The management of acute venous thromboembolism in clinical practice – study rationale and protocol of the European PREFER in VTE Registry

Giancarlo Agnelli1, Anselm K. Gitt2, Rupert Bauersachs3,4, Eva-Maria Fronk5, Petra Laeis5, Patrick Mismetti6, Manuel Monreal7, Stefan N. Willich8, Wolf-Peter Wolf4, Alexander T. Cohen9* and On behalf of the PREFER in VTE investigators

Abstract

Background: Venous thromboembolism (VTE) is a major health problem, with over one million events every year in Europe. However, there is a paucity of data on the current management in real life, including factors influencing treatment pathways, patient satisfaction, quality of life (QoL), and utilization of health care resources and the corresponding costs. The PREFER in VTE registry has been designed to address this and to understand medical care and needs as well as potential gaps for improvement.

Methods/design: The PREFER in VTE registry was a prospective, observational, multicenter study conducted in seven European countries including Austria, France Germany, Italy, Spain, Switzerland, and the UK to assess the characteristics and the management of patients with VTE, the use of health care resources, and to provide data to estimate the costs for 12 months treatment following a first-time and/or recurrent VTE diagnosed in hospitals or specialized or primary care centers. In addition, existing anticoagulant treatment patterns, patient pathways, clinical outcomes, treatment satisfaction, and health related QoL were documented. The centers were chosen to reflect the care environment in which patients with VTE are managed in each of the participating countries. Patients were eligible to be enrolled into the registry if they were at least 18 years old, had a symptomatic, objectively confirmed first time or recurrent acute VTE defined as either distal or proximal deep vein thrombosis, pulmonary embolism or both. After the baseline visit at the time of the acute VTE event, further follow-up documentations occurred at 1, 3, 6 and 12 months. Follow-up data was collected by either routinely scheduled visits or by telephone calls.

Results: Overall, 381 centers participated, which enrolled 3,545 patients during an observational period of 1 year.

Conclusion: The PREFER in VTE registry will provide valuable insights into the characteristics of patients with VTE and their acute and mid-term management, as well as into drug utilization and the use of health care resources in acute first-time and/or recurrent VTE across Europe in clinical practice.

Keywords: Venous Thromboembolism, Anticoagulation, Vitamin K antagonists, Novel Oral Anticoagulants, Prevention, Registry
Background

Acute venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE) is a common disorder with an annual incidence of approximately 1 or 2 cases per 1000 persons in the general population [1–3]. Patients with DVT and PE have increased morbidity and mortality both related to these conditions and also associated co-morbidities such as cancer, medical conditions and surgical procedures [4]. The main objective of anticoagulant therapy for patients with acute VTE is to prevent thrombus extension, embolization and recurrences. According to current practice guidelines the management of patients with acute VTE consists of an initial treatment with bodyweight-adjusted subcutaneous low molecular weight heparin (LMWH); adjusted-dose intravenous or fixed dose subcutaneous unfractionated heparin (UFH); or bodyweight-adjusted subcutaneous fondaparinux followed by long-term treatment with a vitamin K antagonist (VKA) or non-VKA oral anticoagulants (NOACs) [5]. For the treatment of PE the current 2014 European Society of Cardiology Guidelines on the diagnosis and management of acute PE recommend the use of NOACs as alternatives to VKAs [6].

Patients should receive parenteral anticoagulants (either LMWH or UFH or fondaparinux) for at least five days. It is recommended to start VKA on the first treatment day because of the slow onset of action. LMWH, UFH, or fondaparinux therapy may be discontinued when the VKA has reached its therapeutic level as indicated by an international normalized ratio (INR) ≥ 2 at two or more measurements at least 24 h apart. VKA therapy should be continued for at least 3 months. For most patients with a DVT and/or PE secondary to a transient risk factor the currently recommended duration of treatment is sufficient, although extension by another 3 to 6 months of therapy may be indicated in some patients [3]. However, for those with unprovoked DVT or PE, the recommendation is to evaluate the risks and benefits for prolonged therapy. In either case, the VKA dosage regimen needs to be adjusted to maintain the INR in the therapeutic range (target 2.5, range 2.0 to 3.0).

VKAs (such as the coumarins: warfarin, acenocoumarol or phenprocoumon) are indirect coagulation inhibitors, which act by blocking the vitamin K-dependent liver synthesis of the plasma coagulation factors II, VII, IX and X. They were the only oral anticoagulants available for over 50 years. Randomized controlled trials have shown that warfarin, the most commonly used VKA, targeted to an INR between 2.0 and 3.0, reduces the risk of recurrent venous thromboembolic complications in subjects with DVT or PE by 80% to 90% [5,7–9]. However, the use of VKAs is complicated by several inherent problems including a delayed onset of antithrombotic action; a narrow therapeutic window that requires close laboratory monitoring using the INR; an unpredictable and variable pharmacological response; and food and drug interactions requiring frequent monitoring and dosage adjustment [10].

Recently developed oral anticoagulants that are directed against factor Xa or thrombin (factor IIa) overcome some limitations of standard therapy including the need for injections of parenteral anticoagulants and for regular dose adjustments on the basis of laboratory monitoring [11–13]. However, VKAs are still often prescribed and although NOACs are widely approved in Europe, use of NOACs is limited by national guidelines and reimbursement. In Europe, little is known about which factors influence the individual VTE patients’ utilization of health care resources and the corresponding costs derived in hospitals, out of hospitals or in specialized centres during the period between confirmed first-time or recurrent VTE treatment and 12 months of follow-up.

Study aims

The key aims of the PREFER in VTE registry were to assess the real-life acute and mid-term management of patients with VTE, the use of health care resources, and to provide data to estimate the costs for 12-months treatment following a first-time and/or recurrent VTE diagnosis in hospitals or specialized centers in Europe.

In addition, existing anticoagulant treatment patterns, patient pathways, clinical outcomes, treatment satisfaction, and health related quality of life (HR-QoL) were documented.

Primary objectives

The primary objective of this registry was to assess the 12-months direct healthcare resource use and to provide data to estimate the costs following an acute first time or recurrent VTE. In addition, detailed insights into the patients’ characteristics, the management of acute VTE (in particular DVT and/or PE) with specific focus on prevention of VTE recurrences and its treatment-related events such as bleeding, recurrence of DVT/PE, myocardial infarction, stroke, systemic embolic events, post thrombotic syndrome, cardiovascular (CV) events, and death were collected. DVT was defined as DVT alone and PE as PE with or without DVT.

Secondary objectives

The secondary objectives of this study were to 1) describe the treatment satisfaction, HR-QoL, and clinical outcomes following first time or recurrent VTE; 2) to explore the potential relationships between different anticoagulants and duration of therapy, resource use,
estimated costs, treatment satisfaction, HR-QoL, and clinical outcomes; 3) to explore possible geographic variations in the management of VTE patients, duration of therapy, resource use, estimated costs and treatment satisfaction.

Methods and design
The PREFER in VTE registry was a prospective, observational, multicenter study with a follow-up of 12 months and enrolled 3,545 consecutive patients who gave informed consent from 381 centers (311 active centers enrolling ≥1 patient) in seven European countries including Austria, France, Germany, Italy, Spain, Switzerland, and the UK between January 2013 and July 2014. Data were recorded at baseline of the acute VTE and prospectively documented during follow-up at 1, 3, 6 and 12 months (Fig. 1).

Patient information was collected from two different sources: collection of baseline data took place in the hospitals or specialized centers at the time of the diagnosis of the acute VTE. Hospitals or specialized/primary care centers could also opt to follow-up the patients at 1 month. As hospital based investigators do not always see the patient during the following 12 months as part of the routine clinical care, patients were followed by telephone calls. Patients agreed to provide contact details for the planned follow-up calls with the permission to hand the contact details over to the respective local contact research organization (CRO).

This registry was conducted in accordance with the Declaration of Helsinki and adheres to the principles of Good Epidemiology Practice, and applicable regulatory requirements. The responsible ethics committees of the participating countries and the hospital-based institutional review boards approved the protocol of this registry. Patients enrolled into this registry provided written informed consent. Due to the nature of a non-interventional registry, no specific treatments, tests, or procedures were mandated or withheld from the patients. Treatment pattern and treatment initiation, continuation or changes were solely at the discretion of the physician and the patient. There was no attempt to influence the prescribing patterns of any individual treating physician. All medication was prescribed in the usual standard of care and was not provided by the study sponsor. Participation in the study in no way influenced payment or reimbursement for any treatment received by patients during the study. Patients were free to withdraw from the registry at any time.

Selection of sites
Investigator sites were representative for the specific local distribution of primary and secondary care settings in each participating country. A sufficient number of sites were identified including hospitals and specialized centers to best represent current practice of VTE diagnosis and treatment in each particular country. Most centers contacted for participation were randomly selected, others were chosen from experienced centers and all centers were asked to provide institutional details in a short site feasibility questionnaire before being selected. Each active site consecutively recruited at least 1 and up to 60 patients. The enrollment period was 12 months.

Selection of patients
Patients from Austria, France, Germany, Italy, Spain, Switzerland and the UK who gave written informed consent were consecutively enrolled into the registry in hospitals or specialized centers if they were at least 18 years old, had a confirmed first time or recurrent symptomatic VTE defined as either distal or proximal DVT, PE [3] or both, provided telephone contact details for follow-up calls, and were not simultaneously participating in a double blind interventional study.

We expect the parameters measured will vary between patients on the conventional pathway of treatment and those using NOACs and therefore the comparison between those following the conventional pathway and those on the NOACs and the impact of NOACs on QoL, Resource consumption and mostly health care utilization will be examined.

The study aimed to achieve a general ratio of PE:DVT which was approximately 2:3 resulting in a total number of PE (with or without DVT) patients
of \( n = 1,399 \) and a total number of patients with DVT (distal or proximal) of \( n = 2,056 \) (Fig. 2).

**Documented variables**
The enrolling study site documented all patient related baseline data at the time of the acute VTE. The follow-up calls were performed centrally by local CROs. The CROs used standardized questionnaires to get all required information (i.e. recurrence of VTE, bleeding, post-thrombotic syndrome, death, hospitalization, as well as medications and treatments, QoL and patient satisfaction (Perception of Anticoagulant Treatment Questionnaire 2 [PACT-Q2], Venous Insufficiency Epidemiological and Economic Study [Veines-QoL/Sym] or Pulmonary Embolism Quality of Life [PEmb-QoL]), resource consumption / health care utilization). Patient diaries were distributed to facilitate the standardized structured phone calls. The treatment satisfaction questionnaire (PACT-Q2), the disease specific questionnaire (PEmb-QoL or Veines-QoL/Sym) and the QoL questionnaire (EQ 5D–5L) were filled out at baseline, and repeated by post at 1, 3, 6 and 12 months after first diagnosis of acute VTE.

Table 1 displays the variables documented at baseline and at the follow-up visits at 1, 3, 6 and 12 months. The data sources used in this study were clinical records, self-reports, claims, and data from telephone interviews.

**Patients’ treatment satisfaction and quality of life**
Data on patients’ treatment satisfaction and QoL were documented using specific patient-questionnaires. The following questionnaires were part of the evaluation:

**Quality of Life Questionnaire (EQ 5D–5L)**
EQ 5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic assessment [14]. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

**Treatment Satisfaction Questionnaire**
Anticoagulation-specific questionnaire PACT-Q. The ‘Perception of AntiCoagulant Treatment Questionnaire’ was developed to assess patients’ expectations of, and satisfaction with their anticoagulant treatment [15–17].

**Veines-QoL/Sym**
The Veines-QoL/Sym is a patient-based questionnaire designed for self-completion and measures the impact of DVT on symptoms and QoL from the patient’s perspective; this was only completed by patients with DVT [18].

**PEmb-QoL**
The PEmb-QoL questionnaire was modeled on the QoL after DVT (Veines-QoL/Sym) questionnaire. This questionnaire, like the Veines-QoL/Sym, assesses the frequency of symptoms, the time of day which the complaints are their worst, and activities of daily living, as well as work-related problems. However, the PEmb-QoL questionnaire is distinct from the Veines-QoL/Sym in the inclusion of pulmonary-specific symptoms, adding questions on limitations in daily physical activities, and
extending the number of questions on emotional functioning [19].

The PEmb-QoL was only filled out by patients with PE.

**Data management and quality control**

Data entry was performed by the physician or study nurse via a secure website directly into an electronic database. This approach allowed online checks for plausibility and integrity.

There were three strategies for data quality checks: validations that occurred at the time of data entry (i.e., “front-end”), a second, more sophisticated quality control program that ran as a prelude to the creation of the analysis data set and on-site data monitoring by the CRO.

Front-end data checks are advantageous because mistakes are caught and corrected at the time of entry. Certain data elements can be required, while other elements may allow missing values. Additionally, parameters were defined to allow entry of only those records that met the inclusion criteria.

Thirdly, prior to the creation of the analytic dataset, more extensive quality control processes were performed. These checks, programmed in SAS (release 9.2 or higher; Cary, NC, USA), included parent–child edits, consistency edits, and data transformations that facilitated analyses.

**Sample size**

In order to provide meaningful data on reimbursement from different agencies in each participating country, and because significant variation was expected between countries, special care was taken to determine a suitable sample size of patients for each country. As costs are difficult to determine directly and are mostly triggered by the hospitalization of the patients, the sample size calculation was based on the rate of adverse events (AEs) leading to, or prolonging, hospitalization.

Assuming a rate for the AEs that are leading to or prolonging hospitalization and an absolute precision Δ, the sample size N is calculated which is needed if the respective 95% confidence interval (CI) should have a length/precision of 2Δ (±Δ). Concretely, for DVT a

| Variable | Baseline | Follow Up |
|----------|----------|-----------|
| Eligibility criteria | X | | |
| Baseline information | X | | |
| VTE risk factors and co-morbidities | X | | |
| Baseline information on VTE | X | | |
| VTE therapy | X X X X X | |
| Current and previous treatment for prevention of stroke and other thromboembolic events | X X X X X | |
| Quality of life | X X X X X | |
| Patient satisfaction | X X X X X | |
| PEmb-QoL Questionnaire (only PE-patients) | X X X X X | |
| Veines-QoL/Sym Questionnaire (only DVT-patients) | X X X X X | |
| Resource utilization | X X X X X | |
| Clinical events and hospitalizations | X X X X X | |
| Number of days in hospital, work days lost due to VTE, need for nursing/informal help | X X X X X | |

Legend

(1) Objectively confirmed first-time or recurrent VTE; age ≥ 18 years, written informed consent
(2) (Socio-) demographic variables: age, gender, height, weight, BMI, blood pressure, education, employment status, insurance status
(3) Major surgery, bleeding history medical illnesses, multiple trauma, hip fracture, lower extremity paralysis, previous VTE, increasing age, cardiovascular or respiratory failure, prolonged immobility, presence of central venous illness, estrogens, wide Variety of inherited and acquired hematological conditions, cancer, chemotherapy etc.
(4) Date of first diagnosis, lead symptoms, diagnostic pathways, severity
(5) Thrombolysis, Heparin, Vitamin K Antagonist, Embolectomy, Catheter, Insertion of V.cava filter
(6) Physician’s clinical impression of the risk of stroke/ thromboembolic events; physician’s use of algorithm to determine risk; current anticoagulation (by drug, with information on continuation after the visit); discontinued anticoagulation (last 12 months); (Relative) contraindications to anticoagulation; INR (target and achieved value, frequency of tests, percentage of values within target range) D
(7) EQ-5D
(8) PACT-Q2
(9) Number of physician contacts (own office, other physicians); VTE related productivity loss and costs; number and type of VTE diagnostic tests since last visit/call
(10) Specifically due to: VTE, stroke, acute coronary syndrome including myocardial infarction, arterial embolism, decompensated heart failure, syncope, bleeding events
hospitalization rate of 12.3% was assumed [15], while for PE a hospitalization rate of 17.9% was taken [16]. Furthermore, for DVT as well as for PE, a relative precision of 25% was assumed which corresponded to an absolute precision of 0.031 for DVT and an absolute precision for PE of 0.045. Based on these assumptions a minimum of 432 evaluable DVT patients were needed while for PE a minimum of 279 evaluable patients were needed (Table 2). Taking into account a dropout rate of 20% and being aware of the fact that DVT and PE patients were recruited in a ratio of 3:2 (DVT: PE), this resulted in a total of 900 patients recruited (= 540 DVT patients + 360 PE patients) in each region and 4,500 patients in the overall registry. The above sample size consideration is taken from the observational plan and was made before the start of the study. The primary parameters of interest were the “costs” and the “rate for AEs leading to or prolonging hospitalization” was taken as the main trigger for this very general parameter. Therefore, the sample size consideration should be taken as a general guidance and needs to be interpreted in a flexible way. Based on real-life experience, in general a sample of ~600 patients is considered as robust enough for reliable cost estimations.

**Statistical analysis**

This registry collected data under real life conditions. The statistical analysis was performed in an explorative and descriptive way. All variables collected in the electronic case report form as well as the data obtained from the QoL assessments and all derived parameters were used in the statistical analysis.

Binary, categorical, and ordinal parameters were summarized by means of absolute and percentage numbers within the various categories.

Numerical data was summarized by means of standard statistics (i.e. number of available data, number of missing data, mean, standard deviation, minimum, median, maximum, lower and upper quartile).

Time-to-event variables were analyzed via a Cox proportional hazard regression model presenting hazard ratios and the corresponding 95% CIs. No formal statistical tests were performed within the statistical analysis.

A biometrical report using descriptive statistics of all documented parameters was used to describe the overall patient population as well as for each participating country or by region. Patients violating any inclusion/exclusion criteria were identified and documented. There were several variables of interest for additional analyses including: gender, age, weight, diabetes. Details on the selection criteria used were given in the statistical analysis plan and in the statistical section of the report.

As the registry was exploratory in nature, and no hypothesis testing was conducted, there were no significance levels to be adjusted, and there was no requirement to provide stopping rules for the study.

The statistical analysis was performed using SAS (release 9.2 or higher; Cary, NC, USA).

**Discussion**

Little is known about populations of unselected patients with VTE. In Europe there is only minimal data describing individual patient characteristics, management patterns, factors influencing health care resource utilization and the corresponding costs. For completeness these data need to be derived from confirmed cases within hospitals, out of hospitals, in primary care or in specialized centers. The critical period for recurrences and bleeding is the time between first diagnosis and the following 12 months. Including unselected patients with both first time and recurrent VTE allows the burden of disease to be quantified.

The PREFER in VTE registry will help to get a detailed insight into the characteristics and management of patients with VTE (DVT and/or PE) with focus on prevention of events (bleeding, recurrence of DVT; recurrence of PE, post thrombotic syndrome, CV events, other complications and death) in a real life setting. Data were collected from VTE patients during the acute event and followed by an observational period of up to 1 year and were used to assess direct healthcare resource use and estimated costs following acute first-time or recurrent VTE. Patients were therefore treated on the discretion of the physician in charge according to their regular medical care.

In the past, most of the published information on the current therapy and natural history of patients with VTE comes from randomized clinical trials, with strict inclusion and exclusion criteria, fixed doses of anticoagulant drugs, and limited follow-up, mostly focused to obtain data on efficacy and safety. However, a number of

|               | Assumed rate of AE leading to, or prolonging hospitalization | Assumed absolute precision (relative precision) | Sample size (without drop-outs) | Sample size (including drop-outs) |
|---------------|-------------------------------------------------------------|-----------------------------------------------|--------------------------------|----------------------------------|
| DVT           | 0.123                                                       | 0.031 (± 25%)                                  | 432                            | 540                              |
| PE            | 0.179                                                       | 0.045 (± 25%)                                  | 279                            | 349                              |

Sample size (for each region) for the assumed rate of AEs leading to, or prolonging hospitalization 0.123 (DVT) and 0.179 (PE) in order to achieve an absolute precision of 0.031 (DVT) and 0.045 (PE) for a two-sided 95% CI. (Based on normal approximation, calculated by nQuery Advisor® 7.0). AE, adverse event.
patients with VTE are never recruited in clinical trials, particularly, the very young, the very elderly, the pregnant, those with multiple comorbidities, those with a high risk of bleeding and those with polypharmacy. Also there is scarce information on the current therapy in real life (drugs, doses, duration and approach to patients with VTE recurrences and/or bleeding complications). There is also limited information regarding the QoL, utilization of resources, costs, satisfaction of the patient and influence of their willing on the duration of therapy. This information may be very useful for patients, clinicians, healthcare providers, health technology assessors and to the pharmaceutical industry, who will all benefit from the data about many aspects of VTE not previously considered in detail in a broad unselected population. Currently, PREFER in VTE is the only registry evaluating the management of acute VTE in Europe; on an international level, the management of acute VTE has been assessed in the RIETE registry and in the ongoing GARFIELD-VTE registry [20,21].

The observational PREFER in VTE registry aims to address these questions by describing the current anticoagulant treatment patterns, pathways of clinical care, clinical outcomes as well as patient’s treatment satisfaction and HR-QoL in a real world setting. Real life data are of utmost importance to collect information on the safety, efficacy and drug utilization of any novel drug and to link the data with the regulatory mandated phase III data. This is an important stage in the observation and stringent control of all novel drugs. Therefore, there is a need for a European Union wide, international observational registry of VTE patients treated in everyday clinical practice to provide complementary data to that from the trials and to fully understand the treatment pathway of patients.

This large, European registry of acute VTE patients allows the opportunity to answer several research questions that have not previously been investigated within a non-randomized, non-selected population. These questions will address the following six areas:

1. Patient characteristics of consecutive patients with acute VTE in clinical practice including comorbidities, history of thromboembolic/bleeding events, temporary and permanent risk factors including severe medical disorders and interventions with VTE risk
2. Diagnosis of acute VTE (first-time [initial] or recurrent) including timing, symptoms and signs, clinical status and severity
3. Patient pathways including referral details and related time intervals (from primary to secondary care, e.g., internist, hematologist, vascular surgeon or physician, cardiologist and/or hospital) as well as diagnostic pathways
4. Drug utilization/use pattern of drugs for treatment of VTE and prevention of related events
5. Health related quality of life including patient satisfaction and real-world assessments of quality of life
6. Resource consumption/Health care utilization.

Conclusions
The PREFER in VTE registry will provide valuable insights into all these factors in patients with VTE and their acute and mid-term management. The study will provide the opportunity to identify differences in management and outcomes across care settings, and will offer clarity relating to the effectiveness of anticoagulation treatment strategies to treat acute VTE and to prevent recurrent VTE events.

Appendix
List of PREFER in VTE investigators.

Austria
Marianne Brodmann, Peter Rief, Universitätsklinikum Graz, Graz; Lisbeth Eischer, Slagjana Stoshij, Medizinische Universität Wien, Wien; Michael Hirschl, Serge Weinmann, Landesklinikum Zwettl, Zwettl; Peter Marschang, Universitätsklinik Innsbruck für Innere Medizin, Innsbruck.

France
Fabrice Abbadie, Centre hospitalier Jacques Lacarin, Vichy; Antoine Achkar, CH Eure et Seine – Site de Vernon, Vernon; Azeddine Addala, Perrone Reynaldo, Lyon; Frédéric Adnet, Hopital Avicenne, Bobigny; Jean-François Alexandra, Hopital Bichat Claude Bernard, Paris; Sandro Aquilanti, Espace ARTOIS Santé, Arras; Abdelkader Belhassane, Centre Hospitalier de Cambrai, Cambrai Cedex; Anne Benaroya, Pole Sante Des Aspres, Thuir; Toufek Berremili, Marie Chevallier Grenot, CH Annecy Genevois, Pringy Cedex; Virginie Birr, Daniela Holtea, CHU Emile Muller, Mulhouse Cedex; Christophe Bonnin, Le Gibraltar 10–12, Nice; Frederic Bosler, 19 rue Robert Schumann, Sarrebourg; Marie-Gabrielle Bresin Durand, Résid des remparts 7 rue des lombards, Hennebont; Dominique Brisot, Centre Commercial La Croisée, Clapiers; Christophe Brousse, Tarodo De La Fuente, Clinique Du Parc, Castelnau-le-Lez; Richard Cayman, 8 rue des des de l’aire, Bourgoin Jallieu; Michèle Cazaubon, 17, rue Mesnil, Paris; Olivier Champion, 6 Avenue Georges Pompidou, Chalon-sur-Saône; Myriam Chanut, Immeuble Le Clos de Bellande, Aubenas; Pascal Chevalet, Hopital Bellier, Nantes; Jerome Connault, Cecile Durant, CHU Hôtel-
Dieu de Nantes, Nantes; Joel Constans, Hopital St Andre, Bordeaux; Mihaela Cordeau, CHRU Strasbourg, Strasbourg; Francis Couturaud, Karine Lacut, CHRU Hopital Cavale Blanche, Brest; Laure De Dedeker, François Xavier Piloquet, Hôpital Nord Laennec, Saint Herblain; Eric Decoux, Centre Hospitalier de Tourcoing, Tourcoing; Benoit Derrien, Centre Hospitalier, Le Mans Cedex 9; Jean-Marc Diamand, Centre De Medecine Vasculaire, Grenoble; Antoine Diard, 25 Route De Creon, Langoiran; Youssef Douadi, Centre Hospitalier De Saint Quentin, St Quentin; Stephanie Dupas, Santhi Samy Modelier Remond, Marie-Antoinette Sevestre, CHU Amiens Picardie - L’Hôpital Nord, Amiens Cedex 1; Stéphane Edhery, Hôpital Saint Antoine, Paris; Nicolas Falvo CHU Dijon Service De Medecine Interne, Dijon; Claudia Farcas Taralunga, Hôpital Saint Charles, Toulu; Emilie Ferrari, Hôpital Pasteur, Nice; Catherine Gaillard, 14 rue Maurice Devillers, Peronne; Damien Garrigues, Clinique Monie, Villefranche-de-Lauragais; Jean Luc Gillet, 51BIS Avenue Professeur Tixier, Bourgoin Jallieu; Pascal Giordana, L’emprise 29, Boulevard Dubouchage, Nice; Claire Grange, Denis Vital-Durand, Hopital Lyon Sud, Pierre Berite; Frédéric Grare, Espace Medical Torremila, Perpignan; Amine Hadj Henni, CHU Robert-Debré, Reims; Christine Jurus, Clinique du Tonkin, Villeurbanne; Amelie Lacoste, 10, rue Abert Camus, Pontarlier; Jean-Pierre Laroche, Médipôle, Avignon; Myriam Martin, 13 Rue De La Poste, Annecy; Cyrille Mazollier, Pôle Médical, Université J. Fourier, Grenoble; François Xavier Mestres, Clinique Abdou, Universitäts-Hautklinik Hamburg, Hamburg; Thierry Michel, Centre AEGIS, Nantes; Ingrid Michel, Aegina, Paris; Marie-Hélène Michel, Hopital Esquemard, Le Châtelet; Danielle Miquel, L’Aubépine, Rennes; Poulain, 19 rue Vimaine, Vienne; Patrick Ray, Hopital Thonon, Paris; Abed Rifai, Centre Hospitalier, Arras; Pierre-Marie Roy, Angers; Jean-Claude Saby, Clinique du Tonkin, Villeurbanne; Hubert Vodounnon, Hôpital de Dunckerque, Dunkerque.

Germany
Annette Adamczyk, Saskia Schnabl, Universitäts-Hautklinik Tübingen, Tübingen; Wail Al Ahmad, Heinz Weber; Sozial-stiftung Bamberg, Bamberg; Christoph Axthelm, Praxis Axthelm, Pirna; Rupert Bauersachs, Klinikum Darmstadt, Darmstadt; Klaus Bergmann, Nägelsbachstraße 49 c, Erlangen; Ulrich Beschorner, Matthias Knittel, Herzcenter Bad Kreuzingen, Bad Kreuzingen; Karl-Heinz Binias, Martin Pasligh, Ameos Klinikum Schönebeck, Schönebeck; Mehmet Boral, Friederike, Girke, Vivantes Klinikum Neukölln, Berlin; Hermann Bratsch, P7, 13, Mannheim; Gunter Brauer, Berliner Str. 158, Cottbus; Sebastian Burghard, Carl-von-Basedow-Klinikum, Merseburg; Christiane Demann, Carsten Rennebaum, Praxis Emter/ Rennbaum/Demann, Hannover; Anita Demmig, Lindeallee 7, Hoppegarten; Ulrich Eberlein, Ketschengasse 22-24, Coburg; Frank Enger, MVZ Nibelungen (Enger), Bieleheim; Jens, Eschenburg, Jens-Uwe Eschenburg, Neubrandenburg; Lutz Forckmann, MVZ Polymed Forckmann, Chemnitz; Jürgen Frank, In der Schaf 14, Baesweiler; Holger Freischmidt, Martin Gassauer, BGU Ludwigshafen, Ludwigshafen; Ilona Fritsche, Cornelia Kubicke-Hofmann, Vivantes Klinikum im Friedrichshain, Berlin; Mark-Clausdius Goebels, Marien-Hospital Euskirchen, Euskirchen; Stephan Guggenbichler, Stephan Guggenbichler, Frauenstrasse 17, München; Dirk Hättel, Klinikum Detmold, Detmold; Karsten Hartmann, Venenenzentrum Freiburg, Freiburg; Peter, Heilberger, Heilberger, Schweinauer Hauptstr. 12, Nürnberg; Andreas Heinsius, Jüdisches Krankenhaus Berlin, Berlin; Michael Held, Steffen Schnupp, Klinikum Coburg, Coburg; Georg Herman, Am Finkenhügel 1, Osnabrück; Jörg Herold, Universitätsklinikum Magdeburg, Magdeburg; Frank Hertrich, Am Bahnhof 6, Lebach; Henrike Hommel, Privatklinik Robert Schindlbeck, Herrsching; Guntram Hütte, Christoph Kalka, Marienhospital Brühl, Brühl; Katja Jungandreas, Mathias Ramthor, Vivantes Humboldt Klinikum, Berlin; Jan Karcher, Nicolas Werner, Klinikum Ludwigshafen, Ludwigshafen; Susanne Karl-Wollweber, BGU Ludwigshafen, Ludwigshafen; Martin Pasligh, Ameos Klinikum Schönebeck, Schönebeck; Sebastian Werth, Uniklinik Dresden, Dresden; Ute Kopplin, Kirchplatz 10a, Bad Salzungen; Ines Körner, Kathrin Wittig, Praxis Dres. Wittig/Rühlmann/Körner, Leipzig; Knut Kröger, Theodoros Moysidis, Helios Klinik Krefeld, Krefeld; Ulf Kroschel, Herzklinik Ulm, Ulm; Matthias Leschke, Tim zu den Norden, Klinikum Esslingen, Esslingen; Gerhard Lübbert, Krankenhaus Neu-Marienfeld, Marienhospital Brühl, Brühl; Privatklinik Robert Schindlbeck, Herrsching; Guntram Hütte, Christoph Kalka, Marienhospital Brühl, Brühl; Katja Jungandreas, Mathias Ramthor, Vivantes Humboldt Klinikum, Berlin; Jan Karcher, Nicolas Werner, Klinikum Ludwigshafen, Ludwigshafen; Susanne Karl-Wollweber, BGU Ludwigshafen, Ludwigshafen; Martin Pasligh, Ameos Klinikum Schönebeck, Schönebeck; Sebastian Werth, Uniklinik Dresden, Dresden; Ute Kopplin, Kirchplatz 10a, Bad Salzungen; Ines Körner, Kathrin Wittig, Praxis Dres. Wittig/Rühlmann/Körner, Leipzig; Knut Kröger, Theodoros Moysidis, Helios Klinik Krefeld, Krefeld; Ulf Kroschel, Herzklinik Ulm, Ulm; Matthias Leschke, Tim zu den Norden, Klinikum Esslingen, Esslingen; Gerhard Lübbert, Krankenhaus Neu-Marienfeld, Marienhospital Brühl, Brühl; Privatklinik Robert Schindlbeck, Herrsching; Guntram Hütte, Christoph Kalka, Marienhospital Brühl, Brühl; Katja Jungandreas, Mathias Ramthor, Vivantes Humboldt Klinikum, Berlin; Jan Karcher, Nicolas Werner, Klinikum Ludwigshafen, Ludwigshafen; Susanne Karl-Wollweber, BGU Ludwigshafen, Ludwigshafen; Martin Pasligh, Ameos Klinikum Schönebeck, Schönebeck; Sebastian Werth, Uniklinik Dresden, Dresden; Ute Kopplin, Kirchplatz 10a, Bad Salzungen; Ines Körner, Kathrin Wittig, Praxis Dres. Wittig/Rühlmann/Körner, Leipzig; Knut Kröger, Theodoros Moysidis, Helios Klinik Krefeld, Krefeld; Ulf Kroschel, Herzklinik Ulm, Ulm; Matthias Leschke, Tim zu den Norden, Klinikum Esslingen, Esslingen; Gerhard Lübbert, Krankenhaus Neu-Marienfeld, Marienhospital Brühl, Brühl; Privatklinik Robert Schindlbeck, Herrsching; Guntram Hütte, Christoph Kalka, Marienhospital Brühl, Brühl; Katja Jungandreas, Mathias Ramthor, Vivantes Humbold...
Lindenaustr. 5, Altenburg; Kay Nestler, Kleiststr. 5, Grimma; Axel Neumeister, Alexander Schlosser, Helios Klinikum Erfurt, Erfurt; Wolfram Oettler, Carolusstr. 214, Görlitz; Ilka Ott, Deutsches Herzzentrum München, München; Annegret Otto, Alexander-Puschkin-Platz 4c, Riesa; Astrid Pertermann, Polimed Leipzig, Leipzig; Rahel Pfister, Kaiser-Joseph-Str. 262, Freiburg; Lukas Pindur, Gefäßpraxis Leverkusen – Linz, Leverkusen; Siamak Pourhassan, Chirurgische Gemeinschaftspraxis, Klosterstr. 12, Oberhausen; Diethard Predel, Grimmelallee 2c, Nordhausen; Thomas Pudollek, Wiesenstr. 1, Berndorf; Dietrich Reimer, Julius-Lübke-Str. 13, Anderbeck; Cornelia Richter, R 1, 2-3, Mannheim; Eberhard Rieker, S 29, Lauffen; Gabriele Rothenbüber, Zeppelinstraße 16, Dornstadt; Brigitte Rothhagen, Gothaer Straße 1, Waltershausen; Simone Rudolf, Markus Stücker, Maria-Hilf-Kh Bochum (Venenzentrum), Bochum; Andreas Schäfer, Kristina Sonnenschein, Medizinische Hochschule Hannover, Hannover; Wolfgang Schafnitzl, Mönchebergstr. 18, Hamburg; Sebastian Schellong, Birgit Voigts, Krankenhaus Dresden-Friedrichstadt, Dresden; Martin Schiller, Klinikum Ingolstadt, Ingolstadt; Thomas Schmeink, Praxis Schmeink, Aachen; Henrik Schneider, Sana Hanse Klinikum Wismar, Wismar; Norbert Schön, Töginger Straße 27, Mühldorf; Matthias Schulze, Asklepios Klinikum Schwalmstadt, Schwalmstadt; Udo Schumacher, RK Stuttg, Stuttgart; Sabine Sedl, Feldstraße 23a, Schönberg; Harriet Simone Werno, Parcsid medical center – Harriet Simone Werno, Nürnbèrg; Jörg Stachowitz, St. Johannis-stift Paderborn, Paderborn; Marcus Thieme, Medinos Klinik Sonneberg, Sonneberg; Christiane Tiefenbacher, Marien-Hospital Wesel, Wesel; Dimitrios Tsantilas, Halderstraße 23, Augsburg; Petra Vieth, Marienhospital Steinfurt, Steinfurt; Jürgen vom Dahl, Katharina Grün-Himmelmann, Krankenhaus St. Franziskus Mönchengladbach, Mönchengladbach; Peter von Bilderling, Thordis von Maltik, Gefäßpraxis München – Mietasch, München; Katrin Weinrich, Klinikum Augsburg, Augsburg; Marc Weyer, Eduardus Krankenhaus, Köln, Marc Weyer, DRK Kamillus Klinik, Asbach; Peter Wirtz, Kreiskrankenhaus Mechernich, Mechernich; Ina Wittig, Käthe-Kollwitz-Straße 9, Leipzig; Petra Zierock, Vivantes Klinikum Spandau, Berlin.

**Italy**

Walter Agneni, Monica Caprioli, Elena Rancan, U.O. Medicina Interna I, Varese; Giancarlo Agnelli, Francesco Guercini, Valeria Mommi, Dipartimento di Medicina Interna e Vascolare, Perugia (PG); Maria Amitrano, Francesca Cannavacciuolo, Dipartimento Medicina Interna, Avellino; Maurizio Amore, Sebastiano D’Antoni, Ospedale Vittorio Emanuele II, Catania; Ermanno Angelini, Saverio La Forgia, Cardiologia-UTIC, Brindisi (BR); Pier Luigi Antignani, Giuseppe Calandra, Centro Vascolare, Roma; Andrea Arone, Francesco Perticone, Angela Sciacqua, Unità Operativa di Malattie Cardiovascolari Policlinico Mater Domini di Catanzaro, Catanzaro; Giovanni Asaro, Mario Bellisi, U.O. Chirurgia Vascolare, Palermo; Maria Teresa Attanzio, Antonio Pinto, U.O.C. Medicina Vascolare, Palermo; Valerio Attinasi, Enrico Cilliari, Sabrina Solvillo, P.O. Cervello, Palermo; Alberto Balbarini, Claudia Santini, Caterina Violo, U.O. Cardio-Angiologia Universitaria, Pisa; Elena Banfi, Corrado Lodigiani, Istituto di Ricovero e Cura a Carattere Scientifico – Istituto Clinico Humanitas, Rozzano (MI); Doris Barcellona, Stefano Delpin, Silvia Marongiu, Medicina interna 1 e emocoagulopati, Monserrato (Cagliari); Giovanni Barilli, Samantha Pasca, Azienda Ospedaliero Universitaria S. Maria della Misericordia, Udine; Claudia Bartolini, Paolo Verdecchia, Ospedale di Assisi, Assisi (PG); Mosè Bartone, Gerardo Mancuso, Unità Operativa Complessa di Medicina Interna - Presidio Ospedaliero “Giovanni Paolo II”, Lamezia Terme (CZ); Ignazio Bellanuova, Salvatore Felis, Ospedale Garibaldi Centro – Catania, CATANIA (Catania); Annamaria Bellizzi, Luca Masotti, AUSL 6 di Livorno, Cecina (LI); Marina Bianchi, Anna Carugati, Ospedale Valduce, Como; Giuseppe Bianchini, Giorgio Guarnera, Istituto Dermatologico dell’Immacolata, ROMA; Benedetta Boari, Massimo Gallerani, Mauro Pasin, Arcispedale Sant’Anna di Ferrara, Ferrara; Cristiano Bortoluzzi, Roberto Parisi, U.O. Semplice dipartimentale di Angiologia, Venezia; Caterina Brucoli, Giuseppe Palasciano, U.O. Medicina Interna Ospedaliera “Ferrarinini-Pende”, Bari; Giuseppe Camporese, Chiara Tonello, Azienda Ospedaliera di Padova, Padova; Lucia Canafoglia, Serena Rupoli, Clinica di Ematologia, Torrette di Ancona (ANCONA); Emilia Cancellieri, Oriana Paoletti, Sophie Testa, AO Istituti Ospitalieri di Cremona, Cremona; Anita Carlizza, Ospedale S. Giovanni dell’Addolorata, Roma; Marino Carovali, Simona Sada, Anna Samaden, Azienda Ospedaliera “Guido Salvini”, Milano; Chiara Casarsa, Filippo Mearelli, Giulia Pivoti, S.C. Clinica Medica, Trieste; Roberto Catalini, Oriana Zingaretti, Medicina Vascolare, Torrette di Ancona (ANCONA); Stefania Cavazza, Benilde Cosmi, Angiologia e Malattie della Coagulazione “Marino Golini”, Bologna; Caterina Cenci, Domenico Prisco, Elena Silvestri, S.O.D. Patologia Medica, Firenze (FI); Fabrizio Ceresa, Francesco Patanè, Azienda Ospedaliera Ospedali Riuniti, Messina; Antonio Ciampa, Valeria Siniscalchi, Centro Emostasi, Avellino; Tiziana Ciarambino, Giuseppe De Bartolomeo, Ospedale Ferdinando Veneziale, Isernia; Michele Clemente, Presidio Ospedaliero “Madonna delle Grazie” - Matera, Matera; Franco Conti, Laura Paieila, A.O. San Camillo-Forlanini, Roma; Maria D’Avino, U.O.C. Medicina Interna ad indirizzo Angiologico e Cerebrovascolare, Napoli; Aldo D’Alessandro, Marisa Placentino, Vito Sollazzo, Ospedale Civile
di San Severo (FG), San Severo (FG); Armando D’Angelo, Silvana Viganò, Servizio Coagulazione ed Unità Ricerca Trombosi Istituto Scientifico Universitario, Milano; Paolo De Campora, Raffaele Sanguinolo, Ospedale Buonconsiglio Fatebenefratelli, Napoli; Stefano De Franciscis, Raffaele Serra, Università degli Studi Magna Grecia di Catanzano, Catanza; Egidio De Gaudenzi, SOC Medicina Interna, Domodossola (VB); Fernando De Santis, Giovanni Carlo Piccinni, Presidio Ospedaliero Francesco Ferrari-Casarano, Lecce; Italo De Tommaso, U.O. Cardiologia, A.O.R. San Carlo, Potenza; Letizia Di Francesco, Giovanni Maria Vincentelli, U.O.S. Reparto di Breve Osservazione, Roma; Rosario Di Maggio, Giorgia Saccullo, Sergio Siragusa, U.O. Ematologia con trapianto, Palermo; Pierpaolo Di Micco, Andrea Fontanella, Ospedale Buonconsiglio Fatebenefratelli, Napoli; Dario Di Michele, U.O. Medicina Interna - P.O.”G. Mazzini”, Teramo; Giovanni Di Minno, Antonella Tufano, Università Federico II di Napoli, Napoli; Marcello Di Nisio, Ettore Porreca, Dipartimento di Medicina e Scienze dell’invecchiamento, Chieti; Francesca Donadio, Davide Imberti, UOC di Medicina Interna ERI, Piacenza; Iolanda Enea, Azienda Ospedaliera S. Anna e S. Sebastiano di Caserta, Caserta; Fabio Fabbian, Roberto Manfredini, Marco Pala, Arcispedale Sant’Anna di Ferrara, Ferrara; Anna Falanga, Viola Milesi, Centro Di Emostasi e Trombosi, Bergamo; Valerio Fiore, Salvatore Santo Signorelli, Presidio Ospedaliero “Sacro Cuore di Gesù”, Legge; Alessandro Schnone, S.C. Medicina Interna II, Genova; Cosimo Strafino, U.O. Medicina Interna, Termoli (CB); Pietro Tropeano, Centro Diagnosi e Cura Malattie Tromboemboliche Venose, Pordenone; Alfredo Vetrano, Azienda Ospedaliera S. Anna e S. Sebastian di Caserta, Caserta; Nello Zanatta, U.O. Semplice Dipartimentale di Angiologia – Dipartimento di Medicina, Vittorio Veneto (TV).

Spain

Maria Dolores Adarraga Cansino, Hospital de Montilla, Córdoba; Juan Alonso Gutierrez, Francisco Arnaiz de las Revillas, Hospital Valdecilla, Cantabria; Cristina Amado Fernández, Núria Calvo Mijares, Hospital de Serrallana, Cantabria; Maria Ángeles Blanco-Molina, Hospital U. Reina Sofia Córdoba; Maria Angelina Garcia, Dolores Joya Seijo, Hospital Rey Juan Carlos, Móstoles; Rocío Aranda Blazquez, Juan-Bosco López-Sáez, Hospital U. Puerto Real, Puerto Real (Cádiz); Eduardo Arelano Rodrigo, Jaume Villalta Blanch, Hospital Clinic i Provincial, Barcelona; Arola Aragón, Hospital de Galdakao, Galdakao; José Luis Beato Pérez, Hospital de Hellín, Hellín (Albacete); Pedro Bedate Díaz, Andrés Quezada Loaiza, Hospital Central de Asturias, OVIEDO (PRINCIPADO DE ASTURIAS); Marc Cairols Castel-lote, Centro Médico Delfos, Barcelona; Inma Cañas Alcántara, Merixtell Lluis Padierna, Fundación Hospital de Granollers, Granollers; Marina Carrasco Expósito, Juan Antonio Millón Caño, Hospital de la Santa Creu i Sant Pau Barcelona; Amaro Carrasco Mas, Fernando Cereto Castro, Clínica Quirón, Barcelona; Rafael Castro-deza Sanz, Juan Ortiz de Saracho, Hospital El Bierzo, León; Elena Cisneros de la Fuente, Hospital Son Llàtzer, Palma de Mallorca; Cristina de Ancos Aracil, Justo Ruiz Ruiz, Hospital Universitario de Fuenlabrada, Madrid; Maria Dolores de Faborenea González, Alfonso Fernández Iglesias, Hospital U. de Cruces, Bizkaia; Javier de la Fuente Aguado, Lucia González González, Hospital POVISA, Vigo; María del Carmen Fernández-Capitán,
Author details

1University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy.
2Herzstern Ludwigshafen Medical Klinik B, Ludwigshafen, Germany.
3Klinikum Darmstadt GmbH, Darmstadt, Center of Thrombosis and Hemostasis, University of Mainz, Mainz, Germany.
4Center of Thrombosis and Haemostasis, University of Mainz, Mainz, Germany.
5Daichii Sankyo Europe GmbH, Munich, Germany.
6CHU Saint-Etienne Hopital Nord, Saint Etienne Cedex 2, France.
7Hospital Universitari Germans Trias i Pujol, Barcelona, Spain.
8Charité – Universitätsmedizin Berlin, Berlin, Germany.
9King’s College, Guys and St Thomas’ Hospitals NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK.

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