厚生労働省科学研究費補助金

医療安全・医療技術評価総合研究事業

肺血栓塞栓症／深部静脈血栓症の院内発症予防ガイドライン公開後の評価ならびに改定と普及・推進に関する研究

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(研究要旨)
2004年の初版のガイドライン発刊後、一般外科領域、産婦人科領域、整形外科領域では、種々の取り組みが進み、情報も集積した。新しい抗凝固薬も使用可能となっている。一方、内科での取り組みは遅れており、啓蒙が必要である。新しくVTE改訂委員会を編成し、今回検討された情報を十分反映したガイドライン作りが必要である。

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A. 研究目的
2004年に発刊された初版の肺血栓塞栓症／深部静脈血栓症(静脈血栓塞栓症:VTE)予防ガイドラインの改訂作業を行う。

B. 研究方法
初版のVTE予防ガイドラインに改訂のために、ガイドライン発刊後の各領域での取り組みや成果を分析し、また新しいエビデンスを収集して、ガイドライン改訂の基礎資料とする。また、VTE予防ガイドラインに参画が必要となる学会を検討し、改訂作業に対する協力を要請した。

C. 結果と考察
一般外科領域、産婦人科領域、整形外科領域では、2004年以降、臨床現場におけるVTE予防への取り組みは進み、エビデンスも徐々に集積しつつある。新しい薬物も使用可能となったため、これらの情報を改訂ガイドラインに反映させねばならない。一方、内科領域での取り組みは不十分であり、さらに啓蒙活動が必要である。また、精神科領域でのVTE発症報告は増加しており、ガイドラインに加えることを

検討中である。

ところで、わが国のVTEは、高齢化社会などを背景としてさらに増加している。VTE 予防では理学的予防への理解が進み、周術期の VTE の頻度は減少したが、薬物的予防法への抵抗が依然大きい。VTE 診断法は静脈エコーと造影 CT が主流となり、治療に関しては下大静脈フィルターの進歩が著しいが、無症候性下腿静脈血栓症への対処法を検討する必要である。

VTE 予防ガイドライン改訂にあたり、初版への参加 10 学会には同じように参加を依頼し、承諾を得た。さらに日本内科学会、日本呼吸器学会、日本脳神経外科学会、日本救急医学会にも参加を依頼し承諾を得た。更に、日本外科学会、日本循環器学会、日本精神神経学会にも参加を依頼中である。

D. 結果

2004 年の初版のガイドライン発刊後、種々の取り組みが進み、情報も集積した。新しく VTE 改訂委員会を編成し、上記の検討された情報を十分反映したガイドライン作りが必要である。

厚生労働科学研究費補助金(医療安全・医療技術評価総合研究事業)
分担研究報告書

肺血栓塞栓症／深部静脈血栓症の院内発症予防ガイドライン公開後の評価ならびに改定と普及・推進に関する研究
－ 一般外科、産婦人科、整形外科、内科領域の VTE 予防に関する検討 －

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(研究要旨)
一般外科領域、産婦人科領域、整形外科領域では、2004 年以降で臨床現場での VTE 予防への取り組みは進み、エビデンスも徐々に集積しつつある。新しい薬物も使用可能となった。一方、内科領域での取り組みは不十分であるが、精神科領域での VTE 発症報告は増加している。これらの新しい情報を十分に分析して、改訂 VTE 予防ガイドラインに反映させる必要がある。

A. 研究目的
一般外科領域、産婦人科領域、整形外科領域および内科領域におけるわが国の肺血栓塞栓症／深部静脈血栓症(静脈血栓塞栓症: VTE)予防の現状や新しいエビデンスを検討し、予防ガイドライン改訂作業の基礎情報を作成する。

B. 研究方法
初版 VTE 予防ガイドラインが発刊された 2004 年以降の一般外科領域、産婦人科領域、整形外科領域および内科領域におけるわが国の VTE 予防の現状を分析し、また新しいエビデンスを収集して検討した。

C. 結果と考察
2004 年の VTE 予防ガイドラインの発刊以降、診療報酬に「肺血栓塞栓症予防管理料」が収載されたこともあり、全国の一般外科領域、産婦人科領域、整形外科領域の多くの施設で VTE 予防が積極的に行われるようになった。新しいエビデンスもいくつか出てきている。一般外科においては、多施設前向き試験にて腹部手術後 VTE の発生率の検討が行われており、20%以上と欧米と同程度の VTE 発生が見られている。癌などのリスクがより高い手術においては欧米と同程度の予防法が必要である可能性が高い。抗凝固療法による予防の必要性を更に検討する必要がある。
産婦人科領域においては 2001 年から 2005 年に新たに発症した VTE の全国調査が行われている。婦人科の VTE 発症数は 2000 年以前と比して増加しているが、特に卵巣癌術前発症例が一段と増加していた。術後予防は徹底されつつあるが、術前予防やスクリーニングの問題は解決されてはおらず、改訂作業におい

て検討すべき重要課題である。一方、産科のVTE 発症数は減少しており、他の領域と比較して VTE 予防対策が浸透していると考えられた。しかし、妊娠中の DVT への対応が問題になっており、今後、院内発症 VTE と同じように対策が必要であると考えられた。

整形外科領域は VTE 予防が最も進んでいる領域である。新しい抗凝固薬の治験などからエビデンスとなるデータが多く発表されている。例えば、膝関節置換術においては VTE の発生率は 60%以上であり、欧米の報告とほとんど同程度である。他の報告でも同様の結果であり、リスクの高い手術においては日本人と欧米人の VTE 発生率はほとんど相違ない可能性が示唆される。また、2007 年には Xa 阻害薬のフォンダパリヌクスが下肢整形外科手術に保険適応となり、2008 年には低分子量ヘパリンのエノキサパリンが保険適応となった。今回のガイドライン改訂においては、エビデンスが集積した手術のリスクを再検討し、新しい抗凝固療法による予防法をどのリスク段階から推奨するかが、最も重要な検討事項となる。

外科系領域の VTE 予防が全国的に進んでいるのに対して、内科においては認識が低く、依然として VTE 予防施行率は低い。同様に VTE 予防に関する内科領域のエビデンス作りはほとんど進んでおらず、心不全領域での検討がある程度である。一方で、類似領域である精神科での VTE 発症の報告は増加している。全国調査でも発症率が高いことが報告されており、特に入院初期や身体拘束に関連した発症が目立つ。内科領域での VTE 予防対策は簡単ではないが、脳卒中後やICU 入院患者では明らかに VTE の頻度は高く、改訂作業では少しでも合理的な予防法を追求する必要がある。また、2008 年の診療報酬改訂で「肺血栓塞栓症予防管理料」が精神科にも新たに適応されてこともあり、改訂ガイドラインへの精神科領域の追加を検討しなければならない。

E. 結論

外科系診療科では 2004 年以降、臨床現場での取り組みは進み、エビデンスも徐々に集積しつつある。新しい薬物も使用可能となった。一方で、内科領域での取り組みは不十分であるが、精神科での VTE 発症報告は増えている。これらの情報を十分に分析して、改訂 VTE 予防ガイドラインに反映させる必要がある。

厚生労働科学研究費補助金(医療安全・医療技術評価総合研究事業)
研究報告書

肺血栓塞栓症／深部静脈血栓症の院内発症予防ガイドライン公開後の評価ならびに改定と普及・推進に関する研究
－ 肺血栓塞栓症および深部静脈血栓症に関する現状と進歩に関する検討 －

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(研究要旨)
わが国のVTEは、高齢化社会などを背景として年々さらに増加している。VTE予防では理学的予防への理解が進み、周術期のVTEの頻度は減少したが、薬物的予防法への抵抗が依然大きい。VTE診断法は静脈エコーと造影CTが主流となり、治療に関しては下大静脈フィルターの進歩が著しいが、無症候性下腿静脈血栓症への対処法を検討する必要である。

A. 研究目的
肺血栓塞栓症／深部静脈血栓症(静脈血栓塞栓症:VTE)予防に関連したわが国のVTEの疫学や診断・治療に関しての現状や新しいエビデンスを検討し、予防ガイドライン改訂作業の基礎情報を作成する。

B. 研究方法
初版VTE予防ガイドラインが発刊された2004年以降のVTEの発送数や診断・治療の現状を分析し、また新しいエビデンスを収集して検討した。

C. 結果と考察
わが国におけるVTEの発生率は、定期的な全国調査においても、やはり年々増加しており、最近の10年間で2.3倍となっている。これはVTEの診断能が向上した影響もあるが、高齢化社会を背景に、VTEリスクを有する人口が増加し、また食生活の欧米化により肥満人口が増えたことなどが原因と考えられる。日本人と欧米人とのVTEの頻度の違いは未だ解明されていない。欧米人ではFactor V Leidenなどの遺伝子変異が多くのVTE発症に関連するとされ、アジア人には見られない変異である。一方で、日本人に特異性が高い遺伝子変異も見つかっており、例えばProtein S徳島変異はVTEの10%に見られる頻度の高い異常である。
VTEの予防に関しては、弾性ストッキングに関する講習会などの関連学会の活動などにより、理学的予防法に対する理解は深まっている。麻酔科学会などの調査では、VTE予防ガイドラインが発刊された2004年以降、明らかに周術期のVTE発症率は減少している。しかし、周術期の薬物的予防への抵抗は依然高く、そ

の施行率は低いとの報告が多い。フォンダパリヌクスやエキノキパリンといった VTE 予防に対する新しい抗凝固薬がわが国でも使用可能となり、薬物予防に対する啓蒙を十分に進める必要がある。

VTE に対する診断法であるが、画像診断では、深部静脈血栓症に対しては静脈造影に代わって静脈エコーが主流となり、検査技師の養成も進んでいる。また、肺血栓塞栓症の診断検査は肺動脈造影や肺血流シンチから造影 CT にほぼ変わり、多検出器型 CT の発達により診断能力も著しく向上した。しかし、VTE に対する簡便なスクリーニング法がないことが依然として問題であり、診断が難しい疾患であることには変わりない。血液検査では D ダイマーを初期検査に使用する施設も増えているが、その使用法は統一されておらず、改訂ガイドラインにおいても検討が必要と考える。

一方、VTE の治療法に関しては、中枢型の深部静脈血栓症に対するカテーテル的治療が行われるようになり、一定の成果をあげている。しかし、無症候性の下腿静脈血栓が発見された場合の対処法に関しては、意見の集約が不十分である。特に十分なVTE予防施行中に発見された無症候性下腿静脈血栓では経過観察で良いとの意見もあり、改訂作業において十分な検討を必要とする。肺血栓塞栓症に対しては、組織プラズミノーゲンアクチベータであるモンテプラーゼがようやく保険適応となり、重症例への治療選択肢が新たに増えた。しかし、予後改善効果は依然として明らかではなく、今後の検討結果を待たねばならない。一方、下大静脈フィルターは発展を続けており、最近では回収可能型フィルターが主流となっている。その挿入適応は十分に確立していないが、肺血栓塞栓症の急性期に挿入することで予後を改善させる効果も報告されており、最も確実な VTE 治療法として期待されている。

E. 結論

わが国の VTE は年々増加しているが、理学的予防への理解が進み、周術期の VTE の頻度は減少した。薬物的予防法への抵抗が依然大きい。VTE 診断法は静脈エコーと造影 CT が主流となり、治療に関しては下大静脈フィルターの進歩が著しいが、無症候性下腿静脈血栓症への対処法は、今後、検討する必要である。

厚生労働科学研究費補助金(医療安全・医療技術評価総合研究事業)
研究報告書

肺血栓塞栓症／深部静脈血栓症の院内発症予防ガイドライン公開後の評価ならびに改定と普及・推進に関する研究
－ 肺血栓塞栓症/深部静脈血栓塞栓症(静脈血栓塞栓症)予防ガイドラインの改訂委員会の編成に関する検討 －

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(研究要旨)
初版のVTE予防ガイドライン作成委員会への参加10学会には同じように参加を依頼し、承諾を得た。さらに日本内科学会、日本呼吸器学会、日本脳神経外科学会、日本救急医学会にも参加を依頼し承諾を得た。更に、日本外科学会、日本循環器学会、日本精神神経学会にも参加を依頼中である。

A. 研究目的
肺血栓塞栓症／深部静脈血栓症(静脈血栓塞栓症:VTE)予防ガイドラインの改訂において、改訂委員会の編成を検討する。

B. 研究方法
VTE 予防ガイドライン改訂への協力が必要な学会を検討し、協力を依頼する。

C. 結果と考察
まず、2004 年の初版 VTE ガイドラインへの参加学会、すなわち、日本血栓止血学会、日本産科婦人科学会、日本産婦人科・新生児血液学会、日本集中治療医学会、日本静脈学会、日本心臓病学会、日本整形外科学会、日本泌尿器科学会、日本麻酔科学会、肺塞栓症研究会は、これまで同様に改訂委員会への参画が不可欠と考え、参画を依頼した。その結果、ガイドライン改訂への了解を得て、さらに改訂委員会への参加にも承諾を得た。
これらの初期の参加学会のほかに、VTE 予防の中心となる外科関連学会、また今後検討や啓蒙が必要となる内科関連学会の参加が、やはり必要と考えられる。日本内科学会からは産科協力の承諾を得、日本外科学会においては現在検討中である。また、最近、VTE 発症報告が多く、「肺血栓塞栓症予防管理料」の適用も認められた精神科領域でも VTE 予防ガイドラインが切望されている。よって、精神神経学会と連携して、その参画に前向きに検討して頂くこととする。これら以外でリスクが非常に高いと思われる領域、すなわち、救急領域や脳神経外科領域の参画も重要と考えられる。また、肺血栓塞栓症は循環器および呼吸器疾

患としても重要な疾患である。よって、日本救急医学会、日本脳神経外科学会、日本呼吸器学会にも参加協力の依頼を行い、承諾を得、また日本循環器学会では現在検討中である。

E. 結論

初版の VTE 予防ガイドライン作成委員会への参加10学会には同じように参加を依頼し、さらに日本内科学会、日本呼吸器学会、日本脳神経外科学会、日本救急医学会に参加を依頼し、いずれも承諾を得た。

研究成果の刊行に関する一覧表

雑誌

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CHEST Original Research

VENOUS THROMBOEMBOLISM

Venous Thromboembolism Prophylaxis in Acutely Ill Hospitalized Medical Patients*

Findings From the International Medical Prevention Registry on Venous Thromboembolism

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Background: **Evidence-based guidelines recommend that acutely ill hospitalized medical patients who are at risk of venous thromboembolism (VTE) should receive prophylaxis. Our aim was to characterize the clinical practices for VTE prophylaxis in acutely ill hospitalized medical patients enrolled in the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE).**

Methods: **IMPROVE is an ongoing, multinational, observational study. Participating hospitals enroll the first 10 consecutive eligible acutely ill medical patients each month. Patient management is determined by the treating physicians. An analysis of data on VTE prophylaxis practices is presented.**

Results: **From July 2002 to September 30, 2006, 15,156 patients were enrolled from 52 hospitals in 12 countries, of whom 50% received in-hospital pharmacologic and/or mechanical VTE prophylaxis. In the United States and other participating countries, 52% and 43% of patients, respectively, should have received prophylaxis according to guideline recommendations from the American College of Chest Physicians (ACCP). Only approximately 60% of patients who either met the ACCP criteria for requiring prophylaxis or were eligible for enrollment in randomized clinical trials that have shown the benefits of pharmacologic prophylaxis actually received prophylaxis. Practices varied considerably. Intermittent pneumatic compression was the most common form of medical prophylaxis utilized in the United States, although it was used very rarely in other countries (22% vs 0.2%, respectively). Unfractionated heparin was the most frequent pharmacologic approach used in the United States (21% of patients), with low-molecular-weight heparin used most frequently in other participating countries (40%). There was also variable use of elastic stockings in the United States and other participating countries (3% vs 7%, respectively).**

Conclusions: **Our data suggest that physicians' practices for providing VTE prophylaxis to acutely ill hospitalized medical patients are suboptimal and highlight the need for improved implementation of existing evidence-based guidelines in hospitals.** ***(CHEST 2007; 132:936–945)***

Key words: acutely ill; medical patients; prophylaxis; venous thromboembolism

Abbreviations: ACCP = American College of Chest Physicians; ARTEMIS = Arixtra for Thromboembolism Prevention in a Medical Indications Study; DVT = deep vein thrombosis; ES = elastic stockings; IMPROVE = International Medical Prevention Registry on Venous Thromboembolism; IPC = intermittent pneumatic compression; LMWH = low-molecular-weight heparin; MEDENOX = Prophylaxis in Medical Patients with Enoxaparin; PE = pulmonary embolism; PREVENT = Prevention of Recurrent Venous Thromboembolism; UFH = unfractionated heparin; VTE = venous thromboembolism

The vast majority (80%) of hospitalized patients with symptomatic venous thromboembolism (VTE) have not undergone recent surgery.[1–3] Furthermore, 70 to 80% of cases of fatal pulmonary embolism (PE) in the hospital occur in medical (nonsurgical) patients.[4–6] Placebo-controlled studies[7–9] have shown that the incidence of objectively confirmed VTE in acutely ill hospitalized medical patients ranges from 5 to 15%, and can be reduced by between one half and two thirds with appropriate VTE prophylaxis. Despite these data and evidence-based guidelines recommending that prophylaxis should be given to acutely ill hospitalized medical patients who are at risk of VTE,[10,11] it is often underused or used suboptimally in this patient population.[12–15] To date, prophylaxis practices in these patients remain poorly characterized, and published reports[14,16–18] have been limited to single-center or national data. No multinational studies of prophylaxis patterns in acutely ill hospitalized medical patients have been reported.

The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) is an ongoing, multinational, observational study that is designed to assess routine clinical practices in the provision of VTE prophylaxis to acutely ill hospitalized medical patients, and to examine the relationships among patient characteristics, the use of prophylaxis, and clinical end points. The aim of this analysis of the IMPROVE registry is to describe current physician practices for providing VTE prophylaxis to acutely ill hospitalized medical patients. To benchmark observed management practices, we also examined practices in subsets of patients who would have been eligible for enrollment in major randomized controlled trials[7–9] that have shown the benefits of pharmacologic prophylaxis in this population, and in a subset of patients[10] who would have been recommended to receive prophylaxis according to criteria from the American College of Chest Physicians (ACCP) consensus guidelines for VTE prevention.

Materials and Methods

Patient recruitment into the IMPROVE registry took place between July 2002 and September 2006. In contrast to randomized, controlled, clinical studies, no experimental interventions were imposed. Patient management was determined by the treating physicians, and hence the data reflect a real-world approach to VTE prevention.

Study Design

The study was developed and coordinated under the guidance of a Scientific Advisory Board (see Appendix 1) by the Center for Outcomes Research (University of Massachusetts Medical School, Worcester, MA). Physicians or trained study coordinators at each participating hospital systematically enrolled the first 10 consecutive, eligible, acutely ill, hospitalized medical patients at the start of each month. All patients who met the enrollment criteria, including those who died during hospitalization, were considered to be eligible for study enrollment. Patients were enrolled either retrospectively or prospectively. Informed patient consent was obtained when required by the ethics review committee at each participating hospital.

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Patient inclusion criteria were as follows: age ≥ 18 years; admission to the hospital for an acute medical illness; and duration of hospital stay of ≥ 3 days. Patients were excluded from the study if they were enrolled in a therapeutic clinical trial, or if they had received a therapeutic anticoagulant or thrombolytic drug at hospital admission or within 48 h after hospital admission, had undergone major surgery or trauma within 3 months prior to hospital admission, had been admitted to the hospital for the treatment of deep vein thrombosis (DVT) or PE (or diagnosed with DVT or PE within 24 h of hospital admission), had refused to participate in the study, or if follow-up was deemed to be impossible.

Data Collection

Investigators who followed the retrospective enrollment approach used hospital discharge lists to identify eligible patients. Data were then abstracted from the patient's medical records after hospital discharge. Investigators enrolling patients prospectively used hospital admission lists, daily census lists, or both to identify eligible patients. Patients were then enrolled while they were in the hospital, and data were abstracted from their medical records at or after hospital discharge. With both approaches, investigators ensured that patients from a broad range of nonsurgical wards or units in their center were enrolled in the study in order to avoid sample bias. Whenever possible, 3-month posthospital discharge data were obtained from medical records.

Patient data were recorded on standardized case report forms that were completed at or after hospital discharge and at 3 months post-hospital discharge, and were sent to the study coordinating center (Center for Outcomes Research, University of Massachusetts Medical School, Worcester, MA). The recorded data included the following: patient demographics; medications and medical conditions; predefined risk factors for VTE; immobilization (defined as being confined to a bed or chair for > 24 h); history of VTE; predefined potential risk factors for bleeding (*ie*, bleeding at or immediately prior to hospital admission, bleeding disorder, hepatic failure, hemorrhagic stroke, platelet count of $< 100 \times 10^9$ cells/L at hospital admission, bacterial endocarditis, or current gastroduodenal ulcer); types of VTE prophylaxis (*ie*, low-molecular-weight heparin [LMWH], unfractionated heparin [UFH], warfarin, acetylsalicylic acid [aspirin], fondaparinux, direct thrombin inhibitors, elastic stockings [ES], and intermittent pneumatic compression [IPC]); timing and duration of VTE prophylaxis; and hospital discharge disposition. The attending physician's specialty and the hospital setting were also recorded.

Data Quality

Data quality was monitored and documented throughout the study. The study coordinator at each hospital maintained a logbook listing consecutive patients who were considered to be eligible for study enrollment and the reasons for not enrolling eligible patients. A copy of this log was sent to the study coordinating center each month. Patient case report forms with outstanding problems such as missing pages, illegible handwriting, missing fields, and invalid or inconsistent data were queried.

Data Analysis

In these analyses, the data are expressed as numbers and percentages only. Patients who would have been eligible for inclusion in the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study,[7] the Prevention of Recurrent Venous Thromboembolism (PREVENT) study,[8] or the Arixtra for ThromboEmbolism Prevention in a Medical Indications Study (ARTEMIS) study[9] were identified by comparing their characteristics and medical histories with the eligibility criteria for these studies.

Role of Sponsor

The IMPROVE study is supported by an unrestricted educational grant from Sanofi-Aventis to the Center for Outcomes Research at the University of Massachusetts Medical School. The sponsor was not involved in the conduct of the study or in the analysis of data.

RESULTS

Hospital and Patient Characteristics

Between July 2002 and September 2006, 15,156 patients were enrolled in the study from 52 hospitals in 12 countries (Australia, Brazil, Canada, Columbia, France, Germany, Italy, Japan, Spain, the United Kingdom, the United States, and Venezuela). Ten countries had three or more active sites, and 2 countries had two active sites each. Of the 52 hospitals participating, 15% are nonprofit public institutions, 15% are for-profit institutions, 65% are nonprofit private institutions, and the status of 4% is unknown; 67% of sites are hospitals with residency teaching programs. The majority of sites (32 of 50) do not have an IMPROVE advisory board member on their resident staff.

Of patients who were considered for study enrollment, 55% were excluded (Fig 1). The baseline demographics of the enrolled patients are summarized in Table 1. The median age was 68 years, and 50% of patients were women. The most common medical conditions present at the time of hospital admission were infection (32%), respiratory failure (19%), and cancer (11%). Only 4% of patients had a history of VTE, and 33% of patients were immobilized (*ie*, confined to bed or chair for > 24 h) for ≥ 3 days, including immediately prior to hospital admission.

In total, 52% and 43% of patients, respectively, in the United States and other countries met the criteria of the current ACCP guideline recommendations[10] for medical patients who should receive prophylaxis (see Appendix 2). Of the patients who met the ACCP criteria for prophylaxis, 61% of those in the United States and 61% of those in other countries had received some form of prophylaxis.

VTE Prophylaxis Practices

In total, 7,640 patients (50%) received pharmacologic and/or mechanical VTE prophylaxis in the

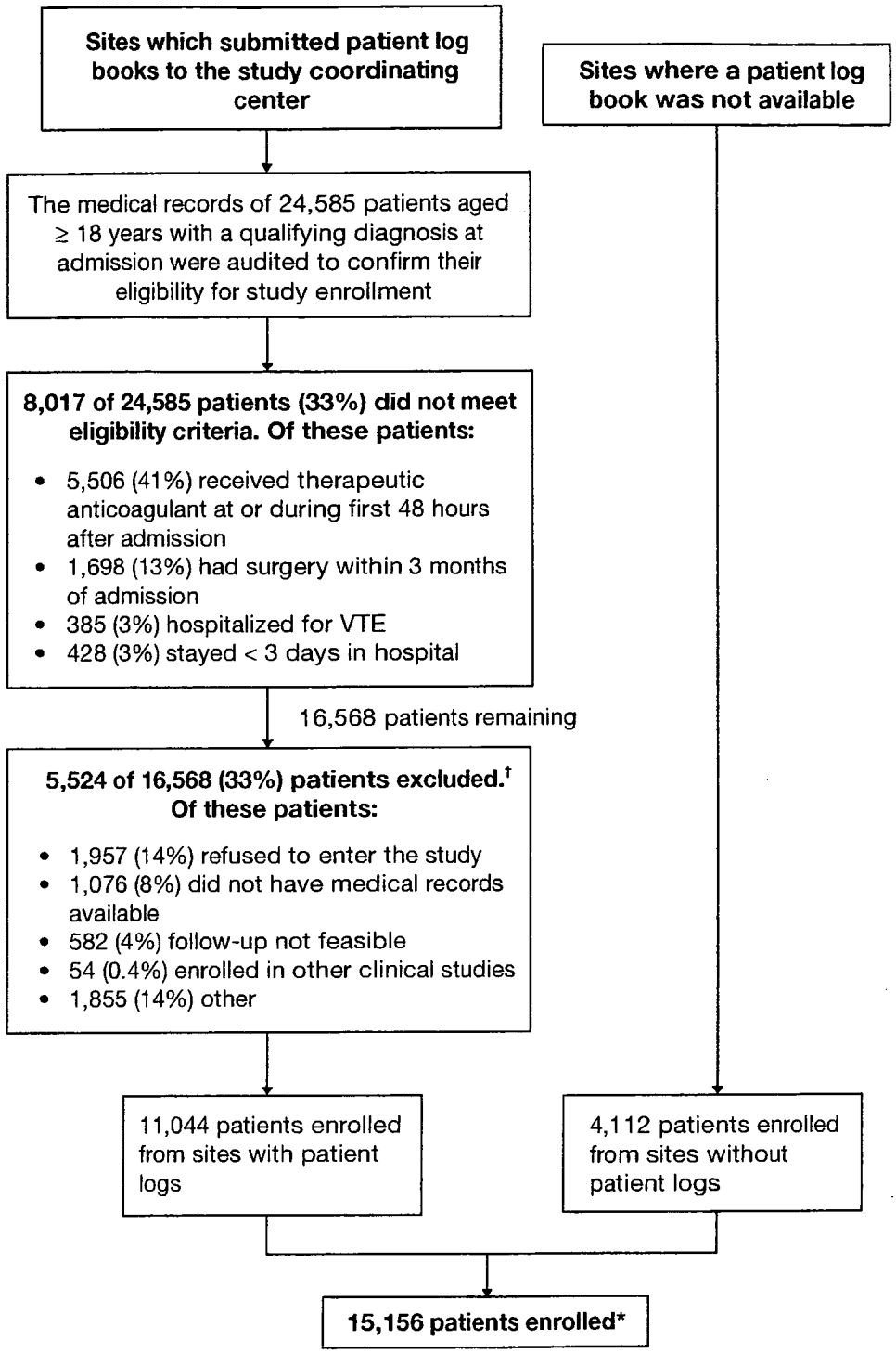

FIGURE 1. Enrollment in the IMPROVE study and reasons for patient exclusion from July 2002 to September 2006 in hospitals where a patient log was available. *To date, 15,156 patients have been enrolled, of whom 11,044 were enrolled in sites that have sent their patient log books to the study coordinating center (see "Data Quality" section). In addition, 4,112 patients were enrolled in sites which did not send patient log books, so reasons for ineligibility or exclusion of patients were not available. The characteristics of patients enrolled in centers which sent patient log books were similar to the characteristics of those in centers which did not send log books. †The reasons for exclusion are mutually exclusive, although this does not mean that a patient did not have more than one of these factors.

Table 1—*Patient Characteristics*

Patient Characteristics	Values
Female, %	50
Age,* yr	68 (52–79)
Weight,*† kg	69 (59–81)
Immobility for ≥ 3 d, %	33
BMI,*‡ kg/m^2	25 (22–29)
Median duration of immobility,*§ d	6 (3–13)
Duration of hospital stay,* d	7 (5–13)
Medical conditions during hospitalization, %	
Infection	32
Respiratory failure	19
Cancer	12
Cardiologic condition	
Ischemic heart disease	12
Congestive heart failure	11
Other cardiologic condition	14
Rheumatic diseases	7
Stroke	6
Severe renal failure	5
Prior VTE	4
Lower extremity paralysis	2
Other disease	37

*Values are given as the median (interquartile range). BMI = body mass index.
†n = 10,433.
‡n = 9,036.
§Includes immobility immediately prior to hospital admission.

hospital (Table 2); the proportion was slightly higher in the United States (54%) compared with other participating countries (49%). However, only 33% of patients in the United States and 47% of patients in other countries received VTE prophylaxis with LMWH or UFH. Overall, LMWH was the most commonly received form of prophylaxis (34%), followed by UFH (11%) [Table 3], although the opposite trend was seen in the United States, where UFH was used more often than LMWH (21% vs 14%, respectively). Of the patients who received LMWH, most (92%) received once-daily doses (Table 2). There were notable differences in the use of LMWH between the United States and other participating countries (*ie*, only 14% of US patients received LMWH, compared with 40% in other countries). However, the LMWH dose regimens used in the United States were similar to those used in other countries. Overall, most patients receiving therapy with UFH received it every 12 h, while a much smaller percentage of patients received it every 8 h. This difference was particularly striking in countries other than the United States (Table 2). Aspirin was used specifically for VTE prophylaxis in a total of 2% of patients (3% of US patients and 1% of those in other countries). Warfarin and fondaparinux were used for VTE prophylaxis in very few patients (< 1%).

Overall, IPC and ES were each used for VTE prophylaxis in 5% and 6% of patients, respectively. There were, however, marked geographic differences in the use of these mechanical methods of prophylaxis. Patients in the United States were more likely to receive IPC than those in other countries (22% vs 0.2%, respectively), but were less likely to receive ESs (3% vs 7%, respectively).

Compared overall with the IMPROVE population, prophylaxis with LMWH or UFH was less commonly used in patients with cancer or risk factors for

Table 2—*Use of VTE Prophylaxis in the Hospital**

Variables	United States	Other Participating Countries
Patients, Total No.	3,410	11,746
Patients receiving one or more types of VTE prophylaxis†	1,852/3,410 (54)	5,788/11,746 (49)
LMWH (all doses)‡	476/3,410 (14)	4,657/11,746 (40)
Once daily	380/457 (83)	4,231/4,589 (92)
q12h	73/457 (16)	347/4,589 (8)
Other	4/457 (0.9)	11/4,589 (0.2)
UFH (all doses)‡	717/3,410 (21)	1,014/11,746 (9)
q12h	282/712 (40)	844/990 (85)
q8h	383/712 (54)	31/990 (3.1)
Other	47/712 (7)	115/990 (12)
Intermittent pneumatic compression	749/3,410 (22)	24/11,746 (0.2)
ES	94/3,410 (3)	794/11,746 (7)
Aspirin	97/3,410 (3)	165/11,746 (1)
Warfarin	77/3,410 (2)	73/11,746 (0.6)
Fondaparinux	11/3,410 (0.3)	5/11,746 (0.04)
Other	130/3,097 (4)	148/9,418 (2)

*Values are given as No. of patients in group/total No. of patients (%).
†Of patients receiving prophylaxis with a parenteral anticoagulant (either UFH or LMWH) in the United States, 36% received LMWH only, 57% received UFH only, and 7% received both; while in other participating countries, 81% received LMWH only, 15% received UFH only, and 4% received both.
‡Denominators for LMWH and UFH do not equal the total number of patients due to missing data on dosing for some patients.

Table 3—*Use of VTE Prophylaxis in Hospital According to Patient Characteristics**

Characteristics	Patients Receiving Prophylaxis						
	Any	LMWH	UFH	IPC	ES	Aspirin	Other
IMPROVE population (n = 15,156)	7,640 (50)	5,133 (34)	1,731 (11)	773 (5)	885 (6)	262 (2)	312 (2)
Medical condition							
Current cancer	789/1,735 (45)	530/1,735 (31)	158/1,735 (9)	113/1,735 (7)	76/1,735 (4)	15/1,735 (0.9)	30/1,735 (2)
ICU stay	1,002/1,296 (77)	531/1,296 (41)	325/1,296 (25)	241/1,296 (19)	98/1,296 (8)	28/1,296 (2)	68/1,296 (5)
Congestive heart failure (NYHA III or IV)	1,063/1,649 (64)	717/1,649 (43)	261/1,649 (16)	98/1,649 (6)	78/1,649 (5)	55/1,649 (3)	60/1,649 (4)
Obese†	1,377/2,421 (57)	830/2,421 (34)	377/2,421 (16)	189/2,421 (8)	162/2,421 (7)	56/2,421 (2)	78/2,421 (3)
Patient characteristics							
Age ≥ 85 yr	1,058/1,750 (60)	722/1,750 (41)	225/1,750 (13)	91/1,750 (5)	136/1,750 (8)	47/1,750 (3)	27/1,750 (2)
Immobile > 3 d‡	2,851/4,334 (66)	1,953/4,334 (45)	632/4,334 (15)	336/4,334 (8)	276/4,334 (6)	130/4,334 (3)	92/4,334 (2)
Presence of potential risk factors for bleeding§	937/2,257 (42)	395/2,257 (18)	177/2,257 (8)	338/2,257 (15)	123/2,257 (6)	17/2,257 (0.8)	49/2,257 (2)

*Values are given as No. (%). NYHA = New York Heart Association.

†Men, body mass index ≥ 30 kg/m^2; women, ≥ 28.6 kg/m^2.

‡Including immediately before admission to hospital.

§Bleeding at or immediately prior to hospital admission, bleeding disorder, hepatic failure, hemorrhagic stroke, platelet count < 100 × 10^9 cells/L at admission to hospital, bacterial endocarditis, or current gastroduodenal ulcer.

bleeding but was more likely to be used if they had stayed in an ICU, had congestive heart failure, or were ≥ 85 years of age or had been immobile for > 3 days (Table 3). LMWH was used more commonly in obese patients. The use of IPC was higher in patients in an ICU or in those with potential risk factors for bleeding (Table 3). Among IMPROVE study patients without potential bleeding risk factors, 52% of patients (6,703 of 12,899 patients) received some form of in-hospital pharmacologic and/or mechanical prophylaxis.

The median durations of VTE prophylaxis in the hospital were 5 and 7 days, respectively, in the United States and other countries, which correlates with the median lengths of hospital stay (5 and 8 days, respectively). Of the patients who received pharmacologic and/or mechanical prophylaxis in hospital, 12% continued to receive it after hospital discharge.

Patients Eligible for Inclusion in VTE Prophylaxis Studies

The inclusion criteria for the MEDENOX,[7] PREVENT,[5] and ARTEMIS[9] studies are summarized in Appendix 2. The most common reasons why IMPROVE study patients would not have been included in the MEDENOX, PREVENT, and ARTEMIS studies were as follows: age < 40 years (MEDENOX and PREVENT studies, 13% each) or < 60 years (ARTEMIS study, 36%); hospitalization for < 6 days in the MEDENOX study (33%) or < 4 days in the PREVENT and ARTEMIS studies (12% each); immobile for > 3 days before hospital admission (MEDENOX and PREVENT studies, 5% each); chronic renal failure and serum creatinine level of > 150 μmol/L or 1.70 mg/dL (MEDENOX and PREVENT studies, 4% each) or serum creatinine level of > 180 μmol/L or 2.04 mg/dL and no volume depletion (ARTEMIS study, 9%); presence of more than one bleeding risk factor (15% in all studies); and stroke (6% in all studies).

Of the patients who would have been eligible for enrollment in the MEDENOX, PREVENT, or ARTEMIS studies, only 62 to 64% received some form of prophylaxis during hospitalization. LMWH was received by 44 to 47% of patients who would have been eligible for these studies and UFH was received by 13 to 15% of patients, while aspirin and ES were each received by 2 to 6% of patients, and IPC was received by 3 to 4% of patients.

Discussion

Half of acutely ill hospitalized medical patients who were enrolled in the IMPROVE study received either mechanical or pharmacologic VTE prophylaxis. Half of patients in the United States and almost half of those in other countries met the criteria of the ACCP guidelines for patients who should receive prophylaxis.[10] Of these, 6 of every 10 patients actually received prophylaxis. A similar proportion of patients who would have been eligible for enrollment in the MEDENOX, PREVENT, or ARTEMIS study[7–9] received some form of prophylaxis.

Large randomized trials such as the MEDENOX study,[7] the PREVENT study,[5] and ARTEMIS study[9]

have shown a reduction in the incidence of VTE with pharmacologic prophylaxis in acutely ill hospitalized medical patients, and the ACCP consensus group guidelines published in 2001[19] and 2004[10] and the international consensus from 2006[11] recommend appropriate prophylaxis in this patient group. Our analyses of prophylaxis in subsets of IMPROVE study patients who met the ACCP guideline criteria for prophylaxis, and in subsets of patients who would have been eligible for enrollment in the MEDENOX, PREVENT, or ARTEMIS trial provide a benchmark comparison for the real-world practices observed in the entire IMPROVE study population. These subsets of patients are those in whom pharmacologic prophylaxis has been shown to be effective, and our observed prophylaxis rates highlight an underuse of prophylaxis in these populations of patients.

There are marked variations in VTE prophylaxis practices in acutely ill hospitalized medical patients. IPC was the most common form of prophylaxis in the United States despite the paucity of data supporting its benefit in this population. The ACCP recommendations suggest that mechanical methods be used in patients in whom there is a contraindication to anticoagulant prophylaxis, but the lack of supportive data from randomized clinical trials is acknowledged.[10] The availability of IPC was very low, and it was rarely used in participating centers outside of the United States. ES were less commonly used in the United States than in other participating countries.

UFH was the most commonly used form of pharmacologic prophylaxis in the United States, while LMWH was most often used in other countries. These differences may be explained, at least in part, by US hospital formularies prioritizing drug acquisition cost rather than downstream cost when making decisions regarding the acquisition and dispensing of LMWH and UFH; analyses have been suggestive of a safety benefit with LMWH compared with UFH.[20–22] The ACCP guidelines[10,19] recommend the use of LMWH for orthopedic surgery prophylaxis, emphasizing that the risk of heparin-induced thrombocytopenia is lower with LMWH prophylaxis than with UFH prophylaxis. The risk of heparin-induced thrombocytopenia was not a consideration in other types of patients, in part because of the perceived economic consequences, particularly in North America.[23] This issue is less likely to drive decisions in Europe, where the difference in cost between LMWH and UFH tends to be relatively smaller than that in the United States. Of patients in the United States who received UFH, doses were given every 12 h in 40% of cases, and every 8 h in 54% of cases. In other participating countries, UFH given every 12 h was almost always used. This contrasts with evidence-based recommendations published in recent consensus guidelines,[11] which advocate the use of UFH every 8 h rather than every 12 h. In patients receiving LMWH (both in the United States and in other countries), dosing was almost always once daily, reflecting the current LMWH label recommendations.

Underuse of VTE prophylaxis in medical patients may be a result of a number of factors. The most common reason appears to be a lack of awareness of both the disease and evidence-based guidelines.[12,24] Hospital audit studies[15,17] have consistently shown that prophylaxis is underprescribed and that there is widespread confusion about appropriate prophylaxis for different levels of risk. Previous studies[13,25–27] conducted at the local or national level have shown that only 35 to 42% of patients in the highest risk groups receive prophylaxis. The complexity of the existing guidelines may also lead to the underuse of prophylaxis; the latest ACCP guidelines on VTE prevention[28] support educational initiatives to increase the awareness and understanding of management guidelines. A further factor is that many hospitals do not have formal protocols for the prevention of VTE in at-risk medical patients. The ACCP recommends that such protocols should be implemented[10] and suggests the implementation of computer-generated reminders, an approach that has been shown to improve the use of prophylaxis and to reduce the rates of DVT and PE in hospitalized patients,[29] or patient-mediated interventions to promote prophylaxis use in appropriate patients.[28]

Studies have also shown that, where institutional guidelines exist, they are often not followed.[30] In a Spanish teaching hospital, 78% of patients received VTE prophylaxis according to the number of risk factors present, as specified in hospital guidelines, but only 37 to 47% of patients received the correct heparin dosage or schedule.[31] Furthermore, the use of appropriate prophylaxis varied considerably, being higher in critical care and surgical wards than in medical wards.[31]

Physicians' fears of potential bleeding complications have also been cited as a reason for not using prophylaxis,[10] and this may encourage increased IPC use. However, there is extensive evidence from randomized clinical studies[7–10] that prophylactic doses of UFH and LMWH are not associated with a significantly increased risk of clinically relevant bleeding. It is noteworthy that when considering

only IMPROVE study patients without risk factors for bleeding, only 52% of patients received some form of prophylaxis.

The IMPROVE registry was designed to enroll a representative population of patients who had been hospitalized for acute medical illnesses. To achieve this, the first 10 consecutive eligible patients were enrolled each month from a broad range of hospital settings. The selection of hospital sites was nonrandomized. Approximately 67% of hospitals did not have an advisory board member on their staff, reducing the potential for bias resulting from physician's practices being influenced by advisory board members with special interests in VTE. Wherever possible, physicians or study coordinators who enrolled patients were not involved in their management, thus reducing the risk of influencing the treating physician's practices. Both prospective and retrospective enrollment are used in the IMPROVE study. Although the choice of prospective enrollment could introduce bias favoring the use of prophylaxis, the rates of prophylaxis were still low.

In conclusion, the results of this analysis of data from the IMPROVE study show that in at-risk, acutely ill, hospitalized medical patients, in whom the benefits of pharmacologic VTE prophylaxis have been demonstrated, such prophylaxis is underutilized and physicians' practices vary considerably. There is clearly room for improving physicians' practices through the implementation of current evidence-based guidelines in hospitals.

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APPENDIX 1

The IMPROVE study is overseen by a medical advisory board of clinicians. Further information about the registry can be found at http://www.outcomes-umassmed.org/improve/.

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Appendix 2

Criteria*	Statement
Criteria of the ACCP guidelines for medical patients who should receive VTE prophylaxis[10]†	"In acutely ill medical patients who have been admitted to the hospital with congestive heart failure, severe respiratory disease, or are confined to a bed and have additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, we recommend LDUFH (grade 1A) or LMWH (grade 1A)" or "In medical patients with risk factors for VTE and in whom there is a contraindication to anticoagulant prophylaxis, we recommend mechanical prophylaxis with GCS or IPC (grade 1C+)"
Inclusion criteria for MEDENOX study[7]	Age > 40 yr; expected hospital stay ≥ 6 d; immobilized ≤ 3 d and Congestive heart failure (NYHA functional class III/IV) or Acute respiratory failure or Acute infection without septic shock; acute rheumatic disorders, including acute lumbar pain, sciatica, or vertebral compression (caused by osteoporosis or a tumor); acute arthritis of the legs or an episode of rheumatoid arthritis in the legs; or an episode of inflammatory bowel disease, plus one risk factor‡
Inclusion criteria for PREVENT study[8]	Age ≥ 40 yr; expected hospital stay ≥ 4 d; immobilized ≤ 3 d and Congestive heart failure (NYHA functional class III/IV) or Acute respiratory failure or Infection without septic shock, acute rheumatologic disorders, or inflammatory bowel disease, plus one risk factor§
Inclusion criteria for ARTEMIS[9]	Age > 60 yr; immobilized for ≥ 4 d and Congestive heart failure (NYHA functional class III/IV) or Acute respiratory illness in the presence of chronic lung disease or Acute infectious disease or Inflammatory disorders such as arthritis, connective tissue diseases, or inflammatory bowel disease

*GCS = graduated compression stockings; LDUFH = low-dose UFH. See Table 3 for expansion of abbreviation.

†For the present analysis, the ACCP guideline recommendations were interpreted as including medical patients hospitalized with a current diagnosis of congestive heart failure or severe respiratory disease (*ie*, COPD or pneumonia) or who were confined to a hospital bed (immobile > 1 day) with one or more additional risk factors for VTE, including age > 75 years, paresis, malignancy, cancer therapy (hormonal, chemotherapy, or radiotherapy), previous VTE, hormone replacement therapy, obesity, varicose veins, central venous catheterization, or other acute medical illness such as inflammatory bowel disease, nephrotic syndrome, myeloproliferative disorders, and inherited or acquired thrombophilia (based on medical risk factors cited in the ACCP guidelines[10]).

‡Age ≥ 75 years, cancer, previous VTE, obesity, varicose veins, hormone therapy, and chronic heart or respiratory failure.

§Age ≥ 75 years, cancer, previous VTE, obesity, varicose veins and/or chronic venous insufficiency, hormone replacement therapy, history of chronic heart failure, chronic respiratory failure, or myeloproliferative syndrome.