The Birmingham and Black Country Cohort of Venous Thromboembolism (BBC-VTE) Registry: Rationale, Design and Preliminary Results

Alexander Sanders MRCP
Wahbi K. El-Bouri PhD
Gregory Y. H. Lip MD
on behalf of the BBC-VTE Investigators*.

Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK

Corresponding author:

Dr Alexander Sanders

E-mail: alexander.sanders1@nhs.net

Funding

There was no funding for this registry, which was conducted as a coordinated quality improvement project by junior medical trainees in West Midlands.

Conflicts of Interest

None specific to this project

Abstract

The Birmingham Black Country Venous Thromboembolism registry (BBC-VTE) is a multi-ethnic cohort of patients who suffered a first episode of venous thromboembolism (VTE) and were admitted to various hospital sites across the West Midlands and Black Country regions in the United Kingdom. The BBC-VTE registry is a retrospective, observational cohort study

which aims to collect data on outcomes including mortality, bleeding and VTE recurrence in this patient cohort. In addition, the comprehensive, structured data collected will allow us to conduct machine learning analyses for risk prediction in such patients and also to compare to previously derived mortality scores such as the PESI and the simplified PESI (sPESI).

Our registry included 2183 patients admitted to hospital between the years 2012-14 and 2016-18 with a first episode of VTE and the mean follow up was 36 months. The cohort was ethnically diverse with 72.5% white Caucasian, 8.2% Asian (including South Asian), 6.7% black, and 11.7% of unknown/other ethnicity. Of those admitted during the collection period 56% had PE, 40% had DVT, with the rest presenting with both PE and DVT. Around 7% of patients went on to develop a bleeding episode and 36% died (all-cause mortality). Of the deaths, 10% of patients died within 30-days of admission (30-day mortality), with 16% dying within 90 days. In summary, this study investigates real-world outcomes of patients after the first index VTE event and attempts to bridge the gap in evidence for contemporary data in this population which will allow to construct more accurate risk prediction tools and management decisions.

1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a severe condition which causes significant morbidity and mortality in hospitalised patients as well as in the community. In population-based studies from the 1990s in the United States the incidence of VTE was estimated to be between 1-2 per 1000 (1-3). The incidence rate rose exponentially with age such that the risk was at least 10 times greater in the >80 age group compared to the <40 age group(1, 2, 4). After the initial VTE event, the risk of recurrence was very high at approximately 13% in the first years (5) and declined thereafter with each year but never reached zero (6-9). Hence, the cumulative rate of VTE recurrence increases with each year and is around 23-25% at 5 years and 30-36% at 10 years follow up (5, 9, 10). The 28-day case-fatality rate is 11% after the first VTE, and is even greater at 25% for cancer patients(7). The incidence of VTE in Caucasians and African Americans was significantly higher than Hispanics and Asians/Pacific (3). In Europe, a community-based study in Western France showed a similar incidence of VTE of between 1-2 per 1000(11). It is important to note that some studies are based on clinical coding data which is likely to have inaccuracies in the recording of the diagnosis. Moreover, most studies are based on North American Caucasian populations making them unrepresentative of global populations.

In the UK, there has been heightened awareness in the last decade about the morbidity and mortality associated with hospital acquired VTE and guidelines have been developed to promote risk assessment of VTE for every hospital admission (15).

The management of patients after a first episode of VTE depends on triaging patients into

groups based on risk of recurrence. There is then a fine balance of bleeding risk from anticoagulation treatment versus ongoing risk of thrombosis. Furthermore, given the high case-fatality rate after incident VTE within the first month, there is a strong emphasis on predicting short-term mortality in such patients. There are various risk prediction tools, and the Pulmonary Embolism Severity Index (PESI) that has been validated to assess probability of 30 and 90 day mortality post PE, allows patients with a low risk of recurrence to be discharged from hospital early and safely(21, 22).

Despite this, there are still many questions left unanswered and there is still sparse evidence for certain aspects of venous thromboembolism diagnosis and management. Many of these are outlined in the "Gaps in the Evidence" section of the European Society of Cardiology guidelines. Of note, there is still debate about the optimal method to adjust the d-dimer threshold required to exclude PE, whether this is based on age or together with clinical risk. This could have the potential to minimise the quantity of unnecessary imaging performed for patients. There is also a lack of prognostic studies in patients found to have isolated sub-segmental filling defects. Subsequently, this means that there is no consensus on how such patients should be managed and followed up. Interestingly, although the PESI and sPESI scores have been validated to predict low risk groups for early PE-related death, the ESC guidelines still identify this area as a gap in the knowledge especially with regards to the intermediate risk of PE group who may qualify for reperfusion therapy. Finally, the optimal anticoagulant treatment in patients with renal insufficiency remains unclear.

Contemporary insights into risk assessments and management in a multi-ethnic cohort in UK are limited, and to address this we established the BBC-VTE (Birmingham Black Country Venous Thromboembolism) registry. This article summarises the design, aims and objectives

of the BBC-VTE registry and planned analyses.

Aims and objectives

The BBC-VTE registry is a retrospective, multi-centre, observational registry designed to be representative of a multi-ethnic cohort. The aims of this contemporary registry are to collect data on, and analyse the relationship and factors affecting mortality, major bleeding, and VTE recurrence after an initial episode of VTE. The secondary aim is to identify any difference that ethnicity may have on the above outcomes. Data collected are broad in scope to allow for statistical and machine learning analysis to predict short-term mortality, bleeding, and recurrence, as well as for comparisons to previously derived mortality scores such as the PESI and simplified PESI (sPESI) scores (21, 23). Machine learning algorithms developed for risk prediction on this dataset will be tested on external VTE datasets to validate their general predictive capability.

Furthermore, the vast data collected will allow us to address some of the gaps in the knowledge as identified in the ESC guidelines and discussed above. In particular, the machine learning algorithms may offer a more precise risk assessment which may allow to improve the diagnostic threshold of the d-dimer and reduce unnecessary imaging. As our registry will collect information on the specific location of PE, it may be possible to shed more light on the prognosis and outcomes of patients based on the location of their PE, for example, for patients with subsegmental filling defects on CTPA. The subgroup of patients with renal insufficiency and their outcomes and management post-PE will also be evaluated.

2. Methods

2.1 Study population

We designed simple inclusion and exclusion criteria, to enable enrolment of a broad range of VTE patients seen in everyday clinical practice, in the Birmingham and Black Country area. Inclusion criteria were: [1] all patients aged ≥18 years; [2] admitted to one of three Trusts (Sandwell and West Birmingham NHS Trust; former Heart of England NHS Foundation Trust; and Walsall Healthcare NHS Trust) between the years 2012-2014 and 2016-2018; [3] with radiologically proven primary or secondary diagnosis of pulmonary embolism (PE) or lower limb deep-vein thrombosis (DVT). Initially the scope of the retrospective data collection was to collect data on admissions during the years 2016-2018. However, the data collection was then expanded to the years 2012-2014 in order to go back in time sufficiently to allow the longer-term outcomes such as recurrence, bleeding and mortality to occur.

Exclusion criteria were: [1] No radiologically proven evidence of venous thromboembolism on current admission; [2] Upper limb DVT or portal vein thrombosis and other non-pulmonary thrombosis including atrial thrombus etc; and [3] pregnant patients. Patient lists at each of the three Trusts have been generated using clinical coding to identify all consecutive patients admitted during the relevant years with a final discharge diagnosis of VTE. Patients from those lists were then randomly allocated to each data collector from our pool of collaborators at each of the Trusts. The data collectors then accessed electronic records for each patient to verify their eligibility as per the above inclusion/exclusion criteria and collected data on the variables of interest as specified below. The date of data collection was recorded in order to calculate the length of follow up and survival.

2.2 Study outcomes

The data collected for each patient can be categorised into six broad groups: patient demographics; physical examination/radiology on admission; past medical history, biochemical analysis on admission; treatment plan; and outcomes (Table 1). The definitions and precise descriptors of the collected variables are detailed in Table 2.

An important aspect of the data collection is that it was performed by clinicians who can interpret the radiology reports in a clinical context. This is most relevant when it comes to decision making on what constitutes a recurrence of VTE versus chronic VTE. The data collectors were trained to determine whether there has been any interval resolution of the clot burden for example as evidenced by any interval radiology reports, prior to constituting any repeat imaging as a recurrence of VTE.

Dates were recorded for subsequent DVT or PE recurrence as well as any subsequent malignancy and the type of malignancy was also recorded. Subsequent bleeding dates and the site of bleeding were recorded for all severities of bleeding. Bleeding with fall in haemoglobin >20 g/L was one of the criteria for major bleeding, based on ISTH criteria (24). Details of whether patients were followed up with regards to reviewing their long-term anticoagulant treatment was recorded from electronic clinic letters and the date of follow up was also recorded. The date of death was recorded from the hospital electronic record if applicable and the cause of death, if available, was recorded from the final discharge summary and not from the death certificate. This information was not always available for every patient.

The limitations of this study are firstly that it was a retrospective data collection and hence not all of the variables were available on record for each patient. Secondly, although the data was gathered from three of the major healthcare providers of this large metropolitan area, there are other hospitals within this area that did not participate in the study. Therefore, data from admissions of patients who re-presented to a non-participating hospital would not be recorded. However, this applies to only a small minority of patients as most patients tend to present to or be taken by ambulance to the usual hospital nearest to their place of residence.

2.3 Study setting and data management

The recruited collaborators for the data collection were practicing doctors and senior specialist nurses at each of the three Trusts in West Midlands, United Kingdom. West Midlands has a multi-ethnic background which ensures representation from a variety of ethnic groups in the study. All data were collected locally by staff already employed at the NHS Trusts and with access to patient data. Each staff member was aware and trained in confidentiality and information governance. Each data collector only accessed part of the data we are collecting, and the data were stored locally in an anonymised fashion without patient identifiable information. This was then amalgamated and statistically analysed centrally.

2.4 Analysis Plan

The primary analysis consists of developing a machine learning algorithm to predict mortality in this group of patients. Prediction models of 30-day mortality, 90-day mortality and 1-year mortality will be developed. Secondary outcomes include prediction of VTE recurrence and bleeding risk in patients. Random Forest algorithms will be used to develop these prediction models, with logistic regression used as a comparator. The dataset will be split into a training and validation set (70:30 ratio) to provide validation of the algorithms. To measure the

efficacy of the algorithm we will report the C-index, sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. Confidence intervals and p-values will be computed through bootstrapping the data.

2.5 Progress to date

The BBC-VTE registry included 2183 patients with dates of admission ranging between 2012 – 2014 and 2016 – 2018. The median age was 68 years (interquartile range 53 – 80) and54% of the cohort were female. The cohort was ethnically diverse with 72.5% white Caucasian, 8.2% Asian (including South Asian), 6.7% black, and 11.7% of unknown/other ethnicity. Of those admitted during the collection period 56% had PE, 40% had DVT, with the rest presenting with both PE and DVT.

After a mean follow-up of 3 years 10 days (1104 days), 7% of patients went on to develop a bleeding episode and 36% died (all-cause mortality). Of the deaths, 10% of patients died within 30-days of admission (30-day mortality), with 16% dying within 90 days (Table 3).

3. Discussion

The BBC-VTE study investigates the contemporary epidemiology of VTE as applicable to an ethnically diverse population of the West Midlands, United Kingdom. Prior epidemiological studies have either been largely performed in the white North American population during the 1990s or as part of international VTE registries such as the GARFIELD-VTE (25). Although these studies recruited large numbers of patients of different ethnicities, the outcomes are not directly comparable due to the variable diagnostic practices as well as treatment patterns and local guidelines which differ around the world and even amongst different hospital groups. In the United Kingdom, most hospitals are under the same

organisation known as the National Health Service which broadly maintains similar standards across all hospital Trusts. Clinical practice is guided by the National Institute for Health and Care Excellence (NICE) guidelines which are applicable for all physicians across the whole country. This ensures a similar baseline for comparison of patient outcomes.

The rate of recurrence of VTE was estimated in previous epidemiological studies to be around 13% in the first year(5). Many of these studies are based on clinical coding data and are therefore prone to error. The BBC-VTE registry is collected by clinicians who confirm the diagnosis by interpreting the radiology reports and correlating them with electronic clinical records. Furthermore, many discharge records do not specify whether the repeat admission was related to complications of the original VTE diagnosis such as chronic VTE and post-DVT or post-pulmonary embolism syndrome, or whether the repeat admission represents a recurrence. This information is impossible to ascertain from the clinical coding or even from clinical records without also confirming the imaging findings. Our rigorous inclusion criteria and data collection technique is likely to reveal a rate of recurrence that is more applicable to a real-world scenario.

Various VTE registries as summarised in Table 4 attempt to estimate outcomes in terms of all-cause mortality, recurrence of VTE and major haemorrhage. The studies are difficult to compare because they were performed during different decades where there was differing availability of the NOACs, not least due to the fact that Apixaban was only introduced after the results of the AMPLIFY study in 2013. Our study does include admissions from as early as the year 2012 and so the anticoagulant choices and their outcomes would be somewhat different from the present day. However, our data is vast in scope and has details of the type of long-term anticoagulant that was prescribed to patients on discharge as well as the date;

and so these differences can be accounted for in the analysis of the statistical data. Furthermore, the VTE registries in Table 4 report all-cause mortality and bleeding rates over different time frames. It is estimated that the highest risk of VTE recurrence or bleeding is within the first month after the initial event and then decreases slowly thereafter (6-9). This makes it difficult to compare the rates across studies that have different follow-up periods. A major outcome measure of the various anticoagulants is the rate of major haemorrhage which is estimated at 1.5 and 1.7% at 12 months post VTE in the PREFER in VTE and GARFIELD-VTE studies (26, 27).

Based on the vast data collected in BBC-VTE about the patient's demographics, laboratory analysis, physical examination and a comprehensive past medical history, we can identify which factors affect the rate of recurrence of VTE, major haemorrhage and mortality using machine learning algorithms.

In conclusion, the BBC-VTE registry will provide insight and contemporary data on the outcomes of patients after a first diagnosis of VTE as well as the clinical data required to construct various machine learning algorithms for risk prediction and clinical decisions.

Acknowledgements:

*BBC-VTE Investigators: Eleanor E. Clarke, Rachel Clements, James M. Roberts, Simerjit Rai, Natalie R. Binfield, OluwabamiseAdewusi, Sumaiya Aziz, Jennifer Durston, ZafraanZathar, Matthew T. Bell, Frederik Priskorn, Anne S. Karunatilleke, TariroMadzima, Abitha M. Illango, Datapwa P. Mujong, Farishta Khan, SannidhyaMisra, Stephanie J. Dyson, Lloyd Edwards, Alice Castle, Elena A.Y.L. Un, Radia Choudhury, Rachael K. Penrose, Michael P. Leeming, GurvinChander, Callum Oakley, Benjamin M Olley

References

1.Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158(6):585-93.

2.Spencer FA, Emery C, Lessard D, Anderson F, Emani S, Aragam J, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med. 2006;21(7):722-7.

3.White RH, Zhou H, Murin S, Harvey D. Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. Thromb Haemost. 2005;93(2):298-305.

4.Kniffin WD, Jr., Baron JA, Barrett J, Birkmeyer JD, Anderson FA, Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. Arch Intern Med. 1994;154(8):861-6.

5.Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160(6):761-8.

6.Albertsen IE, Nielsen PB, Søgaard M, Goldhaber SZ, Overvad TF, Rasmussen LH, et al. Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study. Am J Med. 2018;131(9):1067-74.e4.

7.Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004;117(1):19-25.

8.Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Pengo V, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med. 2010;170(19):1710-6.

9.Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. Bmj. 2019;366:l4363.

10.Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. J Thromb Haemost. 2010;8(11):2436-42.

11.Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost. 2000;83(5):657-60.

12.Martinelli I, Mannucci PM, De Stefano V, Taioli E, Rossi V, Crosti F, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood. 1998;92(7):2353-8.

13.Rodeghiero F, Tosetto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. Ann Intern Med. 1999;130(8):643-50.

14.Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. Arch Intern Med. 2007;167(14):1471-5.

15.Excellence NIfHaC. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline [NG89]. London: NICE; 2018.
16.Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484-8.
17.De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Chiusolo P, Casorelli I, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med. 1999;341(11):801-6.
18.Eichinger S, Pabinger I, Stümpflen A, Hirschl M, Bialonczyk C, Schneider B, et al. The risk of recurrent venous thromboembolism in patients with and without factor V Leiden. Thromb Haemost. 1997;77(4):624-8.
19.Miles JS, Miletich JP, Goldhaber SZ, Hennekens CH, Ridker PM. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol. 2001;37(1):215-8.
20.Ridker PM, Miletich JP, Stampfer MJ, Goldhaber SZ, Lindpaintner K, Hennekens CH. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation. 1995;92(10):2800-2.
21.Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172(8):1041-6.
22.Howard L, Barden S, Condliffe R, Connolly V, Davies CWH, Donaldson J, et al. British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE). Thorax. 2018;73(Suppl 2):ii1-ii29.
23.Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-9.
24.Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4.
25.Weitz JI, Haas S, Ageno W, Angchaisuksiri P, Bounameaux H, Nielsen JD, et al. Global Anticoagulant Registry in the Field - Venous Thromboembolism (GARFIELD-VTE). Rationale and design. Thromb Haemost. 2016;116(6):1172-9.
26.Cohen AT, Gitt AK, Bauersachs R, Fronk EM, Laeis P, Mismetti P, et al. The management of acute venous thromboembolism in clinical practice. Results from the European PREFER in VTE Registry. Thromb Haemost. 2017;117(7):1326-37.
27.P. Angchaisuksiri S-MB, H. Fryk, C.-E. Chiang, Z.-C. Jing, S. Wang, K. Kondo, J. Sathar, E. Tse, S. Goto, A. Kakkar, on behalf of the GARFIELD-VTE Investigators. Venous thromboembolism in Asia and worldwide: Emerging insights from GARFIELD-VTE. International Society of Thrombosis and Haemostasis; 6th July - 10th July, 2019; Melbourne2019.
28.Nishimoto Y, Yamashita Y, Morimoto T, Saga S, Amano H, Takase T, et al. Validation of the VTE-BLEED score's long-term performance for major bleeding in patients with venous

thromboembolisms: From the COMMAND VTE registry. J Thromb Haemost. 2020;18(3):624-32.
29.Turpie AGG HS, Weitz JI, Ageno W, Angchalsuksiri P, Bounameaux H, Goldhaber SZ, Goto S, Kayani G, Dalsgaard Nielsen J, Schellong S, Mantovani LG, Prandoni P, Kakkar AK. 6 month outcomes of patients: Results from GARFIELD VTE. International Society of Thrombosis and Haemostasis; 8th July - 13th July, 2017; Berlin2017.
30.Agnelli G, Gitt AK, Bauersachs R, Fronk EM, Laeis P, Mismetti P, 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.
31.Willich SN, Bauersachs R, Gitt AK, Mismetti P, Monreal M, Wolf WP, et al. Treatment Satisfaction In Patients With Venous Thromboembolism As Measured With Pact-Q2: Prefer In Vte Registry. Value Health. 2014;17(7):A496-7.
32.Bikdeli B, Jimenez D, Hawkins M, Ortíz S, Prandoni P, Brenner B, et al. Rationale, Design and Methodology of the Computerized Registry of Patients with Venous Thromboembolism (RIETE). Thromb Haemost. 2018;118(1):214-24.
33.Mahé I, Sterpu R, Bertoletti L, López-Jiménez L, Mellado Joan M, Trujillo-Santos J, et al. Long-Term Anticoagulant Therapy of Patients with Venous Thromboembolism. What Are the Practices? PLoS One. 2015;10(6):e0128741.
34.Jiménez D, de Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al. Trends in the Management and Outcomes of Acute Pulmonary Embolism: Analysis From the RIETE Registry. J Am Coll Cardiol. 2016;67(2):162-70.
35.Morillo R, Jiménez D, Aibar M, Mastroiacovo D, Wells PS, Sampériz Á, et al. DVT Management and Outcome Trends, 2001 to 2014. Chest. 2016;150(2):374-83.
36.Tzoran I, Brenner B, Papadakis M, Di Micco P, Monreal M. VTE Registry: What Can Be Learned from RIETE? Rambam Maimonides Med J. 2014;5(4):e0037.
37.Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, et al. Anticoagulation Therapy for Venous Thromboembolism in the Real World - From the COMMAND VTE Registry. Circ J. 2018;82(5):1262-70.
38.Yamashita Y, Murata K, Morimoto T, Amano H, Takase T, Hiramori S, et al. Clinical outcomes of patients with pulmonary embolism versus deep vein thrombosis: From the COMMAND VTE Registry. Thromb Res. 2019;184:50-7.
39. Goldhaber S, Visani L, De Rosa M et al. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;354:1386-9

390 **Tables**

391

392 **Table 1** Variables and outcomes measured in the BBC-VTE cohort

Demographics	**Physical examination/ radiology**	**Past medical history**
Age Gender Ethnicity	Heart rate Blood pressure Respiratory rate Temperature Altered consciousness (GCS <15) Hypoxia despite oxygen therapy Oxygen saturations Clinical signs of DVT Weight Height Haemoptysis CTPA and/or V/Q scan results and/or Doppler ultrasound results	Prior immobilisation Hereditary thrombophilia Diabetes mellitus Sickle cell disease/trait Ischaemic heart disease/coronary artery disease Peripheral arterial disease Other venous disease Hypertension Heart failure Hypercholesterolaemia Chronic lung disease Smoking status Alcohol excess Intravenous drug use Stroke Chronic kidney disease Previous venous thromboembolism Previous malignancy
Laboratory analysis	**Treatment plan**	**Outcomes**
D-dimer value and time Haemoglobin White cell count Platelets Neutrophils Monocytes Creatinine C-reactive protein	Whether thrombolysis administered Type of long-term anticoagulant for treatment of VTE Date of follow up	Subsequent VTE type Subsequent malignancy type Subsequent bleeding /site Bleeding with fall in Hb >20 g/L Subsequent death

393 **Table 2**Definitions and descriptions of collected variables

Variable	Description
CTPA	Classified according to the extent of the clot in the pulmonary artery (main pulmonary artery; right/left pulmonary artery; right/left segmental or subsegmental)
Ventilation/Perfusion (V/Q) scan	High/medium/low probability
Doppler ultrasound scan results	Classified according to the extent of the clot in the lower limb (common femoral; superficial femoral; popliteal; posterior tibial; and peroneal)
Physical examination findings	Recorded from the admission document taken within the first few hours of presentation to hospital
Clinical signs of DVT	Interpreted by the data collector based on the admission record and may include the following signs: lower limb pain and tenderness along the deep veins; lower limb swelling/whole leg swelling; presence of collateral vessels; and skin temperature/colour.
Past medical history (PMH)	Obtained from the admission record as well as clinic letters prior to the date of admission
Prior immobilisation	Must have happened within the last 4 weeks and persisted for at least 3 days. Immobilisation had the following subcategories: related to trauma or orthopaedic surgery; any other surgery; neurological disease affecting mobility; acute medical admission; and travel.
Peripheral arterial disease	Includes subcategories of claudication, ulcers, non-healing wounds, amputation, gangrene, renal artery stenosis, carotid stenosis and other.
Other venous disease	Includes varicose veins, chronic venous insufficiency, lymphoedema and other.
Long-term anticoagulant	Recorded as per the discharge summary and is the intended treatment for VTE at the point of discharge from hospital. The categories are: vitamin K antagonist; heparin; rivaroxaban; apixaban; dabigatran; other; or none. The dose of the anticoagulant was also recorded.
Subsequent bleeding	Dates and the site of bleeding were recorded for all severities of bleeding. Major bleeding = fall in haemoglobin >20 g/L

Table 3 Clinical characteristics of included patients

Characteristic	Patients, n (%)
Demographics	
Median Age (years), IQR (25% – 75%)	68 (53 – 80)
Male	1012 (46)
Ethnicity White	1577 (72)
Past Medical History	
Cancer	520 (24)
Previous VTE	246 (11)
Heart failure	172 (8)
Chronic lung disease	449 (21)
Immobilisation†	639 (29)
Hereditary thrombophilia	37 (2)
Clinical Findings	
Altered consciousness‡	59 (3)
Heart rate ≥ 110 bpm	220 (10)
Systolic blood pressure < 100 mmHg	75 (3)
Arterial oxyhaemoglobin saturation< 90%	60 (3)
Temperature < 36°C	138 (6)
Treatment plan	
Long Term Anticoagulant	
Warfarin	919 (42)
Rivaroxaban	282 (13)
Enoxaparin	451 (21)
Apixaban	79 (4)
None	175 (8)
Other	32 (1.5)
Outcomes	
Subsequent VTE	249 (11)
Subsequent bleeding	144 (7)
30-day mortality	215 (10)
90-day mortality	340 (16)
All-cause mortality	793 (36)

VTE venous thromboembolism, IQR interquartile range

†*Immobilised patients are defined as those who have been immobilised for ≥ 3 days in the 4 weeks prior to a VTE.*

‡ *Altered consciousness is defined as any patients with a Glasgow Coma Score (GCS) < 15*

Table 4List of global VTE registries with their demographics, choice of anticoagulant treatment and patient outcomes.

(Rx – Treatment; F/U – Follow-up; VKA – Vitamin K antagonist; DOAC – Direct Oral Anticoagulant; LMWH – Low Molecular Weight Heparin)

Author	Study date/place	Design/patients	Aims	Anticoagulant Rx	F/U timeframe	Results	Complications
Ageno et al(25)	GARFIELD-VTE May 2014 – Jan 2017 28 countries in Europe, America, Asia, Africa and Australasia	Prospective observational 10,685 patients Europe (59.3%), Asia (15.0%), North America (9.9%) and the rest of the world (15.7%)(29). 1,822 patients (17.1%) were from Asia (China n=420, Hong Kong n=98, Japan n=148, Malaysia n=244, South Korea n=343, Taiwan n=232, Thailand n=337)	1. Anticoagulation ofVTE around the world 2. VTE recurrence 3. Bleeding 4. All-cause mortality 5. VTE complications	Rx at diagnosis +/- 1 month (27): non-Asians (vs Asians) in %: Parenteral only: 15.9 (23.3) Parenteral + VKA: 27.5 (20.3) VKA only: 5.5 (4.5) DOAC only: 30.0 (31.5) Parenteral + DOAC: 17.9 (10.9) No Rx: 2.7 (6.6)	At 6 months(29)	Rate (per 100 person years) in all ethnic groups of:(29) 1. All-cause mortality: 11.1 2. Major bleeding: 2.8 3. VTE recurrence: 3.6	Most common cause of death at 6 months: cancer 50.9% of cases, PE death: 5.1%
					At 12 months(27)	Rates per 100 person years in Asians (vs non-Asians) of: 1. All-cause mortality: 15 (5.9) p value <0.01 2. Major bleeding: 2.4 (1.7) p value 0.07 3. VTE recurrence: 5.6 (5.1) p value 0.40	
Agnelli et al(30)	PREFER in VTE Jan 2013 – Jul 2014	Prospective observational 3545 patients Seven European countries: Austria, France, Germany, Italy, Spain, Switzerland, and the UK	1.Characteristics of patients with acute VTE 2. Anticoagulation of VTE 3. Quality of life questionnaire	Rx at 1 month:(26) VKA: 53.4% DOACs: 25.4% Heparin: 18.9% DVT only vs PE+/-DVT: VKA: 47.7% vs 61.8% DOAC: 27.6% vs 22.2% Heparin: 20.2% vs 16.9%	12 months(26)	1. All-cause mortality: 6.7% 2. VTE related mortality: 0.3% 3. Recurrent VTE: 5.2% 4. Major bleeding 1.5%	Patients' satisfaction of Rx questionnaire: Patients on NOACs rated their convenience and treatment satisfaction substantially higher than patients on heparin/VKA(31)
Bikdeli et al(32)	RIETE 2001 – 2017 Started in Spain and expanded to 24 other countries in Europe as well as North and South America	Prospective observational 72,107 patients (Spain n = 54,525)	1. Anticoagulation patterns throughout the ages 2. VTE outcomes 3. Prediction scores for bleeding on VTE Rx	During years 2001-2013 the following long term anticoagulant was commenced for non-cancer and (cancer) patients diagnosed with VTE:(33) VKA – 82% (34%) LMWH – 18% (66%)		For PE subgroup (n = 23,858) years 2001-2013:(34) 1.30 day all-cause mortality: 5.9% (decreased from 6.6% to 4.9% over study period) 2. 30 day PE-related mortality: decreased from 3.3% to 1.8% over study period 3. 30 day VTE recurrence: decreased from 1.1% to 0.6 over study period 4. 30 day major bleeding: decreased from 4.0% to 3.1%	Prognostic score for major bleeding within 3 months of anticoagulant Rx (points):(36) 1.Recent major bleeding (2) 2. Creatinine >1.2mg/dL (1.5) 3. Anaemia (1.5) 4. Cancer (1) 5. Clinically overt PE (1)

						For DVT subgroup (n = 26,695) years 2001-2014:(35) 1.30 day all-cause mortality: decreased from 3.9% to 2.7% over study period 2. 30 day bleeding-related mortality: decreased from 0.5% to 0.1%	6. Age >75 (1)
Yamashita et al(37)	COMMAND VTE Jan 2010 – Aug 2014 Japan	Retrospective cohort study 3027 consecutive patients	1. Optimal duration of anticoagulation 2. VTE outcomes	VKA – 88% DOAC – 2.6% Heparin – 1.6% 3-year incidence of recurrent VTE in the unprovoked group was 3.7% vs 12.2% for those who were still on vs off anticoagulation at 1 year post initial VTE event. No difference in transient or cancer risk group		Cumulative 5-year VTE recurrence: Transient risk – 7.9% Unprovoked – 9.3% Cancer – 17.7% Cumulative 5-year incidence all-cause mortality: Transient risk – 17.4% Unprovoked – 15.3% Cancer – 73.1% 30-day all-cause mortality:(38) PE patients: 6.4% DVT patients: 1.4%	Cumulative 5-year incidence major bleeding: Transient risk – 9.0% Unprovoked – 9.4% Cancer – 26.6% VTE-BLEED score of ≥2 (high risk) had a cumulative 5-year major bleeding incidence of 13.2% vs 5.4% for score of <2 (low risk group)(28)
Goldhaber et al(39)	ICOPER Apr 1999 Europe and North America	Prospective observational 2110 patients	1. PE outcomes 2. Effect of risk factors on survival	n/a	3 months	Crude mortality rate: 17.4% Of these: - 45.1% due to PE - 17.6% to cancer	On multiple regression modelling the following were identified as significant prognostic factors: Age>70, cancer, congestive cardiac failure, chronic obstructive pulmonary disease, systolic arterial hypotension, tachypnoea, and right ventricular hypokinesis

404