Features of IMPROVE:

- Prospective, observational registry
- Multinational/multicenter perspective
- Real-world approach to thromboprophylaxis practice patterns
- Comparing prophylaxis practices in patients with acute medical illnesses
- No imposed experimental intervention
- Regular audits
- Quarterly reports
- Three-month follow-up

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IMPROVE

International Medical Prevention Registry on Venous Thromboembolism

Preventing Venous Thromboembolism in Medical Patients Through Real-world Evidence

IMPROVE Scientific Advisory Committee

Preventing Venous Thromboembolism in Medical Patients Through Real-world Evidence

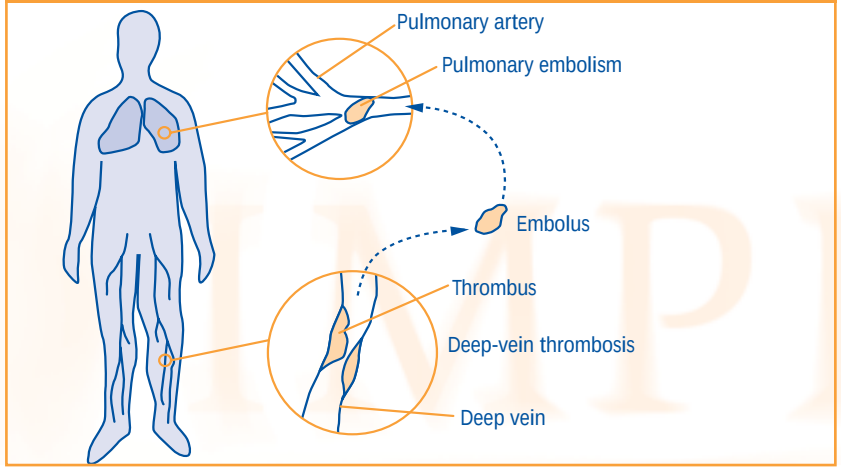
Introduction

Venous thromboembolism (VTE), encompassing deep-vein thrombosis and pulmonary embolism, is the most common cause of preventable death among hospitalized patients (Figure 1). Over the last 30 years, extensive research has shown that patients who undergo major surgery or experience multiple traumas have a high risk of VTE. In addition, it is now becoming widely accepted that hospitalized patients with medical illnesses and predisposing risk factors are also at high risk of developing VTE. However, the risk of VTE in patients with acute medical illnesses, such as acute myocardial infarction, ischemic stroke, cardiopulmonary disease, cancer, inflammatory bowel disease and severe infections, or risk factors such as a history of VTE or cancer, complicating acute infectious disease, or age over 75 years have been less well studied. There are different levels of VTE risk in patients not undergoing thromboprophylaxis with antithrombotic drugs.[1,2]

Recent evidence suggests that medical patients have a similar risk of VTE as surgery patients – the incidence of VTE among general hospitalized medical patients has been reported to be in the range 10–30%,[3–6] while that among general surgery patients is in the range 19–29%.[7] Furthermore, postmortem studies indicate that up to 10% of in-hospital deaths are related to pulmonary embolism, and that only 24% of these deaths occur following surgery.[8] This implies that around three-quarters of patients suffering from pulmonary embolism have not had recent surgery and that hospitalized medical patients are at increased risk of VTE. Elderly patients are at particularly high risk of pulmonary embolism,[9,10] and, as the world's population ages, the impact of VTE on public health and healthcare resources will become increasingly significant.

Venous thromboembolism can be difficult to diagnose because many of the symptoms are nonspecific and the condition may be clinically silent.[11,12] Indeed, in many patients, death may be the first indication of the disease. It is therefore inappropriate to rely on early diagnosis and treatment of VTE.[7,13] The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study demonstrated that patients

Figure 1. Venous thromboembolism



with acute medical illnesses receiving thromboprophylaxis (enoxaparin 40 mg) on a once-daily basis for 6 to 14 days experience significantly fewer venous thromboembolic events than patients who do not receive antithrombotic therapy to prevent VTE.[14] Such a finding suggests that pharmacological thromboprophylaxis remains the key to reducing death and morbidity and the efficacy of low-molecular-weight heparin as thromboprophylaxis is now well established in patients with stroke, recent myocardial infarction, severe infection, and cardiovascular, pulmonary, or inflammatory diseases.[15–18] Although the benefits of thromboprophylaxis appear to be similar for both surgery patients and patients with acute medical illnesses, thromboprophylaxis is substantially underused in patients with acute medical illnesses, even in those with multiple risk factors.[19] In addition, even when thromboprophylaxis is used, it may be employed suboptimally, as suggested by the results of two recent surveys of how French physicians use thromboprophylaxis in medical patients. The College of Internal Medicine of Paris (CIMOP) survey and the Données Epidémiologiques chez les Patients À Risque Thromboembolique (DEPART) study examined practice patterns implemented for hospitalized patients and outpatients with acute medical illnesses, respectively. The studies suggested that there was suboptimal use of thromboprophylaxis, resulting ostensibly from the lack of clear recommendations for healthcare practitioners.[20] For example, there was underuse of thromboprophylaxis in patients with acute medical illnesses and a history of previous thromboembolic events, and in patients with coronary or pulmonary failure.[20]

So far, there has been no systematic attempt to characterize thromboprophylaxis in high-risk medical patients on a multinational basis. A comprehensive registry which details the preventive therapies used and the short-term outcomes associated with this patient group would therefore fulfill an important role. A suitable registry should:

- describe the clinical and demographic characteristics of medical patients who do and do not receive thromboprophylaxis, and document posthospital discharge outcomes, globally and on a hospital- and country-specific basis;
- provide a detailed analysis of the pharmacological therapies and other management strategies used to minimize the short- and long-term complications of VTE following hospitalization for an acute medical illness;
- examine the relationship between the provision of thromboprophylaxis, hospital- and physician-associated outcomes, as well as outcomes following discharge from hospital.

The International Medical Prophylaxis Registry on Venous Thromboembolism (IMPROVE) is the first multinational, multicenter, prospective, observational registry to address these issues. This booklet provides an overview of IMPROVE and gives contact details for further information.

Figure 2. Countries participating in IMPROVE

IMPROVE: Medical Patient Registry

Goal and objectives

IMPROVE provides an opportunity to collect, analyze and disseminate data on the clinical incidence of VTE and the use of thromboprophylaxis in patients with acute medical illnesses. The goal of the registry is to improve patient care through a better understanding of patient demographics, VTE management, and in-hospital and posthospital discharge outcomes. Comparison of individual hospital data with aggregate registry data should help to improve the standard of care for patients with acute medical illnesses by identifying areas for improvement in patient care on both a local and a national scale, so that corrective action can be recommended and necessary changes to patient care implemented.

The objectives of the registry are to:

- provide physicians with timely data on existing and evolving patterns in clinical practice, delivery of patient care, and resource utilization in the management of medical patients at high risk of VTE;
- provide data to support internal and external standards, and benchmarking, of thromboprophylactic patterns and patient outcomes;
- generate hypotheses and design ancillary studies to address important outstanding questions;
- create predictive models for VTE and major bleeding based on patient risk factors;
- disseminate findings through publications in peer-reviewed scientific journals.

Registry management

IMPROVE falls under the auspices of the INvestigators Against ThromboEmbolism (INATE), a worldwide multidisciplinary initiative to improve the management of patients with VTE. The INATE initiative has established a working group to participate in and give direction to registries focusing on patients with VTE. The goal of the INATE Registries Working Group is ultimately to improve patient care: through monitoring the effectiveness of different practices and evaluating the causes of suboptimal outcomes, it will be possible to recommend corrective actions to healthcare professionals who can then implement the changes and help to assess their impact. For more information on INATE please visit the INATE website www.inate.org.

IMPROVE is sponsored by an unrestricted educational grant from Aventis Pharma to the Center for Outcomes Research (COR), based at the University of Massachusetts Medical School in Worcester, Massachusetts, USA. COR serves as the study coordinating center for the registry, which, in turn, is governed by a scientific advisory committee comprising leading physicians and clinical scientists from participating countries. Dr Fred Anderson, Director of COR, is responsible for the proper scientific and ethical conduct of the registry.

Registry design

IMPROVE is a multinational, multicenter, prospective, observational registry that will gather and analyze data on medical patients at high risk of VTE, and the thromboprophylactic methods employed. In contrast to a randomized, controlled clinical trial, there is no imposed experimental intervention: patient management is determined solely by physicians. It is intended that the data collected and reported in this registry will reflect a 'real-world' approach to the prevention of VTE. Approximately 40 centers from 10 countries will participate in the registry, and about 5,000 patients who are hospitalized for an acute medical illness will be enrolled each year (Figure 2).

Patient selection

All patients who meet the enrollment criteria, including those who die during hospitalization, will be considered as potentially eligible for enrollment into the registry. Inclusion and exclusion criteria are outlined in Table 1. To ensure that representative patients are enrolled at each center, the following strategy will be followed:

- patients must fulfill the inclusion criteria;
- enrollment will be limited to the first 10 eligible patients per month at each center;
- consecutive patients will be enrolled beginning on the first day of each month until that month's target enrollment number (10) is met;
- patients may be enrolled in the registry more than once if they have multiple qualifying admissions, but a minimum of 6 months must elapse between each admission.

Table 1. Inclusion and exclusion criteria

Inclusion criteria

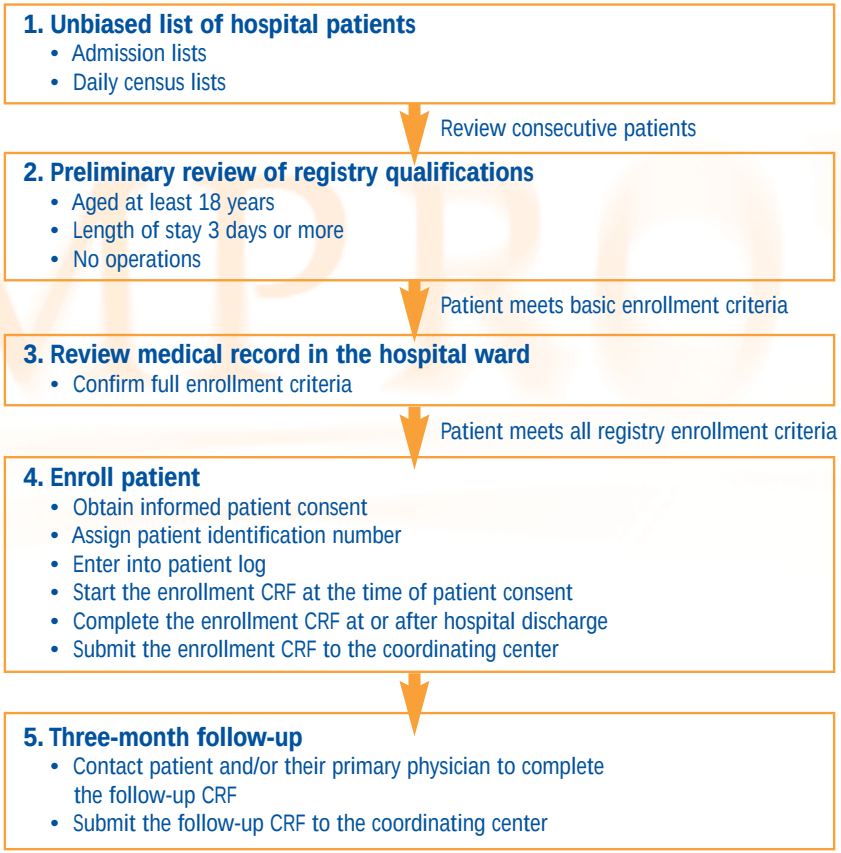
- Admitted for an acute medical illness
- Aged at least 18 years
- Length of hospital stay 3 days or more

Exclusion criteria

- Receiving anticoagulant or thrombolytic therapy on admission or during the first 48 hours following admission
- Major surgery or trauma during admission or within the past 3 months
- Already enrolled in a therapeutic clinical trial
- Admitted for treatment of VTE or diagnosed within 24 hours of admission
- Follow-up is impossible (e.g. patient transferred to another hospital or patient's residence is geographically inaccessible for follow-up)
- Patient does not consent to participate in registry

Eligible patients will be identified through review of each hospital's administrative admission, daily census or discharge records. Ideally, in a multicenter study, all patients should be enrolled using a similar process at all centers. However, experience in the IMPROVE pilot study showed that in-hospital patient enrollment was not feasible at all hospitals, mainly because of the time involved in identifying patients during hospitalization and the need for multiple visits to the ward to collect data during the hospital stay. IMPROVE therefore allows two general approaches to patient enrollment and data collection: patient selection before hospital discharge and patient selection after hospital discharge. For patient selection before hospital discharge eligible patients are identified during hospitalization using hospital admission or daily census lists (Figure 3). For patient selection after hospital discharge eligible patients are identified from hospital discharge lists, and case report forms (CRFs) are completed after hospital discharge (Figure 4). To avoid bias with both approaches, patients are enrolled from a variety of hospital wards/units served by a variety of physicians.

Figure 3. Patient selection before hospital discharge

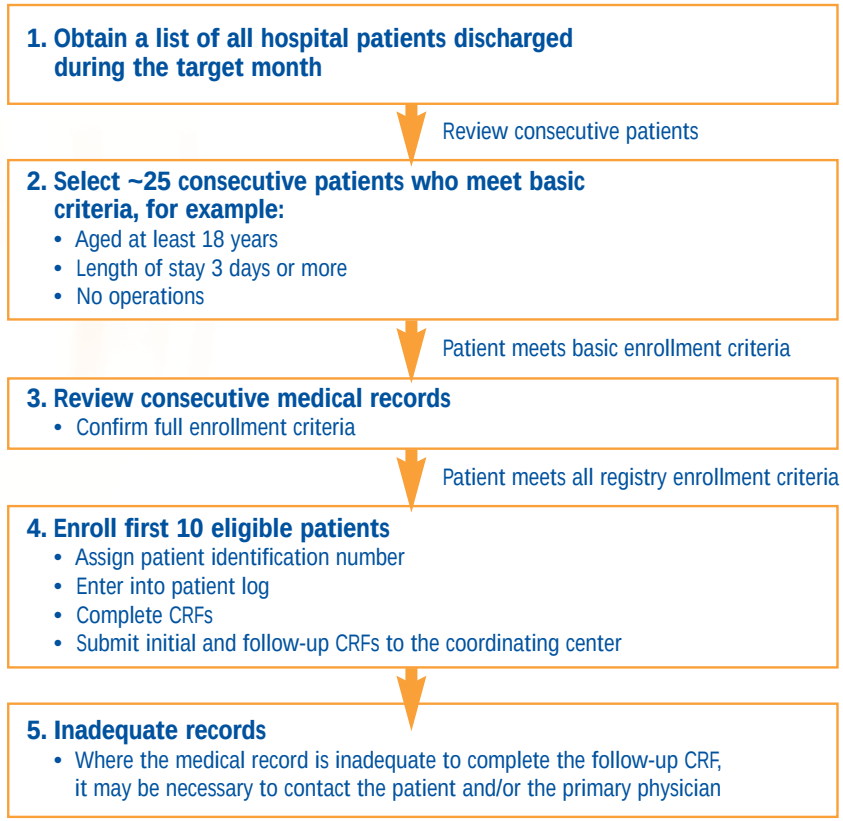


Patient consent, confidentiality and ethics

The need for informed patient consent will depend on the criteria laid down by individual hospital ethics review committees. When necessary, patient consent will be obtained and recorded. At some hospitals, the requirement for patient consent may be waived if adequate data can be obtained from hospital medical records alone and no patient contact is needed.

Patient identities will remain confidential to the participating hospital and physician. No patient identities will be submitted to the registry coordinating

Figure 4. Patient selection after hospital discharge



center. Patients will be identified by use of a unique number assigned to them at enrollment by the registry coordinator at each hospital. All confidential data will be protected by using passwords and firewall software for electronic data, and by storing all paper copies of data in a secure facility. Any registry data submitted through the Internet will be submitted via a secure website at the University of Massachusetts Medical School. Measures employed by IMPROVE to ensure protection of the rights of patients, physicians and centers have been reviewed and approved by the institutional review board of the University of Massachusetts Medical School.

All participating hospitals will inform their institutional review board or ethics committee about their intention to participate in the registry. Where required by national law or local hospital regulations, ethics committees will need to approve the registry protocol before a physician or hospital can participate.

Data collection

Registry data will be collected by physicians and nurses in the hospitals where patients receive their acute medical care. Data will be collected from patients, their physician or nurses, or from medical records. All staff collecting data will be trained to record data on the CRF. To avoid treatment bias, physicians and their research staff who select patients for enrollment or approach patients for consent will ideally not have a role in the routine care of these patients.

Follow-up will be performed at approximately 3 months after discharge from hospital. Follow-up data will be collected during a routine visit to a clinic, via a telephone call to the patient, from the patient's physician or from medical/discharge records.

Quality control

Center for Outcomes Research will be responsible for all data management activities. It will receive CRFs from participating hospitals, and will monitor and document the quality of the data. Inadequate data will be returned to the relevant center for correction or completion. Information on the CRFs will be verified against corresponding medical records in a randomly selected sample of patients enrolled in the registry. A full audit will be performed at centers where the data suggest inadequate compliance with the study protocol.

An Endpoint Committee consisting of experts in the field of VTE will be appointed to apply uniform standards in the assessment of each diagnosed endpoint. The committee will adjudicate the validity of each endpoint on an objective basis.

Data and statistical analysis

It is envisaged that the registry will enroll 5,000 patients per year from 40 hospitals. This will provide an opportunity to observe temporal trends in clinical practices and short-term outcomes. This sample size will give sufficient power to test a number of important hypotheses. Preliminary estimates suggest that an average of 300 patients will be enrolled per year by each 'cluster' of registry hospitals: a cluster will consist of 2–3 hospitals within a region selected to participate in the registry by a member of the IMPROVE Scientific Advisory Board. An annual sample of approximately 100 patients will provide adequate statistical power to determine the proportions of key events at an individual hospital within ±4% and with a 95% confidence interval. Data aggregated across regions and countries will provide even greater validity to the proportions of these key events. This level of statistical power is necessary to address clinically important questions relating to variations in practices and outcomes among the participating hospitals, regions and countries. Data analysis will be tailored to answer specific hypotheses, and will include univariate and multivariate analyses.

Investigators who submit data to IMPROVE will be sent a confidential summary of their data along with the benchmark data from their region, to use as a point of reference, and the aggregate data for all the study sites. These summaries will be sent to participating investigators by courier on a quarterly basis and a helpline will be available should investigators need help interpreting the quarterly report or if they have any questions about the data.

IMPROVE publications

A Publication Committee of the IMPROVE Scientific Advisory Committee will be responsible for guiding the publication process. Peer-reviewed publications will primarily be in the form of abstracts, poster presentations or full manuscripts. Proposals for publications are made by members of the IMPROVE Scientific Advisory Committee or physicians who have enrolled patients at one of the participating hospitals. Members of the Publication Committee are shown on the inside front cover of this booklet.

IMPROVE website

The IMPROVE website can be found at:
www.outcomes.org/improve

The website has been set up to provide information about the registry to all interested healthcare professionals, as well as to facilitate electronic communication between IMPROVE participants. The public section contains a home page, which provides up-to-date information; an overview, including goals and objectives of the registry, and details on the management of the registry; confidentiality information; a list of members of the IMPROVE Scientific Advisory Committee; and links to other VTE resources available on the Internet, including the INATE website.

The Members' Room is password-protected. It provides registry participants with up-to-date analyses of data, meeting minutes and materials, as well as the IMPROVE Instruction Manual. It will also provide facilities for electronic submission of CRFs and publication proposals.

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INVESTIGATORS AGAINST inate THROMBOEMBOLISM

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To find out **more about IMPROVE**, visit the website at www.outcomes.org/improve

E-mail: improve@umassmed.edu
Telephone the IMPROVE HelpLine at: +1 508 856 8837
Send correspondence via **facsimile** to: +1 508 856 5085
Send **mail** to:
IMPROVE
Center for Outcomes Research
University of Massachusetts Medical School
365 Plantation Street, Suite 185
Worcester, MA 01605, USA

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