RE-COVERY DVT/PE: Rationale and design of a prospective observational study of acute venous thromboembolism with a focus on dabigatran etexilate

Walter Ageno[1]; Ivan Casella[2]; Chee Kok Han[3]; Gary E. Raskob[4]; Sebastian Schellong[5]; Sam Schulman[6]; Daniel E. Singer[7]; Karen Kimura[8]; Wenbo Tang[9]; Marc Desch[9]; Samuel Z. Goldhaber[10]

[1]University of Insubria, Varese, Italy; [2]University of Sao Paulo, Sao Paulo, Brazil; [3]University of Malaya, Kuala Lumpur, Malaysia; [4]University of Oklahoma Health Sciences Center, Oklahoma, USA; [5]Stadtisches Klinikum Dresden, Dresden, Germany; [6]Thrombosis and Atherosclerosis Research Institute and McMaster University, Hamilton, Ontario, Canada; [7]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; [8]Boehringer Ingelheim Canada, Burlington, Ontario, Canada; [9]Boehringer Ingelheim, Germany; [10]Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Summary

The therapeutic management of venous thromboembolism (VTE) is rapidly evolving. Following the positive results of pivotal large-scale randomised trials, the non-vitamin K antagonist oral anticoagulants (NOACs) represent an important alternative to standard anticoagulation. In phase III studies, dabigatran was as effective as, and significantly safer than warfarin. Additional information on real-world data of dabigatran is now warranted. RE-COVERY DVT/PE is a multi-centre, international, observational (i. e. non-interventional) study enrolling patients with acute DVT and/or PE within 30 days after objective diagnosis. The study is designed with two phases. Phase 1 has a cross-sectional design, enrolling approximately 6000 patients independently of treatment choice, with the aim of providing a contemporary picture of the management of VTE worldwide. Phase 2 has a prospective cohort design, with follow-up of one year, enrolling 8000 patients treated with dabigatran or vitamin K antagonists (VKAs) with the aim of comparing their safety, defined by the occurrence of major bleeding, and effectiveness, defined by the occurrence of symptomatic recurrent VTE. RE-COVERY DVT/PE will complement both the results of other observational studies in this field and the results of phase III studies with dabigatran, in particular by assessing its clinical benefit in various patient subgroups treated in routine clinical practice.

Keywords

Deep-vein thrombosis, pulmonary embolism, dabigatran, anticoagulation

Correspondence to:
Walter Ageno, MD
Department of Clinical and Experimental Medicine
University of Insubria, Varese, Italy
E-mail: walter.ageno@uninsubria.it

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Introduction

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), causes a major global disease burden (1). The incidence of PE is increasing over time, and short-term morbidity and mortality rates remain high (2, 3). VTE carries a substantial risk of recurrence, with a cumulative incidence of recurrence after 10 years of about 40 % (4). Other long-term complications of VTE include the post-thrombotic syndrome, which may affect 30–50 % of patients with lower limb DVT and chronic thromboembolic pulmonary hypertension, which occurs in up to 4 % of patients with PE (5, 6).

Anticoagulants are the mainstay of therapy. Traditionally, the standard of treatment for the majority of patients with VTE has been initial parenteral anticoagulation with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), overlapping with and followed by a vitamin K antagonist (VKA) for the long-term management (7). However, VKAs are associated with multiple food and drug interactions, and require coagulation monitoring and dose adjustment, which may contribute to low treatment adherence (8). The annual incidence of major bleeding with VKAs ranges between 2 and 8 per 100 patients (7). Case-fatality rates for major bleeding after the first three months of treament range from 9 % in randomised controlled trials to 18 % in observational studies (9, 10)

The non-vitamin K antagonists oral anticoagulants (NOACs) offer simplified alternatives to standard anticoagulation in the treatment of VTE (11). Their rapid onset of action and predictable pharmacokinetics and pharmacodynamics, obviate the need for routine coagulation monitoring, In pivotal randomised trials of acute and extended treatment of VTE, NOACs were non-inferior in efficacy and were associated with fewer major bleeding complications compared to standard treatment (12–14). Based on these results, the NOACs are recommended by international guidelines, and have been recently suggested as the treatment of choice over VKAs (15, 16).

Dabigatran is a direct thrombin inhibitor that binds to the active site of the thrombin molecule, therefore inactivating both free and fibrin-bound thrombin (17). Dabigatran etexilate is a prodrug that is hydrolysed into the active form, dabigatran, by non-specific esterases in the gut, plasma and liver (18). After oral intake, its plasma level peaks within 1–2 hours (h). The half-life is 14–17 h

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(19). Approximately 80% is excreted unchanged through the kidney, while the remaining 20% is conjugated with glucuronic acid and excreted through the biliary system (18). Dabigatran is not metabolised by the cytochrome P450 enzymes, but it is a substrate for the efflux transporter P-glycoprotein (P-gp), located in the intestine and kidneys. Therefore, potent inhibitors of P-gp (e.g. quinidine, ketoconazole, amiodarone, and verapamil) can increase and potent inducers (e.g. rifampicin) can decrease dabigatran absorption (17, 20).

Two randomised controlled trials, RE-COVER and RE-COVER II, compared dabigatran 150 mg twice daily with warfarin for the treatment of VTE (21, 22). In both trials, during six months of treatment, dabigatran was non-inferior to warfarin in the primary efficacy outcome of recurrent symptomatic VTE or VTE-related death. When the results of the two trials were pooled, the rate of major bleeding was significantly lower with dabigatran than with warfarin (23).

In the RE-MEDY trial, dabigatran was compared to warfarin in patients who had completed at least three months of anticoagulation (14). After a median treatment duration of about 16 months, dabigatran was non-inferior to warfarin for the primary endpoint of recurrent or fatal VTE. The composite outcome of major or clinically relevant bleeding was significantly lower in patients who received dabigatran compared with warfarin. The efficacy of dabigatran in the secondary prevention of VTE was also shown by the RE-SONATE trial, where patients for whom there was equipoise for stopping or continuing anticoagulation were randomised to dabigatran or placebo for a median treatment duration of 5.5 months (14).

Dabigatran is now approved in many countries worldwide for VTE treatment and secondary prevention of recurrent VTE in a dose of 150 mg twice daily after at least 5 days of parenteral anticoagulation.

Design of the RE-COVERY DVT/PE Study

Following regulatory approval of the NOACs for the treatment of VTE, agencies requested additional data on real-world safety and effectiveness. The safety of dabigatran in populations more representative of clinical practice has been extensively assessed in patients treated for nonvalvular atrial fibrillation (24, 25) but not in VTE patients. RE-COVERY DVT/PE was designed to evaluate dabigatran in patients with VTE managed in routine clinical practice.

Study questions and design

RE-COVERY DVT/PE is a multi-centre, international, observational (i.e. non-interventional) study enrolling patients with acute DVT and/or PE within 30 days after objective diagnosis. The type, dose, and duration of anticoagulant therapy is decided by the attending physician.

The study is structured in two different phases. Phase 1 aims to provide a contemporary picture of the management of patients with DVT and PE and will have a cross-sectional design, enrolling approximately 2000 consecutive patients with VTE per year for a total of 6000 patients, independently of treatment choice. This phase will describe currently used therapeutic strategies for patients with DVT and PE, rates and duration of hospitalisation for VTE, and identify factors associated with various management strategies. It will also explore geographical variations across several participating countries.

Phase 2 aims to compare the safety and effectiveness of dabigatran with VKAs over one year of follow-up and will have a prospective cohort design. In particular, it will assess the safety and effectiveness of on-label and off-label doses of dabigatran in a broad VTE population in routine clinical practice as well as in special populations that are often underrepresented in phase III clinical trials. Patients enrolled in phase 1 and treated with dabigatran or VKAs will be also eligible for phase 2. The study design is summarised in ▶Figure 1.

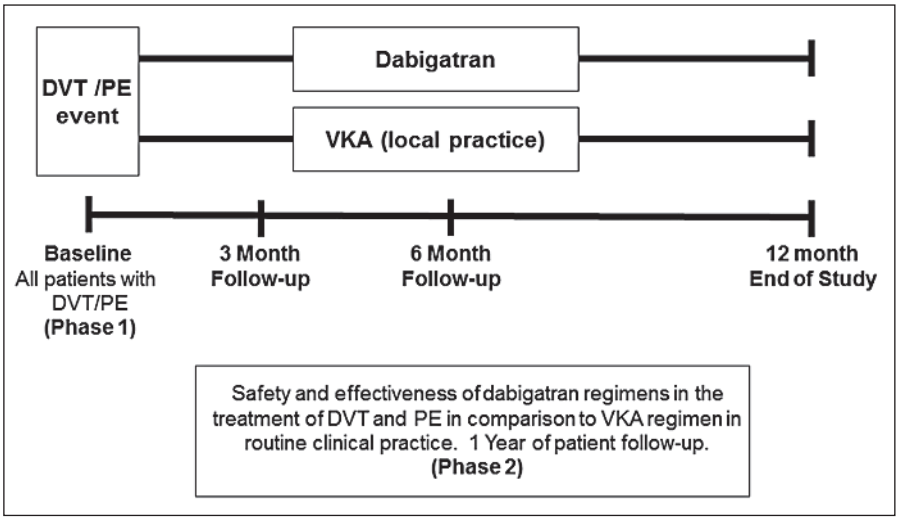

Figure 1: Design of the RE-COVERY DVT/PE study.

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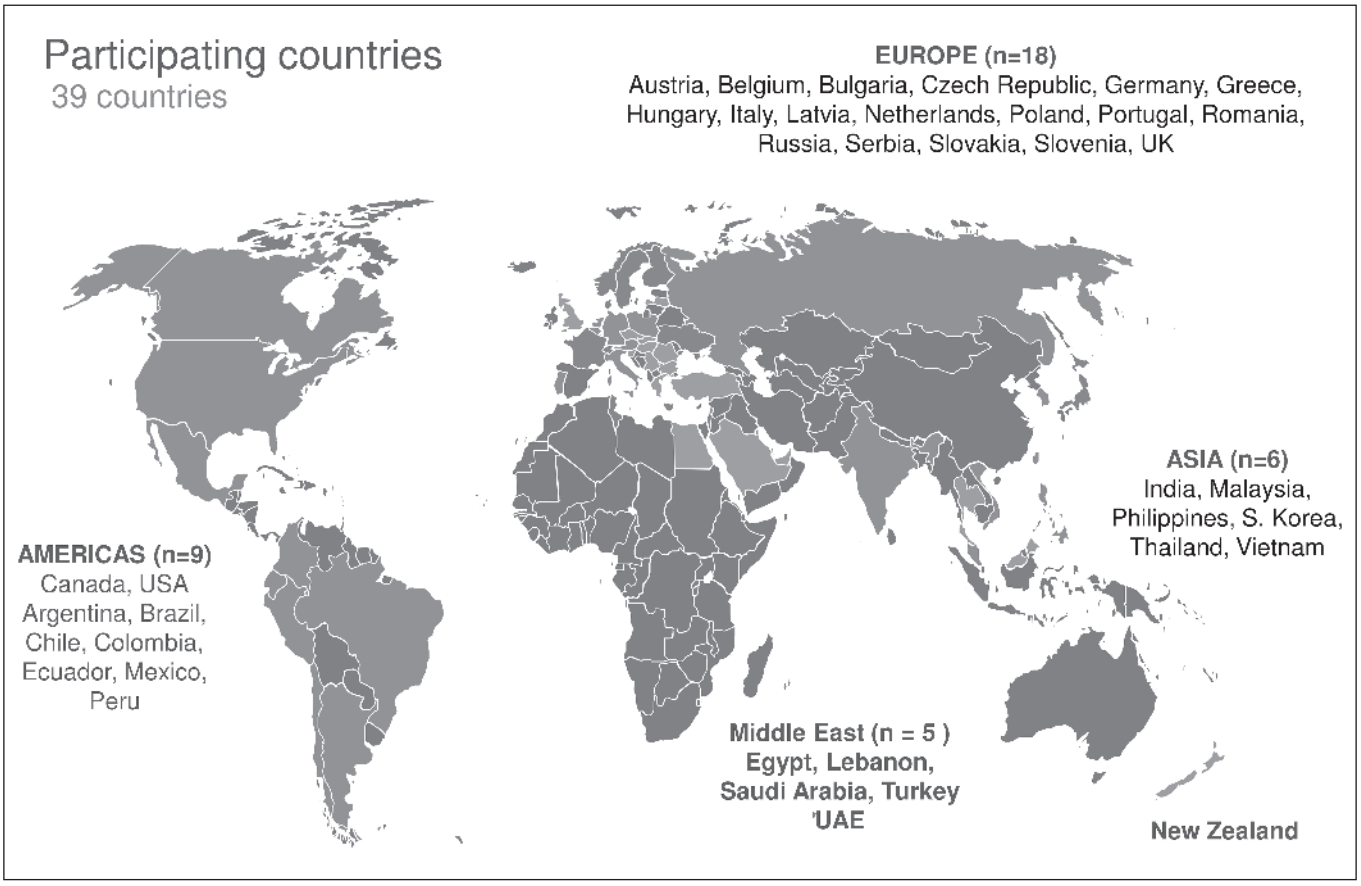

Figure 2: Map of the countries involved in the RE-COVERY DVT/PE study.

Centre and patient selection

The countries selected for this study will represent different regions of the world to provide a broad picture of VTE management that will be more comprehensive than in phase III clinical trials. A map of the participating countries is shown in ▶Figure 2.

The selected sites will represent the standard of practice in each country. For this reason, different facilities are involved, including general practice offices, different specialists offices, hospitals, outpatient-care centres and anticoagulation clinics.

Centre participation requires protocol review by Ethics Committees or Institutional Review Boards. The study is registered at clinicaltrials.gov (NCT02596230).

Inclusion and exclusion criteria

Consecutive adult patients with objective documentation of acute DVT and/or PE are eligible for inclusion if they provide written informed consent. For Phase 1, patients are eligible regardless of the treatment provided and should be enrolled ideally within 14 days, but not more than 30 days after their acute VTE. For Phase 2, patients are eligible if treated with dabigatran or VKA, if available for the long-term follow-up (via clinic or phone) and if anticoagulant therapy is planned for at least three months (▶Figure 3). Patients are not eligible for inclusion if they have other indications for anticoagulant therapy, if they are already participating in a clinical trial on VTE, or if they are currently using an investigational, unapproved drug. To ensure a balanced enrollment approach, it is suggested that for each dabigatran patient enrolled for Phase 2, the next VKA patient with the same index event (DVT/PE) should be recruited ideally at the same study site. To ensure global representation, regional recruitment caps will be employed.

Study outcomes

Phase 1 will describe demographic characteristics, presence of comorbidities and specific risk factors for VTE, risk factors for bleeding, information on the index event including diagnostic approach and management, need for hospitalisation and length of hospital stay.

For Phase 2, the primary outcome for safety is the occurrence of major bleeding. The primary outcome for effectiveness is the occurrence of symptomatic recurrent VTE, including VTE-related mortality. Additional study outcomes include recurrent DVT and/or PE, VTE-related mortality, all-cause mortality, life-threatening bleeding, including fatal bleeding, clinically relevant non-major bleeding, acute coronary syndromes, including ST elevation myocardial infarction, non-ST elevation myocardial infarction, and

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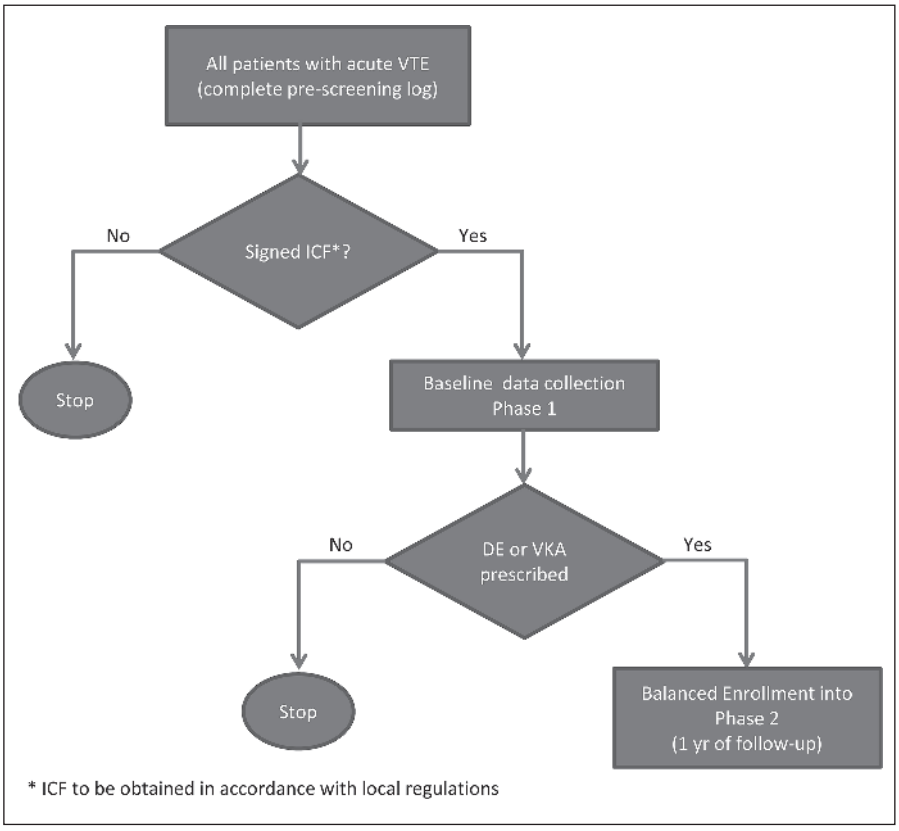

Figure 3: Enrollment of patients into the study.

unstable angina, serious adverse drug reactions, satisfaction with anticoagulant treatment, treatment adherence, and health care resource utilisation. Definition of the study outcomes is shown in ►Table 1.

Data acquisition

Patients are managed according to local clinical practice. No additional medical procedures are required. Baseline data are collected at one visit or over a series of contacts occurring after the acute VTE event, based on information in the patient medical record and/or information that is reported by the patient. The flowchart for the cross sectional part of the study is shown in ►Table 2. For the prospective cohort study, information is collected during follow-up after three months, six months, and one year (►Table 3).

Sample size and statistical analysis

The sample of 6000 patients for the cross-sectional study is not based on formal calculations as there are no hypotheses to be tested. This sample of convenience was considered sufficient to allow robust estimates for each of the considered variables. Further, the sample of 2000 patients per year over a three-year period was considered sufficient to capture treatment trends over time. Descriptive analysis will be used to report baseline demographics, patient characteristics, and anticoagulation treatment. This analysis will be repeated in each enrollment period to assess trends over time. and by region. If eligible, patients included in the cross-sectional assessment and treated with dabigatran or VKA will be also rolled over into the prospective cohort study for phase 2.

To support the sample size determination for the prospective cohort study, assessments were performed for the primary safety outcome of major bleeding, based on the results from the pooled analysis of the RE-COVER and RE-COVER II trials (23). We specified a 1: 1 allocation ratio of dabigatran and VKA patients. We calculated sample size estimates using a one-sided alpha of 0.025 and 30% loss to follow-up rate. With a total sample size of 6380 patients, the study will have 80% power to detect that the upper limit of the 95% confidence interval for the hazard ratio for major bleeding with dabigatran versus VKA is less than 1.3. Thus, a total sample size of up to 8000 patients (i.e. 4000 patients per group) is deemed appropriate for the planned analyses for the prospective cohort study. Data from the longitudinal follow-up will be summarised descriptively, and dabigatran patients will be analysed in comparison to VKA patients using multivariable regression, as well as propensity score analysis. The primary comparative analyses will be based on the actual anticoagulation treatment received ("as treated" analysis). Patients who complete the planned anticoagulant treatment prior to one year or discontinue initial anticoagulant treatment permanently will be censored at the date of last drug intake plus six days for both dabigatran and VKA, or at first intake of another anticoagulant treatment, whichever occurs first.

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Table 1: Definitions of study outcomes.

- **Major bleeding:** overt bleeding associated with a reduction in haemoglobin levels of at least 20 g/l,
or leading to a transfusion of at least 2 units of blood or packed cells; or bleeding occurring in a critical site (intraocular, intracranial, intraspinal, retroperitoneal, intraarticular, pericardial, or intramuscular with compartimental syndrome)[1]
- **Life-threatening bleeding:** symptomatic intracranial bleeding, reduction in haemoglobin levels of at least 50 g/l, transfusion of at least 4 units of packed cells associated with hypotension requiring the use of intravenous inotropic agents, necessitating surgical intervention, or fatal
- **Clinically relevant non-major bleeding:** any overt bleeding not fitting the criteria for major bleeding, but requiring medical intervention, hospitalization, or prompting evaluation
- **Recurrent VTE:** deep venous thrombosis objectively confirmed by compression ultrasonography or
venography: PE objectively confirmed by V-Q lung scan, pulmonary angiography, or spiral CT scan for suspected PE
- **VTE related death:** VTE events that contributed to death based on investigator clinical judgment
- **Satisfaction with anticoagulant treatment:** will be assessed using the PACT-Q2[2]
- **Treatment adherence:** will be assessed using the Morisky Medication Adherence Scale[3]
- **Health care resource utilisation:** will be assessed as number of hospital admissions, emergency room visits, and physician office visits calculated per-patient per-month.

[1] Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Commiyttee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692–694; [2]Prins MH, Marrel A, Carita P, Anderson D, Bousser MG, Crijns H, Consoli S, Arnould B. Multinational development of a questionnaire assessing patient satisfaction with anticoagulant treatment: the "Perception of anticoagulant treatment questionnaire" (PACT Q). Health Qual Life Outcomes 2009; 7: 9; [3]Morisky DE, DiMatteo MR. Improving the measurement of self reported medication nonadherence: Final response. J Clin Epidemiol 2011; 64: 258–263.

Table 2: Flowchart for phase 1 of the study.

Data collection time point	Baseline	At hospital discharge (or 14 days)1
Informed consent	X	
Review of in- / exclusion criteria	X	
Demographics	X	
Medical history	X	
VTE disease characteristics	X	X
Treatment for VTE	X	X
Height	X	
Weight	X	
Blood pressure and heart rate	X	
Collect Laboratory data (if available)	X	
Adverse drug reactions	X	X
Concomitant therapy	X	
Completion of patient participation		X

[1] Data will be collected at the date of hospital discharge or at 14 days post diagnosis, whichever is later.

Discussion

While the use of the NOACs for the treatment of VTE is rapidly increasing, it is important to describe the patients who actually are prescribed these drugs in a setting more likely to be representative of usual clinical practice. Our prospective observational cohort will obtain safety and effectiveness data garnered from routine clinical practice.

Rivaroxaban was the first NOAC to receive approval for patients with DVT, and XALIA was the first prospective, observational, real-world study to investigate the safety and effectiveness of a NOAC in this setting (26). This study, conducted in 19 European countries, Israel, and Canada, found that patients who received rivaroxaban were younger, and fewer had renal impairment, underlying cancer, or concomitant PE than those who received standard anticoagulation therapy. Major bleeding and recurrent VTE event rates in rivaroxaban treated patients were low and similar to those reported in phase III trials, and, after propensity score adjustment, safety and effectiveness were similar between patients treated with rivaroxaban and with standard anticoagulation. This finding was consistent across different patient subgroups. Ongoing prospective registries include the XALIA-LEA study, which is enrolling patients in Latin-America, the Middle-East, and Asia with the same aim and design of XALIA, the European PREFER registry in VTE, RIETE, and GARFIELD-VTE. In all these registries, patients with acute VTE are enrolled and followed for up to 3 years.

The RE-COVERY DVT/PE study has the potential to provide useful incremental information for practicing clinicians. First, this study will complement the results of other completed and ongoing registries. The results of RE-COVERY DVT/PE will provide a worldwide, contemporary cross-sectional picture of the current management of VTE patients and of trends in VTE treatment over a three-year time period. Second, this study will complement the results of phase III studies with dabigatran and will explore the safety and effectiveness of dabigatran in different patient groups, including those poorly represented in randomised controlled trials. These include, for example, patients with cancer and the multimorbid elderly patients. In subgroup analyses of the RE-COVER studies, dabigatran was similarly effective to warfarin across all age groups. Overall bleeding was less frequent in patients receiving dabigatran compared to patients treated with warfarin, irrespective of age (27, 28). Similar results were found in relation to renal function and to the presence of active cancer (29, 30).

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However, real-life data are needed to corroborate these findings. Third, RE-COVERY DVT/PE will assess for the first time the safety and effectiveness of the 110 mg BID dabigatran dose in patients with VTE, since this dose was never tested in phase III studies, but was requested by some health authorities (e.g. EMA) for use in clinical practice and is currently approved in this setting for fragile patients. Finally, RE-COVERY DVT/PE will provide additional data on the safety of dabigatran in the long-term secondary prevention of VTE, following the favourable results of the RE-MEDY trial. This information is clinically relevant given the safety concerns with the long-term use of VKAs and the recommendation of international guidelines to stop anticoagulation at three months in patients defined at high risk of bleeding, including elderly patients (9, 10, 16).

Some limitations that are intrinsic in the design of the RE-COVERY study need to be taken into account. Despite the careful selection of a high number of centres representing the standard of practice in each country and the involvement of a large number of countries worldwide, we cannot exclude that different therapeutic approaches are used in centres or countries that are not involved in this study. Further, although observational studies provide more comprehensive pictures of patients managed in the "real world" than phase III studies, we cannot exclude that for different reasons (including for example early mortality or failure to obtain written informed consent) some patients managed at the participating centres will not be enrolled in the study. However, a pre-screening log will be completed at each centre to provide an estimate of the number of missed patients and of the reasons for exclusion. All investigators will be asked to ensure the enrollment of consecutive patients. Finally, a selection bias in treatment allocation and a subsequent imbalance of patients between treatment groups is expected, and will be addressed by the propensity score analysis.

In conclusion, RE-COVERY DVT/PE is a large, obervational study with a two-phase design that will describe management strategies for patients with VTE. This observational trial will assess the safety and effectiveness of dabigatran in the short-term and long-term treatment of VTE. The results of the RE-COVERY DVT/PE study will add important information to our knowledge on the role of the NOACs in this setting.

Table 3: Flowchart for phase 2 of the study.

Data collection time point	Baseline	At hospital discharge (or 14 days)[1]	3 months	6 months	1 year
Informed consent	X				
Review of in- / exclusion criteria	X				
Demographics	X				
Medical history	X				
VTE disease characteristics	X	X			
Treatment for VTE	X	X	X	X	X
Concomitant diseases		X	X	X	X
Height	X				
Weight	X		X	X	X
Blood pressure and heart rate	X				
Collect Laboratory data (if available)	X	X	X	X	X
Adverse drug reactions	X	X	X	X	X
Outcome events		X	X	X	X
Morisky Medication Adherence Scale			X	X	X
Health resource utilisation			X	X	X
PACT-Q2			X	X	X
Concomitant therapy	X	X	X	X	X
Completion of patient participation					X
Vital status collection[2]			X	X	X

[1] Data will be collected at the date of hospital discharge or at 14 days post diagnosis, whichever is later.
[2] Vital status will be collected if the patient declines further clinic visit.

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Conflicts of interest

W. Ageno has received research support from Bayer, and Boehringer Ingelheim, and has served on advisory boards for Bayer, Boehringer Ingelheim, and Daiichi Sankyo. I. B. Casella is a current or former consultant and/or speaker for Boehringer Ingelheim (Brazil and Germany), EMS (Brazil), Farmoquimica (Brazil), and Pfizer (Brazil). G. Raskob has received consultancy fees from Boehringer Ingelheim, Bayer, BMS, Daiichi Sankyo, Janssen, J&J, Pfizer, Portola, and Eli Lilly. S. Schellong has received consultancy fees and speaker fees from Bayer Healthcare, Boehringer Ingelheim, BMS, Pfizer, and Daiichi Sankyo. S. Schulman has received honoraria and research grants from Boehringer Ingelheim. D. E. Singer has served as a consultant and/or the advisory boards of Boehringer Ingelheim, BMS, Merck,, Johnson & Johnson, and Pfizer, and has received research grants from Boehringer Ingelheim, and BMS. K. Kimura is an employee of Boehringer Ingelheim Canada Ltd. W. Tang is a full-time employee of Boehringer Ingelheim Pharmaceuticals Inc. M. Desch is an employee of Boehringer Ingelheim. S. Goldhaber is a consultant for Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, and Portola and has received research support from BiO2 Medical, Boehringer Ingelheim, BMS, BTG EKOS, Daiichi Sankyo, and Janssen. C. Han declares no conflicts of interest.

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