Global Anticoagulant Registry in the Field – Venous Thromboembolism (GARFIELD-VTE)

Rationale and design

Jeffrey I. Weitz[1]; Sylvia Haas[2]; Walter Ageno[3]; Pantep Angchaisuksiri[4]; Henri Bounameaux[5]; Joern Dalsgaard Nielsen[6]; Samuel Z. Goldhaber[7]; Shinya Goto[8]; Gloria Kayani[9]; Lorenzo Mantovani[10]; Paolo Prandoni[11]; Sebastian Schellong[12]; Alexander G. G. Turpie[13]; Ajay K. Kakkar[9,14]

[1]McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada; [2]Formerly: Technical University of Munich, Munich, Germany; [3]University of Insubria, Varese, Italy; [4]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [5]Division of Angiology and Hemostasis, University Hospitals of Geneva, Switzerland; [6]Bispebjerg-Frederiksberg Hospital, Copenhagen, Denmark; [7]Harvard Medical School, Boston, Massachusetts, USA; [8]Tokai University, Kanagawa, Japan; [9]Thrombosis Research Institute, London, UK; [10]University of Milano-Bicocca, Milan, Italy; [11]University of Padua, Padua, Italy; [12]Municipal Hospital Friedrichstadt, Dresden, Germany; [13]McMaster University, Hamilton, Canada; [14]University College London, London, UK

Summary

Venous thromboembolism (VTE) is a common disorder associated with significant rates of morbidity and mortality. VTE management aims to reduce mortality, the risks of recurrence, and long-term complications. VTE treatment is evolving with the introduction of non-vitamin K antagonist anticoagulants (NOACs). The Global Anticoagulant Registry in the FIELD – Venous Thromboembolism (GARFIELD-VTE) is a prospective, multicentre, observational study that will enrol 10,000 patients treated for acute VTE from ~500 sites in 28 countries. Identified sites reflect the diversity of care settings, including hospital and outpatient settings. Patients will be managed according to local practices and followed for at least three years. The primary objective is to determine the extent to which VTE treatment varies in the real-world setting and to assess the impact of such variability on clinical and economic outcomes. Evolving patterns of care will be captured using two sequential cohorts. The GARFIELD-VTE registry will provide insights into the evolving global treatment patterns for VTE, both deep-vein thrombosis and pulmonary embolism. By enrolling patients from diverse care settings, the registry will provide information on adherence to national and international guidelines, identify good practice as well as treatment deficiencies, and relate patient outcomes to clinical management. The incidence of death, recurrent VTE, bleeding, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension will be documented. By capturing information during and after anticoagulation treatment, the registry will not only define aspects of the natural history of VTE, but also its economic and societal impact at a regional and global level.

Keywords

Registry, venous thromboembolism, deep-vein thrombosis, pulmonary embolism, anticoagulation, thrombolysis

Correspondence to:
Jeffrey I. Weitz, MD
Thrombosis and Atherosclerosis Research Institute
237 Barton Street East, Hamilton, ON L8L 2X2, Canada
Tel: +1 905 574 8550, Fax: +1 905 575 2646
E-mail: weitzj@taari.ca

Financial support:
The GARFIELD-VTE registry is an independent academic research initiative sponsored by the Thrombosis Research Institute (London, UK) and supported by an unrestricted research grant from Bayer Pharma AG (Berlin, Germany).

Received: April 27, 2016
Accepted after minor revision: August 23, 2016
Epub ahead of print: September 22, 2016

http://dx.doi.org/10.1160/TH16-04-0335
Thromb Haemost 2016; 116: 1172–1179

Introduction

Deep-vein thrombosis (DVT) and pulmonary embolism (PE), either as the primary event or a complication of DVT, are known collectively as venous thromboembolism (VTE). VTE is a leading cause of morbidity and mortality worldwide (1). Moreover, the risk of recurrence is high (2–4) and VTE is associated with serious long-term complications, including post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH) (5).

The annual incidence of VTE in the general population of western countries ranges from 1-2 cases per 1000 persons and increases with age (6–8). Although the incidence of VTE in Asia is reported to be lower than that in western countries, the data supporting this concept are limited (9). In Europe, the annual mortality rate from VTE is more than double that for AIDS, breast cancer, prostate cancer and traffic accidents combined (10).

The goal of VTE treatment is to reduce the risk of acute and long-term sequelae such as progression of DVT, fatal PE, recurrent VTE, PTS and CTEPH. The risk of recurrent VTE is highest in the first 6-12 months after cessation of anticoagulant therapy, but a heightened risk persists for at least 10 years, reaching about 25 % at five years and 30 % to 50 % at 10 years (11). Up to 25 % of all VTE events occur in those with a previous event. Patients with

unprovoked VTE have a higher risk for recurrence than those with VTE provoked by transient risk factors such as major surgery, trauma, acute medical illness and others (12). Morbidity and mortality increase with each VTE recurrence (13) and anticoagulation, the foundation of VTE therapy, can cause major bleeding, which contributes to the morbidity and mortality.

PTS is the most common long-term complication of DVT. The incidence of PTS ranges from 20% to 50% within two years of the index DVT (14, 15). PTS is severe in approximately 10% to 15% of cases, costs society billions of euros per year in time lost from work and in medical expenses and leads to functional disability and reduced quality of life (QoL) (16–18). The incidence of CTEPH is less certain. In PE patients followed for two years, one study reported a cumulative incidence of symptomatic CTEPH of 1% at six months, 3.1% at one year and 3.8% at two years (19).

The mainstay of VTE treatment is anticoagulant therapy, which is given for three months in patients with VTE provoked by a transient and reversible risk factor and for longer in those with unprovoked VTE or with ongoing risk factors such as cancer (20). Until recently, VTE treatment consisted of a parenteral anticoagulant, usually low-molecular-weight heparin (LMWH) and a vitamin K antagonist (VKA). The two treatments are overlapped for at least five days and LMWH is stopped when the international normalised ratio (INR) is therapeutic. Although effective, such treatment is cumbersome because LMWH administration requires daily subcutaneous injection, which can be difficult for some patients, and VKAs require frequent coagulation monitoring and dose adjustment, which is burdensome for patients and healthcare providers.

The recent introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), which include rivaroxaban, apixaban, edoxaban and dabigatran, has streamlined VTE treatment. Compared with conventional therapy, meta-analyses of the phase III VTE trials reveal that the NOACs are as effective as VKAs for the prevention of recurrence, but are associated with less bleeding (21–27). Furthermore, the NOACs are more convenient than VKAs because they can be given in fixed doses without routine coagulation monitoring. Whereas edoxaban and dabigatran are initiated after at least five days of parenteral anticoagulant therapy, therapeutic doses of rivaroxaban and apixaban can replace parenteral anticoagulation, thereby enabling all oral therapy. In the face of this changing clinical landscape, it is important to capture the impact of the NOACs on VTE treatment and long-term outcomes on a global level. The Global Anticoagulant Registry in the FIELD – Venous Thromboembolism (GARFIELD-VTE) will provide insights into the evolving global treatment patterns and outcomes for VTE patients across a wide range of clinical settings.

The Garfield-VTE Registry

Registry design

The GARFIELD-VTE (ClinicalTrials.gov identifier: NCT02155491) is a global, prospective, multicentre, observational study of patients requiring treatment for acute VTE. It is an independent academic research initiative sponsored by the Thrombosis Research Institute (London, UK) and supported by an unrestricted research grant from Bayer Pharma AG (Berlin, Germany). The quality assurance processes employed in the registry are subject to independent review by an Audit Committee which, in turn, reports to the scientific Steering Committee. The primary aim of the registry is to observe initial, long-term and extended management strategies and clinical and economic outcomes in patients treated in a real-world setting. Data are captured from the time of diagnosis and over 36 months of follow-up in the various care settings.

The registry began recruiting patients in July 2014 and aims to enrol 10,000 patients within 30 days of diagnosis of DVT and/or PE from approximately 500 sites in 28 countries (►Figure 1). To capture temporal trends in VTE management, patients are being

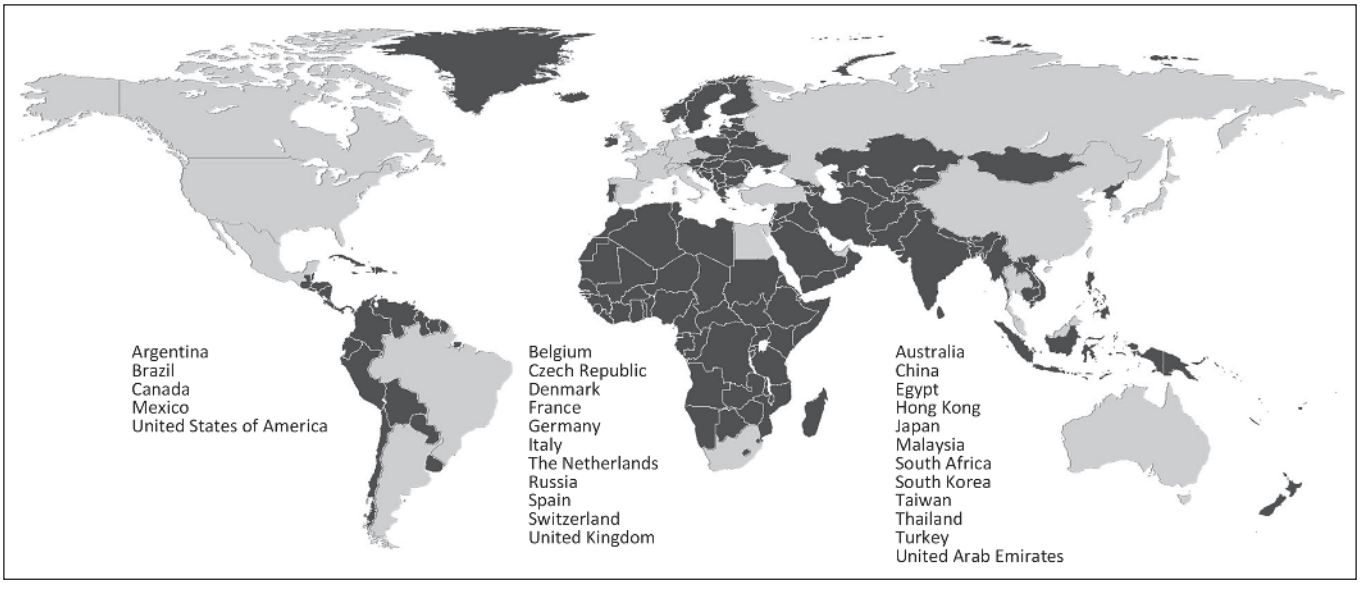

Figure 1: The global reach of GARFIELD-VTE.

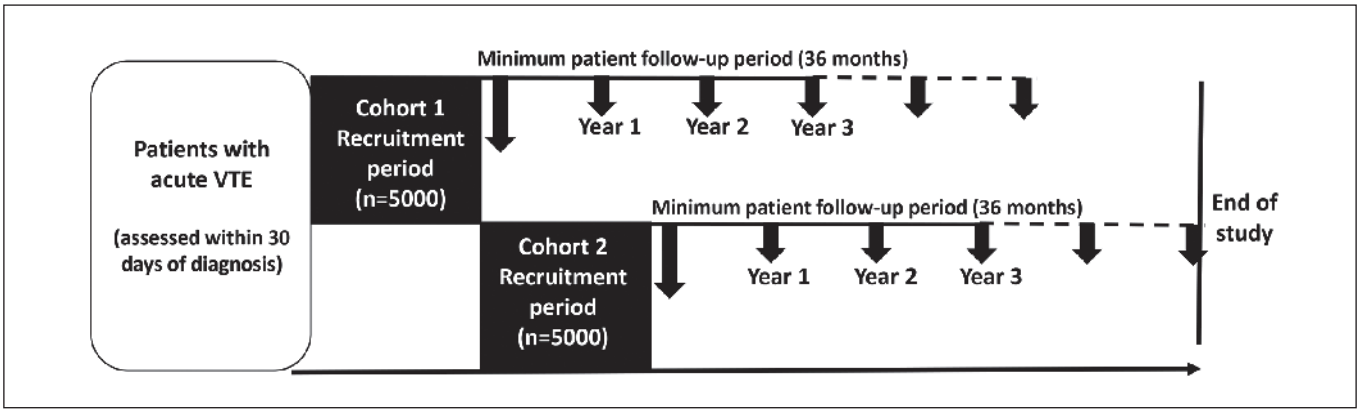

Figure 2: A diagram illustrating the design of GARFIELD-VTE. The dotted line indicates possible annual check-up for up to two years after the minimum 36-month follow-up period.

enrolled in two consecutive cohorts, and are followed for at least three years (▶Figure 2). Recruitment into the second cohort commenced in January 2016 when recruitment of the first cohort was completed.

Coordinators in each participating country provided advice on the national distribution of VTE care settings to ensure that the chosen sites are representative of care in each country. Patients are treated according to standard local practices and no additional visits, tests or procedures are required by the protocol (except for the collection of data using QoL instruments). Data are collected from medical records according to specifications outlined in the electronic case report form (eCRF); the time points defined in the protocol are used as prompts for collection of data from the medical records from the preceding period and the frequency of visits is not specified. The registry has set predefined standards for remote data monitoring and onsite source data verification. Registry monitors will review 5% of all eCRFs against source documentation. All data modifications in the database will be recorded electronically in an audit trail. Variables defined as critical to the statistical analysis will periodically be subjected to a 100% electronic audit for the duration of the study.

Independent ethics committee and hospital-based institutional review board approvals were gained, as necessary, for the protocol. The registry is conducted in accordance with the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation Good Clinical Practice and Pharmacoepidemiological Practice guidelines.

Registry population

The study population consists of males and females from randomly selected sites. All eligible patients are required to be 18 years of age or older and are being treated for VTE, having had a confirmed diagnosis of VTE (either as a primary or recurrent event) within 30 days of assessment for entry into the registry. Patients with recurrent VTE must have completed treatment for the previous VTE episode. The registry does not include patients with superficial vein thrombosis (SVT) or those for whom long-term follow-up is not envisaged. The registry also excludes patients participating in any study that dictates treatments, visit frequency, or diagnostic procedures.

Site selection

Sites were identified at random (using a computer-generated process) from a representative list reflecting treatment patterns in each country and were selected after completion of a qualification question or a qualification call. In some countries, after the process for random selection was exhausted, a few sites were chosen by the national coordinators to meet the site target for the country. Patients are identified from multiple sources, including hospital and outpatient settings from different specialities, such as: vascular medicine, general practice, and internal medicine (including haematology and intensive care). The identifying clinician registers the patient using the eCRF. Physicians involved in the initial diagnosis may transfer or refer patients to other physicians who will report treatment and follow-up to the registry.

Data capture

Data on outcomes relevant to the registry are collected through review of clinical records and patient notes. For the first VTE event recorded in the registry, and for each subsequent VTE event, the following information is captured: patient demographics, medical history, predisposing and provoking VTE risk factors during the past three months (including, for example, the presence of active cancer and thrombophilia), nature of VTE (extent and location), date and method of diagnosis, and symptoms. For patients with a prior episode of VTE, data are recorded before entry into the registry on: the nature of this VTE, the time since this episode as well as associated complications (such as symptoms of PTS and CTEPH, and recurrent VTE). The patient care management settings are defined according to specialty, location, and medical insurance. Routinely performed tests are documented (including INR, haemoglobin, platelet count and creatinine). Relevant medications taken prior to the date of VTE diagnosis and ongoing concomitant

medications taken after VTE diagnosis are described. For patients treated with VKAs, the following data are also collected: INR, INR frequency and outcomes related to INR fluctuation. Data are collected over 36 months of follow-up. Treatment decisions for the first VTE event and each subsequent event are recorded over 36 months. Information is collected on initial and extended therapy for each VTE episode, including start and stop dates, dosing, changes in therapy, overall expected duration of therapy, and the reason for suspending or terminating therapy sooner than intended (such as bleeding, patient decision, and/or physician decision).

All hospitalisations are captured on the eCRF. The data include the duration of hospital stay, reason for hospitalisation, any VTE-related thrombosis or bleeding, whether the hospitalisation was expected or unexpected and the required intervention for VTE, if any.

Over the 36 months of follow-up, the data that will be collected from the medical records at regular intervals include: all PE-related deaths and all other causes of death (for example, due to strokes, cardiac- or cancer-related morbidity or bleeds), all bleeds and their sequelae, all VTE events and their sequelae (recurrent non-fatal PE or symptomatic DVT, PTS and CTEPH), healthcare resource consumption (hospitalisations, medical consultations, INR testing, diagnostic and interventional procedures for VTE) and any cardiovascular event (e.g. transient ischaemic attack, stroke, myocardial infarction or unstable angina). Both physician- and patient-reported outcomes are captured in order to gauge health status, patient treatment satisfaction, cost-effectiveness of treatment and burden of disease. At the start of study (baseline or month 1) and at regular intervals thereafter (month 3, month 6, month 12, month 24 and month 36), data will be collected from the medical records on patients' rating on the Villalta scale (from 0 [none] to 10 [most severe]), and the symptoms (pain, cramps, heaviness, paraesthesia, and pruritus) and signs of PTS (swelling, induration, hyperpigmentation, venous ectasia, redness and pain during calf compression) (28). The physician also assesses the severity of PTS using the Villalta scale (28) at the end of the study (either at month 36 or at the time when the patient withdraws from the study). Patients also complete a modified Short Form Health Survey (SF-12) QoL questionnaire to evaluate the overall burden of illness at baseline/month 1, month 3, month 6, and month 24 and the Anti-Clot Treatment Scale (ACTS) questionnaire to evaluate the burdens and benefits of anticoagulation therapy (28) at baseline/month 1, month 3 and month 6 in selected countries (where local language versions are available). The ACTS instrument, which includes a 12-item burdens scale and a 3-item benefits scale, has been shown to consistently and reliably report on patients' satisfaction with anticoagulation treatment, irrespective of their underlying condition (28).

Registry outcomes

The main objectives of the registry are to capture the treatment patterns for acute VTE (either conventional anticoagulation therapy, NOAC therapy or other treatment modalities); and the rate and nature of VTE recurrence, VTE complications (including PTS and CTEPH), bleeding complications, and all-cause mortality.

Other objectives include: the assessment of the rates of stroke and acute coronary syndrome, health-related QoL and other patient-reported outcomes using the Villalta scale, and the SF-12 and ACTS instruments.

Based on the data collected from the eCRF, healthcare resource consumption will be captured so that the economic burden of VTE can be computed both overall and per patient per year from the perspective of the payer, e.g. national health service, public/private/statutory insurance etc. Healthcare resource consumption includes: drugs, hospitalisations, medical consultations, INR/laboratory testing, and diagnostic and interventional procedures. Data from the eCRF describes, measures and quantifies treatment patterns and related costs longitudinally at the patient level. As appropriate, healthcare resources consumption will be presented in terms of the number, occurrence, length of stay and type of medical contact, i.e. outpatient care visits including: GP visits, office-based care and hospital-setting outpatient visits; and inpatient care including full- and day-case hospital admissions. In the main economic analysis, all costs will be presented as cost per patient per year, expressed in the local currency and translated into Euros and USD using appropriate conversion rates (e.g. PPP's). Overall cost will also be referenced to each country's healthcare expenditure by dividing the cost per VTE patient per year by the average per capita healthcare expenditure in that country.

Data management

Data are submitted to the registry coordinating centre via a secure web-based electronic database capture system, CLINPAL™ (designed by eClinicalHealth Services, Stirling, UK) and are analysed by the Thrombosis Research Institute, London, UK. All patients are assigned a unique identifier, and personally identifiable data are removed at the hospital source, ensuring anonymity and protecting confidentiality. The eCRFs are examined by the registry coordinating centre to ascertain completeness and accuracy, and data queries are sent to participating sites. Source data verification is undertaken in 10% of all cases.

Statistical analysis plan

The Full Analysis Set (FAS) includes patients eligible for the analysis with baseline data locked as complete. Patients who consented to participate in the study and are subsequently found to be ineligible will not be included in the registry database.

The statistical analysis, which will include a description of the population characteristics and outcome variables, will be exploratory, descriptive and summarised into frequency tables (ordinal or nominal data) or summary statistics with mean, standard deviation, minimum, maximum, median, lower and upper quartiles. Confidence intervals (CI) rather than p values will be the standard method for presenting statistical results. The inclusion of both continuous and categorical demographic data will allow for the application of principal component analysis (PCA) and other multivariate statistical methods. Such techniques enable modelling of the impact of lifestyle factors on disease. All analyses will be

performed for the total study sample and separately for each country and region (as appropriate). Events of special interest will be analysed using descriptive statistics, and event rates based on person-time and time-to-event models will be calculated.

Occurrence of disease

Analysis of data from a cohort study involves estimation of the rates of diseases of interest that occur among cohort members during the study period. Occurrence is most appropriately measured in terms of incidence rates. Rates of mortality, recurrence, major bleeding, and other clinical outcomes (person-time event rates and 95 % CI) are described using the population at risk identified at the beginning of the follow-up. In addition, the total number of events including first events and repeated events (cumulative incidence) will be recorded.

Time-to-event endpoints

The analysis of time-to-event is measured from the date of enrolment to the date of first occurrence of the relevant event in patients with an event of interest, unless indicated otherwise. If the

Table 1: Comparison of the features of GARFIELD-VTE registry with those of other ongoing prospective VTE registries.

Registry	Population size	Patient enrolment – key design features	Follow-up
GARFIELD-VTE[a]	• Target: 10,000 • To date: 7030 • Estimated last follow-up: 2019	• Enrolment: Treated patients enrolled within 30 days of a diagnosis of acute VTE (either primary or recurrent) in two sequential cohorts • Setting: About 500 sites in 28 countries from nationally representative clinical settings (hospital and community). Patients are managed according to local standard practice • Endpoints: Treatment of acute VTE; rates of VTE recurrence, complications (including PTS and CTEPH), bleeding, and all-cause mortality at 6 months; rates of stroke and ACS; health-related QoL, costs of hospitalisation and interventions for VTE	≥3 years
VTEval[b] (32)	• Target: 2000 • To date: unknown • Estimated last follow-up: July 2023	• Enrolment: Adults with a clinical suspicion of either: acute PE (with or without DVT) (cohort 1), acute DVT (without symptomatic PE) (cohort 2) or with an incidental diagnosis of VTE (PE or DVT) (cohort 3) • Setting: Single-centre study at University Medical Centre of the Johannes Gutenberg University Mainz, Germany. Both active (defined investigational plan – medical-technical diagnostic/follow-up examinations) and passive follow-up of patients • Endpoints: Short- and long-term mortality (PE-related and all-cause mortality) and rate of recurrent symptomatic recurrent non-fatal PE or DVT.	5 years
PREFER-VTE[c] (33)	• Target: 3600 • To date: 3545 (July 2014) • Estimated last follow-up: unknown	• Enrolment: Adults with diagnosis of acute VTE (primary or recurrent); recruitment aim – ratio of PE:DVT of 2:3 • Setting: European registry of 381 sites in 7 countries (Austria, France, Germany, Italy, Spain, Switzerland, and the UK). Sites are locally representative of primary and secondary care settings. Patients managed according to local standard practice • Endpoints: 12-month direct healthcare resource utilisation; assessment of the real-life acute and mid-term management of patients with VTE (prevention of VTE recurrence, treatment of bleeding), incidence of recurrent DVT/PE, myocardial infarction, stroke, systemic embolic events, PTS and death	≥1 year
PERCEIVE[a]	• To date: 6822 (initiated in February 2005) • Last follow-up: July 2015	• Enrolment: Adults with newly diagnosed malignancy of the breast, colon and rectum, pancreas, lung, prostate or ovary • Setting: Nine hospital cancer centres in 6 countries (Austria, India, Italy, Singapore, UK, USA). Patients are treated according to local best practice • Endpoints: Incidence of VTE, stroke, myocardial infarction, bleeding and mortality over 10 years from diagnosis of cancer	10 years or until death
RIETE[d] (34)	• To date: >45,000 (initiated in 2001 in Spain) • Estimated last follow-up: ongoing – not defined	• Enrolment: Patients with documented symptomatic DVT or PE, confirmed by objective tests • Setting: Computerised registry of patients from hospitals in 16 countries (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Belgium, Czech Republic, Republic of Macedonia, Greece, Canada, Brazil, United States, Argentina, and Ecuador). Patients are managed according to clinical practice • Endpoints: Short-term (3-month) mortality and bleeding; long-term symptomatic recurrent VTE (non-fatal PE or DVT) and PE-related death	≤2 years (5000 patients) ≤1 month (10,000 patients)

[a]Thrombosis Research Institute http://www.tri-london.ac.uk/garfield/information. Accessed January 2016. [b]VTEval Project – Prospective Cohort Studies https://clinicaltrials.gov/ct2/show/NCT02156401. Accessed January 2016. [c]UK research Network Portfolio Database http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=15273. Accessed January 2016. [d]RIETE registry website https://www.riete.org/info/general/index.php. Accessed January 2016. Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; CV, cardiovascular; DVT, deep-vein thrombosis; NOAC, non-vitamin K antagonist oral anticoagulant; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QoL, quality of life; VTE, venous thromboembolism.

event has not occurred prior to the analysis cut-off date, then time is computed from the date of enrolment to the last known date of follow-up unless otherwise specified. The Cox proportional hazards model or parametric time-to-event model is used to estimate the hazard ratio (HR) and 95% CI in subgroups. Comparisons among groups are adjusted appropriately for confounding baseline factors, which may include age, gender, smoking habits, and medical history. Adjusted HRs and 95% CIs will also be presented graphically using forest plots. For each analysis, the proportional hazards assumption in the Cox model will be tested using appropriate graphical procedures. If the proportionality assumption is not valid, it may be necessary to include a time-varying covariate in the model.

Discussion

The results from GARFIELD-VTE will complement data from the large multinational clinical trials and phase IV studies in VTE (21–27, 29–31). Although randomised clinical trials (RCTs) are the gold standard for evaluating the safety and efficacy of new therapies, they are subject to rigorous inclusion and exclusion criteria, and therefore may not be geographically or clinically applicable to real-world settings. In contemporary clinical research, there is a move towards collecting evidence to evaluate drug safety and effectiveness from observational studies. Large prospective disease registries, such as GARFIELD-VTE, have a number of advantages over RCTs. These include a) avoiding bias and allowing the full range of clinical evidence to be explored in terms of patient types, clinical settings and outcomes; b) informing clinicians and policy makers about less well represented groups, such as the elderly, women during pregnancy and those with existing comorbidities (for example, renal impairment or high risk of bleeding), for whom disease management may be challenging; and c) documenting routine clinical management at a national and global level.

It has yet to be determined how NOACs are being used in clinical practice and their impact on short- and long-term complications of VTE remains uncertain. Several registries in Europe (e.g. PREFER-VTE) are seeking to record the impact of NOAC treatment on VTE; however, these registries are often limited by small patient numbers and short durations of follow-up (►Table 1). The sequential recruitment of patients (between 2014 and 2017) into the GARFIELD-VTE registry shortly after diagnosis of an acute VTE event (whether primary or recurrent) is expected to record the evolving treatment patterns during a time when NOACs are becoming more widely adopted.

Due the global nature of the registry, GARFIELD-VTE will document the regional heterogeneity in the clinical presentation of the index and recurrent VTE events and the incidences of recurrent VTE, bleeding, PTS and CTEPH. In addition to reporting on pre-specified clinical and economic outcomes, analyses from GARFIELD-VTE will be hypothesis generating, allowing the exploration of some aspects of the natural history of VTE as well as the economic and societal impact of VTE. The degree of patient involvement in the generation of data is expected to provide unique insights into the QoL of patients with VTE and the aspects of this disease that most impact on patients' lives. It is expected that findings from this registry will inform new avenues for patient-oriented research.

It is important to recognise that registries differ in their design, recruitment strategies, care setting, geographic spread and duration of follow-up (►Table 1) (32–35). Compared with other ongoing prospective registries in VTE, the global GARFIELD-VTE registry has the potential to capture the burden of disease in large-scale populations by employing broad inclusion criteria in a widely representative populations of patients with VTE (across a range of clinical settings) and to capture long-term follow-up data in the community as well as the hospital setting. The value of the GARFIELD-VTE registry is enhanced by high-quality data collection due to the supervision of an independent Audit Committee, which oversees site-dependent verification, remote site monitoring and electronic database monitoring to ensure data quality.

There are inherent limitations to the design of the GARFIELD-VTE registry. For example, GARFIELD-VTE will not provide the same level of insight into the pathogenesis and nature of VTE as single-centre registries such as VTEval (32), which has a defined investigational plan for medical-technical diagnostic/follow-up examination of patients. In addition, 36 months of follow-up may be too short to capture the natural history of VTE in all patients. Nonetheless, the large sample size, the global recruitment and the

What is known about this topic?

- Venous thromboembolism (VTE) is a leading cause of morbidity and mortality worldwide.
- The treatment of VTE is evolving with the recent introduction of the non-vitamin K antagonist oral anticoagulants (NOACs) and updated guideline recommendations for treatment of pulmonary embolism (PE).
- The extent of uptake of the NOACs in the real world is unknown as is their impact on the short- and long-term complications of VTE.

What does this paper add?

- To capture real world information, the Global Anticoagulant Registry in the FIELD – Venous Thromboembolism (GARFIELD-VTE) will enrol 10,000 patients with documented acute VTE from about 500 centres in 28 countries.
- Patients will be managed according to local practice and will be followed for at least three years.
- The incidences of death, recurrent VTE, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension will be documented as will the incidence and nature of bleeding complications.
- By capturing information during and after anticoagulation treatment, the registry will not only define the natural history of VTE, but also its economic and societal impact at a national and global level.

36 months of follow-up are unique features of the GARFIELD-VTE registry.

Acknowledgements

We thank the physicians, nurses, and patients involved in the GARFIELD-VTE registry. JIW holds the Canada Research Chair (Tier I) in Thrombosis and the Heart and Stroke Foundation J.F. Mustard Chair in Cardiovascular Research.

Conflicts of interest

Jeffrey I. Weitz: Honoraria from Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Ionis, Janssen, Merck, Portola, Pfizer. Sylvia Haas: Honoraria from Aspen, Bayer Healthcare, BMS, Daiichi, Sankyo, Pfizer, Sanofi. Walter Ageno: Honoraria from Boehringer-Ingelheim, Bayer Pharmaceuticals, BMS-Pfizer and Daiichi Sankyo. Research support from Bayer Pharmaceuticals and Boehringer-Ingelheim. Henri Bounameaux: Research grant, speaker's fees and honoraria for studies with edoxaban from Daiichi-Sankyo. Research grant, speaker's fees and honoraria for studies with rivaroxaban from Bayer Healthcare. Honoraria from Sanofi-Aventis. Samuel Z. Goldhaber: Grants from BiO2 Medical, Boehringer-Ingelheim, Bristol Myers Squibb, BTG EKOS, Daiichi Sankyo, National Heart Lung and Blood Institute of the National Institutes of Health, Janssen and the Thrombosis Research Group. Personal fees (all consultancy less than $10k) from Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Portola, Zafgen. Shinya Goto: Honoraria from Sanofi, AstraZeneca and Bayer. Research funding from Sanofi. Lorenzo Mantovani: Grants and personal fees from Bayer Healthcare, Boehringer-Ingelheim, Pfizer and Daiichi Sankyo. Paolo Prandoni: Personal fees from Bayer Pharma, Pfizer, Daiichi-Sankyo, Sanofi and Boehringer-Ingelheim. Sebastian Schellong: Speaker fees from Bayer Healthcare, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Sanofi Aventis and Pfizer. Consultancy fees from Bayer Healthcare, Boehringer-Ingelheim, Daiichi Sankyo, Sanofi Aventis and Pfizer. Alexander G.G. Turpie: Personal fees from Bayer Pharma AG, Janssen. Ajay K. Kakkar: Personal fees from Bayer Healthcare, Boehringer-Ingelheim, Daiichi Sankyo Europe, Sanofi S.A., Janssen. Research Grant from Bayer Healthcare. Pantep Angchaisuksiri, Joern Dalsgaard-Nielsen and Gloria Kayani declare that they have no conflicts of interest in the research.

References

1. Jha AK, Larizgoitia I, Audera-Lopez C, et al. The global burden of unsafe medical care: analytic modelling of observational studies. BMJ Qual Saf 2013; 22: 809–815.
2. Huang W, Goldberg RJ, Anderson FA, et al. Occurrence and predictors of recurrence after a first episode of acute venous thromboembolism: population-based Worcester Venous Thromboembolism Study. J Thromb Thrombolysis 2016; 41: 525-538.
3. Martinez C, Cohen AT, Bamber L, et al. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost 2014; 112: 255–263.
4. Galanaud JP, Sevestre MA, Genty C, et al. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. J Thromb Haemost 2014; 12: 436–443.
5. Poch DS, Auger WR. Chronic thromboembolic pulmonary hypertension: detection, medical and surgical treatment approach, and current outcomes. Heart Fail Rev 2016; 21: 309-322.
6. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 2005; 3: 1611–1617.
7. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. Thromb Haemost 2001; 86: 452–463.
8. Tagalakis V, Patenaude V, Kahn SR, et al. Treatment patterns of venous thromboembolism in a real-world population: the Q-VTE study cohort. Thromb Res 2014; 134: 795–802.
9. Cohen A, Chiu KM, Park K, et al. Managing venous thromboembolism in Asia: winds of change in the era of new oral anticoagulants. Thromb Res 2012; 130: 291–301.
10. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost 2007; 98: 756–764.
11. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998; 158: 585–593.
12. Zhu T, Martinez I, Emmerich J. Venous thromboembolism: risk factors for recurrence. Arterioscler Thromb Vasc Biol 2009; 29: 298–310.
13. Spencer FA, Gore JM, Lessard D, et al. Patient outcomes after deep vein thrombosis and pulmonary embolism: the Worcester Venous Thromboembolism Study. Arch Intern Med 2008; 168: 425–430.
14. Tick LW, Kramer MH, Rosendaal FR, et al. Risk factors for post-thrombotic syndrome in patients with a first deep venous thrombosis. J Thromb Haemost 2008; 6: 2075–2081.
15. Kahn SR, Kearon C, Julian JA, et al. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. J Thromb Haemost 2005; 3: 718–723.
16. Ruppert A, Steinle T, Lees M. Economic burden of venous thromboembolism: a systematic review. J Med Econ 2011; 14: 65–74.
17. Kahn SR, Elman EA, Bornais C, et al. Post-thrombotic syndrome, functional disability and quality of life after upper extremity deep venous thrombosis in adults. Thromb Haemost 2005; 93: 499–502.
18. MacDougall DA, Feliu AL, Boccuzzi SJ, et al. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. Am J Health Syst Pharm 2006; 63: S5–15.
19. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004; 350: 2257–2264.
20. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)Endorsed by the European Respiratory Society (ERS) 2014; 35: 3033–3073.
21. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 361: 2342–2352.
22. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012; 366: 1287–1297.
23. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013; 369: 799–808.
24. Buller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369: 1406–1415.
25. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499–2510.
26. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014; 129: 764–772.
27. Yamada N, Hirayama A, Maeda H, et al. Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism – the J-EINSTEIN DVT and PE program. Thromb J 2015; 13: 2.
28. Cano SJ, Lamping DL, Bamber L, et al. The Anti-Clot Treatment Scale (ACTS) in clinical trials: cross-cultural validation in venous thromboembolism patients. Health Qual Life Outcomes 2012; 10: 120.
29. Ageno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic

deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol 2016; 3: e12–21.
30. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev 2015; 12: Cd010957.
31. Cohen AT, Hamilton M, Mitchell SA, et al. Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis. PLoS One 2015; 10: e0144856.
32. Frank B, Ariza L, Lamparter H, et al. Rationale and design of three observational, prospective cohort studies including biobanking to evaluate and improve diagnostics, management strategies and risk stratification in venous thromboembolism: the VTEval Project. BMJ Open 2015; 5: e008157.
33. Agnelli G, Gitt AK, Bauersachs R, et al. The management of acute venous thromboembolism in clinical practice – study rationale and protocol of the European PREFER in VTE Registry. Thromb J 2015; 13: 41.
34. Tzoran I, Brenner B, Papadakis M, et al. VTE Registry: What Can Be Learned from RIETE? Rambam Maimonides Med J 2014; 5: e0037.
35. Beyer-Westendorf J, Forster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood 2014; 124: 955–962.