of objective information from Japanese patients is urgently needed, and approval to use new anticoagulants is eagerly awaited. Fondaparinux, an anti-Xa agent, and enoxaparin, a low molecular weight heparin, became available for use in Japan in the spring of 2007 and 2008, respectively. It is expected that in the near future pharmaceutical prophylaxis with new anticoagulants will become mainstream [46, 47].

Future Outlook

The most significant development in research and practice relating to VTE is that it has been recognized as a more common disease than was previously considered. However, it is still difficult to diagnose VTE unless suspected, although diagnostic modalities are improving. A diagnostic device that can be used at the bedside to easily identify VTE is needed. The management and prophylaxis of VTE will move forward with the development of new agents. Antithrombotic agents with a lower risk of bleeding are needed because VTE is a condition that is associated with easy bleeding. The quality of diagnosis and treatment in Japan has reached Western standards. The next goal is to gather evidence that provides the foundation for guidelines of treatment and prophylaxis. Full-scale research studies such as those performed in the West should be carried out to elucidate the pathological mechanism of VTE and improve its management.

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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

Victor F. Tapson, MD, FCCP; Hervé Decousus, MD; Mario Pini, MD; Beng H. Chong, MD, PhD; James B. Froehlich, MD, MPH; Manuel Monreal, MD; Alex C. Spyropoulos, MD, FCCP; Geno J. Merli, MD; Rainer B. Zotz, MD; Jean-François Bergmann, MD; Ricardo Pavanello, MD; Alexander G.G. Turpie, MD; Mashio Nakamura, MD; Franco Piovella, MD; Ajay K. Kakkar, MD, PhD; Frederick A. Spencer, MD; Gordon FitzGerald, PhD; and Frederick A. Anderson, Jr, PhD; for the IMPROVE Investigators

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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All authors significantly contributed to the concept and design of the study, the interpretation of data, and critical revision of the manuscript. All authors approved the final version of the manuscript. Dr. FitzGerald performed all statistical analyses of data from IMPROVE.

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Dr. Bergmann has received honoraria from Sanofi-Aventis and AstraZeneca. Dr. Froehlich has served as a consultant for Sanofi-Aventis. Dr. Kakkar has received consultancy/research funding from Sanofi-Aventis, sponsors of the IMPROVE registry. Dr. Merli has participated in research studies with AstraZeneca, Sanofi-Aventis, and Boehringer Ingelheim; has served on advisory boards with Bayer, Bacchus Scientific, AstraZeneca, and Sanofi-Aventis; and has been a speaker for AstraZeneca and Sanofi-Aventis. Dr. Pini has received fees from Sanofi-Aventis for being a member of the IMPROVE advisory board, and for conducting clinical studies and for lectures. Dr. Spencer has been a consultant for and has received a grant from Sanofi-Aventis. Dr. Spyropoulos has received grants/research support from and has been a consultant for Sanofi-Aventis and Astra-Zeneca. Dr. Tapson has received grants/research support from and has been a consultant for Sanofi-Aventis. Drs. Decousus, Chong, Monreal, Zotz, Pavanello, Turpie, Nakamura, Piovella, FitzGerald, and Anderson have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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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

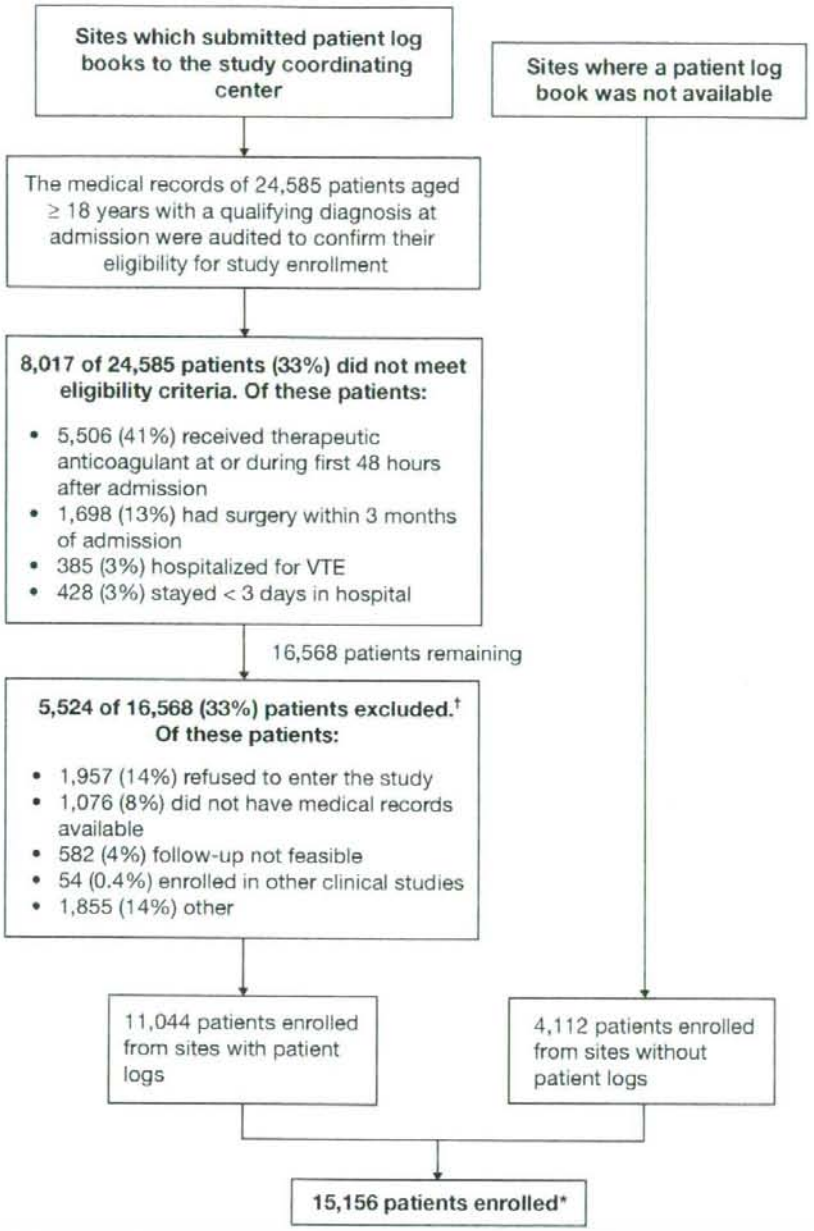

FIGURE 1. Enrollment in the IMPROVE study and reasons for patient exclusion from July 2002 to September 2006 in hospitals where a patient log was available. *To date, 15,156 patients have been enrolled, of whom 11,044 were enrolled in sites that have sent their patient log books to the study coordinating 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)	888 (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,[8] 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,[8] 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.

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Venous Thromboembolism Prophylaxis in Acutely Ill Hospitalized Medical Patients: Findings From the International Medical Prevention Registry on Venous Thromboembolism

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Unusual Pulmonary Embolism
—— Septic Pulmonary Embolism and Amniotic Fluid Embolism ——

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Background Septic and amniotic fluid emboli are rare sources of pulmonary embolism (PE), so the present study sought to elucidate the background of these cases.

Methods and Results A total of 11,367 PE cases were identified from 396,982 postmortem examinations. The incidence of septic PE was 247 (2.2%) of the total. The origin of infection was found in 85.6% of the cases. Fungal embolus was detected more often than bacterial embolus. The most frequently detected fungus was aspergillus (20.8%). The primary disease associated with fungal embolus was leukemia (43.2%). The incidence of PE cases associated with pregnancy and/or delivery was 89 (0.8%) of the total PE cases. Among them, amniotic fluid embolism was found in 33 (73.3%) of 45 PE cases with vaginal delivery, and in 7 (21.2%) of 33 PE cases with cesarean delivery ($p<0.0001$).

Conclusion Fungal embolus was more frequent than bacterial embolus, and leukemia was most frequent as the primary disease in cases of fungal embolus. The main cause of PE in cesarean section cases was thrombotic embolism, and the main cause in vaginal delivery cases was amniotic fluid embolism. (*Circ J* 2007; **71:** 772–775)

Key Words: Amniotic fluid embolism; Bacterial embolism; Cesarean section; Fungal embolism; Leukemia

The incidence of thrombotic pulmonary embolism (PE) is increasing and the interest is increasing in Japan. Generally, PE means thrombotic, but not all emboli causing PE are thrombotic. We recently reported unusual PE induced by tumor! Septic PE (SPE) is also rare but has been clinically diagnosed as peripheral nodules (in some cases, with cavity) by computed tomography.[2,3] Amniotic fluid embolism (AFE) is another kind of PE associated with pregnancy and delivery. There are no reports of SPE and limited reports of AFE from large-scale autopsy studies.[4,5] Therefore, the aim of the present study was to clarify the characteristics of SPE and PE associated with pregnancy and delivery.

Methods

A total of 11,367 PE cases (2.9%) were identified from 396,982 published postmortem examinations.[6–17] PE was defined as critical (critical PE) when it was the primary cause of death or the main diagnosis! AFE was diagnosed by the presence of fetal squamous cells, mucin, meconium, vernix caseosa, or lanugo hairs in the maternal pulmonary vasculature.

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 (SPSS Inc, Chicago, IL, USA). Non-ordinal categorical data were analyzed using the chi-square test.

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Table 1 Primary Focus of Infection in Septic Pulmonary Embolism

Origin of infection	*No. of cases*
Pneumonia	*84 (34.0%)*
*Sepsis*1*	*56 (22.7%)*
Infectious endocarditis	*28 (11.3%)*
Liver abscess	*10 (4.0%)*
Lung abscess	*7 (2.8%)*
Pyelonephritis	*6 (2.4%)*
Cholecystitis	*4 (1.6%)*
Pancreatitis	*4 (1.6%)*
Enteritis	*4 (1.6%)*
Septic thrombophlebitis	*3 (1.2%)*
Necrotizing fasciitis	*2 (0.8%)*
*Others*2*	*4 (1.6%)*
Unidentified	*35 (14.6%)*
Total	*247*

Total percentages do not equal 100% because of rounding off Figs.
**1Sepsis was clinically proved but the cause was unknown.*
**2One case each of infected central venous catheter, retroperitoneal abscess, scrotal abscess, and candida esophagitis.*

Table 2 Cause of Septic Pulmonary Embolism

Cause	No. of cases
Fungal	
Aspergillus	36 (14.6%)
Mucor	31 (12.6%)
Candida	18 (7.3%)
Unidentified	88 (35.6%)
Bacterial	74 (30.0%)

Total percentages do not equal 100% because of rounding off Figs.

Table 3 Relationship Between Malignancy and Septic Pulmonary Embolism

	Fungal (173 cases)	Bacterial (74 cases)
Leukemia	76 (43.9%)	5 (6.8%)
Adenocarcinoma	12 (6.9%)	13 (17.6%)
Lymphoma	12 (6.9%)	1 (1.4%)
Hepatoma	0 (0.0%)	3 (4.1%)
Others	9 (5.2%)	2 (2.7%)
Not described	2 (1.2%)	2 (2.7%)
Not malignancy	62 (35.8%)	48 (64.9%)

Total percentages do not equal 100% because of rounding off Figs.

Table 4 Underlining Diseases, Other Than Malignancy, in Patients With Septic Pulmonary Embolism

	Fungal	Bacterial
Blood diseases	22*1	4
Respiratory diseases	23*2	9*3
Renal diseases	11*4	6*5
Cardiovascular diseases	10	12
Liver diseases	4	2
Connective tissue diseases	3	2
Cerebral diseases	2	4
Infectious diseases	4	9*6
Miscellaneous	8	8

*Diseases with a subclass of 5 or more cases are: *1including 9 cases with myelodysplastic syndrome and 9 aplastic anemia, *2including 19 pneumonia, *3including 7 pneumonia, *4including 11 renal failure, *5including 5 renal failure, *6including 8 sepsis.*

Table 5 Pulmonary Embolism and Delivery

	Spontaneous delivery	Cesarean delivery
Thrombotic pulmonary embolism	12 (26.7%)	26 (78.8%)
Amniotic fluid embolism	33 (73.3%)	7 (21.2%)

$p<0.0001$.

Results

There were 4,363 cases of critical PE. The origin of infection was proven in 211 (85.4%) of 247 cases of SPE (143 males, 104 females) (Table 1). There were 173 cases of fungal emboli, including 36, 31 and 18 cases of Aspergillus, Mucor, and Candida, respectively, and in 88 cases there were no descriptions of the type of fungus (Table 2). Bacterial embolus was found in 74 cases. Critical SPE was found in 119 cases (48.2% of all SPE [119/247]) including 88 cases (50.9% [88/173]) with fungal emboli and 31 (41.9% [31/74]) with bacterial emboli ($p=0.21$). Fungal emboli were reported in 81.0% (111/137) of SPE cases among cancer patients and in 56.4% (62/110) of non-cancer patients ($p<0.0001$). SPE was found more in association with leukemia, adenocarcinoma and lymphoma in that order (Table 3). The rate of fungal emboli in SPE varied among the different types of cancer (93.8% in leukemia, 92.3% in lymphoma, and 48.0% in adenocarcinoma; $p<0.0001$).

The incidence of PE associated with pregnancy and/or delivery was 89 (0.8%) of the total PE cases and included 49 cases of AFE, 39 of thrombotic PE, 4 of fat emboli, 3 of bone marrow emboli, and 1 of tumor embolus (some cases had overlapping causation). When PE cases were limited to those found during and just after delivery, PE was related more to AFE with vaginal delivery, and to thrombotic PE with cesarean delivery ($p<0.0001$) (Table 5).

Discussion

Origin of Infection in SPE

In the present study the main causes of SPE were pneumonia, sepsis and infectious endocarditis. SPE is rare, usually found in patients with tricuspid valve endocarditis (eg, intravenous drug users), indwelling catheter, pacemaker wires, peripheral septic thrombophlebitis, and infection after organ transplant.

SPE resulting from intravenous drug abuse is declining in Western countries[18–20] In 1978, MacMillan et al reported that 78% of SPE cases occurred in drug users;[18] whereas a recent report analyzing 14 cases indicated that the origins of SPE were Lemierre syndrome (SPE caused by peritonsillar abscess) in 4 cases, central venous catheter infection in 3, prosthetic pulmonary valve endocarditis in 2, infected pacemaker or lead wire in 2, and dental abscess, perinephric abscess, and intravenous drug abuse in 1 case each![19] In the United States, 23.5% (12/51) of pulmonary complications in illegal drug users was SPE in 1988;[21] and 1.3% (1/17) in 1992–1993;[22]

However, the origins of SPE in Korea are somewhat different from those in Western countries. Lee et al analyzed 21 clinical cases of SPE and identified the primary site of infection in 15 (3 cases with infective endocarditis, 2 with central venous catheter infection, 2 with liver abscess, 3 with other abscess, 2 with cellulitis, 2 with pneumonia, and 1 with septic arthritis)[23] Diabetes mellitus was found in 28.6% of cases and malignant tumor in 19%. Pneumonia was not considered as a cause of SPE, but there were 2 such cases. There were no cases of intravenous drug abuse in that Korean study. Our study also did not include any cases of SPE and illegal drug abuse.

Liver abscess is not usual as an origin of SPE. Kamano et al reported 7 SPE cases with liver abscess;[24] but since then only 2 such cases have been reported.[23] In the present study liver abscess was the cause of SPE in only 4%, but there were 10 cases.

Fungal PE

Fungal PE resulted from Aspergillus, Mucor, and Candida infection, in that order. Aspergillus and Mucor are angioinvasive organisms. An autopsy examination in Germany indicated that angioinvasive aspergillosis has been increasing in recent years, mainly because of hematological malignancies or acquired immunodeficiency syndrome.[25]

Mucor infection, a rare disorder, progresses slowly, so

antemortem diagnosis is difficult. It invades the small pulmonary arteries and causes hemorrhage, thrombus, and distal infarction. When Mucor invades the large pulmonary arteries, a pulmonary artery pseudoaneurysm is formed.[26] The most commonly associated conditions are diabetes mellitus, renal insufficiency, hematological disorders, including leukemia and lymphoma, as well as immunosuppressive states. In the present study, 63% of cases of fungal PE had cancer and 50.9% had hematological malignancies. A clinical study showed that hematological malignancies were involved in almost all cancer patients with zygomycosis (including Rhizopus, Mucor and Absidia) or angioinvasive aspergillosis (15 of 16 and 28 of 29, respectively).[27]

SPE and Cancer

SPE was found more in cases of leukemia, adenocarcinoma and lymphoma, in that order. Over 90% of SPE cases with leukemia or lymphoma had fungal emboli. Immunocompromised patients are vulnerable to fungal infection and lung infections with Aspergillus and Candida are often found in patients with leukemia or lymphoma.[28]

AFE

Our results indicated that the cause of PE in cesarean section cases was thrombotic PE, and in vaginal delivery cases it was AFE. AFE occurs when amniotic fluid and/or fetal elements (including fetal squamous cells, mucin, meconium, vernix caseosa, and lanugo hairs) enter the maternal blood stream, and is confirmed by proving their existence in the maternal pulmonary vasculature at autopsy.[4,5] Besides the fetal elements, mediators such as histamine, bradykinin, cytokines, prostaglandins, thromboxane, and many others induce an anaphylactoid response.[29] AFE presents as dyspnea and shock either during labor and delivery or in the immediate postpartum period. In 50% of cases this is followed by respiratory and cardiac failure within few hours, and then death. The other half suffers from disseminated intravascular coagulation and multiple organ failure. Three-fifths of the patients died, and only two-fifths survived. Of course, the mechanism of AFE is absolutely different from that of thrombotic PE in pregnancy, but both types are associated with delivery, and thrombotic PE is a differential diagnosis of AFE.[30]

Cesarean section has a higher risk for thrombotic PE than transvaginal delivery.[31–33] Kobayashi et al reported that in Japan the incidence of thrombotic PE in obstetrics consisted of 0.02% of total deliveries, 0.003% of vaginal deliveries, and 0.06% of cesarean deliveries.[32,33] The ratio of cases with cesarean section has been increasing annually in Japan: in 1991 the ratio of cases with cesarean section was 15.9%, and 22.9% in 2000.[32] The Ministry of Health, Labour and Welfare, Japan estimated that the ratio of cases with cesarean section was 6.1% in 1984, 8.3% in 1990, and 17.9% in 2002.[34–36] Furthermore, Kobayashi et al reported that 84.7% (50/59) of cases were associated with cesarean section among cases of postpartum thrombotic PE.[32] These data are comparable to our data (26/38; 68.4%) from the present study.

Vaginal delivery was the source in 33/40 (82.5%) of cases of AFE. A previous report showed that 70% of AFE occurred during labor but before delivery, 11% after vaginal delivery (81% in spontaneous delivery), and 19% during cesarean section.[29] Our data are comparable to these.

Study Limitations

It is known that lung abscess is one of the SPE complications,[18] so it can not be denied that lung abscess is not the cause of SPE but the outcome. Sepsis was an antemortem clinical diagnosis, and cases of sepsis in this study meant that the origin of infection could not be identified. In these cases, catheter infection may be included.

Our subjects were autopsy cases and analysis of fatal cases only has some potential biases. For example, it may result in the inclusion of cases with fungal embolus more frequently than those with bacterial embolus. Therefore, further clinical studies of cases with mild or moderate SPE are needed to eliminate the potential biases and to reach a conclusion.

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