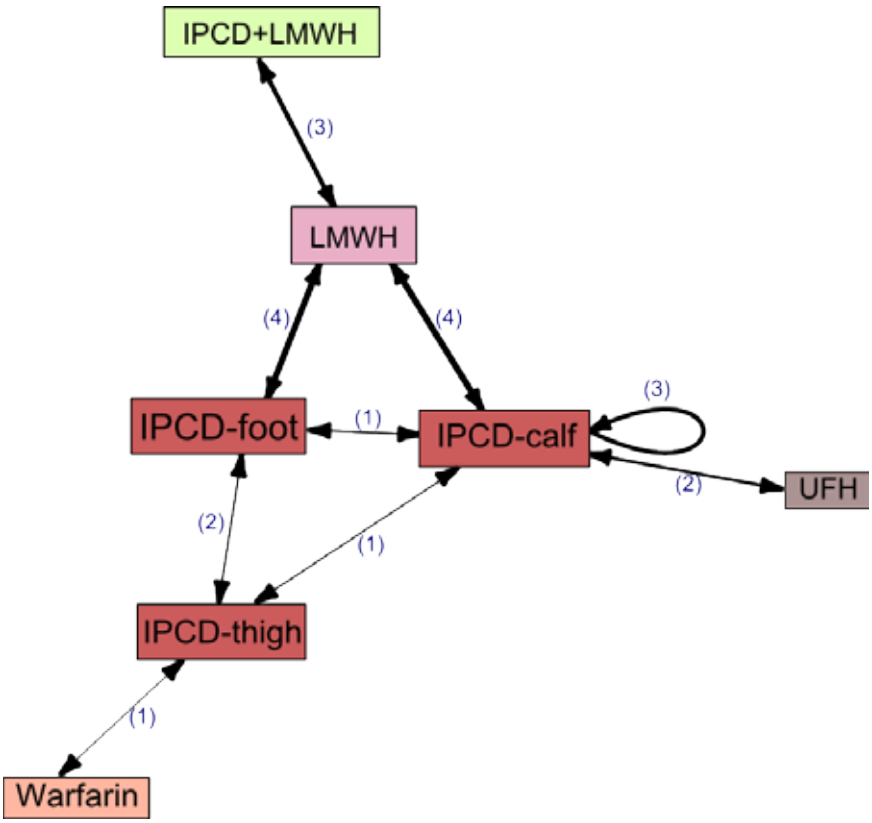
*Two studies applied to both KQ 3 and KQ 4.

Abbreviations: KQ=key question; n=number of studies.

We attempted to contact 14 authors for additional study information; 5 could not be reached, and only 6 others supplied the requested data. A search of ClinicalTrials.gov to ascertain publication bias revealed no additional or completed but unpublished trials.

Eighteen RCTs (3666 subjects), conducted primarily in patients undergoing joint replacement surgery, compared the effectiveness of intermittent pneumatic compression devices (IPCDs) to anticoagulation (n=14) or other IPCDs (n=7) (Figure 2).

Figure 2. Numbers of Comparisons between Interventions (RCTs only, n=18)



Abbreviations: IPCD=intermittent pneumatic compression device; LMWH=low molecular weight heparin; UFH=unfractionated heparin

There were no RCTs comparing antiplatelet agents to IPCDs. Four RCTs and the 3 observational studies (1040 subjects) reported on adherence or ease of use (KQ 4). Devices from 7 different manufacturers were represented (Table 2); however, the brand name of the device and the name of the manufacturer were not always provided. The most commonly studied named devices were the Kendall SCD™ (7 studies) and the Novamedix A-V Impulse System™ (5 studies). Study characteristics are described in greater detail in Appendix D. Further characteristics of the devices are provided in Appendix E.

Table 2. Devices Evaluated in Included Studies

Manufacturer*	Device Name†	Device Characteristics;‡ Sleeve Location(s)§	Number of Studies
Kendall	Kendall SCD™	Multi-chamber, sequential compression, slow inflation, portable and **non-portable** options available, no hour meter Sleeve location(s) available: Foot, **calf, calf-thigh**	7 studies: Lachiewicz, 2004[46] Murakami, 2003[23] Pagella 2007[47] Robertson, 2000[48] Rokito, 1996[49] Stannard, 2001[50] Wood, 1997[51]

Manufacturer*	Device Name†	Device Characteristics;‡ Sleeve Location(s)§	Number of Studies
Novamedix	A-V Impulse System™	Single chamber, constant pressure, rapid inflation, non-portable, hour meter Sleeve location(s) available: **Foot**	5 studies: Blanchard, 1999[52] Pitto, 2004[18] Warwick, 2002[19] Warwick, 1998[53] Windisch, 2011[54]
Huntleigh	Flowtron®	Single chamber, constant compression, slow inflation, portable and **non-portable** options available, no hour meter Sleeve location(s) available: Foot, **calf,** calf-thigh	3 studies: Ginzburg, 2003[55] Pagella, 2007[47] Stone, 1996[56]
NuTech	PlexiPulse®	Multi-chamber, constant compression, rapid inflation, non-portable, **hour meter (1 study)** and **no hour meter (2 studies)** Sleeve location(s) available: **Foot,** calf, **foot-calf**	3 studies: Robertson, 2000[48] Stannard, 2001[50] Wood, 1997[51]
Aircast	VenaFlow®	Multi-chamber, sequential compression, rapid inflation, non-portable, hour meter Sleeve location(s) available: Foot, **calf,** calf-thigh	2 studies: Lachiewicz, 2004[46] Silbersack, 2004[57]
Medical Compression Systems (MCS)	ActiveCare DVT®	Multi-chamber, sequential compression, slow inflation, portable CECT, hour meter Sleeve location(s) available: Foot, **calf**, calf-thigh	1 study: Edwards, 2008[58]
	ActiveCare+S.F.T.®	Multi-chamber, sequential compression, slow inflation, portable CECT, hour meter Sleeve location(s) available: Foot, **calf,** calf-thigh	1 study: Colwell, 2010[17]
	WizAir DVT™ CECT	Multi-chamber, sequential compression, slow inflation, portable CECT, hour meter Sleeve location(s) available: **Calf**	1 study: Murakami, 2003[23]
Jobst	Anthrombic Pump (System 2500)‖	Multi-chamber, sequential compression, slow inflation, non-portable, no hour meter Sleeve location(s) available: **Calf,** calf-thigh	1 study: Pambianco, 1995[59]

Manufacturer*	Device Name†	Device Characteristics;‡ Sleeve Location(s)§	Number of Studies
Unnamed	Unnamed	–	3 studies (8 devices): Bockheim, 2009[60] Greenfield, 1997[61] Proctor, 2001[62]

*Manufacturers of the various IPCDs have changed over time. We report the manufacturer at the time of the study, as accurately as we were able to ascertain this.

†Device names are given as reported in the study, sometimes revised/augmented to reflect trademarked device names at the time of the study, as accurately as we were able to ascertain these.

‡Device characteristics are given as reported in the study, sometimes augmented to reflect the characteristics of trademarked devices at the time of the study, as accurately as we were able to ascertain these. Device characteristics may have changed over time. In particular, some devices that were non-portable at the time of the included studies may now be available in a portable form. Where more than one option was available for a given device characteristic (*eg*, portable and non-portable, hour meter and no hour meter), the option(s) listed in **bold** font were used in the included studies.

§Sleeve locations in **bold** font were used in the included studies.

‖Specific information on this device was not provided in the published study report, but rather by Huntleigh, the company that most recently bought out Jobst. They sent us a copy of the manual for the specific Jobst model used in the Pambianco, 1995 study.[59]

Abbreviations: CECT=continuous enhanced circulation therapy device; DVT=deep vein thrombosis; SCD=sequential compression device; S.F.T.=Synchronized Flow Technology

As Table 2 indicates, the IPCDs evaluated in the included studies primarily used foot or calf sleeves. The mean age of patient samples ranged from 39.5 to 73 years old (median 53.7 years). On average, 47% (range, 24% to 91%) of samples were men. In 16 trials evaluating DVT, routine imaging (typically with ultrasound, 75% of studies) at 3 to 8 days was used for diagnosis, while evaluation for PE was normally triggered by symptoms and was diagnosed by ventilation/perfusion (V/Q) scan or computed tomography in only 44% of studies. Post-hospitalization VTE was diagnosed by history, sometimes supplemented with medical records. Approximately 95% of VTE events were due to DVT. In the 13 studies reporting the distribution of DVT, 18.5% were proximal and 81.5% were distal. Most studies reported the combined rate of symptomatic and asymptomatic DVT, but when reported separately, only 3.2% of DVTs were symptomatic. Only 7 studies reported major bleeding, 5 of which[17,18,52,55,56] conformed to the International Society on Thrombosis and Haemostasis (ISTH) definition.[63] Studies were rated moderate (n=14) or high (n=7) risk of bias (Appendix B).

KEY QUESTION 1: In hospitalized surgical patients at high risk for venous thromboembolism (VTE), what is the comparative effectiveness of VTE prophylaxis with intermittent pneumatic compression devices versus VTE prophylaxis with pharmacologic agents for VTE events, VTE-related mortality, and adverse events?

Description of Included Studies

Ten RCTs (1905 patients) evaluated IPCDs versus anticoagulation for VTE prophylaxis. Seven studies compared IPCDs alone versus anticoagulation,[17-19,49,52,53,56] while 3 studies compared an IPCD in combination with anticoagulation versus anticoagulation alone.[54,57,58] IPCDs were primarily evaluated in joint replacement patients. Only one study evaluated IPCDs in spinal surgery patients. The remaining 9 studies were conducted on patients undergoing total knee arthroplasty (TKA; 3 studies) or total hip arthroplasty (THA; 4 studies); 2 studies combined patient populations undergoing TKA and THA. One of the latter[58] reported results separately for TKA and THA, resulting in a total of 11 comparisons.

The following types of IPCDs were evaluated: foot devices (5 studies), calf devices (4 studies), and a calf-thigh device (1 study). All 10 studies reported the brand name of the devices studied; these were the A-V Impulse System™ foot device (5 studies), the ActiveCare® portable continuous enhanced circulation therapy (CECT) calf device (2 studies, possibly 2 slightly different models), the VenaFlow® rapid-inflation calf device (1 study), the Flowtron® calf device (1 study), and the Kendall SCD™ calf-thigh device (1 study). Foot devices used rapid inflation modes, while all but one calf devices used gradual inflation modes. Devices were typically started intra-operatively or immediately post-operatively, and duration of use ranged from 5 to 12 days or until hospital discharge. Anticoagulation included the LMWHs enoxaparin (7 studies) and nadroparin (2 studies), and the vitamin K antagonist warfarin (1 study). The duration of anticoagulation was less than 10 days in all included studies except for one, which reported use of 30 days or less.[57] Patients excluded from the trials were primarily those with a high risk of bleeding, a prior history of VTE, a history of malignancy, revision of surgery, or painful joints precluding the use of the foot device.

The risk of bias was judged to be moderate in 8 studies[17-19,49,53,54,56,57] and high in 2 studies.[52,58] Appendix B provides details of the quality ratings for each study.

Outcomes

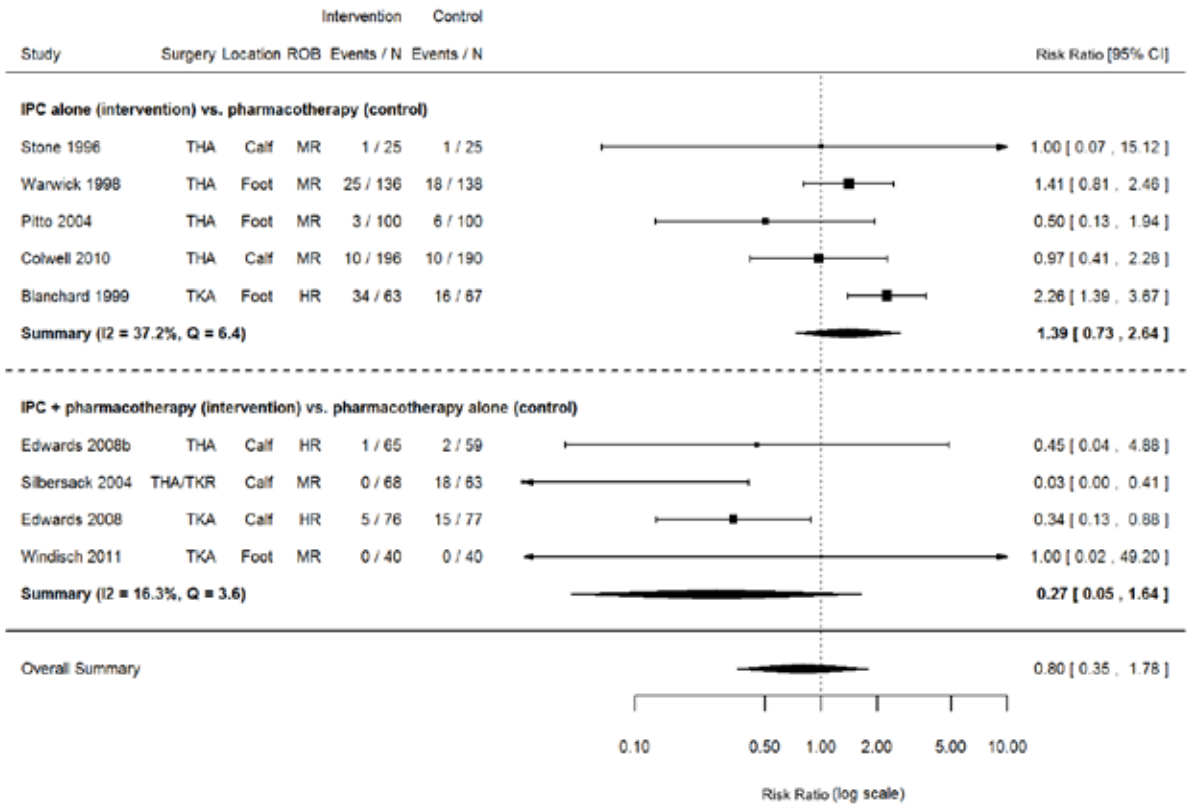
Outcomes included VTE events (DVT and/or PE), any DVT (symptomatic or asymptomatic), symptomatic DVT, PE, all-cause mortality, and major bleeding adverse events. The duration of follow-up for all VTE outcomes and mortality was from 4 weeks to 1 year. We report VTE outcomes separately for joint replacement surgical patients and other surgical patients. Subgroup analyses were feasible only for VTE and DVT outcomes in studies of joint replacement. Additionally, we qualitatively synthesized data on IPCD adherence.

VTE Outcomes in Surgical Joint Replacement Patients

VTE Events (DVT and/or PE)

Among patients undergoing joint replacement surgery, VTE events were identified in 163 patients (11%). VTE events were more common in TKA patients (20%) than in THA patients (8%). Eight of the 10 RCTs in our sample examined the role of IPCDs alone (4 studies) or IPCDs used in combination with anticoagulation (4 studies) in preventing VTE events. One study reported results separately for TKA and THA patients, resulting in 9 comparisons for this analysis. In patients who underwent THA or TKA, there was no statistically significant difference between IPCDs and anticoagulation for VTE events (RR 0.80; 95% confidence interval [CI], 0.35 to 1.78; Figure 3), but intervention effects varied substantially across studies (Q=23.4; p=0.003; $I^{2=}$66%). A sensitivity analysis restricted to studies at moderate risk of bias did not change the pooled estimate substantially (RR 0.78; 95% CI, 0.25 to 2.38). As noted above, the pooled estimate for this outcome was highly heterogeneous. Subgroup analyses separately evaluating IPCDs alone versus anticoagulation (RR 1.39; 95% CI, 0.73 to 2.64; I^2=37%) and IPCDs plus anticoagulation versus anticoagulation alone (RR 0.27; 95% CI, 0.05 to 1.64; I^2=16%) suggested that the combination of IPCDs plus anticoagulation may provide a large protective effect against VTE events, but the confidence interval included the possibility of a chance association (Figure 3).

Figure 3. Risk for VTE Events with IPCD versus Anticoagulation Prophylaxis in Joint Replacement Patients

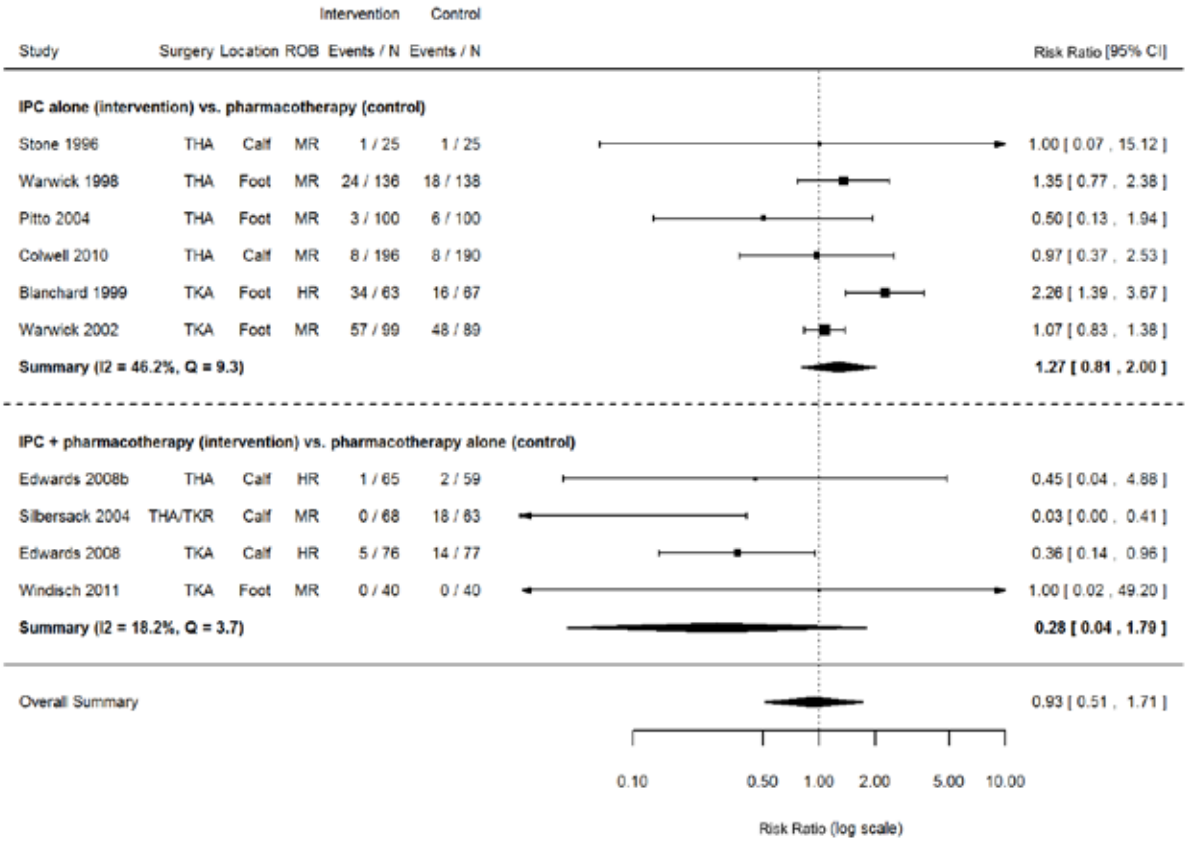


Subgroup analysis of gradual versus rapid inflation devices showed consistent effects for gradual inflation devices (RR 0.61; 95% CI, 0.24 to 1.56; I^2=0%), but inconsistent effects for rapid inflation devices (RR 0.80; 95% CI, 0.35 to 1.78; I^2=71%). We examined outliers qualitatively. Two small studies differed substantially from the pooled estimate. One study at high risk of bias[52] found increased risk of VTE events in TKA patients with an AV Impulse foot device compared to LMWH (RR 2.26; 95% CI, 1.39 to 3.67). In contrast, a study by Silbersack and colleagues,[57] judged to be at moderate risk of bias, found a protective effect against VTE events in a combined population of TKA and THA patients using a VenaFlow rapid inflation calf device plus LMWH versus LMWH alone (RR 0.03; 95% CI, 0.00 to 0.41).

Any DVT Events (Symptomatic or Asymptomatic)

Ten RCTs examined IPCDs alone (6 studies) or IPCDs plus anticoagulation (4 studies) versus anticoagulation alone and reported any DVT events. A total of 264 DVT events (15%) were identified; most DVTs were distal (81%). Proximal DVTs were more common in THA patients (53%) than in TKA patients (7%). There was no important difference in the risk of any DVT event between IPCDs and anticoagulation (RR 0.93; 95% CI, 0.51 to 1.71; Figure 4), but intervention effects varied substantially across studies (Q=23.0; p=0.006; $I^{2=}$61%). A sensitivity analysis restricted to studies at moderate risk of bias did not change the pooled estimate substantially (RR 0.97; 95% CI, 0.53 to 1.78). Subgroup analyses separately evaluating IPCDs alone versus anticoagulation (RR 1.27; 95% CI, 0.81 to 2.00; I^2=46%) and IPCDs plus anticoagulation versus anticoagulation alone (RR 0.28; 95% CI, 0.04 to 1.79; I^2=18%) suggested that the combination of IPCDs plus anticoagulation may provide a large protective effect against VTE events, but the confidence interval included the possibility of a chance association (Figure 4).

Figure 4. Risk for any DVT Events with IPCD versus Anticoagulation Prophylaxis in Joint Replacement Patients



Additional subgroup analyses explain some but not all variability. Subgroup analyses by surgical site showed that heterogeneity was primarily driven by TKA studies. Among the TKA studies, one small study at high risk of bias[52] was different from others in this group. This study found that the AV Impulse System foot device compared to LMWH increased the risk for any DVT (RR 2.26; 95% CI, 1.39 to 3.67). In this study, both lower limbs, as opposed to only the ipsilateral surgical limb, were assessed for DVT. THA studies showed consistent treatment effects and no difference between IPCDs and anticoagulation for risk of DVT events (RR 1.08; 95% CI, 0.66 to 1.76; I^2=0%). Because of the high correlation between device location and inflation mode, subgroup analyses by inflation mode yielded similar results to the analysis of calf versus foot location.

Symptomatic DVT

Although a clinically important outcome, few studies examined symptomatic DVT. Six RCTs (4 studies IPCD alone, 2 studies combination IPCD plus anticoagulation) reported symptomatic DVTs in TKA and THA patients. A total of 6 (0.5%) symptomatic DVTs were identified (n=1143), 3 each in THA and TKA patients. There was no statistically significant difference in symptomatic DVT events when an IPCD was used instead of or in addition to anticoagulation (RR 1.02; 95% CI, 0.48 to 2.14; I^2=0%).

Pulmonary Embolism (PE)

Eight RCTs evaluated IPCDs versus anticoagulation for the prevention of PEs. A total of 7 PEs (0.4%) were identified (n=1596); 5 were in THA patients, and 2 in TKA patients. IPCDs, either alone (4 studies) or in combination with anticoagulation (4 studies), offered no advantage in reducing PE events compared to anticoagulation in THA or TKA patients (RR 1.11, 95% CI 0.83 to 1.49; I^2=0%). We found consistent results, but analyses were limited by the small number of events.

VTE Outcomes in Other Surgical Patients

IPCDs were compared to anticoagulation in only one other surgical population. A small RCT (n=110)[49] performed in spinal surgery patients compared a Kendall SCD calf-thigh device to warfarin and found no significant difference in treatment effect for outcomes of VTE events (DVT and/or PE), any DVT (symptomatic or asymptomatic), symptomatic DVT, or PE. The risk of bias was judged to be moderate.

Mortality

A subset of 4 RCT studies (869 patients) examined all-cause mortality in patients undergoing joint replacement; the length of follow-up ranged from 4 weeks to 3 months. Only one of the 4 RCTs reported any deaths (4 patients),[19] finding no difference in mortality between the A-V Impulse System foot device and LMWH. The overall pooled effect estimate for the 4 RCTs found no difference in the risk of all-cause mortality between IPCDs and anticoagulation (RR 1.57; 95% CI, 0.76 to 3.26; I^2=0%), but the confidence intervals were wide and did not exclude a clinically important difference.

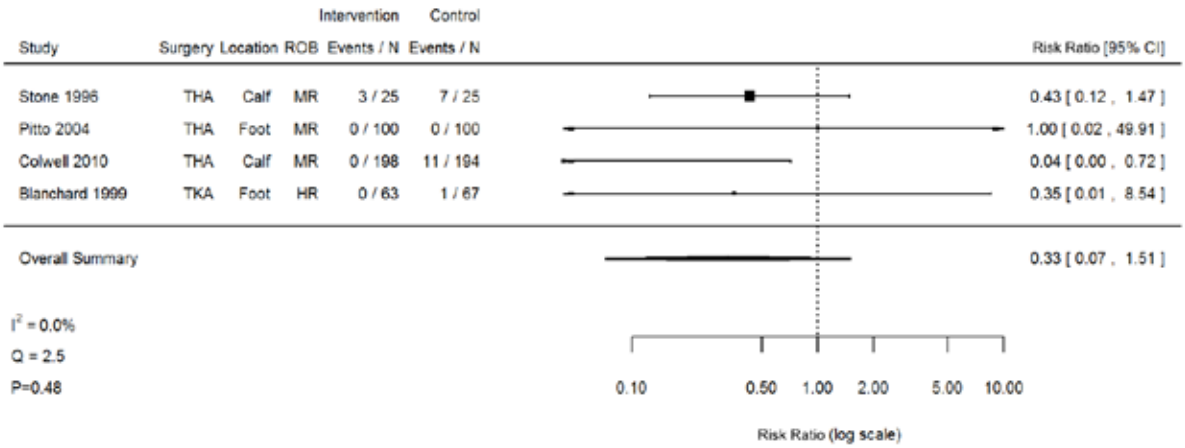
Adverse Events

Adverse events were defined as clinically relevant major bleeding (defined using ISTH criteria for major bleeding in surgical patients), any bleeding, or skin or nerve damage. Meta-analysis was performed only for the outcome of major bleeding.

Major Bleeding

Six RCTs evaluated major bleeding outcomes, but only 4 of these used ISTH criteria for major bleeding in surgical patients (total n=791). Major bleeding was reported in 22 (3%) joint replacement patients (19 patients randomized to anticoagulation versus 3 patients randomized to IPCD). Meta-analysis of these 4 studies suggest that IPCDs may reduce the risk of major bleeding events compared with anticoagulation (RR 0.33; 95% CI, 0.07 to 1.51; I^2=0%; Figure 5). The only individual study to find an IPCD protective against major bleeding events was conducted by Colwell et al,[17] who studied 392 THA patients and compared a portable CECT calf device (ActiveCare+S.F.T.®) versus LMWH. Risk of bias was moderate. Patients in both treatment groups were allowed to receive 81 mg aspirin daily. Patients in the IPCD group had a RR of developing a major bleed of 0.04 (95% CI, 0.0 to 0.72) compared with those who received LMWH. This was also the largest of the studies examining major bleeding outcomes, suggesting that smaller trials may have been underpowered to detect major bleeding outcomes.

Figure 5. Risk for Major Bleeding Events with IPCD versus Anticoagulation Prophylaxis in Joint Replacement Patients



Any Bleeding

Any bleeding was reported in 3 RCTs of patients undergoing joint replacement and one study of patients undergoing spine surgery (total n=710). Bleeding was reported in 83 (23.3%) patients randomized to IPCD and in 105 (29.6%) patients randomized to anticoagulation.

Skin and Nerve Damage

Skin and nerve damage was assessed in 3 studies; however, no patients were identified with this injury.

IPCD Adherence

Adherence was described as rates of discontinuation and average duration of use per day of ICPDs. Four RCTs reported rates of discontinuation, all of which examined the A-V Impulse System foot device. This device was discontinued in 42 of 543 patients (8%). Average duration of use per day was examined in 6 RCTs, including the study by Edwards et al,[58] which reported results separately for TKA and THA patients, resulting in 7 total comparisons. IPCDs were worn for an average of 14.5 hours per day (range 11 to 22). The ActiveCare portable CECT calf device was worn for an average of 20 hours per day (range 19 to 20), whereas the non-portable A-V Impulse System foot device was worn for an average of 16 hours per day (range 11 to 22).

KEY QUESTION 2: In hospitalized medical patients at high risk for VTE, what is the comparative effectiveness of VTE prophylaxis with IPC devices versus VTE prophylaxis with pharmacological agents for VTE events, VTE-related mortality, and adverse events?

Description of Included Studies

Three eligible RCTs (n=855) compared IPCDs to anticoagulation in high-risk medical inpatients.[55,59,61] VTE prophylaxis was initiated within 24 to 48 hours post-admission in 2 studies;[55,61] time to initiation was not specified in the other study.[59] All 3 trials continued VTE prophylaxis until hospital discharge or for 4 weeks, the entire study duration. The first study (n=360) compared a calf IPCD (Jobst Anthrombic Pump) to standard dose LMWH in stroke patients with lower extremity weakness.[59] The second study (n=442) compared a calf IPCD (Flowtron) to unfractionated heparin, dose-adjusted to a therapeutic partial thromboplastin time (PTT) level, in a high-risk, heterogeneous group of trauma patients.[55] The third study was a small feasibility study (n=53) that compared 4 study arms, 2 different IPCDs (calf compression devices and arteriovenous foot devices, manufacturers not specified) and 2 forms of heparin prophylaxis (unfractionated and LMWH) in a high-risk trauma sample.[61] Although this trial met eligibility criteria, it did not report outcomes separately for each study arm, precluding valid interpretation of results.

The risk of bias was judged to be moderate for 2 trials,[55,59] mainly because of higher rates of attrition in the IPCD group and exclusion of these patients from analyses,[59] and because participants were excluded due to non-compliance with the assigned intervention.[55] The third study[61] was judged to be at high risk of bias because of lack of clarity on key methodological criteria. Appendix B provides details of the quality ratings for each study. No eligible study examined other populations of interest with an elevated risk of thromboembolic complications, such as medical intensive care unit patients or patients with malignancy.

VTE Outcomes

VTE Events (DVT and/or PE)

Two trials did not find a statistically significant difference in DVT incidence between IPCD and heparin treatment groups. For stroke patients, the incidence of proximal DVT events was 6.8% versus 4.2% with IPCDs versus heparin, respectively.[59] For trauma patients, the overall incidence of DVT events (proximal and distal) was 2.7% versus 0.5% with IPCDs versus heparin, respectively.[55] Neither study indicated whether DVT events diagnosed by ultrasound were symptomatic or asymptomatic, which limits the clinical usefulness of these results. Only one of the 2 trials reported PE events.[55] The incidence of PE events was similar: one event in the IPCD group compared to one in the heparin treatment group.

Mortality

Only one of the 2 trials reported mortality.[55] There were no deaths in this study.

Adverse Events

Only one study reported the rate of any bleeding or major bleeding.[55] The incidence of bleeding did not differ significantly between the dose-adjusted heparin group (5.0%) and the IPCD group (3.6%; p=0.237). The incidence of major bleeding events was identical (1.8%) in the 2 study groups.

KEY QUESTION 3: In hospitalized surgical and medical patients at high risk for VTE, what is the comparative effectiveness of different IPC devices when compared to one another for preventing VTE events?

Description of Included Studies

Three RCTs (666 patients) directly compared 2 different IPCDs.[46,50,51] Devices from 3 manufacturers, including those using foot, calf, and thigh sleeves, were compared in surgical populations undergoing joint replacement, spinal surgery, or repair of a traumatic acetabular or pelvic fracture. VTE prophylaxis was initiated intraoperatively[46,51] or shortly following admission.[50] Only one study specified treatment duration,[51] continuing the IPCD until the day of discharge. Risk of bias was moderate in 2 studies[46,50] and high in the third.[51] In 2 studies, outcome assessors were not blinded to the type of IPCD.[46,51] Baseline risk profiles in the 2 randomized groups were not comparable in one study.[51]

VTE Outcomes

VTE Events (DVT and/or PE)

A large study (moderate risk of bias) randomized 423 patients undergoing TKA to a calf rapid inflation asymmetrical compression (RIAC) device (VenaFlow) or to a calf sequential compression device (SCD) (Kendall SCD).[46] The rate of VTE events was significantly lower in the Venaflow arm than in the Kendall SCD arm (6.9% vs 15%, respectively; p=0.007); all but one VTE events were DVTs, and it was not specified whether the DVTs were symptomatic. The study authors concluded that thromboprophylaxis using VenaFlow was associated with a significantly lower risk of VTE compared to the Kendall SCD.

Two studies compared a slow-gradual inflation SCD (Kendall SCD) to rapid inflation devices (PlexiPulse).[50,51] In a study of 107 patients undergoing pelvic fracture surgery (moderate risk of bias), the overall rate of VTE events was 14%; all but one VTE events were DVTs, and it was not specified whether the DVTs were symptomatic.[50] Patients received either a calf-thigh SCD (Kendall SCD) or a combination calf and foot rapid inflation device(PlexiPulse). The rate of VTE events in the Kendall SCD arm was not significantly different from that in the PlexiPulse arm (10 [19%] vs 5 [10%]; p=0.265). In another study (high risk of bias), 136 patients undergoing spinal surgery were randomized to receive either a calf-thigh SCD (Kendall SCD) or a sequential rapid inflation foot device (PlexiPulse).[51] No patients randomized to the Kendall SCD were diagnosed with a VTE compared to 2 patients in the PlexiPulse arm (1 DVT and 1 PE).

Mortality

One study reported one death (0.2%) due to myocardial infarction, but no VTE-related mortality.[46] The other studies did not report mortality outcomes.

Adverse Events

None of the included studies reported major bleeding events as an outcome. In one study, 36 patients (26%) complained of redness, itching, or discomfort associated with IPCDs.[51] Of these, 18 (24%) were using the PlexiPulse system and 18 (31%) were using the Kendall SCD ($p>0.5$). In the TKA study,[46] one patient with pigmented synovitis required post-operative aspiration.

KEY QUESTION 4: When used for VTE prophylaxis, do different IPC devices differ in ease of use or adherence?

Description of Included Studies

Four RCTs (374 patients)[23,47,50,51] and 3 observational studies (1724 patients)[48,60,62] compared different IPCDs to one another and reported data on ease of use or adherence. All but one study were conducted in surgical populations. At least 5 devices were included, and specific device names were reported (or obtained through correspondence with study authors) for all but 2 studies.[60,62] Studies were judged to be at moderate (n=3)[23,47,50] or high (n=4)[48,51,60,62] risk of bias. Important limitations in the 3 observational studies were: sequential rather than contemporaneous comparisons of devices; analyses that did not adjust for potential confounders; and use of unvalidated measures to assess comfort or ease of use.

Ease of Use

Four studies reported patient-rated comfort and 2 reported staff-rated ease of use. A PlexiPulse rapid inflation foot device was compared to a Kendall SCD calf-thigh device in 2 studies, one moderate-sized RCT finding no difference in comfort ratings,[51] and a larger observational study finding the PlexiPulse device rated more favorably.[48] Another small RCT compared the Kendall SCD calf and Flowtron calf devices.[47] Patients rated the Flowtron breathable sleeve more comfortable than the Kendall SCD thick stiff plastic sleeve on 1 of 6 items. Staff rated the Flowtron device easier to use (by approximately 1 point on a 5-point Likert Scale) on each of 6 different items. An observational study comparing 5 manufacturers with multiple different sleeves found differences in patient-rated comfort and staff-rated ease of use, but the device-sleeve combinations were not described in a manner that would allow the preferred devices or device type to be identified.[62]

Adherence

Six studies compared adherence for 2 or more IPCDs as reported by patients, staff observation, or counters installed on the devices. There were no consistent associations between specific named devices or location of the sleeve and adherence. Two observational studies found greater adherence with a foot device compared to other IPCDs.[48,60] A small RCT found greater adherence with the portable WizAir DVT CECT calf device (77.7%), which includes a battery pack, compared to a Kendall SCD calf device (58.9%).[23] Other studies found no important differences between a Kendall SCD using a thick plastic sleeve and a Flowtron device using a

breathable plastic sleeve,[47] did not identify the devices evaluated,[62] or did not perform statistical analyses because of missing data.[50]

In KQ 1, we reported adherence in studies comparing an IPCD to anticoagulation. These studies also found longer use with a portable device (mean of 20 hours) compared to the A-V Impulse System foot device, a non-portable device.

SUMMARY AND DISCUSSION

We identified 18 RCTs and 3 observational studies in post-operative surgical and high-risk medical patients that evaluated the comparative effectiveness of IPCDs in reducing VTE events or that rated ease of use or adherence. Most studies compared IPCDs to anticoagulation. Only 3 RCTs in high-risk surgical patients directly compared different IPCDs; there were no head-to-head comparisons in high-risk medical patients. IPCDs were comparable to anticoagulation for major clinical outcomes, but confidence intervals were typically wide and clinically important differences could not be excluded. Subgroup analyses did not show significant differences by device location or mode of inflation. The current evidence base to guide selection of a specific device or type of device is limited, and comparative effectiveness studies are needed to address this gap in evidence. This meta-message is consistent with the findings from another review.[30]

In Table 3 and sections below, we summarize the main findings and strength of evidence by key question (KQ).

Table 3. Strength of Evidence for ICPD Effectiveness in Reducing VTE Events

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)*	Strength of Evidence
	No. of Studies (Patients)	Study Design/Risk of Bias	Consistency Directness	Precision Publication Bias		
KQ 1: IPCDs vs Anticoagulation in Surgical Patients						
Mortality	4 (869)	RCT/High	Consistent Direct	Imprecise None detected	RR 1.57 (0.76 to 3.26)	Insufficient
VTE Events	8 (1528)	RCT/ Moderate	Inconsistent Indirect	Imprecise None detected	IPCD alone: RR 1.39 (0.73 to 2.64) RD=23 more/1000 (16 fewer to 98 more) IPCD+LMWH: RR 0.27 (0.05-1.64) RD=44 fewer/1000 (57 fewer to 38 more)	Low

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)*	Strength of Evidence
	No. of Studies (Patients)	Study Design/Risk of Bias	Consistency Directness	Precision Publication Bias		
Any DVT	10 (1716)	RCT/ Moderate	Inconsistent Indirect	Precise None detected	IPCD alone: RR 1.27 (0.81 to 2.00) RD=5 more/1000 (4 fewer to 20 more) IPCD+LMWH: RR 0.28 (0.04 to 1.79) RD=14 fewer/1000 (19 fewer to 16 more)	Low
Major bleeding	4 (772)	RCT/ Moderate	Consistent Direct	Imprecise None detected	RR 0.33 (0.07 to 1.51) RD=25 fewer/1000 (34 fewer to 19 more)	Low
KQ 2: IPCDs vs Anticoagulation in Medical Patients						
Mortality	1 (442)	RCT/High	Consistent Direct	Imprecise None detected	No events	Insufficient
VTE Events	1 (442)	RCT/High	Consistent Indirect	Imprecise None detected	More events with IPCD (7 vs 2) but p=NS	Insufficient
Any DVT	2 (679)	RCT/High	Consistent Indirect	Imprecise None detected	More events with IPCD (14 vs 6) but p=NS	Insufficient
Major bleeding	1 (442)	RCT/High	Consistent Direct	Imprecise None detected	Equal number of events	Insufficient
KQ 3: Direct Comparisons of IPCDs in Surgical and Medical Patients						
Mortality	1 (423)	RCT/ Moderate	Consistent Direct	Imprecise None detected	1 death	Insufficient
VTE Events	1 (423) 2 (143)	RCT/ Moderate RCT/High	Consistent Indirect Consistent Indirect	Imprecise None detected Imprecise None detected	Fewer VTE events with VenaFlow vs Kendall SCD* No difference between Kendall SCD and PlexiPulse	Low Insufficient

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)*	Strength of Evidence
	No. of Studies (Patients)	Study Design/Risk of Bias	Consistency Directness	Precision Publication Bias		
Any DVT	1 (423)	RCT/ Moderate	Consistent Indirect	Imprecise None detected	Fewer VTE events with VenaFlow vs Kendall SCD*	Low
	2 (143)	RCT/High	Consistent Indirect	Imprecise None detected	No difference between Kendall SCD and PlexiPulse	Insufficient
Major bleeding	None	NA	NA	NA	NA	Insufficient

*Risk differences (RDs) were calculated for outcomes with pooled estimates of effect and strength of evidence ratings of low or higher.

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; IPCD(s)=intermittent pneumatic compression device(s); KQ=key question; LMWH=low molecular weight heparin; NA=not applicable; No.=Number; NS=not statistically significant; RCT=randomized controlled trial; RD=risk difference; RR= risk ratio; SCD=sequential compression device; VTE=venous thromboembolism

SUMMARY OF EVIDENCE BY KEY QUESTION (KQ)

KQ 1: IPCDs versus Anticoagulation in Surgical Patients

The majority of these studies were performed in patients undergoing joint replacement, with one study in other surgical populations. The A-V Impulse System foot device and the portable ActiveCare CECT devices were the IPCDs most commonly compared to anticoagulation. There was no difference between IPCDs and anticoagulation for the outcomes of VTE events, DVT events, and mortality, but confidence intervals were wide and did not exclude clinically important differences for some of these outcomes. There was also no clear pattern of differences in the studied outcomes by type or location of IPCD (foot, calf, thigh), surgical indication (TKA vs THA), or IPCD only versus combined therapy (IPCD plus anticoagulation), although some evidence suggests that combination of IPCD plus anticoagulation may be more effective than IPCD alone. IPCDs compared to anticoagulation may lower the risk of major bleeding.

KQ 2: IPCDs versus Anticoagulation in Medical Patients

There are few studies examining IPCD performance for VTE prophylaxis in high-risk medical patients. We identified studies only in stroke and trauma patients, and calf IPCDs were the most commonly studied devices in these patients. Although there is limited evidence suggesting similar incidence rates of VTE events (DVT or PE) with IPCDs and anticoagulation, we judged the strength of evidence to be insufficient because of important risk of bias and wide confidence intervals that do not exclude clinically important differences in treatment effects.

KQ 3: Direct Comparison of IPCDs in Surgical and Medical Patients

There are few studies that directly compare IPCDs for VTE prophylaxis in surgical patients, and none meeting our inclusion criteria in medical patients. One large study (moderate risk of bias) in TKA patients found evidence that a rapid inflation calf device (VenaFlow) was associated with

lower VTE risk compared to a gradual inflation calf device (Kendall SCD). Two other studies in pelvic fracture and spinal surgery patients, comparing rapid inflation foot or foot-calf devices (PlexiPlus) to gradual inflation thigh-high devices (Kendall SCD), did not show significant differences in VTE event rates. No VTE-related mortality or major VTE-related complications were reported in any of these studies. With few studies reporting on the direct comparison of IPCDs, and indirect comparisons infeasible due to variability in study designs, we considered the strength of evidence to be insufficient to low.

KQ 4: Ease of Use and Adherence in Surgical and Medical Patients

We examined RCTs and observational studies that compared IPCDs and reported data on ease of use or adherence in surgical and medical patients. One small RCT found greater adherence with use of a portable calf device (WizAir DVT CECT) compared to a non-portable calf device (Kendall SCD). Another RCT found no difference in adherence between a rapid inflation foot device (PlexiPlus) compared to a calf-thigh gradual inflation device (Kendall SCD). Observational studies found that foot devices had greater adherence compared to other IPCDs. However, observational studies had important methodological limitations. Overall, there were no consistent associations between specific brand-name IPCDs or sleeve location and ease of use or adherence.

CLINICAL AND POLICY IMPLICATIONS

The prevalence of total joint replacements in the United States is increasing rapidly. By 2030, it is projected that the number of primary THAs in the United States will grow 174% to 572,000, and primary TKAs by 673% to 3.48 million procedures per year.[64] Similar growth in these procedures is likely in the VA Health System since it serves an older population with a high prevalence of orthopedic conditions. However, appropriate prophylaxis is suboptimal in this high-risk population, and there is a growing gap between consensus guidelines and clinical practice.[65-67] Among medically ill hospitalized Veterans, missed opportunities for VTE prophylaxis are also frequent and often include inappropriate mechanical prophylaxis or inadequate use of anticoagulation.[68]

Suboptimal utilization of mechanical prophylaxis with IPCDs is a patient safety issue that has significant cost implications for health systems. Therefore, there is health system interest in improving the quality of mechanical VTE prophylaxis prescribing to ensure that all surgical and medically ill hospitalized patients receive the most appropriate, safe, and cost-effective VTE prophylaxis possible. In the next section, we summarize recommendations from the 2 major U.S. clinical guideline panels that have addressed this issue and then provide a framework for selecting IPCDs in the face of uncertain evidence.

Clinical Practice Guidelines

Surgical Patients

Both the American Academy of Orthopaedic Surgeons and the American College of Chest Physicians (ACCP) have recently issued guidelines on thromboprophylaxis.[14-16] Recommendations for thromboprophylaxis are related to the surgery, the risk of bleeding, and the risk of VTE. IPCD prophylaxis is recommended for orthopedic and non-orthopedic patients

at high risk of bleeding. For non-orthopedic procedures in patients at low risk of bleeding, IPCD prophylaxis is recommended for patients who are also at low risk of VTE. For orthopedic procedures, portable battery-powered IPCDs and devices capable of recording wear time are recommended as an option for patients at low risk of bleeding, but pharmacological prophylaxis with or without IPCD is preferred.[16] Overall, however, these clinical guidelines do not recommend for or against specific IPCDs for VTE prophylaxis and were based on low-quality evidence. Relevant to these guidelines are our findings that IPCDs, compared to anticoagulation, may have decreased risk of major bleeding complications, and that the combination of IPCD and anticoagulation may be more effective at preventing VTE than anticoagulation alone.

Medical Patients

According to the 2012 ACCP guidelines, optimal use of mechanical thromboprophylaxis with IPCDs is recommended in acutely ill medical inpatients at increased risk for thrombosis, who are bleeding, or who are at high risk for major bleeding.[13] These are consensus-based recommendations. The VA patient population has more medical conditions than the general patient population,[69] placing our patients at high risk for VTE and bleeding complications. Given the limited data on mechanical IPCD use in high-risk medical patients, we judged the strength of evidence to be insufficient to determine the effects on clinically important outcomes in this population.

FRAMEWORK FOR SELECTING IPC DEVICES

Making clinical and policy recommendations in the face of uncertain evidence is challenging. Our review was structured to consider 3 types of evidence: 1) head-to-head comparisons of IPCDs; 2) indirect comparisons of IPCDs to a common comparator (*eg*, foot vs calf devices, each compared to anticoagulation); and 3) data on ease of use or adherence from patients or staff. An additional type of evidence is simply the frequency with which particular devices or device types have been evaluated.

Although there are mechanistic differences between ICPDs, such as sleeve location (foot, calf, thigh) and inflation and compression cycle patterns, as well as conceptual differences, such as device portability, we did not find definitive evidence to suggest that any of these factors are associated with clinically important differences in VTE rates or patient- or staff-rated ease of use. When the strength of evidence from published studies is insufficient for confident decision making, other criteria may be applied. In 2007, the Emergency Care Research Institute (ECRI Institute) evaluated selected IPCDs and proposed the following evaluation criteria: safety features, patient comfort, performance (*eg*, inflate to specified pressure), quality of construction, battery life and other battery related features (if battery equipped), and ease of setup and other ease-of-use features.[70] In addition, the guideline-recommended use of portable, battery-powered IPCDs with hour meters in joint replacement patients[16] may be applicable to other surgical and medical populations, but further study of this is needed. Additional considerations are costs and flexibility. If a single device can be used in a variety of modes and with a variety of compression bladders, then that device may serve a broader range of clinical needs. An updated evaluation that describes these features for devices currently on the market could inform decision making.

LIMITATIONS

Limitations can be categorized broadly into those related to the methods of the review and those related to the included studies. Our review differs from prior reviews in important ways. We limited eligibility to studies reporting VTE outcomes at 4 weeks or greater, a period of clinically important elevated risk for VTE. By excluding short-duration studies, we prioritized the most clinically relevant time-point, but excluded trials that may have contributed some useful data. We also imposed geographical limits to restrict the review to medical systems most similar to the United States, but this led to exclusion of at least 2 trials that would otherwise have been eligible.[71,72] A sensitivity analysis (data not shown) that included these studies for the outcomes "any DVT" and "major bleeding" had no important effect on the estimates of effect. In other ways, our eligibility criteria were more expansive. We included surgical and medical populations at elevated risk of VTE and observational studies to better evaluate ease-of-use outcomes. We also conducted novel subgroup analyses by device characteristics to explore whether these characteristics could guide policymakers or health systems in device selection. The devices studied may, however, not be the same as those currently on the market; furthermore, in some instances, we do not know all the features of the devices studied. Our search of ClinicalTrials.gov did not identify any completed but unpublished studies, but statistical methods to evaluate publication bias were limited due to the relatively small number of studies.

The chief limitations of the literature were the paucity of head-to-head comparisons of IPCDs and the focus on DVT assessed by screening imaging studies, resulting primarily in the identification of asymptomatic DVTs of uncertain clinical importance. Other limitations include important methodological limitations in both RCTs and observational studies. However, sensitivity analyses did not show important differences in pooled estimates when studies at high risk of bias were excluded. We also found important heterogeneity in treatment effects for VTE and DVT outcomes, heterogeneity that was only partly explained by subgroup analyses. This unexplained heterogeneity decreased our confidence in the strength of evidence. Finally, changes in manufacturers over time made it difficult to identify some devices and their characteristics accurately.

Despite these limitations, men and women were well-represented in the included studies, and the median average age was 54 years, somewhat younger than the average patient admitted to VA hospitals. Other than age, which is associated with risk for VTE, these results should be applicable to VA patients and VA hospitals.

RESEARCH GAPS/FUTURE RESEARCH

We used the framework recommended by Robinson et al[73] to identify gaps in evidence and prioritize future needs (Table 4). This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps.

Table 4. Evidence Gaps and Future Research Needs

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Effects of IPCDs in medically ill patients	Insufficient information	RCTs or multi-site observational studies
Effects of IPCDs in non-orthopedic high-risk surgical groups (bariatrics, gynecological, or robotic surgeries)	Insufficient information	Large RCTs or multi-site observational studies
Interventions		
Optimal IPCD type or category	Insufficient information	RCTs or quasi-experimental studies of head-to-head comparisons of IPCD sleeve locations, compression patterns, and inflation times
Comparator		
Effectiveness of IPCDs compared to newer oral anticoagulants	Insufficient information	RCTs or observational studies
Outcomes		
Accuracy of treatment effects beyond 4 weeks	Insufficient information	Trials with more careful assessment of VTE rates at 1 month and beyond, outcomes assessed blinded to treatment assignment
Effects on clinically relevant outcomes	Insufficient information	Trials with proximal and symptomatic DVT outcome assessments, trials with standard approaches to assessing/reporting bleeding
Effects on adherence and patient/staff tolerability	Insufficient information	Trials using standard, validated questionnaires for patient/staff assessment of ease of use outcomes

Abbreviations: DVT=deep vein thrombosis; IPCD(s)=intermittent pneumatic compression device(s); RCTs=randomized controlled trials; VTE=venous thromboembolism

CONCLUSIONS

Although IPCDs differ in practical features and in effects on physiology, current evidence does not show a clear difference in effects on clinically important outcomes. As a strategy for thromboprophylaxis, we found that IPCDs may decrease the risk of major bleeding compared to anticoagulation, and when used in combination with LMWH, may decrease the risk of VTE. We conclude that IPCDs are a viable option for VTE thromboprophylaxis when used in accordance with current clinical guidelines. When choosing a specific IPCD, focusing on device flexibility, acceptability by nursing staff and patients, and the most frequently studied devices, as well as on cost, can help direct selection of appropriate IPCDs. Comparative effectiveness studies are urgently needed to address current gaps in evidence.

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