Advances in the prevention of thrombosis: Investigations into atrial fibrillation related stroke and venous thromboembolism

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I would like to thank all the researchers and site staff whose input led to the successful completion of the research included in this thesis. Thanks also to all my co-authors for their contribution in achieving the publications.

I would like to acknowledge my beloved parents - my lovely Mum and my late Dad - for their commitment to my personal and academic development since my early years.

Thank you to my family for the unending support of my work, my aspirations and this PhD.

Submission declaration

I declare that the submitted material as a whole is not substantially the same as published or unpublished material that I have previously submitted, or am currently submitting, for a degree, diploma or similar qualification at any University or similar institution. No parts of the work submitted has been submitted previously for any aforementioned qualification.

Summary

This thesis brings together research undertaken by the author on prevention of two thrombotic disease conditions: atrial fibrillation (AF) related stroke and venous thromboembolism (VTE). The research presented is based on five publications from three studies using mixed methods.

The first study was the UK component of a global prospective observational longitudinal cohort study of patients newly diagnosed with AF (GARFIELD-AF). Globally GARFIELD-AF recruited 52,080 patients newly diagnosed with AF, of which 3,879 were UK participants. Notably the unique objective published in the UK protocol to assess the performance of existing risk stratification tools in AF management led to the development of the GARFIELD-AF risk tool, an improved risk stratification tool that predicts mortality, stroke and bleeding in patients with AF. Further, the UK data indicated a substantial increase in the use of anticoagulants for the prevention of AF-related stroke following updates to AF management guidelines and the availability of non-vitamin K oral anticoagulants.

The second study, an observational cohort study, determined for the first time the incidence of VTE in UK care homes. The VTE incidence in the study (0.71 to 2.48 per 100 person years) was substantial compared to known incidence in the community. This study contributed to national dialogue on VTE prevention and I was invited to present the findings at the All-Party Parliamentary Group on Thrombosis 2016 conference.

The third study, a qualitative study, explored the prevention of hospital-associated thrombosis through interviews with patients and primary care professionals. The study identified a need for improved patient education on VTE, including how patients can recognise signs and symptoms of VTE. The related publication was instrumental in new recommendations on information giving on admission and discharge in the updated 2018 national VTE guidelines.

Further research from gaps in knowledge identified in this thesis will complement ongoing initiatives and lead to improvements in the prevention of AF-related stroke and VTE in the UK and globally.

Table of publications submitted for consideration of PhD by Published Work and candidate's contribution to the publications

Paper	**Authorship**
Paper 1 An international longitudinal registry of patients with atrial fibrillation at risk of stroke (GARFIELD): the UK protocol. *BMC cardiovascular disorders. 2013 Dec;13(1):31.* Patricia Apenteng contributed to the development of the study protocol and conceived the idea of the paper. She led in writing the paper in liaison with Ellen Murray and David Fitzmaurice and the contribution of other co-authors.	*Apenteng PN* *Murray ET* *Holder R* *Hobbs FR* *Fitzmaurice DA*
Paper 2 Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry *BMJ open. 2018 Jan 1;8(1):e018905* Patricia Apenteng conceived the idea of the paper and led in writing the paper in liaison with her co-authors. She supervised data collection, contributed to analysis and interpretation of the data, and responded to reviewers as corresponding author.	*Apenteng PN* *Gao H* *Hobbs FR* *Fitzmaurice DA*
Paper 3 Incidence of venous thromboembolism in care homes: a prospective cohort study *Br J Gen Pract.* 2017 Jan 17:bjgpfeb-2017 Patricia Apenteng contributed to the conception of the study, wrote the protocol, and led on the development of the research tools. She obtained ethics and regulatory approvals, supervised data collection, and contributed to data analysis. She led in writing the paper and responded to reviewers in liaison with corresponding author David Fitzmaurice.	*Apenteng PN* *Hobbs FR* *Roalfe A* *Muhammad U* *Heneghan C* *Fitzmaurice D*
Paper 4 Patients' perceptions and experiences of the prevention of hospital-acquired thrombosis: a qualitative study *BMJ open. 2016 Dec 1;6(12):e013839* Patricia Apenteng led on developing the concept of the paper and the data analysis. She led in writing the paper in liaison with her co-authors and responded to reviewers as corresponding author.	*Apenteng PN* *Fitzmaurice D* *Litchfield I* *Harrison S* *Heneghan C* *Ward A* *Greenfield S*

Paper	Authorship
Paper 5 Prevention of hospital-acquired thrombosis from a primary care perspective: a qualitative study *Br J Gen Pract. 2016 Aug 1;66(649):e593-602* Patricia Apenteng contributed to developing the concept of the paper. She contributed constructively to the thematic analysis of the data and provided detailed comments and amendments on successive drafts of the manuscript.	*Litchfield I* *Fitzmaurice D* *Apenteng P* *Harrison S* *Heneghan C* *Ward A* *Greenfield S*

Copies of these statements of contribution, signed by co-authors can be found in Appendix A.

List of abbreviations and acronyms

Acronym	Meaning
AF	Atrial fibrillation
VTE	Venous thromboembolism
DVT	Deep vein thrombosis
PE	Pulmonary embolism
VKA	Vitamin K antagonist
NOACs	Non VKA oral anticoagulants, more recent publications may refer to them as DOACs (Direct-acting oral anticoagulants)
DOACs	Direct-acting oral anticoagulants
GARFIELD-AF	Global GARFIELD study (**G**lobal **A**nticoagulant **R**egistry in the **FIELD – A**trial **F**ibrillation)
GARFIELD UK	UK component of global GARFIELD study
VTEC	Study to determine the incidence of **V**enous **T**hrombo**e**mbolism in **c**are homes
ExPeKT	Study **Ex**ploring **p**r**e**vention and **k**nowledge of venous **t**hromboembolism
NICE	National Institute for Health and Care Excellence
CHA_2DS_2VASc	Stroke risk classification tool (**C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75, **A**ge 65-74, **D**iabetes mellitus, **S**troke/TIA/thromboembolism, **Va**scular disease, **S**ex Female)
HAS -BLED	Bleeding risk classification tool (**H**ypertension, **A**bnormal liver function or , Abnormal renal function, **S**troke, **B**leeding, **L**abile INRs, **E**lderly (Age >65), **D**rugs or Alcohol)
ONS	Office of National Statistics
PI	Principal Investigator
CRN	Clinical Research Network
NHS	National Health Service
NIHR	National Institute of Health Research
HAT	Hospital-associated thrombosis
APPGT	All-Party Parliamentary Group on Thrombosis
PY	Person years

Chapter 1. Introduction to the thesis

This thesis represents a programme of research related to prevention of the thrombotic conditions atrial fibrillation (AF) related stroke and venous thromboembolism (VTE). Both conditions are potentially preventable through prophylactic treatments for patients identified as high risk, yet their incidence remains high.[1] An understanding of how well strategies for the prevention of these thrombotic conditions are working will optimise their effectiveness and reduce the burden of thrombosis.

Thrombosis may be defined as the formation of a blood clot in the circulatory system.[2] This clot can block or obstruct blood flow in the affected area, and can cause serious medical complications if the clot moves to a critical part of the circulatory system, such as the brain or the lungs. Thrombosis can be broadly classified as either venous thrombosis or arterial thrombosis, according to where the blood clot presents in the body. Venous thrombosis occurs in the veins and arterial thrombosis occurs in the arteries.[1] Thrombosis is the underlying pathology of ischemic heart disease, stroke and venous thromboembolism.[2 3]

Thrombosis is a leading cause of significant morbidity and mortality, and one in four people worldwide die from conditions caused by thrombosis.[4] An ischemic stroke is a condition caused by blockage to part of the brain due to blood clots in one of the arteries supplying blood to the brain. The loss of blood flow to the brain damages tissues in the brain and may cause brain damage, long-term disability, or death. AF is a common type of irregular heart rhythm that can cause blood not to be pumped out properly from the heart, causing it to pool and form a clot. This clot can then travel in the arteries to the brain, obstructing blood flow and causing a stroke. Contemporary studies indicate that 20-30% of all strokes are due to AF.[5]

The term venous thromboembolism (VTE) is used to describe blood clot which starts in a vein and is usually used to collectively refer to the conditions deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT occurs when a blood clot occurs in the deep veins, usually the lower legs. The clot, or part of it, can break off and travel to the lungs, causing a PE. A PE is potentially life threatening as it can prevent blood flow from reaching the lungs and can lead to sudden death in severe cases.

This PhD by Published Work brings together papers published between 2013 and 2018 from applied health research evaluating the effectiveness of the prevention of AF-related stroke and venous thromboembolism. The work I present is based on five publications from three studies. The first study is the UK component of a global study that evaluated the clinical management and outcomes of patients newly diagnosed with atrial fibrillation and at risk of stroke (GARFIELD-AF). The second study is an observational study that determined the incidence of venous thromboembolism in UK care homes. The third study explored prevention and knowledge of venous thromboembolism using mixed methods as part of a NIHR funded Programme Grant for Applied Research.

This commentary serves as a supporting statement for the portfolio of published work and is presented in five chapters. The aim is to present a narrative that explains how the published work fits together and critically appraises the submitted work. This chapter is an introduction to the thesis and explains how AF-related stroke and VTE are linked by the underlying pathology of thrombosis. Chapter 2 presents the background to the research covered by the published work, introduces the research the published work is based on, and defines the candidate's role in the research. Chapter 3 describes the methodologies for each of the studies and their appropriateness. Chapter 4 highlights the key findings of the studies and outlines the original contributions of the research. Chapter 5 presents implications of the research, recommendations for future research and reflections of the research process. The publications included in the thesis are in Appendix B.

Chapter 2: Background

This chapter presents the two thromboembolic conditions covered in the research, the rationale for the research and introduces the research and the candidate's role in the research.

2.1 Atrial fibrillation related stroke

2.1.1 Atrial fibrillation (AF)

AF is the most common clinically significant arrhythmia in the adult population worldwide, and a major cause of stroke.[6] AF affects 1-2% of the global population; prevalence of AF increases steeply with age. People aged 40 and above have a 25% lifetime risk of developing AF.[7] There are two main types of AF: valvular AF and non-valvular AF. Valvular AF refers to AF that is caused by a heart valve problem and predominantly refers to patients with rheumatic valvular disease.[8] Non-valvular AF refers to AF that is not caused by a heart valve problem and is the most common type of AF. AF may also be into classified according to presentation, duration and spontaneous termination of AF episodes. Paroxysmal AF refers to AF that self terminates within 7 days, persistent AF is AF that last more than 7 days and permanent AF if AF that is continuous and does not end.

In the US, the prevalence of AF increases from 0.1% in those aged <55 years to 9% in those aged ≥80 years.[9] In the UK, the prevalence of AF found in one study was 7.2% of those aged 65 and over, and 10.3% in those aged 75 and over.[10] The estimated global number of prevalence cases of AF in 2010 was 33.5 million with approximately 5 million new cases occurring each year.[11] AF is a growing epidemic and its incidence of AF is projected to rise significantly over the next few decades as populations' age.[5]

2.1.2 AF-related stroke

AF increases the risk of ischaemic stroke five-fold and the risk of death two-fold, compared to patients without AF.[6] AF-related strokes constitute about 20% of strokes, with 12,500 strokes per years in England directly attributable to AF.[12] AF-related strokes are more severe than strokes in people without AF and are more

likely to be fatal, lead to long-term disability, extended hospital stay and increased healthcare costs.[13]

Data from several randomized controlled clinical trials have proven that anticoagulation therapy with Vitamin K antagonists (VKAs) reduces the risk of AF-related stroke and other serious sequelae, with a 68% relative risk reduction for ischaemic stroke and 25% reduction in the relative mortality.[14] The risk of stroke in patients with AF is dependent on the presence of other risk factors and evidence based guidelines recommend long-term anticoagulation for patients with AF and at risk of stroke.[5 15] However, anticoagulation comes with a risk of bleeding complications and the decision for oral anticoagulation requires balancing the benefits of stroke prevention with the risks of bleeding. The current National Institute for Health and Care Excellence (NICE) guidelines, published in 2014 recommend using the CHA_2DS_2VASc and HAS-BLED risk scores to guide decisions on anticoagulation.[15] The CHA_2DS_2VASc stroke risk score is a sum of points from congestive heart failure, hypertension, diabetes, vascular disease, age 65-74 years, female sex category (one point each), and age ≥75 years and stroke/transient ischemic attack/thromboembolism (two points each), evaluates stroke risk in people with AF (Table 1). The guidelines recommend oral anticoagulation in men and women with a $CHA_2DS_2VASc \geq 2$ and a consideration of anticoagulation for men with a score of 1. The guidelines do not recommend anticoagulation for men with a score of 0 or women with a score of 1.[15]

The HAS-BLED bleeding risk score is a sum of points from uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (age ≥65 years), drugs/alcohol concomitantly (Table 2). The guidelines recommend modification and monitoring of patients with uncontrolled hypertension, labile INRs, concominant mediation and harmful achohol use.[15] Other AF guidelines such as European Society of Cardiology (ESC) guidelines and the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) also recommend anticoagulants to reduce the risk of AF-related stroke.[5 16]

Table 1. The CHA_2DA_2SVASc scoring system

Risk factors	**Score**
Congestive heart failure	1
Hypertension	1
Age ≥ 75	2
Age 65-74	1
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Sex Female	1

Patients with CHA2DS2VASc ≥ 2 are considered high risk of stroke

Adapted from Lip et al[17]

Table 2. HAS-BLED score scoring system

Clinical characteristic	**Points awarded**
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (Age >65)	1
Drugs	1
Alcohol	1

Adapted from Pisters et al[18]

2.1.3 Challenges in the prevention of AF-related stroke

Despite the effectiveness of anticoagulation therapy in reduction of stroke in patients with atrial fibrillation, anticoagulation in patients with AF is has historically been suboptimal, both globally and in the UK. Many studies report a long-standing problem of under treatment of patients with AF at risk of stroke.[19,20] A systematic review of studies published between 1997 to 2008 on treatment practices for the prevention of AF-related stroke reported underuse of anticoagulants for high risk AF patients in most of 54 studies with over two thirds of studies of AF patients with prior stroke/TIA reporting treatment levels of under 60% of eligible patients.[19] Underuse of anticoagulation in patients with AF has been attributed to patient, physician, and healthcare related barriers including inadequate risk stratification, perceived bleeding risk and risk of falls.[19 21 22]

Up until 2009 VKAs, mostly warfarin in the UK, were the only anticoagulants available for AF-related stroke. VKAs have limitations due to inherent properties such as narrow therapeutic window, variable dose response and the need for frequent monitoring. Non-VKA anticoagulants (NOACs), more recently known as direct-acting oral anticoagulants (DOACs), became available from 2009, providing a wider range of options, particularly for patients in whom warfarin is not suitable. Randomised clinical trials demonstrated that DOACs are at least as good as warfarin for preventing stroke and systemic embolism, with major bleeding events similar to or less frequent than warfarin.[23-26] These randomised controlled trial findings need to be validated by real world evidence, particularly as the management of anticoagulant therapy in clinical trials is generally superior compared to that in clinical practice resulting in lower rates of therapeutic failure than usually seen in real life clinical practice.

2.1.4 Study 1

An international longitudinal registry of patients with atrial fibrillation at risk of stroke: the UK study (GARFIELD UK)

GARFIELD-AF (Global Anticoagulant Registry in the FIELD), an international longitudinal registry of patients with atrial fibrillation at risk of stroke was designed to fill this gap. GARFIELD-AF was conducted in 35 countries worldwide, including

the Americas, Europe, Africa, Asia-Pacific and the Middle East between 2009 and 2018. The aim of the registry was to determine the real world clinical management and outcomes of patients newly diagnosed patients with non-valvular AF with at least one additional risk factor for stroke.[27] The objectives of the global study were to assess the rate of stroke and systemic embolisation, the incidence and characteristics of bleeding complications, therapy persistence, and fluctuations in INR for patients on VKAs. The UK protocol included the unique objectives to evaluate the performance of the CHA_2DS_2VASc and HAS-BLED scores in predicting stroke and bleeding risk in the UK study population. In addition, UK study sought to determine the clinician and patient factors associated with the decision to anticoagulated, any variations in anticoagulation associated with ethnicity, and care settings of diagnosis of AF in the UK. GARFIELD-AF was sponsored by the Thrombosis Research Institute, London, and funded through an educational research grant from Bayer Pharma AG. My involvement in the study and the publications submitted as part of this PhD are based on the UK component of GARFIELD-AF.

2.2 Venous thromboembolism (VTE)

2.2.1 VTE

VTE is a global health problem associated with significant morbidity and mortality.[28] VTE comprises the acute conditions of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as the chronic conditions which may arise after acute VTE-such as post thrombotic syndrome and pulmonary hypertension. DVT is the formation of a blood clot in the deep veins (most commonly in the legs), and a PE commonly occurs when part of the blood clot in the legs detaches and travels up to the lung, causing a blockage in the pulmonary artery.

VTE is associated with a significant disease burden with 10 million cases occurring worldwide annually – across low, middle and high income countries.[29] In the U.S. and Europe, VTE-related events kill more people than HIV/AIDS, breast cancer, prostate cancer and motor vehicle crashes combined.[30] The estimated annual incidence rate of VTE among people of European ancestry range from 104 to 183

per 100,000 person years, rates that are similar to that of stroke.[29] DVT has an incidence of approximately 1 per 1,000 per annum.[29] It is associated with significant mortality and serious morbidity, particularly PE and post-thrombotic syndrome which can lead to chronic venous insufficiency and ulceration. 10% to 30% of people die within one month of diagnosis of VTE and 25% of PEs present with sudden death.[28 31-33] Untreated DVT has a mortality rate of 30%, dropping to between 2 and 8% with appropriate preventative therapy.[34] Post thrombotic syndrome develops in 20-50% of patients with DVT.[31 35] VTE recurs frequently with about 30% of patients with VTE experiencing recurrence within 10 years.[29 36]

2.2.2 VTE risk

VTE incidence rates rise markedly with age.[1 29 32] Independent risk factors for VTE include major surgery, active cancer with or without chemotherapy, neurological disease with leg paresis, hospitalisation for acute illness, nursing home confinement, trauma or fracture, pregnancy or puerperium, oral contraception, non-contraceptive oestrogen plus progestin, oestrogen, progestin and BMI.[37 1 32]

Hospitalised patients have a >100 fold increased incidence of VTE compared to residents in the community,[38] and up to 60 percent of VTE cases occur during or after hospitalization.[29] Hospital-associated thrombosis (HAT) is defined as VTE that occurs in hospital and within 90 days after a hospital discharge.[30] It is a common and potentially preventable problem. The risk of VTE in hospitalised patients can be stratified on the basis of age, obesity, previous VTE, thrombophilia, cancer, recent trauma or surgery, tachycardia, acute myocardial infarction or stroke, leg paresis, congestive heart failure, prolonged immobilisation, acute infection or rheumatological disorder, hormone therapy, central venous catheter, admission to an intensive or coronary care unit, white blood cell count, and platelet count.[29] At least two-thirds of cases of HAT are potentially preventable through VTE risk assessment and the administration of appropriate prophylaxis.[39-42 43] VTE prophylaxis is determined by the level of risk and includes mechanical methods (such as anti-embolism stockings, foot impulse and intermittent pneumatic compression devices) and pharmacological treatments (such as heparin and other anticoagulant drugs).

2.2.3 National VTE prevention

A National VTE Prevention Programme in England was launched in 2010, comprising mandatory VTE risk assessment for hospitalized patients and the provision of appropriate prophylaxis.[44 45] The launch of the programme was the culmination of a series of actions in response to a House of Commons Health Select Committee report in 2005 which identified VTE as a significant preventable cause of morbidity and mortality associated with hospitalization.[45] The National VTE prevention programme currently requires that every person aged 16 and over that is admitted to hospital is assessed for VTE risk using the national VTE risk assessment tool, and appropriate thromboprophylaxis prescribed where required (Table 3).[46] The Programme is supported by resources including a national VTE prevention website, and an e-learning resource and the National VTE Exemplar Network which aims to share best practice and improve patient care through more effective prevention and treatment of VTE.[45]

Table 3. Department of Health VTE risk assessment tool

Mobility – all patients (tick one box)	**Tick**		**Tick**		**Tick**
Surgical patient		Medical patient expected to have ongoing reduced mobility relative to normal state		Medical patient NOT expected to have significantly reduced mobility relative to normal state	
Assess for thrombosis and bleeding risk below				**Risk assessment now complete**	

Thrombosis risk			
Patient related	**Tick**	**Admission related**	**Tick**
Active cancer or cancer treatment		Significantly reduced mobility for 3 days or more	
Age > 60		Hip or knee replacement	
Dehydration		Hip fracture	
Known thrombophilias		Total anaesthetic + surgical time > 90 minutes	
Obesity (BMI >30 kg/m2)		Surgery involving pelvis or lower limb with a total anaesthetic + surgical time > 60 minutes	
One or more significant medical comorbidities (e.g. heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)		Acute surgical admission with inflammatory or intra-abdominal condition	
Personal history or first-degree relative with a history of VTE		Critical care admission	
Use of hormone replacement therapy		Surgery with significant reduction in mobility	
Use of oestrogen-containing contraceptive therapy			
Varicose veins with phlebitis			
Pregnancy or < 6 weeks post partum			

Bleeding risk			
Patient related	**Tick**	**Admission related**	**Tick**
Active bleeding		Neurosurgery, spinal surgery or eye surgery	
Acquired bleeding disorders (such as acute liver failure)		Other procedure with high bleeding risk	
Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2)		Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours	
Acute stroke		Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours	
Thrombocytopaenia (platelets< 75x109/l)			
Uncontrolled systolic hypertension (230/120 mmHg or higher)			
Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)			

Adapted from Department of Health[46]

2.2.4 Gaps in national VTE prevention

If 60% of VTE is hospital acquired, it can be argued that the remaining 40% of VTE occurs in residents in the community; the national VTE prevention programme is focused on HAT and it is important to define high-risk patients in the community that may benefit from thromboprophylaxis. Active cancer accounts for almost 20% of all incident VTE occurring in the community,[29] and high risk groups such as patients with cancer and pregnant and post-partum women are now covered in VTE prevention guidelines. Nursing home stay has been identified as an independent risk factor for VTE[47], and US data suggest an eight fold risk of VTE associated in residence with long-term care facility,[28] yet the epidemiology of VTE in care homes remains unclear. Further, it can be argued that care home residents have VTE risks profiles similar to medical inpatients.[48 49] An investigation of rates of VTE in care homes in the UK could advance the prevention of VTE by providing evidence to determine if a systematic approach for identifying care home residents at risk of VTE for VTE prevention is warranted.

Another undeveloped aspect of the national VTE programme is the role of primary care and patients in the prevention of VTE. Patient involvement is an important aspect of the prevention of HAT; yet, to date, much of the focus on preventing HAT has been on health professionals' implementation of the VTE prevention strategy and associated outcomes, and there is little understanding of patients' perceptions and experiences of HAT prevention. HAT can occur up to 90 days post-discharge, yet implementation of the national VTE programme is secondary care orientated and there is no designation of the role of primary care in the national VTE programme. It is recognised that patients are at increased risk during this time with most cases of HAT occurring following discharge.[50] In addition a significant proportion of hospitalised patients at risk of VTE are discharged with mechanical prophylaxis (usually anti-embolism stockings) and/or pharmacological prophylaxis (usually injections of low molecular weight heparin or more recently DOACs).[46 51-53] As such, patients are responsible for appropriate use of VTE prophylaxis and recognition and timely reporting of possible VTE episodes. It is therefore important to understand how well the VTE prevention programme is working from the perspective of patients and how primary care can contribute.

2.2.5 Study 2

Incidence of venous thromboembolism in care homes: a prospective cohort study (VTEC)

The VTEC study was an observational prospective cohort study which aimed to determine the incidence of VTE among care home residents, conducted in care homes in Birmingham and Oxford between 2013 and 2015. A cohort of care home residents were recruited consecutively and followed up for one year. The main outcome of interest was the rate of VTE events per 100 person years. Key secondary outcomes included associated non-hospital interventions, hospital admissions and deaths. The study was funded by the Primary Care Research Trust of Birmingham and Midlands Research Practices Consortium (PCRT) and the NIHR School of Primary Care Research (NSPCR).

2.2.6 Study 3

Exploring prevention and knowledge of venous thromboembolism (ExPeKT)

The ExPeKT study was a mixed methods investigation of barriers to implementation of thromboprophylaxis against hospital acquired VTE.[54] The study included surveys with primary healthcare professionals and patients, as well as interviews with primary healthcare professionals, patients, acute trusts and other relevant organisations. The qualitative component of the study is included in this PhD by Published Work. The qualitative study consisted of semi-structured interviews with patients and primary healthcare professionals in Birmingham and Oxford.

Interviews with recently hospitalised patients explored patients' understanding of VTE risk and their experiences as to how this risk was assessed and managed and health professional interviews explored clinicians awareness of HAT, and views on the current management of HAT, and the role of primary care in managing it. The ExPeKT study was funded by the National Institute for Health Research (NIHR) as part of a larger Programme Grant for Applied Research for the research programme entitled 'Improving the prevention and treatment of venous thromboembolism in hospital and the community'.

2.3 My contribution to the research studies

GARFIELD-UK has been a major focus of my academic work since 2011. My role was UK coordinator and lead researcher responsible for delivering the UK study under the supervision of the Chief Investigator for the UK, Professor David Fitzmaurice. I led on project management of the UK study, with tasks including leading the UK project team, monitoring progress, managing reports and study documentation. I was also responsible for refinement of the UK protocol according to changes in the global study, ethics amendments, training of site staff – comprising of delivering training on the study protocol, GCP training, and the study database. This involved running a number of investigator meetings and also travelling around the country to train CRN nurses, GPs and research nurses over the duration of the study.

I also led on acquisition of data and following initiating the first UK site in June 2011, I went on to successfully engage with and manage a total of 220 UK sites, leading to the UK being the second highest recruiting country out of 35. I led on the operational aspects of transferring study centre from University of Birmingham to University of Warwick in 2017 and set up a new study team. My original contributions to the study include the developing the monitoring plan for the UK, leading on the implementation of corrective and preventative actions, and leading on data cleaning to ensure complete data capture.

In terms of data analysis and dissemination I was instrumental in the development of a publication plan for the UK data in liaison with the UK Chief Investigator, and also made original contributions to global publications plan. In particular, I made intellectual contributions to the global study by offering input on new areas of data analysis to improve understanding and inform practice. For example, I initiated analysis of factors affecting patient refusal of anticoagulation and outcomes of patients who refused anticoagulation which has never been reported, and I'm currently leading a global paper on this. I also leading on comparing outcomes of earlier cohorts with lower rates of anticoagulation with cohorts in which over 70% received anticoagulation in order to understand the impact of the changes in anticoagulation on outcomes. My UK paper on patterns of antithrombotic therapy was the first of the GARFIELD publications to report reasons

why patients with a $CHA_2DS_2VASc \geq$ did not receive anticoagulation, offering insights to gaps that need to be addressed in order to improve the uptake of anticoagulation. Further, I am lead author of the UK publications including ongoing and planned publications not included in this PhD and have regularly presented UK data at several national UK conferences to date (see Appendix D).

I was involved in the VTEC study from the development stage and contributed to the research design and the grant application. I was co-investigator and Research Fellow on the study, and led the academic and operational aspects of the study. I led on writing the study protocol, initial ethics application and subsequent amendments, development and refinement of the case report forms for data collection, and data management, and data analysis.

I played a critical part in data analysis, leading data cleaning and the endpoint adjudication process. This involved personally checking each of the 1011 CRFs for completeness of data, querying any anomalies and actioning cases requiring further data to ensure there was adequate data for endpoint adjudication. For example, cases with a referral for a VTE related test for which the results had not been reported, or cases with an unexplained prescription for anticoagulants. I was responsible for gathering data for endpoint adjudication, for deaths this involved extracting the ONS cause of death data to add to study data, and for hospital admissions it involved ensuring discharge summary and related documents were included in the case notes. With GP consultations I reviewed the available data for each case to identify any consultations related to symptoms suggestive of VTE to put them forward for adjudication. Drawing on my knowledge on VTE from extensive training at the National Centre of Anticoagulation Training (NCAT), I looked for any indication of symptoms of DVT and PE from the consultation as well as insight from the context of care home notes VTE for any changes that could predispose VTE, for example a case with unilateral leg swelling that was hot to touch, or a case with pleuritic chest pain and hemoptysis with a history of a recent period of immobility, infection or dehydration in care home notes.

I also presented the study at regional and national conferences (see Appendix D). At the operational level I supervised and line managed a team of research

nurses, dealt with recruitment challenges, managed the study data including routine data cleaning and securing and managing Office of National Statistics (ONS) cause of death data.

My role in the ExPeKT study was to analyse the qualitative data and get them published. This involved reviewing the study documentation, double-checking consent forms, doing quality checks on the transcripts and extracting participant characteristics from the survey data. I led on the data analysis of the patient interviews, worked with a sub team of qualitative researchers to identify emerging themes, coded the data using Nvivo and analysed the data using framework analysis. I also contributed constructively to the thematic analysis of the health professionals interviews.

This chapter has defined this thesis as a commentary bringing together a portfolio of published Work. It defined the conditions the research covers, discussed the background to the research, highlighted the gaps in knowledge that the research sought to address and introduced the three studies the published work is based on. Together the three studies presented investigate gaps in the systemic prevention of AF-related stroke and VTE and with the overarching aim to reduce the burden of thrombosis.

Chapter 3. Methodology

This chapter discusses the methodology of each of the three studies included in this thesis. A range of diverse research methods are used including quantitative and qualitative research methods and epidemiological approaches.

3.1 An international longitudinal registry of patients newly diagnosed with atrial fibrillation at risk of stroke (GARFIELD-AF): the UK study

3.1.1 Study design

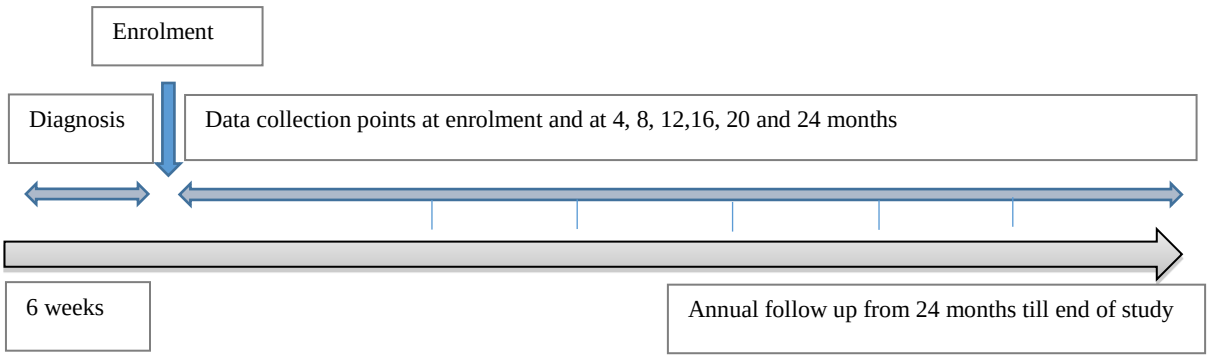
GARFIELD AF was an observational, multi-centre, international, longitudinal, prospective study of men and women newly diagnosed with non-valvular AF with at least one additional risk factor for stroke.[27] Non-valvular AF was defined as AF that was not caused by a heart valve problem. The determination of additional risk factor for stroke was not pre-specified and left to the judgement of the clinician.

Participants were enrolled in five sequential prospective cohorts, and the first cohort included a retrospective validation cohort. The inclusion criteria for the prospective cohorts were: patients aged 18 or older with a diagnosis of non-valvular AF within the past 6 weeks and at least one investigator determined risk factor for stroke. The inclusion criteria for the retrospective cohort were: patients with a diagnosis of non-valvular AF within 6 to 24 months before enrolment and at least one investigator determined risk factor for stroke. The exclusion criteria for both prospective and retrospective cohorts were: patients with valve disease, patients with AF secondary to a reversible cause and patients who did not have capacity to consent for themselves.

The UK component of GARFIELD-AF study (GARFIELD UK) was based in the primary care setting and conducted concurrently with the global study. The primary care setting was chosen because in the National Health Service (NHS) system GPs maintain a complete medical history of their patients and therefore capture patients diagnosed with AF regardless of the care setting in which they were diagnosed and managed. GP practices were recruited from England, Wales, Scotland and Northern Ireland through regional Clinical Research Networks (CRNs) across the UK.

Site Principal Investigators (PIs) and clinical site staff were trained on study procedures and completion of the electronic case report from by either the study team or a research facilitator from their local clinical research network. Participating GP practices identified eligible patients through periodic search of electronic clinical records for new diagnosis. Eligible patients were sent a participant information sheet and invitation to participate. Interested patients called the practices to confirm their interest and book a consent visit with a site staff. After enrolment an electronic case report form was completed from electronic records and follow up data was completed every four months for a minimum of 24 months. Patients were not required to attend the GP practices for the four monthly reviews and data completion was via electronic data capture from GP records. Patients in cohorts 1 to 4 were also followed up until the last patient in cohort five completed the 24-month follow up.

Figure 1. GARFIELD-AF enrolment and data collection (prospective cohorts)



3.1.2 Data collection

Data collected at baseline included demographics, medical history, body mass index, type of AF (new onset AF, paroxysmal AF, persistent AF, permanent AF), treatment strategy initiated at diagnosis. Follow up data included the clinical events and their outcomes- stroke (all types), systemic embolism, coronary syndromes, bleeding events; as well as treatment changes, AF consultations and hospital admissions. The full data collected and clinical outcomes are listed in Appendix C, GARFIELD-AF key facts.

3.1.3 Appropriateness of chosen methodologies

The registry design was appropriate as observing newly diagnosed patients regardless of treatment provides real-world evidence to fill the knowledge gap between clinical trials and real-world practice. Registries are useful in identifying opportunities to improve the quality of care as well as optimise implementation of guideline recommended therapies. In comparison with clinical trials, data from observational registries provides information on a non-selected population, and the extended follow up will provide evidence on what happens to patients over a longer period than other study types. Findings from GARFIELD-AF will therefore support advancements towards better care for patients.

3.1.4 Data analysis

UK data were analysed at baseline for each of the five cohorts. Patient characteristics and medical history were described by cohort. Treatment patterns were analysed by cohort, and by cohort, CHA_2DS_2VAsc, and HAS-BLED scores. Follow up data were analysed overall according the primary study endpoints stroke and systemic embolism, major bleeding, and mortality, and summarised by treatment groups. Statistical analysis was performed using both SAS software V.9.4 and Stata Statistical Software V.14.

A prospective registry is a robust model for collecting data because they identify patients with predefined characteristics and collect outcomes data as and when they occur during the study period. The inclusion of a retrospective validation cohort enabled data for practice prior to sites engaging with the study.

3.2 Incidence of venous thromboembolism in care homes: a prospective cohort study

3.2.1 Study design

A prospective cohort observational study of care home residents in Birmingham and Oxford was conducted to determine incidence rates of VTE. Care homes included care homes with nursing and care homes without nursing as defined by the Care Standards Act.[55] A sample of care homes were recruited to include care homes with

and without nursing, small, medium and large capacity care homes and private/for profit care homes and not for profit care homes. Each resident in the participating care homes was accessed for eligibility and eligible residents were invited to participate in the study. Inclusion criteria were care home resident aged above 18 years and able to provide consent either by personally or via consultee declaration (asking a family member to advise whether a person who lack mental capacity would want to participate). Temporary care home residents and residents with a life expectancy of less than 6 months were excluded. GPs of enrolled participants were recruited to the study in order to access their GP records.

The study endpoint was development of VTE during the study period. VTE events were categorised into three levels of diagnostic certainty: definite VTE where there was clinical evidence of VTE (including radiological or post-mortem diagnosis, evidence of treatment, PE listed as main cause of death in death certificate), probable VTE (high clinical suspicion but no radiological diagnosis), and possible VTE where it could not be ruled out. Each death, hospital admission and GP consultation where there was any indication of VTE symptoms was reviewed independently by two research nurses for any indication they could be VTE related, and any difference of opinion was decided by the chief investigator. All events that could be VTE related were then independently adjudicated by a panel comprising two haematologists and a GP according to the diagnostic criteria definite, probable or possible VTE. Two of the independent referees adjudicated on each event and difference of opinion was judged by a third member.

3.2.2 Data collection

A team of clinical researchers extracted data from participants care home notes and GP records, at baseline and at 12 months follow up, or earlier if the participants died or moved away from the participating care home during the 12 months study period. Baseline data included demographic data, medical history, comorbidities, current medications, and mobility was accessed with the Rivermead Mobility Index.[56] Follow up data comprised hospital admissions (including accident and emergency attendances), deaths and GP consultations. Study data were supplemented with Office of National Statistics (ONS) mortality data.

3.2.1 Appropriateness of chosen methodologies

The care home population is a fragile patient group with a significant proportion lacking mental capacity. The prospective observational cohort study is an appropriate non-invasive study design for this population, and allowed an unselected group of care home residents with individual medical histories to be followed up in their natural environment without any biases.

The use of multiple data sources ensured complete data capture; the care home and GP notes complemented each other and the addition of NHS digital cause of death data flagged up deaths as they occurred so follow up reviews could be completed immediately before care home notes were archived.

3.2.4. Data analysis

Risk of VTE at baseline was calculated using the Department of Health VTE risk assessment tool for hospitalised patients[57] and the QThrombosis score[58] a risk prediction model that quantifies absolute risk of thrombosis at 1 and 5 years (Table 4). VTE incidence was calculated according to 100 person years (PY) of observation with corresponding 95% confidence intervals. The incidence of VTE was calculated according to definite, probable or possible VTE events. Statistical analysis was performed using SAS (version 9.4).

Table 4. QThrombosis predictor variables

Category	Predictor variable
Patient characteristics	Age
	BMI
	Smoking status
	- Non smoker
	- Ex-smoker
	- Light smoker
	- Moderate smoker
	- Heavy smoker
Medical history	Varicose veins
	Congestive cardiac failure
	Chronic renal disease
	Any cancer
	Chronic obstructive airways disease
	Inflammatory bowel disease
	Hospital admission in past 6 months
Current medication	Antipsychotic drugs
	Tamoxifen
	Oral contraceptives
	Hormone replacement therapy

Adapted from Hippisley-Cox J et al[60]

3.3 Exploring prevention and knowledge of venous thromboembolism: a two-stage mixed methods study

3.3.1 Study design

A two-stage, mixed-method study was conducted using surveys with primary healthcare professionals and patients followed by interviews with primary healthcare professionals, patients, acute trusts and other relevant organisations. The study aimed to understand the current practice of thromboprophylaxis for the prevention of HAT, and the knowledge and experience of VTE prevention. The qualitative study with patients and primary healthcare professionals are included in this thesis.

Participants for the qualitative study were identified from the first part of the study; a survey on VTE which also asked participants if they will be willing to be interviewed. The survey was administered to inpatients assessed to be at high risk of VTE, recruited from medical, surgical and orthopaedic wards in two acute trusts in Oxford and Birmingham. Interview participants were purposefully selected according to age, gender, condition requiring hospital stay and site, in order to ensure that the sample reflected a varied range of patients and minimise the risk of the study being distorted to one perspective. A topic guide was developed through discussion with the research team, and comprised open-ended questions that drew reflections on patients' recent hospital admissions with particular reference to their understanding of VTE risk and their experiences of how this risk was assessed and managed.

Similarly, participants for the primary healthcare professional interviews were drawn from respondents of a postal survey that was sent to all GPs and practice nurses and included an invitation to participate in individual interview. The survey was sent to all GPs and practice nurses within the study area. Respondents who had expressed interest in participating in interviews were invited for interview. A topic guide was developed to explore primary healthcare professionals' awareness of HAT, and their perceptions of the role of primary care in preventing HAT.

3.3.2 Data collection

Face-to-face interviews were carried out with patients classed by hospital staff as being at high risk of developing VTE during a recent hospital admission. Telephone interviews were carried out with GPs and practice nurses. A female non-clinical researcher trained in qualitative research carried out both patient and primary healthcare professional interviews and all interview participants provided informed consent. All the interviews were audio recorded and transcribed verbatim.

3.3.3 Appropriateness of chosen methodologies

It is important to understand patient experience in addition to epidemiological data. The rationale of using interviews was to allow detailed exploration of personal perceptions and individual experiences without the contamination of other

participants' views. Interviews allow in depth exploration of patients with lived experience of national VTE programme, as well as the perceptions of primary healthcare professions on the national VTE prevention programme and the role of primary care.

3.3.4 Data analysis

The qualitative data were analysed using framework analysis.[59] Three researchers read a selection of transcripts to familiarise themselves with the interviews and identify merging themes. They then met to compare, discuss and finalise a thematic framework for coding the interviews. The author of this thesis coded the data patient interviews using Nvivo software and a second researcher coded the healthcare interviews manually. The research team interpreted the data by discussing the data in each category and making connections between the data.

This chapter has described the methodologies of the three studies included in this thesis. The studies use different methodologies comprising two observational cohort studies: a multi-site registry study that set standards for quality in registries, and a pioneer study to determine incidence of VTE in care homes, as well as a qualitative study to explore lived experience of patients who received thromboprophylaxis for the prevention of HAT.

Chapter 4. Contributions of the Published Work

This chapter highlights the main results in the Published Work and their contributions to knowledge.

4.1 GARFIELD UK (Paper 1 and Paper 2)

4.1.1 Summary of main results

The GARFIELD-UK protocol paper (Paper 1) provided a scientific record of the novel methodology as adapted to the UK context and demonstrated the strengths of GARFIELD-UK. An original objective in the UK protocol to evaluate the performance of the CHA_2DS_2VASc and HAS-BLED tools generated interest in improved understanding of risk stratification for the global study and was instrumental in the development of the GARFIELD-AF risk tool. The GARFIELD-AF risk tool is a novel risk prediction tool developed using data from 39,898 patients in the global GARFIELD-AF registry and predicts mortality, stroke and bleeding in patients with AF better than the existing tools.[60] The GARFIELD-AF tool offers a more accurate and integrated method to facilitate decisions on anticoagulation of patients with AF and could be incorporated into primary care electronic systems to improve risk stratification of patients with AF.

Whilst the UK has previously participated in international AF registries, GARFIELD-AF is the first international AF registry to plan for enough patients to allow for meaningful national level analyses with comparable global data to understand differences. Methodologically it showcased strengths of primary care research in the UK and adaptation to fit the context with the inclusion of UK specific objectives to maximise benefits to research to the UK. The publication enabled peer review of the methodology for the UK study, enhanced transparency of the research and clarified planned analysis.

The GARFIELD-UK antithrombotic treatment patterns paper (Paper 2) described risk profiles and evolving treatment patterns of UK patients newly diagnosed with AF. It presented baseline risk profiles and antithrombotic therapy initiated at diagnosis for patients enrolled to Cohorts 2 to 5, according to cohort; Cohort 1 was not included as it predominantly consisted of retrospective patients.

The paper documented a significant change in the prescribing after DOACs became available for stroke prevention in AF and also gave an indication of changes in clinical practice after the 2014 update to the NICE AF guidelines.[15] The proportion of patients prescribed with anticoagulants at diagnosis, with or without an antiplatelet, increased consistently from cohort 2 (diagnosed between September 2011 and April 2013) to cohort 5 (diagnosed between June 2015 and July 2016), (C2:54.7%, C3:60.3%, C4:73.1% and C5:73.9% with a corresponding decrease in the use of antiplatelet monotherapy (36.4%, 25.5%, 11.9% and 10.5%). NOAC use increased from a slow uptake of 1.3% in C2 to 43% in C5.

Despite the increase in the use of anticoagulants, a quarter of high-risk patients in the most recent cohort did not receive anticoagulation. The main known reasons why anticoagulants were not given in patients at high risk of stroke were patient refusal and physician choice, with patient refusal accounting for 11.2% of high risk patients in cohort 5 not receiving anticoagulation. On the other hand a substantial proportion of patients at low risk received anticoagulation (up to 50% in the most recent cohort), indicating there are still improvements to be made in reducing the risk of stroke in patients with AF. Over 10% in each cohort received both an anticoagulant and an antiplatelet which may unnecessarily increase bleeding risk.

4.1.2 Impact

The GARFIELD-AF tool could potentially improve risk stratification of patients with AF and ensure patients who need anticoagulants receive them and those that do not need anticoagulants do not receive them. External validation of clinical prediction models is essential prior to implementation in clinical practice in order to verify the robustness and generalisability. Following a successful funding application to the NIHR, I am currently leading a study to validate the GARFIELD-AF tool in UK primary care electronic records.

The treatment patterns paper is a leading source of current practice in the UK on treatment patterns for stroke prevention in AF and reports a shift from the long-standing problem of underuse of anticoagulation in patient with AF and improved

adherence to AF management guidelines.[61] Findings indicate that patients are more often receiving guideline recommended therapy, but they also highlight issues such as co-prescription of anticoagulants and antiplatelets, and anticoagulation of patients at low risk of stroke. Prior to this publication the available evidence was limited to the VKA only era until 2009 and indicated underuse of anticoagulation with less than 70% of patients receiving anticoagulation.[19]

A review of the literature on treatment practices for stroke prevention in patients published in 2016 concluded that oral anticoagulant use was still suboptimal in patients with AF with poor compliance to AF guidelines despite transition into a new era of anticoagulation.[62] A review of contemporary literature of anticoagulation prescription in AF published in 2019 reported an improvement in adherence to AF guidelines with our paper having the most contemporary UK cohort.[61] A systematic review search carried out by the author of this thesis in January 2019 identified a further UK study published in 2019 based on electronic patient records validates our findings and reported a statistical significant increase in prescribing of anticoagulants in AF from 2000 to 2016.[63] In addition, the most recent Quality and Outcomes Framework data (2018-2019) indicates that nationally 86% of patients who were registered with AF and who had been assessed as having $CHA_2DS_2VASc \geq 2$ were being treated with anticoagulation.[64] Further, a more recent publication outside the scope of the literature search indicates that nationally, prescribing of DOACs for patients with AF steadily increased from 9% of all anticoagulants in 2014 to 74% in 2019.[65] These new data indicate there have been further increase since 2016 in the proportion of patients with AF receiving anticoagulation, overall and for DOACs in particular.[64,65] The take up of DOACs is expected to increase further in the current QOF period as DOACs are being initiated routinely instead of VKA and patients on VKA are being switched to DOACs to minimise need for regular INR monitoring during the Covid-19 pandemic.

Overuse in patients at low risk is noticeable in post 2010 literature[62] and the GARFIELD UK data indicates this still persists. What the GARFIELD paper adds that is not addressed by any of the contemporary post 2010 UK studies[63-68] is insight to the reasons why patients at high risk of stroke did not receive AC. Reasons for patients with AF not receiving anticoagulation are generally attributed to the

clinician decision and our finding regarding the role of patient refusal is important in efforts to improve stroke prevention in AF.[22 69]

In sum, the GARFIELD UK publications have made significant original contributions to knowledge, through introducing a focus of analysis that led to the development of the GARFIELD-AF risk tool and the provision of contemporary evidence on prevention of AF-related stroke in the UK.

4.2 Incidence of VTE in care homes (Paper 3)

4.2.1 Summary of main results

The paper on incidence of VTE in care homes was the first publication to report VTE risk profile of UK care home residents and the incidence of VTE in UK care homes. Findings indicated that VTE risk factors common in the care home population; residents had a mean age of 85 years (SD 8.6 years) and the most common risk factors were significantly reduced mobility (58.7%), active cancer (11.6%), obesity (14%), and personal history of VTE (10.1%). However, there was no evidence of VTE risk assessment and use of VTE prophylaxis was virtually non-existent with 0.7% on heparin, 5.5% on anticoagulants for AF, and 5% using compression stockings.

The incidence of definite VTE was 0.71 per 100 PY (95% CI = 0.33 to 1.54), the incidence of definite and probable VTE was 0.83 per 100 PY (95% CI = 0.33 to 1.70) and the incidence of definite, probably and possible VTE was 2.48 per 100 PY (95% CI = 1.53 to 3.79). The incidence of definite and probable VTE was higher in care homes without nursing compared to care homes with nursing (1.10 per 100 PY vs 0.70 per 100 PY). Majority of the definite and probable VTE events were DVTs (71.4%) with PEs accounting for the remaining (16.6%). The incidence of definite and probable VTE related death was 0.12 per 100PY.

4.2.2 Impact

The paper contributes to the discourse on understanding VTE risk outside of the hospital setting in the UK and will inform future research on VTE in care homes.

Prior to this the evidence on VTE in care homes was limited to studies in the US and Israel; the previously reported rates range from 1.30 per 100 PY[70] to 3.68 per 100 PY.[71-73] These rates are higher than the rates of definite and probably VTE in the VTEC study, however these were retrospective studies which relied on administrative data subject to misclassification, and included VTE events that occurred before care home admission. VTEC was the first prospective study on VTE in care homes with robust standards for ascertainment of VTE events and all events verified to have occurred during care home stay. However the VTE incidence we reported is likely to be an underestimate because VTE is often silent and the study did not include post mortems.[74-76] A previous post mortem study of nursing home deaths found undiagnosed VTE to be cause of death in 8% of residents with up to 40% unsuspected prior to death.[74] Nevertheless the incidence of definite and probable VTE found by the VTEC study was seven times higher than the community incidence of 0.117 per 100 person-years[28] and twice as high as the incidence in people aged ≥ 70 years.[77]

In 2016 the All Party Parliamentary Group on Thrombosis (APPGT) identified lack of guidance on VTE prevention in care homes based on an information request from CCGs across the country on current standards for the prevention and management in care homes. A report based on the findings emphasised the need for academic studies are needed to clinically establish the extent to which care home residents in England are at an increased risk of preventable blood clots, and what the appropriate threshold for thromboprophylaxis should be.[78] Following the interest of the APPGT on research I was invited to present the study findings at the 2016 APPGT conference at the House of Commons. VTE in the care home setting remains under-researched and the VTEC publication remains the only primary research on VTE in care homes in the UK and internationally the only prospective study on VTE in care homes. A US study published in 2018 found an incidence rate nearly of 3,653 per 100,000 nursing home person-years, representing nearly 30 times the published incidence rates for that community.[79] The APPTG's 2015 Annual Survey of hospital trusts in England found that found care home residents were disproportionately represented in patients admitted to hospital for VTE, with an average of 4% of patients (and up to 14% in one area) admitted to hospital for VTE in 2014/15 being residents of elderly care

homes whilst care home residents only comprise approximately 0.5% of the population of England and Wales.[78] These data together with evidence from VTEC indicates that better understanding of VTE risk in the care home population can lead to improvements in VTE prevention.

4.3 Exploring patients and primary care health professionals perspectives of VTE prevention (Paper 4 and Paper 5)

4.3.1 Summary of main results

The paper on patients' perspectives of the prevention of HAT (Paper 4) provided an improved understanding of patients' knowledge and perceptions of HAT and their experiences of the national VTE prevention program. The key themes that emerged from the patient interviews are presented in Table 5. All the participants were surgical patients and most were hospitalised due to planned admission (87.1%). Patients who received prophylaxis for HAT were aware of a risk of blood clots; however they lacked a good understanding of VTE and the individual conditions DVT and PE. Patients with planned surgery were more knowledgeable of VTE compared to patients on emergency admission due to attendance at a pre-surgical assessment which usually included patient education on VTE.

Most of the participants were discharged with VTE prophylaxis; experiences of VTE prophylaxis were characterised with good adherence to heparin injections and poor adherence to anti-embolism stockings, largely due to perceived lack of clarity in guidance from health professionals in terms of whether they were required to wear them post discharge and / or how long to continue wearing them for. Reasons for discontinuation included discomfort and the perception that they were no longer required due to heparin injections or improved mobility. Participants recognised that experiencing VTE symptoms was a medical emergency, however they had limited knowledge on the signs and symptoms of VTE, particularly of the potentially fatal complication of PE, and side effects of anticoagulants.

Table 5. Themes and subthemes from patient interviews

Patients' perceptions and experiences of HAT

Awareness of VTE risk	**Experience of VTE prophylaxis**	**Knowledge of VTE symptoms**	**Post discharge support**	**Perceived gaps in patient education**
VTE risk assessment	Injections (perceptions and adherence)	Inadequate knowledge of symptoms	Perceived role of primary care	Patient education and public awareness
	Stockings (perceptions and adherence)	Reaction in the event of symptoms		

The primary care perspective paper (Paper 5) was based on interviews with 12 GPs and two primary care nurse practitioners drawn from a mix of urban/rural practices with list sizes ranging from small to large. Findings were centred around two key themes; influences on HAT prevention in primary care and suggestions for improving current systems. Factors influencing HAT prevention in primary care included limited awareness of VTE among GPs, poor coordination between primary and secondary care, and logistical constraints. Whilst primary care professionals were aware of HAT risk, their awareness of guidelines for VTE prevention and VTE risk factors was limited. GPs reported they had not received training on prevention of VTE and their only related experience was warfarin management. Primary care professionals were of the opinion that VTE prevention was the responsibility of clinicians in secondary care and would not routinely be involved except in special cases flagged up for GP involvement such as patient requiring extended prophylaxis or when a patient self-reports with any issues.

Whilst GPs acknowledged a potential role in patient education, this was limited by lack of training in VTE prevention. Further GP post-discharge involvement was dependent on appropriate communication from secondary care, both in the form of discharge communication and patients receiving adequate information so they are aware of when they need to seek medical review or GP involvement. Whilst GPs felt VTE prevention best managed in secondary care, they

acknowledged that GPs could contribute to VTE prevention and this would require training, funding and improved discharge communication in primary care.

4.3.2 Impact

The findings from the patient interviews highlight the significance of patient involvement in VTE prevention. Our study identified the need for improved education of hospitalised patients on HAT, particularly around the signs and symptoms of VTE and clarity on the use of thromboprophylaxis post-discharge. Improved patient education will optimise prevention of HAT under the National VTE prevention programme.

The main contribution of the primary care interviews is the conclusion that providing VTE training to primary care professionals and improved discharge communication specifying patients VTE risk and prophylaxis prescribed will enable primary care to contribute effectively to the prevention of HAT.

The patients' perspectives paper is making an impact in VTE prevention and is cited as a source of as evidence in 2018 update on VTE prevention guidelines for adult and young people aged 16 and over.[46] The updated guidelines includes new recommendations on giving information and planning for discharge related to the findings reported in the paper. This includes recommendations around discharge on giving patient and their family member verbal and written information on the signs and symptoms of DVT ad PE and the importance of seeking help if these or any adverse event are suspected, and recommendations on giving people discharged with VTE prophylaxis the importance of using it correctly, continuing treatment for the recommended duration.[46]

This chapter has presented the key findings from the research studies and provided a commentary on the contributions of the research.

Chapter 5. Conclusions

This PhD by Publication on the prevention of thrombosis focused on three research studies on the prevention of AF-related stroke and VTE. This thesis has presented the rationale for the research, discussed the methodology and how the research has contributed to knowledge. This final chapter highlights the implications of the research, describes the research questions that emerge from this PhD and ways to address these, and reflects on the research process.

5.1 Implications of the research

The findings from this PhD has a number of implications for patients, clinicians and practice. Findings from GARFIELD UK indicate an improvement in the management of AF with patients more often receiving guideline recommended therapy. At the same time, a quarter of patients at high risk of stroke do not receive anticoagulation; findings also raise questions regarding overtreatment in patients at low risk of stroke, co-prescription of anticoagulants and antiplatelets, which may put patients at an unnecessary increased risk of bleeding, and patient refusal of anticoagulation. Patient refusal of anticoagulation, whilst an acceptable outcome of shared decision-making, has implications on clinical outcomes of patients and national efforts to reduce the burden of AF-related stroke.

Findings from the VTEC study indicate care home residents are at increased risk of VTE. VTE risk assessment is not routinely conducted in care homes; therefore, it is important for clinicians to consider VTE risk in their care of care home residents. This has implications for clinicians in terms of training, particularly as the ExPeKT primary care interviews indicated that primary care professionals lack adequate knowledge of VTE prevention. VTE training for primary care professionals would also carve a role for primary care on the prevention of VTE in the community and better equip primary care professionals to support the prevention of HAT. Further, extending VTE training to care home staff will enable them recognise the signs and symptoms of VTE and facilitate detection and management of VTE in care homes. In terms of service delivery, it is important for commissioners of health services to define tailored pathways for assessment and

diagnosis of VTE in care home residents as care home residents may have barriers to accessing the conventional routes for investigating suspected VTE.

Patients' perspectives of the prevention of HAT highlighted gaps in patient education, which hinders patient involvement in VTE prevention. This has implications for practice in terms of adopting a systematic approach to patient education on VTE; the findings are already having an impact on practice following the incorporation of detailed recommendations regarding patient education in the updated NICE VTE prevention guidelines.

5.2 Future research

5.2.1 Prevention of AF-related stroke

Despite an improvement in management of patients with AF, anticoagulation remains sub-optimal due to patients at low risk being anticoagulated and missed opportunities to prevent AF-related stroke due to patient refusal and clinician factors. Research questions emerging from this PhD include queries around why a quarter of high risk patients do not receive anticoagulants but half of patients at low risk of stroke receive anticoagulants, what are the outcomes of patients who are co-prescribed anticoagulants and antiplatelets, why do patients refuse anticoagulants, and what are the outcomes of patients who refuse anticoagulation. GARFIELD-AF will provide insight into some of these issues; ongoing analysis of GARFIELD-UK data will inform on outcomes of patients in relation to the antithrombotic treatment received, and I am leading an analysis of global GARFIELD-AF data on factors associated with patient refusal of anticoagulation and outcomes of patients who refuse anticoagulation. Further appropriate investigation of patient refusal of anticoagulation would be a qualitative study to explore patients' beliefs around AF-related stroke and anticoagulation and clinicians experiences.

5.2.2 Prevention of VTE

The primary research question emerging from the VTEC study is - which care home residents are at increased risk? Further evidence on risk stratification will inform

guideline development for prevention of VTE in care homes. A secondary analysis of primary care electronic health records linked with hospital episode data and ONS mortality data would be an appropriate way to determine comparable VTE incidence rates in the care homes, in the community and among age groups, as well as determination of risk factors for each of the population groups of interest. Differences in methodological approaches affect incident rates reported by VTE studies, making comparison of VTE incidence across studies and patient populations difficult; the proposed methodology will address challenges of interpreting the data.

Findings from the patients' perceptions study emphasise the importance of patient insight in evaluating evidence-based approaches to the prevention of thrombosis. At the time of the qualitative study, DOACs had not been approved for the prevention of HAT; DOACs are a convenient option for patients with difficulty in administering heparin injections' however little is known on patients' experiences of DOACs for this purpose. Research on patients' perspectives of DOACs for the prevention of HAT will further inform on success of the national VTE prevention strategy.

5.3 Reflections of the research

5.3.1 Strengths and limitations

GARFIELD UK

The strengths of GARFIELD-AF lie in the strategies employed to minimise the limitations usually associated with registry studies. Firstly, patients were consented and enrolled within 6 weeks of diagnosis; this eligibility criterion ensured the sample included patients who may not survive long after AF diagnosis by capturing disease burden early on. Secondly, GARFIELD-AF was conducted to high quality standards with 20% source data verification under the supervision of an independent Audit Committee.[80] Corrective and preventative actions were implemented to address any discordance between the study protocol and findings from the audit.

A limitation of the GARFIELD-AF study is that it did not engage with patients and clinicians to explore some of the patterns of prescribing and the

patient's role. A qualitative exploration would have given insight into the reasons behind some of the clinical practices that were contrary to AF guidelines.

VTEC

The main strengths of the VTEC study was the prospective nature of the study design and the ascertainment and adjudication of VTE events according to pre-specified clinical criteria. Although the VTEC findings gave an indication of increased VTE risk in care home residents, the study was limited by the small number of definite VTE events. A larger number of definite VTE events would have allowed for further understanding of VTE in care homes and possibly the development of a clinical prediction model for estimating the probability of the occurrence of VTE in the VTE population.

It is clear the study probably missed many VTE events due to its observational nature with data collection limited to case notes reviews only. There was a high prevalence cases with inconclusive symptoms indicative of VTE which were not explored further. For example many patients had episodes of red, hot, and swollen leg(s) attributed to cellulitis which remained unresolved despite repeated courses of antibiotics. If I had the opportunity to do the study again, I would include measures to actively detect VTE in patients presenting with symptoms such as the Wells score,[81,82] d-dimers to be measured at baseline and monitored routinely during the study. I would explore the use of less invasive point of care finger prick d-dimer devices and trained sonographers to scan legs of participants with symptoms suggestive of DVT with a portable Doppler scan on site to improve detection of VTE, and referral of participants with a high clinical suspicion of VTE for a CT pulmonary angiogram. Further, theoretically it would be worth considering exploring conducting post mortems in such a follow up study, particularly as a quarter of participants died within the one year follow up although the sample did excluded residents with a life expectancy of less than 6 months, and data from a care home post mortem study of nursing home residents reported undiagnosed VTE as cause of death in 8% of residents.[74]

ExPeKT

Face-to-face interviews with patients provided in-depth exploration of the issues, and analysis was independent of the interviewing researcher. The research team was multidisciplinary and offered different perspectives which enhanced interpretation of the data.

The study sample was not representative of hospitalised patients as it did not include medical in-patients. Also the sample did not include patients on DOACs which are now routinely used for the prevention of HAT, however the thromboprophylaxis used by the study sample was a reflection of practice at the time the study was undertaken.

5.3.2 Challenges in conducting the research

Each of the studies faced unique challenges in the conduct of the research. The key challenge for GARFIELD UK was site retention - the study took place over a period of 7 years with the first UK patient enrolled in 2011 and final follow up completed in 2018, over the course of the a number of sites withdrew from the study due to PIs or staff issues. As the lead researcher I sought to minimise the loss of data by negotiating with withdrawing sites to complete the minimum follow up period of 24 months for patients already enrolled in the registry and engaging with local CRNs provided support data completion for sites unable to do so. In order to maintain patient recruitment numbers, replacement sites were recruited on a rolling basis. The study sought to maintain site retention by engagement through newsletters and annual investigator meetings to update site staff and report interim findings.

The VTEC study had a number of challenges; firstly, the NHS research ethics committee initially declined the inclusion of care home residents without capacity. This was reversed after the study team made a case to the ethics committee on the importance of including this patient group in order to achieve a sample that was representative of the care home population. Secondly, recruitment of residents without capacity was initially challenging as family members who would provide consultee declaration generally visited at weekend and evenings when research nurses were not on site. This was resolved by using postal consultee declarations following an amendment approved by the ethics committee. The designated

consultee of all eligible patients without capacity were sent information about the study with a consultee declaration form to be returned in a prepaid envelope to the research team.

Further there was a problem accessing GP records for some participants as a few GPs declined to give access to GP records altogether whilst some engaged with the study but declined access to notes of patients who had died. There was also a problem with attrition and some participants were lost to follow up after moving to a different care home due to a need to nursing care or being discharged to a different care home following a hospital admission.

The main challenge with ExPeKT was the recruitment of GPs; even though sufficient numbers expressed an interest in being interviewed, it was difficult to find suitable time for the telephone interview, as many GPs were too busy to find time for the interviews.

5.3 Concluding remarks

This PhD has covered prevention of thrombosis by drawing on five publications from three studies on AF-related stroke and VTE. The last decade has seen advances in the prevention of these two thromboembolic conditions. Firstly the prevention of AF-related stroke has seen the introduction of new guidelines, availability of a wider range of anticoagulant options, and improved prescribing of anticoagulants for patients with AF in the UK and internationally. Secondly, 2020 marks the 10th anniversary of the National VTE prevention programme. Over the past decade, the VTE prevention programme has embedded systematic VTE prevention into the NHS and achieved substantial reduction in mortality and morbidity associated with HAT.[45 83-86] In spite of these advances there are ongoing challenges and the need to improve prevention of AF-related stroke and VTE persists. This can be achieved through improved application of existing AF guidelines and VTE guidelines from both the patient and clinician perspective as well as further investigations on VTE risk in the community in order to extend the VTE guidelines to high-risk patients outside the hospital setting. The research presented here and the further research

recommended will complement scientific research to further advance the prevention of thrombosis in the UK and globally.

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Appendices

Appendix A. Statement of candidate's contribution to the publications signed by co-authors

Appendix B. Publications included in the thesis

Appendix C. GARFIELD-AF key facts

Appendix D. List of candidate's conference proceedings for research included in this PhD by Published Work

Appendix E. Full bibliography of candidate

Appendix A. Statement of candidate's contribution to the publications signed by co-authors

Paper 1

An international longitudinal registry of patients with atrial fibrillation at risk of stroke (GARFIELD): the UK protocol

Apenteng PN, Murray ET, Holder R, Hobbs FR, Fitzmaurice DA. An international longitudinal registry of patients with atrial fibrillation at risk of stroke (GARFIELD): the UK protocol. BMC cardiovascular disorders. 2013 Dec;13(1):31.

Patricia Apenteng contributed to the development of the study protocol and conceived the idea of the paper. She led in writing the paper in liaison with Ellen Murray and David Fitzmaurice and the contribution of other co-authors.

I agree that Patricia Apenteng made the aforementioned contribution to this paper		
Name	*Signature*	*Date*
Dr Ellen Murray	[redacted]	18/02/20
Dr Roger Holder		
Professor Richard Hobbs	[redacted]	23/1/20
Professor David Fitzmaurice	[redacted]	10/12/19

Paper 2

Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry
Apenteng PN, Gao H, Hobbs FR, Fitzmaurice DA. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. BMJ open. 2018 Jan 1;8(1):e018905.

Patricia Apenteng conceived the idea of the paper and led in writing the paper in liaison with her co-authors. She supervised data collection, contributed to analysis and interpretation of the data, and responded to reviewers as corresponding author.

I agree that Patricia Apenteng made the aforementioned contribution to this paper		
Name	*Signature*	*Date*
Dr Haiyan Gao	[redacted]	05 February 2020
Professor Richard Hobbs	[redacted]	23/1/20
Professor David Fitzmaurice	[redacted]	10/12/19

Paper 3

Incidence of venous thromboembolism in care homes: a prospective cohort study
Apenteng PN, Hobbs FR, Roalfe A, Muhammad U, Heneghan C, Fitzmaurice D. Incidence of venous thromboembolism in care homes: a prospective cohort study. Br J Gen Pract. 2017 Feb 1;67(655):e130-7.

Patricia Apenteng contributed to the conception of the study, wrote the protocol, and led on the development of the research tools. She obtained ethics and regulatory approvals, supervised data collection, and contributed to data analysis. She led in writing the paper and responded to reviewers in liaison with corresponding author David Fitzmaurice.

I agree that Patricia Apenteng made the aforementioned contribution to this paper		
Name	*Signature*	*Date*
Professor Richard Hobbs	[redacted]	23/1/20
Mrs Andrea Roalfe	[redacted]	13/1/2020
Mr Muhammad Usman		
Professor Carl Heneghan	[redacted]	18/1/20
Professor David Fitzmaurice	[redacted]	10/12/19

Paper 4

Patients' perceptions and experiences of the prevention of hospital-acquired thrombosis: a qualitative study

Apenteng PN, Fitzmaurice D, Litchfield I, Harrison S, Heneghan C, Ward A, Greenfield S. Patients' perceptions and experiences of the prevention of hospital-acquired thrombosis: a qualitative study. BMJ open. 2016 Dec 1;6(12):e013839.

Patricia Apenteng led on developing the concept of the paper and the data analysis. She led in writing the paper in liaison with her co-authors and responded to reviewers as corresponding author.

I agree that Patricia Apenteng made the aforementioned contribution to this paper		
Name	*Signature*	*Date*
Professor David Fitzmaurice	[redacted]	10/12/19
Dr Ian Litchfield		17.12.19
Dr Sian Harrison		7/1/20.
Professor Carl Heneghan		18/1/20
Dr Alison Ward		
Professor Sheila Greenfield	[redacted]	17/12/19

Paper 5

Prevention of hospital-acquired thrombosis from a primary care perspective: a qualitative study
Litchfield I, Fitzmaurice D, Apenteng P, Harrison S, Heneghan C, Ward A, Greenfield S. Prevention of hospital-acquired thrombosis from a primary care perspective: a qualitative study. Br J Gen Pract. 2016 Aug 1;66(649):e593-602.

Patricia Apenteng contributed to developing the concept of the paper. She contributed constructively to the thematic analysis of the data and provided detailed comments and amendments on successive drafts of the manuscript.

I agree that Patricia Apenteng made the aforementioned contribution to this paper		
Name	*Signature*	*Date*
Dr Ian Litchfield	[redacted]	17.12.19
Professor David Fitzmaurice		4/2/19
Dr Sian Harrison		7/1/20
Professor Carl Heneghan		18/1/20
Dr Alison Ward		
Professor Sheila Greenfield	[redacted]	17/12/19

The following co-authors were uncontactable:

- Dr Roger Holder (Paper 1) has retired and uncontactable.
- Mr Muhammad Usman (Paper 3) has left the University of Birmingham and is uncontactable.
- Dr Alison Ward (Paper 4 and Paper 5) has retired and is uncontactable.

Appendix B. Publications included in the thesis

BMC Cardiovascular Disorders

STUDY PROTOCOL Open Access

An international longitudinal registry of patients with atrial fibrillation at risk of stroke (GARFIELD): the UK protocol

Patricia N Apenteng[1], Ellen T Murray[1], Roger Holder[1], F D Richard Hobbs[2], David A Fitzmaurice[1*] and UK GARFIELD Investigators and GARFIELD Steering Committee

Abstract

Background: Atrial fibrillation (AF) is an independent risk factor for stroke and a significant predictor of mortality. Evidence-based guidelines for stroke prevention in AF recommend antithrombotic therapy corresponding to the risk of stroke. In practice, many patients with AF do not receive the appropriate antithrombotic therapy and are left either unprotected or inadequately protected against stroke. The purpose of the Global Anticoagulant Registry in the FIELD (GARFIELD) is to determine the real-life management and outcomes of patients newly diagnosed with non-valvular AF.

Methods/design: GARFIELD is an observational, international registry of newly diagnosed AF patients with at least one additional investigator-defined risk factor for stroke. The aim is to enrol 55,000 patients at more than 1000 centres in 50 countries worldwide. Enrolment will take place in five independent, sequential, prospective cohorts; the first cohort includes a retrospective validation cohort. Each cohort will be followed up for 2 years. The UK stands to be a significant contributor to GARFIELD, aiming to enrol 4,582 patients, and reflecting the care environment in which patients with AF are managed. The UK protocol will also focus on better understanding the validity of the two main stroke risk scores ($CHADS_2$ and $CHA_2DS_2VAS_C$) and the HAS-BLED bleeding risk score, in the context of a diverse patient population.

Discussion: The GARFIELD registry will describe how therapeutic strategies, patient care, and clinical outcomes evolve over time. This study will provide UK-specific comprehensive data that will allow a range of evaluations both at a national level and in relation to global data and contribute to a better understanding of AF management in the UK.

Trial registration: ClinicalTrial.gov: NCT01090362

Keywords: Anticoagulation, Atrial fibrillation, Registry, Stroke, Vitamin K antagonists

Background

Atrial fibrillation (AF) is the most common clinically significant arrhythmia in the adult population; it is an independent risk factor for stroke and mortality. People with AF have a fivefold increased risk of stroke and a twofold increased risk of death [1]. Prevalence of AF increases throughout life, affecting less than 1% of individuals under 60 years, approximately 4% of individuals over 60 years, and up to 10% of over those aged 80 years [2,3].

The estimated diagnosed prevalence of AF in the UK is around 1.4% [4,5], and more than 46,000 new cases of AF are diagnosed every year [6]. About 15% of all strokes are caused by AF, and 12,500 strokes each year in England are thought to be directly attributable to AF [7]. Furthermore, AF-related strokes are more serious: they are more likely to be fatal than strokes in patients without this arrhythmia; among patients who survive, these strokes cause more disability with less likelihood of independent recovery [8]. For example, findings from

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the Framingham study indicate that mortality is increased 1.84-fold in strokes in people with AF compared to those in sinus rhythm, and recurrence is more frequent [9]. The Copenhagen stroke study found that patients with AF require longer hospital stays (50 days versus 40 days, $P < 0.001$) and a lower discharge rate to their own homes (odds ratio 1.7; 95% confidence interval [CI] 0.44 to 0.85) with poorer neurological and functional outcomes [8]. Further, data from the European community stroke project show that AF increased by 50% the probability of remaining disabled (odds ratio 1.43; 95% CI 1.13 to 1.80) or handicapped (odds ratio 1.51; 95% CI 1.13 to 2.02) [10].

Management of AF requires either a rate-control strategy to slow the ventricular rate or a rhythm-control strategy in an attempt to maintain sinus rhythm. Regardless of whether the rate-control or the rhythm-control strategy is pursued, antithrombotic therapy for prevention of stroke and thromboembolism is a fundamental management tool.

Oral anticoagulants are effective in the reduction of stroke and thrombolytic events among patients with AF. Vitamin K antagonists (VKAs) are the most widely used anticoagulants and adjusted-dose warfarin has been shown to reduce the risk of stroke by approximately 60% in patients with AF [9]. However, in practice the use of VKAs is not universal [10]. As a result, only about one-half of the patients who should receive antithrombotic therapy to prevent thromboembolic stroke actually receive it [11].

Risk stratification is important when considering anticoagulation, as the risk of stroke in AF patients is dependent on clinical predictors [12]. A recent stroke risk stratification scheme, CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]), has been proposed as an alternative to $CHADS_2$ [13]. CHA_2DS_2-VASc adds further variables to $CHADS_2$ – age 65–74, female sex, and vascular disease, and thromboembolism in addition to stroke/ transient ischaemic attack (TIA).

Anticoagulant therapy carries a risk of bleeding, and major bleeding such as intracranial bleeds can be catastrophic. Bleeding risk-stratification schemes assess the risk of major bleeding for patients on anticoagulation to help determine the risk–benefit balance in AF. A novel bleeding risk score – HAS-BLED (Hypertension, Abnormal renal/liver function [1 point each], Stroke, Bleeding history or predisposition, Labile international normalised ratio [INR], Elderly [>65], Drugs/alcohol concomitantly [1 point each]) [14] – is gaining recognition internationally [12] and in the UK, and could potentially improve assessment of bleeding risk in patients with AF.

In 2006 the National Institute for Health and Clinical Excellence (NICE) published guidelines for the management of AF, with priorities on identification and diagnosis of AF, treatment of AF, and provision of antithrombotic therapy [15]. One of the key recommendations of the guidelines is a formal assessment of the risk of thromboembolism using a stroke risk stratification and thromboprophylaxis algorithm (Figure 1). The guideline proposes routine anticoagulation with warfarin for patients at high risk of stroke, and aspirin for those at low risk of stroke.

The prevalence of AF in the UK is increasing, probably due to the ageing population and improved survival from conditions predisposing to AF, including, for example, myocardial infarction. A large population-based study of the epidemiology and treatment of AF in the UK found prevalence of diagnosed AF rose steadily (0.84% in men in 1994 compared with 1.49% in 2003, compared with 0.83% and 1.29%, respectively, in women) [4]. The number and proportion of AF patients in the UK prescribed antithrombotic therapy has progressively increased over time [4,16]. An analysis of national data from 1994 to 2003 found under one-half of all AF patients received any antithrombotic treatment in 1994 but around 80% received some sort of stroke prevention in 2003 [4]. Also, treatment of AF with oral anticoagulants more than doubled from 1994 to 2003 in men (25% to 53%) and has increased significantly women (32% to 40%) [4]. However, the use of anticoagulants remains inappropriate [4,17] and the NICE 2006 costing report estimated that 46% of patients who should be on warfarin are not receiving it [18]. There is also evidence to suggest underuse of anticoagulation in the elderly; for example, in one study elderly patients (age >85 years) were less likely to initiate warfarin (relative rate 0.16, 95% CI 0.15 to 0.18) and more likely to start aspirin (relative rate 1.66, 95% CI 1.47 to 1.88) compared with patients aged 40–64 years [17].

Much of the UK evidence is based on retrospective cross-sectional studies and was derived from prevalence data. As such, there is limited evidence on persistence of treatment with antithrombotic therapy and it has been indicated that only 60% of patients prescribed warfarin continue for at least 2 years [17]. Also, much of the available evidence relates to AF management prior to the publication of the NICE guidelines in 2006. It is not clear how well clinicians adhere to these guidelines and what impact this has had. There is an absence of contemporary longitudinal data on the clinical management of AF in the UK, including the key therapeutic area of antithrombotic therapy, persistence of therapy, and related clinical outcomes.

Importance of GARFIELD UK

The Global Anticoagulant Registry in the FIELD (GARFIELD) is an observational, international, longitudinal registry of patients newly diagnosed with AF at risk of

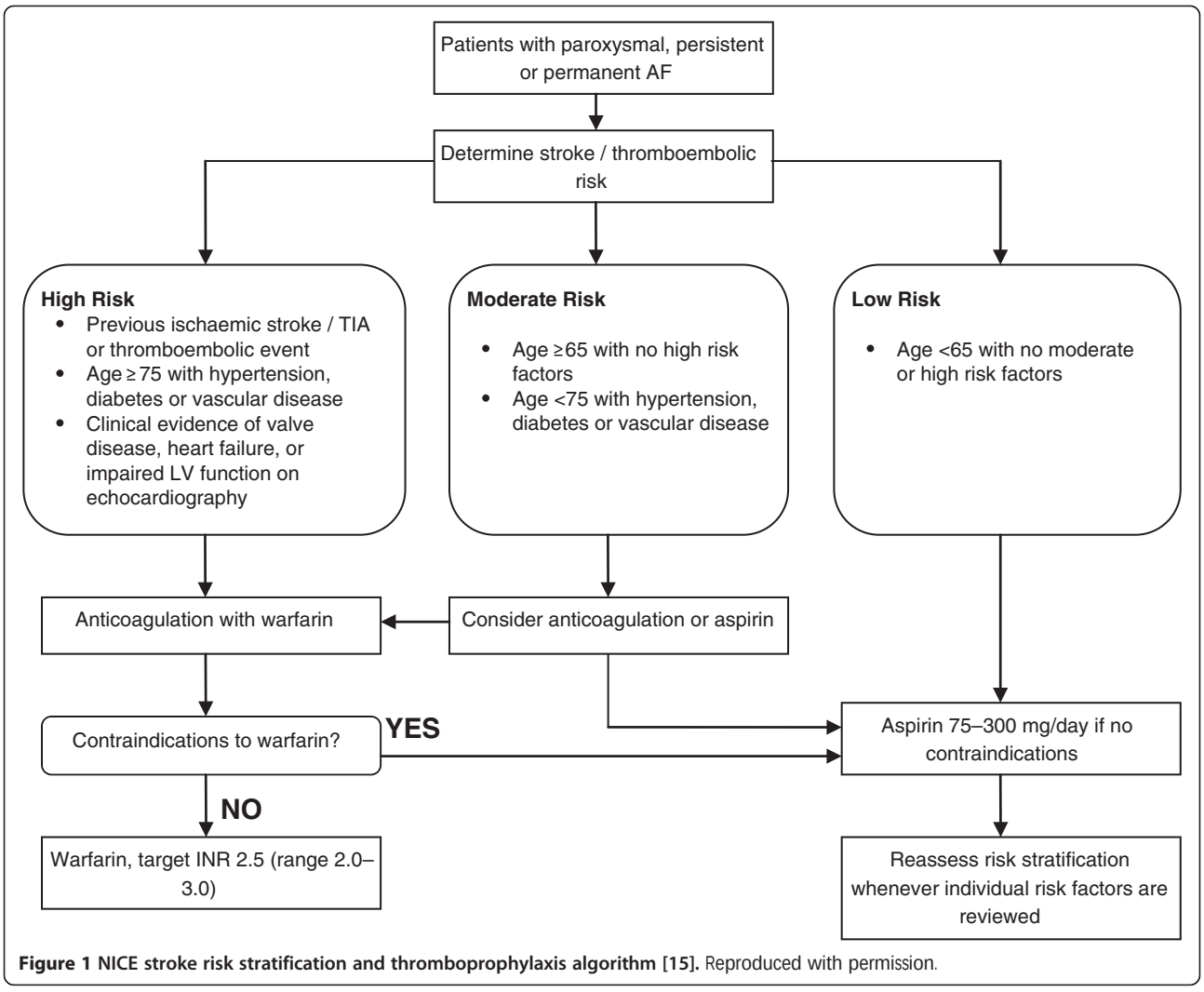

Figure 1 NICE stroke risk stratification and thromboprophylaxis algorithm [15]. Reproduced with permission.

stroke, and aims to determine real-life treatment patterns and clinical outcomes. The global study aims to recruit 55,000 patients in five sequential cohorts of 10,000 patients each, alongside a validation cohort of 5000 patients. The methods for the global study have been published [19]. The UK is the only country undertaking GARFIELD to have its own protocol; the UK protocol was developed from the global protocol and adapted to the UK context to maximise the value of GARFIELD to the UK. It therefore has a slightly different design and includes important and original specific research questions relevant to the UK population. Tailoring the protocol to the UK allowed it to be adopted by the Primary Care Research Network portfolio of research. A number of publications will emanate from the UK-specific data over the course of the study to provide real-life contemporary evidence. As such, this paper is an important point of reference for the UK study. Principally, the UK study will review the management of AF in the UK and evaluate clinical practice against guideline recommendations.

Methods/design

Study design

GARFIELD in the UK is primary care based and aims to recruit 4,582 patients at more than 100 sites across the UK. Enrolment will take place in five independent sequential cohorts, parallel to the global study. Similar to the global study, Cohort 1 will include a retrospective validation cohort of patients diagnosed with AF between 6 months and 24 months previously. Data will be extracted through a case notes review at baseline, and at every 4 months until 24 months after diagnosis. The data will be collected using an electronic case report form (eCRF). A summary of the UK study design is provided in Figure 2.

Study aims

The key aims of the GARFIELD registry are to determine the real-life treatment patterns and clinical outcomes of newly diagnosed patients with non-valvular AF with at least one additional risk factor for stroke.

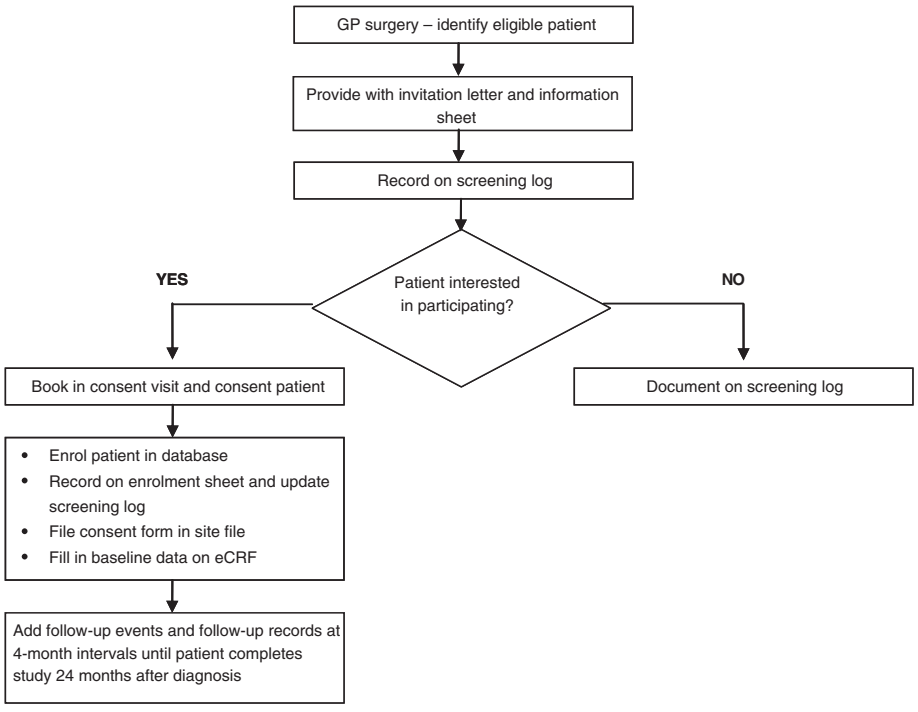

Figure 2 Summary of UK study design.

In accordance with the global objectives, the study will assess the rate of stroke and systemic embolisation, and assess the outcome of these events with specific reference to:

- The incidence and characteristics of bleeding complications (e.g. location and severity, classified as major, clinically relevant non-major, and minor);
- Therapy persistence, including discontinuation, interruption, and changes of therapy regimen;
- For patients on VKAs, fluctuations in the INR over time.

The UK protocol has additional objectives that will inform the management on AF. GARFIELD in the UK seeks to evaluate the performance of the novel stroke risk score CHA_2DS_2-VASc in comparison with $CHADS_2$ in predicting stroke risk in the UK study population. Likewise it will evaluate the effectiveness of the bleeding risk score HAS-BLED in predicting bleeding risk within the UK study population. In addition, the study will determine the clinician and patient factors associated with the decision to anticoagulate patients. Another unique objective of the UK study is to determine any variations in levels of anticoagulation associated with ethnicity. Furthermore, the study will determine where patients are principally diagnosed with AF and assess the role of primary care in the management of AF in the UK.

Study setting

In the UK, all healthcare delivery is centred on the general practitioner (GP), with referrals for specialists and for routine admission to hospital organized at the GP level. As a result of the National Health Service structure, GPs maintain in their surgeries a complete medical history of their patients. Recruiting from the general practices will therefore capture all patients diagnosed with AF regardless of their care settings, and in the UK, these include hospital departments (cardiology) and emergency settings. The UK is therefore recruiting solely from the primary care setting; nevertheless, we expect to achieve a representative sample of patients with AF being cared for in the UK, comparable to the sample recruited in the global study.

Investigator sites (GP practices) will be representative of the UK, and will include sites in England, Wales, Scotland, and Northern Ireland, with the aim of achieving a sample representative of the geographical distribution of the UK population. Practices will be recruited and trained in collaboration with national research networks. The Primary Care Research Network (PCRN) England provides a world-class infrastructure to conduct clinical research in primary care settings in the NHS by supporting and facilitating recruitment and set up of sites. PCRN England is delivered through eight local research networks that cover the whole of England. Similar networks operate in Scotland (Scottish PCRN), Northern

Ireland (Northern Ireland Clinical Research Network), and Wales (National Institute for Social Care and Health Research). Expressions of interest will be sent to practices by the research network for each region, and sites will be selected from the responses received.

Registry population

The details of the registry population are given in full in the global GARFIELD methods paper [19].

Prospective cohorts

The eligibility criteria for the prospective cohorts are: patients aged 18 years or older with a diagnosis of non-valvular AF within the past 6 weeks and at least one additional risk factor for stroke [19].

Retrospective cohort

The eligibility criteria for the retrospective cohort are: patients with a diagnosis of non-valvular AF within the 6–24 months before enrolment, and at least one additional risk factor for stroke [19].

Patient recruitment

Each participating GP will identify eligible patients using a search of the computerised clinical record and will invite them by standard letter to be enrolled in the GARFIELD registry. GPs will also opportunistically inform patients in the practice and give them a participant invitation letter and information sheet.

For the retrospective cohort, a practice computer search for all patients with a current diagnosis of AF (between 6 months and 2 years prior to inclusion) will be undertaken. Once identified, patients will be assessed according to the inclusion/exclusion criteria and eligible patients invited to participate.

For the prospective cohort, a computer search will be undertaken at least once a month at each practice to identify newly diagnosed patients with non-valvular AF. Once identified, the patient will be assessed according to the inclusion/exclusion criteria. Eligible patients will be sent a participant invitation letter and information sheet and asked to contact the practice if they are interested in participating. A screening log of all patients invited to participate in the registry will be maintained at each site. A consent visit is arranged for interested patients, after which they are enrolled in the registry and baseline data are completed.

Collection of baseline and follow-up data

Data collected at baseline include: demographics (e.g. ethnicity, sex, date of birth); body mass index; vital signs at diagnosis; AF symptoms; type of AF (new, paroxysmal, persistent, permanent); method and site of diagnosis; treatment strategy initiated at diagnosis; antithrombotic therapy; treatment decision (patient and physician factors); and medical history (cardiovascular, medical, bleeding).

Follow-up data include clinical events (stroke/TIA, peripheral embolism, acute coronary syndrome) and outcome of event; AF-related medical consultation and/or hospitalisation and outcome; AF treatment change; change in antithrombotic therapy (discontinuation, duration on therapy, reasons for discontinuation); bleeding events (classified as major, clinical relevant non-major, and minor); bleeding location of treatment (e.g. Accident and Emergency, GP practice); outcome of bleeding (recovered, permanently disabled, fatal); bleeding healthcare utilisation (hospitalisation, Accident and Emergency, physician, etc.); medical history update; mortality, including sudden cardiac death and non-cardiovascular death; and INR records in relation to therapeutic range, and location of INR monitoring.

Clinical outcomes and data quality

The study outcomes comprise clinical events (stroke, TIA, systemic and pulmonary embolism, myocardial infarction), bleeding events, therapy persistence, hospital visits and INR monitoring, and are listed in below:

- Cerebrovascular events defined as stroke including:
  - Primary ischaemic stroke
  - Primary intracerebral haemorrhage
  - Secondary haemorrhagic ischaemic stroke
- TIAs
- Systemic embolism
- Pulmonary embolism
- Mortality
- Acute coronary syndromes including:
  - Unstable angina
  - ST-elevation myocardial infarction
  - Non-ST-elevation myocardial infarction
- Bleeding events including:
  - Frequency
  - Location
  - Severity (classified as major [clinically overt bleeding associated with a fall in haemoglobin of ≥2 g/dl OR a transfusion of ≥2 packed red blood cells or whole blood OR a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal OR a fatal outcome], clinical relevant non-major and minor)
- Therapy persistence, including:
  - Rate of discontinuation
  - Duration of time on therapy
  - Reasons for discontinuation
  - Duration and cause of treatment interruption or suspension

- Analysis of events listed with regard to hospitalisation and outcomes
- Any other hospital visits (inpatient, outpatient, emergency department)
- Major adverse cardiac events
- For patients treated with VKA:
  - Frequency and timing of monitoring required in maintaining therapeutic anticoagulation
  - INR recordings in relation to therapeutic range
  - Location of INR monitoring and medical consultations due to INR testing
  - Use of bridging anticoagulation necessitated by VKA interruption
  - Outcomes in relation to INR fluctuation.

Source data verification will be undertaken in 20% of all cases to verify adherence to the protocol and assess the level and accuracy of data recording.

Funding

The GARFIELD Registry is sponsored by the Thrombosis Research Institute, London, UK. Funding of the registry is provided through an educational research grant from Bayer Pharma AG, Berlin, Germany.

Sample size and data analysis

The total projected sample size for the UK is 4,582, comprising 417 retrospective patients for Cohort 1 and 833 prospective patients for Cohorts 1 to 5. With these projected sample sizes the precision of estimated incidence of stroke is set out in Table 1 for different levels of incidence.

An interim analysis will be done at the UK level for the baseline data in each cohort and after all patients in each of the first four cohorts have completed the study. For a full analysis, baseline data, follow-up data, and study endpoint data will be summarised overall and by treatment groups, cohort, and region. Summaries of categorical data will be presented as frequency counts, percentages, and 95% confidence intervals. Continuous data will be presented as means (standard deviations), medians (with 95% confidence intervals), interquartile ranges, minimum, maximum, and number of patients.

Comparison of follow-up and outcome data between treatment groups, cohorts, and regions will be made using linear (for continuous outcomes) or non-linear (for categorical outcomes) mixed modelling with practice included as a random effect. Association between outcome variables and baseline data will be explored using the same method. For continuous data, normality of residuals will be tested using the Kolmogorov–Smirnov test and transformation or bootstrapping will be implemented where required. Time-to-event analysis will use Kaplan–Meier and Cox regression analyses to summarise and explore the association with baseline and other pertinent data. Comparison of $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED risk measures will be compared on the basis of receiver-operating characteristic curve analyses. The baseline characteristics of the patients – who have been classified as at risk of stroke according to physician-perceived risk factors or combinations of factors – will be reported.

Table 1 Precision of estimated incidence of stroke for different levels of incidence, and confidence intervals on effect sizes for quantitative measures

	Width of 95% confidence interval		
Expected incidence of stroke	Sample size of retrospective patients: 417	Cohort size of prospective patients: 833	Total sample size of 4,582
2.5%	±1.5%	±1.1%	±0.5%
5%	±2.1%	±1.5%	±0.6%
10%	±2.9%	±2.0%	±0.9%
20%	±3.8%	±2.7%	±1.2%
30%	±4.4%	±3.1%	±1.3%
40%	±4.7%	±3.3%	±1.4%
50%	±4.8%	±3.4%	±1.4%

Width of 95% confidence interval		
Sample size of retrospective patients: 417	Cohort size of prospective patients: 833	Total sample size of 4,582
0.14	0.10	0.04

Discussion

The development of this large, ongoing registry allows the opportunity to answer several research questions that have not previously been investigated within a non-randomised, non-selected population. These questions will pertain to:

- Clinical risks within a non-selected population of newly diagnosed patients with AF, compared with data from randomised trials in which prevalent, stable VKA users were preferably enrolled [20];
- Risks and benefits associated with oral anticoagulation;
- Quality of INR control in everyday clinical practice;
- Persisting barriers to prescribing oral anticoagulation;
- The economic burden of AF;
- The main diagnostic pathways, including the real-life identification and management of patients at various levels of risk for ischaemic stroke.

GARFIELD UK data will provide a comprehensive description of AF management and insights into the rationale for decisions relating to anticoagulation. The findings will establish how well the NICE guidelines have been implemented in the UK. Whilst NICE guidelines

are not mandatory, they are evidence-based and internationally recognised to reflect best practice. Further, GARFIELD will inform on the effectiveness of the NICE treatment guidelines and allow an evaluation of such guidelines and patient outcomes.

The global data will provide comparable information within which to consider national data and models of best practice, and the significance of the context in interpreting findings. The range of data will also provide evaluation of any inequalities in the UK in terms of AF diagnosis, management, and possibly clinical outcomes. 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 INR control within the various test settings in the UK, as well as the effectiveness of the recent stroke (CHA_2DS_2VASc) and bleeding (HAS-BLED) risk scores.

The study will provide real-world prospective data that will allow an evaluation of clinical practices and related outcomes in the VKA-only era, but will also report on outcomes relating to any novel anticoagulants or new therapies licensed for use in the UK during the duration of the study.

Appendix

UK GARFIELD Investigators

David A Fitzmaurice at the University of Birmingham and the UK Clinical Research Network (Primary Care). Will Murdoch, Naresh Chaunan, Daryl Goodwin, Richard McManus, Ramila Patel, Philip Saunders, Bennett Wong, Richard Evans, Philip Saunders, Janet Leese, Prem Jhittay, Andrew Ross, Manjit Kainth, Kevin Douglas, Gill Pickavance, Joanna McDonnell, Andrea Williams, Trevor Gooding, Helga Wagner, Geert Van Zon, Kevin Jones, Shoeb Suryani, Matt Thomas, Emily Watson, Arun Singal, William Wilcock, Subharsi Sircar, John Cairns, Drew Gilliland, Roman Bilas, Elizabeth Strieder, Peter Hutchinson, Anne Wakeman, Michael Stokes, Alistair Howitt, Bhaskhar Vishwanathan, Nigel Bird, Dominic Gray, Paul Evans, Matt Clark, John Bisatt, Jennifer Litchfield, Elizabeth Fisher, Tim Fooks, Richard Kelsall, Neil Paul, Elizabeth Alborough, Michael Aziz, Cobarsanellore Ramesh, Peter Wilson, Simon Franklin, Sue Fairhead, Julian Thompson, Vivien Joseph, Gary Taylor, Huw Charles, Dawn Tragen, Wendy Molefi-Youri, David Seamark, Carolyn Paul, Mark Richardson, Angus Jefferies, Helen Sharp, Hywel Jones, Claire Giles, Michael Page, Olaleye Oginni, Jehad Aldegather, Simon Wetherell, William Lumb, Phil Evans, Frances Scouller, Neil Macey, Stephen Rogers, Yvette Stipp, Richard West, Stephen Thurston, Paul Wadeson, John Matthews, Preeti Pandya, Andrew Gallagher, Raj Priyadharshan, Jayne Oliver, Tammy Railton, Emyr Davies, Steven Sayers, Claire Hutton, Nick Walls, Richard Thompson, Bijoy Sinha, Keith Butter, Susan Barrow, Helen Little, David Russell, Jason Davies, Ikram Haq, Paul Ainsworth, Claire Jones, Phil Weeks, Jane Eden, David Kernick, Janet Glencross, Alison MacLeod, Karen Poland, Connor Mulholland, Alison Warke, Paul Conn, Gerry Burns, Richard Smith, Simon Lowe, Rakee Kamath.

Abbreviations

AF: Atrial fibrillation; CHA_2DS_2-VASc: Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]); CHA_2DS_2-VASc: Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]; $CHADS_2$: Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled); GARFIELD: Global Anticoagulant Registry in the FIELD; GP: General practitioner; HAS-BLED: Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly (1 point each); INR: International normalised ratio; TIA: Transient ischaemic attack.

Competing interests

PA, ETM, and RH declare that they have no competing interests.
DAF has received honoraria from Bayer, Pfizer, Leo Laboratories, Roche Diagnostics.
FDRH has no direct competing interests but has received sponsorship or consulted for companies with an interest in anticoagulation including Bayer, Boehringer Ingelheim and Pfizer.

Authors' contributions

PA contributed to the development of the study protocol, drafted the manuscript and is managing the UK cohorts. ETM is a co-investigator for the UK and is involved in supporting the management of the UK cohorts. ETM contributed to drafting of the study protocol and provided comments on the draft manuscript. RH is a statistician involved in data analysis of the UK cohorts, performed sample size calculations and contributed to drafting of the manuscript. FDRH is a co-investigator for the UK and contributed to the drafting of the UK protocol. FDRH also provided comments on the draft manuscript. DAF is a Steering Committee member and the UK National Coordinator for the GARFIELD Registry. DAF participated in the conception of the project and the study design, drafting of the study protocol, and provided comments on the draft manuscript. All authors have read all of the different versions and approved the final version of this manuscript.

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A full list of the UK GARFIELD Investigators is given in the Appendix.

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Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry

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ABSTRACT

Objective To investigate evolving patterns in antithrombotic treatment in UK patients with newly diagnosed non-valvular atrial fibrillation (AF).

Design Prospective, multicentre, international registry.

Setting 186 primary care practices in the UK.

Participants 3482 participants prospectively enrolled in four sequential cohorts (cohort 2 (C2) n=830, diagnosed September 2011 to April 2013; cohort 3 (C3) n=902, diagnosed April 2013 to June 2014; cohort 4 (C4) n=850, diagnosed July 2014 to June 2015; cohort 5 (C5) n=900, diagnosed June 2015 to July 2016). Participants had newly diagnosed non-valvular AF and at least one risk factor for stroke, were aged ≥18, and provided informed consent.

Main outcome measures Antithrombotic treatment initiated at diagnosis, overall and according to stroke and bleeding risks. Stroke risk was retrospectively calculated using CHA_2DS_2-VASc (cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female)) and bleeding risk using HAS-BLED (hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, elderly (>65), drugs/alcohol concomitantly (1 point each)).

Results 42.7% were women and the mean age was 74.5 years. The median CHA_2DS_2-VASc score was 3 in all cohorts and the median HAS-BLED score was 2 in all cohorts. There was a statistically significant increase in the use of anticoagulant therapy from C2 to C5 (C2 54.7%, C3 60.3%, C4 73.1%, C5 73.9%; P value for trend <0.0001). The increase in the use of anticoagulant was mainly in patients with CHA_2DS_2-VASc ≥2. The use of vitamin K antagonists (VKAs)±antiplatelet (AP) drugs decreased from C2 to C5 (C2 53.3%, C3 52.1%, C4 50.3%, C5 30.6%), while the use of non-vitamin K antagonist oral anticoagulants (NOACs)±AP increased (C2 1.3%, C3 8.0%, C4 22.7%, C5 43.3%). The use of AP only decreased (C2 36.4%, C3 25.5%, C4 11.9%, C5 10.5%), as did the combination therapy of VKA+AP (C2 13.6%, C3 11.0%, C4 9.6%, C5 5.8%).

Conclusion There has been a progressive increase in the proportion of patients newly diagnosed with AF receiving guideline-recommended therapy in the UK, potentially driven by the availability of NOACs.

Trial registration number NCT01090362; Pre-results.

Strengths and limitations of the study

- This study describes real-world clinical practice in the UK for treatment initiated at atrial fibrillation (AF) diagnosis in patients with AF and at least one risk factor for stroke.
- Eligible patients were enrolled prospectively and consecutively without exclusions according to comorbidities or treatment.
- Patients were recruited in primary care in the UK, encompassing patients diagnosed in a comprehensive range of national care settings.
- This study does not include patients without capacity to consent.

INTRODUCTION

Atrial fibrillation (AF) is a potent risk factor for stroke and mortality; people with AF have a fivefold increased risk of stroke and a twofold increased risk of death.[1 2] AF-related strokes are more serious and are more likely to be fatal or lead to long-term disability than strokes in people without this arrhythmia.[3] Stroke prevention is therefore a principal goal in the treatment of AF[4] and is a major public health priority.[5] Fortunately, there are effective therapies, with anticoagulation shown to mitigate up to two-thirds of this stroke risk.

Since 2010, changes in treatment guidelines from the European Society of Cardiology and the National Institute for Clinical Excellence (NICE) have widened the criteria for patients with AF that should be considered for antithrombotic therapy and now advocate

Table 1 Baseline characteristics of patients in cohorts 2 to 5

Variable	Cohort 2 (n=830) (2011–2013)	Cohort 3 (n=902) (2013–2014)	Cohort 4 (n=850) (2014–2015)	Cohort 5 (n=900) (2015–2016)	Total C2 to C5 (n=3482)
Women, n/N (%)	376/850 (45.3)	391/902 (43.3)	343/850 (40.4)	378/900 (42.0)	1488/3482 (42.7)
Age at diagnosis, years, mean (SD)	75.2 (9.7)	73.8 (9.7)	74.2 (9.6)	74.8 (9.0)	74.5 (9.5)
Age at diagnosis, years, median (IQR)	77.0 (70.0 to 82.0)	75.0 (68.0 to 81.0)	75.0 (69.0 to 81.0)	75.0 (69.0 to 81.0)	75.0 (69.0 to 81.0)
Age group, n/N (%)					
<65	110/830 (13.3)	133/902 (14.7)	116/850 (13.6)	96/900 (10.7)	455/3482 (13.1)
65–74	222/830 (26.7)	315/902 (34.9)	293/850 (34.5)	322/900 (35.8)	1152/3482 (33.1)
≥75	498/830 (60.0)	454/902 (50.3)	441/850 (51.9)	482/900 (53.6)	1875/3482 (53.8)
Caucasian race, n/N (%)	804/816 (98.5)[a]	867/884 (98.1)[b]	832/837 (99.4)[c]	853/860 (99.2)[d]	3356/3397 (98.8)[e]
Medical history, n/N (%)					
Congestive heart failure	70/830 (8.4)	69/902 (7.6)	56/850 (6.6)	57/900 (6.3)	252/3482 (7.2)
Coronary artery disease	166/830 (20.0)	165/902 (18.3)	164/850 (19.3)	174/900 (19.3)	669/3482 (19.2)
Acute coronary syndrome	87/830 (10.5)	74/896 (8.3)[f]	90/847 (10.6)[g]	89/897 (9.9)[h]	340/3470 (9.8)[i]
Vascular disease	109/830 (13.1)	112/895 (12.5)[j]	125/848 (14.7)[k]	125/898 (13.9)[l]	471/3471 (13.6)[m]
Systemic embolism	9/830 (1.1)	4/893 (0.4)	3/842 (0.4)	6/893 (0.7)	22/3458 (0.6)
Stroke/TIA	101/830 (12.2)	105/902 (11.6)	116/850 (13.6)	106/900 (11.8)	428/3482 (12.3)
History of bleeding	28/830 (3.4)	26/899 (2.9)	23/845 (2.7)	27/895 (3.0)	104/2574 (3.0)
Hypertension	607/830 (73.1)	637/899 (70.9)	566/847 (66.8)	607/897 (67.7)	2417/3473 (69.6)
Diabetes mellitus	136/830 (16.4)	156/902 (17.3)	168/850 (19.8)	154/900 (17.1)	614/3482 (17.6)
Moderate to severe CKD*	244/830 (29.4)	241/902 (26.7)	199/850 (23.4)	196/900 (21.8)	880/3482 (25.3)
Risk scores					
CHA_2DS_2-VASc, median (IQR)	3.0 (2.0 to 4.0)[n]	3.0 (2.0 to 4.0)[o]	3.0 (2.0 to 4.0)[p]	3.0 (2.0 to 4.0)[q]	3.0 (2.0 to 4.0)[r]
CHA_2DS_2-VASc, 0–1, n/N (%)	73/795 (9.2)	93/844 (11.0)	90/801 (11.2)	81/835 (9.7)	337/3275 (10.3)
HAS-BLED, median (IQR)	2.0 (1.0 to 2.0)[s]	2.0 (1.0 to 2.0)[t]	2.0 (1.0 to 2.0)[u]	2.0 (1.0 to 2.0)[v]	2.0 (1.0 to 2.0)[w]
HAS-BLED, 0–2, n/N (%)	437/574 (76.1)	510/641 (79.6)	535/638 (83.9)	524/615 (85.2)	2006/2468 (81.3)

Patients missing: [a]14, [b]18, [c]13, [d]40, [e]85, [f]6, [g]3, [h]3, [i]12, [j]7, [k]2, [l]1, [m]11, [n]35, [o]58, [p]49, [q]65, [r]207, [s]256, [t]261, [u]212, [v]285, [w]1014.
*Includes NKF KDOQI stages III–V.
CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female); CKD, chronic kidney disease; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, elderly (>65), drugs/alcohol concomitantly (one point each); NKF KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; TIA, transient ischaemic attack.

anticoagulants (ACs) as the only appropriate antithrombotic therapy in patients with AF.[4 5] ACs include vitamin K antagonists (VKAs; typically warfarin) and, recently, non-VKA oral anticoagulants (NOACs), comprising factor Xa inhibitors and direct thrombin inhibitors. Whereas the only anticoagulant previously recommended was warfarin, the updated AF guidelines from NICE include recommendations for NOACs for patients with non-valvular AF.

In 2014, NICE updated its guidelines on the management of AF, recommending the CHA_2DS_2-VASc (cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female)) stroke risk tool for assessing stroke risk in patients with AF and further recommending anticoagulation therapy for patients at high risk (CHA_2DS_2-VASc ≥2), a consideration of anticoagulant therapy for patients at moderate risk (CHA_2DS_2-VASc=1) and no anticoagulant or antiplatelet (AP) treatment for patients at low risk (defined as CHA_2DS_2-VASc=0 for men and CHA_2DS_2-VASc=1 for women).[5] In addition, the emergence of NOACs in the UK since 2012 has provided a wider range of AC options, particularly for patients for whom warfarin may not be appropriate. The change in guidelines coupled with the emergence of NOACs has the potential to transform clinical practice; however, the impact on the use of ACs in patients with AF in the UK is unclear.

More than 46 000 new cases of AF are diagnosed in the UK every year. Many studies have reported a long-standing problem of undertreatment with ACs of patients at high risk of stroke[6 7]; UK studies in the last decade also report suboptimal treatment,[8–11] though there is limited

evidence of AF management since the introduction of NOACs. Little is known about the contemporary real-world management of patients newly diagnosed with AF who are perceived to be at risk of stroke by their physicians. The Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) aims to determine real-life treatment patterns and clinical outcomes of patients with newly diagnosed non-valvular AF and at least one investigator-determined risk factor for stroke.[12 13] This paper investigates the evolving patterns of antithrombotic treatment of UK patients enrolled in the GARFIELD-AF registry from September 2011 to July 2016.

METHODS

Study design

GARFIELD-AF is an ongoing, prospective, non-interventional, international registry of adults (≥18 years) diagnosed with AF. Patients were recruited into five independent cohorts; the first cohort also included a validation cohort of retrospective patients.

Participants

Inclusion criteria for the prospective cohort comprised a new diagnosis of non-valvular AF of up to 6 weeks prior to entry into the registry and an investigator-determined risk factor for stroke. Eligible patients were recruited consecutively at participating sites in order to prevent selection bias. The retrospective cohort comprised patients diagnosed 6–24 months before enrolment. Patients are followed up for a minimum of 2 years. Patients with transient AF, secondary to a reversible cause, and patients for whom follow-up was not possible were excluded from the registry. Full methods of the GARFIELD-AF registry have been previously reported.[12 13]

This paper reports baseline characteristics and treatment patterns in UK participants enrolled into cohorts 2 to 5; participants enrolled into cohort 1 were excluded as it consisted predominantly of a retrospective validation cohort.

Setting

Enrolment of UK patients into cohorts 2 to 5 was undertaken between September 2011 and July 2016 at 186 general practices (GPs) across the UK (161 in England, 8 in Wales, 8 in Northern Ireland and 9 in Scotland). The necessary regulatory approvals were obtained prior to recruitment, and all patients provided written informed consent prior to enrolment into the registry. The standard national diagnostic criteria for AF apply for GARFIELD-AF, and for the UK this was by electrocardiographic confirmation.

Data sources

Data collected at baseline comprised demographics, body mass index, type of AF, care setting of diagnosis, treatment strategy initiated at diagnosis, reason for treatment decision and medical history. Data were collected through review of medical records by trained site staff using an electronic case report form.

Stroke risk was calculated retrospectively using CHA_2DS_2-VASc score-based variables: heart failure, hypertension, age ≥75 years and 65–74 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA), left ventricular ejection fraction <40%, prior thromboembolism, vascular disease and female gender. HAS-BLED scores were calculated retrospectively using the variables hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly (>65) and drugs/alcohol concomitantly.

Data for the analysis in this report were extracted from the study database on 28 July 2016.

Definitions

ACs include VKAs and NOACs. NOACs include oral direct factor Xa inhibitors and oral direct thrombin inhibitors.

Vascular disease was defined as peripheral artery disease and/or coronary artery disease (CAD) with a history of acute coronary syndromes. Hypertension was defined as a documented history of hypertension or blood pressure >140/90 mm Hg. Chronic kidney disease (CKD) was classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines[14]: moderate to severe includes stages III to V; none or mild includes all other patients.

Statistical analysis

Patient characteristics and medical history are described by cohort. Continuous variables are expressed as number of patients and mean±SD and or median and IQR. Categorical variables are expressed as frequencies and percentages. Treatment patterns were analysed by cohort, and by cohort and CHA_2DS_2-VASc or HAS-BLED. Trends were assessed using an extension of the Wilcoxon rank-sum test.

Logistic regression models were used to assess the risk factors associated with the prescribing of NOACs (vs VKA). The following risk factors were included in the model: gender, age group, race, smoking, congestive heart failure, hypertension, diabetes, CAD, vascular disease, dementia, moderate to severe CKD, non-steroidal anti-inflammatory drug (NSAID) usage, history of bleeding, previous stroke/TIA/systemic embolism (SE) and cohort. ORs with 95% CIs were estimated to describe the associations of the risk factors and prescribing of NOACs versus VKA, as well as AP and no treatment (No ACs) versus ACs.

Multiple Imputation by Chained Equations was used to fill in missing values, creating five complete datasets.[15 16] Logistic regression was performed using the imputed datasets. First-degree interaction between comorbidities and time (cohort) was tested using likelihood ratio tests. Only significant interactions were included in the final model.

Statistical analysis was performed using both SAS software V.9.4 (SAS Institute, Cary, NC, USA) and Stata Statistical Software V.14 (StataCorp, College Station, TX, USA).

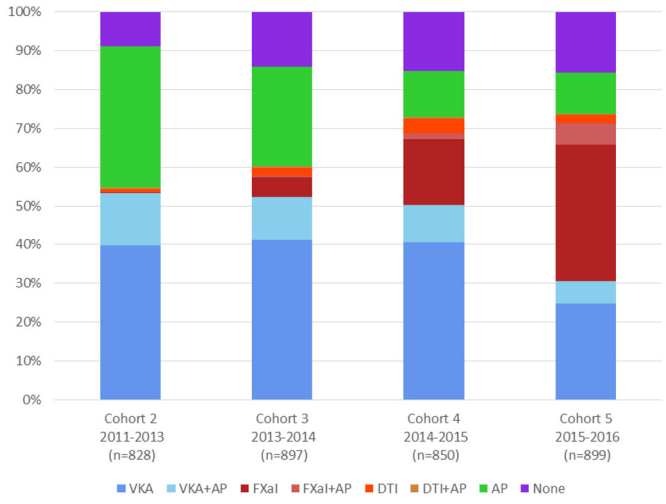

Figure 1 Antithrombotic treatment at diagnosis by cohort. AP, antiplatelet; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; VKA, vitamin K antagonist.

RESULTS

Patient distribution and characteristics

In the UK, 3482 patients were enrolled into cohorts 2 to 5 between September 2011 and July 2016: cohort 2 (C2) consisted of 830 patients diagnosed with AF between September 2011 and April 2013, cohort 3 (C3) consisted of 902 patients diagnosed between April 2013 and June 2014, cohort 4 (C4) consisted of 850 patients diagnosed between July 2014 and June 2015, and cohort 5 (C5) consisted of 900 patients diagnosed between June 2015 and July 2016. Overall, 42.7% of patients were women, mean age (SD) at diagnosis was 74.5 years (9.5) and 89.7% had a CHA_2DS_2-VASc score of ≥2 (table 1).

Participants were diagnosed in a broad range of care settings representative of those in the UK: more than half of the patients (2124/3482; 61.0%) were diagnosed in primary care. The remainder were diagnosed in internal (general) medicine (21.9%), cardiology (15.2%), geriatrics (1.8%) and neurology (0.1%). Of the 3482 participants, 1370 (39.3%) had new or unclassified AF, 640 (18.4%) had paroxysmal AF, 272 (7.8%) had persistent AF and 1200 (34.5%) had permanent AF. There were some variations in baseline characteristics across the four cohorts (table 1), though the median CHA_2DS_2-VASc and HAS-BLED scores were similar.

Antithrombotic therapy use by cohort

Figure 1 shows the treatment patterns at diagnosis in each of the four cohorts. The proportion of patients prescribed AC therapy at diagnosis, with or without an AP, increased consistently from C2 to C5 (54.7%, 60.3%, 73.1% and 73.9%; for trend <0.0001), whereas the use of AP only decreased (36.4%, 25.5%, 11.9% and 10.5%). At the same time, there was an increase in the proportion of patients receiving NOACs with or without AP from C2 to C5 (1.3%, 8.1%, 22.7%, 43.3%); the proportion of patients not receiving any antithrombotic therapy increased from C2 to C4 (8.9%, 14.4%, 15.1%) then stayed similar in C5 (15.7%). Co-prescription of AC and AP was variable (C2 14.0%, C3 11.8%, C4 11.4%, C5 11.7%). Table 2 shows selected baseline characteristics for all patients (C2 to C5 combined) according to treatment group. Patients receiving no treatment generally had a lower incidence of comorbidities, apart from history of bleeding; however, patients aged ≥75 years were more likely not to receive treatment.

Overall, 19.1% (666/3482) of patients were prescribed NOACs. Table 3 shows the baseline characteristics of patients on NOACs by cohort. There were no clear patterns of NOAC use by patient characteristics; however, patients diagnosed in cardiology in the earlier cohorts were more likely to be given NOACs than those in the later cohorts, while among patients diagnosed in primary care the later cohorts were more likely to receive NOACs than earlier cohorts. Of the patients prescribed either NOACs or VKA, those with dementia were significantly more likely to receive NOACs than VKA compared with patients without a history of the condition (table 4). Also, patients were more likely to receive NOACs over VKA as the cohorts progressed, from C2 to C5; however, no interaction between cohort and covariates was statistically significant.

Table 5 shows the baseline characteristics of patients who received no AC therapy (34.3%, 1195/3482) by cohort. There were no clear changes over time in 'no AC' use when considering individual patient characteristics. Nevertheless, in the whole population, 'no AC' was less likely (relative to AC therapy) in patients aged 65–80 years, with diabetes, or a history of vascular disease and previous stroke/TIA/SE than in patients without these conditions or other age groups (table 6). 'No AC' was more likely if patients had a history of bleeding or with NSAID usage. Over time, UK physicians became increasingly less likely to choose 'no AC' with each successive cohort of patients enrolled between 2011 and 2016.

Antithrombotic therapy use according to risk score

Figure 2 shows the use of antithrombotic therapy according to CHA_2DS_2-VASc score and cohort. Notably, the registry includes a few patients classified as low risk according to the CHA_2DS_2-VASc score (ie, 0 for men, 1 for women) because the determination of risk factors was left to the clinician's judgement and not prespecified in the protocol. The use of AC±AP increased from C2 to C4 for patients at all levels of stroke risk (low, moderate and high risk), though the increase was highest in patients with a CHA_2DS_2-VASc of ≥2 (C2 56.7%; C4 75.6%). At the same time, there was a decline in the proportion of patients receiving AP only and an increase in the proportion of high-risk patients not receiving any antithrombotic therapy. The overall use of antithrombotic therapy decreased in patients with low risk of stroke from C2 to C4, driven by a decline in the use of AP only from 35.7% in C2 to 11.8% in C4.

Table 2 Baseline characteristics of patients in cohorts 2 to 5 by antithrombotic treatment type

Variable	None (n=470)	AP alone (n=725)	VKA alone (n=1267)	NOAC alone (n=587)	AC+AP (n=425)	AC±AP (n=2279)
Women, n (%)	201 (42.8)	291 (40.1)	565 (44.6)	262 (44.6)	167 (39.3)	994 (43.6)
Age, mean (SD)	73.3 (10.5)	75.3 (9.7)	74.2 (9.4)	75.0 (9.4)	74.7 (8.2)	74.5 (9.2)
Age 65–74, n (%)	153 (32.6)	217 (29.9)	430 (33.9)	198 (33.7)	150 (35.3)	778 (34.1)
Age ≥75, n (%)	227 (48.3)	417 (57.5)	676 (53.4)	319 (54.3)	234 (55.1)	1229 (53.9)
Medical history, n (%)						
Heart failure (any)	22 (4.7)	46 (6.3)	97 (7.7)	36 (6.1)	49 (11.5)	182 (8.0)
Hypertension (any)	325 (78.1)	531 (77.7)	961 (79.2)	451 (80.0)	331 (80.3)	1743 (79.6)
Diabetes mellitus	51 (10.9)	105 (14.5)	249 (19.7)	94 (16.0)	112 (26.4)	455 (20.0)
Stroke	12 (2.6)	55 (7.6)	78 (6.2)	46 (7.8)	52 (12.2)	176 (7.7)
Systemic embolism	–	5 (0.7)	12 (1.0)	1 (0.2)	4 (1.0)	17 (0.8)
CAD (any)	37 (7.9)	187 (25.8)	168 (13.3)	90 (15.3)	182 (42.8)	440 (19.3)
Vascular disease	23 (4.9)	120 (16.6)	125 (9.9)	64 (10.9)	137 (32.5)	326 (14.4)
History of bleeding	34 (7.3)	35 (4.9)	14 (1.1)	15 (2.6)	6 (1.4)	35 (1.5)
Moderate to severe CKD*	94 (20.0)	208 (28.7)	331 (26.1)	128 (21.8)	117 (27.5)	576 (25.3)
Risk scores						
CHA_2DS_2-VASc, mean (SD)	2.8 (1.4)	3.3 (1.5)	3.3 (1.4)	3.3 (1.4)	3.8 (1.5)	3.4 (1.4)
CHA_2DS_2-VASc, median (IQR)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	4.0 (3.0 to 5.0)	3.0 (2.0 to 4.0)
CHA_2DS_2-VASc, 0–1, n (%)	75 (18.1)	73 (10.8)	107 (8.9)	57 (10.1)	24 (5.9)	188 (8.6)
HAS-BLED, mean (SD)	1.4 (0.9)	2.4 (0.8)	1.4 (0.8)	1.4 (0.8)	2.4 (0.8)	1.6 (0.9)
HAS-BLED, median (IQR)	1.0 (1.0 to 2.0)	2.0 (2.0 to 3.0)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	2.0 (2.0 to 3.0)	2.0 (1.0 to 2.0)
HAS-BLED, 0–2, n (%)	249 (88.7)	306 (61.3)	855 (90.2)	398 (91.9)	193 (63.9)	1446 (85.8)

*Includes NKF KDOQI stages III–V.
AC, anticoagulant; AP, antiplatelet; CAD, coronary artery disease; CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female); CKD, chronic kidney disease; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, elderly (>65), drugs/alcohol concomitantly (1 point each); NKF KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Also, the proportion of low-risk patients not receiving any antithrombotic therapy increased from 21.4% to 35.3%. There was a slightly different pattern from C4 to C5; there was a decrease in the use of AC±AP in patients at low risk (C4 53.0%, C5 40.0%) and C5 had the largest proportion of low-risk patients not receiving treatment (50.0%). C5 saw an increase in NOAC use across all stroke risk levels, along with a decrease in the use of VKA.

Figure 3 shows the use of antithrombotic therapy according to HAS-BLED score and cohort. There was an increase in AC use over the study period for patients with a HAS-BLED score of 0 to 2; notably, there was a steady increase in AC±AP use in patients with HAS-BLED ≥3, peaking at C4 (C2 40.1%, C3 46.7%, C4 66.0%, C5 58.2%) at the expense of AP use.

Main reason anticoagulant was not used in patients with CHA_2DS_2-VASc ≥2

The main reasons why ACs were not used in patients with a CHA_2DS_2-VASc score of ≥2 are shown in table 7. The top two known reasons were patient refusal and physician's choice. Patient refusal was variable, and in the most recent cohort (C5), it accounted for 11.2% of high-risk patients not receiving AC. There were also some variations in the reasons for physicians choosing not to give high-risk patients ACs across the cohorts; the main reason in C2 was fall risk, whereas the main reason in C5 was bleeding risk.

DISCUSSION

These findings from the UK cohort of the GARFIELD-AF registry indicate a progressive improvement in the

Table 3 Baseline characteristics of patients on NOACs by cohort

Variable	Cohort 2 (n=11)	Cohort 3 (n=73)	Cohort 4 (n=193)	Cohort 5 (n=389)	Total C2 to C5 (n=666)
Female, n (%)	4 (36.4)	42 (57.5)	80 (41.5)	165 (42.4)	291 (43.7)
Age at diagnosis, years, mean (SD)	75.9 (10.3)	74.8 (9.2)	74.7 (10.1)	74.7 (9.0)	74.7 (9.4)
Age at diagnosis, years, median (IQR)	75.0 (69.0 to 86.0)	74.0 (69.0 to 81.0)	76.0 (68.0 to 82.0)	75.0 (69.0 to 81.0)	75.0 (69.0 to 82.0)
Age group, n (%)					
<65	2 (18.2)	8 (11.0)	30 (15.5)	43 (11.1)	83 (12.5)
65–74	3 (27.3)	29 (39.7)	59 (30.6)	138 (35.5)	229 (34.4)
≥75	6 (54.5)	36 (49.3)	104 (53.9)	208 (53.5)	354 (53.2)
Care setting at diagnosis, n (%)					
Internal medicine	2 (18.2)	18 (24.7)	53 (27.5)	108 (27.8)	181 (27.2)
Cardiology	4 (36.4)	11 (15.1)	21 (10.9)	59 (15.2)	95 (14.3)
Neurology	–	–	1 (0.5)	1 (0.3)	2 (0.3)
Geriatrics	–	2 (2.7)	2 (1.0)	7 (1.8)	11 (1.7)
Primary care/general practice	5 (45.5)	42 (57.5)	116 (60.1)	214 (55.0)	377 (56.6)
Medical history, n (%)					
Congestive heart failure	2 (18.2)	4 (5.5)	14 (7.3)	23 (5.9)	43 (6.5)
History of hypertension	10 (90.9)	48 (65.8)	139 (72.8)	276 (71.1)	473 (71.3)
Diabetes mellitus	2 (18.2)	9 (12.3)	35 (18.1)	69 (17.7)	115 (17.3)
Stroke	–	7 (9.6)	16 (8.3)	32 (8.2)	55 (8.3)
Systemic embolism	–	–	1 (0.5)	2 (0.5)	3 (0.5)
Coronary artery disease	1 (9.1)	11 (15.1)	43 (22.3)	73 (18.8)	128 (19.2)
Vascular disease	1 (9.1)	7 (9.7)[a]	37 (19.3)[b]	50 (12.9)	95 (14.3)[c]
History of bleeding	–	3 (4.1)	2 (1.0)	11 (2.8)	16 (2.4)
Moderate to severe CKD*	–	26 (35.6)	47 (24.4)	70 (18.0)	143 (21.5)
Risk scores					
CHA_2DS_2-VASc, mean (SD)	3.3 (1.7)	3.3 (1.4)[d]	3.4 (1.5)[e]	3.3 (1.4)[f]	3.3 (1.5)[g]
CHA_2DS_2-VASc, median (IQR)	4.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)
CHA_2DS_2-VASc, 0–1, n (%)	2 (18.2)	7 (9.9)	19 (10.4)	37 (9.9)	65 (10.2)
HAS-BLED, mean (SD)	1.2 (0.8)[h]	1.7 (0.8)[i]	1.5 (0.8)[j]	1.4 (0.8)[k]	1.5 (0.8)[l]
HAS-BLED, median (IQR)	1.0 (1.0 to 2.0)	2.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)
HAS-BLED, 0–2, n (%)	6 (100)	52 (86.7)	129 (89.0)	255 (92.4)	442 (90.8)

Patients missing: [a]1, [b]1, [c]2, [d]2, [e]10, [f]16, [g]28, [h]5, [i]13, [j]48, [k]113, [l]179.
*Includes NKF KDOQI stages III–V.
CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female); CKD, chronic kidney disease; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, elderly (>65), drugs/alcohol concomitantly (1 point each); NKF KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; NOAC, non-vitamin K antagonist oral anticoagulant.

clinical management of AF, with newly diagnosed at-risk patients with AF more often receiving guideline-recommended therapy. The proportion of patients on AC increased (C2 54.5%, C3 60.1%, C4 72.9%, C5 73.9%) and the increase in the use of AC was mainly in patients with CHA_2DS_2-VASc ≥2. There was a notable increase in the use of NOACs±AP (C2 1.3%, C3 8.0%, C4 23.0%, C5 43.3%), with the main increase in NOAC prescribing being driven by the prescribing of factor Xa inhibitors; C5 saw a change in VKA prescribing, with NOACs being prescribed in place of VKA. The use of AP only decreased (C2 36.5%, C3 25.3%, C4 11.9%, C5 10.5%); however, the co-prescription of AC+AP did not change much (C2 14%, C3 11.8%, C4 11.4%, C5 11.7%). AC use decreased with bleeding risk, with people with HAS-BLED ≥3 less likely to be anticoagulated; nevertheless, use of AC in patients with HAS-BLED ≥3 increased notably from 40.1% in C2 to the peak of 66.0% in C4.

In addition, there was a decline in AP use in patients at low risk, with a corresponding increase in the proportion of patients in this category not receiving any antithrombotic therapy. However, an important proportion of low-risk patients received AC over the period, with 50% of low-risk patients receiving AC in the most recent cohort.

Table 4 Use of NOACs in relation to baseline characteristics for patients on an AC at baseline

Variable	Cohorts 2 to 5 OR (95% CI)
Gender	
Female	1
Male	0.90 (0.72 to 1.12)
Age (years)	
65	1
65–80	0.66 (0.47 to 0.92)
80–85	0.71 (0.48 to 1.07)
>85	1.02 (0.66 to 1.59)
Medical history*	
Congestive heart failure	0.88 (0.58 to 1.34)
Hypertension (history or >140/90 mm Hg)	1.23 (0.93 to 1.62)
Diabetes	0.78 (0.59 to 1.02)
Coronary artery disease	1.14 (0.80 to 1.65)
Vascular disease	1.14 (0.76 to 1.71)
Dementia	3.58 (1.15 to 11.15)
Moderate to severe CKD†	0.85 (0.65 to 1.10)
NSAID usage	0.57 (0.44 to 0.74)
Bleeding	1.90 (0.86 to 4.19)
Previous stroke/TIA/SE	1.29 (0.96 to 1.75)
Smoking	
Never	1
Ex-smoker	1.03 (0.82 to 1.29)
Current smoker	0.61 (0.38 to 0.97)
Cohort	
2	1
3	6.14 (3.28 to 11.52)
4	7.24 (9.43 to 31.53)
5	55.21 (30.29 to 100.62)

*Reference group is patients with no history of disease (for congestive heart failure, hypertension, diabetes, coronary artery disease, vascular disease, dementia, moderate to severe CKD, NSAID usage, bleeding, previous stroke/TIA/SE).
†Includes NKF KDOQI stages III–V; none or mild (reference group) includes all other patients.
An OR >1 implies that NOACs are more frequent than VKAs, while an OR <1 means that VKAs are more frequent than NOACs. No interaction between cohort and covariates was statistically significant.
AC, anticoagulant; CKD, chronic kidney disease; NKF KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

For patients with a CHA_2DS_2-VASc score of 1, there was a notable increase in AC prescribing from C2 to C5 and a steep decline in the use of AP only.

Our findings are, to a large extent, consistent with changes in AF management guidelines. In the UK, NICE guidelines up until 2014 recommend that high-risk patients should be on warfarin, those at moderate risk should receive warfarin or aspirin, and low-risk patients should not be on warfarin (but could be prescribed aspirin).[17] The current (2014) guidelines no longer recommend aspirin; patients should receive anticoagulation or not.[5] The notable increase in AC use and corresponding decline in AP use fall within the guidelines; our data suggest patients that would have been given aspirin in earlier cohorts are now given AC, also that the increase in AC use is potentially driven by the availability of NOACs.

This is the first UK study to describe the reasons for not anticoagulating real-world patients in relation to stroke risk, and the findings corroborate our deduction that guidelines have influenced clinical practice. The data suggest that patient refusal (11.2% for high-risk patients in the most recent cohort) may be the main patient factor affecting rates of anticoagulation. There is little UK evidence on AC treatment rates in the post-VKA-only era; nevertheless, co-prescription of ACs and APs (15.1%) is higher than reported by Kassianos *et al*[11] (11% initiated on ACs plus APs within 12 weeks of diagnosis of AF).

Strengths and limitations

This study describes real-world clinical practice in the UK for treatment initiated at AF diagnosis in patients with AF and at least one risk factor for stroke. Recruiting patients from primary care captures patients regardless of the care setting of diagnosis, therefore providing a pool of patients representative of UK patients diagnosed with AF. Study sites sought to recruit consecutive eligible patients, thereby reducing the risk of selection bias. In addition, the 6-week period between diagnosis and enrolment minimises the risk of excluding deceased patients.

The study is subject to the limitations inherent to observational studies, although efforts were made to standardise definitions and reduce missing data. Ethical approval for the study does not cover patients without the capacity to consent. The data on low-risk patients need to be interpreted with caution due to the low numbers in the UK sample. Comorbidities are likely confounders in treatment strategies; however, these were not comprehensively incorporated in this analysis.

Comparison with global GARFIELD-AF data

Evolving antithrombotic treatment patterns up to C4 for the global GARFIELD-AF population have previously been published[18]; our comparison is in relation to UK patients enrolled during the corresponding recruitment period (C2 to C4). Globally, a total of 34 170 patients were enrolled into C2 to C4 in 34 countries. UK patients were older than patients in the global study: mean age of 74.7 years compared with 69.9 years in the global study.[18] UK patients had less heart failure (7.6% vs 19.8%), higher prevalence of CKD (26.5% vs 10.3%), but similar rates of

Table 5 Baseline characteristics of patients not on AC by cohort

Variable	Cohort 2 (n=375)	Cohort 3 (n=356)	Cohort 4 (n=229)	Cohort 5 (n=235)	Total C2 to C5 (n=1195)
Women, n (%)	166 (44.3)	140 (39.3)	89 (38.9)	97 (41.3)	492 (41.2)
Age at diagnosis, years, mean (SD)	75.2 (9.8)	74.0 (9.9)	73.8 (10.7)	74.9 (9.9)	74.5 (10.0)
Age at diagnosis, years, median (IQR)	77.0 (69.0 to 82.0)	75.0 (69.0 to 81.0)	74.0 (68.0 to 81.0)	75.0 (69.0 to 82.0)	75.0 (69.0 to 82.0)
Age group, n (%)					
<65	51 (13.6)	60 (16.9)	38 (16.6)	32 (13.6)	181 (15.1)
65–74	102 (27.2)	114 (32.0)	78 (34.1)	76 (32.3)	370 (31.0)
≥75	222 (59.2)	182 (51.1)	113 (49.3)	127 (54.0)	644 (53.9)
Care setting at diagnosis, n (%)					
Internal medicine	66 (17.6)	73 (20.5)	49 (21.4)	37 (15.7)	255 (18.8)
Cardiology	54 (14.4)	53 (14.9)	30 (13.1)	29 (12.3)	166 (13.9)
Neurology	–	–	1 (0.4)	1 (0.4)	2 (0.2)
Geriatrics	7 (1.9)	8 (2.2)	3 (1.3)	4 (1.7)	22 (1.8)
Primary care/general practice	248 (66.1)	222 (62.4)	146 (63.3)	164 (69.8)	780 (65.3)
Medical history, n (%)					
Congestive heart failure	25 (6.7)	18 (5.1)	10 (4.4)	15 (6.4)	68 (5.7)
History of hypertension	269 (71.7)	245 (68.8)	135 (59.2)	141 (60.3)	790 (66.2)
Diabetes mellitus	46 (12.3)	50 (14.0)	29 (12.7)	31 (13.2)	156 (13.1)
Stroke	23 (6.1)	20 (5.6)	7 (3.1)	17 (7.2)	67 (5.6)
Systemic embolism	2 (0.5)	2 (0.6)	–	1 (0.4)	5 (0.4)
Coronary artery disease	80 (21.3)	57 (16.0)	44 (19.2)	43 (18.3)	224 (18.7)
Vascular disease	46 (12.3)	34 (9.6)[a]	31 (13.5)	32 (13.7)[b]	143 (12.0)[c]
History of bleeding	23 (6.1)	19 (5.4)	13 (5.7)	14 (6.0)	69 (5.8)
Moderate to severe CKD*	108 (28.8)	82 (23.0)	47 (20.5)	65 (27.7)	302 (25.3)
Risk scores					
CHA_2DS_2-VASc, mean (SD)	3.2 (1.5)[d]	3.0 (1.4)[e]	3.0 (1.5)[f]	3.2 (1.5)[g]	3.1 (1.5)[h]
CHA_2DS_2-VASc, median (IQR)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)
CHA_2DS_2-VASc, 0–1, n (%)	41 (11.6)	46 (13.8)	34 (16.5)	27 (13.4)	148 (13.5)
HAS-BLED, mean (SD)	2.2 (0.9)[i]	2.1 (0.9)[j]	1.7 (1.0)[k]	1.9 (1.1)[l]	2.0 (1.0)[m]
HAS-BLED, median (IQR)	2.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)	2.0 (1.0 to 2.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)
HAS-BLED, 0–2, n (%)	164 (66.6)	173 (71.1)	122 (77.7)	96 (71.6)	555 (71.2)

Patients missing: [a]1, [b]1, [c]2, [d]22, [e]24, [f]22, [g]34, [h]102, [i]129, [j]113, [k]72, [l]101, [m]415.
*Includes NKF KDOQI stages III–V.
AC, anticoagulant; CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female); CKD, chronic kidney disease; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, elderly (>65), drugs/alcohol concomitantly (1 point each), NKF KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative.

coronary artery disease and acute coronary syndromes. UK patients had a higher proportion of those with CHA_2DS_2-VASc score of 0–1 (10.5% vs 14.7%) and a lower proportion with HAS-BLED of 0–2 (81.3% vs 88.7%).

Despite starting from a lower baseline, the use of AC in the UK in the most recent cohort is comparable to that in the global study (UK 54.7% to 73.1%, global 62.1% to 71.1%).[18] Nevertheless, the uptake of NOACs is higher in the global study, with NOACs being prescribed in place of VKA, whereas VKA prescribing in the UK hardly changed up until C4 (NOAC use in C4: global 37.2%, UK 22.7%). In C5, however, UK data illustrate a decline in VKA prescribing matched by an increase in NOAC use. As in the UK population, overtreatment of patients at low risk of stroke was observed in the global population, and over 50% of low-risk patients in C4 received AC. This may be due to clinicians' perception of stroke risk as all participants were deemed by the recruiting clinician to have an investigator-determined risk factor for stroke. Co-prescription of AC+AP was also an issue in the global population, with 6.8% affected in C4; however, the UK seems to have responded better to the renunciation of AP only as a treatment option: in C4, 11.7% of high-risk UK patients were given AP only compared with 16.0% in the global population.

Table 6 Use of antiplatelet and no treatment (no AC) versus anticoagulant in relation to baseline characteristics

Variable	Cohorts 2 to 5 OR (95% CI)
Gender	
Female	1
Male	1.09 (0.91 to 1.30)
Age (years)	
<65	1
65–80	0.70 (0.54 to 0.90)
80–85	0.75 (0.55 to 1.02)
>85	0.98 (0.70 to 1.36)
Medical history*	
Congestive heart failure	0.73 (0.52 to 1.03)
Hypertension (history or >140/90 mm Hg)	0.89 (0.72 to 1.09)
Diabetes	0.57 (0.45 to 0.72)
Coronary artery disease	0.84 (0.64 to 1.11)
Vascular disease	0.63 (0.46 to 0.87)
Dementia	0.72 (0.28 to 1.84)
Moderate to severe CKD†	0.92 (0.75 to 1.12)
NSAID usage	5.85 (4.89 to 7.00)
Bleeding	6.30 (3.90 to 10.18)
Previous stroke/TIA/SE	0.47 (0.36 to 0.62)
Smoking	
Never	1
Ex-smoker	0.96 (0.81 to 1.15)
Current smoker	1.04 (0.73 to 1.48)
Cohort	
2	1
3	0.84 (0.67 to 1.05)
4	0.55 (0.43 to 0.70)
5	0.52 (0.41 to 0.66)

*Reference group is patients with no history of disease (for congestive heart failure, hypertension ,diabetes, coronary artery disease, vascular disease, dementia, moderate to severe CKD, NSAID usage, bleeding, previous stroke/TIA/SE)
†Includes NKF KDOQI stages III–V; none or mild (reference group) includes all other patients.
Please note: An OR > 1 implies that No ACs are more frequent than ACs, while an OR < 1 means that ACs are more frequent than No ACs. Odds ratios were adjusted for all variables in the model.
AC, anticoagulant; CKD, chronic kidney disease; NKF KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; NSAID, non-steroidal anti-inflammatory drug; SE, systemic embolism; TIA, transient ischaemic attack.

Implications for practice

These data indicate progressive concordance with evidence-based guidelines and clinical practice in the UK for patients newly diagnosed with AF. More UK patients are receiving guideline-recommended therapy; this is significant, given the increasing prevalence of AF in the UK. Although the proportion of high-risk patients taking an AC in the most recent cohort is unprecedented, nearly a quarter of high-risk patients still do not receive AC therapy, indicating that there is further scope for improvement. It is important to elucidate the reasons why some high-risk patients do not receive anticoagulation; in particular, the reasons and circumstances for patient refusal need to be explored (and documented). An important proportion of low-risk patients are still receiving AC despite the proven capability of the CHA_2DS_2-VASc score to identify patients at truly low risk. Further attention to

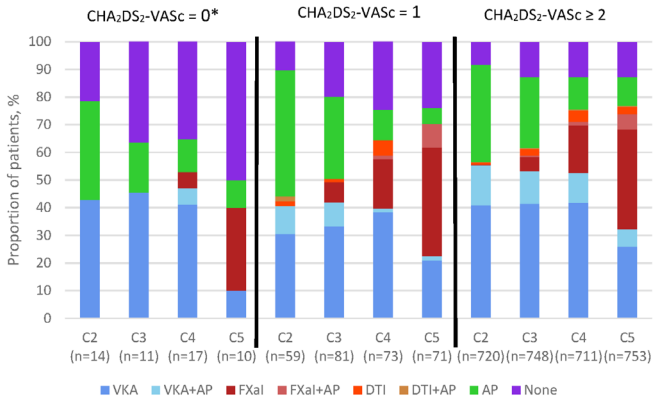

Figure 2 Antithrombotic treatment at diagnosis by CHA_2DS_2-VASc and cohort, for patients with a score of 0, 1 and ≥2. *Includes women with no other risk factors. The total population represented by n excludes unknowns. Patients with missing CHA_2DS_2-VASc score: C2, 35; C3, 58; C4, 49; C5, 65. AP, antiplatelet; CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female); DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; VKA, vitamin K antagonist.

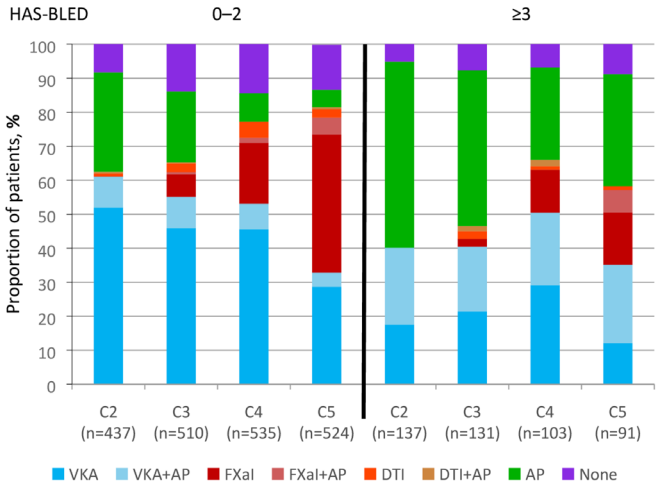

Figure 3 Antithrombotic treatment at diagnosis by HAS-BLED score and cohort, for patients with a score of 0–2 and ≥3. AP, antiplatelet; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, elderly (>65), drugs/alcohol concomitantly (1 point each); VKA, vitamin K antagonist.

Table 7 Main reason anticoagulant not used in patients with CHA_2DS_2-VASc ≥2

Variable	Cohort 2 (n=307) n %	Cohort 3 (n=279) n %	Cohort 4 (n=171) n %	Cohort 5 (n=170) n %
Main reason anticoagulant not used*				
Already taking antiplatelet drugs for other medical condition	30 (9.8)	11 (3.9)	5 (2.9)	9 (5.3)
Patient refusal	44 (14.3)	51 (18.3)	24 (14.0)	19 (11.2)
Previous bleeding event	6 (2.0)	5 (1.8)	7 (4.1)	5 (2.9)
Taking medication contraindicated or cautioned for use with VKA or AC	1 (0.3)	2 (0.7)	1 (0.6)	2 (1.2)
Other	113 (36.8)	100 (35.8)	73 (42.7)	79 (46.5)
Unknown	70 (22.8)	72 (25.8)	46 (26.9)	36 (21.2)
Physician's choice†	43 (14.0)	38 (13.6)	15 (8.8)	20 (11.8)
Bleeding risk	8 (18.6)	10 (26.3)	9 (60.0)	13 (65.0)
Concern over patient compliance	3 (7.0)	1 (2.6)	–	–
Guideline recommendation	8 (18.6)	6 (15.8)	1 (6.7)	1 (5.0)
Fall risk	13 (30.2)	12 (31.6)	2 (13.3)	5 (25.0)
Low risk of stroke	11 (25.6)	9 (23.7)	3 (20.0)	1 (5.0)

*Percentages are calculated with the column 'n' as denominator;
†Percentages in each category of the physician's choice are calculated with the available (non-missing) data of the variable as denominator.
AC, anticoagulant; CHA_2DS_2-VASc, cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)–vascular disease, age 65–74 and sex category (female); VKA, vitamin K antagonist.

patients in this category will be beneficial. Also, patients are being co-prescribed ACs and aspirin (11.7% of high-risk patients in most recent cohort), a combination that is rarely indicated since it increases bleeding risk by over 50%; it might be worth exploring the rationale for this in future research.

The clinical management of patients with AF is evolving and treatment outcomes will become clearer with time. GARFIELD-AF provides real-world data on evolving treatment patterns, and further data will provide insight into corresponding treatment outcomes.

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Collaborators A full list of the UK GARFIELD-AF Investigators is given in the online supplementary appendix 1.

Contributors PNA contributed to the acquisition, analysis and interpretation of data for the study, and drafted the manuscript. HG contributed to the analysis and interpretation of the data and revised the work critically for intellectual content. FDRH contributed to the interpretation of the data and revised the work critically for intellectual content. DAF contributed to the acquisition, analysis and interpretation of the data and revised the work critically for intellectual content. FDRH and DAF contributed to the initial methods of GARFIELD-AF in the UK. DAF is also the Principal Investigator and guarantor for the UK study. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

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Competing interests FDRH personal fees and other from BMS/Pfizer, personal fees and other from BI, personal fees and other from Bayer, outside the submitted work.

Patient consent Obtained.

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Incidence of venous thromboembolism in care homes:

a prospective cohort study

Abstract

Background
Care home residents have venous thromboembolism (VTE) risk profiles similar to medical inpatients; however, the epidemiology of VTE in care homes is unclear.

Aim
To determine the incidence of VTE in care homes.

Design and setting
Observational cohort study of 45 care homes in Birmingham and Oxford, UK.

Method
A consecutive sample of care home residents was enrolled and followed up for 12 months. Data were collected via case note reviews of care home and GP records; mortality information was supplemented with Health and Social Care Information Centre (now called NHS Digital) cause of death data. All potential VTE events were adjudicated by an independent committee according to three measures of diagnostic certainty: definite VTE (radiological evidence), probable VTE (high clinical indication but no radiological evidence), or possible VTE (VTE cannot be ruled out). (Study registration number: ISTCTN80889792.)

Results
There were 1011 participants enrolled, and the mean follow-up period was 312 days (standard deviation 98 days). The incidence rate was 0.71 per 100 person years of observation (95% confidence interval [CI¡ ¢ 0.2› to 1.54) for definite VTE, 0.83 per 100 person years (95% CI ¢ 0.33 to 1.70) for definite and probable VTE, and 2.48 per 100 person years (95% CI ¢ 1.53 to 3.79) for definite, probable, and possible VTE.

Conclusion
The incidence of VTE in care homes in this study (0.71–2.48 per 100 person years) is substantial compared with that in the community (0.117 per 100 person years) and in people aged ≥70 years (0.44 per 100 person years). £urther research regarding risk stratification and VTE prophylaxis in this population is needed.

Keywords
care home residents; deep vein thrombosis; nursing home residents; pulmonary embolism; venous thromboembolism; VTE incidence.

INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious global health problem associated with significant morbidity and mortality.[1,2] VTE risk significantly increases with advancing age, and age ≥75 years has been established as an independent risk factor.[3–›] Other important risk factors include immobilisation, hospitalisation, malignancy, previous VTE, and comorbidities such as heart failure, stroke, chronic obstructive pulmonary disease (COPD), and diabetes mellitus.[7–14]

Approximately 50% of VTE is associated with hospital admission, and VTE risk assessment of hospitalised patients is strongly recommended by evidence-based guidelines.[15] It could be argued that care home residents have VTE risk profiles similar to those of medical inpatients,[1›,17] although the impact of VTE risk factors in the UK care home population is unknown.[1›] Nursing home stay is an independent risk factor for VTE;[8] moreover, US data suggest an eightfold risk of VTE associated with residence in a long-term care facility.[18]

The epidemiology of VTE in care homes remains unclear and accurate data are needed on rates of VTE in care homes. The present study is a prospective cohort observational study to determine, for the first time, the incidence of VTE in UK care homes.

METHOD

Study design
This was an observational cohort study. Study staff extracted clinical data from case notes of participants' care home and GP records over 12 months for all events of interest. Mortality data were complemented with cause of death data from the Health and Social Care Information Centre (HSCIC) (now called NHS Digital), the national provider of population data relating to health and social care. The main outcome of interest was the rate of VTE events per 100 person years (PYs).

Setting and participant selection
'Care home' as used in this study, in accordance with the UK definition,[19] included care homes with nursing and care homes without nursing. A sample of care homes was recruited in Birmingham and Oxford, stratified by type, size, and ownership to increase generalisability. Care homes with fewer than 10 beds were excluded. Each resident from participating care homes was assessed for study inclusion. Inclusion criteria were care home resident and able to provide consent (either by consenting personally or via consultee declaration; that is, asking a family member to advise whether a person who lacks mental capacity would want to participate). Temporary residents and residents with a life expectancy of <› months were excluded. GPs were asked to provide access to participants' medical records.

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How this fits in

/esidence in a nursing home is an independent risk factor for venous thromboembolism (VTE). The incidence of VTE in care home residents (with and without nursing) may be up to 21 times the community incidence and five times that of people aged ≥70 years. Care home residents are not risk assessed for VTE.

Data collection

Clinical researchers reviewed the care home and GP medical records for each participant at baseline and at 12 months' follow-up, or when the participants died or moved away. Baseline data comprised demographic data, medical history, comorbidities, and current medications. The /ivermead Mobility Index (/MI)[20] was administered by care home staff. £ollow-up data comprised hospital admissions (including accident and emergency attendances), deaths, and GP consultations.

Outcomes

Endpoint definition. The study endpoint was defined as development of VTE during time in the study. VTE events were categorised into three levels of diagnostic certainty: definite VTE (clinical evidence of VTE, including radiological or post-mortem diagnosis, evidence of treatment, PE listed as main cause of death on death certificate); probable VTE (high clinical suspicion or indication of VTE but no radiological diagnosis); and possible VTE (no clinical suspicion of VTE recorded in patient's notes, although VTE could not be ruled out, for example, due to pleuritic chest pain or haemoptysis).

Endpoint adjudication. £irst, two research nurses with VTE training reviewed the complete case report form for each patient and adjudicated on each death, hospital admission, and GP consultation where there was any suggestion that there were VTE symptoms. Events that were not VTE related were adjudicated as probably not VTE or definitely not VTE, and cases with insufficient information for a sensible decision were adjudicated as 'VTE unknown'. The principal investigator adjudicated where there was a difference of opinion. All events adjudicated as definite VTE, probable VTE, and possible VTE were then referred to a second stage of adjudication: an independent adjudication panel comprising two haematologists and a GP; two members assessed anonymised information to adjudicate on events and any difference of opinion was judged by the third member.

Statistical analysis

Person time at risk commenced from date of enrolment until 12 months, lost to follow-up, or death. Incidence of VTE was calculated per 100 PYs of observation with corresponding 95% confidence intervals (CIs), using the Poisson exact method. The incidence of VTE was calculated based on definite, probable, and possible VTE events. Participants' baseline VTE risk was calculated for both the Department of Health risk assessment tool[21] and ¤Thrombosis' score.[22] The individual risk of VTE was assessed for selected factors using Poisson regression, reporting relative risks, associated 95% CI, and *P*-values. Statistical analysis was performed using SAS (version 9.4).

RESULTS

Sites

£orty-five care homes in Birmingham and Oxford participated. Participating care homes varied according to type, size, and ownership, and were representative of UK care homes (Table 1). Eighty-three out of 8› GPs granted access to participants' medical records.

Table 1. Characteristics of study care homes[a]

Care home characteristics	All Birmingham and Oxford care homes[b]	Study care homes
Number	231	45
Type		
" ith nursing	119 (52)	27 (›0)
" ithout nursing	112 (48)	18 (40)
Size, number of beds		
<30 (small)	89 (39)	15 (33)
30–49 (medium)	82 (35)	15 (33)
≥50 (large)	›0 (2›)	15 (33)
Mean number of beds (SD)	NA	43.9› (21.38)
Ownership		
Private«for profit	14› (›3)	35 (78)
Not for profit	85 (37)	10 (22)
Location		
Birmingham	144 (›2)	27 (›0)
Oxford	87 (38)	18 (40)
Study participants per care home		
Mean (SD) participants per home	NA	22.47 (10.00)
Median number participants per home (I¤/)	NA	20 (15–29)
Number of participants per home (range)	NA	›–45

[a]Data are n *or* n *(%) unless otherwise specified. [b]All care homes in Birmingham and Oxford registered on the Care ¤uality Commission website during the care home recruitment phase of the study in 2013. I¤/ ¢ inter‹uartile range. NA ¢ not applicable. SD ¢ standard deviation*

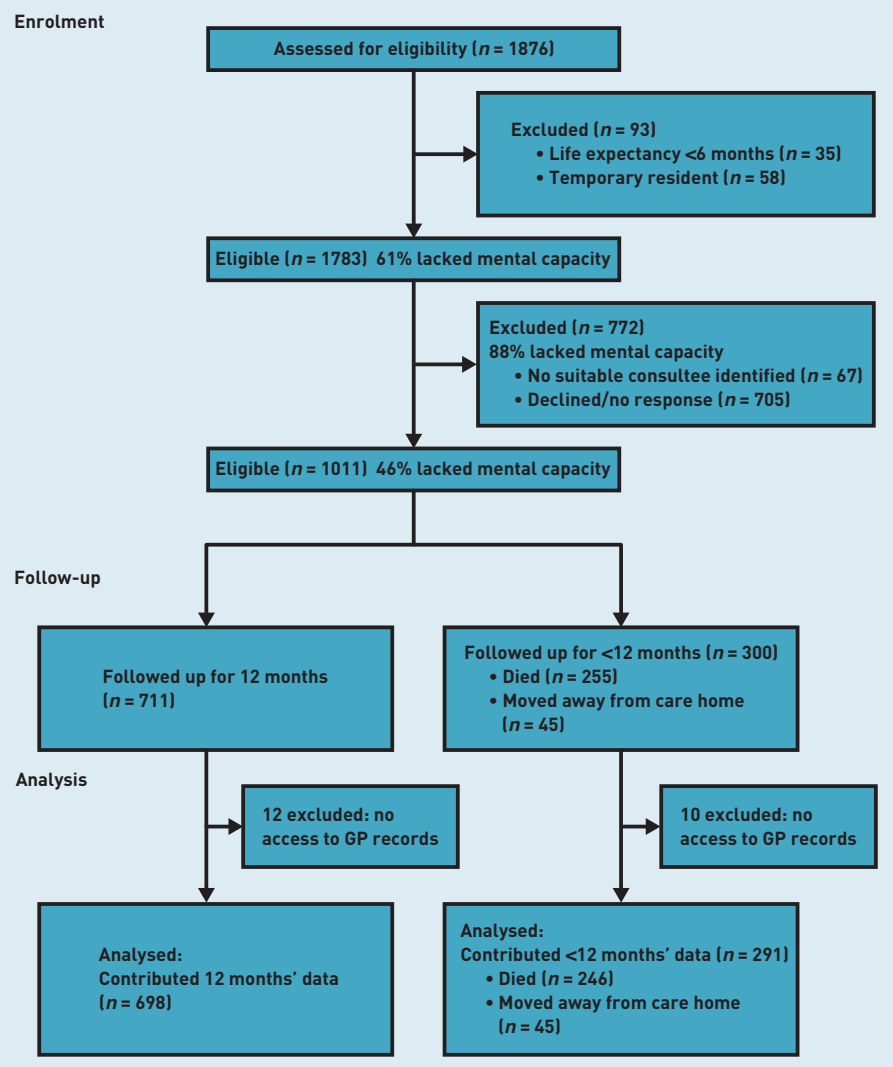
£igure 1 reports the numbers of individuals at each stage of the study. All residents in participating care homes were assessed for eligibility (*n* ¢ 187›); 95.0% (1783 out of 187›) were eligible. /easons for exclusion were life expectancy <› months (*n* ¢ 35) and being temporary residents (*n* ¢ 58). Sixty-seven patients were excluded as they lacked capacity to consent and no suitable consultee was identified. Of eligible residents, 5›.7% (1011 out of 1783) invited to participate were consented and enrolled to the study between August 2013 and §une 2014; 4›› (4›.1%) of those enrolled lacked capacity.

Baseline data were obtained for 1011 participants. £ollow-up analysis consisted of 989 participants (22 patients were excluded from follow-up analysis because of restricted access to GP records). Six-hundred and ninety-eight out of the 989 were followed up for 12 months, 45 moved away, and 24› died while in the study (after less than 12 months). The total follow-up period was 847.52 PYs with median (I¤/) follow-up period 3›5 (300–3›5) days.

Participants

The mean age (standard deviation [SD¡) was 85.1 (8.›) years, 58.1% (587 out of 1011) were aged ≥85 years; mean BMI was 24.4 kg«m^2 (SD ›.1), with 14.1% (142 out of 1011) having BMI ≥30 kg«m^2 and 11.8% (119 out of 1011) having a BMI <18.5 kg«m^2 (Table 2). Most of the participants, 9›.8% (979 out of 1011), were of white ethnic group and 71.4% (722 out of 1011) were female; 52.7% (530 out of 1011) had dementia. Of the participants, 22.2% (224 out of 1011) were completely bedridden (/MI score ¢ 0) and a further 3›.5% (3›9 out of 1011) had significantly reduced mobility (/MI score ¢ 1–›).

The main reason for re‹uiring care home admission was mental health conditions (41.4%, 419 out of 1011), with 89.3% (374 out of 419) of this being caused by dementia.



›igure 1. Study flow diagram.

Table 2. Participants' characteristics

N = 1011	*n*	%
Age, years		
<›5	34	3.4
›5–74	85	8.4
75–84	305	30.2
≥85	587	58.1
£emale	722	71.4
" hite ethnic group	979	9›.8
Dementia[a]	530	52.7
Main condition requiring care home admission		
Mental health condition	419	41.4
Social«emotional problems	187	18.5
Somatic disorders	340	33.›
Other	›5	›.4
Length of stay since admission		
<1 year	378	37.4
1 year to <5 years	528	52.2
≥5 years	105	10.4
Do-not-resuscitate order in place	320	31.7
BMI,[b] kg/m^2		
<18.5 (Underweight)	119	11.8
18.5–24.9 (Normal weight)	438	43.3
25.0–29.9 (Overweight)	23›	23.3
≥30 (Obese)	143	14.1
Smoking status		
Ex-smoker	334	40.3
Current smoker	3›	4.4
Mobility[c]		
Bedridden (/MI ¢ 0)	224	22.2
Significantly reduced mobility (/MI ¢ 1–›)	3›9	3›.5
Mobile (/MI ¢ 7–15)	417	41.3
Care home		
Type		
" ith nursing	›91	›8.3
" ithout nursing	320	31.7
Size, number of beds		
<30	23›	23.3
30–49	294	29.1
≥50	481	47.›
Ownership		
£or profit	739	73.1
Not for profit	272	2›.9

[a]Data were missing for five patients. [b]Data were missing for 75 patients. [c]Data were missing for one participant. BMI ¢ body mass index. /MI ¢ /ivermead Mobility Index.

Participants had been in the present care home for a mean time of 2.8 years (SD 8.2), with a median time of 1.5 years. Of the participants, ›8.3% (›91 out of 1011) resided in care homes with nursing and 31.7% (320 out of 1011) in care homes without nursing; overall 31.7% (320 out of 1011) had a do-not-resuscitate order in place.

Baseline VTE risk

" hen the Department of Health VTE risk assessment tool[21] for hospitalised patients was applied to baseline data, 58.7% of participants (593 out of 1011) were classed as high risk and eligible for consideration of either mechanical or pharmacological prophylaxis in the hospital setting (Table 3). The ¤Thrombosis risk tool,[22] a risk prediction model designed for primary care, indicated that participants had an increased 1-year risk of VTE with 9›.0% (971 out of 1011) having an absolute risk of ≥0.3, three times the general risk.

VTE prevention strategies at baseline

Prompted by a recent VTE or hospitalisation, 0.7% of participants (7 out of 1011) were on heparin, and another 5.5% (5› out of 1011) were on oral anticoagulants, mainly for atrial fibrillation. Compression stockings were used by 5.0% (51 out of 1011). There was no evidence in any participant's records of VTE risk assessment.

Identification of VTE events during follow-up period

Data for 989 participants in the follow-up analyses were reviewed by the internal adjudication team. There were 991 events: 24› deaths, 574 hospital admissions (relating to 345 patients), and 171 GP consults involving symptoms suggestive of VTE. Out of these, the internal adjudication process identified 132 potential VTE events; there was insufficient information to make a judgement on six events. £inally, independent adjudication confirmed 21 VTE events (› definite, 1 probable, 14 possible).

Incidence of VTE

Table 4 shows the number of VTE events according to diagnostic certainty and associated incidence rates. The incidence of definite VTE was 0.71 per 100 PY (95% CI ¢ 0.2› to 1.54), definite and probable VTE was 0.83 per 100 PY (95% CI ¢ 0.33 to 1.70), definite, probable, and possible was 2.48 per 100 PY (95% CI ¢ 1.53 to 3.79). The incidence of definite and probable VTE varied according to type of care home (care home with nursing: 0.70 per 100 PY, care home without nursing: 1.10 per 100 PY). Table 5 shows supplementary data according to the type of VTE. Most of the definite and probable VTE events were DVTs (71.4% [5 out of 7¡), and PE accounted for 1›.›% (1 out of ›) of definite VTE compared with 57.1% (8 out of 14) of possible VTE. The incidence of VTE-related deaths was 0.12 per 100 PY for definite VTE as well as definite and probable VTE, and 0.35 per 100 PY definite, probable, and possible VTE. The rate of hospital admissions caused by VTE was 0.34% (2 out of 574) for definite VTE, 0.52% (3 out of 574) for definite and

Table 3. Department of Health VTE risk assessment

Risk assessment criteria	*n*	%
Mobility		
Significantly reduced mobility	593	58.7
Thrombosis risk (based on 5›3 patients with reduced mobility)		
Active cancer or cancer treatment	›9	11.›
Age >›0 years	587	99.0
Dehydration	NM	NM
Known thrombophilias	2	0.3
Obesity (BMI >30 kg«m^2)	83	14.0
One or more significant medical comorbidities[a]	425	71.7
Personal history of VTE	›0	10.1
Use of hormone replacement therapy	1	0.2
Use of oestrogen-containing contraceptive therapy	0	0.0
Varicose veins with phlebitis	2	0.3
Pregnancy or <› weeks postpartum	0	0.0
Number with at least one thrombosis risk factor	593	100%

[a]*Heart disease; metabolic, endocrine, or respiratory pathologies; acute infectious diseases; inflammatory conditions. BMI ¢ body mass index. NM ¢ not measured. VTE ¢ venous thromboembolism.*

Table 4. Incidence of VTE according to diagnostic certainty

Characteristic	Number of events	*n*	Person years	Incidence rate per 100 person years	9¡% CI
Diagnostic criteria					
Definite VTE	›	989	847.52	0.71	0.2› to 1.54
Definite and probable VTE	7	989	847.52	0.83	0.33 to 1.70
Definite, probable and possible VTE	21	989	847.52	2.48	1.53 to 3.79

VTE ¢ venous thromboembolism.

probable VTE, and 1.21% (7 out of 574) for definite, probable, and possible VTE.

Table › compares the event rates across age groups, sex, mobility, type of care home, length of residency, previous VTE event, and presence of one or more significant medical comorbidities. In summary, the data suggest that the risk of a recurrence is increased with having a previous VTE (relative risk [//¡ 3.17 95% CI ¢ 1.1› to 8.››¡, *P* ¢ 0.02) and with having one or more significant medical comorbidities (// 4.87 [95% CI ¢ 1.›4 to 14.49¡, *P* ¢ 0.004). Although the risk of VTE is likely to be increased with being female, aged ≥85 years, resident in a nursing home, and resident in care home for <1 year, the confidence intervals are wide and include the possibility of reduced risk.

DISCUSSION

Summary

This is the first prospective study to determine the incidence of VTE in care homes and evaluate incidence of VTE in UK care homes. There was an incidence of 0.83 per 100 PY for definite and probable VTE, significantly higher (seven times) than the community incidence of 0.117 per 100 PY,[18]

Table ¡. Incidence of VTE according to type of VTE and diagnostic certainty

Characteristic	Definite VTE £*n*= 6⁄		Definite and probable VTE £*n*= 7⁄		Definite¢ probable¢ and possible VTE £*n*= 21⁄	
Type of event	*n*£%⁄	Incidence rate £9¡% CI⁄	*n*£%⁄	Incidence rate £9¡% CI⁄	*n*£%⁄	Incidence rate £9¡% CI⁄
DVT	5 (83.3)	0.59 (0.19 to 1.38)	5 (71.4)	0.59 (0.19 to 1.38)	11 (52.3)	1.30 (0.›5 to 2.32)
PE	1 (1›.›)	0.12 (0.003 to 0.››)	2 (28.›)	0.24 (0.03 to 0.85)	10 (47.›)	1.18 (0.57 to 2.17)
£atal PE	1 (1›.›)	0.12 (0.003 to 0.››)	1 (14.2)	0.12 (0.003 to 0.››)	3 (14.2)	0.35 (0.07 to 1.03)
⁄ecurrent VTE	2 (33.3)	0.24 (0.03 to 0.85)	2 (28.›)	0.24 (0.03 to 0.85)	5 (23.8)	0.59 (0.19 to 1.38)

DVT ¢ deep vein thrombosis. PE ¢ pulmonary embolism. VTE ¢ venous thromboembolism.

Table 6. VTE event rates according to selected participant characteristics

Characteristics		Number of events[a]/ person years	Relative risk £9¡% CI[b]/	*P*-value
Sex	Male (reference)	4«240	1	–
	£emale	17«›08	1.›7 (0.5› to 4.99)	0.350
Age, years	<75 (reference)	2«10›	1	–
	75–84	1«258	0.21 (0.02 to 2.27)	0.200
	≥85	18«483	1.98 (0.4› to 8.51)	0.3›0
Rivermead Mobility Index	0 (reference)	3«183	1	–
	1–›	8«301	1.›2 (0.43 to ›.11)	0.480
	7–15	10«3›4	1.›8 (0.4› to ›.09)	0.430
Length of stay since admission	<1 year	9«30›	2.74 (0.35 to 21.59)	0.340
	1 to 5 years	11«448	2.28 (0.29 to 17.›9)	0.430
	>5 years (reference)	1«93	1	–
Type of care home	“ ith nursing	17«575	2.02 (0.›8 to ›.00)	0.210
	“ ithout nursing (reference)	4«273	1	–
Previous VTE	Previous VTE	5«7›	3.17 (1.1› to 8.››)	0.024
	No previous VTE (reference)	1›«772	1	–
Malignancy	Malignancy	3«114	1.07 (0.32 to 3.›4)	0.910
	No malignancy (reference)	18«733	1	–
Obesity, body mass index	>30 kg«m^2	3«125	0.99 (0.29 to 3.41)	0.990
	≤30 kg«m^2 (reference)	1›«››3	1	–
Significant medical comorbidities[c]	0 (reference)	4«453	1	–
	≥1	17«395	4.87 (1.›4 to 14.49)	0.004

[a]Definite, probable, and possible VTE. [b]Poisson exact CI. [c]Heart disease; metabolic, endocrine, or respiratory pathologies; acute infectious diseases; inflammatory conditions. VTE ¢ venous thromboembolism.

rising to 2.48 per 100 PY when including possible VTE. The incidence of definite and probable VTE is also twice as high as the rate of VTE in people aged ≥70 years (0.44 per 100 PY).[23] The study population was classed as high risk according to conventional available VTE risk assessment tools; however, there was no demonstrable use of VTE risk assessment.

Strengths and limitations

The current study has several strengths; the clear definitions for VTE according to diagnostic certainty and independent adjudication of study endpoints minimised bias in the ascertainment of VTE events. Data collection comprised complete notes review of both care home and GP records; GP records in UK contain the complete medical history including all hospitalisations, investigations, results, and medications, therefore providing a robust data source for identification of VTE events. £urthermore, HSCIC cause of death data provided reliable data for adjudication on deaths. The study sample is drawn from a mix of care homes across Birmingham and Oxford, and reflects a considerable proportion of care home residents without mental capacity. Nevertheless, the small number of definite and probable VTE events meant that there was insufficient data to develop a reliable clinical prediction model for estimating the probability of the occurrence of VTE in a care home population.

Comparison with existing literature

The incidence rate of definite and probable VTE in the present study is lower than that found in previous studies; however, if possible VTE is included the rate is much higher.[24–27] Gomes and colleagues found an incidence of 1.30 events per 100 PY,[24] Gatt *et al* found an incidence of 1.4 to 1.› per 100 PY,[25] and ¥eibson and colleagues found an incidence of 1.2 to 1.5 per 100 PY.[2›] These studies, however, relied on nursing home administrative data and diagnostic codes, and were, therefore, subject to diagnostic uncertainty and misclassification. £urthermore, Gomes *et al* and ¥eibson and colleagues were unable to disentangle VTE events that occurred during nursing home residence from those that occurred before admission, as conditions were recorded as active at time of assessment. This is important, as /eardon *et al* found that 1 in 25 patients admitted to care homes had a current diagnosis of VTE.[27] On the other hand, the present study included only VTE events

that occurred during participants' time in the study. Patients were also excluded with life expectancy of <› months, and this group may have had a higher likelihood of developing a VTE.

A more recent study found a higher incidence of 3.›8 per 100 PY.[27] This again may be a result of methodological differences, although the authors attributed this to possible conse‹uences of differences in the pool of nursing homes studied, and improved diagnostics for asymptomatic VTE such as the portable Doppler ultrasound. Portable Doppler was not available to care home residents in the current study. Nevertheless, incidence rates found in this and previous studies are likely to underestimate the real incidence of VTE in the care home population as death caused by PE is underdiagnosed while post-mortem-proven fatal PE rate in hospital inpatients is 2.5%.[28] Additionally, a post-mortem study of 234 nursing home residents found undiagnosed VTE to be the cause of death in 8%, while 40% of PE events were not suspected before death.[29] In the present study, only one out of the 24› deaths had objectively confirmed PE as the cause of death, giving a fatal PE rate of 0.4%. Moreover, the studies are subject to under-recognition of VTE as symptoms may be nonspecific and masked by comorbidity in older patients.[30–34] Also VTE is often silent,[35–37] and a previous study found prevalence of 13.5% DVT by ultrasonography screening of institutionalised older individuals.[38]

Implications for practice

Despite robust standards for ascertainment of VTE events, the incidence in care home residents in this study is high compared with incidence in the community overall, as well as incidence in older people. The substantial VTE rate in care home residents re‹uires consideration by clinicians responsible for their care; this has implications on national health care in terms of the UK's ageing population, particularly as none of the residents in the present study had been risk assessed for VTE.

Current guidelines have no provision for care home residents; further evidence is needed to inform guideline development. flarowitz and colleagues developed a VTE risk stratification tool for care homes,[39] although this has not been validated. Many of the characteristics of care home residents are also associated with adverse events from pharmacological thromboprophylaxis. Although it is difficult to argue for formal risk assessment in care homes at this stage, there is a need to explore risk stratification and the benefit of VTE prophylaxis in this population.

›unding

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Ethical approval

Ethical approval for the study was granted by the National /esearch Ethics Service (N/ES) committee "est Midlands fi Black Country (reference 13« "M«0118). Informed consent was obtained for all study participants.

Provenance

£reely submitted; externally peer reviewed.

Competing interests

Carl Heneghan has received expenses from the "orld Health Organization ("HO) and holds grant funding from the NIH/, the NIH/ SPC/, the "ellcome Trust, and the "HO. He is also a member of the advisory group of the "HO International Clinical Trials /egistry Platform and also organizes the Evidence¥ive conference with the *BM§*. The other authors have declared no competing interests.

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Patients' perceptions and experiences of the prevention of hospital-acquired thrombosis: a qualitative study

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ABSTRACT

Objective: To examine patients' understanding of hospital-associated thrombosis, and their experiences of thromboprophylaxis.

Design: Qualitative study using semi-structured interviews with 31 patients requiring venous thromboembolism (VTE) prophylaxis following a recent hospital admission. Interviews were audio-recorded, transcribed verbatim and analysed thematically using framework analysis.

Setting: 4 hospitals in Birmingham and Oxford.

Results: All the participants received thromboprophylaxis following surgical procedures. Participants were aware of a risk of blood clots; however, they lacked a good understanding of VTE and its components. Experiences of VTE prophylaxis were characterised with good adherence to heparin injections and poor adherence to elastic compression stockings, largely due to perceived lack of clarity in guidance from health professionals. Participants had limited knowledge of the signs and symptoms of VTE and would value improved education on VTE.

Conclusions: Findings suggest that patient education is often inadequate and impacts negatively on patients' involvement in VTE prevention. An enhanced patient education programme incorporating a consistent message on the appropriate use of elastic compression stockings and description of VTE symptoms is likely to optimise the effectiveness of the prevention of hospital-associated thrombosis. Physicians may use the results of this study to improve individual patient education.

Strengths and limitations of this study

- Mixed variety sample of patients requiring venous thromboembolism prophylaxis following a recent hospital admission.
- Interviews were audio recorded, transcribed verbatim and independently checked for accuracy.
- Data analysis was iterative and independent of the interviewing researcher.
- Over-representation of surgical patients.
- Participants were predominantly of white British ethnicity.

INTRODUCTION

Patient involvement is an important aspect of the prevention of hospital-associated thrombosis (HAT) yet, to date, much of the focus on preventing HAT has been on health professionals' implementation of the venous thromboembolism (VTE) prevention strategy and associated outcomes, and there is little understanding of patients' perceptions and experiences of HAT prevention. HAT can occur up to 90 days postdischarge from hospital, and it is recognised that patients are at increased risk during this time with most cases of HAT occurring following discharge.[1] With current trends towards enhanced recovery and early postsurgery hospital discharge, a significant proportion of hospitalised patients at risk of VTE are discharged with mechanical prophylaxis (usually antiembolism stockings) and/or pharmacological prophylaxis (usually self-administered injections of low molecular weight heparin).[2–5] Therefore, a lot of responsibility falls on the patient with regard to appropriate use and adherence to VTE prophylaxis and recognition of possible VTE episodes for timely medical intervention.

VTE comprises the acute conditions deep vein thrombosis (DVT) and pulmonary embolism (PE); DVT occurs when a blood clot forms in the deep veins (usually lower legs) and PE is a potentially fatal complication which occurs when some or the entire clot detaches and travels to the lungs. A recent US study found that while patients were generally aware of the benefits of antithrombotic therapy, only 6 out of 12 interviewed patients had a clear understanding of DVT and PE.[6] Also adherence has been identified as a problem with patients prescribed thromboprophylaxis both internationally and in the UK.[7–10] It has been hypothesised that patients

are not adequately educated about the rationale for thromboprophylaxis; however, this has not been fully elucidated and no qualitative research has explored HAT prevention from the patients' perspective. This qualitative study, embedded within a larger study exploring the prevention and knowledge of VTE (ExPeKT) aimed to explore patients' awareness of VTE and their experiences VTE prophylaxis.[11]

METHODS

Face-to-face interviews were carried out with patients classed by hospital staff as being at high risk of developing VTE during a recent hospital admission. The rationale of using interviews was to allow detailed exploration of personal perceptions and individual experiences without the contamination of other participants' views. Participants were drawn from respondents to a survey conducted as part of the broader ExPeKT study.[11] The survey was distributed to 868 inpatients assessed to be at high risk of VTE, recruited from medical, surgical and orthopaedic wards in two acute trusts in Oxford and Birmingham. Of these, 564 patients returned completed questionnaires and 238 confirmed they would be prepared to be interviewed.

Purposeful sampling[12] was employed to select interview participants of maximum variety of age, gender, condition requiring hospital stay and site. This was to ensure that the sample reflected a varied range of patients to minimise the risk of the study being distorted to one perspective. A topic guide was developed through discussion with the research team, and comprised open-ended questions that drew reflections on patients' recent hospital admissions with particular reference to their understanding of VTE risk and their experiences of how this risk was assessed and managed (see online supplementary appendix 1).

Data collection continued until theoretical saturation was attained.[13] Semistructured interviews were conducted with a total of 31 patients and they all took place in the patients' homes. All participants provided informed consent prior to the interviews. The interviewer was a woman, a non-clinical researcher (PhD) trained in qualitative research; she was not known to participants prior to the study, and participants were made aware that she was conducting the interviews as part of her job. The interviews lasted between 10 and 45 min; all were audio recorded and transcribed verbatim. Verification of interview data was completed through triangulation with the corresponding survey responses to establish credibility and dependablity.[14]

Analysis

PNA, IL and SG independently read through the same three interview transcripts to familiarise themselves with the interviews and identify emerging themes. They then met to compare, discuss and finalise themes for the coding frame.[15] Based on this PNA subsequently coded the remaining interviews using NVivo software to manage the data which was analysed using framework analysis[16] (see online supplementary appendix 2).

RESULTS

Participant characteristics

Participants' characteristics were extracted from patient questionnaires administered as part of the wider ExPeKT study[11] (table 1). Of the 31 participants, 55% were men and ages ranged from 38 to 81 years with a mean age of 63. The majority (94%) were of white British ethnicity and 87% had received at minimum an 'O level' education or earned a professional qualification.

All the participants were surgical patients, 87% were planned admissions and the remainder were emergency admissions. In total, 58% underwent orthopaedic surgery (hip or knee replacement). All the participants received VTE prophylaxis, with 77% receiving both compression stockings and heparin injections.

Findings are presented in five main themes: awareness of VTE risk, experience of VTE prophylaxis, knowledge

Table 1 Participants' characteristics

Variable	N=31	Per cent
Male, n (%)	17	54.8
Age groups (years)		
≤40	3	9.7
41–64	11	35.5
65–74	12	38.7
≥75	4	12.9
Not known	1	3.2
White British ethnicity	29	93.5
Highest level of education received		
O or A level	6	19.4
Degree	9	29.1
Professional/commercial	12	38.7
Not known/none	4	12.9
Admission		
Planned admission	27	87.1
Emergency admission	4	12.9
Length of hospital stay, number of days		
≤3	7	22.6
1–6	17	54.8
≥7	7	22.6
Condition requiring hospital admission		
Orthopaedic surgery	18	58.1
Gastrointestinal surgery	7*	22.6
Other surgery	6†	19.3
VTE prophylaxis		
Stockings only	5	16.1
Injectable prophylaxis only	2	6.5
Both stockings and injectable prophylaxis	24	77.4

*One was oncology related.
†Three were oncology related.
VTE, venous thromboembolism.

of VTE symptoms, postdischarge support and perceived gaps in patient education (figure 1).

Awareness of VTE risk

Patients reported being aware of risk of blood clots associated with their recent hospital admission; though they did not refer specifically to the terms DVT or PE. In particular, patients booked for planned orthopaedic surgery described a presurgical assessment which entailed a discussion on all the risks relating to their surgery including risk of blood clots.

> I just remember the general things that there is obviously a substantial risk of clotting and that they take certain precautions to ensure that they manage that sort of during and after the process. Female aged 69, total hip replacement

> Yes they were very good. They covered all those points honestly, they did point out lower limb surgery, increased risk etc. Best thing to do, and that's come through repeatedly, is keep moving. Male aged 56, total hip replacement

However, information given to a patient in the preassessment for non-orthopaedic surgery seemed to miss out the emphasis on blood clots:

> I mean I know when you have your pre-op they do your blood pressure and everything, yes. But at no time, in fact, were blood clots actually mentioned. Female aged 68, stoma reversal

Patients' source of awareness of VTE appeared to be mainly from information given in work up to the recent surgical admission or a previous surgery of themselves or a family member.

> Q: Before you went into hospital were you aware of the risks of blood clots associated with being in hospital?
>
> A: Yes, I think so, largely because, I'm having been in previously for various bits and pieces over my life, y'know, I was aware that they can happen but fortunately there's no family history so, not too concerned. And also everyone explains these things at each time, all the various risks that are associated. Female aged 62, knee replacement

VTE risk assessment: Patients appeared not to be aware of undergoing a VTE risk assessment and many presumed that the VTE prophylaxis was part of a general approach rather than a tailored treatment due to their being at high risk.

> I had a pre-med, they checked my blood pressure and everything, but no I wasn't aware of being risk assessed for that particular condition (blood clots). Female aged 63, ovarian cysts

Experience of VTE prophylaxis

Patients described their perceptions and experiences of heparin injections and compression stockings.

Injections: perceptions and adherence: Twenty-four out of 26 patients given heparin injections as part of their

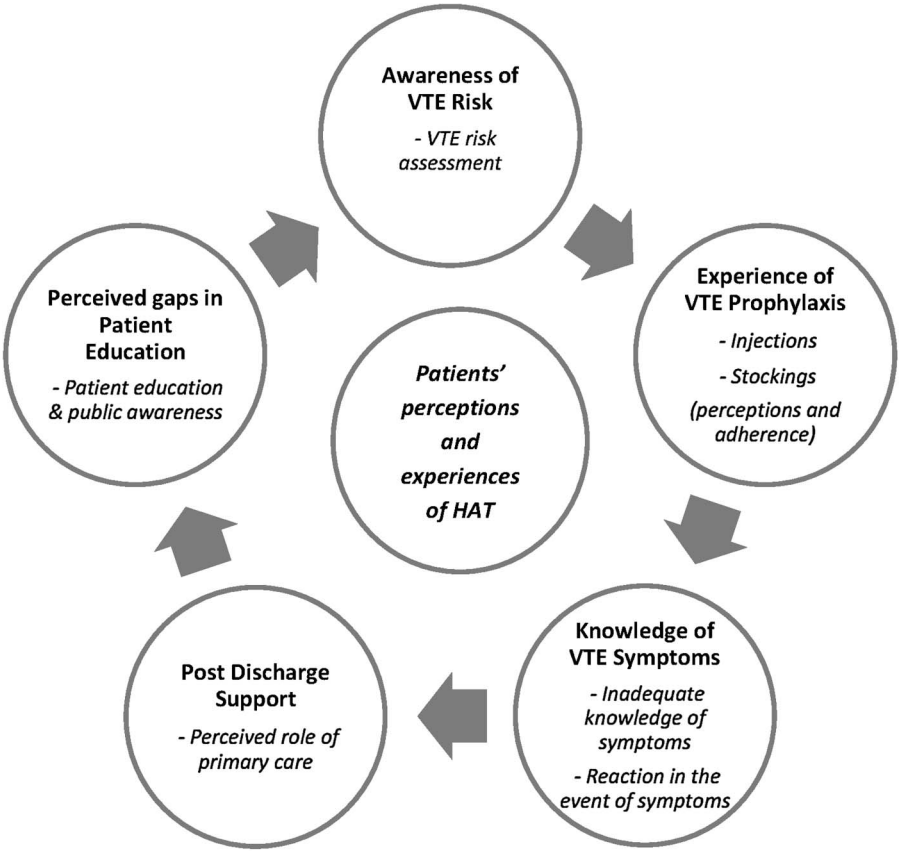

Figure 1 Themes and subthemes. HAT, hospital-associated thrombosis; VTE, venous thromboembolism.

hospital admission had to self-administer the heparin injections at home postdischarge. Patients' narratives portrayed mixed views of having to self-inject; some reported they were not keen on self-administering the injections while others had no problem with it and did it routinely. Patients described the differing levels of guidance provided on injecting the chemoprophylaxis. Some received training by a nurse that included a demonstration and observation while others recalled being handed the injection set on discharge and instructed to maintain the course of injections. Despite these discrepancies all participants discharged with heparin injections reported completing the course of injections though some had help from an adult child or partner.

> I mean I'm not particularly a squeamish kind of person, so I wasn't particularly nervous about it. I didn't like the idea when I first had to do them the first time, but, realising effectively that there isn't a choice, just get on and do it. So…y'know 6 o'clock every night the ol' thing came out…I had quite a few bruises on my tummy…as time went on I suppose y'know, it did become more painful. But y'know, needs must, if that's what you've got to do, that's what you've got to do. Female aged 62, knee replacement

Generally patients understood that the injections were to prevent blood clots; however, two patients had limited understanding of the rationale for the injections and viewed them as part of the treatment of their condition, and did not necessarily associate them with VTE prevention.

> Q: So what treatment did you receive, to prevent blood clots?
>
> A: Now, was I given any pills, the week before. On that visit, we were given some pills…no I don't think before the operation I had anything specific for blood clots.
>
> Q: Did you have anything whilst you were in hospital do you know?
>
> A: I'm sure they were giving me something, they were giving me various pills, but again, they didn't necessarily tell me, as I recall, what it was for.
>
> Q: What about when you left the hospital. Did they give you anything to bring home?
>
> A: I don't think so; I mean I had the support stockings…
>
> Q: Did you have any injections? Injections in the stomach?
>
> A: Yes, ah, is that, was that, I'd forgotten that now. I was given these—I had to inject myself for, a month?
>
> Q: Yes, now that is an anticoagulant
>
> A: Right, perhaps I had forgotten that. Male aged 63, total hip replacement

Elastic compression stockings: perceptions and adherence: A total of 29 patients reported receiving elastic compression stockings during their hospital admission and described their experiences. Overall, there was inconsistency in the administration of the stockings and some participants described coming round from surgery to find the stockings on, with no explanations. Patients' narratives pointed to a lack of clarity on the use of stockings and few patients (7/29) wore them for prescribed length of time. Patients described multifaceted reasons for non-adherence; guidance on stockings use seemed to be rather potluck—very few were clear that they were to continue to wear them postdischarge and/or how long they were to wear them for.

> Q: Did you wear the stockings all of time?
>
> A: For the full length I was in there, yeah.
>
> Q: And when you came out?
>
> A: Didn't wear them when I came out.
>
> Q: Were you supposed to?
>
> A: Well no I don't think so…I didn't wear them when I came out no, no. Although they did give me four or five pairs. Male aged 38, lump removed from right leg

Some patients discontinued wearing stockings after a while due to discomfort, choosing to exercise and/or stay mobile in place of the stockings or a perception that their personal risk of VTE was low.

> I carried on for a little while, but they made my legs worse. I felt they were too tight…My daughter in law is a physiotherapist- because I was so active, she thought I would be alright without sort of thing…so uncomfortable they bit into you around the top here leg and all that y'know. Male aged 73, knee replacement

Patients also reported contradictions in information received regarding stockings, with conflicting information from nurses, doctors and information leaflets. This made it difficult for patients to know the correct course of action, and one patient was told he no longer needed to wear the stockings once the injections were started.

> The nurse said wear them for a fortnight which is what I did and then reading the leaflet afterwards it said keep wearing the stockings for after six weeks but I only wore them for a fortnight. Male aged 69, hip replacement
>
> I suppose that's probably the most unclear part of the whole procedure. The injections were fine, I was quite happy with y'know, doing and administering it and that whole process. Obviously the stockings were worn in the hospital sort of continuously and then I think the information you get, the information sheets is wear of up to four weeks post op, but there was definitely conflicting

advice from the nursing staff. Some of the nurses were, 'well it's not that serious if you don't wear them' others were 'absolutely must wear them.' So, y'know there was definitely conflicting advice. Female aged 40, hip replacement revision

Some of the patients who wore elastic compression stockings for the prescribed period (often 6 weeks) also reported of discomfort in terms of tightness and challenges of getting them on and off, and many required help from a spouse or partner.

Interestingly many patients reported saving their stockings for flying.

Knowledge of VTE symptoms

Inadequate knowledge of symptoms: One-third of the interviewed patients were of the opinion that they would not recognise symptoms of a blood clot. The other two-thirds described vague symptoms relating to DVT with 'pain in lower leg' being the most cited symptom, with a few mentioning tenderness, soreness, redness and swelling. Patients' responses demonstrated a lack of awareness of potentially fatal PE and only two patients described symptoms of PE, describing it as 'when the clot travels to the lungs' and cited symptoms such as shortness of breath, and tachycardia.

I mean, I know there is a risk but I wouldn't know how to assess whether or not I was having a blood clot. Female aged 63, ovarian cysts

Well if you're gonna ask me now what are the symptoms I'm gonna say I can't remember. I think discolouration, and probably pain in your leg. I don't know if you get to the stage of passing out do you? Male aged 63, hip replacement

Reaction in the event of symptoms: All participants said they would seek medical attention if they thought they were having a blood clot, some opting to go to the general practitioner (GP) and others recognising it as a medical emergency.

I would, I don't know, it depends how bad it was I suppose. I might go straight to A and E or, go to the doctor. But I would know that it's urgent. Male aged 79, knee replacement

Postdischarge support

Perceived role of primary care: The interviews explored the need for postdischarge support from GP/district nurse. Generally patients were of the opinion that it was not necessary to routinely activate GP involvement postdischarge, and many could not see the point and found it difficult to envision a role for primary care in this area. Patients reported that they had all coped fine with the current system and were empowered to contact their GP if they had any concerns. A few said they would find it reassuring just to know they were doing the right thing due to the long time period between discharge from surgery and follow-up consultations.

That's quite interesting actually, I think I never thought about in terms of the GP but the one thing I did sort of think about during the whole recovery process is you kind of sort of leave hospital and that's it until you have your check-up so, you do hit moments where I think you do wonder is everything going ok even if you've got no reason to be, to question it. Am I doing the right thing? Should I be doing this? Shouldn't I be doing that? And there isn't really anyone to call. So whether it's a visit from the GP that would be, a good idea or whether it's a district nurse or whether even it's a physio, I think in that period between sort of discharge and you follow up consultation I think, it's too long a gap without some, just reassurance really, nothing more than that. Female aged 40, hip replacement revision

Perceived gaps in patient education

Patient education and public awareness: Patients would however value more education on VTE, in terms of how the VTE prophylaxis works, clarity on stockings use and some information on symptoms in order to recognise if they were having a blood clot. One patient who had experienced a minor bleeding episode said it would have been useful to have been warned about possible side effects of pharmacological prophylaxis. Patients also touched on lack of public awareness of VTE and suggestions to deal with this included public campaign.

Y'know there's the sort of checklist that they have to fill before you're discharged. Y'know have you got your meds? Have you got this have you got that? Maybe that's the point at which they just need to sit with patients again and say, 'right, let's just remember some key things y'know, do you know how to identify infection or blood clot?'…Y'know take an extra ten minutes per patient on discharge to go through a number of key risk areas is probably the one thing that could be, looked at. Female aged 40, hip replacement revision

DISCUSSION

The findings of this qualitative study give insights into patients' experiences of VTE prevention. Despite an awareness of VTE risk, patients did not appear to have a good understanding of the components of VTE and its potentially fatal complications. Patients were aware it was important to seek medical advice if they thought they had a VTE but appeared to lack the knowledge to assess its onset and important knowledge on signs and symptoms of VTE was limited.

Though our study found good adherence to injectable prophylaxis, there was poor adherence to antiembolism stockings due perhaps to a lack of clarity in patient education.

The National Institute for Health and Care Excellence (NICE) guidelines for VTE prevention recommend that patients discharged with VTE prophylaxis are offered

verbal and written information on the signs and symptoms of DVT and PE, and the correct and recommended duration of use of VTE prophylaxis at home. It also recommends patients are educated about the importance of using VTE prophylaxis correctly, adherence and the importance of seeking help if they have any problems using the prophylaxis or DVT, PE or other adverse events are suspected.[2] Our findings are inconsistent with these recommendations with patients having huge gaps in knowledge of symptoms and requirements relating to stockings use.

The finding relating to high adherence to injectable prophylaxis must be interpreted within the context of the study sample which was predominantly orthopaedic patients who had presurgical a session involving education on VTE prevention. Similarly this accentuates the significance of the finding relating to limited knowledge on signs and symptoms of VTE.

The literature supports the premise that improving a patient's understanding of the rationale for a medication increases adherence,[17] and this has been proven to apply to VTE prevention—a US study found individualised patient education sessions on thromboprophylaxis was associated with higher adherence to injectable prophylaxis.[18] Another study found that discharge counselling was associated with improved adherence after hospital discharge for myocardial infarction.[19]

Strengths and limitations

To the best of our knowledge, this is the first qualitative study to explore hospitalised UK patients' perceptions and experiences of VTE prevention, incorporating awareness of VTE risk and VTE prophylaxis. Face-to-face interviews provided in-depth exploration of the issues, and analysis was iterative and independent of the interviewing researcher. The research team was multidisciplinary and offered different perspectives which enhanced interpretation of the data.

Surgical patients were over-represented, and inclusion of medical patients would have provided a broader representation of hospitalised patients; however, this was a feature of the composition of the survey respondents and findings have been interpreted in the context of this. The sample was also predominantly of white British ethnicity. Nevertheless, a maximum variety sample[20] allowed a mix of participants from the sampling frame, and interviews were conducted to the point of theoretical saturation. Given the high proportion of orthopaedic surgical patients who often have VTE education embedded into the presurgical assessments, findings may overestimate the VTE awareness and adherence to VTE prophylaxis.

Comparison with existing literature

Patients in our study had inadequate knowledge of symptoms of DVT and PE to enable appropriate self-assessment and self-reporting of possible VTE episodes. In addition, they did not appear to recognise the real personal risk of VTE.

Our finding that patients lack a clear understanding of VTE is consistent with previous research; a recent US study found that while hospitalised patients were aware of risk of VTE following orthopaedic surgery and the benefits of VTE prophylaxis many did not have a clear understanding of VTE.[6] A survey in Canada found that only 6% patients who had received thromboprophylaxis as part of a hospital stay were aware of the complication of a blood clot travelling to the lungs, and 20% were not able to correctly identify a single symptom of DVT.[21] The communication of risk is a difficult part of clinical practice[22] and evidence suggests that the format in which risk information is presented affects patients' understanding and perception of risk.[23] Some areas of risk communication still lack strong evidence,[23] nevertheless the communication of VTE risk should aim to influence patient awareness of VTE and correct inappropriate risk perception to facilitate patients to reduce their risk. It is therefore important for patients to be aware that they have been assessed as high risk of VTE. The literature also suggests inadequate public knowledge of VTE and a recent UK street survey reported limited public knowledge of DVT and highlighted the need for raising general awareness of DVT with particular focus on its complications.[24]

Our finding relating to injectable prophylaxis is contrary to the literature which indicates suboptimal adherence to heparin injections[7 8] with non-adherence ranging from 21% to 37%.[7] Our study also found that patients often did not receive enough information to support proper use of elastic compression stockings resulting in poor adherence. This is consistent with the literature and other researchers have observed that some inpatients are offered stockings in a perfunctory manner with poor or limited patient education on VTE.[25 26]

Provider–patient communication in hospitals is frequently problematic and often further complicated during hospital discharge.[27 28] Incorporating the patient's perspective enriches and improves communication between providers and patients, and integrating collaboration and patient empowerment has positive outcomes in relation to patient satisfaction and healthcare outcomes.[29]

CONCLUSION

This study addresses an important aspect of VTE prevention and identifies gaps in patient education that hinder patients' role in VTE prevention. While some patients are aware of the appropriate use of pharmacological and mechanical prophylaxis postdischarge, many lacked important knowledge on the use of antiembolism stockings and symptom recognition of DVT and PE. Patients need a basic but comprehensive understanding of VTE and appropriate use of VTE prophylaxis to complete their participation in VTE prevention.

Suboptimal adherence to VTE prophylaxis and the lack of awareness of VTE symptoms compromise VTE

prevention and puts patients at risk of adverse events; therefore, more attention must be paid to patient involvement in VTE prevention. Improved patient education incorporating VTE risk will motivate adherence to VTE prophylaxis, and education on recognition of symptoms will equip patients to self-assess and self-report possible VTE events. Ongoing initiatives such as Thrombosis UK and World Thrombosis Day may help to increase awareness and improve the understanding of venous thrombosis. Nevertheless, patient education must be systematic and standardised across the National Health Service (NHS) to optimise the effectiveness of the national VTE prevention strategy.

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Ian Litchfield, David Fitzmaurice, Patricia Apenteng, Sian Harrison, Carl Heneghan, Alison Ward and Sheila Greenfield

Prevention of hospital-acquired thrombosis from a primary care perspective:

a qualitative study

Abstract

Background
Although there is considerable risk for patients from hospital-acquired thrombosis (HAT), current systems for reducing this risk appear inefficient and have focused predominantly on secondary care, leaving the role of primary care underexplored, despite the onset of HAT often occurring post-discharge.

Aim
To gain an understanding of the perspectives of primary care clinicians on their contribution to the prevention of HAT. Their current role, perceptions of patient awareness, the barriers to better care, and suggestions for how these may be overcome were discussed.

Design and setting
Qualitative study using semi-structured interviews in Oxfordshire and South Birmingham, England.

Method
Semi-structured telephone interviews with clinicians working at practices of a variety of size, socioeconomic status, and geographical location.

Results
A number of factors that influenced the management of HAT emerged, including patient characteristics, a lack of clarity of responsibility, limited communication and poor coordination, and the constraints of limited practice resources. Suggestions for improving the current system include a broader role for primary care supported by appropriate training and the requisite funding.

Conclusion
The role of primary care remains limited, despite being ideally positioned to either raise patient awareness before admission or support patient adherence to the thromboprophylaxis regimen prescribed in hospital. This situation may begin to be addressed by more robust lines of communication between secondary and primary care and by providing more consistent training for primary care staff. In turn, this relies on the allocation of appropriate funds to allow practices to meet the increased demand on their time and resources.

Keywords
prevention and control; primary health care; qualitative research; thrombosis.

INTRODUCTION

Hospital-acquired thrombosis (HAT) is a substantial healthcare problem resulting in significant mortality, morbidity, and economic cost.[1,2] Recent estimates put the figures for hospital deaths from venous thromboembolism (VTE) in England and Wales in excess of 3› 000[3] out of some 16 million admissions,› although the introduction of the VTE risk assessment tool has led to a reduction in these numbers.[5] It is a disorder that can occur across race, ethnicity, age group, and sex, with many of the known risk factors, such as advanced age, immobility, surgery, and obesity, on the increase. HAT can occur up to 90 days after admission,[6] yet, to date, much of the focus on preventing HAT has fallen on the secondary care environment and there is little to no understanding of the role of primary care. However, a recent study that incorporated primary care data found that over 50% of deaths from VTE occurred after hospital discharge.[7]

This risk of developing HAT is influenced by the specific medical condition of the patient[8] and thromboprophylaxis has been shown to reduce the risk of VTE by 75% in surgical patients[9] and by around 50% in medical patients.[9,10]

Current UK guidelines for preventing HAT[11] (Figure 1) recommend using the Department of Health's risk assessment tool[12] to inform the prescription of the appropriate thromboprophylaxis.[13] The risk assessment tool uses factors, such as significant comorbidity, age, and pregnancy, alongside the risks associated with hospital admissions, such as reduced mobility for >3 days or undergoing surgery that lasts >60 minutes. The prophylaxis that is recommended consists of mechanical devices, such as antiembolism stockings, often used in combination with a pharmacological element including low molecular weight heparin (LMWH), sometimes prescribed for several months following surgery.[11] Previous research abroad has indicated that non-adherence to guidelines is an issue for both physicians[1›] and patients.[15,16] There is some evidence of similar issues of adherence among patients in the UK,[17] with some reporting adherence to LMWHs as low as 23%.[18] The guidelines also stipulate a supporting role for GPs, based on their notification of when patients are discharged and the prophylaxis prescribed. This type of communication between care settings is known to be problematic,[19–23] leaving patients vulnerable to adverse events following discharge,[2›–29] and the role performed by primary care being unclear.

If primary care is to contribute more effectively to the prevention of HAT, then a better understanding of its current role and of the factors that influence this role is required. The ExPeKT study was designed to explore existing knowledge of thromboprophylaxis among patients,

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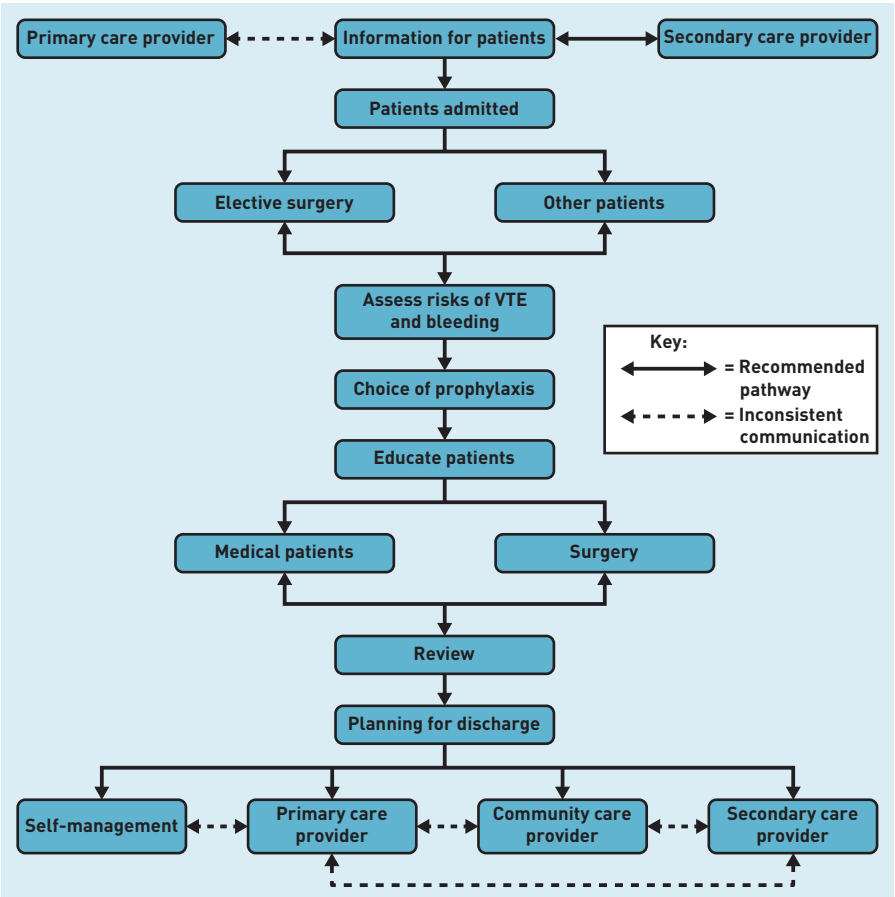
How this fits in

Large numbers of patients are affected by hospital-acquired thrombosis. There is a clear need to improve current mechanisms for managing the issue. Primary care can fulfil this need, although currently its role is poorly defined and it remains underutilised. The authors conducted a series of semi-structured interviews with primary care clinicians to explore perceptions of the current processes for preventing HAT across primary and secondary care. In doing so, ideas were gleaned on how the current management of HAT might be improved. Participants spoke of their limited role, both in educating patients and assessing the risk of HAT before admission, and the lack of contact with patients post-discharge. A number of reasons for this emerged, including a lack of clarity on the responsibility for patients, poor levels of communication, and, as a result, poor coordination of care between different settings. If a broader role for primary care is to be adopted, then there must be improved training for the relevant staff and the provision of appropriate resources.

Figure 1. Management of VTE risk in hospitalised patients (after NICE 2010).[11] VTE ¡ venous thromboembolism.



clinicians, and related staff in primary and secondary care, and other relevant organisations.[30] Here the authors report on a qualitative exploration of the perspectives of primary care clinicians on the factors that influence HAT prevention, including potential barriers to improving current systems and how they may be overcome.

METHOD

The study sample was drawn from two former primary care trusts in Oxfordshire and South Birmingham. All 817 GPs and 583 practice nurses within the study area were sent a postal survey as part of the broader ExPeKT study and invited to participate in a semi-structured interview. From the 111 surveys that were returned, a total of 37 professionals confirmed they would be prepared to be interviewed. Following further contact by telephone, it was determined that, of these, three had retired and a further 20 were either unable to find a convenient time to take part or requested an online interview, which they failed to complete. A final total of 1› interviews took place⁄ 12 GPs and two advanced nurse practitioners. Informed consent was obtained prior to conducting the interviews, which lasted between 10 and 50 minutes.

The study used semi-structured telephone interviews[31] and a topic guide developed to explore clinicians' awareness of hospital-associated VTE, their perceptions of the awareness of patients, and the role of primary care in managing this problem, including any limiting factors and ways in which current systems of managing the issue might be improved (see Box 1 for topic guide). The interviews were conducted by a research fellow experienced in qualitative research, recorded using a telephone recording adaptor with a digital recorder, and transcribed verbatim.

Analysis

Each transcript was read and the findings analysed by two of the authors, who agreed on themes and decided upon the coding framework. Transcripts were analysed using a framework analysis.[32]

RE›ULT›

The sex of the participating clinicians are provided in Table 1, alongside a description of each practice, including the number of patients registered, Index of Multiple Deprivation ranking (IMD code),[33] and an indication of rurality.[3›] The interviewed male and female GPs were from across eight practices. The practices were predominantly

Bo£ 1. Topic guide for semi-structured telephone interviews

- To what extent are GPs aware that hospital-acquired thrombosis (HAT) is a problem'
  - What is your awareness of existing guidelines'
- To what extent are patients aware of HAT'
  - Are there any characteristics of patients that affect this awareness'
  - Do they recognise symptoms'
- Where do you feel responsibility lies for preventing HAT'
- What is the role of primary care in managing HAT in the community'
  - Do you have contact with a patient either prior to admission or following discharge'
  - What are the factors that influence this patient contact'
- What are the factors that limit your role in managing HAT
  - What is the level of contact with other care providers'
  - What are the time and financial pressures'
  - Have you received any training for HAT risk assessment and management'
  - Do you feel that you receive adequate information from secondary care'
- How can the risk of HAT in the community be reduced'
  - Can primary care play a useful role'
  - What can facilitate any change in role'

situated in urban environments; the IMD code varied from ›.29 to 39.69 and the number of patients from 3375 to 27 261. In addition, two advanced nurse practitioners at a large ¡HS community healthcare trust, which clinically manages people in their own homes to prevent an avoidable hospital admission, were interviewed.

The factors that influence the prevention and management of HAT in primary care are described here within five key themes⁄ GP awareness, patient characteristics, designation of responsibility, communication across care settings, and logistical constraints. In discussing suggestions for the way in which the risk of HAT might be reduced, ideas emerged within two key themes⁄ either clinical innovation or organisational innovation. The key themes and associated subthemes are described in Box 2.

Table 1. Characteristics of clinicians interviewed and their practices

Clinician	›tudy practice	›e£	IMD code	Patient list	Urban/rural
GPs					
GP01	Practice 1	Male	15.10	9595	A1 (Urban)
GP02	Practice 2	Male	39.69	936›	A1 (Urban)
GP03	Practice 3	Male	11.05	13 097	C1 (Urban)
GP0›	Practice 3	Male	11.05	13 097	C1 (Urban)
GP05	Practice ›	Male	29.››	27 261	A1 (Urban)
GP06	Practice 5	Female	›.29	11 321	C1 (Urban)
GP07	Practice 6	Female	5.02	5917	E1 (Rural)
GP08	Practice 7	Female	10.08	3375	E1 (Rural)
GP09	Practice 8	Female	37.80	›115	C1 (Urban)
GP10	Practice 8	Male	37.80	›115	C1 (Urban)
GP11	Practice 8	Male	37.80	›115	C1 (Urban)
GP12	Practice 8	Male	37.80	›115	C1 (Urban)
Nurse practitioners					
¡P01	Community healthcare trust 1	Male	31.70	n⁄a	A1 (Urban)
¡P02	Community healthcare trust 1	Female	31.70	n⁄a	A1 (Urban)

IMD § Index of Multiple Deprivation.

Influences on HAT prevention in primary care

GP awareness of HAT. The clinicians interviewed discussed their overall awareness of HAT and the nature of their specific role in its prevention. There appeared to be a general awareness of the risk of HAT to patients⁄

¥I'm aware that it's becoming a huge problem because I know that they screen everybody now, pretty much everybody has to be on prophylaxis.' (GP06)

¥I'm sure that the GPs are aware of it as a problem, yes.' (¡P02)

There appeared, however, little training specific to HAT other than that associated with the use of related medication⁄

¥I've probably not received official training along those lines, apart from warfarin, but no, no official training.' (GP01)

¡or were several of those interviewed aware of the existing guidelines for reducing the risk of HAT, including the risk factors that would require extended prophylaxis following discharge⁄

¥There are hopefully protocols in place to prevent post-op VTE.' (GP02)

¥Right now certainly I don't know which operations do and don't need extended prophylaxis.' (GP03)

Patient characteristics⁄ clinical dependency and patient awareness. Clinicians described how clinical dependency and patient education would influence the level of involvement of primary care providers.

A patient whom the practice recognises as being particularly vulnerable would be reviewed either prior to admission or following discharge⁄

¥We don't often see them unless either there's something that's flagged up in pre-op assessments, or if they've got particular concerns. I mean, we wouldn't routinely see someone, you know, before they go in for an operation.' (GP02)

Bo£ 2. Themes and subthemes

Influences on hospital-acquired thrombosis prevention in primary care					› uggestions for improving current systems	
GP awareness	Patient characteristics	Designation of responsibility	Coordination of care	Logistical constraints	Clinical innovation	Organisational innovation
Current role	Awareness	Secondary care	Communication with primary care and secondary care	Pre-admission risk assessment	Oral-based medication	Improved auditing
Training	Clinical dependency	Primary care	Communication with primary care and community care	Increasing patient awareness	Software-based clinical support tool	Increased role of primary care
				Post-discharge appointments		Unified commissioning

¥I think people who've had a prolonged admission or people who have multiple comorbidity or who are generally quite frail, you know, we might go and do a review post-discharge, particularly people on the Gold Standards Framework.' (GP02)

Where patients were vulnerable, GPs would either administer prophylaxis or otherwise enlist the support of district nurses✓

¥"es, we're more than happy to give that «Clexane ' fi *out to our patients fl those patients who are elderly and are unable to administer it.'* (GP01)

¥We get involved sometimes in arranging district nurses to administer extended courses of antithrombotics but it is very limited at the moment.' (GP09)

¥We also get our district nurses to go out and give them their Clexane injections.' (GP01)

The GPs described how some of the patients were vaguely aware of the issue, but not to the extent that they would recognise the symptoms✓

¥I think they're well aware that DVT involves getting a clot in your leg somewhere. I don't think they're too clued up about what the true symptoms are.' (GP01)

¡ one of those interviewed felt that the patients were appropriately informed. Some questioned the effectiveness of the communication of educational information✓

¥I don't think they're educated when they go into hospital.' (GP03)

¥They will always pretend that nobody has said anything, because they don't understand a lot of it. They say, –Oh no, nobody's ever said anything to me†, and you know right well they have. They often say, –I haven't been told anything†, because they just don't understand what's being said.' (¡ P01)

Designation of responsibility. Opinions varied on where responsibility for various aspects of HAT prevention should lie.

In considering educating patients, it was felt that the consultant within secondary care should bear responsibility✓

¥If a hospital consultant is tabling somebody for surgery that is risky for DVT; they should be the one that is counselling the patient about DVT.' (GP06)

There were various opinions on who was responsible for patients adhering to their HAT prophylaxis prescription✓

¥A difficult one, I mean it's been initiated in hospital and it's prescribed in hospital, so I would guess in the current system, it would have to be the hospital that was responsible.' (¡ P02)

¥I think once they've had their operation done, I think it's a grey area, in terms of where the responsibility lies. Does it lie with consultants who've done the operation to make sure that they've sent patients home with prophylaxis, or whether it's our job then to just make sure they are on prophylaxis when they come out ' ' (GP01)

Others believed that, following discharge, the responsibility automatically falls on primary care, based on the assumption that patients had previously received the appropriate information✓

¥Once they're discharged on a 2-week course, it's obviously the GP's responsibility if they run into any problems. So as long as they've been advised what to look out for, then they would contact us if there are any problems.' (GP02)

Communication with primary care, secondary care, and community care. GPs reported difficulties in coordinating care with colleagues in secondary and community-based care, primarily as a result of poor communication.

This poor communication appeared to be an issue, both before admission and following discharge. Clinicians reported that, though they would generally receive notification of admission, the detail it contained could vary/

¥"es, we know they're going in invariably, if it's a planned admission ‡ sometimes we know the date, sometimes we don't know the date.' (GP08)

The inconsistent quality of the discharge summary was also reported, as was the lack of information the practice received relating to extended prophylaxis/

¥That's completely pot luck. Some discharge summaries are very good, they tell you the dose of Clexane that they want you to give and for how many weeks and what they're treating for ‡ and then, on the other hand, you just don't really get any feedback at all.' (GP01)

Another GP also noted the lack of precise information on extended prophylaxis/

¥Some of my patients have had, for example, a hip replacement and have had 35 days of injections; unless the patient tells you, you are not necessarily aware they are still taking it.' (GP09)

One GP attributed the variation in the quality of the discharge summary to the inexperience of the author/

¥Well the problem is the hospital discharge notes are written by very junior staff, they're writing them and they probably didn't know what they were writing it for.' (GP03)

One of the GPs interviewed reported the problems of liaising with district nurses over the care of discharged patients/

*¥The district nurse still comes in «*butfi *it's completely fragmented now. District nurses don't work with you any more, they are in a separate team. They are employed by the hospitals now and communication is extremely poor.'* (GP09)

Logistical constraints. Several of the GPs interviewed described how the pressure on resources in primary care precluded increased involvement in preventing HAT/

¥It's not part of the core services of a GP and one can't keep taking on sort of secondary care work without a funding stream.' (GP08)

Another GP described how current demands on their time meant they were unwilling to assume responsibility for educating patients about the risks of HAT/

¥At the moment we are seriously swamped with other work we've already got from the hospital and it would need a nurse's appointment for every patient going into hospital. So we would have to see them specifically to do this and so we absolutely, totally don't want to take it on.' (GP06)

There were also concerns voiced over the amount of time it would take to visit immobile patients following discharge/

¥It would require a lot of time ‡ the patients don't want to come in to the GP surgery when they've just had an operation so you're talking about sending doctors out to people's homes to go and talk to them about injecting low molecular weight heparin and preventing VTE.' (GP02)

›uggestions for improvement

The suggestions for improvement can be placed in one of two groups. The first, organisational innovations, consists of improved auditing, an increased and appropriately funded role for primary care, and unified commissioning of HAT.

The second group can be considered clinical innovations, namely clinical support tools and orally administered medication.

Improved auditing. One GP suggested that an important step was the systematic gathering of information on the time and cost issues of mismanaging HAT as a way of raising awareness and encouraging the appropriate investment/

¥I guess probably looking at the time and cost issues and putting that in front of the healthcare professionals and saying/ –Look, this is something worthwhile doing because it does have financial and health costs if we don't do it.†' (GP01)

Increased role of primary care. It was acknowledged that an increased role for primary care could see benefits in a number of areas, including increased patient awareness and better coordination of care between primary and secondary care settings.

'Raising awareness of patients with planned admissions ... that they ought to raise this issue ... with the treating hospital ... that would make a lot of sense.' (GP09)

GPs also felt that they could take a more proactive role in communicating with consultants following major surgery.

'I think we as GPs should question discharges a bit more, especially after big operations. I think, at the moment, we do leave it in the hands of the consultants.' (GP01)

The greater involvement of staff would require improved training of relevant staff.

'Training, I think, would be good generally across all staff members, nurses, and doctors.' (GP01)

Unified commissioning. It was also suggested that the commissioning could be unified and provision of prophylaxis should become the responsibility of a single organisation.

'I would definitely commission the whole lot, not a week here and the rest prescribed by someone else.' (GP09)

Clinical support tools. Software-based tools were mentioned as a means of supporting GPs to undertake any risk assessment.

'Something like ... HS Improvement should pick this up. Getting a risk assessment tool, a software tool, would be quite useful.' (GP09)

Oral medication. Others felt that a more easily-administered medication would prove significant, reducing the need for clinician-mediated administration.

'I mean, I'm looking forward to the time when oral anticoagulation will come and I know that that is available.' (... P02)

DI›CU››ION

›ummary

Despite having the opportunity to actively reduce the occurrence of HAT, the current role of GPs and, more broadly, primary care, appears limited, whether in educating patients and assessing risk of HAT prior to admission, or in the management of patients on prophylaxis following discharge. The clinicians interviewed described a number of factors that influence prevention of HAT in primary care. These included limited awareness among GPs and poor coordination of care with colleagues in community or secondary care settings, exacerbated by a lack of clarity concerning their role and frequent inconsistencies in the quality and timing of communication between care settings.

A number of constructive suggestions did emerge to improve the current system, and there was a broad consensus that there was opportunity for an increased role for primary care both pre-admission and post-discharge. Those interviewed were equally clear that due to current logistical constraints, any extended role for primary care would require additional and targeted funding.

›trengths and limitations

There is a growing understanding of the importance of managing HAT, though this is the first study to gain the perspectives of primary care providers. It cannot be commented on as to how representative these views are of the wider GP population; however, the practices represented a wide variety of IMD codes, list sizes, and geographical locations. Although telephone interviews were chosen over face-to-face interviews for practical reasons, short telephone interviews have been found to be equally as productive as short face-to-face interviews.[35]

Theoretical saturation was reached within the 1› interviews.[36] The authors suggest that this comparatively small number could be explained by 'consensus theory', where 'experts' with shared knowledge about the topic under discussion are more likely to exhibit common values.[37] The fact that so many GPs were too busy to be interviewed also supports the finding that the current demand for GP services limits the time available for undertaking additional activities.

Comparison with e£isting literature

Patients were reported as being neither aware of the risk of HAT, nor how it might best be managed following discharge, despite recommendations to the contrary.[11] Previous work indicates that appropriate patient education can improve outcomes and adherence to medication.[16,38,39] Tools,

such as enhanced medication plans, can improve information transfer and increase patient knowledge of individual drug treatment.[10]

The GPs interviewed also felt that this information might be better provided within the primary care environment. In hospital, patients can be flooded with information from doctors, frequently beyond their capacity to assimilate and memorise it,[11] and, with shorter lengths of stay, ward staff are finding it harder to assess and meet the information needs of the patients,[12] further inhibited by the complexity of the modern healthcare team.[13] It has previously been suggested that greater responsibility for patient education should lie with primary care,[14] where the quiet surroundings,[15] managerial support,[16,17] and the allocation of undisturbed time[14] can facilitate improved communication.

Improving the coordination of HAT prevention between care settings would appear critical, considering the trend towards shorter hospital stays and increased delivery of care in the community.[18–51] The coordination of care is key considering previous evidence of patients unprepared for their self-management role,[19] and vulnerable to adverse events following discharge.[2,19–29] However, the clinicians interviewed reported that any coordination was hindered by the fragmentation of their relationship with community care, and issues with the timeliness and content of the information they received from secondary care.

Of particular concern to many of the GPs interviewed was the quality of the discharge summary. These should be timely and contain information on newly prescribed medication or specific follow-up needs.[11,29] However, many of the interviewed clinicians described them as late and frequently incomplete, reflecting previous evidence of GPs not routinely notified about patient admissions, discharges, or complications during the course of the hospital stay,[52–55] and patients unable to access an appropriate healthcare practitioner in possession of their discharge summary.[20–22] It was noted that summaries received from junior doctors were often poor, echoing previous research, which reported that junior doctors felt inadequately prepared for writing discharge summaries and needed improved training in the area.[56] More robust systems of communication[57,58] and increased involvement of informatics might benefit the production and dissemination of discharge summaries; both of these strategies have proven successful in other ¥high-risk' circumstances.[59] Another important aspect of the successful transition of patients is the mutually agreed transfer of responsibility from hospital to primary care provider;[29] however, those interviewed offered conflicting opinions of where this responsibility should lie.

The ¡ational Institute for Health and Care Excellence (¡ICE) guidance is explicit in its recommendation for prompt and accurate communication with GPs, yet it would appear that this is not routinely followed. Though strategies have emerged that address HAT-specific barriers, such as continued education of junior doctors and giving greater prominence to medicated stockings on prescription charts,[60,61] the means by which communication with primary care can be improved has yet to be explored.

It was acknowledged that primary care could support HAT prevention but it became clear that this was unlikely to happen without additional resources being available. Other suggestions to support the extended role for primary care advocated by some of those interviewed, such as improved training or the introduction of software-based clinical support, all have cost implications for an already stretched service.[62] It was suggested that, in order to secure these funds, empirical evidence of the impact of HAT would help raise awareness of the issue and the financial implications of its mismanagement. In the absence of increased funding, the option remains to use existing resources more effectively. Recently, the use of pre-admission healthcare data has been successful in identifying high-risk cases of HAT,[63] and it may be in the interim that this approach could help focus resources more precisely.

Implications for practice

The number of patients with HAT is high and onset frequently occurs post-discharge. Despite this, the level of awareness among GPs varied and many of those interviewed agreed that improved training of GPs and other relevant staff is needed. With that in place, primary care staff would be better equipped to raise awareness of HAT in patients, undertake a potentially better informed risk assessment, and support vulnerable groups in adherence to the prescribed thromboprophylaxis.

There appeared to be a lack of clarity of what was expected from primary care. This included confusion about where the responsibility for preventing HAT lay, and when and how primary care providers

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might be involved. An improved definition of the role of primary care would be useful and is reliant on the provision of the appropriate training.

This better-defined role for primary care should be predicated on prompt and accurate communication of patient information between primary and secondary care. Currently, GPs reported reliance on second-hand information from patients. With access to the appropriate information, those patients at most risk from HAT can be more closely monitored and supported by GPs. Previous work has demonstrated the positive impact of a simple educational intervention for raising patient awareness on prophylaxis adherence following urology surgery.[18] Piloting a similar intervention across a range of sites, involving a broader range of at-risk patient groups, should be considered.

There appears to be a useful role for primary care in the prevention of HAT. Gathering evidence of the impact of mismanaging HAT may encourage policymakers and commissioning bodies to prioritise the issue and provide the additional resources that would be required.

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Appendix C. GARFIELD-AF key facts

GARFIELD-AF key facts

Global **A**nticoagulant **R**egistry in the **FIELD (GARFIELD-AF)**

An international longitudinal registry of patients newly diagnosed with non-valvular atrial fibrillation

Study attributes

Non interventional study design, describing real-world clinical practice and outcomes
57,262 patients enrolled
>1000 sites in 35 countries, from the Americas, Europe, Africa, Asia-Pacific and the Middle East
5 sequential prospective cohorts
Minimum of 2 years follow up (2 to 9 years)
First patient in December 2009
Last patient in July 2016
Final follow up July 2018
Minimum of 2 years follow up

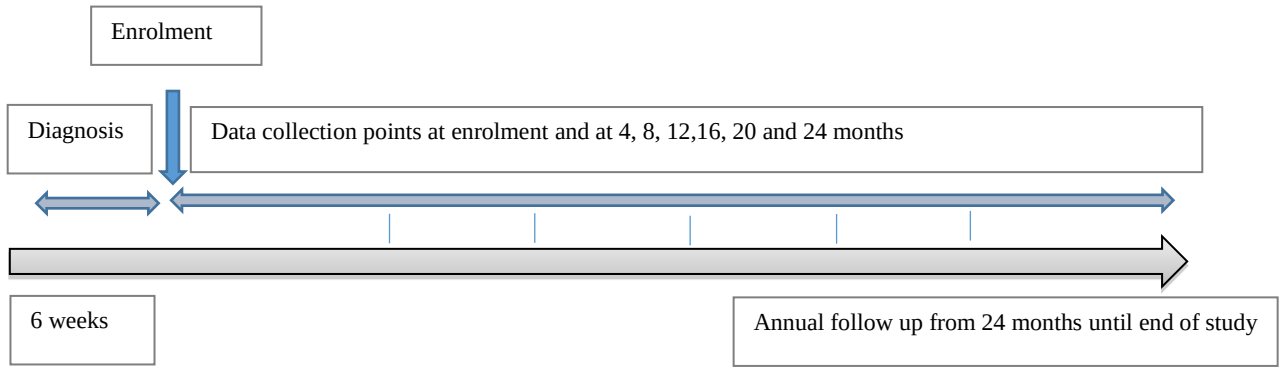
Inclusion criteria

Patients aged ≥18 years
Newly diagnosed with non-valvular AF (within 6 weeks) and at least one additional investigator determined risk factor for stroke

Exclusion criteria

Patients with AF secondary to a reversible cause
Patients without capacity to consent

Data collection



Baseline data

Patient demographics
Medical history
Type of AF (paroxysmal, persistent, permanent, new/undetermined)
Date of diagnosis
Method of diagnosis
Symptoms
Care setting of diagnosis
Drug therapy at diagnosis (cardiac, non-cardiac, rate or rhythm control)
Antithrombotic therapy at diagnosis (anticoagulant, antiplatelets)
Reason patient not anticoagulated

Follow up data

Clinical events during follow up period
Changes to AF treatment and antithrombotic therapy
Hospitalisation and healthcare utilisation
Medical history update
Patient treatment satisfaction (selected countries)

Main outcome measures

Stroke (ischemic and hemorrhagic)
Transient ischemic attack
Systemic embolism
Pulmonary embolism
Heart failure
Myocardial infarction
Hospitalisation
Cardiovascular death
Non-cardiovascular death
Major bleeding
Non-major clinically relevant bleeding
Minor bleeding
Therapy persistence for patients on anticoagulant therapy
INR recordings for patients treated with VKA

Achievements

The largest global prospective AF registry
Comprehensive programme of audit and quality control, with 20% source data verification under the supervision of an independent audit committee
Development of the first AF risk score assessing stroke, bleeding and mortality in a single tool using artificial intelligence and machine learning
Record of real-world temporal changes in prescribing practice over 8 years
Examines treatment effects of VKAs and NOACs

Appendix D. List of candidate's conference proceedings for research include in PhD by Published Work

GARFIELD-AF presentations

Oral presentations

Apenteng PN, Accetta G, Hobbs FDR, Kakkar AK, Fitzmaurice DA. *One-year outcomes of patients with newly diagnosed atrial fibrillation: UK findings from the GARFIELD-AF registry*. Paper presented at the Society of Academic Primary Care (SAPC) Annual Scientific Meeting, 2017, Coventry

Apenteng PN, Accetta G, Hobbs FDR, Kakkar AK, Fitzmaurice DA. (2016) *Evolving antithrombotic treatment patterns in patients newly diagnosed with atrial fibrillation: UK findings from the GARFIELD-AF registry*. Paper presented at the XXXVI World Congress of the International Society of Hematology, Glasgow

Apenteng PN, Accetta G, Hobbs FDR, Kakkar AK, Fitzmaurice DA. Evolving antithrombotic treatment patterns in patients newly diagnosed with atrial fibrillation: UK findings from the GARFIELD-AF registry. SAPC Annual Scientific Meeting 2016, Dublin

Apenteng PN, Murray ET, Hobbs FDR, Roalfe A, Usman M, Heneghan C, Fitzmaurice DA. Incidence of Venous Thromboembolism in care home residents (plenary). NSPCR 10 year event 2016, London

Apenteng PN, Murray ET, Hobbs FDR, Roalfe A, Usman M, Heneghan C, Fitzmaurice DA. An observational study to determine the incidence of Venous Thromboembolism in care home residents. Joint 2016 BSHT, AiP & UK Platelet Group Annual meeting 2016, Leeds

Apenteng PN, Murray ET, Hobbs FDR, Kakkar AK, Fitzmaurice DF. Have non-vitamin K antagonist oral anticoagulants made an impact in terms of stroke prevention in atrial fibrillation? An analysis of the UK cohort of the GARFIELD-AF registry. SAPC Annual Scientific Meeting 2015, Oxford

Apenteng PN, Murray ET, Hobbs FDR, Kakkar AK, Fitzmaurice DF. Antithrombotic treatment patterns for stroke prevention in relation to age: insights from the UK cohort of the international GARFIELD Registry. SAPC Annual Scientific Meeting 2014, Edinburgh

Apenteng PN, Murray ET, Hobbs FDR, Kakkar AK, Fitzmaurice DF. Patterns of antithrombotic therapy in relation to type of atrial fibrillation: insights from the UK cohort of the global GARFIELD registry. Heart Rhythm Congress 2014, Birmingham

Apenteng PN, Murray ET, Hobbs FDR, Kakkar AK, Fitzmaurice DF. Does gender impact the use of antithrombotic therapy in patients with atrial fibrillation? An analysis of a UK cohort of the global AF registry GARFIELD. SAPC Annual Scientific Meeting 2013, Glasgow

Poster presentations

Apenteng PN, Murray ET, Hobbs FDR, Kakkar AK, Fitzmaurice D. Global Anticoagulant Registry in the FIELD: a snapshot of atrial fibrillation in the UK. SAPC Annual Scientific Meeting 2012, Bristol

VTEC presentations

Oral presentations

Apenteng PN, Fitzmaurice DA. Incidence of Venous Thromboembolism in care home residents. All-Party Parliamentary Thrombosis Group annual conference 2016, London

Apenteng PN, Murray ET, Hobbs FDR, Roalfe A, Usman M, Heneghan C, Fitzmaurice DA. Incidence of Venous Thromboembolism in care home residents (plenary). NSPCR 10 year event 2016, London

Apenteng PN, Murray ET, Hobbs FDR, Roalfe A, Usman M, Heneghan C, Fitzmaurice DA. An observational study to determine the incidence of Venous Thromboembolism in care home residents. Joint 2016 BSHT, AiP & UK Platelet Group Annual meeting 2016, Leeds

Poster presentations

Apenteng PN, Murray ET, Hobbs FDR, Heneghan C, Roalfe A, Usman M, Fitzmaurice DA. Risk of venous thromboembolism in care home residents. XXXVI World Congress of the International Society of Hematology 2016, Glasgow

Apenteng PN, Murray ET, Deller R, Bradburn P, Gibbons M, Stant K, Batki A, Talbot L, Hobbs FDR, Fitzmaurice DA. A prospective cohort observational study to determine the incidence of VTE among care home residents: study design and progress to date. NSPCR Showcase 2014, Oxford

Appendix E. Full bibliography of candidate

Publications

Peer reviewed articles

Apenteng PN, Gao H, Hobbs FR, Fitzmaurice DA. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. BMJ open. 2018 Jan 1;8(1):e018905**.**

Apenteng PN, Hobbs FDR, Roalfe A, Usman M, Heneghan C, Fitzmaurice D. Incidence of venous thromboembolism in care homes: a prospective cohort study Br J Gen Pract. 2017 Jan 16; doi: 10.3399/bjgp17X688873

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Research reports

Denny E, Culley L, Papadopoulos I, Apenteng P. (2010) Endometriosis and cultural diversity: improving services for minority ethnic women. Final Report for Research for Patient Beneit Grant PB-PG-0906-11145. Birmingham: Birmingham City University

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