ANTICOAGULATION CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

By

HANIS HANUM BINTI ZULKIFLY

A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF BIRMINGHAM

Institute of Cardiovascular Sciences
College of Medical and Dental Sciences
University of Birmingham
Edgbaston
United Kingdom

March 2019

Abstract

The studies contained in this thesis highlight key issues relating to knowledge, psychological aspects and quality of life among newly anticoagulated atrial fibrillation (AF) patients. In addition, it also included objective measures of the quality of vitamin K antagonist (VKA) therapy among atrial fibrillation and operated valvular heart disease (VHD) patients on long term VKA therapy. Three studies were conducted in separate cohorts to achieve these objectives.

Study 1 (TREAT-2) examined self-report assessment of depression, anxiety, beliefs about medication and knowledge of AF, and quality of life among 139 newly anticoagulated AF patients at baseline and 105 patients at six months follow up. Findings suggest that patients appear to have low levels of depression and anxiety and had positive beliefs about medication. However, AF knowledge and quality of life was poor. These findings remained unchanged at 6 months follow up. Nevertheless, more patients were aware of AF consequences and had improvements in AF symptoms.

Study 2 (TTR in relation to ethnicity) investigated objective measures and predictors of quality of anticoagulation control (time in therapeutic range, TTR) and adverse clinical outcomes in 991 AF patients on VKA therapy over 5.2 years. TTR was compared among patients in different ethnic groups, elderly (≥80 vs. <80 years), and patients with different categories of kidney disease (eGFR≥90 vs. 60-89 vs. ≤59ml/min/1.73m^2). TTR was significantly lower in South-Asians [60.5% (95% CI 58.0-63.0)] and Afro Caribbeans [61.3% (95% CI 58.2-64.4)] compared to Whites [67.9% (95% CI 67.1-68.8); p<0.001] despite similar INR monitoring intensity. No significant difference in TTR was seen among the elderly or patients with different categories of kidney disease within this cohort. Non-white ethnicity was the strongest independent predictor of poor TTR after adjusting for demographics and clinical variables [OR 2.62 (95% CI 1.67-4.10); p<0.001].

Study 3 (TTR in operated VHD) examined TTR, predictors and adverse clinical outcomes among 456 operated VHD patients with and without AF over 6.2 years. Results showed that TTR was significantly poorer in operated VHD patients with AF (TTR 55.7%) compared to those without AF (TTR 60.1%; p=0.002). Independent predictors of poor TTR included female sex, AF and anaemia/bleeding history.

Findings from Study 1 suggest that among newly anticoagulated AF patients, improvements are needed in AF knowledge. Although their quality of life is reduced, they were not anxious or depressed and they hold positive beliefs about their medication. Interventions (educational

and motivational) are required so that enhancements in knowledge and quality of life can be achieved among newly anticoagulated AF patients. Studies 2 and 3 indicate that good anticoagulation control is more difficult to achieve in non-white AF patients and operated VHD patients with AF, respectively. This suggests that more frequent INR checks and closer examination of the individual reasons for poor anticoagulation among these patients is required to improve quality of anticoagulation control so that adverse events can be prevented. The findings and conclusions provide a platform for future research to develop interventions to improve quality of life among anticoagulated AF patients and to improve INR control, particularly among ethnic minority patients with AF and those with VHD.

Publications arising from thesis

Papers

1. Zulkifly H, Lip GY, Lane DA. Bleeding Risk Scores in Atrial Fibrillation and Venous Thromboembolism. **Am J Cardiol** 2017; 120 (7): 1139-1145
2. Zulkifly H, Lip GY, Lane DA. Use of the SAMe-TT_2R_2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients treated with vitamin K antagonists: A review. **Heart Rhythm.** 2018; 15 (4): 615-623
3. Zulkifly H, Lip GY, Lane DA. Epidemiology of AF. **Int J Clin Pract.** 2018; 73 (3): e13070.

Abstracts

1. Zulkifly H, Cheli P, Lutchman I, Bai Y, Lip GYH, Lane DA. Quality of and predictors of anticoagulation control among multi ethnic cohorts receiving VKA therapy for stroke prevention in atrial fibrillation: Heart Rhythm Congress, Birmingham, UK, 8 October 2018 [Poster]
2. Zulkifly H, Cheli P, Lutchman I, Bai Y, Lip GYH, Lane DA. Anticoagulation control in elderly AF patients receiving vitamin K antagonists for stroke prevention in atrial fibrillation: the West Birmingham AF Project: European Society of Cardiology, Munich, Germany, 27 August 2018 [Poster]
3. Zulkifly H, Cheli P, Lutchman I, Bai Y, Lip GYH, Lane DA. Anticoagulation control in different ethnic-minority patients receiving vitamin K antagonists for stroke prevention in atrial fibrillation: the West Birmingham AF Project: Festival of Graduate Research, University of Birmingham, UK, 10 April 2018 [Poster]
4. Zulkifly H, Cheli P, Lutchman I, Bai Y, Lip GYH, Lane DA. Anticoagulation control in different ethnic-minority patients receiving vitamin K antagonists for stroke prevention in atrial fibrillation: the West Birmingham AF Project: Midlands Cardiovascular Scientific Meeting, University of Leicester, 23 November 2017 [Poster]
5. Zulkifly H, Cheli P, Lutchman I, Bai Y, Lip GYH, Lane DA. Anticoagulation control in different ethnic-minority patients receiving vitamin K antagonists for stroke prevention in atrial fibrillation: the West Birmingham AF Project. European Society of Cardiology, Barcelona, Spain 28 August 2017 [Poster]
6. Zulkifly H. Use of the SAMe-TT_2R_2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients treated with vitamin K antagonists: A review. MySecon, London, 14th May 2017 [Poster]

Dedication

I dedicate this thesis to my husband, Naza and my two daughters, Raina and Raisha.

Acknowledgements

I would like to say a very-very big thank you ('terima kasih') to both of my supervisors, Dr Deirdre Lane and Professor Gregory Lip for their guidance, patience and support over the past three years of my PhD journey. This would not have been possible without you.

I am grateful to the staff of the Anticoagulant Clinic, Sandwell and West Birmingham Hospitals and University Hospital Birmingham for being very helpful and cooperative whilst I was recruiting patients from their clinics. Also, for giving me access to their anticoagulation management software to identify patients needed for all my studies. Not to forget to all the patients who participated in the TREAT-2 study, staff, doctors, nurses and others who helped me at the AF clinic. A big thank-you to you all.

Special thanks to my friends whom I've met along this journey: Paola, Marco, Daniele, Ivana, Maria, Josemy, Reem, Mazaya, Aeron, Kazuo, and Amy. You have been incredible in giving me support, strength and motivation to finish this work.

A very big thank you to my family, mum, dad, Hanani, Faiz, Faizal and Naufal for coming all the way from Malaysia for emotional support and inspiring me to persist in difficult times. To mom and dad, a very big thank you for keeping me in your prayers and always believing in me. To dad, special thanks for inspiring me to write in a better way. You have always been my strength. To Aunt Misbah, a very special thank you for always being there for me, right from the beginning until the end. You have supported me all the way and encouraged me to persevere throughout my ups and downs.

Not to forget, a very big thank you to my sponsors, Universiti Teknologi MARA and Kementerian Pendidikan Tinggi for funding my PhD study as well as my family here in the UK.

Last but not least, to my lovely husband, Naza and my two daughters, Raina and Raisha. A very-very big thank you to you all for being with me throughout this journey. You have been very patient with me, my shoulder to cry on and my pillar of strength! Thank you for your sacrifices, your prayers, your support and for keeping me sane! I could have not made it without you.

List of tables

List of figures

List of abbreviations

AC	Anticoagulant clinic
ACCP	American College of Chest Physicians
ACV	Anticoagulant variability
AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life
ALP	Alkaline phosphatase
ALT	Alanine transferase
AV	Atrioventricular
AVR	Aortic valve replacement
BDI	Black Depression Inventory
BMQ	Beliefs about medication
CABG	Coronary Artery Bypass Graft
CAVD	Calcific aortic valve disease
CCS	Canadian Society of Cardiology
CDA	Clinical data archive
CI	Confidence interval
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CRNMB	Clinically relevant non-major bleed
cTnT-hs	High sensitive cardiac troponin
CV	Cardiovascular
CYP2C9	Cytochrome P450 2C9
DASS	Depression Anxiety Stress Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EHRA type 1 VHD	Evaluated Heart valves, Rheumatic or Artificial type 1 valvular heart disease
EHRA type 2 VHD	Evaluated Heart valves, Rheumatic or Artificial type 2 valvular heart disease
ESC	European Society of Cardiology
ESRD	End stage renal disease
GAD-7	Generalised Anxiety Disorder-7
GDF-15	Growth differentiation factor 15
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
Hct	Haematocrit
HR	Hazard ratio
HRA	Health Research Authority
HRQoL	Health related quality of life
ICD	International Classification of Diseases
ICM	Implantable cardiac monitoring
INR	International normalised ratio
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
KDIGO	Kidney Disease Improving Global Outcomes
MACE	Major adverse clinical events
MD	Mean difference
mEHRA	Modified European Heart Rhythm Association
MI	Myocardial infarction

MTAC	Medication Therapy Adherence Clinic
MVR	Mitral valve replacement
NICE	The National Institute for Health and Care Excellence
NNT	Number needed to treat
NNH	Number needed to harm
NOAC	Non-vitamin K antagonist oral anticoagulants
NVAF	Non-valvular atrial fibrillation
NYHA	New York Heart Association
OAC	Oral anticoagulant
OR	Odds ratio
PAF	Paroxysmal atrial fibrillation
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PHQ-9	Patient Health Questionnaire-9
PINRR	Percentage of INRs in range
PMAS	Pharmacist managed anticoagulant services
POC	Point of care
PSM	Patient self-monitoring
PST	Patient self-testing
PTCA	Percutaneous transluminal coronary angioplasty
QoL	Quality of life
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RHD	Rheumatic heart disease
RR	Relative risk
SA	Sinoatrial
SD	Standard deviation
SE	Systemic embolism
SF-36	Short Form Health Survey
STAI-S	State-Trait Anxiety Inventory
SWBH	Sandwell and West Birmingham Hospitals
TE	Thromboembolism
TIA	Transient ischemic attack
TTR	Time in therapeutic range
UC	Usual care
UHB	University Hospitals Birmingham
UI	Uncertainty intervals
USA	United States of America
VHD	Valvular heart disease
VKA	Vitamin K antagonist
VKORC1	Vitamin K Epoxide Reductase Complex Subunit1
VTE	Venous thromboembolism

Table of Contents

Chapter 1. Literature review

1.1 Epidemiology of atrial fibrillation

This section summarises the literature on the epidemiology of atrial fibrillation (AF) worldwide according to continents, age and ethnicity/race, and also includes the prevalence of AF in stroke patients. This has been published in the International Journal of Clinical Practice (1).

Atrial fibrillation (AF), the most common form of arrhythmia with clinical significance, is a major global health burden worldwide (2). In the United States (US) and European countries, one in every four middle-aged adults will develop AF. Most importantly, AF is associated with a five-fold greater risk of stroke, increased risk of death and development of heart failure, and a greater risk of hospital admission, with 10-40% of AF patients hospitalised annually. Additionally, irrespective of other cardiovascular-related conditions, AF patients have poorer quality of life and unfortunately, despite anticoagulation for stroke prevention, they can still develop vascular dementia and a decline in cognitive function (3).

1.1.1 Incidence and prevalence of atrial fibrillation worldwide

According to the Global Burden of AF(4), worldwide, the projected number of people with AF in 2010 was 33.5 million, consisting of 20.9 million males (UI, 19.5-22.2 million) and 12.6 million females (UI, 12.0-13.7 million), with higher incidence and prevalence rates in developed countries (**Table 1.1**). Mortality associated with AF globally is higher in females, primarily driven by higher mortality among females in developing countries (**Figure 1.1**).

Table 1.1: Incidence and prevalence of AF and AF- associated mortality rate with 95% uncertainty intervals (UI) (per 100,000) for males and females (data extracted from Chugh 2014) (4)

	1990	2010	1990	2010
	Male		Female	
Incidence of AF				
Globally, all ages	60.7 (49.2-78.5)	77.5 (65.2-95.4)	43.8 (35.9-55.0)	59.5 (49.9-74.9)
Developed Countries	78.4 (67.5-91.9)	123.4 (107.6-141.5)	52.8 (45.0-62.9)	90.4 (77.8-104.5)
Developing Countries	50.0 (33.8-76.8)	53.8 (38.7-79.8)	36.0 (24.5-54.7)	40.0 (27.2-62.6)
Prevalence of AF				
Globally, all ages	569.5 (532.8-612.7)	596.2 (558.4-636.7)	359.9 (334.7-392.6)	373.1 (347.9-402.2)
Developed Countries	608.2 (547.0-693.5)	660.9 (597.1-738.2)	362.5 (329.3-422.3)	387.7 (343.8-450.0)
Developing Countries	546.6 (503.0-599.6)	656.7 (522.9-617.6)	358.2 (329.8-393.0)	366.1 (337.4-400.8)
Mortality rate				
Globally, all ages	0.8 (0.5-1.1)	1.6 (1.0-2.4)	0.9 (0.7-1.2)	1.7 (1.4-2.2)
Developed Countries	1.3 (0.9-1.9)	2.7 (1.9-4.3)	1.1 (1.0-1.3)	2.4 (2.0-3.0)
Developing Countries	0.4 (0.2-0.8)	0.7 (0.4-1.3)	0.7 (0.4-1.4)	1.0 (0.6-1.7)

AF=atrial fibrillation

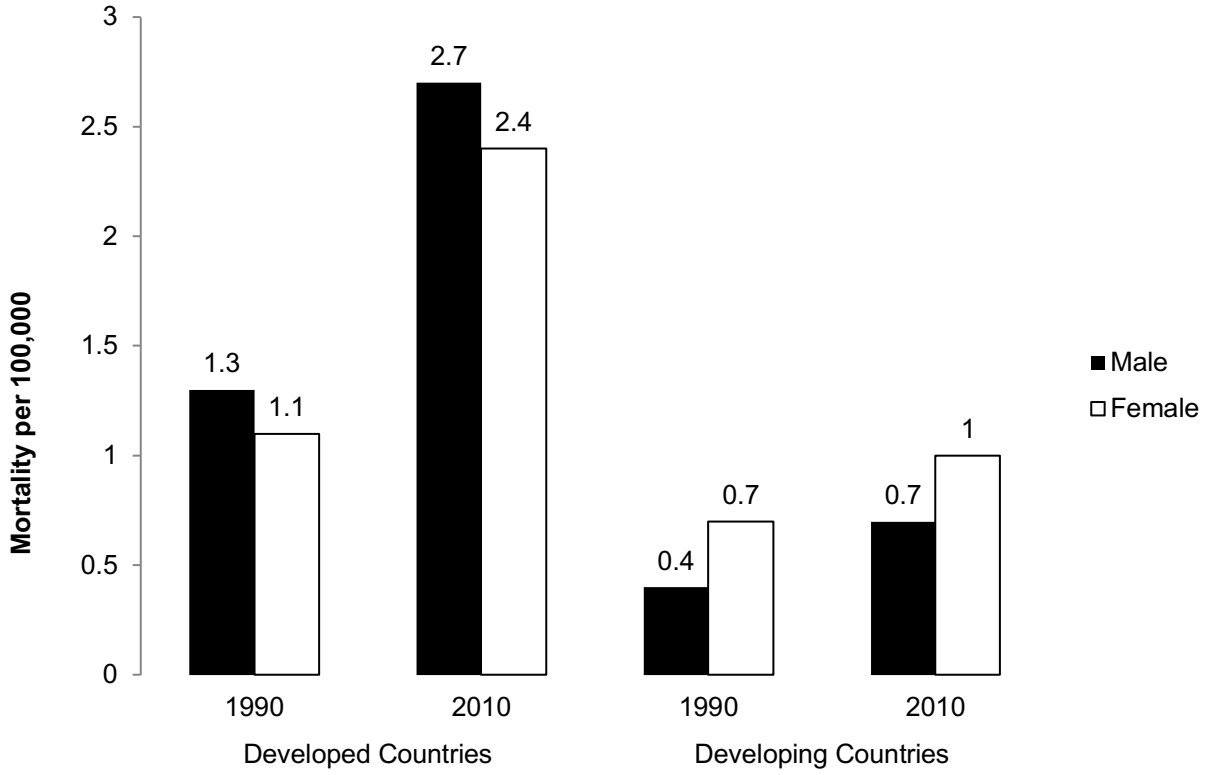


Figure 1.1: AF associated mortality stratified by sex and region (developed and developing countries)

1.1.2 Prevalence of atrial fibrillation by continents

In Europe, AF currently affects eight million people and is expected to rise drastically, 2.3-fold by 2060 (5, 6). In the United Kingdom, projections from the Clinical Practice Research Database suggest that AF will affect between 1.3 and 1.8 million people by 2060 (7). In the United States, about 3-5 million people are currently affected by AF and by 2050 this figure is expected to be greater than 8 million people (8). In Australia, Europe and the USA, the current estimated prevalence of AF is between 1-4% (2, 5). **Table 1.2** and **Figure 1.2** illustrate the prevalence of AF in nine countries, stratified by continents worldwide. Australia has the highest prevalence of AF i.e., 5.4% followed by Africa 4.6%, (although the prevalence was lower (0.7%) in another African study) (9) then Iceland (2.4%) and lowest in Asian countries (0.49%-1.9%).

A recent review (10) on AF epidemiology of 58 studies from five Asian (China, Japan, South Korea, India, Malaysia) and eight Middle Eastern countries (Turkey, Bahrain, Qatar, Kuwait, Saudi Arabia, Oman, United Arab Emirates and Yemen)(10) reported the annual incidence of AF to be 5.38 per 1000 person-years. These are mainly from Chinese, Japanese and Korean studies (10 studies in total) (11-20) conducted from 1991-2012, with study populations ranging from 1485 (15) to 471,446 (13). Prevalence of AF varies between hospital-based and community-based studies; being higher in the latter (0.37%-3.56% vs. 2.8%-15.8%) (10).

Table 1.2: Worldwide prevalence of AF by continent

Country	Study	-Years data obtained -Study design	Sample size	Study population		Prevalence (%) total, (men and women)
				Data source	Age (SD) years [Men, women (%)]	
Africa						
Africa	Sliwa et al 2010 (21)	-2006-2008 -Prospective	5328 cardiac cases	Hospital-based, single centre, urban population	59 (18) [39, 61% AF]	4.6 (†)
Kenya	Shavadia et al 2013 (9)	-2008-2010 -Retrospective	44, 144	One hospital admission in Nairobi	≥18 [56, 44% AF]	0.7 (†)
Asia						
Malaysia	Lim et al 2016 (22)	-2007-2014 -Prospective	10,805	18 urban, 22 rural communities across Malaysia	52.6 (11.6)	0.49 (†)
Singapore	Yap et al 2008(23)	† -Prospective	1,839	Community-based study	≥55	1.4 (†)
Thailand	Phrommintikul et al 2016 (24)	† -Prospective	1,277	Cross section of Maerim District, Chiang Mai	≥65 [45.8, 54.2% AF]	1.9 (†)
Australia						
Australia	Ball et al 2015(25)	-June 2014	6,140,651	7 international epidemiology study	≥55	5.4 (5.97, 4.79)
Australia	Sturn et al 2002 (26)	-2000 -Prospective	14, 194	50 consecutive patients at 321 general practices	≥30	4.0 (6.0, 4.0)

Table 1.2 continued

Country	Study	-Years data obtained -Study design	Sample size	Study population		Prevalence (%) total, (men and women)
				Data source	Age (SD) [Men, women (%)]	
Europe						
England	Health & Social Care Information Centre 2014-2015 (27)	-2014-2015 -Retrospective	56,939,507	National primary care practice database	†	1.6 (†)
United Kingdom	Lane et al 2017 (7)	-1998-2010 -Retrospective	57, 818	UK Clinical Practice Research Datalink (CPRD)	≥18 [51.7, 48.3% AF]	1.26 (1.33, 1.18) per 1000 pt-yrs [age-adjusted incidence]
Iceland	Stefansdottir et al 2011(6)	-1987-31 December 2008 -Retrospective	4905-AF cases	The National University Hospital of Iceland	20–99	2.4-age and sex standardised
North America						
USA	Naccarelli et al 2009(28)	-2004-2005 -Retrospective	242, 903	National databases of employer-funded insurance and Medicare	≥20	1.1 (†)
South America						
Brazil	Marcolino et al 2015(29)	-Jan-December 2011 -Retrospective	262 685	658 municipalities, primary Care	50.3 (19.3) [40.4, 59.6]	1.8 (2.4, 1.3)

† Not reported

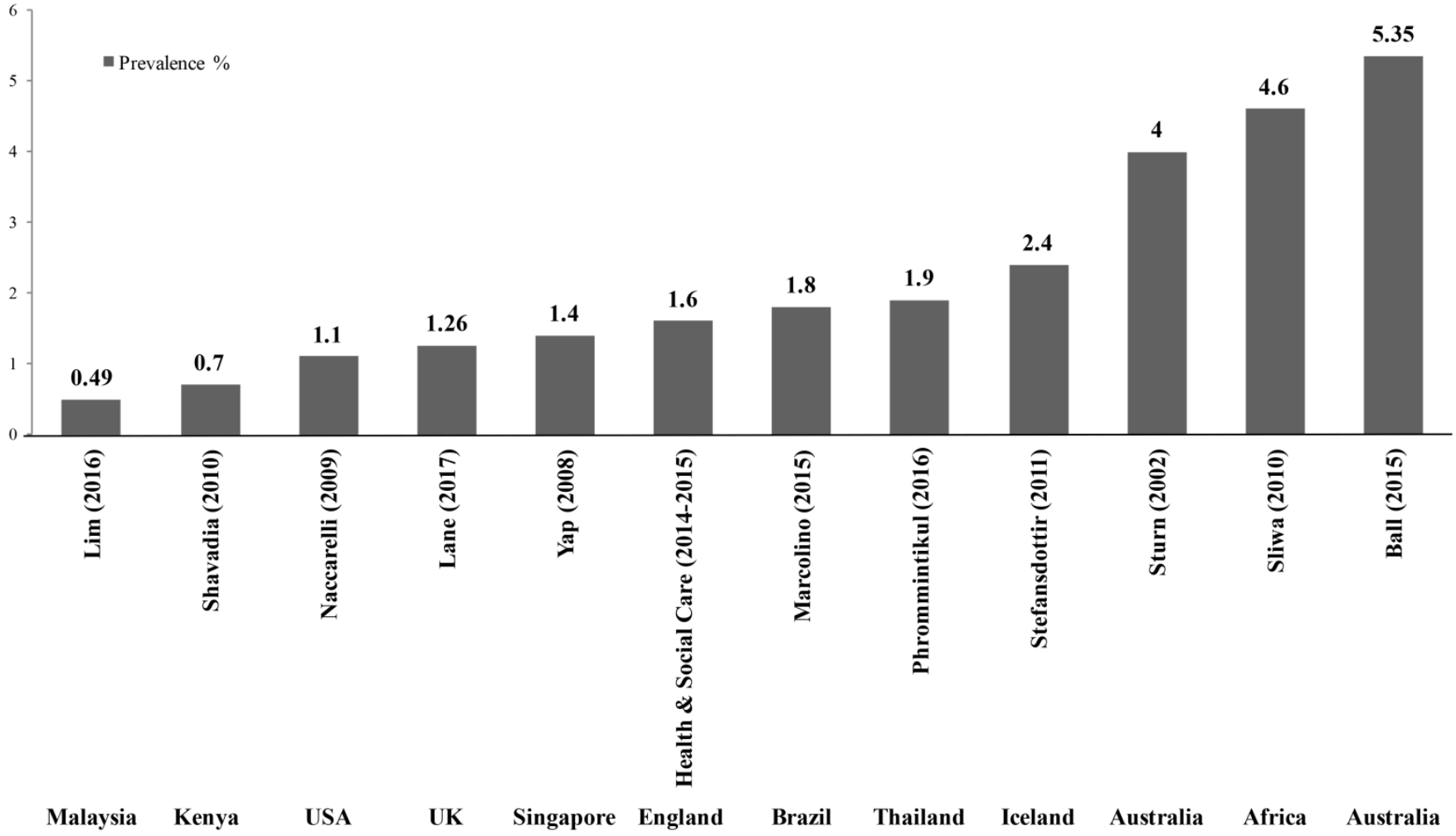


Figure 1.2: Prevalence of AF by country

Differences in the incidence and prevalence rates between studies is likely dependent on the time the study was conducted, the design (nationwide studies, medical insurance databases etc., retrospective, prospective, cross-sectional) and the study population (age of patients, urban compared to remote areas as their risk factors may vary, for example the prevalence of rheumatic heart disease is higher in rural populations in India)(30) which in turn affect the quality of data obtained (5).

1.1.3 Ethnicity, age and prevalence of atrial fibrillation

The prevalence of AF across different ethnic groups differs, although most of the studies investigating these differences have been conducted in the United States. For the purpose of this thesis, ethnicity is classified as Whites, (Europeans, Americans) Afro-Caribbeans, (Blacks, Black British, African-American) East Asians, (Chinese, Japanese, Malaysian and other Asians) South Asians, (Indian, Pakistani, Bangladeshi) Hispanics, (Hispanic or Latino) and others, as reported in individual studies (31, 32).

Table 1.3 shows the prevalence of AF by race and ethnicity according to 11 studies,(33-43) conducted in the United States and one (33) multicentre study conducted in North America, Europe and Asia. In all studies, the prevalence of AF was highest among the Whites compared to Afro-Caribbeans, East Asians and Hispanics, ranging from 42% (42) to 2.5% (41) among the Whites, and 21%(41) to 1.7% (40) among Afro-Caribbeans. Only three studies (33, 35, 43) reported AF prevalence among East Asians which ranged from 3.9% (35) to 10.1% (33), while only one study reported AF prevalence among Hispanics (3.9%) (35). A meta-analysis of 10 studies examining the prevalence of AF among African-Americans compared to Whites in the United States, concluded that being African-American was associated with a 'protective effect' from AF [OR 0.51 (95% CI 0.44-0.59); $p<0.001$]. Despite the lower prevalence of AF, African-Americans in the US have twice the risk of first ever stroke compared to Whites and this might be due to higher risk factor burden of stroke, for example, hypertension (44).

Table 1.3: Prevalence of AF by ethnicity and race

Country/State	Study	a) Study design b) Follow up c) Sample size	Mean (SD) age study population	Prevalence of AF (%)			
				Whites	Afro-Caribbeans	East Asians	Hispanics
North America, Europe, Asia	Lau et al 2013(33)	a) Prospective b) 2.5 years c) 2580	Europeans: 76.2 (6.6) Black African: 75.2 (6.2) Chinese: 76.2 (6.7) Japanese: 78.4 (7.0)	18	8.3	10.1 Chinese, 9.5 Japanese	N/A
Michigan, USA	Lahiri et al 2011(34)	a) Retrospective b) N/A c) 1001	African American: 33.0% ≥70 European American: 35.4% ≥70	29	19	N/A	N/A
USA	Winkelmayer et al 2011(43)	a) Cross sectional b) 15 years c) 2,483,199	70.9 (11.8)	14	6.5	9.0*	N/A
California, USA	Shen et al 2010(35)	a) Cross-sectional b) N/A c) 430, 317	White: 70 (64-77) Black: 68 (64-74) Asian: 67 (63-73) Hispanic: 67 (61-71)	8	3.8	3.9	3.6
15 U.S states, Washington, DC	Marcus et al 2010(36)	a) Combination of CHS and ARIC study b) – c) 19, 784	**CHS** African American: 73 (6) Whites: 73 (6) **ARIC** African Americans: 53 (6) Whites: 54 (6)	23	15	N/A	N/A

Table 1.3 continued

Country/State	Study	a. Study design b. Follow up c. Sample size	Mean (SD) age study population	Prevalence of AF (%)			
				Whites	Afro-Caribbeans	East Asians	Hispanics
Maryland, Minnesota, Mississippi, N. Carolina, USA	Alonso et al 2009(37)	a) Prospective b) 228,976 person-years c) 15, 407	Whites: 54.4 (5.7) African Americans: 53.6 (5.8)	7.9	4.8	N/A	N/A
Ohio, USA	Smith et al 2006 (38)	a) Prospective b) - c) 9671	N/A	24	17	N/A	N/A
California, USA	Ruo et al 2004 (39)	a) Retrospective and prospective b) – c) 1373	73 overall	38	20	N/A	N/A
Georgia, USA	Upshaw et al 2002(40)	a) Retrospective b) – c) 2123	14% age 70-79	7.8	2.5	N/A	N/A
California, USA	Go et al 2001(41)	a) Cross sectional b) N/A c) 17, 974	71.2 (12.2) whole cohort	2.5	1.7	N/A	N/A
Michigan, USA	Afzal et al 1999(42)	a) Prospective b) 6 months c) 163	Blacks: 63.8 (13.7) Whites: 70.8 (13.1)	42	21	N/A	N/A

Pt-yrs = patient years; *Asian Americans; N/A = not applicable

In addition to ethnic differences, age distribution of AF diagnosis may also differ between regions. More than 70% of AF patients in Western Europe, Australia and North America were aged >65 years (2). A different pattern in the average age of AF diagnosis is evident from other regions. AF patients are younger from the Arabic (45), Ethiopian (46), South Korean (2) and South African (21) studies with mean age ranging from 41-65 years. Results from the RE-LY AF registry which enrolled AF patients from the 164 emergency departments worldwide to evaluate the differences in the presentation and management of AF, also shows some regional variation in terms of age at AF diagnosis; patients from America and Europe countries were on average 10-12 years older than those from Africa, India and the Middle East (47).

1.1.4 Incidence and prevalence of atrial fibrillation in stroke patients

AF increases the risk of stroke approximately 5 times compared to those without AF (3). The presence of AF was 24.6% in patients [mean (SD) age 78.8 (13.3) years] with ischemic stroke in one Italian population-based study. In this study, AF was more frequent in women, elderly patients (>80 years), those with coronary heart disease and peripheral arterial disease. AF was also an independent predictor of 30-day and 1-year mortality in Cox regression analysis (48).

Another prospective study in Germany reported an overall prevalence of AF slightly higher than the Italian study, i.e., 28.6% in patients (N=692) with ischemic stroke or transient ischemic attack, with prevalence increasing with age (49). The prevalence of AF in ischaemic stroke patients in the USA (i.e., 23% in acute ischaemic stroke patients from eight states) (50), two European studies (24.6 and 28.6% respectively) (29, 30) and one Australian study (25%; study population 26,960) (51) was similar to that reported by the Italian study. However, the prevalence of AF was reportedly lower in some Asian countries, approximately 10% in China (52), 5.8-6% in India (53, 54), but higher in Japan (32%) (55).

Sposato et al conducted a meta-analysis of 50 studies in 2015 (56) to estimate the proportion of newly diagnosed AF patients experiencing stroke or transient ischemic attack (TIA) after undergoing four sequential phases of cardiac monitoring; phase 1: electrocardiogram (ECG) at admission, phase 2: continuous inpatient ECG, phase 3: Holter monitoring and phase 4: mobile cardiac outpatient telemetry. In this study, they reported an overall presence of AF in 23.7% (95% CI 17.2-31.0) of their post-stroke patients and an estimated prevalence of AF in post-stroke patients with either known or newly diagnosed AF of about 39.0%, higher than previously reported studies (56).

The prevalence of AF worldwide is increasing steadily although large variation can be seen between studies and countries. A larger proportion of ischemic stroke patients are also found to have AF either during admission or upon investigation post-discharge that becomes a major concern as AF related to stroke has poorer outcomes and prognosis (3, 5). This increase in the prevalence of AF may be explained by the fact that better detection methods have been used to detect AF (2, 3, 57) and also greater awareness among physicians and other healthcare providers who are able to detect patients with AF during routine check-ups, flu injections and also during hospital admissions.

Further epidemiological studies should be undertaken globally, especially in Asian and African countries, in urban and rural areas, so that a more accurate picture of the incidence and prevalence of AF can be captured, thereby allowing appropriate implementation of stroke prevention strategies to reduce stroke risk and burden.

The next section summarises the pathophysiology, diagnosis, pattern and symptoms of risk and general treatment of AF.

1.2 Overview of atrial fibrillation

Atrial fibrillation is a condition where there is an ineffective atrial contraction that results from an uncoordinated atrial activation. The sino-atrial (SA) node which sends electrical impulses to the atria for atrial contraction (thus forcing the blood to enter the ventricles) and is also responsible for controlling and coordinating the heart rate, is no longer functioning in an organised manner, thereby causing an irregular and rapid heart rate (58).

1.2.1 Pathophysiology of atrial fibrillation

Atrial fibrillation occurs when the electrical signalling pathway is abnormal (3). The signals are generated from all over the atria causing a fibrillating or quivering atrial activity. The signals are no longer systematically triggered via the SA node (58). Specifically, the pulmonary veins located in the left atrium generate multiple impulses in majority of AF cases (3). The generated impulses can be fired at a very rapid rate of about 300-600 beats per minute, however, not all of the impulses can be filtered by the atrioventricular (AV) node (59). The signals originating from multiple areas within the atria are chaotic, fast and irregular, leading to inadequate atrial emptying. Excessive signals passing through the AV node causes the ventricular rate to be increased (59). The emptying of the ventricles is affected by the increase in ventricular activity (60-130 beats per minute) and if this continues, it leads to reduced general circulation of the blood causing symptoms of fatigue, light-headedness, breathlessness and chest pain (59).

Hypertension, diabetes, heart failure, coronary artery disease, and ageing are among the factors that can lead to changes to the pathophysiology of the atria, including hypo-contractility, inflammation, vascular remodelling, inflammation, fatty infiltration and ion channel dysfunction (3). These changes can cause conduction disturbances and thus lead to the development of AF. Some of these changes are also involved in the manifestation of a hypercoagulable state in AF.

1.2.2 Pathophysiology atrial fibrillation related thromboembolism

Tissue factor exposure in the blood stream as a result of hypocontractility and ischemia induces inflammation and adds to the thrombogenic environment in the atria of AF patients, thus leading them to have an increased risk of thromboembolic events such as stroke or transient ischemic attack (TIA) (3). Along with the structural remodelling, the rhythm of AF itself predisposes the atrial myocardium to a prothrombotic state (60). Additionally, the myocardial damage within the atrium that develops within short periods of AF stimulates the release of prothrombotic factors onto the endothelial surface causing platelet aggregation. This could partly elucidate the reason of long-term stroke risk even in short episodes of AF (61, 62).

1.2.3 Diagnosis and detection of atrial fibrillation

AF diagnosis is made using the ECG that shows a typical pattern of AF involving irregular RR intervals and no distinct P waves. Any episode of AF lasting at least 30 seconds is considered as a diagnosis of AF (3). Patients with AF can be symptomatic or asymptomatic ('silent AF'). Silent AF can have severe consequences such as stroke and death just as with symptomatic AF (63-65). Such events can be avoided or reduced with early detection and OAC initiation. Suggestions have been made to screen AF in a more widespread manner including within community healthcare practices (66) and using sophisticated diagnostic tools which could detect short and long episodes of AF. One systematic review (67) of eight trials (N=18,189) conducted in the GP/outpatient clinic and community setting identified a 1.4% incidence of undiagnosed AF using a single time point screening AF method (pulse palpation or ECG) of patients aged ≥65 years (67). The pulse palpation method was reported to have a sensitivity of 94% and a specificity of 72% in detecting AF (68) while the handheld single lead ECGs have higher sensitivity and specificity ranging from 94%-98% and 76%-97% respectively (69).

Evidence has shown that detection of undiagnosed AF can be obtained by prolonged ECG monitoring (70, 71). In 2014, two trials (70, 72) were conducted to investigate whether long

term ECG monitoring is superior to conventional 24-hour monitoring in detecting AF in patients with cryptogenic stroke. The EMBRACE-AF trial (72) included 572 patients with cryptogenic stroke within the previous 6 months and investigated the benefits of longer monitoring periods (30 days) versus conventional 24-hour ECG monitoring. In the study, at least 16.2% of patients had AF for 30 seconds over 90 days of monitoring compared to just 3.2% for those undergoing 24-hour monitoring (an absolute difference of 12.9 percentage points [95% CI (8.0 to 17.6); p<0.001])(72).

The CRYSTAL AF trial (70), with a slightly lower number of participants (N=447), examined if 'conventional follow-up' was better than continuous cardiac monitoring via implantable cardiac monitor (ICM) in detecting AF in patients with cryptogenic stroke after 3 months of the event. At 6 months, it was similarly shown that the rate of AF detection is higher in patients receiving ICM compared to the conventional group [8.9% vs. 1.4%, (HR 6.4; 95% CI 1.9 - 21.7; p<0.001)] (70). Essentially, the benefit of continuous monitoring was also seen at 12 months with a 12.4% AF detected in patients with ICM compared to 2.0% in the conventional group (70). Despite the available evidence to date, the best method for detecting and screening AF is still unclear.

Evidence demonstrates the benefits of continuous ECG monitoring, the current guideline (3) recommends ECG rhythm strip and pulse palpation for primary prevention and at least 72 hours of monitoring in post stroke/TIA patients.

1.2.4 Patterns of atrial fibrillation

In most cases, AF progresses from infrequent, short episodes to longer and more frequent episodes, and a sustained form of AF can develop eventually over time. Five types of AF are classified based on the presentation, duration, and spontaneous termination of AF episodes **(Table 1.4).** Currently, guidelines do not differentiate between types of AF and stroke prophylaxis as observational studies suggest that stroke risk is dependent on concomitant stroke risk factors regardless of AF type (73, 74). However, a recent meta-analysis (75)

suggests that the risk of stroke may differ between patients with paroxysmal AF and non-paroxysmal AF. Twelve studies (10 RCTs and 2 prospective studies) involving almost 100, 000 patients evaluated the impact of AF type (PAF vs. non-PAF) on thromboembolic (TE) events, bleeding and death. After adjustment for stroke risk factors (hypertension, heart failure, age, gender, previous thromboembolism and diabetes) the hazard ratio for TE events was 1.38 (95% CI 1.19–1.61; $p<0.001$); bleeding events was 1.03 (95% CI 0.90–1.17; $p=0.715$) and all-cause mortality was 1.22 (95% CI 1.09–1.37; $p<0.001$) respectively in non-PAF vs. PAF patients (75). Results from this meta-analysis showed that thromboembolism and mortality were significantly higher in non-PAF compared to PAF patients (75).

Table 1.4: Patterns of atrial fibrillation (taken directly from ESC guideline 2016)

AF pattern	Definition
First diagnosed AF	Undiagnosed AF before, irrespective of duration of arrhythmia or presence and severity of AF-related symptoms
Paroxysmal AF	AF that self-terminates usually within 48 hours. Some paroxysms can occur for up to 7 days OR AF episodes that are cardioverted within 7 days
Persistent AF	AF episodes lasting longer than 7 days, including episodes terminated by cardioversion (pharmacological or direct current cardioversion), after 7 days or more
Long-standing persistent AF	Prolonged AF lasting for ≥1 year when a rhythm control strategy is adopted
Permanent AF	AF accepted by patients and physicians and rhythm control strategy is not pursued. If rhythm control therapy is to be adopted, AF should be classified as long-standing persistent AF

1.2.5 Symptoms of atrial fibrillation

Some AF patients (25-40%) report no symptoms or very minimal symptoms while others (15-30%) report severe disabling symptoms. Symptoms include palpitations, lethargy, shortness of breath, chest tightness, sleeping difficulties and psychological distress. Symptomatic AF patients tend to report poorer quality of life than asymptomatic patients (3). The modified European Heart Rhythm Association (EHRA) symptom scale **(Table 1.5)** can be used to categorise the severity of AF symptoms.

Table 1.5: Modified European Heart Rhythm Association symptom scale (3)

Modified EHRA score	Symptoms	Description
1	None	No symptoms
2a	Mild	Symptoms related to AF are not affecting normal daily activity
2b	Moderate	Patients are troubled by symptoms of AF but normal daily activity is not affected
3	Severe	Symptoms related to AF are affecting normal daily activity
4	Disabling	Discontinuation of normal daily activity

1.2.6 Risk of developing atrial fibrillation

Many concomitant conditions and cardiovascular diseases increase the risk of AF development. **Table 1.6** lists the most common concomitant disease associated with AF. Identifying these risk factors and managing them is crucial to prevent AF and its burden of the disease (3).

Table 1.6: Comorbid conditions/risk factors associated with AF (3)

Comorbidities/risk factors	
• Genetic predisposition	• Obstructive sleep apnoea
• Older age	• Chronic kidney disease
• Hypertension	• Smoking
• Heart failure	• Alcohol consumption
• Valvular heart disease	• Vigorous exercise
• Myocardial infarction	
• Thyroid disorder	
• Obesity	
• Diabetes mellitus	
• Chronic obstructive pulmonary disease	

The original Framingham Heart Study (76) (38 years follow up) investigated the predictors of AF development has shown that men had 1.5 times higher risk of developing AF. Other risk factors identified from the study include: hypertension (OR 1.5 men and OR 1.4 women), congestive heart failure (OR 4.5 men and 5.9 women), myocardial infarction (OR 1.4 men), valvular heart disease (OR 1.8 men and OR 3.4 women), aging and diabetes (OR 1.4 men and 1.6 women) were all independent predictors of AF development (76). Other studies also showed that obesity (HR 1.37) (77), thyroid dysfunction (78), COPD (FEV1<60%: RR 2.53) (79), chronic kidney disease (stage 4/5: OR 3.52) (80), current smoker (RR 2.05) (81) and >21 drinks of alcohol per week (RR 1.39)(82) were also associated with AF development.

1.2.7 Treatment of atrial fibrillation

Essentially, there are five targets of treatment in AF patients: 1) acute rate and rhythm control to achieve hemodynamic stability, 2) managing precipitating factors which involves lifestyle changes and treating underlying conditions for the purpose or cardiovascular risk reduction, 3) assessing stroke risk and offering oral anticoagulants (OAC) therapy in patients with stroke risk factors (this will be discussed in more detail in section 1.4), 4) assessing heart rate with rate control therapy and lastly symptoms assessment with anti-arrhythmic drugs, cardioversion or catheter ablation. These targets are set for the benefits of patients to improve life expectancy, quality of life autonomy and social functioning (3).

1.2.7.1 Rate and rhythm control therapy

Essentially, rate control therapy is often offered to patients to improve AF-related symptoms. Very little evidence exist that showed the best type and intensity of rate control therapy compared to stroke prevention. Most data were derived from observational studies and short-term cross over trials (83-86). Medical treatment options for rate control therapy for acute or long-term rate control are beta blockers (bisoprolol, carvedilol), non- dihydropyridine calcium

channel blockers (diltiazem and verapamil), digoxin and some rhythm control agents which have rate control properties, for example amiodarone, dronedarone and sotalol (3).

Another part of AF management involves restoring and maintaining sinus rhythm either with pharmacological agents or with catheter ablation or in combination. At the moment, rhythm control therapy is indicated in patients who are still symptomatic despite on adequate rate control therapy (3). When anti-arrhythmic drugs are ineffective, electrical cardioversion is usually offered in symptomatic AF patients. Evidences comparing rate and rhythm control therapy versus rate control therapy alone have shown neutral outcomes (87-89). Pharmacological rhythm control therapy options include amiodarone, flecanide and propafenone. However, long term use of rhythm control therapy should be considered based on the safety of each agent. For example, amiodarone could cause QT prolongation so it should be avoided (if possible) with drugs causing the same effect. In addition, dronedarone is contraindicated in patients with decompensated heart failure or patients with NYHA class IV heart failure as these patients are prone to negative inotropic action and ventricular proarrhythmic effects of anti-arrhythmic drugs (3).

1.2.8 Pathways to management of atrial fibrillation

1.2.8.1 The ABC pathway

Recently, 'The Atrial Fibrillation Better Care (ABC)' pathway was introduced for the management of AF patients in an integrated manner (90) (**Figure 1.3**). The **'A'** in the ABC pathway stands for '**A**void' stroke, which can be achieved by implementing the 'Birmingham 3 step' approach (**Figure 1.3**). The **'B'** acronym stands for '**B**etter management of symptoms' including offering rate or rhythm control therapy and lastly **'C'** stands for managing cardiovascular and other **C**omorbidities. Simply, the 'Birmingham 3 step approach' involves:

1) Identifying low risk patients
2) Offering appropriate stroke prevention (OAC) to patients not in the 'low risk group and assessing bleeding risk (using the HAS-BLED score)
3) Deciding on OAC therapy either with a NOAC or VKA, emphasising anticoagulation control (TTR ≥70%) in those receiving VKA

1.2.8.2 National Institute for Health and Care Excellence (NICE) AF care pathway and European Society of Cardiology (ESC) integrated pathway

Similarly, the NICE AF care pathway (91, 92) (**Figure 1.4**) and the ESC integrated pathway (3) (**Figure 1.5**) suggest offering stroke prevention strategy to all AF patients at risk of stroke and better management of AF symptoms with either rate or rhythm control strategy. The ABC pathway (90) and the ESC integrated pathway (3) adds the ability to manage cardiovascular risk factors and other comorbidities. The ESC integrated pathway necessitates changes in lifestyle that will result in a better quality of life and improved life expectancy. All three pathways were created to guide physicians to manage AF patients in a more integrated and efficient manner.

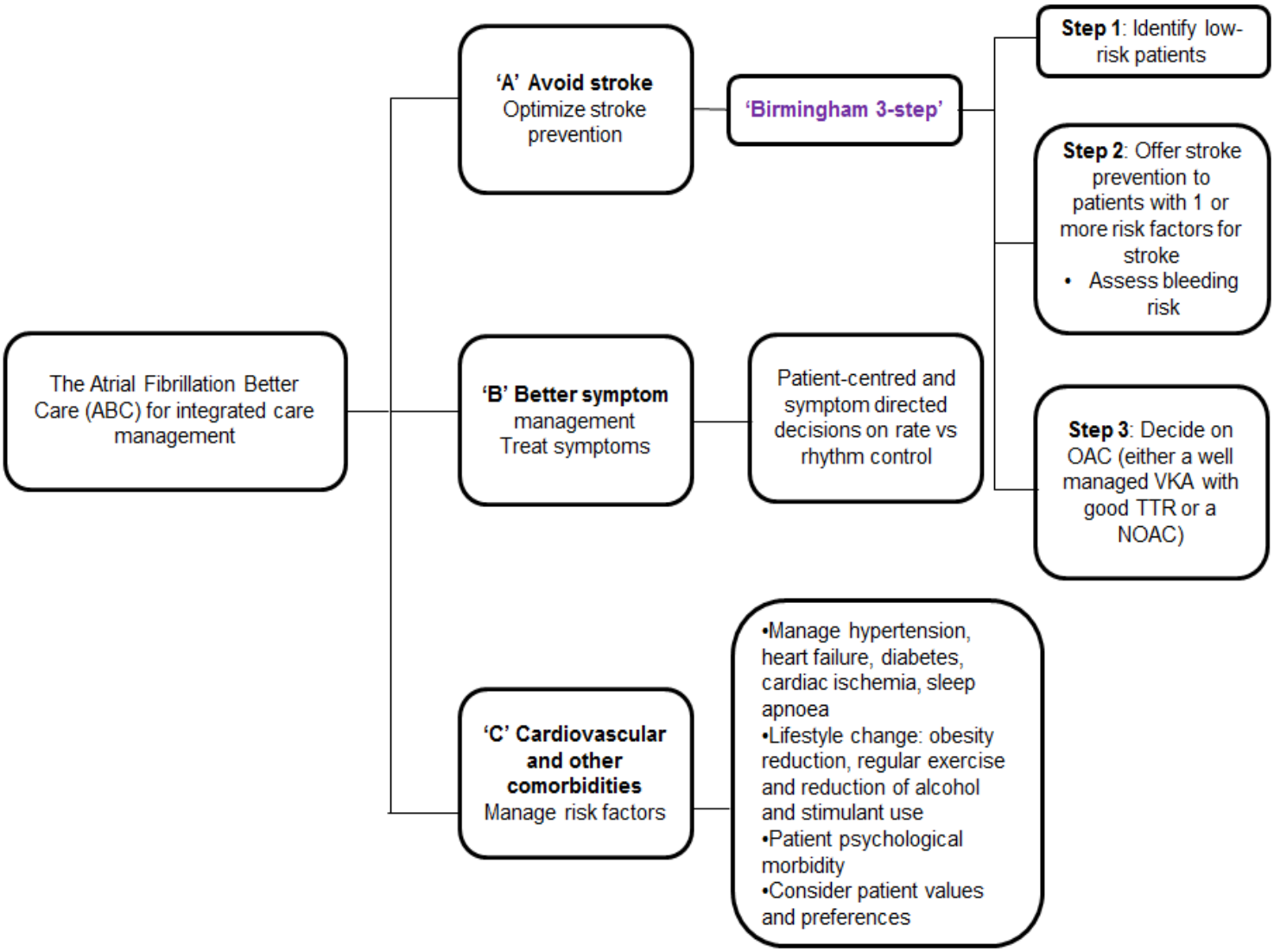
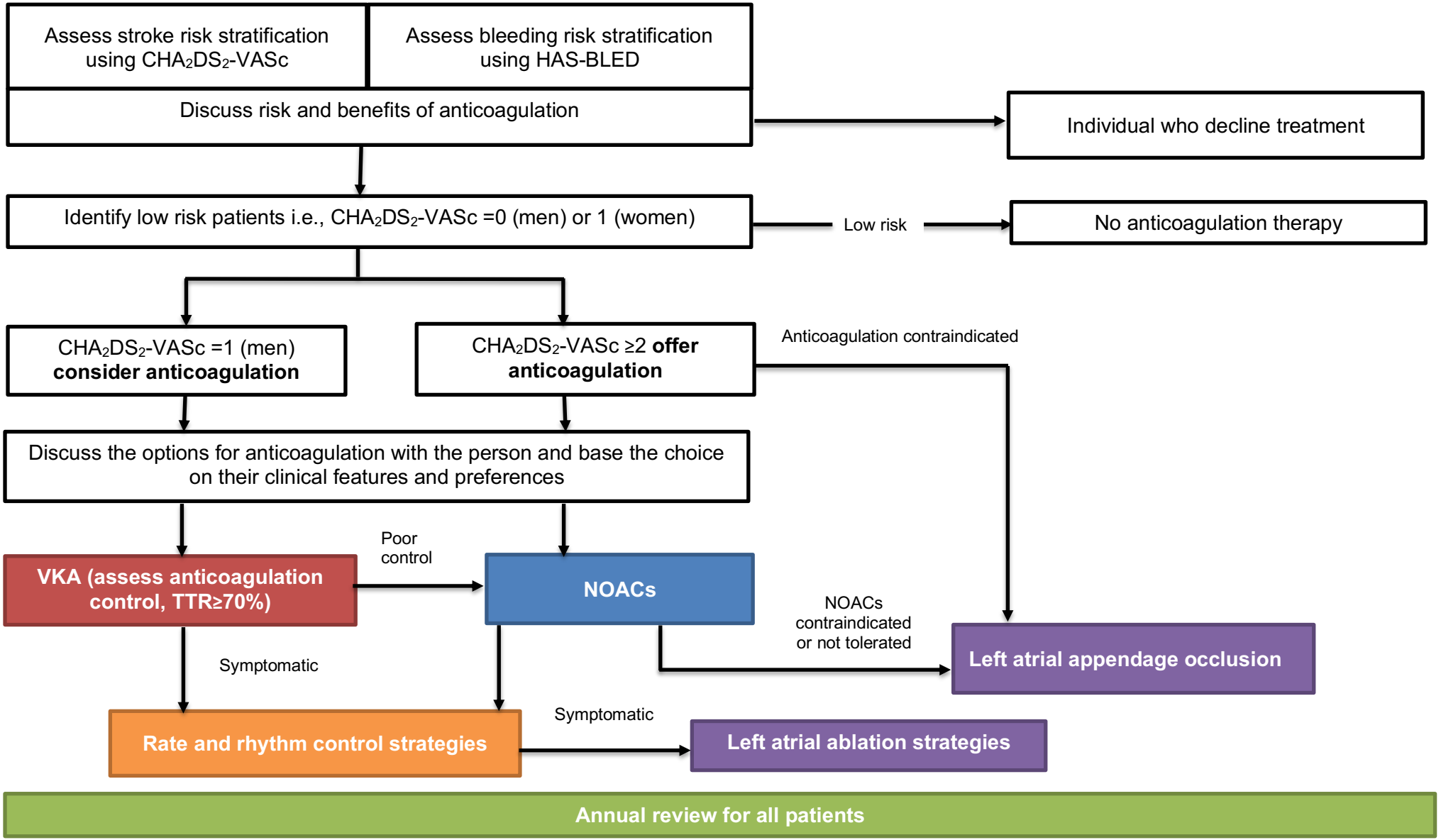


Figure 1.3: ABC pathway [taken directly from Lip 2016 (90)]

NOAC: Non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; TTR: time in therapeutic range; VKA: vitamin K antagonist



AF: atrial fibrillation; NOACs: non-Vitamin K antagonist oral anticoagulants; TTR: time in therapeutic range; VKA: vitamin K antagonist

Figure 1.4: NICE-AF care management pathway taken from NICE-AF guideline 2014 (91, 92)

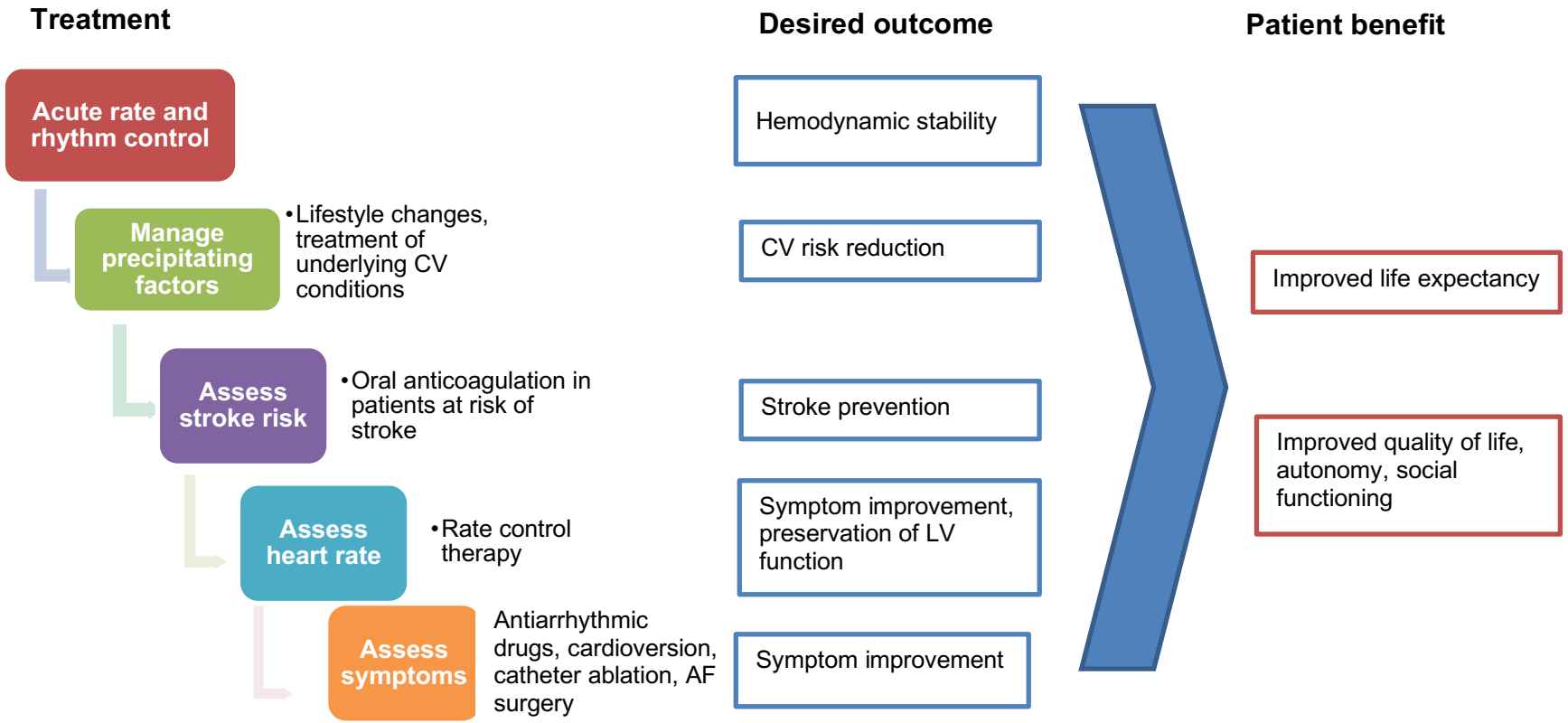


Figure 1.5: European Society of Cardiology integrated pathway adapted from the ESC AF Guidelines 2016 (3)

1.3 Psychological aspects in patients with atrial fibrillation and the impact on quality of life

1.3.1 Depression and anxiety

Studies have reported psychological distress among patients with AF (93). Five studies (94-98) have reported the prevalence of depression in AF cohorts which ranged from 10%-38% measured using validated questionnaires [Beck Depression Inventory (BDI) (3-5) and Hospital Anxiety and Depression Scale (HADS)] (94, 98). Meanwhile, the prevalence of state and trait anxiety is reported as between 28-35% and 35%-38%, respectively, among AF patients, in other studies, using the State-Trait Anxiety- Inventory (STAI-S) questionnaire (96, 99).

Recently, one Greek study of 170 permanent AF patients (94) found that depression and anxiety were associated with patients' age and number of years since diagnosis; those aged >70 years who had the disease for 6-10 years were more anxious and depressed than those aged <70 years who had AF for less than 6 years. Elderly AF patients are likely to be more anxious and depressed perhaps due to various factors like cognitive impairment, physical impairment, and poor treatment adherence (100, 101). In this study, poor/no knowledge of the state of their health and having moderate/poor relationship with medical staff were also associated with depression. Patients may be more depressed if they are unsure about the disease, their prognosis and management. However, with adequate knowledge, patients tend to have better control of their disease, present with fewer symptoms and are emotionally less distressed (102, 103). In this study, females were also found to be more anxious compared to males. This could be due to the differences in the type of AF and severity of symptoms and outcomes of cardiac disease, as well as daily living or health behaviours (94, 104). For example, females may be more prone to distress after facing an emotional trauma (example divorce or death of family members) and perhaps this added stress would further cause negative impact to their current comorbid condition.

Research has shown that quality of life (QoL) is poorer among AF patients with anxiety and depression. Thrall et al (96) compared 101 AF and 97 hypertensive patients (age and sex matched) and reported that AF patients were significantly more anxious (mean trait anxiety score 37.4 vs. 33.3; p=0.02 in AF vs. hypertensive patients) than hypertensive patients at baseline and this persisted 6 months later (mean trait anxiety score 36.9 vs. 32.6; p=0.03 in AF vs. hypertensive patients). Symptoms of depression were also present in 38% of AF patients at baseline and this also persisted at 6 months. Furthermore, symptoms of depression and anxiety were independently related to health related quality of life (HRQoL) at baseline but at 6 months, only symptoms of depression predicted HRQoL (96). In this study, AF patients were more anxious and depressed than hypertensive patients probably because AF is an illness associated with symptoms and an increased risk of stroke whereas hypertension is without any specific symptoms and patients may have the perception of hypertension being a benign condition. Studies (105-107) have shown that AF patients with greater severity of symptoms (106, 107) and with recurrence of AF (108) have higher rates of depression and/or anxiety.

Similarly in 2009, Lane et al (99) reported that lone AF patients presented with more anxiety symptoms (38% state and 41% for trait anxiety) and had poor QoL, however, depression level was low [median score 2.0 (0-3.0)] at baseline. In contrast to Thrall et al, (who did not investigate the beliefs about medication)(96), Lane et al (99) reported that beliefs about medication and number of AF symptoms predicted their physical quality of life.

1.3.2 Anticoagulation and quality of life

Despite the marked improvement in the prevention of stroke with the use of oral anticoagulation therapy, studies (109, 110) have shown that the QoL among patients with VKA therapy is affected as it requires behaviour and lifestyle modification.

Several studies (109, 111-113) from Brazil, Argentina and Spain among anticoagulated patients (N=72 to 905) mainly for AF and mechanical heart valves, have assessed QoL using

the SF-36 tool. They reported overall SF-36 scores ranging from 54-62 indicating poor QoL. These studies (109, 111-113) reported that patients have more limitations in daily activity compared to emotional health evident by lower scores in physical domain compared to emotional domains. This indicates that anticoagulated patients appear to have greater impairment in their physical health rather than emotional health.

However, other studies (109, 111, 114, 115) from Brazil, Turkey, Malaysia and Spain (N=72 to 339) among mostly anticoagulated AF patients using VKA showed a relatively better QoL with scores ranging from 67-86 with the Duke Anticoagulation Satisfaction Scale (DASS) (109, 111-113). Three studies (109, 111, 114) showed that patients were more limited and had higher burden in their physical activity, however, only one study (115) showed patients were more psychologically affected by their anticoagulation therapy. Although the studies differed methodologically (small sample size, cross-sectional study), they suggest that anticoagulated patients are more likely to be affected by treatment inconvenience rather than by their emotional health.

Another Turkish study (116) compared HRQoL using the SF-36 tool among 182 NOAC and warfarin patients (91 patients in each group). They showed that even after adjustment for age, gender, adherence, and duration of OAC therapy, warfarin treated patients had significantly lower HRQoL scores in all domains ($p<0.05$); self-reported symptoms of anxiety (HADS-A: 6.2 vs. 4.6; $p<0.001$) and depression (HADS-D: 4.9 vs. 3.6; $p<0.001$) were significantly higher among warfarin treated patients compared to NOAC patients respectively. (116) This may be expected given that NOACs have fewer drug interactions, no known food interactions and do not require frequent INR monitoring, which have all been shown to impact patient's QoL (109, 111, 114, 115).

The next section discusses stroke prevention in AF including identifying stroke risk factors, different treatment strategies (VKA vs. NOACs) and guideline recommendations.

1.4 Stroke prevention in atrial fibrillation

1.4.1 Antithrombotic therapy in stroke prevention in atrial fibrillation

Currently, there are five types of OAC therapy available for stroke prevention in AF patients, including Vitamin K antagonists (VKA e.g., warfarin) and non-VKA oral anticoagulants (NOACs e.g., dabigatran, rivaroxaban, apixaban and edoxaban) (3).

1.4.1.1 Vitamin K antagonist (VKAs)

The principal priority in managing patients with AF is stroke prevention. Warfarin and other types of VKAs (for example acenocoumarol, phenprocoumon) were among the first anticoagulants used in AF patients. Clinical trials (117) have shown that compared to placebo, dose-adjusted VKA reduces the risk of stroke and systemic embolism by 64% (95% CI 49-74) (**Table 1.7**) and all-cause mortality by 26% (95% CI 3-43) (117). Compared to antiplatelet therapy, dose-adjusted VKA was also more efficacious in a reduction of TE complication [relative risk reduction 39% (95% CI 22-52) from 12 trials, 12, 963 participants] (117). However, VKAs have a narrow therapeutic index requiring dose adjustments and frequent monitoring of the international normalised ratio (INR) to achieve maximum therapeutic effect and minimise harm. Furthermore, individual response to VKA can be influenced by many factors (**see section 1.5, pages 78-100 for more detail**) (3). Nonetheless, VKA is still the recommended OAC of choice in AF patients with severe renal impairment (CrCl<15ml/min) and patients with valvular heart disease requiring mechanical valve prosthesis (3). When VKA is used, attention needs to be given on the quality of anticoagulation reflected by the time in therapeutic range (TTR) of the INR (3). To maximise effectiveness and safety of VKA, the European guidelines (3) have recommended a TTR of ≥70% while the NICE guideline (118) recommended TTR of ≥65%. Several studies (119-122) have also shown that TTR independently predict thromboembolic (120, 122), bleeding events (120, 121) and improves survival (119, 122) in AF patients prescribed with VKA therapy.

Table 1.7: Adjusted-dose warfarin versus placebo or no treatment, taken directly from Hart 2007 (117)

Study, year	Patients, N	Target INR	Strokes/patients, n/n a. warfarin b. placebo or control	Relative risk reduction (95% CI), %
AFASAK I, 1989(123), 1990(124)	671	2.8-4.2	a. 9/335 b. 19/336	54 *
BAATAF, 1990(125)	420	1.5-2.7	a. 3/212 b. 13/208	78*
SPAF 1, 1991(126)	421	2.0-4.5	a. 8/210 b. 19/211	60*
CAFA, 1991(127)	378	2.0-3.0	a. 6/187 b. 9/191	33*
SPINAF, 1992(128)	571	1.4-2.8	a. 7/281 b. 23/290	70*
EAFT, 1993(129)	439	2.5-4.0	a. 20/225 b. 50/214	68*
6 trials	2900	-	a. 53/1450 b. 133/1450	64 (49-74)

INR: international normalized ratio; * 95% CI not stated in the Hart 2007 meta-analysis (117)

1.4.1.2 Non-vitamin K antagonist oral anticoagulants (NOACs)

With the emergence of non-VKA oral anticoagulants (NOACs), the practice of antithrombotic management has shifted toward prescribing NOACs for stroke prevention in patients with AF given the relative efficacy, safety and convenience of NOACs compared to VKAs (26). Four NOACs including the direct thrombin inhibitor, dabigatran and factor Xa inhibitors rivaroxaban, apixaban and edoxaban are suitable alternatives to VKAs for stroke prevention in AF. **Table 1.8** list the different characteristics of warfarin and the four NOACs and **Table 1.9** summaries the baseline characteristics of the four major NOAC trials. NOACs have a more targeted mode of action, shorter time to reach the maximum anticoagulant effect, shorter half-life, less drug-drug interactions and no food restrictions compared to warfarin. **Tables 1.10** and **1.11** present the efficacy and safety results, respectively, from the four NOAC trials. Compared to warfarin,

dabigatran 150mg twice daily [RR 0.66 (95% CI 0.53-0.82)] and apixaban 5mg twice daily [RR 0.79 (95% CI 0.66-0.95)] are associated with a lower risk of ischemic stroke and systemic embolism. All four NOACs significantly reduced the risk of haemorrhagic stroke [dabigatran 150 mg RR 0.26 (95% CI 0.14-0.49); rivaroxaban 20 mg RR 0.59 (95% CI 0.37-0.93); apixaban 5 mg RR 0.51 (95% CI 0.35-0.75); edoxaban 60 mg RR 0.54 (95% CI 0.38-0.77)] and intracranial haemorrhage [dabigatran 150 mg RR 0.40 (95% CI 0.27-0.60); rivaroxaban 20 mg RR 0.67 (95% CI 0.47-0.93); apixaban 5 mg RR 0.42 (95% CI 0.30-0.58); edoxaban 60 mg RR 0.47 (95% CI 0.34-0.63)] compared to warfarin. A meta-analysis (3) of the four major Phase 3 NOAC trials have also concluded that compared to warfarin, NOACs significantly reduced the risk of stroke and systemic embolism by 19% [RR 0.81 (95% CI 0.73-0.91; $p<0.0001$)], and this is largely due to a significant reduction in haemorrhagic stroke [RR 0.49 (0.38-0.64; $p<0.0001$)] (130). NOACs also significantly reduce intracranial haemorrhage [RR 0.48 (0.39-0.59; $p<0.0001$)] and all-cause death [RR 0.90 (0.85-0.950; $p=0.0003$)] but were also associated with increased risk of GI bleeding [RR 1.25 (1.01-1.55); $p=0.04$)] when compared to warfarin (3).

Table 1.8: Pharmacokinetics of warfarin versus NOACs and baseline characteristics for four randomised controlled trial cohorts comparing warfarin versus NOACs

	Warfarin (131)	Dabigatran (132)	Rivaroxaban (133)	Apixaban (134)	Edoxaban (135)
Mechanism of action	Interfere with synthesis of vitamin K dependent clotting factors by inhibiting VKORC1	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Bioavailability, %	98	3-7	66 without food 100% with food	50	62
Time to reach peak level, hours	1.5-3 days	3	2-4	3	1-2
Half-life, hours	20-60	12-17	5-13	9-14	10-14
Clearance	Renal	80% renal	66% liver, 33% renal	27% renal	50%
Dosing in AF	Variable dose, once daily	150mg or 110mg twice daily	20mg or 15mg once daily	5mg or 2.5mg twice daily	60mg or 30mg or 15mg once daily
Not recommended if	-	CrCl<30ml/min	CrCl<15ml/min	CrCl<15ml/min	CrCl<15ml/min
Antidote	Vitamin K	Idarucizumab	Not available	Not available	Not available

Table 1.9: Baseline characteristics of the four randomised controlled trial cohorts comparing warfarin versus NOACs

	Dabigatran (132)	Rivaroxaban (133)	Apixaban (134)	Edoxaban (135)
Patients, N	18,113	14,264	18,201	21,105
Mean/median age	71.5 (8.7)	73 (65-78)	70 (63-76)	72 (64-78)
Male, %	63.6	60.3	64.5	61.9
Follow up, years	2	1.9	1.8	2.8
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.8
Median individualised TTR	67 (54-78)	58 (43-71)	66 (52-77)	68 (57-77)

AF: atrial fibrillation; CrCl: creatinine clearance; CHADS score: 1 point each for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and 2 points for stroke/TIA; TTR: time in therapeutic range; VKORC1: vitamin K epoxide reductase

Table 1.10: Efficacy outcomes in the four major randomised controlled trials comparing warfarin versus NOACs in AF populations

	Dabigatran (132) (RE-LY)		**Rivaroxaban (133) (ROCKET-AF)**		**Apixaban (134) (ARISTOTLE)**		**Edoxaban (135) (ENGAGE AF-TIMI 48)**	
Efficacy Outcomes								
	Dabigatran 150mg N=6076	**Warfarin**, N=6022	**Rivaroxaban** 20mg	**Warfarin**	**Apixaban** 5mg N=9120†	**Warfarin**, N=9081†	**Edoxaban** 60mg, N=7035†	**Warfarin**, N=7036†
Stroke/ systemic embolism, N (%/yr)	134 (1.11)	199 (1.69)	269/7081† (2.1)	306/7090† (2.4)	212 (1.27)	265 (1.60)	296 (1.57)	337 (1.80)
Relative risk (95% CI)	**0.66 (0.53-0.82); p<0.001**		0.88 (0.75-1.03); p=0.12*		**0.79 (0.66-0.95); p=0.01***		0.87 (0.73-1.04)§; p=0.08	
Ischemic stroke, N (%/yr)	111 (0.92)	142 (1.20)	149/7061‡ (1.34)	161/7082‡ (1.42)	162 (0.97)	175 (1.05)	236 (1.25)	235 (1.25)
Relative risk (95% CI)	0.76 (0.60-0.98); **p=0.03***		0.94 (0.75-1.17); p=0.581*		0.92 (0.74-1.13); p=0.42		1.00 (0.83-1.19); p=0.97	
Haemorrhagic stroke, N (%/yr)	12 (0.10)	45 (0.38)	29/7061‡ (0.26)	50/7082‡ (0.44)	40 (0.24)	78 (0.47)	49 (0.26)	90 (0.47)
Relative risk (95% CI)	**0.26 (0.14-0.49); p<0.001***		**0.59 (0.37-0.93); p=0.0248**		**0.51 (0.35-0.75); p=<0.001***		**0.54 (0.38-0.77); p<0.001**	
All-cause mortality, N (%/yr)	438 (3.64)	487 (4.13)	208/7061‡ (1.87)	250/7082‡ (3.53)	603 (3.52)	669 (3.94)	773 (3.99)	839 (4.35)
Relative risk (95% CI)	0.88 (0.77-1.00); p=0.051*		0.85 (0.70-1.02); p=0.073*		**0.89 (0.80-0.998); p=0.047***		0.92 (0.83-1.01); p=0.08	

* p for superiority; † based on intention to treat population; ‡based on safety on-treatment population; §97.5%CI was used

Table 1.11: Safety outcomes in the four major randomised controlled trials comparing warfarin versus NOACs in AF populations

	Dabigatran (RE-LY) (132)		**Rivaroxaban (ROCKET-AF) (133)**		**Apixaban (ARISTOTLE) (134)**		**Edoxaban (135) (ENGAGE AF-TIMI 48)**	
Safety outcomes								
	Dabigatran 150, N=6076	**Warfarin**, N=6022	**Rivaroxaban** 20, N=7111	**Warfarin**, N=7125	**Apixaban** 5, N=9088	**Warfarin,** N=9052	**Edoxaban** 60, N=7012	**Warfarin,** N=7012
Major bleeding N (%/yr)	375 (3.11)	397 (3.36)	395 (3.6)	386 (3.4)	327 (2.13)	462 (3.09)	418 (2.75)	524 (3.43)
Relative risk (95% CI)	0.93 (0.81-1.07); p=0.31		1.04 (0.90-1.20); p=0.58		**0.69 (0.60-0.80); p<0.001**		**0.80 (0.71-0.91); p<0.001**	
Intracranial haemorrhage, N (%/yr)	36 (0.30)	87 (0.74)	55 (0.5)	84 (0.7)	52 (0.33)	122 (0.80)	61 (0.39)	132 (0.85)
Relative risk (95% CI)	**0.40 (0.27-0.60); p<0.001**		**0.67 (0.47-0.93); p=0.02**		**0.42 (0.30-0.58); p<0.001**		**0.47 (0.34-0.63); p<0.001**	
GI bleed, N (%/yr)	182 (1.51)	120 (1.02)	224 (3.15%) ¶	154 (2.16%)¶	105 (0.76)	119 (0.86)	232 (1.51)	190 (1.23)
Relative risk (95% CI)	**1.50 (1.19-1.89); p<0.001**		-		0.89 (0.70-1.15); p=0.37		**1.23 (1.02-1.50); p=0.03**	
Net clinical outcome, N (%/yr)	832 (6.91)†	901 (7.64)†	-	-	1009 (6.13)‡	1168 (7.20)‡	1323 (7.26)§	1462(8.11)§
Relative risk (95% CI)	**0.91 (0.82-1.00); p=0.04**		**-**		**0.85 (0.78-0.92); p<0.001**		**0.89 (0.83-0.96); p=0.003**	

†composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding, ‡ composite of stroke, systemic embolism, major bleeding or all-cause death; §composite of stroke, systemic embolic event, major bleed, all-cause death;¶ percentage not %/yr and p<0.001

Another meta-analysis of 'real-world' high quality studies (28 studies included only from nationwide or health insurance claims database with adjusted or matched findings) of dabigatran, rivaroxaban and apixaban compared to warfarin for stroke prevention in AF has produced findings consistent with the RCTs (**Table 1.12**) (136). Dabigatran, rivaroxaban and apixaban all reduced the risk of intracranial bleed compared to warfarin, with similar risk of ischemic stroke and ischemic stroke/systemic embolism. Mortality risk was lower with dabigatran and apixaban. There was less gastrointestinal (GI) bleeding and major bleeds with apixaban but higher risk of GI bleed with dabigatran and rivaroxaban, and similar risk of myocardial infarction with dabigatran and rivaroxaban compared to warfarin **(Table 1.12).** (136) Edoxaban was not included in this meta-analysis as no real world studies assessing edoxaban was published at the time of the searches.

Table 1.12: Meta-analysis of real word studies comparing dabigatran, rivaroxaban and apixaban to warfarin for efficacy and safety outcomes [from Ntaios et al(136)]

Efficacy outcomes		**Dabigatran vs. warfarin**		**Rivaroxaban vs. warfarin**		**Apixaban vs. warfarin**	
Ischemic stroke		(HR, 0.96; 95% CI, 0.80–1.16)		(HR, 0.89; 95% CI, 0.76–1.04)		(HR, 0.95; 95% CI, 0.75–1.19)	
Number of studies	No of patients	9	476, 924	5	108, 810	3	48, 549
Ischemic stroke/systemic embolism		(HR, 1.17; 95% CI, 0.92–1.50)		(HR, 0.73; 95% CI, 0.52–1.04)		(HR, 1.07; 95% CI, 0.87–1.31)	
Number of studies	No of patients	7	234, 739	4	54, 577	1	24, 993
Any stroke/systemic embolism		(HR, 0.93; 95% CI, 0.77–1.14)		HR, 0.87; 95% CI, 0.71–1.07		**(HR, 0.67; 95% CI, 0.46–0.98)**	
Number of studies	No of patients	2	66, 992	2	50, 620	1	15, 390
Myocardial infarction		(HR, 0.96; 95% CI, 0.77–1.21)		(HR, 1.02; 95% CI, 0.54–1.89)		-	
Number of studies	No of patients	5	316, 180	2	24, 621	-	-
Safety outcomes							
Intracranial haemorrhage		**(HR, 0.42; 95% CI, 0.37–0.49)**		**(HR, 0.64; 95% CI, 0.47–0.86)**		**(HR, 0.45; 95% CI, 0.31–0.63)**	
Number of studies	No of patients	12	606, 855	7	136, 221	4	66, 482
Gastrointestinal bleed		**(HR, 1.20; 95% CI, 1.06–1.36)**		**(HR, 1.24; 95% CI, 1.08–1.41)**		**(HR, 0.63; 95% CI, 0.42–0.95)**	
Number of studies	No of patients	10	537, 770	4	71, 368	2	33, 323
Major bleed		(HR, 0.83; 95% CI, 0.65–1.05)		(HR, 1.00; 95% CI, 0.92–1.08)		**(HR, 0.55; 95% CI,0.48–0.63)**	
Number of studies	No of patients	13	348, 896	8	167, 532	4	89, 036
Death		**(HR, 0.63; 95% CI, 0.52–0.76)**		(HR, 0.67; 95% CI, 0.35–1.30)		**(HR, 0.65; 95% CI, 0.56–0.75)**	
Number of studies	No of patients	6	319, 486	2	51, 795	1	41, 785

1.4.2 Assessing risk factors for stroke

Assessing risk factors for stroke in AF patients is essential before starting anticoagulation treatment. Stroke risk factors related to AF have been reported in various systematic reviews (137, 138). History of stroke/TIA [RR 2.5 (95%CI 1.8-3.5)], increasing age [RR 1.5 per decade; (95% CI 1.3-1.7)], history of hypertension [RR 2.0 (95% CI 1.6-2.5)] and diabetes mellitus [RR 1.7 (95%CI 1.4-2.0)] were the most consistent risk factors for stroke as reported by the Stroke in AF Working group study (137). Female sex, vascular disease and heart failure have been less consistently associated with stroke risk in AF. One systematic review and meta-analysis reported an increased risk of strokes among females with AF [RR 1.31 (95%CI 1.18-1.46)] (139), while in another non-anticoagulated AF population, only females ≥75 years were at increased the risk of stroke [HR 1.20 (95%CI 1.12-1.28)] (140). Stroke risk in women is age-dependent where women age <65 with no other stroke risk factors are classified as being at low risk of stroke (141). Recently, another nationwide registry showed that female and male (with no additional risk factor) AF patients have similar thromboembolic risk. In addition, female gender acts as a 'risk modifier' rather than a risk factor whereby risk of TE is only higher in females with ≥2 non-gender stroke related risk factors with the acronym CHA_2DS_2-VA (heart failure, hypertension, aged 75 years, diabetes, stroke, vascular disease and age 65-74). Furthermore, in this registry, the risk of stroke differs by different score categories; the risk increases significantly with a score ≥2 (but not 3) thus modifying the stroke risk. [CHA_2DS_2-VA score 2: HR 1.21 (1.08-1.34); score 3: HR 1.03 (0.93-1.13); score 4: HR 1.25 (1.14-1.36); score 5: HR 1.41 (1.27-1.56)] (142).

In terms of vascular disease, the OPTIMAL trial showed increased risk of stroke [adjusted HR of 14.6 (95% CI 5.87-36.3)] among new-onset AF patients 30 days after acute myocardial infarction (143), while another Danish study also reported increased risk of stroke among patients with peripheral arterial disease [HR 1.93 (95% CI 1.70-2.19)] (144). Left ventricular dysfunction (moderate to severe) was also seen as risk factor for stroke (RR 2.5 95% CI 1.5-4.4) in one study (92) while another study showed no difference in the risk of stroke or

thromboembolism between different categories of ejection fraction (EF) [HR 0.75 (95% CI 0.44-1.30) for EF <35% and HR 1.25 (95% CI 0.83-1.93) for EF 35-49% (145).

1.4.3 Predicting stroke risk with clinical risk scores

Various clinical risk scores to predict stroke, TIA or thromboembolism (TE) in AF patients have been developed since the 1990's **(Table 1.13).** The risk scores were developed based on common demographic and clinical factors found in AF patients (141). **Table 1.13** presents eleven risk scores to predict stroke in AF population. The most common risk factors present in these risk scores are prior thromboembolic events and diabetes mellitus (present in all eleven risk scores). Increasing age and hypertension were present in ten of the risk scores followed by female sex and heart failure (in 6 scores), and vascular disease (5 scores).

1.4.3.1 CHA_2DS_2-VASc score

Among all the risk scores mentioned in **Table 1.13**, only the CHA_2DS_2-VASc score will be discussed in more detail as it is the most widely validated risk score and is recommended by most major AF clinical guidelines (**see next section**). The CHA_2DS_2-VASc score (**Table 1.14**) was developed in 2010 (146), almost a decade after the development of $CHADS_2$ score. Compared to the $CHADS_2$ score, it included three additional stroke risk factors: female sex, age 65 to 74 and vascular disease. In addition, the CHA_2DS_2-VASc score more clearly defined the 'congestive heart failure' factor to include those with moderate to severe LV dysfunction (ejection fraction<40%), recent decompensation of heart failure either with preserved or reduced ejection fraction. Furthermore, 2 points was awarded for those aged ≥75 years (146) as increasing age is a strong predictor of stroke (137).

The CHA_2DS_2-VASc score was first validated in the Euro Heart Survey cohort of 1084 non-valvular, non-anticoagulated AF patients (146). In this study, increasing rates of TE can be seen as the CHA_2DS_2-VASc score increases **(Table 1.15).** The same trend was also seen when it was validated in the SPORTIF III and IV cohort (147) but lower TE rates from the

anticoagulated cohort were evident compared to the non-anticoagulated cohort. Slight improvement in the ability to predict stroke with the CHA_2DS_2-VASc score compared to the $CHADS_2$ score were shown in both studies [C index 0.60 vs. 0.56 in Euro Heart Survey cohort (146) and C index 0.65 vs. 0.64 for in the SPORTIF III and IV cohort (147) for CHA_2DS_2-VASc and $CHADS_2$ respectively].

The CHA_2DS_2-VASc score was further validated in several other cohorts (118, 144, 148, 149) including in non-Western cohorts (150, 151). Compared to the $CHADS_2$ score, the CHA_2DS_2-VASc score was able to predict stroke events in two Chinese studies [C index: 0.53 (150) and 0.72, respectively] (151).

Table 1.13: Risk factors in stroke risk stratification schemes, updated from Lip et al 2015 (141)

	Risk factors							Other factors
Scores	Age, y	Female sex	Prior TE event	Hypertension	Heart failure	Diabetes mellitus	Vascular disease	
AFI, 1994(152)	65-75, >75		✓	✓		✓		
SPAF, 1999(153)	>75†	✓†	✓	✓		✓		
$CHADS_2$, 2001(154)	≥75		✓	✓	✓	✓		
Framingham, 2003 (155)	✓	✓	✓	✓		✓		
vanWalraven, 2003(156)			✓	✓		✓	✓	
Rietbrock, 2008 (157)	✓	✓	✓			✓		
CHA_2DS_2-VASc, 2010(146)	65-74, ≥75	✓	✓	✓	✓	✓	✓	
QStroke, 2013(158)	✓	✓	✓	✓	✓	✓	✓	Many other‡
ATRIA, 2013(159)	✓	✓	✓	✓	✓	✓	✓	Proteinuria, eGFR
$CHADS_2$, 2013, Japan(160)	≥65		✓	✓	✓	✓	✓	Cardiomyopathy
CHADS65, 2014 (161)	≥65		✓	✓	✓	✓		

eGFR: estimated glomerular filtration rate; TE: thromboembolism; vascular disease: prior myocardial infarction, aortic plaque or peripheral arterial disease
†age and female sex is combined as a single factor; ‡ ethnicity (self-assigned), smoking status, ratio of total serum cholesterol to high density lipoprotein, cholesterol concentrations, body mass index, family history of coronary heart disease in first degree relative under 60 years, Townsend deprivation score, treated hypertension, diabetes type I and II, renal disease, rheumatoid arthritis, valvular heart disease and atrial fibrillation

Table 1.14: CHA_2D_S2-VASc score components

CHA_2DS_2-VASc components	
CHF or LVEF ≤40%	1
Hypertension	1
Age ≥75 years	2
Diabetes	1
Stroke/TIA/ thromboembolism	2
Vascular Disease*	1
Age 65-74	1
Female **s**ex	1
Total score:	**9**
Low risk:	**0 male**
	1 female
High risk:	**≥ 1 male**
	≥2 female

LVEF: left ventricular ejection fraction*prior myocardial infarction, peripheral artery disease or aortic plaque

Table 1.15: CHA_2DS_2-VASc score and thromboembolic risk taken directly from Lip et al from the European Heart survey (146) and SPORTIF III and IV trial (147)

CHA_2DS_2-VASc score	**European Heart survey cohort (146)**		**SPORTIF III and IV cohort (147)**	
	TE rate at 1 year (95% CI)	**Adjusted 1 year TE rate, %#**	**TE rate at 1 year (95% CI)**	**Adjusted 1 year TE rate, %†**
0	0	0	0	0
1	0.6 (0.0-3.4)	0.7	0.46 (0.10-1.34)	1.3
2	1.6 (0.3-4.7)	1.9	0.78 (0.44-1.29)	2.2
3	3.9 (1.7-7.6)	4.7	1.16 (0.79-1.64)	3.2
4	1.9 (0.5-4.9)	2.3	1.43 (1.01-1.95)	4.0
5	3.2 (0.7-9.0)	3.9	2.42 (1.75-3.26)	6.7
6	3.6 (0.4-12.3)	4.5	3.54 (2.49-4.87)	9.8
7	8.0 (1.0-26.0)	10.1	3.44 (1.94-5.62)	9.6
8	11.1 (0.3-48.3)	14.2	2.41 (0.53-6.88)	6.7
9	100 (2.5-100)	100	5.47 (0.91-27.0)	15.2

TE: thromboembolic events # Theoretical TE rates without therapy: corrected for the % of patients receiving aspirin within each group, assuming that aspirin provides a 22% reduction in TE risk, based on Hart et al. (1) †Theoretical TE rates without therapy: assuming that warfarin provides a 64% reduction in TE risk, based on Hart et al. (1); CI indicates confidence interval.

All of the 'clinical factor' based risk scores have modest predictive ability (C-index approximately 0.6) for identifying 'high risk' groups thus addition of biomarkers (such as D-dimer, natriuretic peptides, von Willebrand factor) has been shown to improve the predictive ability of identifying the high-risk group (141, 162-164). However, despite addition of several biomarkers, only slight improvement in the predictive abilities of the scores can be seen changing the C-index to 0.65-0.70 (162-164). Measurement of biomarkers results in additional cost and loss of simplicity in risk score calculation making such scores less easy to use in everyday clinical practice (141).

1.4.4 Guidelines and recommendations for stroke risk stratification and antithrombotic therapy

Previously, the focus of the older risk scores was to divide patients into low risk, moderate risk and high risk of stroke. However, evidence has shown that identifying 'high risk' patients leads to under treatment with OAC in these groups (165, 166). Thus, the focus now has shifted towards identifying 'low risk' patients (CHA_2DS_2-VASc =0 in males or 1 in females). Many studies (167-169) have demonstrated that the CHA_2DS_2-VASc score is best at identifying the 'truly low risk' patients for whom the risk of stroke or systemic embolism is <1% per year. Due to this, the latest European Society of Cardiology (ESC)(3), the National Institute for Health and Care Excellence (NICE) (118), American (170), Australian (150) and Asia Pacific (171) guidelines **(Table 1.16)** have recommended using the CHA_2DS_2-VASc score to stratify stroke risk. The Canadian Cardiovascular Society (CCS) 2016 (172) recommends the modified CHADS65 score, although it acknowledges that other risk factors (also present in CHA_2DS_2-VASc score) such as age >65, prior myocardial infarction, aortic plaque and peripheral arterial disease.

All of the latest AF guidelines recommend OAC, with either a NOAC or well-controlled VKA (TTR ≥70%), for all AF patients who are not deemed 'low risk', with preference for a NOAC in most guidelines (1, 28-30). The recommendation for no antithrombotic therapy for low risk

patients and use of OAC in high-risk patients (those with ≥2 stroke risk factors) is consistent in all guidelines (except in the Australian guideline (150), where the recommendation is no antithrombotic or aspirin in the low risk group). However, AF guidelines (3, 150, 170, 173) have conflicting recommendations for patients in the intermediate risk groups with a single stroke risk factor where some (3, 173) considered OAC based on patient preferences and others (150, 170) with the recommendation of 'No antithrombotic therapy or treatment with OAC or aspirin may be considered'.

Table 1.16: Guideline recommendations for stroke prevention in AF

	Risk score		Risk categories (scores)	Recommendations
APHRS 2017(171)	CHA_2DS_2-VASc	**Asia pacific**	CHA_2DS_2-VASc =0 or 1 in female	No antithrombotic therapy
			CHA_2DS_2-VASc=1 in male	NOAC preferred (D, R, A, E) or well controlled VKA
			CHA_2DS_2-VASc ≥2	NOAC preferred (D, R, A, E)
ESC 2016 (3)	CHA_2DS_2-VASc	**European**	CHA_2DS_2-VASc =0 or 1 in female	No antithrombotic therapy
			CHA_2DS_2-VASc = 1 in male and 2 in female	OAC should be considered depending on individual characteristics or patient preference
			CHA_2DS_2-VASc ≥2 in male ≥3 in female	NOAC (preferred) or well controlled VKA
CCS 2016 (172)	CHADS65	**Canada**	Age <65 without $CHADS_2$ risk factors, CAD/ coronary, aortic or peripheral vascular disease	No antithrombotic therapy
			Age <65, no $CHADS_2$ risk factor but have CAD/coronary, aortic or peripheral vascular disease	OAC- NOAC preferred over to VKA
			Age <65 and one of $CHADS_2$ risk factors -Heart failure -Hypertension -Diabetes Mellitus -Stroke/TIA/peripheral embolism	OAC- NOAC preferred over to VKA
			Age ≥65	OAC- NOAC preferred over to VKA

Table 1.16 continued

NICE 2014 (118)	CHA_2DS_2-VASc	**United Kingdom**	**Low risk** (0 male) (1 female)	No antithrombotic therapy
			High risk (1 male) (≥2 female)	Well controlled VKA or NOAC
2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation (170)	CHA_2DS_2-VASc	**America**	CHA_2DS_2-VASc =0	No antithrombotic therapy
			CHA_2DS_2-VASc score =1	No antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered
			With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2	VKA, D, R, A
			CHA_2DS_2-VASc score ≥2 and end stage CKD (CrCL<15ml/min) or on haemodialysis	VKA
			CHA_2DS_2-VASc score ≥2 moderate to severe CKD	Reduced doses of direct thrombin or factor Xa inhibitors may be considered
CCS 2014 (161)	CHADS65	**Canada**	Age <65 without $CHADS_2$ risk factors, CAD/ coronary, aortic or peripheral vascular disease	No antithrombotic therapy
			Age <65, no $CHADS_2$ risk factor but have CAD/coronary, aortic or peripheral vascular disease	ASA

Table 1.16 continued

			Age <65 and one of $CHADS_2$ risk factors -Heart failure -Hypertension -Diabetes Mellitus -Stroke/TIA/peripheral embolism	OAC- NOAC preferred over to VKA
			Age ≥65	OAC- NOAC preferred over to VKA
Atrial Fibrillation Information for the Health Practitioner (2014)(150)	CHA_2DS_2-VASc	**Australia**	Age <65 without $CHADS_2$ risk factors, CAD/ coronary, aortic or peripheral vascular disease	No antithrombotic therapy or aspirin only
			CHA_2DS_2-VASc=1 1 clinically relevant non-major risk factor	Evidence of treatment is limited but options include: -No antithrombotic treatment, aspirin 75-300mg daily or OAC. Aspirin and OAC is unlikely to have a net clinical benefit unless HAS-BLED score is low
			CHA_2DS_2-VASc ≥2 1 'major' risk factor or ≥ 2 clinically relevant non-major risk factor	-New OAC is preferred to warfarin (target INR 2.5)
APHRS 2013 (174)	CHA_2DS_2-VASc	**Asia pacific**	CHA_2DS_2-VASc =0	No antithrombotic therapy
			CHA_2DS_2-VASc 1	NOAC (D/A) W/R (alternative)
			CHA_2DS_2-VASc ≥2	OAC (D/R/A/W)
ESC 2012 (173)	CHA_2DS_2-VASc	**European**	CHA_2DS_2-VASc =0	No antithrombotic therapy

Table 1.16 continued

			CHA_2DS_2-VASc= 1	Well controlled VKA or NOAC OAC should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.
			CHA_2DS_2-VASc ≥2	Well controlled VKA or NOAC When patient refuse any form of OAC, antiplatelet therapy with combination of ASA and clopidogrel or less effectively ASA
ESC 2010(173)	$CHADS_2$ score	**European**	**Low risk** -No risk factor (<65 with lone AF)	ASA or no antithrombotic
			Intermediate risk 1 '**clinically relevant non-major'** -Heart failure (moderate to severe LV systolic dysfunction, LVEF <40%) -Hypertension and/or diabetes mellitus -Female sex and/or age 65-74 years -Vascular disease	Adjusted dose VKA (target INR 2.5) OR ASA 75-325 mg daily
			High risk ($CHADS_2$≥2) OR 1 'major' or ≥2 'clinically relevant non-major'	VKA with target INR 2.5
			Major risk factor -Previous stroke, TIA, systemic embolism -Age ≥75	

Table 1.16 continued

NICE 2006 (175)	NICE	**United Kingdom**	**Low risk** Age <65 with no moderate or high-risk factors	ASA 75-300 mg daily
			Moderate risk -Age ≥65 with no high-risk factors -Age <75 with hypertension, diabetes, vascular disease	Consider anticoagulation or ASA 75-300mg daily
			High risk -Previous thromboembolic event -Age ≥75 with hypertension, diabetes, vascular disease -Clinical evidence of valve disease, heart failure or impaired LV function	VKA with target INR 2.5
ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation(58)		**America**	**No risk factors**	ASA 81 to 325 mg daily
			One moderate-risk factor -Age ≥75 -hypertension -heart failure (EF ≥35%) -Diabetes mellitus	ASA 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
			Any high-risk factor or more than 1 moderate-risk factor	VKA (target INR 2.5)
			High risk factors Previous stroke. TIA, embolism Prosthetic heart valves	

AF: atrial fibrillation; ASA: Aspirin; A: apixaban; D: dabigatran; E: edoxaban; R: rivaroxaban; CAD: coronary artery disease; CHADS score: 1 point each for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and 2 points for stroke/TIA; CHA_2DS_2-VASc score: 1 point each congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age 65-74, diabetes mellitus, vascular disease and 2 points each for age>75 years and prior stroke/TIA; CrCl: creatinine clearance; EF: ejection fraction; INR: international normalised ratio; HAS-BLED: 1 point each for uncontrolled hypertension, abnormal renal or liver function, stroke, prior bleeding labile INR, age >65, interacting drugs and alcohol excess; LV: left ventricular; NOAC: non-vitamin K antagonist; TIA: transient ischemic attack; TTR: time in therapeutic range; VKA: vitamin K antagonist

1.4.5 Assessing bleeding risk in atrial fibrillation

This section will summarise bleeding risk and the various bleeding risk scores developed for AF. The review has been published in the American Journal of Cardiology (176).

Assessing bleeding risk is also important before prescribing OAC therapy to AF patients. Over the last decade, several risk scores have been proposed to predict bleeding events in AF patients on anticoagulant therapy. These scores have been tested and validated worldwide in many cohorts of AF (177-185) to support physicians in assessing bleeding risks (186). Recently, the ESC Guidelines on the management of AF 2016 has summarised bleeding risks (into modifiable and non-modifiable) and encouraged prompt attention to common modifiable bleeding risk. This includes hypertension (especially when systolic blood pressure is >160 mmHg), labile INR or TTR <60% (in patients on VKA), medications predisposing to bleeding such as antiplatelet and non-steroidal anti-inflammatory drugs and lastly excessive alcohol consumption (≥8 drinks/week) (3, 141).

1.4.5.1 Risk factors of bleeding

Many risk factors of bleeding are included in the various bleeding scores shown in **Table 1.17.** The number of risk factors included in the bleeding risk scores ranges from three (177) to 12 (181). All bleeding scores (177-182, 187) include common clinical factors that influence the risk of bleeding for example age, utilising different age ranges and cut-offs (ranging from above 50 years old to above 85 years old) to indicate greater risk of bleeding; three scores include age ≥75 (178, 179, 181). After age, the most common bleeding risk factors included in the scores are as follows: (i) previous/remote bleeding (reported in 7 scores) (177-182, 187), (ii) renal disease (included in 5 scores) (178-181, 187), and (iii) anaemia (in 5 scores) (178, 179, 181, 182, 187), hypertension (179-181), stroke (180, 181, 187), combined antiplatelet therapy (178, 180, 182) and alcohol excess (180-182) (all included in 3 scores). Two scores included diabetes (182, 187) and liver disease (180, 181) and one score included malignancy (181), reduced platelet count (181) and female sex (182).

Table 1.17: Risk factors for bleeding included in each bleeding risk score

Risk factor	ABC [177]	ORBIT[178]	ATRIA [179]	HAS-BLED [180]	HEMORR$_2$HAGES[181]	Shireman [182]	OBRI [187]	Total
Age≥75		✓	✓		✓			3
Age≥70						✓		1
Age≥65				✓			✓	2
Age≥50	✓							1
Biomarkers	✓							1
Previous/remote bleed	✓	✓	✓	✓	✓	✓	✓	7
Recent bleed						✓		1
Anaemia		✓	✓		✓	✓	✓	5
Renal disease		✓	✓	✓	✓		✓	5
Liver disease				✓	✓			2
Hypertension			✓	✓	✓			3
Myocardial infarction							✓	1
Diabetes						✓	✓	2
Malignancy					✓			1
Stroke				✓	✓		✓	3
Combined antiplatelet therapy		✓		✓		✓		3
Labile INR				✓				1
Alcohol excess				✓	✓	✓		3
Excessive fall risk					✓			1
Genetic factors					✓			1
Reduced platelet count					✓			1
Female sex						✓		1
Total risk factors	**3**	**5**	**5**	**9**	**12**	**8**	**7**	

ICU/CCU: intensive coronary care unit/ coronary care unit; INR: international normalised ratio; PE: pulmonary embolism

Two bleeding risk scores, HEMORR$_2$HAGES (181) and the ABC bleeding score, (177) included factors that are not routinely available in daily clinical practice. HEMORR$_2$HAGES included genetic testing, although this was not available in their cohort, and the ABC score included 3 biomarkers, GDF-15, cTnT-hs and haemoglobin.

1.4.5.2 Derivation and validation studies for the bleeding risk scores

Seven bleeding (177-182, 187) risk scores have been developed and validated between 1989 to 2016. Six were developed in AF patients (177-182), and one in a mixed disease cohort of patients (valvular heart surgery, mitral valve disease, AF, stroke, TIA, pulmonary embolism (PE), deep vein thrombosis (DVT), and other thromboembolism) (187).

The mean/median age of study population in the derivation cohort ranged from 61(187) to 80.2 years(181) **(Table 1.18).** Almost half of the population in the derivation studies were female and only three studies (178, 179, 187) reported ethnicity, which was predominantly White. Five out of six (177-180, 182) studies from the AF cohort reported hypertension as the common co-morbid disease present in their population whereas one study from the mixed cohort (187) reported kidney disease to be more prevalent in their patient population.

Table 1.18: Baseline patient characteristics of the derivation cohorts for each bleeding risk score

Patients, %	ABC	ORBIT	ATRIA	HAS-BLED	HEMORR$_2$HAGES[†]	Shireman	OBRI
Number of patients	14,537	7411	6123	3456	1604	19,875	556
Mean age (SD)/median (IQR)	70 (19-97)	75(68-82)	-	66.8(12.8)	80.2	88% ≥70 years	61 (14)
Sex (female)	36	42.4	41.8	39.3	57	52.5	53
White ethnicity	-	89.6	86.6	-	-	-	93
History/ diagnosis of cancer	-	23.9	15.2	-	4.8	2.5	-
Anaemia/abnormal Hb/Hct	-	36.6	12.4	-	8.5	7.5	-
Hypertension	87	84.9	62.0	65.6	0.4	72	-
Diabetes	25	30.6	20.6	18	-	29.6	8
CHF	31	34.7	-	29.5	-	59.8	-
MI	13	15.8	0.4	34.6[#]	-	68.5[#]	4
Prior stroke/TIA	19	9.5	12.6	10.4	37.2	32.1	12
GI bleed	-	8.0	7.1	1.8[‡]	-	11.9	10
eGFR <60ml/min	-	32.1	2.9[α]	5.3[§]	-	0.6[¥]	18
Antiplatelet	-	37.9	1.0	-	-	22.3	-
Warfarin	-	93.5	-	-	42.3	28.7	-
NOACs	-	6.5	-	-	-	-	-

CAD: coronary artery disease; CHF: congestive heart failure; GI: gastrointestinal; hb: haemoglobin; hct: haematocrit; MI: myocardial infarction; NOACs: newer oral anticoagulant;
† warfarin users only; [‡] major bleed; [#] CAD; [α]<30ml/min; [§] renal failure; ¥ hepatic/renal failure; (-) not reported

Table 1.19 presents the characteristics of derivation and validation studies of bleeding risk scores for AF. A prospective study design was used in three (177, 178, 180) out of six scores for AF populations. Two (179, 182) studies used a retrospective analysis and one study (181) derived their score from the previous bleeding score available in AF, while one retrospective study design was used in mixed population (187).

Most had follow-up for at least 1 year except by the first score developed by Shiremen et al (182) which followed their patients for the first 90 days following hospital discharge following AF diagnosis. All studies derived their risk score using bleeding risk factors from large cohorts of patients ranging from 3456 (180) to almost 20,000 (182) patients, apart from one study, Landefield et al which only included 556 patients (187).

All bleeding risk scores stratified patients into three categories of bleeding risk (low, intermediate and high) except for the HAS-BLED score which initially categorised bleeding risk as high (score ≥3) and low-moderate risk (0-2) (141). These bleeding risk scores showed major bleeding rates ranging from 0.6%-3% in the low risk group and 4.9%-30% in the high-risk group in the validation cohorts **(Table 1.20).**

Table 1.19: Characteristics of the Derivation and Validation cohorts for each of the bleeding risk scores and composition of each score

Author, year, country	Derivation cohort a. Study design b. Sample size c. Length of follow up d. Indication of anticoagulation	Validation cohort a. Study design b. Sample size c. Length of follow up d. Indication of anticoagulation	Major Bleed definition
ABC (177) 2016 Sweden	a. Prospective b. 14, 537 c. 1.7 years (median) d. AF	a. Prospective b. 8468 c. 1.9 years (median) d. AF	ISTH criteria: clinically overt bleeding with at least one of (i) decrease haemoglobin concentration 2 g/L or more; (ii) transfusion of 2 or more units of packed RBC; (3) that was fatal or occurred in critical area or organ (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal)
ORBIT (178) 2015 USA	a. Prospective b. 7411 c. 2 years d. AF	a. Prospective b. 14264 c. Median 1.9 year d. AF	(i) fatal bleeding and/or (ii) symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or (iii) bleeding causing haemoglobin level to fall of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.
ATRIA (179) 2011 USA	a. Retrospective b. 6123 c. 6 years d. AF	a. Retrospective b. 3063 c. 6 years d. AF	Fatal, requiring transfusion of 2 U packed blood cells, or haemorrhage into a critical anatomic site (e.g., intracranial, retroperitoneal)

Author, year, country	Derivation cohort	Validation cohort	Major Bleed definition
HAS-BLED (180) 2010 UK	a. Prospective b. 3456 c. 1 year a. AF	a. Prospective b. 3071 c. 1 year d. AF	Any bleeding requiring hospitalization and/or causing a decrease in haemoglobin level of >2 g/L and/or requiring blood transfusion that was not a haemorrhagic stroke
HEMORR$_2$HAGES (181) 2006 USA	a. Score derived from 3 previously published bleeding scheme	a. Retrospective b. 3791 c. 36 months d. AF	Any hospitalisation for haemorrhage determined by Medicare claims
Shireman et al (182) 2006 USA	a. Retrospective b. 19,875 c. 3 months d. AF	a. Retrospective b. 6,470 c. 3 months d. AF	Hospital admission for either a GI haemorrhage or intracranial haemorrhage according to the DRG and ICD-9 CM codes
OBRI (187) 1989 USA	a. Retrospective b. 556 c. 48 months d. Valvular heart surgery, mitral valve disease, AF, stroke, TIA, PE, DVT, other thromboembolism	a. Prospective b. 264 c. 48 months d. VTE, prosthetic heart valve, others	Overt bleeding that led to the loss of at least 2.0 units in 7 days or less, or was otherwise life-threatening

AF: atrial fibrillation; DRG and ICD-9 CM codes: Diagnosis Related Group and International Statistical Classification of Disease and Related Health Problems; GI: gastrointestinal; ISTH: International Society on Thrombosis and Haemostasis; PE: pulmonary embolism; RBC: red blood cell; TIA: transient ischemic attack; U: units; VTE: venous thromboembolism

Table 1.20: Risk factors, risk categories and bleeding events in the validation cohorts

	Risk factors and points awarded		Risk categories	Bleeding events in validation cohort (per 100 patient years)
ABC	**A**ge			
	Biomarkers		Low: <1%	0.62
	GDF-15		Medium: 1-2%	1.67
	cTnT-hs		High: >3%	4.87
	Haemoglobin			
	Clinical history (previous bleeding)			
ORBIT	**O**lder age ≥75 years	**1**	Low : 0-2	2.4[a]
	Reduced haemoglobin/ hct/anaemia	**2**	Medium : 3	4.7
	Bleeding history	**2**	High : ≥4	8.1
	Insufficient kidney function	**1**		
	Treatment with antiplatelet	**1**		
	Total	**7**		
ATRIA	**A**naemia	**3**	Low : 0-3	0.83
	Renal disease	**3**	Intermediate : 4	2.41
	Age ≥75 years	**2**	High : 5-10	5.32
	Prior bleeding	**1**		
	Hypertension	**1**		
	Total	**10**		

Table 1.20 continued

	Risk factors and points awarded		Risk categories	Bleeding events in validation cohort (per 100 patient years)
HAS-BLED	Elevated systolic **H**ypertension	**1**	Low : <3	0=1.13
	Abnormal renal and liver function (1 pt each)	**1/2**	High : ≥3	1=1.02
	Stroke	**1**		2=1.88
	Bleeding	**1**		3=3.74
	Labile INR	**1**		4=8.70
	Elderly >65 years	**1**		5=12.50
	Drugs or alcohol (1 pt each)	**1/2**		6=0.0
	Total	**9**		7=-
				8=-
				9=-
				Any score=1.56
HEMORR$_2$HAGES	Hepatic or renal disease	**1**	Low : 0-1	1.9-2.5
	Ethanol abuse	**1**	Intermediate : 2-3	5.3-8.4
	Malignancy	**1**	High : ≥4	10.4-12.3
	Older age >75 years	**1**		
	Reduced platelet count or function	**1**		
	Re-bleeding risk	**2**		
	Hypertension (uncontrolled)	**1**		
	Anaemia	**1**		
	Genetic factors	**1**		
	Excessive fall risk	**1**		
	Stroke	**1**		
	Total	**12**		

Table 1.20 continued

	Risk factors and points awarded		Risk categories	Bleeding events in validation cohort (per 100 patient years)
Shireman et al	Age ≥70 years	**0.49**	Low: ≤1.07	0.9% Within 90 days
	Female	**0.31**	Moderate : >1.07 but <2.19	2.0% within 90 days
	Remote bleeding	**0.58**	High : ≥2.19	5.4% within 90 days
	Recent bleeding	**0.62**		
	Alcohol/drug abuse	**0.71**		
	Diabetes	**0.27**		
	Anaemia	**0.86**		
	Antiplatelet	**0.32**		
	Total	**4.16**		
OBRI	Age ≥65 years	**1**	Low : 0	3% at 12 month
	History of stroke	**1**	Intermediate: 1-2	8% at 12 months
	History of GI bleed	**1**	High : 3-4	30% at 12 months
	Recent MI, anaemia, DM, creatinine>1.5mg/dl	**1**		
	Total	**4**		

cTnT-hs: Troponin T; DM: diabetes mellitus; GDF-15: growth differentiation factor-15; GI: gastrointestinal; hct: haematocrit; INR: international normalised ration; MI: myocardial infarction; PE: pulmonary embolism; P/Y: person years; pt: point

[a] bleeding event in original derivation cohort; [b] clinically important bleeding: sum of major bleed and clinically relevant non-major; (-) not available

The earliest bleeding score developed by Landefeld et al (187) in 1989 derived five predictive factors of major bleeding in a mixed population. One of the original risk factors was AF but this was later removed when the score was validated in 1989, as its association with major bleeding in the derivation cohort was no longer significant in the validation cohort. Diabetes mellitus was substituted instead of AF as a new predictor of major bleeding.

1.4.5.3 Performances of bleeding risk scores

The ability of the bleeding risk scores to predict bleeding risk has been validated in both similar cohort where the score was derived (3 studies) (179, 180, 182) and in independent validation cohort (4 studies) (177, 178, 181, 188). In the validation and comparison study by Hijazi et al (177), the ABC score statistically outperformed the HAS-BLED and ORBIT scores in predicting major bleeding in both the derivation cohort [0·68 (95% CI 0·66–0·70) vs. 0·61 (0·59–0·63) vs. 0·65 (0·62–0·67) respectively; ABC-bleeding vs. HAS-BLED p<0·0001 and ABC-bleeding vs. ORBIT p=0·0008] and the external validation cohort [0·71 (95% CI 0·68–0·73) vs. 0·62 (0·59–0·64) for HAS-BLED vs. 0·68 (0·65–0·70) for ORBIT; ABC-bleeding vs. HAS-BLED p<0·0001 and ABC-bleeding vs. ORBIT p=0·0016](177). Although the ABC score performed better than the HAS-BLED and ORBIT scores in this report, the complexity of the algorithm and testing for biomarkers which are not routinely performed in daily clinical practice, may make it difficult and costlier, for physicians to apply routinely.

One recent meta-analysis (189) compared the diagnostic accuracy between HAS-BLED and HEMORR$_2$HAGES, ATRIA, CHADS$_2$ or CHA$_2$DS$_2$-VASc scores in anticoagulated patients with AF. The findings revealed that the HAS-BLED score performed better than the HEMORR$_2$HAGES and ATRIA bleeding scores, as well as being superior to CHADS$_2$ or CHA$_2$DS$_2$-VASc in predicting bleeding. Despite having better performance when compared to HEMORR$_2$HAGES, ATRIA and ORBIT, an additional advantage of the HAS-BLED score over the other five bleeding scores is the inclusion of quality of anticoagulation control (the 'L'

acronym for labile INR or poor TTR<65%). TTR reflects anticoagulation control in patients taking a VKA; a target TTR of ≥70% is optimal for efficacy and safety (173).

In a post-hoc analysis evaluating the performance of HAS-BLED, ATRIA and ORBIT bleeding risk scores in the AMADEUS trial (190), TTR was strongly correlated with clinically relevant bleeding events in patients using the ATRIA and ORBIT score, thus demonstrating that incorporating TTR in bleeding scores improves their ability to predict future bleeding events. Another comparison of four bleeding risk scores (HAS-BLED, ORBIT, ATRIA and HEMORR$_2$HAGES) in the SPORTIF cohort (191) also investigated whether the addition of 'labile INR' (TTR<65%) improved bleeding risk prediction (with the exception of the HAS-BLED score which already contains labile INR). Addition of 'labile INR' to ORBIT, ATRIA and HEMORR$_2$HAGES bleeding risk scores, significantly improved the predictive performance of each score for major bleeding [integrated discriminatory improvement (IDI) 0.0023, p=0.0092 vs. IDI 0.0020, p=0.00014 vs. IDI 0.0015, p=0.0016 respectively](191).

Apostolakis et al (192) compared the predictive performance of HAS-BLED with HEMORR$_2$HAGES and ATRIA in the AMADEUS trial and demonstrated that the HAS-BLED score performed better than HEMORR$_2$HAGES and ATRIA score in predicting any clinically relevant bleeding, with only the HAS-BLED score demonstrating significant improvement for intracranial haemorrhage(192). In another ancillary analysis of the same trial (193), the HAS-BLED score performed better than the ORBIT score in predicting any clinically relevant bleed in a non-oral anticoagulant (idraparinux)(193).

More recently the predictive ability of the HAS-BLED score was also investigated in patients receiving NOAC therapy, with rivaroxaban, in a small retrospective case-control study(194); the HAS-BLED score demonstrated some diagnostic ability to predict major bleeding events although this was not statistically significant (C statistics=0.68; p=0.07) (194). Analyses have demonstrated that the HAS-BLED score not only performs well in predicting bleeding events

in VKA treated patients with AF, it can also be used to predict bleeding events in non-VKA treated patients which is very useful as more AF patients are being treated with NOACs.

The next section will summarise factors affecting anticoagulation control in stroke prevention in AF.

1.5 Anticoagulation control in stroke prevention

Studies (119, 122, 195) have shown that good anticoagulation control is associated with reduction of thromboembolic complications while the risk of intracranial haemorrhage is significantly higher in patients with high INR values (INR>4.0) (196). Therefore, it is important to identify factors that might affect anticoagulation control in patients taking oral anticoagulants.

1.5.1 Factors affecting anticoagulation control

These factors can be divided to demographic and clinical factors **(Table 1.21)** and non-clinical factors **(Table 1.22).**

Table 1.21: Demographic and clinical factors affecting anticoagulation control

Demographic factors	**Lab parameters**
Sex (female) (197-203)	Albumin, g/dL† (204)
Age † (198-200, 204-207)	Neutrophil, %† (204)
Younger age (<50 years) (198-200, 204-207)	Red blood cell count, $x10^6$/mcL† (204)
Tobacco use (within 2 years) (199, 205, 208)	Red blood cell distribution width, %† (204)
Ethnicity (non-white)(195, 198, 209, 210)	
Alcohol (204)	
Clinical factors	
Warfarin naïve (195)	Non-standardised target INR (201) (211)
Medical history* (200, 201) (131, 204, 212)	Changes in gut flora (131)
Pneumonia (213)	Numerous drug interaction (e.g., amiodarone, antibiotics, pain medications, aspirin) (131, 199, 204, 213)
Bleeding history (213)	Genetics (214-217)
Hospital stays ≥7days (213)	Uncontrolled systolic blood pressure, mm Hg†
No enhanced anticoagulation care¥ (213)	Body mass index kg/m^2 † (204)
Paroxysmal AF (195)	

†continuous variable; * hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke (ischemic or haemorrhagic), pulmonary disease, and hepatic or renal disease, venous thromboembolism, thrombocytopenia, anaemia; ¥lack of participation (no access or plan) in a dedicated anticoagulation management when VKA is initiated

Table 1.22: Non-clinical factors affecting anticoagulation control

Patient factors	Physician factor	Health care system factors
Knowledge and behavioural factors (218-220)	Bleeding risk(221)	Hospital based vs. community-based vs. clinical trial (206, 222, 223)
Adherence (224-227)	Lower targeted INR range (1.6-2.5) (221)	Models of care (228-232)
Socioeconomic status (200, 233)	Different treatment priorities (221)	
Dietary and herb interaction (234, 235)		
Fasting (236, 237)		

1.5.1.1 Demographic and clinical factors affecting anticoagulation control

1.5.1.1.1 Female sex

Differences in the quality of anticoagulation therapy between males and females have been observed in some studies while other studies have not confirmed this. Seven studies (197-203) investigating predictors of TTR have demonstrated that women have poorer anticoagulation control compared to men although the precise mechanism remains unclear and should be investigated further (199). Poor anticoagulation control can be translated to poorer clinical outcomes among women. The SPORTIF trial comparing warfarin vs. ximelagatran (238) has shown that compared to males, females with AF were older, had more stroke risk factors and had higher risk of stroke and thromboembolic events [2.08%/year, (95% CI 1.60–2.56%/year vs. 1.44%/year, 95% CI 1.18–1.71%/year in men; p=0.016)] (238). A meta-analysis (139) has also shown that female patients have higher residual risk of stroke and systemic embolism despite the use of warfarin [OR 1.3, (95% CI 1.11 to 1.47); p=0.001] as compared to the male patients (239). It can be speculated that maybe females have more interruptions (238) (probably due to menopausal transitions), have more stroke risk factors

(238) and have the fear of the bleeding complications while on anticoagulation therapy leading to poorer anticoagulation control compared to males.

1.5.1.1.2 Younger age (<50-60 years)

Some studies (198-200, 204-207) have shown that younger patients, in particular those <50 years old (206, 207, 240), have poorer anticoagulation control compared to older patients, although the precise mechanism remains uncertain. It could be speculated that perhaps younger patients have more active lifestyle, are less motivated to manage their AF due to competing demands on their time (job, less leisure time) (199, 200) and have medication adherence issues which might impact their quality of anticoagulation control.

1.5.1.1.3 Older age

Although studies have shown that younger patients have poorer anticoagulation control with VKA therapy, the quality of anticoagulation control among the very elderly (aged ≥80 years) is also perceived to be low (241-244). This perception leads to a lower prescription rate among the very elderly patients (241, 245, 246). The ageing population with AF is increasing; they too require effective anticoagulation therapy. However, anticoagulation in the elderly is not a simple matter due to the increased risk of bleeding associated both with age per se and the greater risk of co-morbidities and polypharmacy (241, 247, 248). Also, VKA therapy may be more difficult among the elderly due to the frequency of INR monitoring required (which may be more problematic if it requires travel to an anticoagulant clinic), dietary intake and drug interactions (249).

Among the studies in the elderly anticoagulated population, few report anticoagulation control with the exception of the WASPO (250) and BAFTA (251) trials with mean TTR 67 and 69 respectively. Good anticoagulation control (mean TTR 71% in both studies) was seen in another two Italian studies of their elderly cohort of ≥80 (247) and ≥75 (252) years. However, a much lower TTR (mean age 77, mean TTR 58%) can be seen in another study (241) of

elderly patients in the inception warfarin period. None of these studies (241, 247, 252) investigated the association of age with TTR but two studies (241, 247) showed that increasing age (age ≥80 years for both studies) was significantly associated with bleeding events [adjusted OR 2.0 (1.1-4.0); p=0.05 (247) and unadjusted incidence rate 2.75 (1.27-5.95) (241)].

1.5.1.1.4 Medical history

Numerous studies have shown that comorbid diseases influence patients' quality of anticoagulation with warfarin therapy. Poorer anticoagulation control is associated with heart failure (197-202, 253-255), diabetes (197-200, 202, 205, 256), kidney disease (198, 199, 201, 213, 257), liver disease (198, 199, 254, 257), lung disease (199, 201, 204, 205), coronary artery disease (199, 201), peripheral vascular disease (199, 201), stroke (199, 204), pneumonia (205, 213), cancer (201, 258), major depression (201, 259), venous thromboembolism (204, 258), previous bleeding (213), thrombocytopenia (204), bipolar disorder (259), and psychosis (259). The exact mechanism of this relationship is unclear but perhaps this reflects greater illness burden and complexity, more medications leading to increased risk of non-adherence, polypharmacy and drug interactions **(will be described in more detail in section 1.5.1.1.9 page 86)**, poorer quality of life which all might lead to poorer anticoagulation control (200).

1.5.1.1.5 Chronic kidney disease (CKD)

Among all the other comorbid disease affecting anticoagulation control, the impact of CKD towards anticoagulation control will be discussed in more detail. This is because studies have shown an increased risk of bleeding among AF patients with CKD (especially those with severe renal impairment and on dialysis) while using OACs (260-262). Nonetheless, studies (263-266) have also shown that good anticoagulation control while on VKA therapy among CKD patients is associated with reduced risk of stroke [HR 0.60 (95%CI 0.39-0.93)], major

bleeding [HR 0.58 (95%CI 0.42-0.80)] and mortality [HR 0.61 (95% CI 0.46-0.82). (264) To date, eight studies (263-270) have presented information on anticoagulation control among AF patients with CKD. All studies showed a decrease in TTR as the kidney function worsened. Indeed, the presence of CKD was negatively associated with achieving good TTR [OR 0.75 (0.67-0.92)] in the SPORTIF III and V trial cohort (264). Similarly, CKD was also as independent predictor of TTR in the Current Perspective of Anticoagulation in Clinical Practice in the Primary Care Setting (PAULA) study [unstandardized coefficient -3.4 (95% CI -5.51 to -1.29); p=0.002] (270).

The exact mechanism of poor TTR among CKD patients in unknown but studies have shown (270-272) patients with CKD are usually at risk for under- or over- anticoagulation; among the latter this is a result of reduced clearance of S-warfarin in CKD patients (273). Indeed, patients with end stage renal disease (ESRD) have a 50% increase in plasma warfarin S/R ratio compared to patients with normal renal function (274). This could perhaps reflect a decrease in CYP2C9 activity in patients with renal failure, thus necessitating a lower dose in these patients (274). Following that, Limdi et al (268, 275) showed that after accounting for clinical and genetic factors, patients with reduced kidney function were able to maintain therapeutic anticoagulation with lower warfarin dosage (average dose 3.9mg/day in severe group vs. 4.8mg/day in normal group; p=0.0002) (268, 275).

1.5.1.1.6 Treatment with interacting drug (e.g.: amiodarone)

Pharmacological rhythm control strategies in AF, particularly with amiodarone, are known to have some effect on INR readings. Amiodarone, a potent inhibitor of both the S-enantiomer and R-enantiomer of warfarin (276) is known to inhibit the metabolism of warfarin thus potentiating an enhanced anticoagulant effect of warfarin (277). In addition, amiodarone has a long half-life thus causing this potential drug interaction to occur for several weeks or months after cessation of amiodarone (277). This might lead to an increase in INR values in patients taking warfarin together with amiodarone thus translating into poorer TTR among these

patients. Apostolakis et al (199), in the original cohort of the SAMe-TT_2R_2 score, reported 14.3% of patients were prescribed Amiodarone (for rhythm control) and this was associated with low TTR (ß=-0.03 95%CI (-0.06 to 0.0); p=0.05) (199).

1.5.1.1.7 Smoking history

Smoking is not only a predictor of poor anticoagulation control in three studies (199, 205, 208); it also has also been shown to predict severe bleeding in patients treated with warfarin therapy [HR 1.32; (95%CI 1.04-1.67; p=0.02)] in the Loire Valley AF Project (278). Meanwhile, a meta-analysis of 13 studies (279) assessing the interaction between smoking and warfarin has shown that warfarin clearance might be enhanced by the effects of smoking, which in return leads to a reduction in the effects of warfarin. This meta-analysis also found that a significantly higher dose of warfarin was required in active smokers compared with non-smokers to achieve a therapeutic INR (279) which might explain the increased risk of bleeding among smokers. The exact relationship between smoking and anticoagulation control is unclear but it may reflect less interest in maintaining good health (among smokers) that may translate into poorer adherence to OACs, thus resulting in poor TTR.

1.5.1.1.8 Ethnicity

Studies have shown that ethnic minority groups (Blacks, Hispanics and Asians) have poorer anticoagulation control compared to Whites. Three studies (198, 209, 210) conducted in the United States and two trials (280, 281) comparing TTR among the Blacks and Whites have shown that mean TTR among Blacks was lower compared to Whites **(Table 1.23).** Similarly, in the SPORTIF III and IV trials (195), the proportion of patients from Black/African Americans was greater in the poor anticoagulation control group compared to moderate and good anticoagulation control group **(Table 1.23).**

These observations may be due to various reasons for example differences comorbid disease, socioeconomic status, poor understanding of therapy, adherence issue and genetic

background. Ethnic differences in anticoagulation control were evident in a cohort of 98,053 patients (210) receiving warfarin therapy for various indications (AF, VTE and other mixed conditions), with lower mean TTR among the Blacks compared to Whites. Blacks were younger and lived in areas of highest quartile of poverty, had higher illness burden including more comorbid disease, requiring more medications and hospitalisations to manage those conditions compared to White patients (210). After accounting for all these factors, which are mostly non-modifiable, Black patients still had a recorded TTR 2.3% lower than White patients (210) **(Table 1.23).**

In terms of pharmacogenetics, warfarin metabolism and dose requirements might differ between ethnic groups. Studies have shown that warfarin dosage requirements are higher in Blacks compared to Whites partly due to racial differences in genotype frequencies (216). Blacks have been found to have additional CYP2C9 alleles which are associated with reduced function of the CYP2C9 activity and thus might contribute to dose variability (216). In addition, issues like health literacy, adherence to medication might also contribute to the differences in quality of anticoagulation therapy among different ethnic groups (210).

Table 1.23: Major studies reporting anticoagulation control in different ethnic groups

	Patients	Study design	Follow up	Ethnicity	Mean TTR, %	Poor INR control (TTR≤60)	Moderate INR control (TTR 60-75)	Good INR control (TTR≥75)
SPORTIF III and IV trial, USA (195)	3587 AF	RCT	16.6 (6.3) months	White	-	87.3	93.7	96.1
				Asian	-	9.6	4.5	3
				Black/African American	-	2.5	1.6	0.8
IMPACT trial, North America, Europe, Australia (280, 281)	2718 but 229 with INR results	RCT	2 years	White	55	-	-	-
				Black	44	-	-	-
				Asian	68	-	-	-
				Non-Hispanic	54	-	-	-
				Hispanic	48	-	-	-
VARIA study, USA (198)	98,053 AF, VTE, others	Retrospective	2 years	White	62.3	-	-	-
				Black	55.8	-	-	-
TREAT-AF study, USA (209)	184, 161 AF	Retrospective	90 days	White	59 (18)	-	-	-
				Black	52 (20)	-	-	-
				Asian	59 (18)	-	-	-
ORBIT-AF, USA (210)	10, 132 AF	Prospective	2.1 years	White	68 (53-80)	-	-	-
				Black	59 (41-75)	-	-	-
				Hispanic	62 (46-78)	-	-	-

AF: atrial fibrillation; INR: International normalised ratio; RCT: randomised controlled trial; TTR: Time in therapeutic range; VTE: venous thromboembolism

1.5.1.1.9 Other clinical factors affecting anticoagulation control

As seen in **Table 1.21** there are other clinical factors that may affect anticoagulation control. Seven studies (199, 200, 204, 205, 208, 213, 254) have demonstrated that numerous drug interactions with warfarin such as amiodarone, aspirin, pain medications, and antibiotics might impact the quality of anticoagulation therapy. This can be explained by the fact that these medications are inhibitor (amiodarone, analgesics, antibiotics, ex macrolides, quinolones and azoles groups) or inducer of CYP2C9 (carbamezipine) enzyme that is involved in warfarin metabolism, thus concomitant use of these drugs might cause potentiation or inhibition of the warfarin effect (282). The concomitant use of these medications with warfarin should be avoided but if essential, they should be used with caution (dose adjustment of warfarin required) and with careful, regular monitoring of INR (277, 282).

Warfarin is mainly metabolised in the liver by the enzyme cytochrome-P450 2C9 (CYP2C9) and it exerts its anticoagulant effect by inhibiting the protein VKORC1. Anticoagulant effects of warfarin have been found to be influenced by the effect of three single nucleotide polymorphism (SNPs); two in the CYP2C9 gene (CYP2C9*2 and CYP2C9*3) and one in the VKORC1 gene. Patients with CYP2C9*2 (more commonly in Whites), CYP2C9*3 and VKORC1 variants will metabolise warfarin less efficiently thus require lower doses of warfarin (216). Although patients with CYP2C9*2, CYP2C9*3 and VKORC1 variants are at risk of over anticoagulation during the initiation phase, (214, 215) the impact on TTR among the maintenance phase remains debatable (217).

Combining common clinical and demographic predictors of INR control together, Apostolakis et al (199) developed a scoring system, known as the SAMe-TT_2R_2 score. In 2017, Lin et al (213) and Williams et al (204) published two novel scoring systems; the former with seven factors known as the PROSPER score (213), the latter (204) with 15 and the SAMe-TT_2R_2 score (199) with six predictors of anticoagulation control **(Table 1.24).**

All three scores (199, 204, 213) included concomitant medical history and potential drug interaction as predictors of anticoagulation control. Both SAMe-TT_2R_2 score (199) and Williams et al (204) included demographic factors of age, whereas SAMe-TT_2R_2 score included additional demographic factors such as tobacco use and ethnicity while Williams et al (204) included body mass index and alcohol. PROSPER score and Williams et al included more clinical factors where there might be an overlap between pneumonia and prescription of antibiotics in the PROSPER score (213) and the latter included more laboratory variables (204) as compared to the SAMe-TT_2R_2 score **(Table 1.24).**

In the SAMe-TT_2R_2 (199) and PROSPER (213) score, if patients had a score of >2, they are predicted to have poor TTR with the latter (213) being emphasized for the geriatric population. Whereas in the model by Williams et al (204), if patients have ≥4 and ≥7 poor TTR factors, their estimated TTR will be <60% and <50% respectively **(Table 1.24).** NOAC is the preferred anticoagulant of choice rather than VKAs if patients had high scores in all three scores (199, 204, 213). These scores were developed to identify patients at risk of having good/poor anticoagulation control with warfarin and thus can aid physicians to choose the appropriate anticoagulant therapy for stroke prevention in AF. Although the two new scores (204, 213) seem very comprehensive, they are very complex and are not ‘user friendly’ especially in a busy clinical setting.

Table 1.24: Scores to predict anticoagulation control

SAMe-TT_2R_2	Points	PROSPER	Points	Williams et al	
Sex (female)	1	Pneumonia	1	Age, y[¥]	
Age (<60 years)	1	Renal dysfunction[†]	2	Systolic BP, mmHg[¥]	
Medical history*	1	Oozing blood (bleeding history)	1	Body mass index, $kg/m^{2¥}$	
Treatment (interacting drugs, e.g., amiodarone)	1	Staying in hospital ≥7 days	1	Albumin, g/dL[¥]	
Tobacco use (within 2 years)	2	Pain medications	1	Neutrophil, %[¥]	
Race (non-white)	2	No enhanced anticoagulation care[‡]	4	Red blood cell count, x 10^6/mcl[¥]	
		Prescription for antibiotics	1	Red blood cell distribution width, %[¥]	
				Alcohol problem[£]	
				Anaemia[£]	
				Lung disease[£]	
				Stroke haemorrhagic[£]	
				Thrombocytopenia[£]	
				Venous thromboembolism[£]	
				Any antiarrhythmic[£]	
				Aspirin[£]	
Cut offs					
Scores 0-2	Good INR control[§]	Scores 0-2	Good INR control[§]	≥4 poor factors	TTR <60%
Scores >2	Poor INR control[§]	Scores >2	Poor INR control[§]	≥7 poor factors	TTR <50%

*Two or more of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease. [¥]continuous variable; [£]binary variables; [†]Having records of acute kidney injury, chronic kidney disease, or end stage kidney disease prior 180 days
[‡]lack of participation (no access or plan) in a dedicated anticoagulation management service when initiating a VKA; [§] on probability

1.5.1.2 Non-clinical factors

1.5.1.2.1 Patient factors

Studies have shown that patient's comprehension and acceptance of the complex regimen required with warfarin therapy might also affect the quality of VKA treatment (283). Evidences have shown that in the general AF population, patients have minimal knowledge about their medical condition (284-289), poor understanding of the benefits and risk of specific treatment in particular OAC therapy (285-291), and are usually not aware of factors that can influence the effectiveness and safety of the treatment (284-287). However, one recent survey conducted in eight European countries showed different results (292). Most of their patients (91-94%) have good knowledge of anticoagulation (in terms of indication and INR target range). Furthermore, patients with college or university grades had lower frequent deviations of their target INR range (2.8% vs. 5.1%, $p<0.05$) and had higher awareness (57% vs. 38.5%, $p<0.05$) of the anticoagulation related risk of bleeding compared to those without schooling respectively (292). However, this survey did not indicate the proportions of patients with different education level thus this might affect their results (probably they had higher proportions of patients with college or university grades).

Recently, the ESC guideline has recommended a tailored patient education in all phases of AF management (3). Patient education is important to ensure accurate information is delivered about AF and its treatment. Apart from that, obtaining feedback from patients regarding any concerns or barriers (for example food and drug interactions, the need to modify lifestyle habits and the risk of bleeding complications) that prevent them from taking warfarin (283) are also crucial. The concerns should be addressed so that any barriers to medication taking can be avoided and thus optimal outcome of anticoagulation therapy can be achieved. In the recent years, several patient information tools (for example phone apps or structured face to face

educational session) have been developed focusing on oral anticoagulation therapy (293, 294). Evidences have shown that these educational tool or intervention was effective at improving the quality of anticoagulation therapy (219, 293, 295, 296). The TREAT (219) educational intervention (an educational-behavioural intervention), was effective at improving the quality of anticoagulation therapy (TTR) among patients receiving it compared to usual care (TTR at 6 months 76.2% vs. 71.3%, p=0.035 respectively) (293). Two recent surveys conducted in Serbia (218) and Singapore (220) demonstrated that better knowledge, quality of life, adherence rate and higher satisfaction to VKA therapy resulted in good TTR at follow up; however these studies were not designed to measure the impact of an educational intervention on TTR.

Despite overwhelming evidence showing the effectiveness of oral anticoagulation in stroke prevention in AF, the demonstrable benefits of the OACs, in terms of stroke prevention, will not be translated if patients do not adhere to, or fail to persist with their medications (226). A recent extensive review of 30 studies (226) assessing adherence and persistence towards OACs reported that within the five NOAC trials (132-135, 297), the discontinuation rate for patients who were on warfarin was similar to each of the NOACs ranging between 13-34%. (132-135, 297) In the same review, 13 'real-world' [9 NOACs (298-306) and 4 warfarin (227, 307-309)] studies were also included (226). The adherence rate to warfarin was lower (40-56%) in three of the warfarin studies (227, 307, 308), compared to 63-99% adherence in the nine NOAC studies (298-306). Among all these studies, only two studies (227, 300) demonstrated the impact of non-adherence on treatment outcomes. Although retrospective and with a relatively short duration of follow up (median 0.67 years), Shore et al (300) demonstrated that even a 10% decrease in adherence to dabigatran therapy was associated with 13% increase in the combined outcome of all-cause mortality and stroke. In a larger number of population (N=64, 661), with a slightly longer follow up (median 1.1 year), Yao et al (227) showed an increased risk of stroke in patients with CHA_2DS_2-VASc score of ≥2 not taking OACs for ≥6 months.

Other patient-related factors that might influence anticoagulation control are socioeconomic status. Rose et al (200) has demonstrated that patients living in the poorest area (based on the zip code of residence) was predicted to have poor TTR control compared to the wealthiest during the first 6 months of warfarin therapy. This relationship persisted even after 6 months being on warfarin therapy (200). In another population based study of 166,742 patients, lower socioeconomic status (based on the median neighbourhood income quantiles) was also a risk factor for bleeding and bleeding related to mortality among older individuals taking warfarin therapy (233).

Common concerns among patients receiving VKA relate to food and drug interactions. Patients receiving warfarin are advised to reduce intake of food that is rich in vitamin K, for example, green leafy vegetables (spinach, broccoli etc.) as this might impact INR stability. Vitamin K-rich food might counteract the anticoagulant effects of warfarin and dose adjustment is required in patients presenting with low or high INR values after drastic changes in dietary intake of vitamin K. A recent systematic review (234) (two intervention trials and nine observational studies) summarising current evidence on the interaction between dietary vitamin K intake and warfarin concluded that the evidence available does not support the restriction of dietary intake of vitamin K but encourages patients to have a stable dietary habit and avoidance of dramatic changes in dietary vitamin K (234).

Due to the narrow therapeutic index of warfarin, concomitant use of warfarin and herbal remedies results in a major safety concern (235). Warfarin accounted for 26% of cases of drug-herb interaction from clinical cases (310). A review on clinical evidences of herb and warfarin interaction has highlighted clinical effects, severity of interaction and quality of clinical evidences (235). They have identified thirty-eight selected herbs, four were evaluated with Level I evidence as ‘highly probable’ to interact with warfarin, three were ‘probable interaction’ with Level II evidence, ten were ‘possible’ (Level III evidence) and twenty-one were ‘doubtful

interaction' (Level IV evidence). The concomitant use of warfarin should be strongly avoided in 'highly probable' (Cranberry, Soya, St John's wort and Danshen) and 'probable herbs' (coenzyme Q10, Chinese Angelica, Ginger). Whereas for 'possible' (for example Ginko and Chamomile) and 'doubtful' (for example Fenugreek and Parsley) interaction, for safety reason, close monitoring of INR is recommended (235). For example, Cranberry juice commonly used for blood and digestive disorder has been found to be linked to a major bleeding and high INR (due to potentiation of warfarin effect) in a case report in the US involving a man who took warfarin after drinking 710 ml of cranberry juice (311). Despite the available case reports about warfarin and herb interaction, the intensity of the interaction might be overestimated. Future studies or trials are needed to ascertain the magnitude and the clinical impact of these interactions.

The impact of fasting on anticoagulant control is debatable. A prospective Singaporean (236) study investigated the effect of fasting among 32 patients taking warfarin pre-Ramadhan, during Ramadhan, and post Ramadhan. Although underpowered, a decrease in TTR was seen from 81.0% to 69.6% before Ramadhan to during Ramadhan, respectively. In contrast, another recent study (237) showed that TTR was better during the Ramadhan period compared to pre-Ramadhan period (TTR 82.1% vs. 70%; $p<0.001$). More studies with larger sample size are needed to ascertain the impact of fasting towards anticoagulation control among warfarinised patients.

1.5.1.2.2 Physician factors

Bleeding risk is the most commonly cited (221) reason for not initiating or delaying warfarin treatment. In some older patients, some physicians prefer to target a lower INR range (INR 1.6-2.5) to avoid bleeding complications as elderly (>65 years in HAS-BLED score) is a risk factor for bleeding complications.

The benefit of oral anticoagulation in an elderly population has been demonstrated in several studies. Focks et al (312) reported the rate of major bleeding and ischemic stroke of 2.8 and 2.3 per 100 patient years respectively, in his cohort of the very elderly (≥80years) AF patients. Based on number needed to treat (NNT: 91) and number needed to harm (NNH: 22) a total of four strokes/TIAs can be prevented based on every major bleed caused by VKA. Meanwhile, Friberg et al (313) has shown a positive net clinical benefit from treatment with warfarin (adjusted net clinical benefit >6%/y) in nearly all AF patients except those at lowest risk of stroke as the benefit of preventing a stroke far outweighs the smaller risk of bleeding even in patients with high HAS-BLED scores.

Bleeding risk should not be used as a reason to withhold anticoagulant treatment; instead anticoagulation treatment should be used with caution and strict control even in patients at high risk of bleeding complications (3, 314). Some physicians would prefer to avoid a major bleeding event than to prevent stroke, whereas patients are prepared to accept the risk of bleeding rather than to suffer from a stroke (221, 315). Currently there are five options for OAC therapy for stroke prevention in AF (VKAs, dabigatran, apixaban, edoxaban, rivaroxaban). The availability of NOACs allows physicians to choose the best NOAC that would fit into their patient's criteria. In the case of patients with high risk of bleeding (HAS-BLED>3), dabigatran 110 mg, apixaban 5mg or edoxaban 60 mg can be offered to patients (316).

1.5.1.2.3 Health care system factors

1.5.1.2.3.1 Hospital vs. community-based vs. clinical trial

To date, 16 studies have validated the SAMe-TT_2R_2 score in AF cohorts. These studies are described in detail in the next section **(section 1.6, page 101)**. In these studies **(Table 1.25 and Figure 1.6)**, seven (199, 317-322) used hospital anticoagulation clinics to monitor patient's INR, four (323-326) stated hospital monitoring without specifying whether it was performed by an anticoagulation clinic or not, three (199, 280, 327) were from clinical trial

settings and one from primary care (328) and cardiology outpatient clinic each. (329) Anticoagulation control was highest in patients monitored by hospital anticoagulation clinics, with TTRs ranging from 58% (319) to 78% (322). In the hospital setting (without information on anticoagulant clinic involvement), TTR ranged from 38.2% (325) to 58% (326). In the clinical trial settings, TTR was 53.6% (280) to 68.5%(327) and lastly, TTR was 69%(328) in primary care.

A 2006 meta-analysis of 67 studies (222) compared the effect of study setting on anticoagulation control in a mixed group of patients (on OAC for AF, valvular disease, VTE, cerebrovascular disease, peripheral vascular disease) and showed that anticoagulation control was significantly lower in the community setting compared to those from anticoagulation clinic and in RCTs [unadjusted mean TTR 56.7 (51.5-62.0) vs. 65.6 (63.7-67.7) vs. 66.4 (59.4-73.3), $p>0.0001$ respectively]. Similarly, another meta-analysis of eight studies from 14 participating centres in the United States reported that AF patients who are managed in the community setting had a lower mean TTR (51%) compared to those managed by the anticoagulant clinic i.e. TTR 63% (223). In contrast, in the Auricula registry of 18,391 patients in 67 different centres, found no significant difference in the mean TTR among hospital based centres versus community based centres (TTR 75.7% vs. 80.3% respectively) and their mean TTR in the entire population was 76.2%, higher than reported in clinical trials (206).

Table 1.25: Mean TTR% in studies validating the SAMe-TT_2R_2 score

	a. Study design b. Length of follow-up	Population	Method INR monitoring	Mean (SD)/ Median (IQR) TTR
Pivatto Junior, 2017, Brazil (317)	a. Retrospective b. 1 year	263	Anticoagulant clinic-hospital	62.5 (44.2-79.5)
Bernaitis, 2016, Singapore (326)	a. Retrospective b. -	1137	Hospital based	58.0 (34.3)
Chan, 2016, Hong Kong (325)	a. Retrospective b. 4.7 ± 3.6 years (mean)	1428	Hospital based	38.2 (24.4)
Gorzelak-Pabis, 2016, Poland (324)	a. Prospective b. -	104	Hospital based	51 (32)
Lip, 2016, USA (280)	a. Prospective b. 438 days on OAC	229	Trial setting	53.6 (23)
Lobos-Bejarano, 2016, Spain (328)	a. Retrospective b. >12 months	1524	Primary care	69 (17.7)
Proietti, 2016, Europe, Asia, Australasia(327)	a. Prospective b. 563 days (median)	3665	Clinical trial centre	68.5 (55.17-79.32)
Szymanski, 2016, Poland (323)	a. Retrospective b. N/A	211	Hospital	51.8 (25.0-71.2)
Abumuaileq, 2015, Spain (319)	a. Retrospective b. 10 months (mean)	911	Anticoagulant clinic-hospital	PINRR 58 (18)

Table 1.25 continued

	a. Study design b. Length of follow-up	Population	Method INR monitoring	Mean (SD)/ Median (IQR) TTR
Roldán, 2015, Spain (318)	a. Prospective b. 6 months	459	Anticoagulant clinic-hospital	64 (17)
Ruiz-Ortiz, 2015, Spain (329)	a. Retrospective b. 27 months (median)	1056	Cardiology outpatient clinic-hospital	63.8 (25.9)
Gallego, 2014, Spain (322)	a. Prospective b. 952 days (median)	972	Anticoagulant clinic-hospital	78 (19.98)
Lip, 2014, France (330)	a. Prospective b. 1016±1018 days (mean)	8120	Clinicians -hospital	-
Poli, 2014, Italy (321)	a. Prospective b. 4.6 years (mean)	1089	Anticoagulant clinic-hospital	73 (62.5-82.0)
Skov, 2014, Denmark (320)	a. Prospective b. 1 year	182	Anticoagulant clinic-hospital	76 (-)
Apostolakis, 2013, UK (199)	a. Retrospective and prospective b. 3.5 years (mean)	1305	Derivation- clinical trial Internal-clinical trial External: anticoagulant clinic-hospital	Derivation cohort 64.2 (18) Internal validation 63.0 (19) External validation 66 (16)

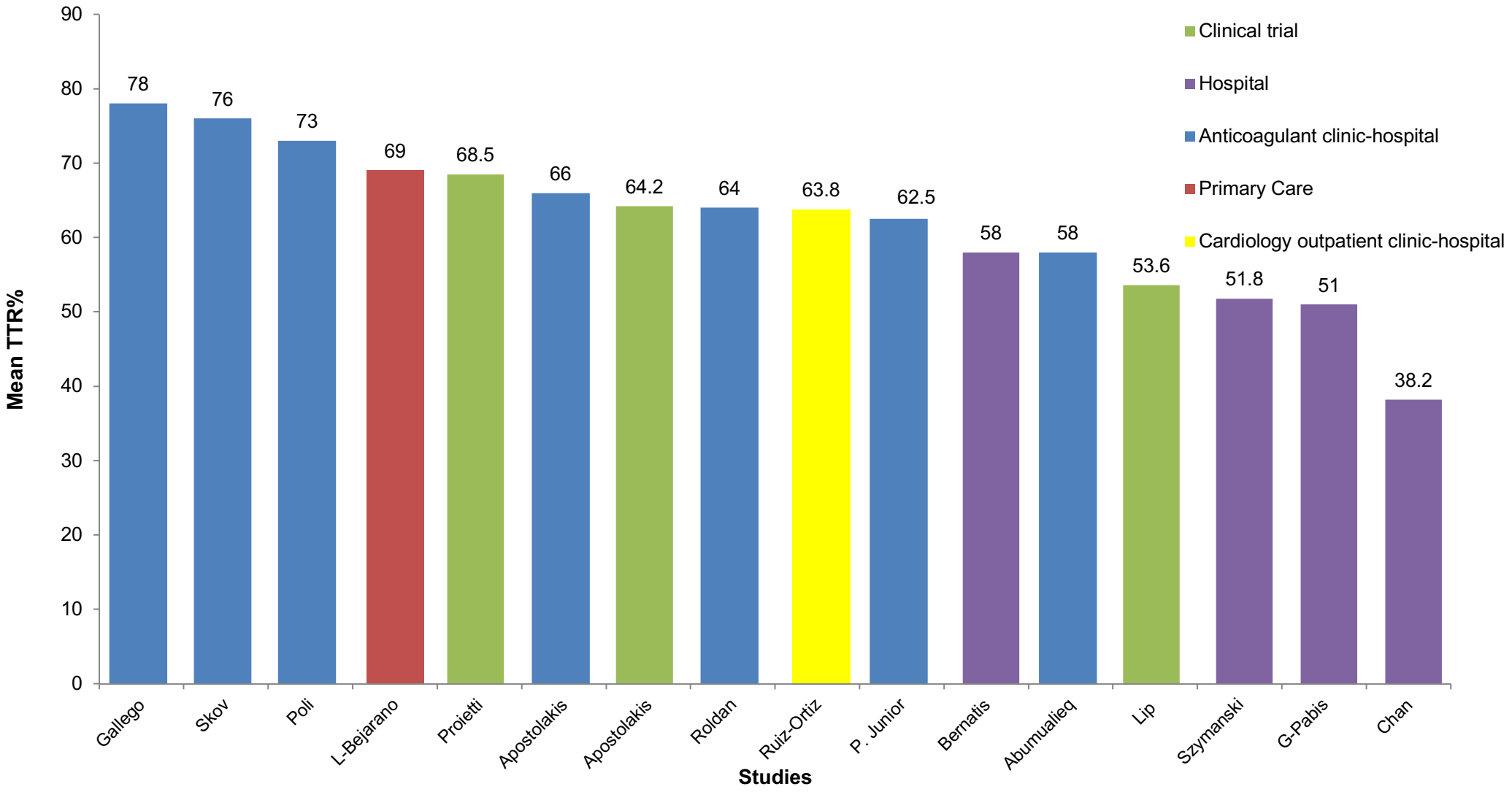


Figure 1.6: Mean TTR% among studies that validated the SAMe-TT_2R_2 score

1.5.1.2.3.2 Models of care

A variety of models of care known as usual care (UC) model, anticoagulant clinic (AC) model and patient self-testing (PST) model (also known as home monitoring) were developed due to the complexity of managing patients on warfarin therapy. In the UC model, patients are managed by physicians without formal systematic monitoring procedures or policies to focus on dose management. In the AC model, patients are usually managed by specialised nurses or pharmacist under physicians' supervision with systematic policies and procedures on initiating, optimising and maintaining warfarin therapy. Lastly in PST model, patients self-manage their own INR test at home using a portable point of care (POC) instrument. Patients either receive instruction on dose from a healthcare provider or self-managed their own dose (PSM) (331).

Studies have shown that different models of care might influence patient's quality of anticoagulation therapy and impact adverse clinical outcome. A recent systematic review (228) of 25 studies (3 RCTs and 22 non-RCTS) involving 12,252 participants evaluated the quality of anticoagulation control among pharmacist-managed anticoagulant services (PMAS) compared with routine medical care. Quality of anticoagulation therapy was significantly better in the PMAS group (TTR 66.9%) compared to usual care (TTR 56.7%), evidenced by a higher TTR in the former compared to the latter in 23 of 25 studies. Adverse clinical outcomes were also lower in the PMAS group compared to routine medical care, evidenced by lower or equal risk of major bleeding (N=10 of 12 studies) and lower rates of thromboembolic events (in nine out of 10 studies). (228) Another meta-analysis of eight RCTs (229) comparing the effectiveness of PMAS versus other models of care (including UC by physicians, nurses and other healthcare professional) in a mixed group of patients also showed better TTR in standard therapeutic range for patients in the PMAS compared to UC group. However, safety and mortality data were inconclusive; instead patients in PMAS group were most satisfied (229) **(Table 1.26).** The findings from the two meta analyses showed the benefits of PMAS over UC

towards improving TTR however more studies are needed to confirm the benefits of PMAS in terms of adverse clinical outcomes.

Evidence has shown that more frequent INR testing results in a reduction of thromboembolic and bleeding events (332). With the difficulties associated with frequent INR visits to an anticoagulant clinic in short interval of time, the concept of patient self-testing (PST) was introduced. Since 2004, the American College of Chest Physicians (ACCP) have recommended PST to be implemented 'for patients who are motivated and can demonstrate competency' (Grade 2B) (333). Several meta-analyses of clinical trials showing the advantages of PST/PSM have been conducted in 2011 (232) and 2012(231) **(Table 1.26).** Bloomfield et al (232) demonstrated that in highly motivated adult patients requiring long term anticoagulation therapy with warfarin, PST alone or in combination of PSM was associated with significantly reduced risk of thromboembolic events (42%) and deaths (26%) without an increased risk of major bleeding events compared to patients receiving UC (232). Similarly, Heneghan et al (334) conducted a systematic review including 28 trials in 2016 also showed a significant reduction of TE events in the PSM or PST groups [RR 0.58, (95% CI 0.45 to 0.75)]; but no significant reduction in major bleeding [RR 0.95, (95% CI, 0.80 to 1.12)] or all-cause mortality [RR 0.85, (95% CI 0.71 to 1.01)] (231). Results from the two meta-analyses suggest the benefits of PST and/or PSM towards reducing TE and mortality compared to UC.

Another small randomised trial (N=159) performed in the Netherlands reported that PST and PSM patients had a significantly improved quality of life compared to PST patients or UC (managed in the hospital) only (335).

Table 1.26: Models of care and anticoagulation control and/or clinical events

	No of studies	Population, N	Population	Models	TTR and/or clinical events
Manzoor 2017(228)	25 studies 3 RCT 22 non RCT	12, 252	AF, VTE	PMAS vs. UC	TTR higher in PMAS (66.9%) vs. UC (56.7%) in 23 of 25 studies
Zhou 2016 (229)	8 RCTs	1493	AF, VTE, valvular heart disease, CVA, cardiomyopathy, mural thrombus and others	PMAS vs. UC	TTR PMAS vs. UC: MD 3.66 95% CI (2.2-5.11) for INR 2.5 $\pm$ 0.5 (standard INR range) TTR PMAS vs. UC: MD 2.85 95% CI (-0.56 to 6.26) for INR 2.5 $\pm$ 0.7 (expanded INR range)
Heneghan 2016 (334)	28 trials	8950	AF, valve replacement, DVT	PST and/or PSM vs. UC	TE: PST or PSM: (RR 0.58, 95% CI 0.45-0.74; participants = 7594; 18 studies) Mortality: PST or PSM: (RR 0.85, 95% CI 0.71-1.01; 6358 participants, 11 studies)
Bloomfield 2011(232)	22 trials	8413	AF, mechanical heart valve replacement	PST and/or PSM vs. UC	TE: OR 0.58, 95% CI (0.45-0.75, =<0.001) Mortality: OR 0.74 95%CI (0.63-0.87, p<0.001)

CI: confidence intervals; MD: mean difference; PMAS: pharmacist-managed anticoagulant service; PST: patient self-testing; PSM: patient self-monitoring; UC: usual care

1.6 Use of the SAMe-TT_2R_2 score to predict anticoagulation control in atrial fibrillation treated with vitamin K antagonists

The section summarises studies which have assessed and/or validated the SAMe-TT_2R_2 score in patients treated with VKA for AF. This section has been published in the Heart Rhythm Journal (336).

The original purpose of developing the SAMe-TT_2R_2 score was to produce a simple clinical schema which could be used routinely in everyday practice to help assess the likelihood of an AF patient being able to achieve and maintain good anticoagulation control on VKA therapy, using patient-related clinical parameters which are readily available. The availability of NOACs worldwide has resulted in increased usage due to their advantages. These include faster onset-of-action [average maximum effect approximately three hours after intake (337) compared to VKA (onset 36-72 hours)], greater reduction in stroke/systemic embolism [+19% compared to VKA(3)], avoidance of INR monitoring with NOACs(338), and absence of achieving/maintaining adequate TTR (as with warfarin). Achieving a therapeutic INR can take 2-4 weeks and often longer (131). After termination of study drug in the NOAC trials, of those patients switching to warfarin, <40% achieved a therapeutic INR within 15 days, and <80% after 30 days(339); more strokes occurred during that period in the patients who went from study drug to VKA than from VKA to VKA (339, 340). This strong argues for using NOACs over VKAs where possible, however, VKAs are still widely used globally and will not disappear from use especially for AF patients with severe renal impairment, moderate to severe mitral stenosis or mechanical heart valves (3). In addition, in low- and middle-income countries where cost plays an important role in options available for OAC treatment VKA is still the first-line antithrombotic agent of choice, therefore the SAMe-TT_2R_2 score will remain an important decision-making tool, currently and in the future, to guide physicians choice of anticoagulant treatment (341).

1.6.1 SAMe-TT_2R_2 score validation studies

Current studies (N=16) assessing the SAMe-TT_2R_2 score in AF patients are summarised in **Table 1.27** and the baseline patient characteristics of these cohorts are presented in **Table 1.28**. The majority of the studies (N=9) (199, 280, 318, 320-322, 324, 327, 330) were performed prospectively, with a follow-up duration ranging from six months (318) to 4.7 years (325). Eleven of the studies were performed in European populations (199, 318-324, 327, 328, 330), three in Asian populations (325, 326, 342) and one in the American populations (280). Proietti et al (327) studied a mixed indication clinical trial cohort including patients from Europe, Asia and Australasia.

Most studies to date were performed in elderly (mean or median age ranging from 61 years to 76 years old) Western Caucasian populations, which mainly used warfarin (10 studies) (199, 280, 320, 321, 323, 325-327, 330, 342) as their OAC of choice. The majority of the patients had multiple comorbidities with hypertension being the most common, except for the study by Lip et al (330) where congestive heart failure was most common. All of the studies reported a low prevalence of smoking status and use of amiodarone for rhythm control, with the exception of Lip et al (330), with 35% of patients using amiodarone. As shown in **Figure 1.7**, as the SAMe-TT_2R_2 score categories increase, the mean TTR of their study population decreases.

Five studies (280, 319, 325, 328, 343) investigated the relationship between components included in the SAMe-TT_2R_2 score and TTR. Three studies (280, 319, 328) showed that female sex was associated with poor anticoagulation control; one (319) showed that having ≥2 comorbidities was related to poor TTR and one (280) showed that black ethnicity (as well as NYHA IV) was associated with poorer anticoagulation control. Chan et al (325) also reported that having heart failure and diabetes mellitus independently predicts poor anticoagulation control.

Table 1.27: Studies assessing the SAMe-TT_2R_2 score in atrial fibrillation cohorts

	a. Study design **b. Mean follow-up** **c. Method INR monitoring**	**Population** **a. Number** **b. Mean (SD)/median (IQR) age (range, years)** **c. Race/ethnicity** **d. OAC used**	**SAMe-TT_2R_2 score distribution (%); mean (SD) TTR (%)**	**Percentage of patients with dichotomised TTR (%)**
Pivatto Junior(317) 2017 Brazil	a. Retrospective a. 1 year b. Hospital OAC clinic	a. 263 AF a. 71.2 (64.1-78.5) b. White c. 97.3% Warfarin	0-1: 138 (52.5); 69.2 ≥2: 125 (47.5); 56.3	-
Bernaitis(326) 2016 Singapore	a. Retrospective b. - c. Hospital	a. 1137 AF b. 71 (63-77) c. Asian d. Warfarin	0-1:0 2: 339; 63.2 (34.1) >2:798; 55.8 (34.1)	-
Chan(325) 2016 Hong Kong	a. Retrospective b. 4.7 ± 3.6 years c. Hospital	a. 1428 NVAF b. 76.2 (8.7) c. Chinese d. Warfarin	2: 22 (14.3); 70[†] 3: 80 (51.9); 70 4: 41 (26.6); 70 5: 7 (4.5); 70 6: 4 (2.6);70	TTR≥70: 11 TTR<70: 89
Gorzelak-Pabis(324) 2016 Poland	a. Prospective b. - c. Hospital	a. 104 AF with cognitive impairment b. 75 (10) c. White d. 61% Acenocoumarol	0-1: 64 (26) ≥2: 50 (28)	-
Lip(280) 2016 USA	a. Prospective b. 438 days c. Trial setting	a. 229 AF b. 66.7 (11) c. 80.3% White d. Warfarin	0-1:0.571 (0.22) ≥2: 0.498 (0.24)	-

	a. Study design b. Mean follow-up c. Method INR monitoring	a. Number b. Mean (SD)/median (IQR) age (range, years) c. Race/ethnicity d. OAC used	SAMe-TT_2R_2 score distribution (%); mean (SD) TTR (%)	Percentage of patients with dichotomised TTR (%)
Lobos-Bejarano(328) 2016 Spain	a. Retrospective b. >12 months c. Primary care	a. 1524 NVAF b. 77.4 (8.7) c. White d. 94.8% Acenocoumarol	0-1: 69.6% (17.4) ≥2: 66.6% (18.5)	TTR≥65: 60.6 TTR<65: 39.4
Proietti(327) 2016 Europe, Asia, Australasia	a. Prospective b. Median 563 days (IQR 483-651) c. Trial setting	a. 3665 AF b. 72(66-77) c. Mixed‡ d. Warfarin	0-2: 2914 (80.4); 69.05 (55.63-79.89) >2: 710 (19.6); 66.55 (52.83-77.46)	TTR>70: 46.9 TTR≤70: 53.1
Szymanski (323) 2016 Poland	a. Retrospective b. - c. Hospital	a. 211 AF b. 57.1 (10.2) c. White d. 75.4% warfarin	0-1: 114 (54); 52.3 ≥2: 97 (46); 51.3	TTR>70: 25.2 TTR≤70: 74.8
Abumuaileq(319) 2015 Spain	a. Retrospective b. 10 months c. Hospital OAC clinic	a. 911 NVAF b. 73 (11) c. White d. 93% Acenocoumarol	0-1:672 (74); 59 (18)¶ ≥2: 239 (26); 54 (19)¶	PINRR>65:44 PINRR≤65:55
Roldán (318) 2015 Spain	a. Prospective b. 6 months c. Hospital OAC clinic	a. 459 NVAF b. 76 (70-82) c. White d. Acenocoumarol	<2: 253 (55); 67 (18) ≥2: 206 (44.8); 61 (16)	TTR>65:54 TTR≤65:46
Ruiz-Ortiz(329) 2015 Spain	a. Retrospective b. Median 27 months c. Cardiology clinic	a. 1056 NVAF b. 73.6 (9.8) c. White d. Acenocoumarol	0-1:613 (58); 65.6 (26.2) ≥2: 443 (42); 61.3 (25.3)	TTR≥65:52.7 TTR<65:47.3

Table 1.27 continued

	a. Study design **b. Mean follow-up** **c. Method INR monitoring**	**a. Number** **b. Mean (SD)/median (IQR)age** **c. Race/ethnicity** **d. OAC used**	**SAMe-TT_2R_2 score distribution (%); mean (SD)TTR (%)**	**Percentage of patients with dichotomised TTR (%)**
Gallego(322) 2014 Spain	a. Prospective b. Median 952 days c. Hospital OAC clinic	a. 972 NVAF b. 76 (70-82) c. White d. Acenocoumarol	0-1:431 (44); 79.67 (19.46) ≥2: 332 (34); 78.4 (20.28) >2:208 (21); 74.25 (20.24)	-
Lip(330) 2014 France	a. Prospective b. 1016±1018 days c. Clinicians -hospital	a. 8120 AF†† b. 70 (15) c. White d. Warfarin	0-1: 4504 (55); 77(1.7)§ ≥2: 2252 (28); 52(2.3)§ >2:1364 (17); 43(3.2)§	-
Poli(321) 2014 Italy	a. Prospective b. 4.6 years c. Hospital OAC clinic	a. 1089 AF b. 75 (30-94) c. White d. Warfarin	0-1:624 (57); 72.3 (15.3) 2: 288 (26); 72.0 (15.6) >2:177 (16); 68.2 (16.4)	-
Skov(320) 2014 Denmark	a. Prospective b. 1 year c. Hospital OAC clinic	a. 182 AF b. 70.2# c. White d. Warfarin	0-1:105 (58); 76 ≥2: 77 (42); 76	-
Apostolakis(199) 2013 United Kingdom	a. Retrospective and prospective b. 3.5 years c. Clinical trial (internal-validation)/Hospital OAC clinic (external-validation)	a. 1305 AF b. 69(8)/74(10) c. 8.7%, 19.3 % non-white (internal/external-validation) d. Warfarin	(Internal/External validation) 0: 242 (18); 0.66±0.16/0.7±0.13 1: 413 (31);0.65±0.18/0.66±0.17 2: 303 (23);0.63±0.17/0.66±0.16 3:185 (14); 0.59±0.22/0.65±0.17	**Internal validation** TTR>70:35.7 TTR≤70:64.3 **External validation** TTR>70:44.1 TTR≤70:55.9

AF: atrial fibrillation; CV: cardiovascular; INR: international normalised ratio; IQR: interquartile range; Max: maximum; MI: myocardial infarction; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant/anticoagulation; ROC: area under curve; SD: standard deviation; SAMe-TT_2R_2 score: sex (female), age (<60 years, medical history (≥2 of the following: hypertension, diabetes, coronary artery disease or myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary, hepatic, or renal disease), treatment with interacting drugs (e.g. amiodarone[all 1 point], current tobacco use and race (non-white) [2 points]; TTR: time to therapeutic; TE: thromboembolism; VTE: venous thromboembolism †TTR presented as ≥70% and <70% not mean TTR; ‡mixed population: White, Black, Asian, other; §number of patients with labile INR, (%); ¶PINRR % (mean ± SD); #no SD or IQR reported; †† n=4637 on VKA; - not reported

Table 1.28: Baseline characteristics of all studies assessing the SAMe-TT_2R_2 score in AF population

N (%)	Female	Age <60	Hypertension	Diabetes	HF	Prior stroke/TIA	PAD	Renal disease	CAD	COPD	Smoking	Previous bleeding	Amiodarone
Pivatto(317)	113 (43.0)	41 (15.6)	231 (87.8)	108 (41.1)	149 (56.7)	96 (36.5)	25 (9.5)	7 (2.7)	76 (28.9)	36 (13.7)	37 (14.1)	24 (9.1)	26 (9.9)
Bernaitis (326)	448 (39.4)	172 (15.1)	677 (59.5)	343 (30.2)	88 (7.7)	45 (4.0)	-	156 (13.7)	271 (23.8)	-	84 (7.4)	-	78 (6.9)
Chan(325)	671 (52.5)	48.0 (3.4)	922 (64.6)	387 (27.1)	367 (25.7)	496 (34.7)	102 (7.1)	2.9 (2.0)	407 (28.5)	-	71.0 (5.0)	-	94 (6.6)
Gorzelak-Pabis(324)	63 (60.6)	-	92 (88.5)	30 (28.8)	72 (69.2)	15 (14.0)	-	-	-	-	20 (19.2)	-	8 (7.7)
Lip(280)	47 (20.5)	57 (24.9)	206 (90.0)	106 (46.3)	208 (90.8)	26 (11.4)/ 14 (6.1)	31 (13.5)	-	178 (77.7)	-	-	-	46 (20.1)[#]
L.Bejarano (328)	741 (48.6)	66 (4.3)	1223 (80.2)	473 (31.0)	392.0 (25.7)	209.0 (13.7)	99 (6.5)	92 (6.0)	286 (18.8)	-	100 (6.6)	134 (8.8)	100 (6.6)
Proietti(327)	1116 (30.5)	72[§] (66-77)	2812 (76.7)	860 (23.5)	1372 (37.4)	753 (20.5)	-	-	1619 (44.2)	-	334 (9.1)	208 (5.7)	-
Szymanski (323)	79 (37.4)	108 (51.2)	194 (91.9)	27 (12.8)	8.0 (3.8)	16 (7.6)	-	-	-	-	31.0 (14.7)	-	17 (8.1)
Abumuaileq (319)	306 (33.6)	-	678 (74.4)	220 (24.1)	343 (37.7)	103 (11.3)	92 (10.1)	36[¶] (4)	127 (13.9)	183 (20.1)	77 (8.5)	115 (12.6)	-
Roldán(318)	237 (53.0)	38 (8.0)	368 (80.0)	141 (31.0)	87 (19.0)	67 (15.0)	-	51 (11.0)	70 (15.0)	50 (11.0)	38 (8.0)	37 (8.0)	72 (16.0)
Ruiz-Ortiz(329)	443 (42.0)	-	884 (83.7)	321 (30.4)	235 (22.2)	150 (14.2)	-	153 (14.5)	215 (20.3)	176 (16.7)	76 (7.2)	56 (5.3) [††]	102 (9.7)
Gallego (322)	494 (51.0)	66 (7.0)	796 (82.0)	249 (26.0)	350 (36.0)	182 (19.0)	-	94 (10.0)	182 (19.0)	-	136 (14.0)	79 (8.0)	-

Table 1.28 continued

N (%)	Female	Age <60	Hypertension	Diabetes	HF	Prior stroke/TIA	PAD	Renal disease	CAD	COPD	Smoking	Previous bleeding	Amiodarone
Lip(330)	3,129 (39)	-	3,405 (42.0)	1,244 (15.0)	4,466 (55.0)	674 (8.0)	-	734 (9.0)	2,434 (30.0)	870 (11.0)	1,053 (13.0)	-	1,670 (35.0)
Poli(321)	412 (37.8)	61 (5.6)	745 (68.7)	216 (19.9)	268 (24.7)	313 (28.8)	143 (13.2)	-	239 (22.1)	-	181 (16.6)	-	200 (18.4)
Skov (320)	54 (29.6)	23 (12.6)	-	-	-	-	-	-	-	-	41 (22.5)	-	27 (14.8)
Apostolakis(199)†	382 (37.5)	147 (14.4)	692 (67.9)	200 (19.6)	197 (19.3)	130 (12.8)	57 (5.6)	53 (5.2)‡‡	173 (17.0)§§	-	64.0 (6.3)	-	129 (12.7)
Apostolakis(199)‡	157 (67.1)	30.0 (10.5)	234 (81.8)	64 (22.4)	45 (15.7)	30.0 (12.8)	8 (2.8)	2.0 (0.7)‡‡	44 (15.4)§§	-	140 (49.0)	-	26 (9.1)

CAD: Coronary artery disease; HF: Heart failure; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; TIA: transient ischemic attack; PAD: peripheral arterial disease
*internal validation †external validation; ‡ median age; § eGFR 30 ml/min/1.73m2; ‖ antiarrhythmic; ¶ Major bleed; # hepatic/renal disease; ** history of MI

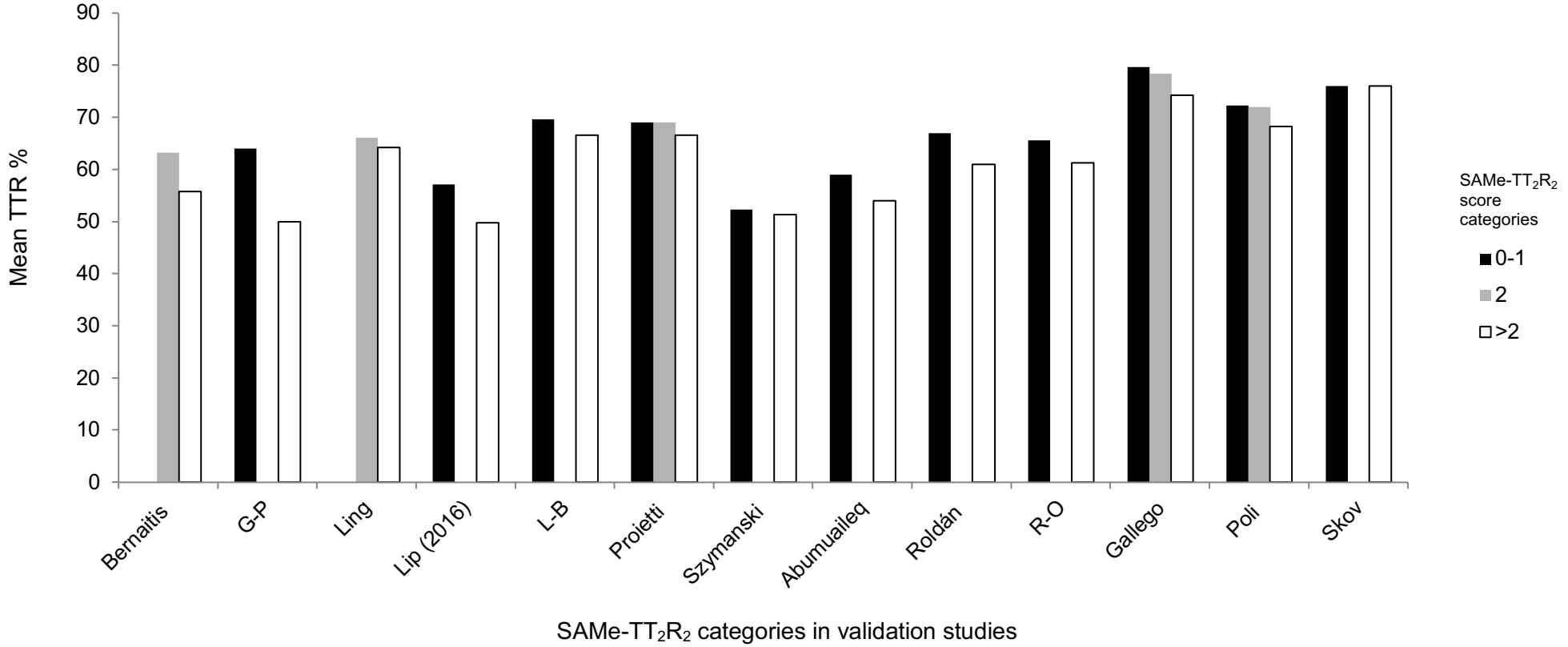


Figure 1.7: Mean TTR vs. SAMe-TT_2R_2 categories in validation studies

Six of the studies (199, 317, 319, 328-330) reported the predictive ability of the SAMe-TT_2R_2 score using C-statistics **(Figure 1.8).** Taken together, these validation studies suggest that the SAMe-TT_2R_2 score is able to predict good or poor anticoagulation control among AF patients better than chance, with C-statistics ranging from 0.56 (328) to 0.72. (199) Many risk scores based on clinical factors such as $CHADS_2$, CHA_2DS_2-VASc, Killip and TIMI scores show broadly similar modest C-indexes (approx. 0.6) when used to predict patients categorised at 'high risk' who actually sustain clinical events (193, 314).

Six studies (319, 321, 322, 325, 327, 330) also examined if the SAMe-TT_2R_2 score could discriminate AF patients with clinical events. Five (319, 322, 325, 327, 330) demonstrated some positive associations for SAMe-TT_2R_2 score predicting clinical events, with C-statistics ranging from 0.55 (330) to 0.62 (322) (**Table 1.29**). As seen in most of the studies, (199, 280, 318, 319, 321-330, 342) increasing SAMe-TT_2R_2 score demonstrated poorer TTR values which might also translate into poorer outcomes. This can be evidenced by studies that showed the SAMe-TT_2R_2 score relating to severe bleeding (322) and major bleeding (defined by the Bleeding Academic Research Consortium) (330), stroke/TE (330), adverse cardiovascular event (322) and death (322, 330) during follow up. In an observational study performed in 911 non-valvular AF Spanish patients, the SAMe-TT_2R_2 score also successfully predicted the composite outcome of major bleeding, TE complications and death (319). A Chinese study also demonstrated that a SAMe-TT_2R_2 score of ≤2 vs. SAMe-TT_2R_2 of 3 vs. SAMe-TT_2R_2 ≥4 is associated with lower annual stroke risk (3.49%/year vs. 4.56% per year vs. 6.41%/year, respectively) (325) .

1.6.2 Importance of good anticoagulation control

Achieving good anticoagulant control (i.e. TTR≥65-70%) as recommended by guidelines (3, 344) is essential for managing AF patients treated with VKA. Indeed, numerous studies have demonstrated that a high TTR translates into lower risk of stroke and bleeding (119, 120, 122, 195, 345). A systematic review demonstrated that a 7% and 12% improvement in TTR can

lead to a reduction in major bleeding and thromboembolic event, respectively, by 1 event per 100 patient years (120). A real-world study (119) of 27,458 warfarin treated patients for AF (with at least 3 INR measurements) showed that in patients with good anticoagulation control (TTR ≥70%), stroke risk was reduced to 79% compared to patients with poor INR control (TTR ≤30%). However, achieving and maintaining a therapeutic INR can be difficult to accomplish and therefore, NOACs are preferred to VKA in the majority of patients requiring OAC initiation (3).

1.6.3 Impact of different methods of calculating TTR

Fauchier and colleagues (346) have raised concern about the different methods used to calculate TTR, whether to use TTR based on the Rosendaal method, percentage of INRs in range (PINRR) (traditional method) or percentage of visits in range on a given date (cross-sectional method), as these methods are not interchangeable. Overall, 14 studies (199, 280, 318, 320-329, 342) reported TTR using the Rosendaal method, only one study (319) utilised PINRR method and another one reported 'labile INR' as their measure of anticoagulation control (330). At the moment, there is no evidence showing which method of calculating percentage of INR in range is best, as each method has its own unique strengths and weaknesses (347). While TTR via the Rosendaal method calculates the exact percentage of days the INR falls within range; its calculation is more complex than the others and is based on linear extrapolation. In contrast, calculating TTR via the PINRR method is simpler as it only looks at the number of INRs that fall within the therapeutic range divided by the total number of INR tests undertaken. However, the PINNR method does not consider the actual number of days of anticoagulant treatment and thus might underestimate control in patients with inconsistent INR monitoring, patients who have temporary discontinued therapy and patients with a long gap between each INR test, in contrast to the Rosendaal method where these factors will be accounted for, resulting in a lower TTR.

The next section discusses about antithrombotic therapy in patients with valvular heart disease.

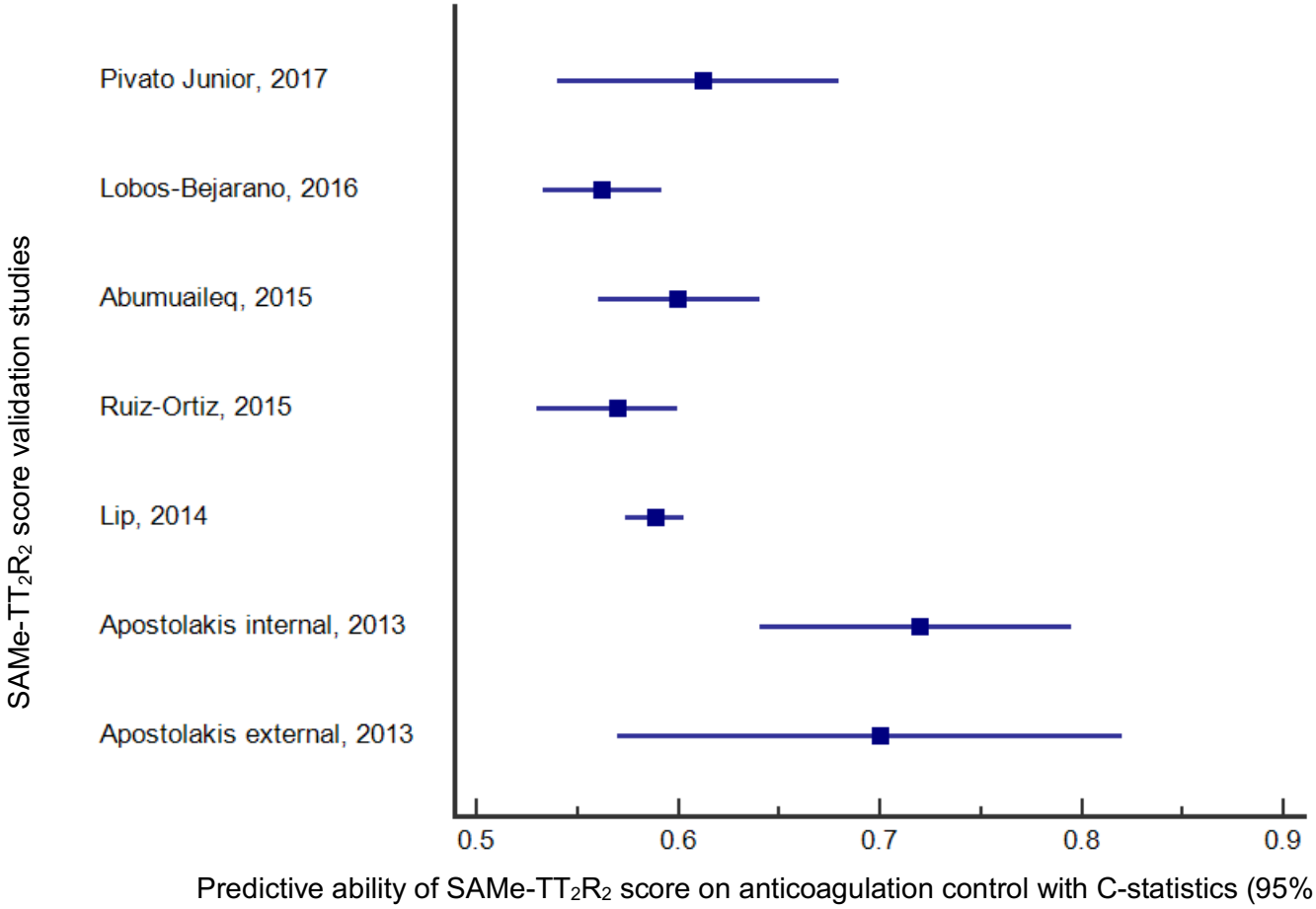


Figure 1.8: Predictive ability (C-statistics and 95% confidence intervals) of SAMe-TT_2R_2 towards anticoagulation control in validation studies

Table 1.29: Predictive ability (C-statistics) of SAMe-TT_2R_2 for anticoagulation control and clinical events

	Anticoagulation control, c-statistics (95% CI)	Clinical events, c-statistics (95% CI)
Pivatto Junior (317)	TTR≥65: 0.612 (0.544-0.681; p=0.002)	-
Chan (325)	-	Stroke: 0.54 (0.52-0.57)
Abumuaileq (319)	PINRR ≤70: 0.60 (0.56-0.64; p<0.01)	Composite major bleeding, thromboembolic complication or death: 0.57 (0.51-0.62); p=0.03
Ruiz-Ortiz (329)	TTR≥65: 0.57 (0.53-0.60; p<0.0005)	-
Gallego (322)	-	Adverse CV event: 0.62 (0.57-0.68; p<0.001) Bleeding: 0.55 (0.49-0.62; p=0.117) All-cause mortality: 0.62 (0.55-0.68; p<0.001)
Lip (330)	Labile INR: 0.589 (0.574-0.603)	Stroke/TE: 0.561 (0.547-0.575) Severe bleeding: 0.552 (0.537-0.566) Major BARC bleeding:0. 574 (0.560-0.589) Death: 0.544 (0.530-0.559)
Apostolakis (199)	TTR 31% internal 0.72 (0.64-0.795) TTR 36% external 0.70 (0.57-0.82)	-

1.7 Antithrombotic therapy in atrial fibrillation associated with valvular heart disease

AF and valvular heart disease (VHD) often coincide and are present in about 2.5% of patients in industrialized countries (348-350). However, the management of patients with both conditions have not been well addressed in large clinical trials. Patients with valvular heart disease are often excluded from most of the clinical trials due to the complexity of their management strategy. Due to this, there is a lack of definitive guidance on how best to manage this group of patients (349, 351).

Recently, new definition to 'valvular AF' has been proposed based on the type of oral anticoagulation to be used in AF patients with valvular heart disease. The term valvular AF is outdated; the new term is Evaluated Heart valves, Rheumatic or artificial (EHRA) type I VHD and EHRA type II VHD (**Table 1.30)** (349, 351). These new terms will be used throughout the thesis except when it is cited as 'valvular AF' from original studies.

Table 1.30: Classification of AF patients with valvular heart disease [taken directly from (356, 358)]

Definition	OAC therapy	Valve type
Evaluated Heart valves, Rheumatic or artificial **(EHRA) type I** VHD	VKA only	• Moderate to severe mitral stenosis of rheumatic origin • Mechanical prosthetic valve replacement
Evaluated Heart valves, Rheumatic or artificial **(EHRA) type II** VHD considering CHA_2DS_2-VASc score	VKA or NOAC	• Mitral regurgitation • Mitral valve repair • Aortic stenosis • Aortic regurgitation • Tricuspid regurgitation • Tricuspid stenosis • Pulmonary regurgitation • Pulmonary stenosis • Bio prosthetic valve replacement • Transaortic valve intervention (TAVI)

1.7.1 Epidemiology of valvular heart disease with atrial fibrillation

Large differences can be seen in the epidemiology of VHD across different types of VHD and between low and high income countries (352). Rheumatic heart disease (RHD) is the most common cause of morbidity and mortality in low income countries while calcific aortic valve disease (CAVD) carries the greatest burden of VHD in high income countries (352). A review reported the prevalence of RHD between 46 per 100,000 in northern India while higher prevalence can be seen in the Solomon Islands, 2400,000 per 100,000 (353). In contrast, in the United States, aortic stenosis (a spectrum of CAVD) accounts for 45% of all deaths from VHD and was the main driver of VHD-related deaths over the past 30 years (354). The risk of ischaemic stroke can be up to 17 times greater in AF patients with rheumatic heart disease compared to patients with AF alone without any significant valvular heart disease (355).

However, limited information is available on the prevalence and incidence of AF associated with VHD. The RELY-AF registry (enrolled AF patients at 164 sites in 46 countries) reported the presence of RHD among AF patients as 31.5% in India, 21.5% in Africa and 2.2% in North America (356). Whereas the ORBIT-AF registry, a multicentre, prospective, outpatient hospital registry included 176 US practices with 9748 AF patients, demonstrated a prevalence of 27.7% with significant VHD in this population. Among them, 4.1% had mitral stenosis/mechanical valve, 4.7% had bioprosthetic valves or balloon valvuloplasty or prior valve repair while a higher prevalence (18.9%) of patients with aortic regurgitation/aortic stenosis, mitral regurgitation or tricuspid regurgitation (357) was found, consistent with other high income countries (354).

1.7.2 Anticoagulation therapy in AF patients with valvular heart disease

Thrombotic events are the most common cause of mortality and morbidity especially after surgery for VHD. This risk is especially higher within the first 3 months, for both bioprosthetic and mechanical devices (348). Therefore, antithrombotic therapy is required to prevent thrombotic events in VHD patients after surgical intervention. Effective measures should also

be made to control modifiable risk factors (for example effective blood pressure control in hypertensive patients) to reduce the risk of thromboembolism, together with the prescription of antithrombotic drugs (358). Anticoagulation therapy is required lifelong in patients receiving a mechanical valve as this confers a life-long thrombotic risk. In addition, AF, a common arrhythmia in VHD, also requires life-long anticoagulation (3, 348, 349, 358). Thus, patients with both AF and mechanical/bioprosthetic device are at risk of thromboembolic and bleeding complications if their anticoagulation therapy is not well optimised (348).

1.7.2.1 Anticoagulation therapy in mechanical heart valves

Exposure to the artificial valve and tissue injury caused by the presence of a prosthetic valve activates the intrinsic and extrinsic coagulation pathways thus inducing the formation of thrombin which in turn facilitates thrombus generation (349, 351). This condition is more pronounced in AF patients, patients with mild to severe stenosis and aortic stenosis, as all these conditions affect the blood flow turbulence thus triggering the coagulation cascade, intensifying the propensity to thrombosis (349, 351). VKA antagonists prevent the coagulation cascade at both the intrinsic and extrinsic pathways thus preventing the formation of thrombin. The European guidelines (3, 349, 351) recommend the use of VKA in patients undergoing mechanical valve transplantation (regardless of presence of AF) and AF patients with moderate to severe mitral stenosis with good anticoagulation control, TTR >65-70% (3, 349, 351). The use of VKA should be monitored according to the INR range and targets based on the prosthesis thrombogenicity and patient-related risk factors **(Table 1.31).** Treatment duration with anticoagulation therapy depends on several factors. Patients with mechanical valves and those with bioprosthetic valves or native valve disease (aortic and mitral stenosis, aortic, mitral and tricuspid regurgitation) with additional (≥2) stroke risk factors require lifelong anticoagulation treatment (Class 1 recommendation) (3, 351). However, the current ACC/AHA guideline (359) recommends VKA therapy with the addition of aspirin (at least 75-100 mg/day) to all patients receiving mechanical valves (Class 1A recommendation), whereas ACCP (360)

recommends addition of aspirin only in high-risk patients with careful monitoring of the bleeding risk (359, 360).

Table 1.31:Target INR values for VKA among patients with prosthetic valves [taken directly from (358, 368)]

Prosthesis thrombogenicity	Valve type	INR target in patients with related factors ≥1*(351)	INR target in patients without risk factor (361)
Low	Carbomedics. Medtronic Hall, St Jude Medical, ON-X	3.0	2.5
Medium	Other bileaflet valves	3.5	3.0
High	Lillehei-kaster, omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves	4.0	3.5

*Risk factors: mitral or tricuspid valve replacement, previous thromboembolism, AF, mitral stenosis of any degree, left ventricular ejection fraction <35%

A meta-analysis from 1994 (362) of 13,088 patients on antithrombotic therapy vs. no antithrombotic therapy investigated thromboembolic and bleeding complications among patients receiving a mechanical heart prosthesis. In this study, the incidence of major embolism (causing death, residual neurological deficit or peripheral ischemia causing surgery) without any antithrombotic therapy was 4.0 per 100 patient-years (95% CI 2.9-5.2) while this incidence was further reduced to 1 per 100 patient-years (95% CI 1.0-1.1) in patients with VKA and 2.2 per 100 patient-years (95% CI 1.4-3.1) for those on antiplatelet therapy (362). For bleeding complications, OAC therapy increased the incidence of total bleeding (cerebral, intracranial, bleeding causing death or hospitalisation and minor bleeding); 1.9 per 100 patient-years (95% CI 1.7-2.0) and the addition of antiplatelet therapy further increased the incidence of total bleeding; 4.6 (95% CI 3.1-6.4) (362).

Another more recent meta-analysis of RCTs by Massel et al (363), comparing VKA alone vs. combination VKA and antiplatelet, of 4122 mechanical valve replacement patients found a reduced risk of TE event [OR 0.43 (0.32-0.59, p<0.00001] and mortality [OR 0.57 (0.42-0.78;

p=0.0004)] in patients with the combination therapy compared to VKA alone. However there was increased risk of major bleeding with the addition of antiplatelet therapy [OR 1.58 (1.14-2.18); p=0.006)] compared to anticoagulation therapy (363).

The use of NOACs in patients with mechanical valve prosthesis is contraindicated (351, 358). There is only one trial, the RE-ALIGN trial, a phase 2 dose study (364) of patients with mechanical heart prosthesis (aortic and mitral) that evaluated the use of dabigatran versus warfarin. Based on the kidney function, the selection dose of dabigatran was 150, 220 or 300mg twice daily to achieve a trough level of 50ng/ml which is based on the pharmacokinetic model from the RE-LY trial. Unfortunately, the trial was terminated early after randomisation of 252 of 405 patients because there was an excess of thromboembolic and bleeding events in the dabigatran group (364). Several explanations have been suggested including inadequate concentration of dabigatran in plasma, varied pharmacodynamics properties of dabigatran and warfarin and over reactive contact coagulation pathway in the early postoperative period induced by the sewing ring (351). No other studies of NOACs (factor Xa) has been tested subsequently. Due to this, currently all patients with mechanical valve prosthesis should be anticoagulated with a VKA (3, 349, 351).

1.7.2.2 Anticoagulation therapy in bioprosthetic valves

Reports have shown that thromboembolism associated with bioprosthetic valves ranged from 0.2%-3.3% per year (360, 365, 366) whereas higher risk can be found among the valves in the mitral, compared to the aortic, position. Similar to that seen in mechanical prostheses, but to a lower extent, TE risk is also higher within the first 3-months post-surgery (367, 368). Due to that, compared to OACs, the use of low dose aspirin is now favoured for those with surgical aortic bioprosthesis (without other indications for OAC, for example AF) for the first three months post-surgery; however, this is based on a low-level of evidence (class IIa, level C) (358). OACs may be considered for the first 3 months after surgery in aortic bioprosthesis patients with class IIB, level C evidence (358, 369-371). In contrast, those with mitral or tricuspid valve replacement with bioprosthesis should still be considered for OAC therapy for the first 3 months after surgical intervention (358).

Lifelong anticoagulation therapy is required in patients with bioprosthesis and with additional risk factors such as venous thrombosis, AF, hypercoagulable state and severely impaired left ventricular function with low evidence (class I, level C) (351, 358). When long term anticoagulation therapy is needed, VKA should be favoured in patients with bioprosthesis (358). Despite the lack of RCT, (351, 372-374) NOACs can be used instead of warfarin in AF patients with bioprosthesis after the third month of the post-operative period (351, 358).

The Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively (DAWA) pilot study (375) compared dabigatran vs. warfarin post bioprosthetic valve replacement in AF patients however due to low enrolment (N=27; 15 dabigatran and 12 warfarin), the trial was terminated earlier and no concrete conclusion was made. One patient from the warfarin group and no patient from the dabigatran group developed intra cardiac thrombus and ischaemic stroke respectively after 90 days of randomisation (375). Other small studies (373, 374) also suggested NOACs as reasonable alternatives to VKA therapy in patients with AF and VHD, but more studies are needed to confirm its efficacy and safety profile (351).

The ARISTOTLE (376) and ENGAGE-AF (373) trials included 82 and 191 patients with a bioprosthesis, respectively. In both trials, the incidence of stroke/systemic embolism was similar; between 1.19-2.9%/year for those receiving either apixaban or low/high dose edoxaban compared to 1.7%/year incidence with warfarin therapy (351, 373, 376). Compared to warfarin, edoxaban low and high dose was associated with similar risk of stroke/SE [HR 0.37 (0.10-1.42) and HR 0.53 (0.16-1.78) respectively compared to warfarin]; however only low dose edoxaban was associated with a lower risk of major bleeding [HR 0.12 (0.01-0.95)]; low and high dose of edoxaban with lower risk of all-cause mortality [high dose edoxaban vs. warfarin: HR 0.46 (0.23-0.91) and low dose edoxaban vs. warfarin: HR 0.43 (0.21-0.88) respectively] (351, 373, 376).

1.7.2.3 Anticoagulation control in patients with valvular heart disease (VHD)

To date, only four (377-380) studies evaluated anticoagulation control by TTR in patients undergoing valve replacement therapy. Two studies from Italy and Denmark (377, 378) that evaluated TTR among mechanical heart valve patients showed relatively low TTR ranging from 55-60% while very good TTR of 71-73% can be seen in another two Swedish studies (379, 380).

Meanwhile, in 2002 one study (381) assessed the effect of anticoagulation control on long term survival after valve replacement with a Medtronic Hall valve among 1532 patients receiving single valve replacement at either the aortic or mitral position. Anticoagulation control variability (ACV) was used and defined as the percentage of INRs outside the 2.0-4.0 range [patients with aortic valve replacement (AVR) had a range of 2.0-3.0 while patients with mitral valve replacement (MVR) had a higher range of 3.0-4.0]. The ACV was further divided into 3 equal sized groups: low (0-19.9% ACV), intermediate (20-29.9% ACV) and high ACV (≥30% ACV); with higher ACV reflecting poor anticoagulation control. Overall, 75.5% of the collected INRs were within the target range. Of those INRs outside of the therapeutic range, 12.0% were below 2.0 and 12.5% were above 4.0. Survival at 15 years was reduced in the high ACV group

with AVR but was similar among the low and intermediate group (28% vs. 59% vs. 55%; p<0.001, respectively). Similarly, as with MVR at 15 years, the survival rate was 56%, 42% and 24%; p<0.001 for the low, intermediate and high ACV groups, respectively; also, significantly reduced in the high ACV group. On multivariate analysis, ACV per 20% increase was associated with increased mortality [HR 1.8, coefficient 0.595; p=0.001]. In this study, although the quality of anticoagulation control was not assessed via the Rosendaal or the percentage of INRs in range methods, better quality of anticoagulation assessed by ACV was associated with reduced mortality (381).

In essence, VHD patients, particularly those with surgical prostheses (regardless of AF), are at increased risk of thromboembolic complications. Long term anticoagulation therapy with VKA is recommended for those with a mechanical prosthesis; whereas those with a bioprosthesis (without additional risk factors) require at least three months of anticoagulation therapy (VKA/NOACs) after surgical intervention. Measures should be taken to ensure the quality of anticoagulation control is optimised level to prevent TE and bleeding complications.

1.8 Aims and objectives

This thesis will include three studies with the main objective of examining anticoagulation control in AF patients from different cohorts. Specific objectives are outlined below. Secondary objectives will be mentioned in each specific study.

1. The original aim was to assess the impact of at behavioural-educational intervention (TREAT-2) on TTR, among patients identified as less likely to establish and maintain adequate TTR (SAMe-TT_2R_2 score >2), receiving warfarin and comparing these patients against those receiving warfarin and usual care alone (SAMe-TT_2R_2 score 0-2). However, due to a change in clinical practice regarding the prescription of NOACs instead of warfarin since 2015, the original aim of this study changed with the focus on assessing depression, anxiety, knowledge about AF, beliefs about medication, and quality of life among newly anticoagulated AF patients in this cohort [see Chapter 2].
2. To examine the quality of VKA control (measured by TTR), predictors of anticoagulation control, and the relationship between INR control and adverse clinical outcomes [thromboembolic (stoke/TIA and systemic embolism), bleeding events, cardiovascular hospitalisation, all-cause mortality and ≥1 composite endpoints (MACE)] in AF patients in a multi-ethnic cohort [see Chapter 3].
3. To examine the quality of VKA control (measured by TTR), predictors of anticoagulation control, and the relationship between INR control and adverse clinical outcomes [thromboembolic (stoke/TIA and systemic embolism), bleeding events, cardiovascular hospitalisation, all-cause mortality and ≥1 composite endpoints (MACE)] in patients with operated valvular heart disease (VHD), with and without AF [see Chapter 4].

Chapter 2. A prospective study examining non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin based on the SAMe-TT_2R_2 score strata in anticoagulant-naïve patients with atrial fibrillation: the TREAT-2 study

2.1 Abstract

Introduction:

To ensure efficacy and safety of OAC therapy with VKA (for example warfarin), the therapeutic range of INR 2.0-3.0 must be achieved. In clinical practice, this is often poorly controlled and could be due to poor adherence, inadequate knowledge and awareness of the importance of OAC therapy. The TREAT intervention (219, 382), a one-off educational-behavioural session, demonstrated a significant improvement in the TTR compared to patients receiving usual care alone.

Objective:

The original aim of this study was to examine the impact of a behavioural-educational intervention (TREAT-2) on TTR among warfarin patients with SAMe-TT_2R_2 score >2 (those predicted to have poor response to warfarin therapy) and compare their TTR among patients with SAMe-TT_2R_2 score 0-2 (those predicted to have good response warfarin therapy). Medication adherence via pill count method was assessed for patients receiving NOAC therapy. Secondary endpoints included assessment of patients' depression, anxiety, knowledge of AF and its treatment, beliefs about medication and quality of life using validated questionnaires at baseline and six months follow up. Due to a change in clinical practice regarding the prescription of NOACs instead of warfarin since 2015, there were insufficient patients initiated on warfarin therapy within the Trust. Therefore, the comparison of the impact

of the TREAT-2 intervention on TTR among warfarin-treated patients could not be examined. Instead the results focus on the secondary outcomes.

Methods:

Prospective, observational and longitudinal study design was employed among patients newly-initiating OAC therapy for stroke prevention in AF (either warfarin or a NOAC). The Patient Health Questionnaire-9 (PHQ-9), Generalised Anxiety Disorder-7 (GAD-7), AF knowledge scale, Beliefs about medication (BMQ) and Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaires were completed among 139 newly anticoagulated AF patients at baseline and 105 patients at six months follow up. The parameters were compared descriptively between warfarin and NOACs patients at both time points. The change in scores between baseline and follow-up were analysed in those who completed the questionnaires at both time points (N=105).

Results:

At baseline the overall median (IQR) depression and anxiety scores were 4.0 (1.0-8.0) and 1.0 (0-5.0) respectively. The mean (SD) AF knowledge score was 5.7 (1.7). Patients had positive perceptions about their medications evident by the mean (SD) positive necessity-concern differential 5.8 (4.1) and poor overall quality of life score, 66.7 (53.7-77.8). There were no significant differences in the depression, anxiety and beliefs about medication scores over time. However, significantly higher proportions of patients answered correctly in the question assessing the consequences of AF (88.6% vs. 50.5%; $p<0.001$) and symptoms score from the quality of life questionnaire has significantly improved at follow up compared to baseline (83.3 vs. 79.2; $p=0.02$)] respectively. Median (IQR) TTR at follow up for patients on warfarin was 77.3% (54.4-84.7) and adherence for 70% of NOAC patients via pill count method was 100%.

Conclusion:

Newly anticoagulated AF patients appear to have low levels of anxiety, depression, poor AF knowledge, positive perceptions about their medication and poor overall quality of life at baseline and these parameters remained the same after six months of follow up. However, significantly more patients were aware of the consequences of AF and symptoms of AF (by the AFEQT questionnaire) improved at follow up. Future research is required in order to determine the impact of educational and behavioural interventions towards improving knowledge, emotional health, quality of life and thus preventing adverse clinical outcomes in patients receiving different types of OAC therapy.

2.2 Background and rationale

Adequate OAC, either with VKA or NOAC is essential for effective stroke prevention in patients with AF with ≥1 additional stroke risk factor (173). NOACs offer efficacy, safety and relative convenience compared to the VKAs (130). However, cost considerations result in variable policies regarding NOACs in different healthcare systems, ranging from unrestricted reimbursement at one end of the spectrum to full payment by AF patients at the opposite end. Some healthcare systems have even adopted 'conditional authorisation' of NOACs prescription, based on (say) 6 months of low quality of anticoagulation with VKAs, as measured by the TTR during a pre-defined period of VKA trial, whilst others still search for optimal criterion for patient selection in the local setting. Indeed, the SAMe-TT_2R_2 score could help aid individual decision-making regarding the choice between VKAs or NOACs in routine clinical practice.

Previous studies by the Birmingham group (284, 383, 384) and others (385, 386) have found that many AF patients possess very little knowledge of their disease and do not understand the risks and/or benefits of anticoagulant therapy, particularly among ethnic minority patients (383, 384). This may contribute to poor INR control, given the complexity of the warfarin regimen, with dosing adjustments, drug-, food- and alcohol- interactions. Few studies have intervened to improve adherence with, and understanding of, warfarin therapy. Thus, a more structured education intervention among patients who are predicted to be less likely to achieve good INR control (SAMe-TT_2R_2 score of >2) may be an alternative treatment strategy which could help improve their TTR.

Patient education has been found to improve INR control (296). Indeed, an earlier pilot study of a brief educational intervention (284) demonstrated a significant improvement in the awareness of target therapeutic INR ($p<0.0001$) and factors which may affect INR levels ($p=0.005$), with a trend towards improvement in awareness of the benefits of anticoagulants

and bleeding risks. Further, the TREAT intervention (see **Table 2.1** for the components of the intervention), a one-off educational-behavioural session, delivered by a health psychologist, demonstrated a significant improvement in the TTR compared to patients receiving usual care alone (76.2% vs. 71.3% respectively; p=0.035) (219, 382).

However, a recent Cochrane systematic review (387) assessing the impact of knowledge and behavioural intervention on TTR showed equivocal results. The mean difference of TTR between patients receiving educational and self-monitoring interventions compared to usual care was 6.31 (95% CI -5.63 to 18.28). This suggest that although TTR appears to be higher in the intervention group vs. usual care, analysis of the pooled data was not in favour (statistically) of the former compared to the latter. Nonetheless, these results were based on only two trials (N=69) with very low quality of evidence, assessing the impact of self-monitoring and education intervention vs. usual care on TTR. Thus, further trials are needed to investigate the benefits of similar interventions (both educational and behavioural) on anticoagulation control in AF patients.

Improving understanding about a disease and its treatment allows patients to make informed decisions about the management of their condition and treatment may make a significant difference to clinical outcomes. Whilst NOACs are a valid alternative to warfarin, the latter will still continue to be used as a treatment for AF, and interventions that can improve anticoagulation control are essential to reduce the risk of adverse events.

Table 2.1: Components of the TREAT intervention

	Content
Educational Booklet	• AF causes and consequences • Warfarin and its metabolism • Stroke risk and risk of bleeding on treatment • Lifestyle changes (diet, alcohol, lifestyle changes)
Patient DVD *Delivered by 'expert patient' narratives and consultant Q&A*	• AF: causes, consequences, side effects, treatment options • Warfarin: INR monitoring, lifestyle changes • Patient barriers: psychological, physical • Consultant Q&A: common questions and answers
Patient worksheet	Including: Calculate your own risk of stroke; personal barriers to warfarin uptake; and discussion of personal goals for lifestyle changes
Self-monitoring diary	Two-week diary monitoring including: Diet; Alcohol intake (in units); Medications; and INR outcomes

2.2.1 Study objective

The initial objective of this study was to perform a prospective observational intervention of NOAC versus warfarin based on SAMe-TT_2R_2 score strata in anticoagulant-naïve patients with AF. In addition, to evaluate the impact of the TREAT-2 educational and behavioural intervention on TTR among patients identified as less likely to establish and maintain adequate TTR (SAMe-TT_2R_2 score >2) receiving warfarin and comparing these patients against those receiving warfarin and usual care alone (those with a SAMe-TT_2R_2 score ≤2).

Secondary objectives included assessment of patients' depression, anxiety, knowledge of AF and its treatment, beliefs about medication and quality of life using validated questionnaires at baseline and six months follow up.

2.3 Methods

Study design

Prospective observational study with a 16-month inclusion period and a 6-month follow-up.

Patients

Anticoagulant-naïve AF patients referred for OAC therapy (see **Figure 2.1**), were recruited from three different sources: (1) OAC clinic at Sandwell and West Birmingham Hospitals (SWBH), (2) AF/Cardiology Clinic at SWBH and (3) OAC clinic, University Hospitals Birmingham (UHB).

Inclusion criteria

Male and female adult (aged ≥18 years) patients with electrocardiographically documented AF without Evaluated Heart valves, Rheumatic or Artificial (EHRA) type 1 VHD, and at least one additional risk factor for stroke (based on the CHA_2DS_2VASc score)(146), who were OAC-naïve (having never taken OAC) and eligible for OAC were considered for inclusion. Men with a CHA_2DS_2VASc score of ≥1 and women with a CHA_2DS_2VASc score of ≥2 were eligible for OAC therapy.

Exclusion criteria

The exclusion criteria were: (1) aged <18 years old, (2) any contraindication to OAC, (3) prosthetic cardiac valve or significant VHD with an indication for heart surgery, (4) likelihood of intermittent or permanent discontinuation of OAC during follow-up (e.g., due to major surgery or post-AF ablation), (5) active malignancy, (6) cognitive impairment, (7) any disease likely to cause their death within 6 months and (8) unable to provide written informed consent.

Ethical approval

This study involved patients from two NHS sites, thus REC approval was applied for. Ethical approvals were obtained from the West Midlands South Birmingham Research Ethics Committee [REC; (REC reference: 16/WM/0339)], the Health Research Authority [HRA; (IRAS ID: 193145); 26th September 2016), and also SWBH Research and Development (R&D; R&D reference: 16CARD06;13th October 2016). The University Hospitals Birmingham was added as a site later and approval from the REC and UHB R&D was obtained (Reference number RRK6149; 12th December 2017). Approval letters can be found in **Appendix 5.** The University of Birmingham acted as the sponsor for this study.

Patient recruitment

Recruitment of patients lasted for 16 months starting from 15th October 2016 to 3rd March 2018. However, the process of obtaining ethical approval at the UHB site began later on and was a lengthy process. Thus, in the 3-month period of recruitment at the UHB site (3rd January – 3rd March 2018), only a limited number of patients were recruited (25 patients were screened for eligibility and only nine patients agreed to participate) (**Figure 2.1**).

2.3.1 Procedure

After initiation of OAC (either warfarin or a NOAC) therapy, patients were seen by an anticoagulant nurse/healthcare professional for an educational session regarding their AF and anticoagulation therapy as per usual care. After that, patients were approached by the researcher to discuss the study and if the patient agreed to participate, written informed consent was obtained and the baseline questionnaire was administered. Individual baseline SAMe-TT_2R_2 score was calculated and patients were allocated to one of four groups on the basis of their SAMe-TT_2R_2 score and OAC (warfarin or NOAC) (see **Figure 2.1**). Patients with a SAMe-TT_2R_2 score ≤2 who were prescribed warfarin (dose-adjusted to achieve a target INR of 2.0 to 3.0) were assigned to Group 1 and patients with a SAMe-TT_2R_2 score ≤2 who were

prescribed NOAC were assigned to Group 2. Patients with a SAMe-TT_2R_2 score >2 who were prescribed warfarin were assigned to Group 3, to receive the intensive education (TREAT-2). Patients with a SAMe-TT_2R_2 score >2 who were prescribed NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) were assigned to Group 4. Baseline demographic and clinical information, including medical, medication history and laboratory information was recorded from the hospital records onto a proforma **(Appendix 1, A1.1).** All patients were informed about AF and the need for anticoagulant therapy by a healthcare professional using the standard warfarin or NAOC-specific education checklist at baseline as per usual care. All patients on warfarin also received the standard Yellow book to identify that they were on warfarin.

Patients in Group 3 would receive a group intervention (between 2-4 patients plus carer/family member) based on the session developed for the TREAT study delivered by the researcher within 4 weeks of warfarin initiation. In addition, patients would receive an educational booklet, self-monitoring diary, worksheet and alert card.

INR monitoring

INR monitoring was performed by the Anticoagulation Services at SWBH and UHB. All patients who received warfarin (usual care and intensive education arms) attended the anticoagulant outpatient clinic at the respective hospital to have their INR checked using a capillary sample. The frequency of the INR visits was at the discretion of the OAC clinic (the OAC clinic staff were blinded to the intervention arm the patient is allocated to enable as 'naturalistic' as possible follow-up and monitoring). Every INR result from baseline to the end of the study (6-months) was recorded. The proportion of time each patient spent in the therapeutic INR range (2.0 to 3.0) (TTR) was calculated by the Rosendaal (using linear interpolation method between two consecutive INR values) and the percentage of INR in range (PINRR) methods (dividing the number of INRs that falls in range by the total number of INR tests). INR data was utilised from months 1 to 6 follow-up (to allow attainment of the

correct dose of warfarin during the first four weeks). More details of the calculation of TTR can be seen in **section 3.3.4.1.1, page 178.**

Six-month follow-up

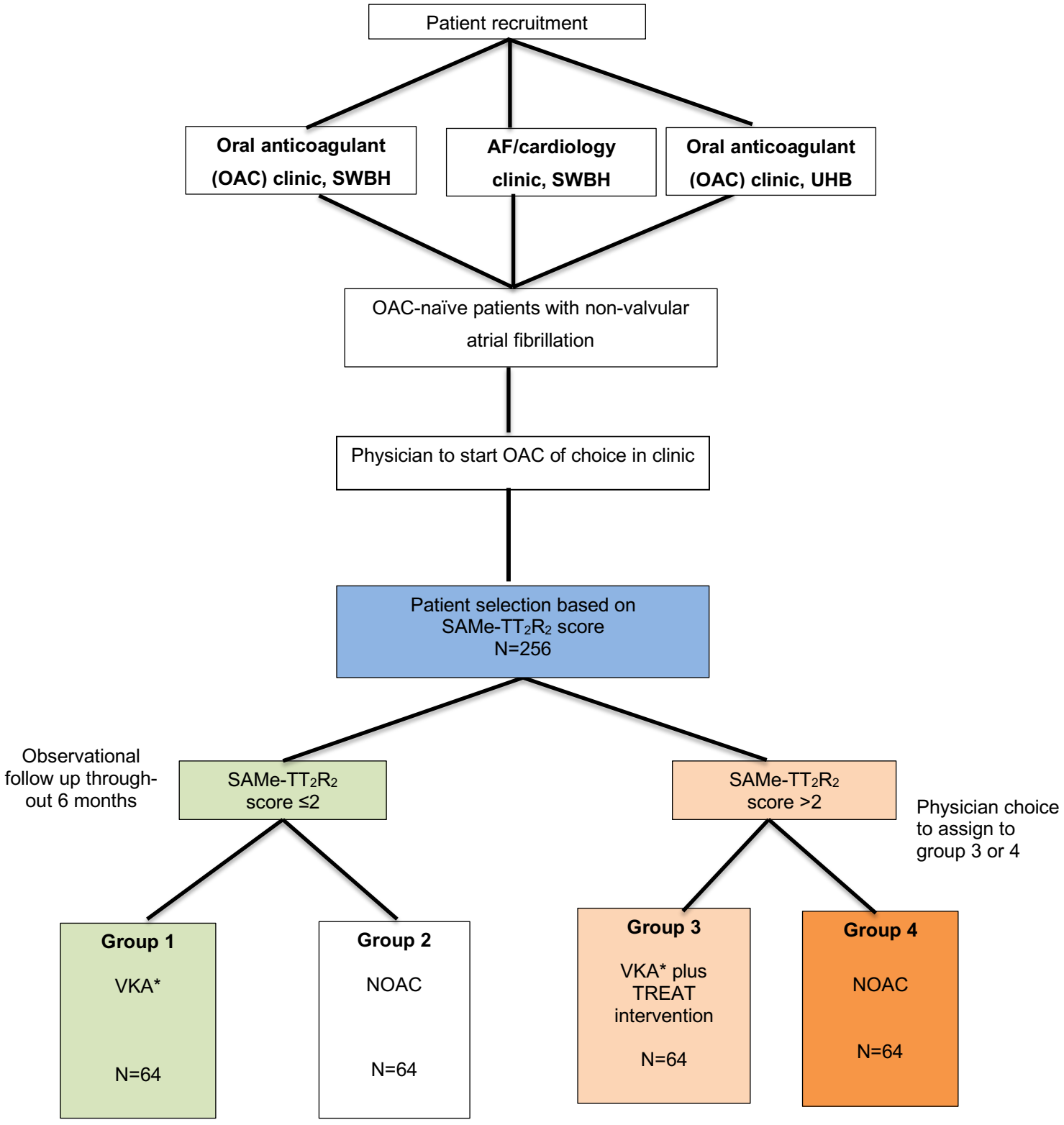
All patients were followed up via phone call at 6 months. Patients receiving NOACs were asked to post back all their pill boxes and blister packs to the researcher. Medication adherence of patients in Groups 2 and 4 were reviewed at 6- months via pill count.

The battery of questionnaires (PHQ-9, GAD-7, AF knowledge scores, BMQ and AFEQT) was posted to all participants at follow up with a stamped addressed envelope for return. If returned questionnaires were not fully completed, the researcher contacted the patient by telephone to facilitate 100% completion of the questionnaires. Patients were sent a reminder questionnaire at both baseline and follow up if they did not respond within 2-3 weeks of receiving the original set of questionnaires.

2.3.2 Assessment of medication adherence

Medication adherence was assessed among patients receiving NOAC therapy via the pill count method. Patients were asked to keep their NOAC boxes and blisters from the point they were recruited into the study until six months of follow up. They were also given stamped-addressed envelopes to return their empty pill boxes and blister packages. Upon receiving the packages, the number of pills remaining in the blister packages were counted. In addition to pill counting, the patients were also asked two questions to assess adherence via a phone call: 1. ‘Do you sometimes forget to take your blood-thinning pills?’ (yes/no answer); 2. ‘Over the past 2 weeks, were there any days when you did not take your blood-thinning medicine?’ (yes/no answer). These two questions were adapted from the self-report questions from the Morisky Green Levine adherence scale, which showed concurrent and predictive validity on

blood pressure control in majority of patients with good adherence to antihypertensive medications (388). Although the pill count method is an indirect measure of adherence, it has higher accuracy compared to other subjective methods (389), cost effective (389) and is commonly used in clinical trials (390, 391).



*All INR measurements under the jurisdiction of SWBH/UHB OAC clinic

Figure 2.1: Study design and patient selection flow chart

2.3.3 Study outcomes

The primary outcome was the proportion of time spent in the therapeutic INR range, 2.0 to 3.0, at 6 months for the two groups commencing warfarin and medication adherence (via pill count) for patients receiving a NOAC. The following secondary outcomes were examined: (1) depression, (2) anxiety, (3) patients' knowledge of AF, (4) beliefs about medication and (5) quality of life.

Ancillary descriptive analyses explored the incidence of bleeding, stroke/TIA, cardiovascular hospitalisation and death (given that the study was not powered to detect these differences). Exploratory analyses determined whether the incidence of bleeding, stroke/TIA, cardiovascular hospitalisation, death and composites (≥1) of these events were similar in patients with SAMe-TT_2R_2 0-2 compared to SAMe-TT_2R_2 >2.

The number of patients with strokes/TIA, bleeding, thromboembolic, CV hospitalisations and death events were determined from hospital records. Stroke was defined as a focal neurologic deficit, from a non-traumatic cause, lasting at least 24 hours and further categorized as ischemic (with or without haemorrhagic transformation), haemorrhagic, or of uncertain type (in the case of patients who did not undergo brain imaging or in whom an autopsy was not performed). Systemic embolism was defined as a thromboembolic event outside the brain, retina, heart or lungs. Stroke and systemic embolism were later combined as thromboembolic events (TE). Major bleeding was classified according to the ISTH criteria (392): fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells) (392). Clinically relevant non-major bleeding (CRNMB) was defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician guided medical or surgical treatment, or a change in antithrombotic therapy (392). Major bleeding and CRNMB were combined as bleeding events. Cardiovascular hospitalisation was defined as a hospitalisation

with a cardiovascular cause: i) heart failure, MI, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled AF/atrial flutter, supraventricular arrhythmia, ii) valve surgery, coronary artery bypass graft (CABG) surgery, percutaneous transluminal coronary angioplasty (PTCA) surgery, pacemaker/ implantable cardioverter-defibrillator (ICD) insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation (393) AND as recorded in patient's medical records.

2.3.3.1 Questionnaires

The following questionnaires were given to the patients to complete at baseline and 6-months later to assess depression and anxiety, knowledge of AF, beliefs about medication, and quality of life (**see Appendix 2 for full questionnaires**). These questionnaires were chosen as they are validated questionnaires and have been used in other cohorts of chronic diseases including asthma, diabetes and cardiovascular diseases including AF (394-396) (397) (398) (399).

2.3.3.1.1 Patient Health Questionnaire (PHQ-9)

Depression was assessed using the Patient Health Questionnaire (PHQ-9) (400). The PHQ-9 is a 9-item scale that contains the diagnostic criteria for depression based on the DSM-IV criteria. It is calculated by assigning scores of 0 to 3 to the response categories of "not at all," "several days," "more than half the days," "and nearly every day," respectively; scores range from 0-27. Scores of 0 indicated no depression and ≥15 signify the presence of major depression. Scores of 5, 10, 15, and 20 represents thresholds demarcating the lower limits of mild, moderate, moderately severe and severe depression, respectively (400).

2.3.3.2.1 The Generalised Anxiety Disorder 7-item (GAD-7)

The Generalised Anxiety Disorder 7-item (GAD-7) questionnaire was used to assess anxiety. It is a 7-item scale and is calculated by assigning scores of 0 to 3 to the response categories of “not at all,” “several days,” “more than half the days,” “and nearly every day,” respectively, and adding the scores together. A total score for the 7 items ranges from 0 to 21. Scores of 0 indicated no anxiety and ≥10 represents the presence of generalised anxiety disorder (GAD). Scores of 5, 10 and 15 are taken as the cut off points for mild, moderate and severe anxiety, respectively (401). The GAD-7 and PHQ-9 scores were chosen because they were recommended by the NICE guidelines as one of the valid measures of anxiety and depression severity (400, 401) among primary care patients (402, 403). Furthermore, both scales have been validated in patients with cardiovascular diseases, (394-396) with good sensitivity and specificity to detect major depressive disorder (81% and 77%, respectively) (395) and generalised anxiety disorder (75% and 89%, respectively) (404).

2.3.3.3.1 Knowledge of AF

Patients’ knowledge of AF was assessed using the Atrial Fibrillation Knowledge scale. (397) This scale consists of 11-items concerning AF in general (3-items), symptoms recognition, (3-items) treatment (3-items) and general attitudes towards AF (2-items). For each question, patient can choose one of three options; only one answer is correct. Scores range from 0 to 11 or 0-100%, with higher correct scores denoting better knowledge of AF(397). This scale has a border line reliability score with Cronbach α of 0.58 in its original derivation cohort. This scale combines three important aspects of AF knowledge: AF management, symptoms and antithrombotic therapy. It can also be used to detect gaps in knowledge and attitude towards AF management (397).

2.3.3.4.1 Beliefs about Medicine Questionnaire (BMQ)

To assess patients' beliefs about medication, the Beliefs about Medicine Questionnaire (BMQ) was used (398). This is an 18-item questionnaire consisting of two parts, one assessing patients' belief about their own medicine (BMQ-specific) and the other assessing patients' beliefs about medicine in general (BMQ-general). The BMQ-specific covers two themes the specific-necessity theme evaluates patients' view about the importance and necessity of their medicines, whilst specific-concern theme comprises patients' beliefs about potential harm and adverse effect of their own medicines. Each sub-scale has a score ranging from 5 to 25. Patients can choose if they 'strongly disagree', 'disagree', 'uncertain', 'agree' and 'strongly agree' with the statements regarding their view of medicines. A high score on the 'necessity' theme indicates that patients think their medicines are important to them; a high score on the 'concern' theme means that patients are worried and concerned about their own medicines. The difference between the necessity and concern domain is obtained by subtracting the two values. Positive values indicate that patients perceive their medication as more important than their concerns about potential side effects of the medication and vice versa for negative values. Likewise, BMQ-general part has two themes as well; general overuse theme assesses how patients perceive the extent of medicine usage, and the general harm theme represents patients' beliefs about the harmful nature of medicines in general. The scores of the last two themes range from 4 to 20; a high score in each theme means negative perception about medicines in general (398). This scale is valid, reliable and has been validated in AF and other cardiovascular diseases, renal, and diabetic populations (398).

2.3.3.5.1 The Atrial Fibrillation Effect on Quality–of-life (AFEQT)

The Atrial Fibrillation Effect on Quality–of-life (AFEQT) questionnaire was used to assess AF patients' quality of life (405). It is a 20-item scale that is further divided to assess symptoms (4-items), daily activities (8-items), treatment concern (6–items) and lastly treatment

satisfaction (2–items). Responses were expressed using a 7-point Likert scale ranging from the most severe limitations/symptoms to no limitation/symptom. The raw score of 1 to 7 was transformed to a 0 to 100 scale. A score of 0 indicates lowest quality of life and a score of 100 indicates highest quality of life. Thus, higher scores on the AFEQT instrument indicate better health status. The responsiveness of this instrument is its ability to detect clinically meaningful changes in a patients' health status over time. Changes in the AFEQT overall and domain scores from baseline to subsequent 6 months were used to evaluate responsiveness to change over time (405). The AFEQT questionnaire was shown to adequately assess quality of life in AF populations evident by demonstrating robust content validity in one systematic review (399).

2.3.4 Hypothesis

It was originally hypothesised that patients with a SAMe-TT_2R_2 score >2 receiving warfarin who received the TREAT-2 intervention (Group 3) would have a significant improvement in TTR compared to those patients with a SAMe-TT_2R_2 score 0-2 receiving warfarin only. Secondly, it was hypothesised that patients with a SAMe-TT_2R_2 score >2 would have more depression and anxiety symptoms, poor knowledge of AF, negative beliefs or perception towards medication and have poorer quality of life than those with SAMe-TT_2R_2 score 0-2.

Unfortunately, due to the change in clinical practice during the study, where prescription rates for NOACs for stroke prevention in AF increased sharply from 2015, there were only 13 patients (Group 1 and 3) prescribed with warfarin therapy of which only four (Group 3) were eligible for the TREAT-2 intervention. However, these four patients did not agree to participate in the TREAT educational intervention within 4 weeks of warfarin initiation; but only agreed to do the questionnaire **(Figure 2.2).** Therefore, the planned analysis of comparing TTR between Group 1 (warfarin and usual care) and Group 3 (warfarin and TREAT-2 educational intervention) could not be undertaken. Hence the analyses focus on the secondary outcomes from the questionnaire data, adverse events and medication adherence in NOAC patients.

Patients were grouped according to the type of OAC they received (warfarin or NOAC) for the questionnaire analyses.

Research questions

- Do patients with a SAMe-TT_2R_2 score >2
    - Have poorer TTR?
    - Have more depression and anxiety symptoms, poorer knowledge of AF and quality of life and negative perceptions of medication?
    - Have more thromboembolic and bleeding events, CV hospitalisations, death and a composite of these events than those with SAMe-TT_2R_2 score 0-2?

Power calculations

Power for the primary endpoint of INR control, evidenced by TTR was calculated based on the results of the TREAT (219) study. In the TREAT study, patients receiving the intensive educational intervention (N=43) and usual care (N=54) had a mean (SD) TTR of 78.5% (20.1) and 66.7% (21.8), respectively. Therefore, a sample size of 54 patients in each of the warfarin groups will provide at least 90% power to detect similar differences at a significance level of 0.05. The same number of patients were recruited for the NOAC groups. To allow for a 20% attrition rate, 64 patients per group were needed, resulting in a total sample size of 256 patients. Data was analysed using IBM SPSS for Windows (Version 23.0) (406).

2.3.5 Statistical analysis

Following a test of statistical normality, by histogram plot method and the Kolmogorov-Smirnov test where a bell-shaped distribution in the former and p-values >0.05 in the latter were indicative of normally distributed data. Continuous variables were presented as mean (SD) and for non-parametric data, median with interquartile range (IQR, 25th to 75th quartile) were reported. Categorical variables were reported as counts with percentages. Descriptive

statistics were presented for baseline demographic and clinical information. Categorical variables were analysed using the chi-square statistic or the Fisher exact test (where expected frequencies are less than five in any cell).

All data were analysed by intention-to-treat. The primary endpoint, TTR, was determined by the method of linear interpolation using the Rosendaal and the PINRR methods, with INR data from months 1 to 6. Overall TTR was also calculated incorporating all available INRs. Differences in the overall TTR and TTR excluding the inception period (INR value from day 1 to day 30) were examined using the Wilcoxon-signed ranked test and were reported as median (IQR) as they were not normally distributed. P-values <0.05 were considered statistically significant.

Data for the secondary endpoints of (1) depression, (2) anxiety, (3) patients' knowledge of AF, (4) beliefs about medication and (5) quality of life at the two time-points (baseline, 6- months) were presented descriptively and graphically to illustrate the change in these variables over time. In this section, patients were grouped according to the type of OAC they received, either warfarin or NOAC, instead of the original SAMe-TT_2R_2 groups. As mentioned previously, there were too few patients in Groups 1 and 3 (N=9 and N=4, respectively) compared to Groups 2 and 44 (N=102 and N=24, respectively), thus making the comparison between SAMe-TT_2R_2 groups inappropriate. However, the results arranged by the original groupings are provided in **Appendix 3**. Paired t-test and Wilcoxon-signed ranked test were used for normally and non-normally distributed data, respectively, to investigate the changes for the questionnaire variables over time for patients who completed the questionnaires at both baseline and six months (N=105).

The number of patients with thromboembolism, major bleeding, CV hospitalisation and all-cause death at 6- months follow up were presented as absolute numbers and percentages. The events were also compared in relation to the SAMe-TT_2R_2 score categories (0-2 vs. >2) and were presented as proportions.

2.4 Results

During the period of patient recruitment, 598 AF patients (573 SWBH and 25 UHB) were screened for eligibility. One hundred and seventy-four patients refused to participate and 255 patients were not eligible due to OAC-experience (N=123), did not attend appointment (N=111), no documented evidence of AF (N=14), cancer (N=4), and cognitive impairment (N=3) (**Figure 2.2).** Of those eligible to participate (N=343), 169 (49.2%) agreed and gave written informed consent. However, only 139 (40.5%) (SWBH 132 and UHB 7) patients returned the baseline questionnaires. At six months follow up, 105 (75.5%) patients returned their questionnaires, with only 67 (70%) NOAC patients returning the empty pill boxes and blister packs **(Figure 2.2).**

2.4.1 Baseline demographics and clinical characteristics of AF patients

Table 2.2 presents the demographics and clinical characteristics of 139 AF patients who were prescribed OAC therapy at baseline stratified by their baseline SAMe-TT_2R_2 score. There were 111 patients (79.9%) with the SAMe-TT_2R_2 score of 0-2, of which 9 patients were prescribed warfarin (Group 1) and 102 patients were prescribed NOACs (Group 2). Only 28 patients (20%) had a SAMe-TT_2R_2 >2, of which only 4 patients were prescribed warfarin (Group 3) and 24 patients received a NOAC (Group 4).

In the overall population, the mean (SD) age was 72.0 (8.5), 56.1% were male, the majority were white (88.8%), married (55.4%), and had secondary school level education (76.3%). Slightly more than half experienced no AF symptoms (54.7%) according to the modified European Heart Rhythm Association (mEHRA) classification system and most (77.0%) had paroxysmal AF. Hypertension (75.5%) was the most common co-morbidity followed by diabetes (28.8%) and chronic kidney disease (26.6%) [defined as creatinine clearance (CrCl) <60ml/min or as stated in the medical notes]. The overall mean (SD) CHA_2DS_2-VASc and HAS-BLED scores were 3.3 (1.5) and 1.9 (1.1) respectively **(Table 2.2).**

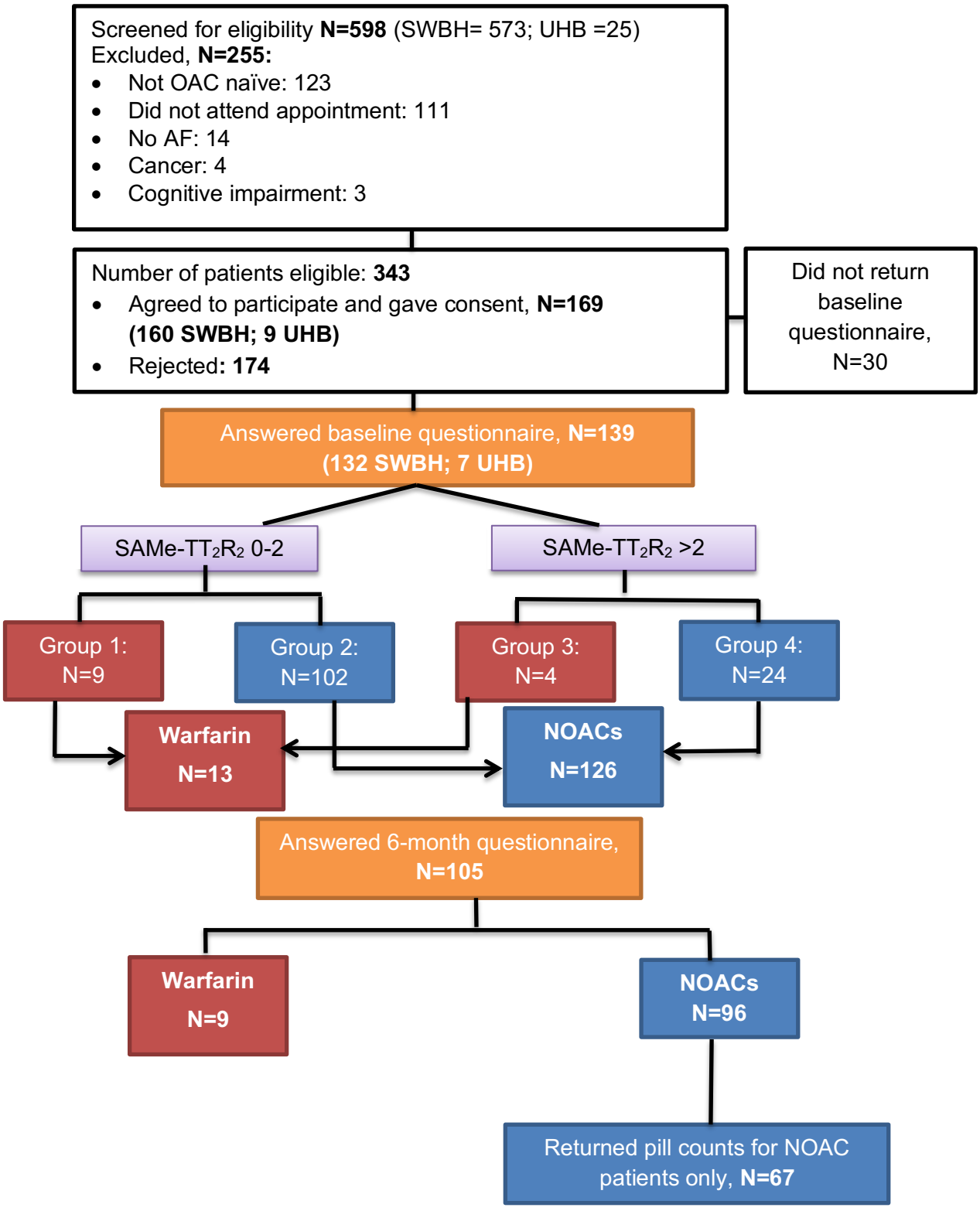


Figure 2.2: Flowchart of patient's inclusion and follow-up in the study

Table 2.2: Baseline demographics and clinical characteristics of newly anticoagulated AF patients stratified by the SAMe-TT_2R_2 score

			SAMe-TT_2R_2 0-2		SAMe-TT_2R_2 >2	
		Overall	**Group 1**	**Group 2**	**Group 3**	**Group 4**
		N=139	N=9	N=102	N=4	N=24
Age at OAC initiation	Mean age (SD)	72.0 (8.5)	72 (6.2)	73.8 (7.9)	68.5 (13.3)	67.2 (9.0)
Age groups	≤64	21 (15.1)	0	10 (9.8)	1 (25.0)	10 (41.7)
	65-74	65 (46.8)	7 (77.8)	48 (47.1)	2 (50.0)	8 (33.3)
	≥75	53 (38.1)	2 (22.2)	44 (43.1)	1 (25.0)	6 (25.0)
Sex	Female	61 (43.9)	4 (44.4)	41 (40.2)	2 (50.0)	14 (58.3)
Ethnic groups	White	123 (88.8)	8 (88.9)	102 (100)	2 (50.0)	11 (45.8)
	South-Asian	7 (5.0)	1 (11.1)	0	0	6 (25.0)
	Afro-Caribbean	9 (6.5)	0	0	2 (50.0)	7 (29.2)
Marital status	Married	77 (55.4)	5 (55.6)	55 (53.9)	2 (50.0)	15 (62.5)
	Single	19 (13.7)	1 (11.1)	16 (15.7)	1 (25.0)	1 (4.2)
	Divorced/separated	12 (8.6)	1 (11.1)	7 (6.9)	1 (25.0)	3 (12.5)
	Widowed	31 (22.3)	2 (22.2)	24 (23.5)	0	5 (20.8)
Educational status	Primary school	5 (3.6)	0	3 (2.9)	0	2 (8.3)
	Secondary school	106 (76.3)	8 (88.9)	75 (73.5)	4 (100)	19 (79.2)
	College	28 (20.1)	1 (11.1)	24 (23.5)	0	3 (12.5)
Age leaving education	Mean age (SD)	16.7 (5.8)	16.7 (3.6)	17.2 (6.2)	15.5 (0.6)	15.9 (4.7)
Alcohol intake	Alcohol>14unit/day	23 (16.5)	0	20 (19.6)	1 (25.0)	2 (8.3)
Smoking status	Smoking/ex-smoker	17 (12.2)	0	4 (3.9)	2 (50.0)	11 (45.8)

Table 2.2 continued

		Overall N=139	Group 1 N=9	Group 2 N=102	Group 3 N=4	Group 4 N=24
Modified EHRA class	Class 1 (none)	76 (54.7)	5 (55.6)	52 (51.0)	4 (100)	15 (62.5)
	Class 2 (mild)	40 (28.8)	3 (33.3)	31 (30.4)	0	6 (25.0)
	Class 3 (severe)	23 (16.5)	1 (11.1)	19 (18.6)	0	3 (12.5)
AF type	Paroxysmal	107 (77.0)	7 (77.8)	77 (75.5)	3 (75.0)	20 (83.3)
	Persistent	9 (6.5)	0	7 (6.9)	0	2 (8.3)
	Permanent	23 (16.5)	2 (22.2)	18 (17.6)	1 (25.0)	2 (8.3)
Past medical history	Heart failure	10 (7.2)	1 (11.1)	7 (6.9)	1 (25.0)	1 (4.2)
	Hypertension	105 (75.5)	6 (66.7)	76 (74.5)	4 (100.0)	19 (79.2)
	Diabetes	40 (28.8)	3 (33.3)	28 (27.5)	2 (50.0)	7 (29.2)
	Stroke/TIA	23 (16.5)	3 (33.3)	13 (12.7)	0	7 (29.2)
	Vascular disease*	21 (15.1)	1 (11.1)	13 (12.7)	1 (25.0)	6 (25.0)
	Lung disease#	26 (18.7)	3 (33.3)	15 (14.7)	1 (25.0)	7 (29.2)
	Kidney disease†	37 (26.6)	4 (44.4)	24 (23.5)	2 (50.0)	7 (29.2)
	Anaemia	29 (20.9)	1 (11.1)	25 (24.5)	0	3 (12.5)
	Previous bleeding	7 (5.0)	0	6 (5.9)	0	1 (4.2)
CHA_2DS_2-VASc score	Mean (SD)	3.3 (1.5)	3.6 (1.9)	3.2 (1.3)	3.5 (2.6)	3.4 (1.7)
CHA_2DS_2-VASc score categories	Low risk	0	0	0	0	0
	Intermediate	22 (15.8)	2 (22.2)	13 (12.7)	1 (25.0)	6 (25.0)
	High risk	117 (84.2)	7 (77.8)	89 (87.3)	3 (75.0)	18 (75.0)
HAS-BLED score	Mean	1.9 (1.1)	1.9 (0.8)	2.0 (1.1)	1.8 (0.5)	1.8 (1.2)
HAS-BLED score categories	Low risk (0-2)	108 (77.7)	7 (77.8)	79 (77.5)	4 (100)	18 (75.0)
	High risk (≥3)	31 (22.3)	2 (22.2)	23 (22.5)	0	6 (25.0)
SAMe-TT_2R_2 score	Mean (SD)	1.7 (1.2)	1.3 (0.7)	1.1 (0.7)	3.5 (0.6)	3.7 (0.8)

Table 2.2 continued

		Overall N=139	Group 1 N=9	Group 2 N=102	Group 3 N=4	Group 4 N=24
Current medications	Warfarin	13 (9.4)	9 (100)	0	4 (100)	0
	NOACs	126 (90.6)	0	102 (100)	0	24 (100)
	Beta-blocker	77 (55.4)	5 (55.6)	53 (52.0)	3 (75.0)	16 (66.7)
	ACEI/ARB	72 (51.8)	3 (33.3)	54 (52.9)	2 (50.0)	13 (54.2)
	Diuretics	44 (31.7)	3 (33.3)	29 (28.4)	2 (50.0)	10 (41.7)
	Amiodarone	3 (2.2)	0	1 (1.0)	0	2 (8.3)
	Concurrent antiplatelet	7 (5.0)	0	2 (2.0)	0	5 (20.8)
	Digoxin	12 (8.6)	2 (22.2)	8 (7.8)	0	2 (8.3)
	Calcium channel blocker	54 (38.8)	3 (33.3)	39 (38.2)	2 (50.0)	10 (41.7)
	Statins	98 (70.5)	7 (77.8)	68 (66.7)	3 (75.0)	20 (83.3)

Group 1: SAMe-TT_2R_2 score 0-2 + warfarin; Group 2: SAMe-TT_2R_2 score 0-2 +NOAC; Group 3: SAMe-TT_2R_2 score >2 +warfarin; SAMe-TT_2R_2 score >2+NOAC

ACEI/ARB: angiotensin converting enzyme inhibitor/ angiotensin receptor blockade; AF: atrial fibrillation; CHA_2DS_2-VASc score - Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75years [2 points], Diabetes, Stroke [2 points], Vascular disease, Age 65–74 years, and Sex category (female). Total scores range between 0-9; low risk CHA_2DS_2-VASc score: 0 male; 1 female, intermediate: 1male, ≥2 female, high risk CHA_2DS_2-VASc score: ≥2 male; ≥3 female; TIA: transient ischemic attack; eGFR: estimated glomerular filtration rate, ml/min/1.73 m^2; HAS-BLED score – uncontrolled Hypertension: systolic ≥160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR ratio/TTR <60, Drugs/alcohol concomitantly. Total scores range between 0-9; low risk of bleeding range between 0-2 and high risk of bleeding ≥3; modified European Heart Rhythm Association symptom scale (mEHRA): 1 no symptoms, 2 mild and moderate, 3 severe, 4 disabling; SAMe-TT2R2 score – Sex female, Age<60, Medical history (more than two comorbidities), Treatment (interacting drug, e.g. Amiodarone), Tobacco use (doubled) and Race (non-white, doubled). Total scores ranged from 0-8; probable good response to VKA therapy range between 0-2 and probable poor response to VKA therapy ranged from ≥3; SD: standard deviation
* Vascular disease: prior myocardial infarction, peripheral artery disease or aortic plaque; # Lung disease: obstructive and restrictive diagnosed lung conditions; †eGFR <60ml/min or as noted in medical notes

2.4.2 Psychological measures, knowledge and beliefs about medication of AF patients overall and according to OAC groups (warfarin vs. NOACs)

2.4.2.1 Depression and anxiety

At baseline, the median (IQR) depression and anxiety scores in the whole cohort were 4.0 (1.0-8.0) and 1.0 (0-5.0), respectively **(Table 2.3).** Most patients had none or minimal symptoms of depression (57.6%) or anxiety (71.9%) **(Table 2.3).** The median (IQR) depression and anxiety scores were higher in patients receiving a NOAC than those receiving warfarin, [depression [4.0 (1.0-8.0) vs. 2.0 (0-4.5)] and anxiety [1.0 (0-5.0) vs. 0 (0-4.5)], respectively.

At the 6-month follow-up, the overall median (IQR) scores of PHQ-9 and GAD-7 were the same [depression 4.0 (0-9.0) and anxiety 1.0 (0-5.0), respectively] **(Table 2.3).** There were no significant differences in the median (IQR) depression and anxiety scores **(Table 2.4 and Figure 2.3)** and the proportion of AF patients in different categories of depression **(Figure 2.4)** and anxiety **(Figure 2.5)** across the two time points.

The prevalence of major depression (PHQ-9 ≥15) at baseline and follow-up was 6.7% **(Table 2.4).** Meanwhile, the prevalence of generalised anxiety disorder (GAD-7 ≥10) was 11.4% at baseline but declined slightly to 9.5% at follow up **(Table 2.4).** There was no significant difference between the proportion of patients with major depression and generalised anxiety disorder over time **(Table 2.4 and Figure 2.6).**

Table 2.3: Baseline and 6 months follow up psychological measures of AF patients overall and according to OAC groups (warfarin vs. NOACs)

Median (IQR)	Baseline (N=139)			Follow up (N=105)		
	Overall, N=139	Warfarin N=13	NOACs N=126	Overall, N=105	Warfarin N=9	NOACs N=96
PHQ-9 (9 items; scores range from 0-27)						
Total score	4.0 (1.0-8.0)	2.0 (0-4.5)	4.0 (1.0-8.0)	4.0 (0-9.0)	3.0 (0-6.0)	4.0 (0.3-9.0)
Minimal 0-4, N (%)	80 (57.6)	10 (76.9)	70 (55.6)	56 (54.4)	7 (77.8)	51 (53.1)
Mild 5-9, N (%)	31 (22.3)	2 (15.4)	29 (23.0)	25 (24.3)	1 (11.1)	24 (25.0)
Moderate 10-14, N (%)	20 (14.4)	0	20 (15.9)	15 (14.6)	0	15 (15.6)
Moderately severe 15-19, N (%)	5 (3.6)	0	5 (4.0)	6 (5.8)	1 (11.1)	5 (5.2)
Severe depression 20-27, N (%)	3 (2.2)	1 (7.7)	2 (1.6)	1 (1.0)	0	1 (1.0)
GAD-7 (7 items; scores range from 0-21)						
Total score	1.0 (0-5.0)	0 (0-4.5)	1.0 (0-5.0)	1.0 (0-5.0)	0 (0-5.0)	1.0 (0-5.0)
Minimal 0-4, N (%)	100 (71.9)	10 (76.9)	90 (71.4)	68 (66.0)	6 (66.7)	64 (66.7)
Mild 5-9, N (%)	23 (16.5)	1 (7.7)	22 (17.5)	25 (24.3)	2 (22.2)	23 (24.0)
Moderate 10-14, N (%)	8 (5.8)	2 (15.4)	6 (4.8)	6 (5.8)	0	6 (6.3)
Severe anxiety 15-21, N (%)	8 (5.8)	0	8 (6.3)	1.0 (1.0)	1 (11.1)	3 (3.1)

GAD-7: The Generalised Anxiety Disorder 7-item; IQR: interquartile range; NOACs: non-vitamin K oral anticoagulants; OAC: oral anticoagulants; PHQ-9: Patient Health Questionnaire

Table 2.4: Changes in psychological measures between baseline and 6 months follow up among overall AF patients (N=105)

Median (IQR) change in score	Baseline N=105	Follow up N=105	Changes in score over time	Differences over time p- value*
PHQ-9 (9 items)				
Median (IQR) score	4.0 (1.0-8.5)	4.0 (0-9.0)	0 (-2.5 to 1.5)	0.53
Major depression PHQ-9≥15, N (%)	7 (6.7)	7 (6.7)	-	1.00
GAD-7 (7 items)				
Median (IQR) score	1.0 (0-5.0)	1.0 (0-5.0)	0 (-1.0 to 1.0)	0.67
Major anxiety disorder, GAD-7≥10, N (%)	12 (11.4)	10 (9.5)	-	0.822

*Wilcoxon-signed ranked test; AF: atrial fibrillation; PHQ-9: Patient Health Questionnaire; GAD-7: The Generalised Anxiety Disorder 7-item; IQR: interquartile range

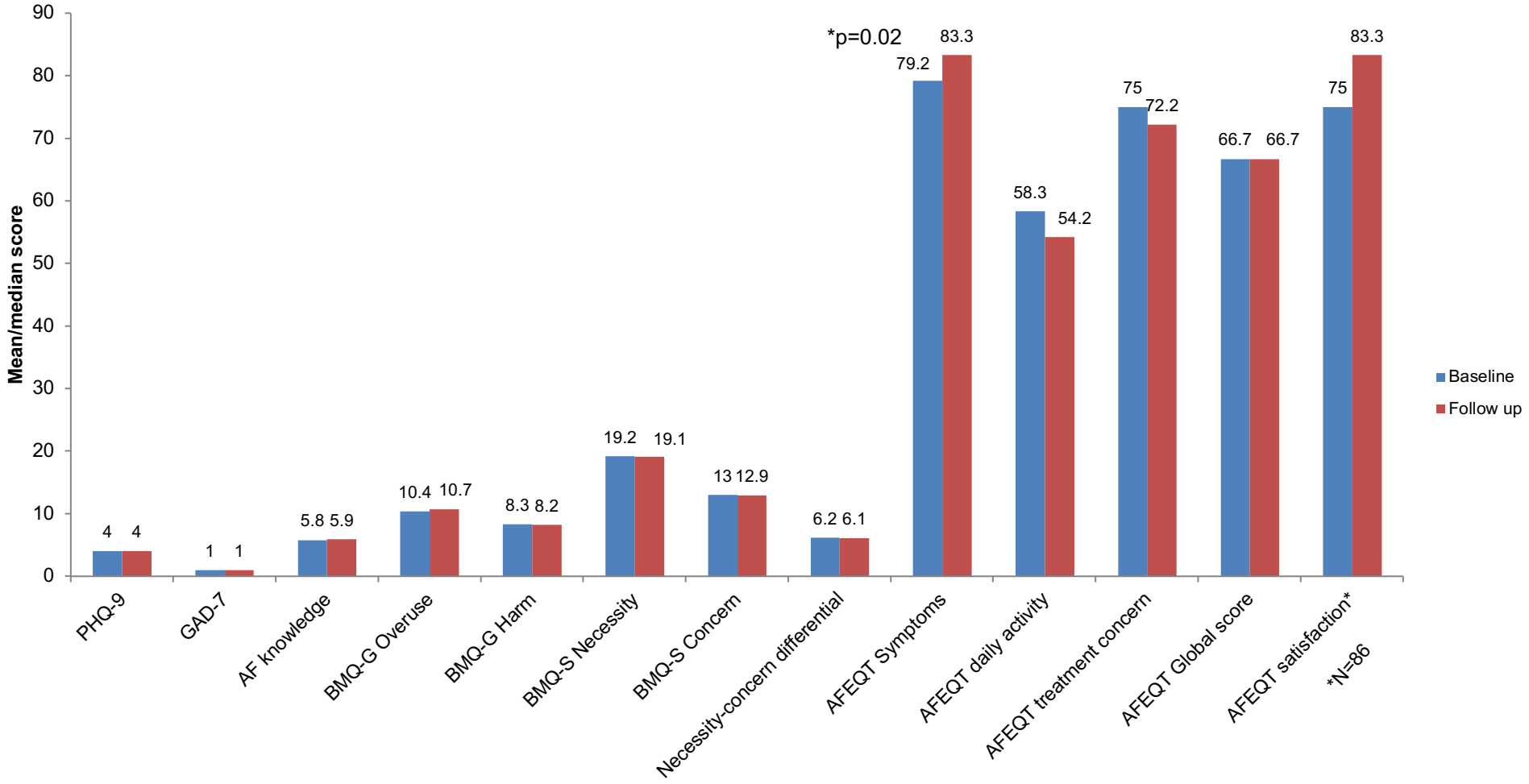


Figure 2.3: Mean/median score at baseline and 6 months follow up for depression, anxiety, knowledge of AF, beliefs about medication and quality of life among overall AF patients who completed the questionnaire at both time points (N=105)

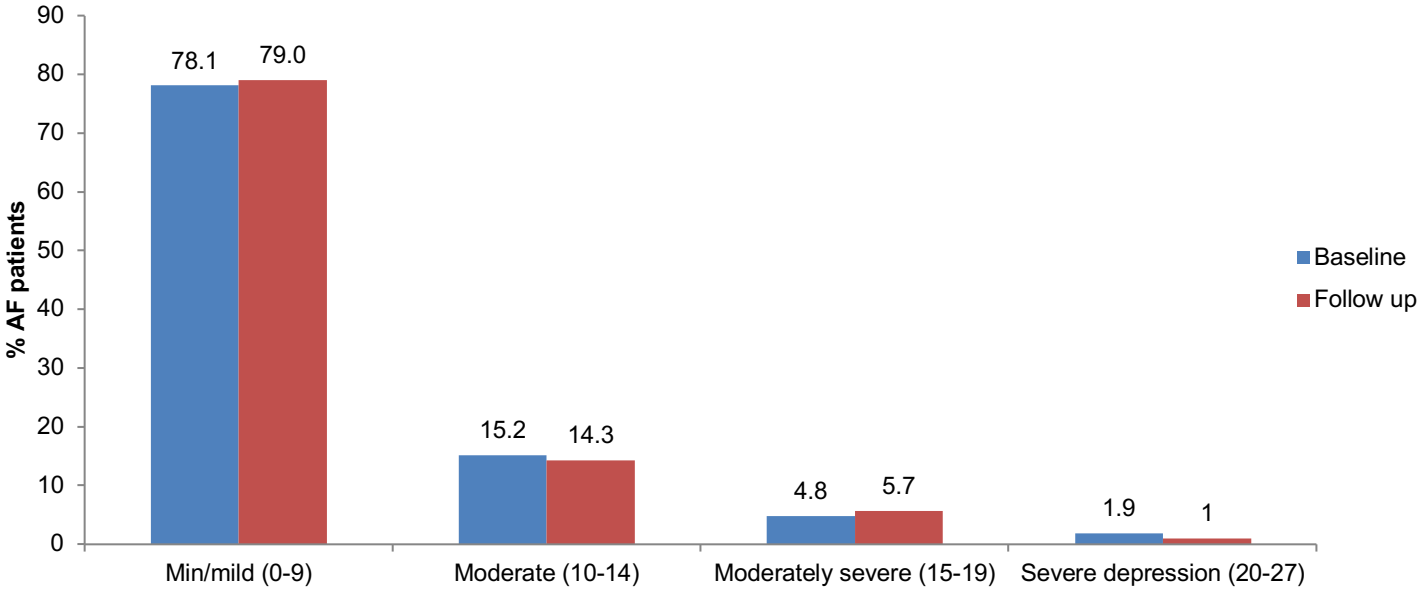


Figure 2.5: PHQ-9 scores in categories among overall AF patients at baseline and 6 months follow up (N=105)

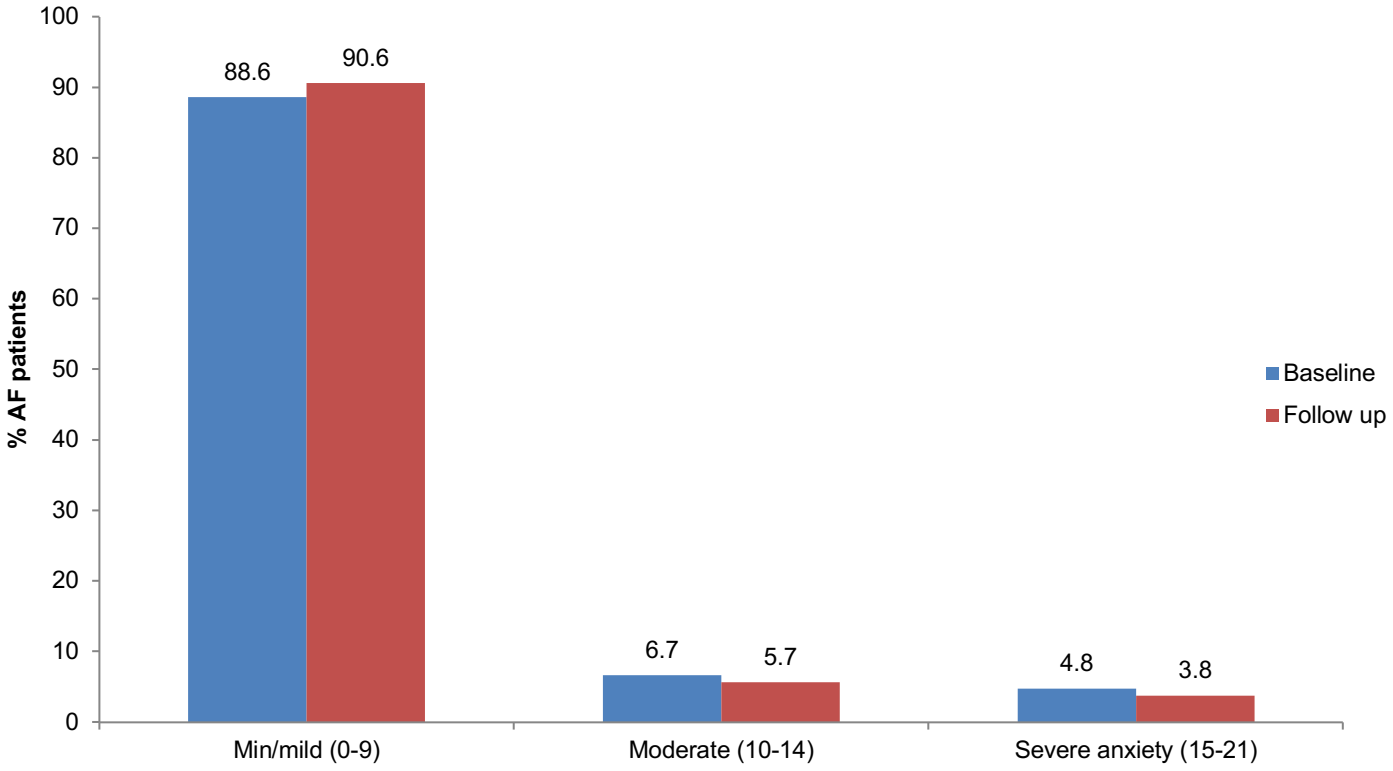


Figure 2.4: GAD-7 scores in categories among overall AF patients at baseline and 6 months follow up (N=105)

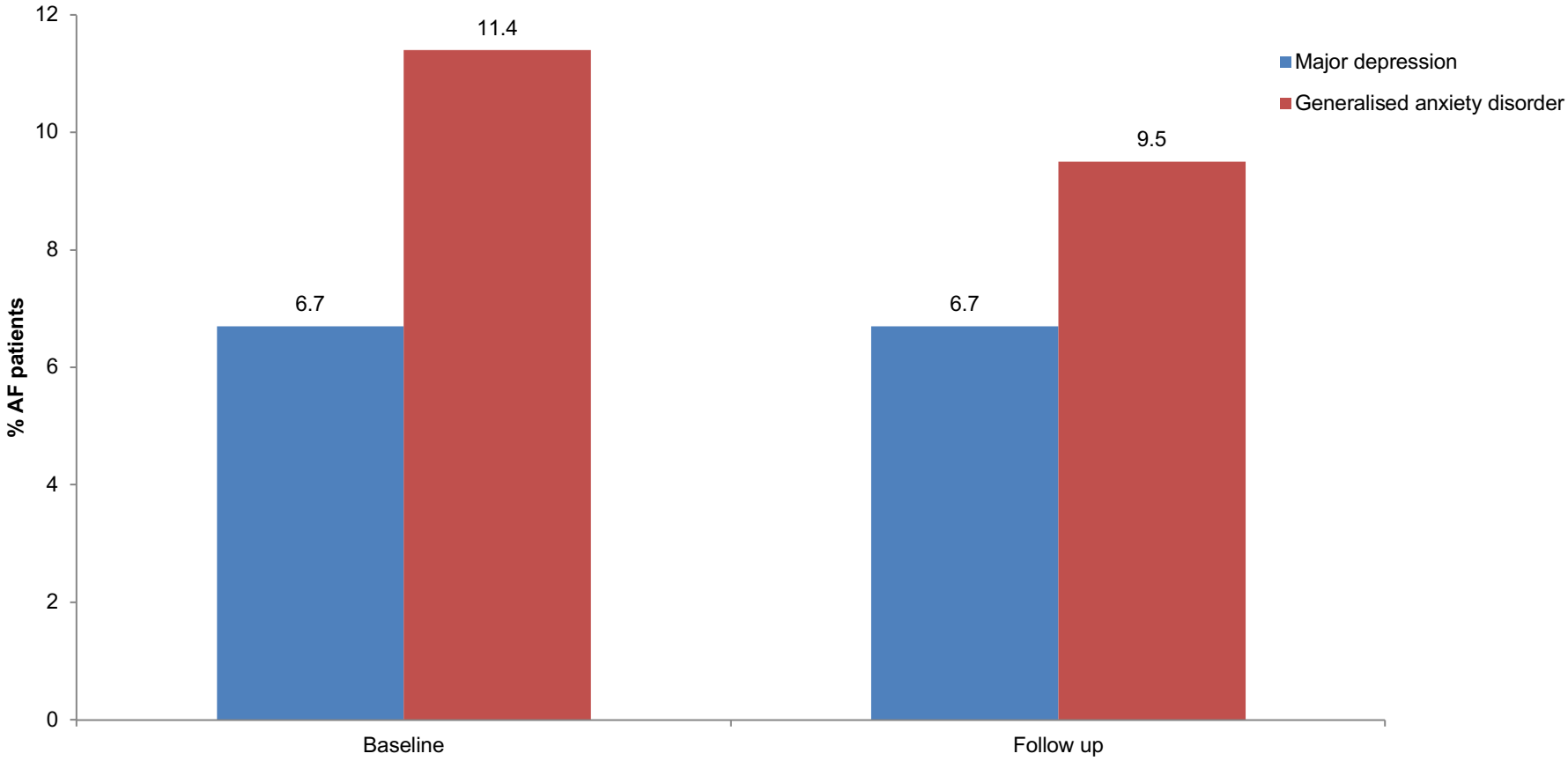


Figure 2.6: Major depression (PHQ-9 ≥15) and generalised anxiety disorder (GAD-7≥10) among overall AF patients at baseline and 6 months follow up (N=105)

2.4.3 AF knowledge

At baseline, the overall mean (SD) score, for AF knowledge was low at 5.7 (1.7) with warfarin patients obtaining slightly higher mean scores overall compared to NOAC patients **(Table 2.5).**

At follow up, the overall mean (SD) score for AF knowledge was similar to the score at baseline, at 5.9 (1.9) **(Table 2.5).** There were no significant differences in the overall mean AF knowledge scores between baseline and 6-months **(Table 2.6).**

Each question of the AF knowledge scale was also analysed specifically among patients who answered the questionnaires at both time points (N=105) **(Table 2.7 and Figure 2.7).** The majority of patients correctly answered the 'reason for OAC prescription' (90.5%) and on the question 'regarding physical activity' (91.4%) at baseline. However, significantly fewer patients correctly answered the 'reason for OAC prescription' at follow up (74.3%) compared to baseline (p=0.002). Conversely, significantly higher proportions of patients were aware of 'the consequences of AF' at follow up (88.6%) compared to baseline (50.5%; p<0.001) **(Table 2.7 and Figure 2.7).**

Table 2.5: Baseline and 6 months follow up knowledge scale of AF patients overall and according to OAC groups (warfarin vs. NOACs)

AF knowledge scale (11 items; scores range from 0-100%)						
	Baseline (N=139)			**Follow up (N=105)**		
Mean (SD), %	**Overall** N=139	**Warfarin** N=13	**NOACs** N=126	**Overall** N=105	**Warfarin** N=9	**NOACs** N=96
Total overall scores **(min-max: 0-11)**	5.7 (1.7)	6.8 (1.2)	5.6 (1.7)	5.9 (1.9)	7.0 (1.3)	5.8 (1.9)
Total overall scores, %	52.0 (15.4)	61.5 (11.2)	51.0 (15.4)	53.9 (16.9)	63.6 (11.1)	52.9 (17.0)

AF: atrial fibrillation; NOACs: non-vitamin K oral anticoagulants; OAC: oral anticoagulants; SD: standard deviation

Table 2.6: Change in knowledge scale between baseline and 6 months follow up among overall AF patients (N=105)

AF knowledge scale (11 items; scores range from 0-100%)	**Baseline** N=105	**Follow up** N=105	**Changes in score over time**	**Differences over time p-value***
Total overall score **(min-max: 0-11)**	5.8 (1.7)	5.9 (1.9)	-0.1 (2.0)	0.50
Total overall score, %	52.6 (15.5)	53.9 (16.9)	-1.2 (18.3)	0.50

*Paired t-test; AF: atrial fibrillation

Table 2.7: Specific questions in the AF knowledge scale and percentages of patients with correct response at baseline and 6 months follow up (N=105)

Questions in AF knowledge score	Baseline	Follow up	p-value*
AF in general			
1. If AF is identified without any complaints, patients should immediately visit hospital	18 (17.1)	17 (16.2)	1.00
2. It is risky if patients do not feel his/her AF	45 (42.9)	33 (31.4)	0.06
3. AF is a rare condition	8 (7.6)	8 (7.6)	1.00
Symptoms recognition			
1. What are the trigger factors for AF	47 (44.8)	58 (55.2)	0.07
2. Why is it important to take my medications properly	50 (47.6)	44 (41.9)	0.43
3. What is atrial fibrillation?	64 (61.0)	69 (65.7)	0.53
AF treatment			
1. Why patients using oral anticoagulation should be careful with the use of alcohol	71 (67.6)	72 (68.6)	1.00
2. What is the function of anticoagulation clinic	61 (58.1)	57 (54.3)	0.61
3. Why is oral anticoagulation prescribed in certain patients with AF	95 (90.5)	78 (74.3)	**0.002**
AF general attitude			
1. Statements regarding physical exercise	96 (91.4)	93 (88.6)	0.61
2. Statements regarding the danger associated with AF	53 (50.5)	93 (88.6)	**<0.001**

*chi-square; AF: atrial fibrillation

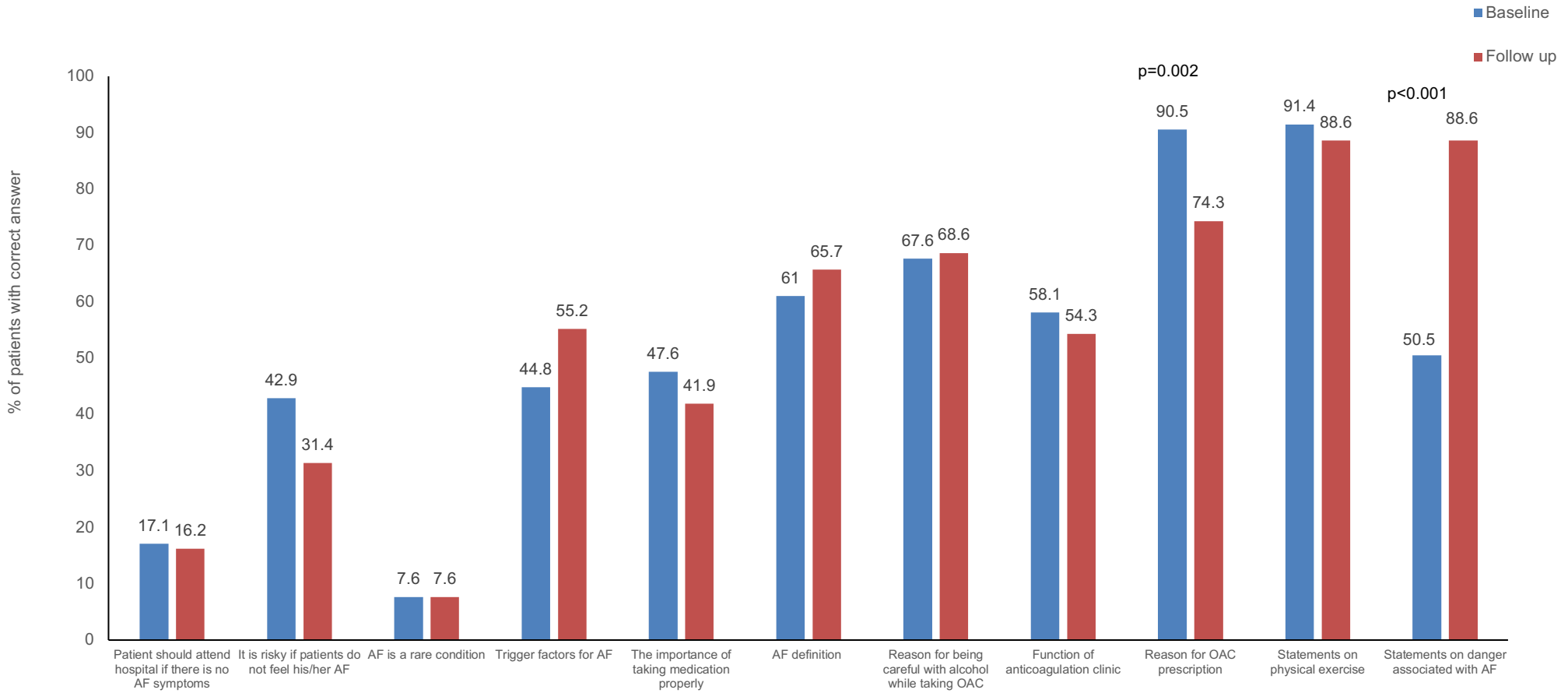


Figure 2.7: Proportion of AF patients with correct answers in each specific question at baseline and 6 months follow up (N=105)

2.4.4 Beliefs about medication

At baseline, the overall mean (SD) score in the general overuse and general harm domains were 10.5 (2.9) and 8.6 (2.9), respectively. In terms of patients' specific beliefs about their anticoagulation therapy, the mean (SD) specific-necessity score was higher [19.0 (3.0)] than the specific-concern score [13.3 (3.5)], with a positive necessity-concern differential [5.8 (4.1)]. This indicates that patients perceived their medications are being more important than their concerns regarding medications. NOAC patients obtained slightly higher scores on the general harm and specific-concerns domains at baseline compared to warfarin patients **(Table 2.8).**

At six months follow up, the scores in the general and specific domains remained the same. Similar scores were seen among warfarin and NOAC patients in the general overuse and general harm domains, while NOAC patients achieved slightly higher scores on the specific necessity and necessity-concern differential **(Table 2.8).** There was no significant difference in either the general and specific domains over time **(Table 2.9).**

Table 2.8: Baseline and 6 months follow up scores on beliefs about medication of AF patients overall and according to OAC groups (warfarin vs. NOACs)

	Baseline scores (N=139)			Follow up scores (N=105)		
Baseline scores, mean (SD)	**Overall,** N=139	**Warfarin** N=13	**NOACs** N=126	**Overall,** N=105	**Warfarin** N=9	**NOACs** N=96
Beliefs about medication (BMQ; 18 items)						
BMQ general (scores range from 4-20)						
General overuse (4-20)	10.5 (2.9)	10.5 (2.9)	10.5 (2.9)	10.7 (2.9)	10.8 (1.4)	10.7 (3.0)
General harm (4-20)	8.6 (2.9)	7.4 (1.7)	8.7 (2.9)	8.2 (2.4)	8.4 (1.2)	8.2 (2.5)
BMQ specific (scores range from 5-25)						
Specific necessity (5-25)	19.0 (3.0)	19.2 (2.4)	19.0 (3.1)	19.1 (3.1)	18.8 (1.4)	19.1 (3.2)
Specific concern (5-25)	13.3 (3.5)	12.2 (2.7)	13.4 (3.6)	12.9 (3.8)	13.3 (4.3)	12.9 (3.8)
Necessity-concern differential	5.8 (4.1)	6.9 (3.9)	5.7 (4.2)	6.1 (4.4)	5.4 (4.2)	6.2 (4.4)

BMQ: Beliefs about medication; NOACs: non-vitamin K oral anticoagulants; OAC: oral anticoagulants; SD: Standard deviation

Table 2.9: Change in score on beliefs about medication between baseline and 6 months follow up among overall AF patients (N=105)

BMQ (18 items) mean (SD) score	Baseline N=105	Follow up N=105	Changes in score over time	Differences over time p- value*
BMQ general‡				
General overuse	10.4 (3.0)	10.7 (2.9)	-0.4 (2.8)	0.20
General harm	8.3 (2.8)	8.2 (2.4)	0.1 (2.4)	0.78
BMQ specific‡				
Specific necessity	19.2 (3.0)	19.1 (3.1)	0.1 (2.4)	0.54
Specific concern	13.0 (3.5)	12.9 (3.8)	0.0 (3.5)	0.91
Necessity-concern differential	6.2 (4.0)	6.1 (4.4)	0.1 (3.9)	0.78

*paired t-test; AF: atrial fibrillation; BMQ: Beliefs about medication; SD: standard deviation

2.4.5 Quality-of-life

The overall global median (IQR) baseline score for quality of life was 66.7 (53.7-77.8). Patients scored lowest in the daily activity domain [60.4 (39.6-79.2)] and highest in the AF symptoms domain [79.2 (58.3-95.8)]. NOAC patients had higher scores in the AF symptoms and treatment satisfaction domains and the overall global score compared to warfarin patients **(Table 2.10).**

At follow up, the median (IQR) global score was also 66.7 (49.1-81.9) and patients continued to score lowest in the daily activity domain **(Table 2.10).** Similarly, NOAC patients had higher scores in the AF symptoms and treatment satisfaction domains compared to warfarin patients. Among patients who completed the questionnaires at both time-points, there was a significant increase in AF symptoms score at follow-up [83.3 (64.6-100) vs. 79.2 (54.2-95.8); p=0.02], with no significant change in the other domains over time **(Table 2.11 and Figure 2.8).**

Table 2.10: Baseline and 6 months follow up quality of life scores of AF patients overall and according to OAC groups (warfarin vs. NOACs)

AFEQT (20 items; scores range from 0-100)						
	Baseline measures (N=139)			**Follow up measures (N=105)**		
Median (IQR)	**Overall,** N=139	**Warfarin** N=13	**NOACs** N=126	**Overall,** N=105	**Warfarin** N=9	**NOACs** N=96
AF symptoms (0-100)	79.2 (58.3-95.8)	58.3 (41.7-97.9)	79.2 (58.3-95.8)	83.3 (64.6-100)	75.0 (54.2-97.9)	83.3 (66.7-100)
Daily activity (0-100)	60.4 (39.6-79.2)	68.8 (31.3-82.3)	60.4 (39.6-77.6)	54.2 (34.4-77.1)	66.7 (21.9-82.3)	54.2 (35.4-76.6)
Treatment concern (0-100)	75.0 (52.8-86.1)	75.0 (68.1-83.3)	75.0 (52.8-88.9)	72.2 (58.3-88.9)	72.2 (52.8-88.9)	72.2 (58.3-88.9)
Treatment Satisfaction† (0-100)	75.0 (66.7-83.3)	66.7 (56.3-85.4)	75.0 (66.7-83.3)	83.3 (66.7-91.7)	75.0 (66.7-91.7)	83.3 (66.7-89.6)
Overall global score (0-100)	66.7 (53.7-77.8)	60.2 (50.9-80.1)	66.7 (53.7-77.8)	66.7 (49.1-81.9)	75.0 (47.2-81.5)	66.2 (48.6-82.2)

† N=111; AFEQT: Atrial Fibrillation Effect on Quality–of-life; AF: atrial fibrillation; OAC: oral anticoagulants; IQR: interquartile range; NOACs: non-vitamin K oral anticoagulants

Table 2.11: Change in quality of life scores between baseline and 6 months follow up among overall AF patients (N=105)

Median (IQR) change in score	**Baseline** N=105	**Follow up** N=105	**Changes in score over time**	**p- value***
AFEQT (20 items)				
Median (IQR) AF symptoms	79.2 (54.2-95.8)	83.3 (64.6-100)	-4.8 (22.2)	**0.02**
Median (IQR) daily activity	58.3 (38.5-80.2)	54.2 (34.4-77.1)	2.8 (18.9)	0.33
Median (IQR) treatment concern	75.0 (52.8-86.1)	72.2 (58.3-88.9)	-0.90 (23.2)	0.57
Median (IQR) treatment satisfaction†	75.0 (66.7-83.3)	83.3 (66.7-83.3)	-4.3 (22.2)	0.07
Median (IQR) overall global score	66.7 (51.9-78.0)	66.7 (49.1-81.9)	-0.3 (16.2)	0.65

† N=86 at both time points; *Wilcoxon-signed ranked test; AFEQT: Atrial Fibrillation Effect on Quality–of-life; AF: atrial fibrillation; IQR: interquartile range

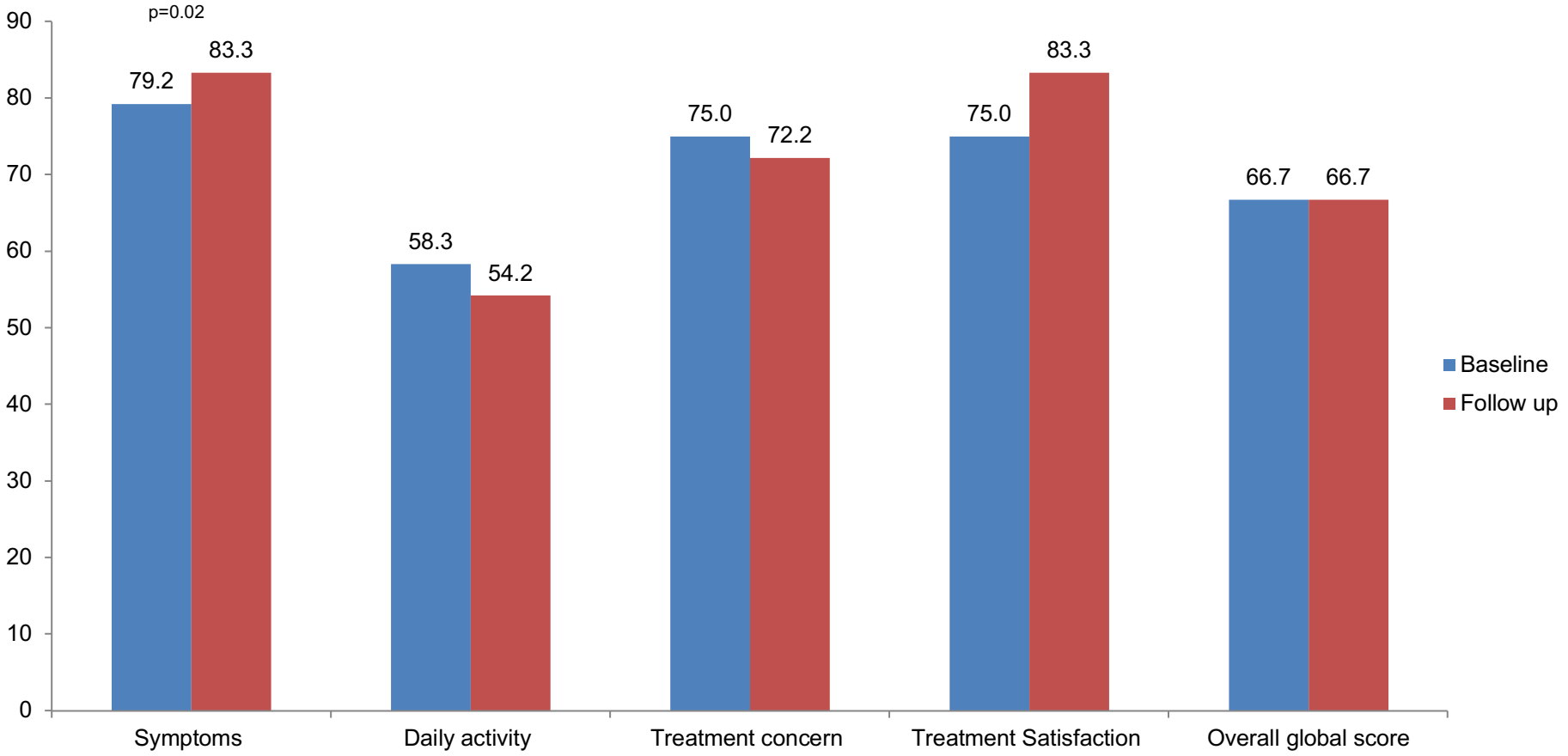


Figure 2.8: Quality of life domain scores assessed by the AFEQT questionnaire in AF patients overall at baseline and 6 months follow up (N=105)

2.4.6 Time in therapeutic range, medication adherence and adverse clinical outcome at 6 months follow up

The overall median (IQR) TTR for warfarin patients at 6 months using the Rosendaal and PINRR methods were 62.6 (49.0-70.3) and 43.1 (33.0-50.0), respectively. When the inception period (the first 4 weeks of warfarin treatment) was excluded, TTR and PINRR were significantly better, 77.3 (54.4-84.7; p=0.004) and 56.4 (45.8-66.7; p=0.004), respectively. Among the 126 patients on NOACs at baseline, 96 patients reached the six months follow up. Among them, 67 patients (70%) returned their pill boxes and blister packages at follow up and the pill count demonstrated 100% adherence. Six patients had their medications prepared from the pharmacy as weekly blister packs thus they are not able to keep their empty NOAC packages/boxes. Moreover, upon questioning, majority of patients (86.5%) claimed that they never forget to take their NOAC medication and only one patient claimed they have forgotten to take it over the past two weeks.

At follow up, there were only 13 patients with ≥1 of the composites of bleeding, CV hospitalisations and death. No thromboembolic events occurred, three patients experienced bleeding events (2 major bleed and 1 CRNMB bleed), 8 patients had CV hospitalisation and 3 patients died. When the events were stratified according to the SAMe-TT_2R_2 score categories (0-2 vs. >2), a non-significant higher proportion of patients with SAMe-TT_2R_2 >2 experienced CV hospitalisation (7.1% vs. 5.4%), death (3.6% vs. 1.8%) and ≥1 of the composites of bleeding, CV hospitalisations and death (10.7% vs. 9.0%) compared to those with SAMe-TT_2R_2 0-2 respectively. However, all bleeding events (2.7%) occurred among those with SAMe-TT_2R_2 0-2.

2.5 Discussion

AF patients who were newly anticoagulated with either warfarin or NOACs for stroke prevention do not appear to have significant depressive or anxiety symptoms at baseline. However, patients had poor knowledge of AF and its treatment, perceived that OAC medication is important and this outweighed their medication concerns, and they also had poor quality of life. At six months, there were no significant changes in depression, anxiety, beliefs about medication and quality of life. However, more patients were aware of the consequences of AF but fewer patients understood the reason of OAC prescription and patients had improvements in AF symptoms at follow up compared to baseline.

In this study, few patients reported depressive and anxiety symptoms at baseline and follow up; consistent with previous studies in the West Midlands assessing depression and anxiety among AF patients using validated questionnaires (99, 407) (219). In the overall population, more patients experienced symptoms of generalised anxiety rather than major depression at baseline (11.4% vs. 6.7%, respectively) and follow up (9.5% vs. 6.7%, respectively). This finding is consistent with studies by Lane et al (99) and Clarkesmith et al (219). Both studies (99, 219) reported a higher prevalence of anxiety (38.5-41.5%) than depression (25.5%) among their AF cohorts at baseline, but were limited by smaller sample sizes (N=70 to 97) and used different questionnaires to assess symptoms of depression and anxiety (BDI, STAI and HADS) than the present study. Taken together, these results suggest that anxiety is the predominant affective trait among AF patients, which might influence the patient's quality of life (96, 99, 219). The presence of higher anxiety symptoms rather than depressive symptoms in the current cohort is difficult to explain but may be influenced by the presence of comorbidities as well as AF symptoms and commencing OAC therapy. A recent systematic review (408) of eight studies (AF vs. control group) assessed the role of psychological factors in AF using validated questionnaires. From the five studies (95, 96, 409-411) assessing the

role of depression in AF patients included in the review, only one study (409) showed a significant difference in the depression level among AF patients compared to healthy controls (effect size 3.08; 95% CI 2.63-3.57) (409). For trait anxiety, two studies (96, 410) showed higher levels of trait anxiety in AF patients compared to hypertensive patients (96) and patients with supraventricular tachycardia (410), although the differences were small for both studies [0.34; 95% CI 0.07-0.61 and 0.41 (0.02-0.80) respectively]. As a result, no clear conclusion was made due to small number of studies and methodological differences (408). For example, types of AF patients studied were different (paroxysmal vs. persistent vs. permanent), different type of questionnaires were used to assess depression and anxiety and conclusions from each study were inconsistent. Hence, future studies in this area are needed to draw a clear conclusion on the involvement of psychological distress in AF patients.

In general, patients in the current study have positive perception towards OAC medication evidenced by high mean (SD) specific-necessity scores [19.0 (3.0)] and a positive necessity-concern differential [5.8 (4.1)] at baseline. This remained unchanged at follow up indicating that patients perceive their OAC medication as more important than their concerns about it. This finding is similar to the TREAT study (219) in the UK and in another study in Palestine (412). Both studies showed higher specific-necessity beliefs than specific-concern beliefs and this was associated with better treatment adherence in both studies (219, 412) and better TTR in the TREAT education intervention group compared to the usual care group (219). In this cohort, patients also disagreed that their medications are harmful. This further strengthens the positive beliefs that patients have towards the importance of taking their medication which could potentially impact their adherence level. In the adherence assessment among patients receiving NOACs via the pill count method at six months, 70% of the patients reported 100% adherence. However, the remainder (N=29) did not return any boxes/blister packages as they had forgotten to keep them for the study purposes. In contrast, one study from Saudi Arabia (413) among patients with multiple chronic diseases (diabetes, hypertension, asthma; N=408) showed higher general harm score [13.6 (2.3)] than the current study and this was significantly

more prevalent among non-adherent patients compared to high adherent patients. This suggests that where patients have negative thoughts about their medication, they are more likely to become non-adherent. In this study, no significant differences were seen in both the general and specific domains of the BMQ over time. Although the available evidence demonstrates consistent results with the current studies, caution must be exercised as there could be differences in terms of medication beliefs, usage and cultural differences between studies conducted in Western countries compared to Middle Eastern countries (412) (413).

In terms of AF knowledge, AF patients in this cohort had poorer knowledge about AF and its treatment reflected by an average score of 5.7 (1.7) and 5.9 (1.9) at baseline and follow up, respectively. There were no significant differences in the AF knowledge score over time. Nevertheless, on assessing each specific question on the AF knowledge questionnaire, more patients were aware of the consequences of AF at follow-up but fewer understood the reasons of OAC prescription at follow up compared to baseline. Clearly, there is a gap in AF knowledge among patients which changes over time in terms of the need of OAC therapy for stroke prevention. These findings are in keeping with other studies investigating knowledge among AF patients (283, 284, 286, 287). Studies showed that AF patients have inadequate knowledge of their condition (284-287), poor understanding of the benefits and risk of their treatment, (285-287) specifically anticoagulation therapy and not aware of the factors that could impact the effectiveness and safety of treatment (284-286). Thus, this could influence their ability to make informed choices of the treatment options and prevent them from being actively involved in management of their own treatment. Lane and colleagues (283) have included strategies to improve knowledge among AF patients entailing: greater awareness among the public of what is AF and the repercussions, better patient support and provisions of educational materials, enhanced understanding of the patients' needs among medical professions, improved communication between physicians and patients and including patients' preferences during the discussion of treatment options (283). Studies (219, 386) have also shown that with better education, emotional distress can be reduced, adherence

and concordance can be enhanced (219, 284, 289) and quality of life can be improved resulting in better treatment outcomes (219, 386).

Overall, AF patients had poor quality of life evident by a median score of 66.7% for the overall global score and this remained the same at 6 months follow up; similar to other studies (99, 219). In contrast, one trial (386) in the Netherlands (N=712) showed higher baseline QoL score in AF patients randomised to the nurse-led group (72%) (with psychosocial support and education intervention at 3,6 and 12 months) but similar QoL scores in the usual care group (68%) compared to the current study. In their study, QoL, including anxiety and depression, improved significantly after 1 year of follow up, irrespective of treatment group. However, patients in the nurse-led group had better knowledge at follow up and quality of life was significantly correlated with knowledge. Taken together, these findings suggest the benefits of a structured educational intervention (involving educational reinforcement and psychosocial support) in promoting better knowledge, emotional health and quality of life. In the current cohort, patients seem to have the greatest limitation in their physical health compared to emotional and clinical health at both baseline and follow up (evident by lowest score in the daily activity domain). Multiple observational studies worldwide (109, 111-113, 116) have shown similar results where AF patients appear to have the greatest impairment in their physical health compared to their emotional health. This could be influenced by ageing, symptoms severity, number of comorbidities, all of which could affect the patients' ability to conduct physical activity and thereby reduce their quality of life (QoL) (386) (109, 111-113, 116). In this study, significant improvement was only seen in the AF symptoms domain at follow up, suggesting that patients were less affected by their symptoms at this point. This could probably be influenced by effective symptom management with either pharmacological or non-pharmacological interventions (cardioversion or ablation) although this is purely speculative. Another explanation is that maybe patients had had time to come to terms with their diagnosis and were therefore less bothered by their symptoms.

There were only thirteen patients on warfarin therapy and their overall median (IQR) TTR at six months was suboptimal at 62.6% (49.0-70.3) however, TTR was significantly better and at the optimal level after excluding the inception period (the first four weeks of therapy to allow attainment of warfarin dose) with 77.3% (54.4-84.7; p=0.004); a finding similar to previous study(219). In terms of adverse events, there were no TE events, however, three patients had bleeding events (2 major bleed and 1 CRNMB), eight patients were hospitalised for CV reason and two patients died at follow up. All adverse events occurred among NOAC patients.

2.5.1 Limitations

This study has several limitations. Firstly, the study contained only 13 patients on warfarin and no patients attended the TREAT educational intervention thus the original planned analyses and hypothesis testing were not possible, due primarily to a change in clinical practice regarding NOAC prescription over warfarin for AF patients newly initiating OAC. The recruitment target was not achieved (N=256) based on the pre-specified SAMe-TT_2R_2 groups (N=64 in each group). Thus, the results for patients on warfarin or NOAC were presented descriptively and no significance testing was undertaken. Secondly, although two centres were utilised for patient recruitment, the overall number of patients included was low compared to other longitudinal studies assessing psychological measures, knowledge and quality of life among AF patients (108, 386, 414). However, the results from the current study are in keeping with previous studies within the West Midlands reporting low levels of anxiety, depression and knowledge among AF patients (99, 407). In addition, there were only 16 non-white patients, thus the results may not be applicable to all AF participants. Thirdly, only 105 (76%) patients completed the 6-month questionnaires; the study had 24% attrition rate at 6 months. It is possible that those who did not return the 6-month questionnaires may have experienced more health problems and/or worsening emotional health and quality of life. The results may have been different if all respondents completed the 6-month questionnaires. However, the 6-month response rate was 76%, which is higher than many previous questionnaire studies (96, 219, 415, 416). Fourth, among the 96 NOAC patients who reached the follow up only 70%

returned their empty pill boxes/packages. The pill count method is not the most robust method of assessing adherence as patients may not have taken all the pills but simply returned the empty boxes and blister packs, however this method is simple, low cost and used in many clinical trials (389). To date, direct measures of adherence including measurement of drugs in plasma or urine were considered the most accurate way to assess adherence however it is expensive, difficult to perform, is dependent on the test used and drug metabolism (389).

2.5.2 Clinical implications and future research

This study will add to the existing literature on the psychological health, quality of life and AF knowledge of patients with AF who receive OAC. Whilst NOACs have sought to overcome the inherent difficulties experienced by patients prescribed with warfarin, the psychological impact on patients (as well as warfarin patients) has not been thoroughly investigated to date. Together, these results will provide important insights into patient's feelings, beliefs and awareness about the OAC, and the impact on their QoL. This information can be used to create innovative strategies to improve health outcomes in AF patients receiving OAC therapy for stroke prevention.

More in-depth studies investigating the psychological impact of OAC therapy in AF patients are needed. Validated questionnaires to collect data on the emotional impact (anxiety and depression) and quality of life could be routinely included as endpoints in large RCTs/multinational registries so that this information is available alongside other endpoints.

Furthermore, the TREAT-2 intervention could be extended to other developing countries like Malaysia where warfarin is the main OAC of choice for stroke prevention in AF. In Malaysia, the majority of VKA patients are being managed by clinical pharmacist in the hospital setting in the Medication Therapy Adherence Clinic (MTAC) (417). This clinic aims to optimise medication therapy, improve medication adherence and prevent/reduce problems related to medication with a pre-specified protocol that incorporates a patient education checklist, INR

testing interval, dosage adjustment and warfarin dispensing (417). To date, no trials are available in Malaysia to determine the impact of MTAC towards TTR however, one retrospective cohort study (418) of mainly AF patients showed that TTR was significantly better in the MTAC compared to usual care group (TTR 65.1 vs. 48.3; $p<0.05$ respectively) while another study (419) of AF patients showed no difference in TTR between the two respective groups. It would be of interest to incorporate the components of TREAT-2 intervention into the MTAC protocol and design a trial to examine TTR in the TREAT-2 intervention group + MTAC (N=50) vs. usual care group (N=50) in Malaysia. The outcome of this study could determine the benefits of the added TREAT-2 intervention into the current MTAC protocol and the impact of such interventions towards psychological health, quality of life and knowledge among patients receiving it.

2.6 Conclusion

Newly anticoagulated AF patients appear to have low levels of anxiety, depression, poor AF knowledge, positive perceptions about their medication and poor overall quality of life at baseline which remains unchanged at six months follow up. However, more patients were aware of the consequences of AF and AF symptoms (by the AFEQT questionnaire) improved significantly at follow up.

Chapter 3. Anticoagulation control in different ethnic groups receiving vitamin K antagonist therapy for stroke prevention in atrial fibrillation: the West Birmingham AF Project

3.1 Abstract

Introduction: Efficacy and safety of VKAs is optimised in AF patients when the INR is 2.0-3.0. Anticoagulation control comparing different ethnic groups has not been well-assessed, although epidemiological studies suggest poorer INR control in non-white cohorts.

Objective: To examine the quality of VKA control (TTR), predictors of anticoagulation control and the prevalence of adverse clinical outcomes [thromboembolic (stoke/TIA and systemic embolism), bleeding events, cardiovascular hospitalisation and all-cause mortality] in AF patients in a multi-ethnic cohort at one acute Trust in the West Midlands, United Kingdom. Ancillary analysis was also undertaken to investigate TTR among elderly (≥80 vs. <80 years) and patients with different categories of kidney disease (eGFR≥90 vs. 60-89 vs. ≤59ml/min/1.73m^2) within this cohort. Exploratory analyses investigated the relationship between INR control and adverse clinical outcome.

Methods: All demographic and clinical data were collected retrospectively from the electronic medical record database. VKA control was assessed retrospectively by TTR using the Rosendaal method and percentage INRs in range (PINRR), among 991 White, Afro-Caribbean and South-Asian AF patients. Predictors included patient's demographics, comorbidities and other clinical data and these were examined by multiple regression analysis. The relationship between INR control and adverse clinical outcome was investigated with chi-square.

Results: The overall mean (SD) age at warfarin initiation was 71.6 (9.4) years; 55% male; mean (SD) CHA_2DS_2-VASc score 3.4 (1.6) and patients were followed up over a median of

5.2 years. The cohort consisted of 807 Whites, 102 South-Asians and 82 Afro-Caribbean patients. Compared to Whites, mean (SD) TTR and PINRR were significantly lower in South-Asians [TTR 67.9% vs. 60.5%, p<0.001; PINRR 58.8% vs. 51.6%, p<0.001 respectively] and Afro-Caribbeans [TTR 67.9% vs. 61.1%, p<0.001; PINRR 58.8% vs. 53.1%, p<0.001 respectively], despite similar INR monitoring intensity. Whites had better anticoagulation control, evidenced by a greater proportion with TTR ≥70% and PINRR ≥70%. Anticoagulation control was significantly more likely to be sub-therapeutic (INR<2.0) among South-Asians and Afro-Caribbeans compared to Whites (30.2%, 30.2%, and 24.7%, p<0.05 respectively).

Ancillary analyses showed that TTR was similar (66.6%) in patients ≥80 vs. <80 years and there were no significant differences in TTR observed among patients with normal kidney function (eGFR≥90), mild (eGFR 60-89) and mild-moderate-severe kidney disease (eGFR ≤59) [64.0% vs. 66.9% vs. 67.0%; p=0.053 respectively].

Logistic regression revealed that non-white ethnicity [OR 2.62 95%CI (1.67-4.10); p<0.001 and OR 3.47 (1.44-8.34); p=0.005] and anaemia [OR 1.65 95%CI (1.00-2.70); p=0.05 and OR 6.27 95%CI (1.89-20.94); p<0.003] were independent predictors of both TTR<70% and PINRR<70%, respectively.

At 5.2 years, 329 (33.2%) patients experienced ≥1 major adverse clinical outcome (MACE). Cardiovascular hospitalisations were significantly higher among South-Asians compared to Whites (32.3% vs. 21.3%; p<0.05). Patients with CV hospitalisations were significantly more likely to have poor TTR (TTR<70%, p=0.002 and TTR<65%, p=0.008).

Conclusions: Ethnic disparities in the quality of anticoagulation control are evident with South-Asians and Afro-Caribbeans having poorer INR control compared to Whites. There were no significant differences in TTR between elderly and younger patients (≥80 vs. <80 years) or between different categories of kidney disease. Non-white ethnicity and anaemia remained the strongest independent predictor of poor TTR and PINRR. CV hospitalisations were more prevalent among South-Asians and were associated with poor TTR.

3.2 Introduction

Vitamin K antagonists (e.g., warfarin) have been used for many decades for the prevention of stroke in patients with AF (131). The efficacy and safety of VKA is determined by achieving the target international normalised ratio (INR) of 2.0-3.0 in AF patients (131). To summarise INR control over time, TTR can be calculated by various methods including Rosendaal's (using linear interpolation to assign INR value to each day between two consecutive INR values) and the percentage of INRs within therapeutic range (PINRR) (420, 421). TTR is a significant and important predictor of thromboembolic and bleeding outcomes in AF patients on VKA (3, 131, 173, 316). A recent European consensus document recommended an individual TTR of ≥70% for optimal efficacy and safety outcomes whilst on a VKA (3), whilst the NICE guidelines on AF recommend a TTR ≥65% (344).

Many factors can influence the quality of anticoagulation control thus affecting TTR, (**see Section 1.5.1, page 78** for a review of predictors of anticoagulation control) (199). Ethnicity has been identified as one of the determinants of anticoagulation control in patients with AF (199) and this has been incorporated in the SAMe-TT_2R_2 score (**see Section 1.5.1.1.8, pages 83-85** for more information on ethnicity and TTR). Apart from ethnicity, studies have also shown that increasing age (247, 252) and chronic kidney disease (263-270) were associated with poor anticoagulation control [**see Section 1.5.1** for more information on the impact of age (**pages 80-81**) and kidney disease (**pages 81-82**) on TTR].

3.2.1 Study objectives

Birmingham is a multi-ethnic city mainly comprised of White British (53.1%), Afro-Caribbean (4.4%), Pakistani (13.5%) and Indian (6%) citizens, and Sandwell and West Birmingham Hospitals NHS Trust serves this tri-ethnic population. The main aim of this study was first to investigate the quality of anticoagulant control; second, to examine predictors of anticoagulation control (TTR) and lastly, to examine the prevalence of adverse clinical outcomes in AF patients in a multi-ethnic cohort. Ancillary analyses were also undertaken to investigate anticoagulation control among elderly patients (≥80 vs. <80 years) and patients with different categories of kidney disease (eGFR≥90 vs. 60-89 vs. ≤59ml/min/1.73m^2). Exploratory analyses also investigated the relationship between INR control and adverse clinical outcomes.

3.3 Methods

3.3.1 Study design

This is a retrospective cohort analysis of a multi-ethnic cohort of AF patients receiving VKA therapy for stroke prevention at one acute Trust in the West Midlands, United Kingdom. Data collection was undertaken from February to December 2016. AF patients receiving VKA therapy for stroke prevention with a target INR range of 2.0-3.0 were selected from the DAWN AC® anticoagulation management software; used by the Trust Anticoagulation Service to manage anticoagulation therapy.

The DAWN AC® anticoagulation management software, a computer assisted dosage program, is clinically validated software designed to manage large anticoagulation clinics in an effective and safe way (422). It contains a complete anticoagulation decision support package that includes induction, maintenance and bridging of warfarin therapy (422). It also contains demographic and clinical information including reasons for anticoagulation, types of

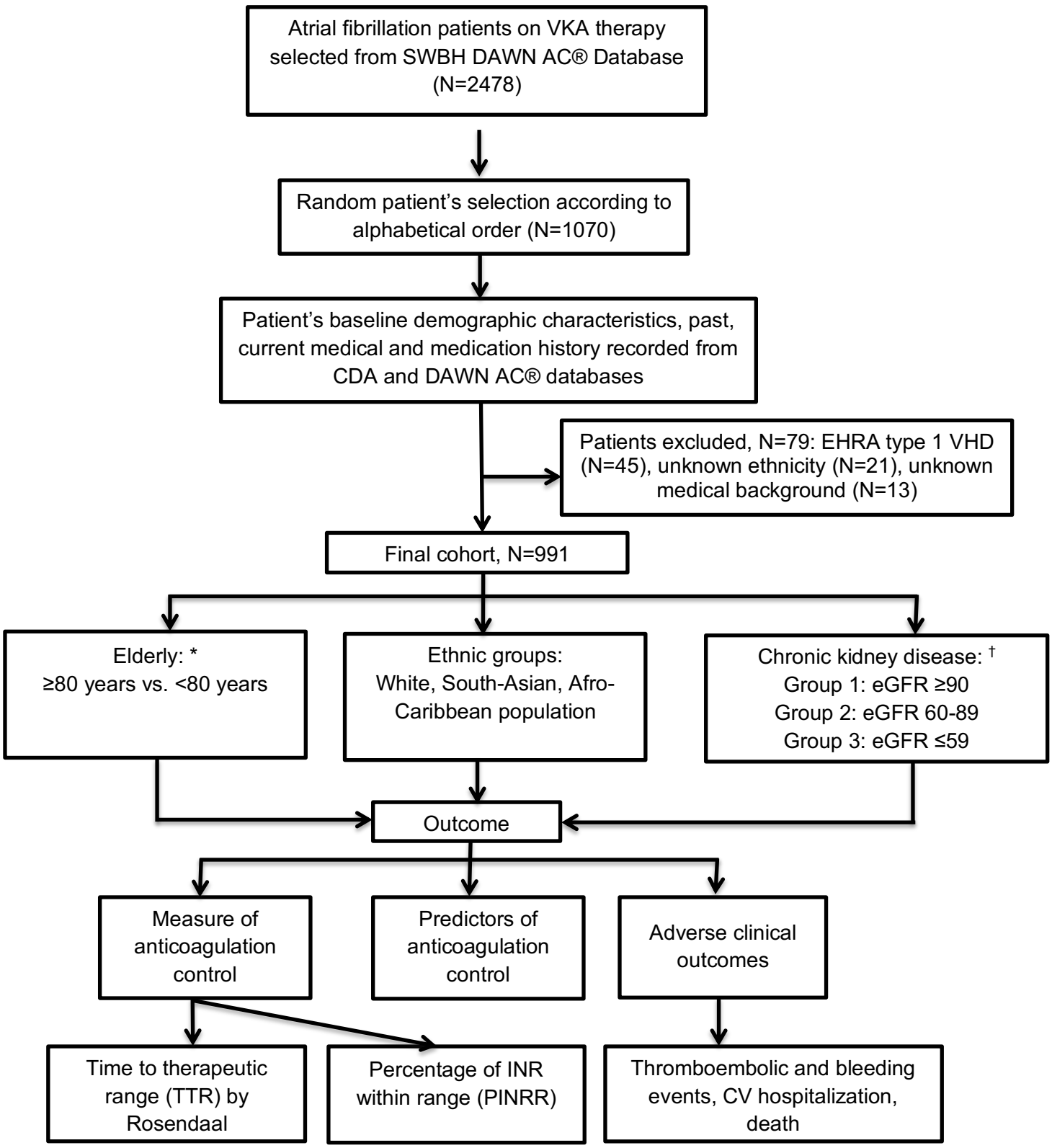
anticoagulant used, target INR range, and the start date of anticoagulation, plus the dosing algorithm, test interval and INR results including history and current INRs for VKA management.

This study was considered as service evaluation by the SWBH Research and Development department and therefore did not require REC approval. However, local R&D approval was obtained (see email confirmation from SWBH R&D Department, **Appendix 5**).

3.3.2 Patient selection

An alphabetical list of patients was generated (N=2478) from DAWN® AC and patients were selected at random by choosing every third, fifth and tenth patient from the patients list. A total of 1070 patients were included constituting 43% of the whole population. The ethnic group distribution of the population in this Trust (AF patients on VKA therapy) generated from the DAWN database is as follows: 78% Whites, 7.4% South-Asian, 5.3% Afro-Caribbeans and 9.5% unknown/other ethnic background. For the purpose of this analysis, the present cohort is representative of the whole AF and VKA cohort at the Trust, i.e., 81.4% White, 10.3% South-Asian and 8.3% Afro-Caribbean.

Patients with EHRA type 1 VHD (N=45), unknown ethnicity (N=21), or unknown medical history (N=13) were excluded from these analyses. EHRA type 1 VHD were defined as patients with a diagnosis of moderate-to-severe mitral stenosis, rheumatic valvular disease or valve replacement requiring VKA therapy. Thus, the final cohort comprises 991 patients (807 White, 102 South-Asian, and 82 Afro-Caribbean). **Figure 3.1** presents the study design flow chart.



*Ancillary analysis 1; †Ancillary analysis 2; CDA: clinical data archive; CV: cardiovascular; INR: international normalised ratio; TTR: time in therapeutic range; PINRR: percentage of INRs in range; SWBH: Sandwell and West Birmingham Hospitals; VKA: vitamin K antagonist

Figure 3.1: Study design and patient selection flow chart

3.3.3 Procedure

A proforma **(see Appendix 4, Table A4.1)** was used to collect all baseline demographic and clinical characteristics of patients including medical history, medication, laboratory results and also information on outcomes of interest, INR results and adverse clinical outcomes. All demographics and clinical information were gathered from the Clinical Data Archive (CDA), an electronic medical record database. The CHA_2DS_2-VASc score (146), HAS-BLED score (180) and SAMe-TT_2R_2 score (199) were calculated for each patient based on the available information and used to predict stroke, bleeding and anticoagulant control, respectively (see **Table 3.1**).

Table 3.1: CHA_2DS_2-VASc, HAS-BLED, and SAMe-TT_2R_2 scores

CHA_2DS_2-VASc		**HAS-BLED**	
CHF or LVF ≤40%	1	Uncontrolled **H**ypertension†	1
Hypertension	1	**A**bnormal kidney/liver function	1/2
Age ≥75 years	2	**S**troke	1
Diabetes	1	**B**leeding‡	1
Stroke/TIA/ thromboembolism	2	**L**abile INR§	1
Vascular Disease*	1	**E**lderly ≥65 years	1
Age 65-74	1	**D**rugs/alcohol excess‖	1/2
Female **s**ex	1		
Total	**9**		**9**

SAMe-TT_2R_2	
Sex (female)	1
Age (<60 years)	1
Medical history¶	1
Treatment strategy#	1
Tobacco use**	2
Race (non-Caucasian)	2
Total	**8**

CHF: congestive heart failure; INR: international normalised ration; LVF: left ventricular function; TIA: transient ischemic attack; * prior myocardial infarction, peripheral artery disease or aortic plaque; †systolic blood pressure ≥160mmHg; ‡ bleeding history, anaemia or predisposition for bleeding; §poor time in therapeutic range (<60%); ||concurrent antiplatelet /non-steroidal anti-inflammatory drugs, ≥8units alcohol/week; ¶Two or more of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease; #interacting drugs, e.g., amiodarone; **within 2 years

3.3.4 Variables and definitions

3.3.4.1 Primary dependent/outcome variables:

3.3.4.1.1 Time in therapeutic range (TTR)

All available INR values from inception to 31st December 2016 or cessation of OAC therapy or death were obtained from the CDA and DAWN AC® databases. The quality of anticoagulation control was calculated as the proportion of TTR (INR 2.0-3.0), using the Rosendaal method (421) (which uses linear interpolation to assign an INR value to each day between two consecutive INR values) and PINRR, calculated by dividing the number of INR in range with the total INR values (420, 423). TTR values were further dichotomized into TTR ≥70% and TTR <70%, according to a recent European consensus document for optimal efficacy and safety outcomes (3) whilst on a VKA, and ≥65% and <65% based on the NICE guidelines (118). The proportion of sub-therapeutic (INR <2.0) and supra-therapeutic (INR >3.0) INRs was also calculated. Years of follow up is defined as the duration of warfarin therapy denoted from the first available INR on the DAWN AC® system until the present.

3.3.4.1.2 Adverse clinical outcome

The adverse clinical outcomes of interest were stroke, transient ischemic attack (TIA), systemic embolism (SE), bleeding events [combination of major and non-clinically relevant non-major bleeding (CRNMB)], cardiovascular (CV) hospitalization and all cause death and these were obtained from the patients' medical records, CDA. All analysis pertaining to adverse clinical outcome were exploratory in nature. A composite endpoint of major adverse clinical event (MACE) encompassed ≥1 of the following: stroke/TIA, systemic embolism, bleeding, cardiovascular hospitalisation or death. Definitions of each outcome can be found in **Section 2.3.3, pages 134-135**.

3.3.4.2 Independent variable: Ethnicity

Self-reported ethnicity was identified directly from the electronic medical records, CDA/DAWN® AC, where available. The different ethnic groups identified were White British, White Irish, White others, Asian British Indian, Asian British Pakistani, Asian British Bangladeshi, other Asians, Black British Caribbean and Black British African, according to the UK Census. These were then recoded into the three main ethnic groups; White, South Asian and Afro-Caribbean respectively. Those without information on ethnicity were excluded from the study (N=21).

Ethnicity was an independent variable for the first part of the analysis examining the quality of anticoagulation control among the different ethnic groups. However, for the second part of the analysis, investigating the predictors of TTR, ethnicity was a covariate along with the other demographics and clinical characteristics.

3.3.4.3 Predictors: Patient demographic and clinical factors

Patients' age was calculated according from the date of the first of INR available from the VKA therapy. Elderly patients were defined as patients who are ≥80 years. Information on gender (male and female), smoking (smoking within 2 years and non-smoking) and alcohol history (no alcohol, alcohol within recommended units i.e.; 14 units per week for both men and women or above recommended units) were obtained directly from CDA. Smoking history was available for 717 patients (72.4%). For calculation of the SAMe-TT_2R_2 score, that required information on smoking status, all missing information on smoking status was coded as non-smoker (N=274). Information on alcohol intake was only available for 58.0% patients, thus this variable was excluded from further analysis. Comorbid conditions at baseline including hypertension, heart failure, coronary artery disease/ischemic heart disease, stroke/TIA, prior bleeding history and anaemia were obtained directly from CDA.

Other comorbid diseases like kidney disease, liver disease and anaemia were also assumed based on available laboratory results at baseline. A correction factor to eGFR values was

made for Afro-Caribbean patients by multiplying the eGFR obtained from CDA by 1.21 (424). Assumption of CKD was made if patients had eGFR <60ml/min or serum creatinine >200umol/L; liver disease if abnormal liver function tests were reported; if alanine transaminase/alkaline phosphatase (ALT/ALP) >x3 upper limit of normal (ULN), and anaemia if the haemoglobin level was <135 g/L for males and <115 g/L for females. Laboratory results and medications taken at baseline were obtained directly from the CDA.

3.3.4.3.1 Chronic kidney disease (CKD)

Further categorisation of kidney disease was made according to the 'Kidney Disease Improving Global Outcomes' (KDIGO) GFR categories adapted by the NICE guidelines, with five categories of kidney disease for the ancillary analysis (**Table 3.2**) (424).

Table 3.2: Categories of chronic kidney disease from the NICE guidelines (424)

GFR category	GFR (ml/min)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mild to moderately decreased
G3b	30-44	Moderate to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

GFR: glomerular filtration rate

3.3.4.4 Other patient clinical factors (not included as predictors of anticoagulation control)

Type of AF, including paroxysmal, persistent, long-standing persistent and permanent, was obtained from the medical notes. If this information was not available, an assumption was made based on the length of time since AF diagnosis and the pattern of ECG recordings available with confirmation from a medical doctor and according to the ESC AF guidelines (3). For example, if the available ECG showed multiple episodes of AF which lasted less than 48 hours, this was categorised as paroxysmal AF. If AF lasted longer than 7 days, including those

terminated by cardioversion (either with drugs or direct current cardioversion), this was categorised as persistent AF. Whereas for long-standing persistent AF, the AF was continuous, lasting ≥1 year and a decision had been made to adopt a rhythm control strategy. Lastly permanent AF was defined when AF was accepted by both physician and patient and a decision has been made to not continue with rhythm control therapy (3). Calculation of stroke risk, bleeding risk and quality of anticoagulation control was made according to the CHA_2DS_2-VASc score, HAS-BLED score, and TTR (Rosendaal and PINNR methods), respectively.

The individual CHA_2DS_2-VASc score (to predict stroke risk) was calculated as follows: one point each for the presence of congestive heart failure, hypertension, diabetes mellitus, vascular disease (defined as peripheral vascular disease, myocardial infarction or aortic plaque), age 65-74 and female sex, and two points each for the presence of age≥75 years and previous stroke/TIA **(Table 3.1).**

The individual HAS-BLED score (to predict bleeding risk) was calculated as follows: one point each for the presence of uncontrolled hypertension (for all cases blood pressure was assumed to be controlled as this is a requirement when on VKA therapy), abnormal kidney was defined as serum creatinine >200umol/L, abnormal liver function as ALT/ALP >x3 ULN) and from the past medical history (i.e., cirrhosis), previous stroke, prior bleeding within 12 months (including recent diverticulitis, gastric ulcer or anaemia defined as haemoglobin level of <135 g/L for male and <115 g/L for female and from the medical history), labile INR or TTR<60%, elderly >65 years and drugs (concurrent antiplatelet or NSAIDs) and/or alcohol (>14 units/week, recommended by the current guidelines; modified from the original HAS-BLED score of >8 units/week). There was insufficient information about alcohol intake, and therefore this variable was not included in the calculation of HAS-BLED score; the maximum HAS-BLED score was eight. A HAS-BLED score of 0-2 was denoted as low risk of bleeding and ≥3 as high risk of bleeding **(Table 3.1).**

The individual SAMe-TT_2R_2 score (to predict quality of anticoagulation control) was calculated as follows: one point each for female sex; presence of ≥2 of the following medical conditions: hypertension, diabetes mellitus, coronary artery disease or myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic disease or renal disease; treatment with interacting drugs e.g. amiodarone for rhythm control; and two points each for tobacco use within 2 years (tobacco use is a combination of current smoking and ex-smoking but with unknown duration as this information is not available); and race (non-white), giving a possible score ranging from 0-8. Patients with SAMe-TT_2R_2 score of 0-2 were defined as being likely to do well on VKA therapy and those with a SAMe-TT_2R_2 score >2 were classified as at risk of suboptimal anticoagulation control (TTR<65%) **(Table 3.1).**

3.3.5 Statistical analysis

Normality tests were performed by histogram plot method and the Kolmogorov-Smirnov test where a bell-shaped distribution in the former and p-values >0.05 in the latter were indicative of normally distributed data. Normally distributed data were expressed as mean (standard deviation, SD) and non-parametric data are presented as median (interquartile range, IQR). Categorical variables were compared using the chi-square test or the Fisher's Exact test (as appropriate) and reported as counts with percentages. Continuous variables comparing >2 groups used the analysis of variance (ANOVA) test for normally distributed data, with post-hoc tests as appropriate (e.g., Bonferroni), while, the Kruskal-Wallis test was utilised for non-parametric data. Independent t-tests and Wilcoxon signed ranked tests were utilised for comparing continuous variables within two groups for normally and non-normally distributed data, respectively.

For baseline demographics, clinical characteristics and adverse clinical outcomes, data were presented as descriptive statistics. Pearson correlation was utilised to investigate the correlation between TTR and PINRR (normally distributed).

Linear regression analysis was conducted to investigate the predictors of TTR and PINRR as a continuous variable. Logistic regression analysis was also used to investigate predictors of poor TTR (TTR<70%) and PINRR (PINRR <70%) as categorical variables as this cut off reflects poor anticoagulation control recommended by the European Guidelines (1). The relationship between INR control (TTR<70% and TTR<65%) and adverse clinical outcomes was investigated using the Chi-squared test and these analyses were exploratory. Predictors of MACE events and composite endpoints (≥1 MACE) were examined using Cox proportional hazard regression models. Survival analysis was also displayed using Kaplan-Meier curves. P-values <0.05 were considered statistically significant. All analyses were confined to complete cases only (except for smoking history) and were conducted using SPSS version 23.0 (IBM, NY, USA) (425).

3.4 Results

3.4.1 Baseline characteristics

3.4.1.1 By ethnicity

The final cohort included 991 AF patients receiving warfarin for stroke prevention, with a median (IQR) length of follow up of 5.2 (3.2-7.0) years. The majority of the population were White (N=807, 81.4%), with 10.3% South-Asian (N=102) and 8.3% Afro-Caribbean (N=82). The overall mean age at warfarin initiation was 71.6 (9.4) years and South-Asian patients were significantly younger than Whites and Afro-Caribbeans (p=<0.05 for group comparison); half the population were male (55.3%) **(see Table 3.3**). Overall, hypertension was the most common co-morbidity (79.2%), followed by chronic kidney disease (37.3%) and diabetes mellitus (20.6%). There was a significant difference in prevalence of diabetes (p<0.001), anaemia (p<0.001), and vascular disease (p=0.007) between ethnic groups. Diabetes mellitus and anaemia were significantly more prevalent among South-Asians and Afro-Caribbeans (p<0.05 for group comparison) compared to Whites and vascular disease was significantly more prevalent among South-Asian compared to Whites and Afro-Caribbeans (p<0.05 for group comparison). Smoking status was only available in 72.4% patients. Smoking (current or ex-smoker within 2 years) appeared to be more prevalent among Whites (51.6%) compared to South-Asian (14.6%) and Afro-Caribbeans (25.9%; p<0.05 group comparison). Type of AF differed by ethnicity (p=0.004), with a greater proportion of Afro-Caribbeans (40.2%) found to be in persistent AF compared to South-Asians and Whites. The only overall significant difference (p<0.001) in medications was calcium channel blocker prescription with a greater prevalence among Afro-Caribbeans compared to South-Asians and Whites.

The overall mean (SD) CHA_2DS_2-VASc score was 3.4 (1.6) and was significantly higher among Afro-Caribbeans compared to Whites and South-Asians [3.9 (1.7) vs. 3.3 (1.6) vs. 3.6 (1.7), respectively; p<0.05 for group comparison]. The overall mean (SD) HAS-BLED score was 1.5 (0.9) and was significantly higher in both South-Asians and Afro-Caribbeans compared to

Whites [mean (SD) HAS-BLED score of 1.8 (0.9) vs. 1.7 (1.0) vs. 1.5 (0.9) respectively; $p<0.05$ for group comparison]. The SAMe-TT_2R_2 score, was significantly higher among South-Asians and Afro-Caribbeans compared to Whites ($p<0.05$ for group comparison) **(see Table 3.3).**

Table 3.3: Baseline characteristics of the study population overall and stratified by ethnicity and age (≥80 vs. <80 years)

	Total, N=991	White, N=807	South-Asian, N=102	Afro-Caribbean, N=82	Age ≥80 years, N=205	Age <80 years, N=786	Overall p-value ethnicity	Overall p-value age
Mean (SD) age	71.6 (9.4)	71.9 (9.3)	68.2 (9.9) [a]	72.9 (9.3) [c]	-	-	**<0.001**	-
<65	209 (21.1)	166 (20.6)	29 (28.4)	14 (17.1)	-	-	**0.004**	-
65-74	355 (35.8)	287 (35.6)	45 (44.1)	23 (28.0)	-	-		-
≥75	427 (43.1)	354 (43.9)	28 (27.5) [a, c]	45 (54.9) [c]	-	-		-
Female	443 (44.7)	343 (42.5)	46 (45.1) [c]	54 (66.0) [b, c]	120 (58.5)	323 (41.1)	**<0.001**	**<0.001**
Male	548 (55.3)	464 (57.5)	56 (54.9)	28 (34.1)	85 (41.5)	463 (58.9)		
White	-	-	-	-	176 (85.9)	631 (80.3)	-	
South-Asian	-	-	-	-	10 (4.9)	92 (11.7)	-	**0.016**
Afro-Caribbean	-	-	-	-	19 (9.3)	63 (8.0)	-	
Heart failure	138 (13.9)	109 (13.5)	14 (13.7)	15 (18.3)	31 (15.1)	107 (13.6)	0.49	0.66
Hypertension	785 (79.2)	631 (78.2)	82 (80.4)	72 (87.8)	176 (85.9)	609 (77.5)	0.12	**0.011**
Diabetes	204 (20.6)	132 (16.4)	44 (43.1) [a]	28 (34.1) [b]	38 (18.5)	166 (21.1)	**<0.001**	0.47
Stroke/TIA	179 (18.1)	145 (18.0)	23 (22.5)	11 (13.4)	40 (19.5)	139 (17.7)	0.27	0.61
VTE	38 (3.8)	32 (4.0)	3 (2.9)	3 (3.7)	7 (3.4)	31 (3.9)	0.88	0.88
PAD	26 (2.6)	24 (3.0)	1 (1.0)	1 (1.2)	8 (3.9)	18 (2.3)	0.35	0.30
Vascular disease*	163 (16.4)	123 (15.2)	28 (27.5) [a]	12 (14.6) [b]	37 (18.0)	126 (16.0)	**0.007**	0.56
Lung disease[#]	196 (19.8)	165 (20.4)	12 (11.8)	19 (23.2)	34 (16.6)	162 (20.6)	0.08	0.23

Table 3.3 continued

	Total, N=991	White, N=807	South-Asian, N=102	Afro-Caribbean, N=82	Age ≥80 years, N=205	Age <80 years, N=786	Overall p-value ethnicity	Overall p-value age
Cardiomyopathy‡	30 (3.0)	25 (3.1)	2 (2.0)	3 (3.7)	4 (2.0)	26 (3.3)	0.77	0.44
Kidney disease†	370 (37.3)	308 (38.2)	40 (39.2)	22 (26.8)	103 (50.2)	267 (34.0)	0.12	**<0.001**
Anaemia	145 (14.6)	101 (12.5)	28 (27.5)[a]	16 (19.5)[b]	34 (16.6)	111 (14.1)	**<0.001**	0.44
Smoker/ex-smoker (N=717)	326 (45.5)	300 (51.6)	12 (14.6)[a]	14 (25.9)[b]	49 (33.8)	277 (48.4)	**<0.001**	**0.002**
Paroxysmal	274 (27.6)	225 (27.9)	31 (30.4)	18 (22.0)	48 (23.4)	226 (28.8)		
Persistent	229 (23.1)	174 (21.6)	22 (21.6)[c]	33 (40.2)[b, c]	47 (22.9)	182 (23.2)	**0.004**	0.26
Permanent	488 (49.2)	408 (50.6)	49 (48.0)	31 (37.8)	110 (53.7)	378 (48.1)		
ACEI/ARB	561 (56.6)	449 (55.6)	62 (60.8)	50 (61.0)	115 (56.1)	446 (56.7)	0.43	0.93
Beta-blocker	455 (45.9)	360 (44.6)	57 (55.9)	38 (46.3)	87 (42.4)	368 (46.8)	0.10	0.30
CCB	350 (35.3)	264 (32.7)	39 (38.2)[c]	47 (57.3)[b, c]	82 (40.0)	268 (34.1)	**<0.001**	0.14
Digoxin	226 (22.8)	194 (24.0)	18 (17.6)	14 (17.1)	43 (21.0)	183 (23.3)	0.15	0.54
Diuretics	439 (44.3)	351 (43.5)	42 (41.2)	46 (56.1)	120 (58.8)	319 (40.6)	0.07	**<0.001**
Amiodarone	58 (5.9)	52 (6.4)	3 (2.9)	3 (3.7)	7 (3.4)	51 (6.5)	0.25	0.13
Concurrent antiplatelet	46 (4.6)	38 (4.7)	6 (5.9)	2 (2.4)	10 (4.9)	36 (4.6)	0.53	1.00

Table 3.3 continued

	Total, N=991	White, N=807	South-Asian, N=102	Afro-Caribbean, N=82	Age ≥80 years, N=205	Age <80 years, N=786	Overall p-value ethnicity	Overall p-value age
Mean (SD) CHA_2DS_2-VASc	3.4 (1.6)	3.3 (1.6)	3.6 (1.7)	3.9 (1.7)[b]	4.4 (1.3)	3.1 (1.6)	**0.002**	**<0.001**
0	29 (2.9)	25 (3.1)	2 (2.0)	2 (2.4)	0	29 (3.7)		
1	81 (8.2)	72 (8.9)	5 (4.9)	4 (4.9)	0	81 (10.3)		
2	185 (18.7)	150 (18.6)	27 (26.5)	8 (9.8)	12 (5.9)	173 (22.0)		
3	238 (24.0)	200 (24.8)	20 19.6)	18 (22.0)	37 (18.0)	201 (25.6)		
4	225 (22.7)	183 (22.7)	17 (16.7)	25 (30.5)	68 (33.2)	157 (20.0)		
5	124 (12.5)	101 (12.5)	12 (11.8)	11 (13.4)	46 (22.4)	78 (9.9)	**0.001**	**<0.001**
6	82 (8.3)	62 (7.7)	13 (12.7)	7 (8.5)	28 (13.7)	54 (6.9)		
7	22 (2.2)	11 (1.4)	6 (5.9)	5 (6.1)	12 (5.9)	10 (1.3)		
8	4 (0.4)	2 (0.2)	0	2 (2.4)	1 (0.5)	3 (0.4)		
9	1 (0.1)	1 (0.1)	0	0	1 (0.5)	0		
CHA_2DS2-VASc categories: Low risk	39 (3.9)	32 (4.0)	3 (2.9)	4 (4.9)	0	39 (5.0)		
Intermediate	71 (7.2)	65 (8.1)	4 (3.9)	2 (2.4)	0	71 (9.0)	0.214	**<0.001**
High risk	881 (88.9)	710 (88.0)	95 (93.1)	76 (92.7)	205 (100)	676 (86.0)		
Mean (SD) HAS-BLED	1.5 (0.9)	1.5 (0.9)	1.8 (0.9)[a]	1.7 (1.0)[b]	1.8 (0.8)	1.5 (0.9)	**<0.001**	**<0.001**
0	93 (9.4)	79 (9.8)	8 (7.8)	6 (7.3)	0	93 (11.8)		
1	443 (44.7)	379 (47.0)	34 (33.3)	30 (36.6)	97 (47.3)	346 (44.0)		
2	326 (32.9)	263 (32.6)	32 (31.4)	31 (37.8)	68 (33.2)	258 (32.8)		
3	107 (10.8)	71 (8.8)	25 (24.5)	11 (13.4)	32 (15.6)	75 (9.5)	**<0.001**	**<0.001**
4	20 (2.0)	13 (1.6)	3 (2.9)	4 (4.9)	7 (3.4)	13 (1.7)		
5	2 (0.2)	2 (0.2)	0	0	1 (0.5)	1 (0.1)		

Table 3.3 continued

	Total, N=991	White, N=807	South-Asian, N=102	Afro-Caribbean, N=82	Age ≥80 years, N=205	Age <80 years, N=786	Overall p-value ethnicity	Overall p-value age
HAS-BLED categories Low risk	862 (87.0)	721 (89.3)	74 (72.5)[a]	67 (81.7)	165 (80.5)	697 (88.7)	**<0.001**	**0.003**
High risk	129 (13.0)	86 (10.7)	28 (27.5)[a, c]	15 (18.3)[b, c]	40 (19.5)	89 (11.3)		
Mean SAMe-TT_2R_2 score	2.3 (1.4)	2.0 (1.2)	3.7 (0.9)[a]	3.8 (0.9)[b]	2.2 (1.2)	2.4 (1.4)	**<0.001**	**0.04**
0	74 (7.5)	74 (9.2)	0	0	14 (6.8)	60 (7.6)	**<0.001**	**0.004**
1	231 (28.6)	0	0	0	49 (23.9)	182 (23.2)		
2	246 (24.8)	236 (29.2)	6 (5.9)	4 (4.9)	72 (35.1)	174 (22.1)		
3	235 (23.7)	167 (20.7)	42 (41.2)	26 (31.7)	36 (17.6)	199 (25.3)		
4	162 (16.3)	87 (10.8)	37 (36.3)	38 (46.3)	31 (15.1)	131 (16.7)		
5	35 (3.5)	12 (1.5)	13 (12.7)	10 (12.2)	3 (1.5)	32 (4.1)		
6	6 (0.6)	0	3 (2.9)	3 (3.7)	0	6 (0.8)		
7	2 (0.2)	0	1 (1.0)	1 (1.2)	0	2 (0.3)		
SAMe-TT_2R_2 categories 0-2	551 (55.6)	541 (67.0)	6 (5.9)[a]	4 (4.9)[b]	135 (65.9)	416 (52.9)	**<0.001**	**0.001**
>2	440 (44.4)	266 (33.0)	96 (94.1)[a]	78 (95.1)[b]	70 (34.1)	370 (47.1)		

ACEI/ARB: angiotensin converting enzyme inhibitor/ angiotensin receptor blockade; CCB: calcium channel blocker; CHA_2DS_2-VASc score - Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75years [2 points], Diabetes, Stroke [2 points], Vascular disease, Age 65–74 years, and Sex category (female). Total scores range between 0-9; low risk CHA_2DS_2-VASc score: 0, intermediate: 1, high risk CHA_2DS_2-VASc score: ≥2; TIA: transient ischemic attack; TE: thromboembolism; HAS-BLED score – uncontrolled Hypertension: systolic ≥160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR ratio/TTR <60, Drugs/alcohol concomitantly. Total scores range between 0-9; low risk of bleeding range between 0-2 and high risk of bleeding ≥3; SAMe-TT_2R_2 score – Sex female, Age<60, Medical history (more than two comorbidities), Treatment (interacting drug, e.g. Amiodarone), Tobacco use (doubled) and Race (non-white, doubled). Total scores ranged from 0-8; probable good response to VKA therapy range between 0-2 and probable poor response to VKA therapy ranged from ≥3.

* Vascular disease: prior myocardial infarction, peripheral artery disease or aortic plaque; † Kidney disease: eGFR<60 ml/min; ‡ Cardiomyopathy: dilated, restrictive and obstructive myocardial conditions; # Lung disease Includes obstructive and restrictive diagnosed lung conditions;

[a] significant difference between White and South-Asian groups ($p<0.05$); [b] significant difference between White and Afro-Caribbean groups ($p<0.05$); [c] significant difference between South-Asian and Afro-Caribbean groups ($p<0.05$)

3.4.1.2 By age (≥80 years and <80 years)

Baseline characteristics of the population grouped by ≥80 years and <80 years are also shown in **Table 3.3.** There were 205 patients (20.6%) who were ≥80 years old and the majority were female (58.5%; p<0.001) and of white ethnicity (85.9%; p=0.016). Hypertension (85.9%; p=0.011) and chronic kidney disease (50.2%; p=<0.001) were significantly more prevalent among elderly patients, whereas smoking history (48.4%; p=0.002) was significantly more prevalent in patients aged <80 years. As expected, the mean (SD) CHA_2DS_2-VASc [4.4 (1.3); p<0.001] and HAS-BLED score [1.8 (0.8); <0.001] were significantly higher among elderly patients, whereas the mean SAMe-TT_2R_2 score was significantly higher in the younger population.

3.4.1 By kidney disease categories

There were 974 patients with eGFR results available at baseline. The distribution of patients according to the classification of the kidney disease is shown in **Table 3.4.** These categories were further dichotomised into normal kidney function with eGFR ≥90 ml/min/1.73m^2; mildly decreased with eGFR 60-89 ml/min/1.73m^2 and combination of group 3a, 3b, 4 and 5 (mild-moderately-severe and kidney failure) with eGFR ≤59 ml/min/1.73m^2.

Table 3.4: Distribution of patients in the current cohort according to the categories of kidney disease, N=974

GFR category	GFR (ml/min/1.73m^2)	N (%)	New dichotomised group in this cohort, eGFR (ml/min/1.73m^2)	N (%)
G1	≥90	133 (13.7)	Normal (≥90)	133 (13.7)
G2	60-89	491 (50.4)	Mild (60-89)	491 (50.4)
G3a	45-59	225 (23.1)	Mild-moderate-severe and kidney failure (≤59)	350 (35.9)
G3b	30-44	98 (10.1)		
G4	15-29	24 (2.5)		
G5	<15	3 (0.3)		

GFR: glomerular filtration rate

For the purpose of the thesis, the description of the different kidney function groups will be patients with eGFR ≥90, eGFR 60-89 and eGFR ≤59. The median (IQR) eGFR at baseline was 66.0 (54.0-79.0) ml/min/1.73m^2. Half of the population had eGFR 60-89 ml/min/1.73m^2, while 35.9% had an eGFR ≤59 ml/min/1.73m^2.

Compared to patients with normal kidney function, AF patients with eGFR 60-89 and eGFR ≤59 were significantly older ($p<0.05$ for group comparison). There were significantly more females and those of white ethnicity in patients with eGFR ≤59 compared to eGFR ≥90 ($p<0.05$ for group comparison) **(Table 3.5).** Heart failure, hypertension and anaemia were significantly more prevalent in patients with eGFR ≤59 compared to eGFR ≥90 and eGFR 60-89 ($p<0.05$ for group comparison). Meanwhile, stroke/TIA was significantly more prevalent in patients with eGFR ≥90 and eGFR ≤59 compared to eGFR 60-89 ($p<0.05$ for group comparison). A significant proportion of AF patients with eGFR ≥90 had concomitant lung disease and also smoked (or used to smoke within 2 years) compared eGFR 60-89 and eGFR ≤59 ($p<0.05$ for group comparison) **(Table 3.5).**

In addition, the use of ACE/ARB and diuretics were significantly more prevalent in patients with eGFR ≤59 ($p<0.05$ for group comparison) while the use of beta blockers ($p<0.05$ for group comparison) was significantly more prevalent in patients with eGFR ≥90. Mean (SD) CHA_2DS_2-VASc score [3.9 (1.6); $p<0.05$ group comparison] and HAS-BLED score [1.7 (0.9); $p<0.05$ for group comparison] was significantly higher in patients with eGFR ≤59 while mean SAMe-TT_2R_2 score was significantly higher in patients with eGFR ≥90 **(Table 3.5).**

Table 3.5: Baseline characteristics of overall population with eGFR results and according to three categories of kidney disease

N (%)		Total, N=974	eGFR≥90 ml/min N=133	eGFR 60-89 ml/min N=491	eGFR ≤59 ml/min N=350	Overall p-value
Age	Mean (SD)	71.6 (9.4)	67.5 (10.1)	70.7 (9.4)[a]	74.4 (8.4)[b, c]	**<0.001**
	<65	205 (21.0)	46 (34.6)	116 (23.6)	43 (12.3)[b]	
	65-74	351 (36.0)	49 (36.8)	191 (38.9)	111 (31.7)	**<0.001**
	≥75	418 (42.9)	38 (28.6)	184 (37.5)	196 (56.0)[b]	
Sex	Female	437 (44.9)	47 (35.3)	209 (42.6)	181 (51.7)[b]	**0.002**
	Male	537 (55.1)	86 (64.7)	282 (57.4)	169 (48.3)[b]	
Ethnic groups	White	792 (81.3)	89 (66.9)	403 (82.1)[a]	300 (85.7)[b]	
	South-Asian	102 (10.5)	13 (9.8)	52 (10.6)	37 (10.6)	**<0.001**
	Afro-Caribbean	80 (8.2)	31 (23.3)	36 (7.3)[a]	13 (3.7)[b]	
Medical history	Heart failure	135 (13.9)	15 (11.1)	55 (11.2)	65 (18.6)[b,c]	**0.006**
	Hypertension	774 (79.5)	101 (75.9)	376 (76.6)	297 (84.9)[b,c]	**0.008**
	Diabetes	202 (20.7)	26 (19.5)	100 (20.4)	76 (21.7)	0.84
	Stroke/TIA	175 (18.0)	26 (19.5)	70 (14.3)[a]	79 (22.6)[b,c]	**0.007**
	VTE	36 (3.7)	4 (3.0)	22 (4.5)	10 (2.9)	0.42
	PAD	26 (2.7)	3 (2.3)	8 (1.6)	15 (4.3)	0.06
	Vascular disease*	160 (16.4)	16 (12.0)	76 (15.5)	68 (19.4)	0.11
	Lung disease[#]	194 (19.9)	36 (27.1)	101 (20.6)[a]	57 (16.3)[b,c]	**0.03**
	Cardiomyopathy[‡]	29 (3.0)	4 (3.0)	16 (3.3)	9 (2.6)	0.85
	Anaemia	145 (14.9)	17 (12.8)	62 (12.6)	66 (18.9)[b,c]	**0.03**
	Smoker/ex-smoker (N=708)	319 (45.1)	54 (51.9)	169 (47.5)	96 (38.7)	**0.03**

Table 3.5 continued

		Total, N=974	eGFR≥90 ml/min N=133	eGFR 60-89 ml/min N=491	eGFR ≤59 ml/min N=350	Overall p-value
Types of AF	Paroxysmal	274 (28.1)	37 (27.8)	143 (29.1)	94 (26.9)	0.59
	Persistent	228 (23.4)	37 (27.8)	114 (23.2)	179 (51.1)	
	Permanent	472 (48.5)	59 (44.4)	234 (47.7)	77 (22.0)	
Medications	ACEI/ARB	553 (56.8)	67 (50.4)	270 (55.0)	216 (61.7)	**0.04**
	Beta-blocker	454 (46.6)	69 (51.9)	207 (42.2)[a]	178 (50.9)[c]	**0.02**
	CCB	347 (35.6)	45 (33.8)	175 (35.6)	127 (36.3)	0.88
	Digoxin	223 (22.9)	25 (18.8)	108 (22.0)	90 (25.7)	0.22
	Diuretics	433 (44.5)	42 (31.6)	192 (39.1)	199 (56.9)[b,c]	**<0.001**
	Amiodarone	58 (6.0)	6 (4.5)	27 (5.5)	25 (7.1)	0.46
	Concurrent antiplatelet	44 (4.5)	6 (4.5)	19 (3.9)	19 (5.4)	0.56
CHA_2DS_2-VASc score	Mean (SD)	3.4 (1.6)	2.9 (1.5)	3.2 (1.6)	3.9 (1.6) [b,c]	**<0.001**
	0	27 (2.8)	9 (6.8)	16 (3.3)	2 (0.6)	**<0.001**
	1	80 (8.2)	14 (10.5)	51 (10.4)	15 (4.3)	
	2	183 (18.8)	29 (21.8)	104 (21.2)	50 (14.3)	
	3	235 (24.1)	35 (26.3)	125 (25.5)	75 (21.4)	
	4	222 (22.8)	25 (18.8)	101 (20.6)	96 (27.4)	
	5	120 (12.3)	14 (10.5)	55 (11.2)	51 (14.6)	
	6	81 (8.3)	6 (4.5)	30 (6.1)	45 (12.9)	
	7	21 (2.2)	1 (0.8)	8 (1.6)	12 (3.4)	
	8	4 (0.4)	0	1 (0.2)	3 (0.9)	
	9	1 (0.1)	0	0	1 (0.1)	

Table 3.5 continued

		Total, N=974	eGFR≥9 ml/min N=133	eGFR 60-89 ml/min N=491	eGFR ≤59 ml/min N=350	Overall p-value
CHA_2DS_2-VASc score categories	Low risk (0)	37 (3.8)	11 (8.3)	23 (4.7)	3 (0.9)[b]	
	Intermediate (1)	70 (7.2)	12 (9.0)	44 (9.0)	14 (4.0)[b,c]	**<0.001**
	High risk (≥2)	867 (89.0)	110 (82.7)	424 (86.4)	333 (95.1)[b]	
HAS-BLED score	Mean	1.5 (0.9)	1.5 (0.9)	1.4 (0.8)	1.7 (0.9)[c]	**<0.001**
	0	91 (9.3)	14 (10.5)	61 (12.4)	16 (9.3)	
	1	434 (44.6)	56 (42.1)	236 (48.1)	142 (40.6)	
	2	322 (33.1)	46 (34.6)	148 (30.1)	128 (36.6)	**<0.001**
	3	106 (10.9)	14 (10.5)	41 (8.4)	51 (14.6)	
	4	19 (2.0)	2 (1.5)	5 (1.0)	12 (3.4)	
	5	2 (0.2)	1 (0.8)	0	1 (0.3)	
HAS-BLED score categories	Low risk (0-2)	847 (87.0)	116 (87.2)	445 (90.6)	286 (81.7)	**0.001**
	High risk (≥3)	127 (13.0)	17 (12.8)	46 (9.4)	64 (18.3)	
	Mean	2.3 (1.3)	2.7 (1.5)	2.2 (1.3)[a]	2.4 (1.2)[c]	**<0.001**
SAMe-TT_2R_2 score	0	69 (7.1)	12 (9.0)	51 (10.4)	6 (1.7)	
	1	230 (23.6)	20 (15.0)	123 (25.1)	87 (24.9)	
	2	244 (25.1)	24 (18.0)	114 (23.2)	106 (30.3)	
	3	228 (23.4)	36 (27.1)	119 (34.2)	73 (20.9)	**<0.001**
	4	160 (16.4)	29 (21.8)	65 (13.2)	66 (18.9)	
	5	35 (3.6)	9 (6.8)	16 (3.3)	10 (2.9)	
	6	6 (0.6)	2 (1.5)	3 (0.6)	1 (0.3)	
	7	2 (0.2)	1 (0.8)	0	1 (0.3)	

Table 3.5 continued

		Total, N=974	eGFR≥90 ml/min N=133	eGFR 60-89 ml/min N=491	eGFR ≤59 ml/min N=350	Overall p-value
SAMe-TT_2R_2 score categories	0-2	543 (55.7)	56 (42.1)	288 (58.7)	199 (56.9)	**0.003**
	>2	431 (44.3)	77 (57.9)	203 (41.3)	151 (43.1)	

eGFR ≥90ml/min/1.73m^2- normal kidney function; eGFR 60-89 ml/min/1.73m^2- mild kidney disease; eGFR ≤59 ml/min/1.73m^2- mild-moderate-severe and kidney failure

ACEI/ARB: angiotensin converting enzyme inhibitor/ angiotensin receptor blockade; CCB: calcium channel blocker; CHA_2DS_2-VASc score - Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75years [2 points], Diabetes, Stroke [2 points], Vascular disease, Age 65–74 years, and Sex category (female). Total scores range between 0-9; low risk CHA_2DS_2-VASc score: 0, intermediate 1, high risk CHA_2DS_2-VASc score: ≥2; TIA: transient ischemic attack; TE: thromboembolism; eGFR: estimated glomerular filtration rate, ml/min/1.73 m^2; HAS-BLED score – uncontrolled Hypertension: systolic ≥160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR ratio/TTR <60, Drugs/alcohol concomitantly. Total scores range between 0-9; low risk of bleeding range between 0-2 and high risk of bleeding ≥3; SAMe-TT_2R_2 score – Sex female, Age<60, Medical history (more than two comorbidities), Treatment (interacting drug, e.g. Amiodarone), Tobacco use (doubled) and Race (non-white, doubled). Total scores ranged from 0-8; probable good response to VKA therapy range between 0-2 and probable poor response to VKA therapy ranged from ≥3.
* Vascular disease: prior myocardial infarction, peripheral artery disease or aortic plaque; ‡ Cardiomyopathy: dilated, restrictive and obstructive myocardial conditions; # Lung disease: obstructive and restrictive diagnosed lung conditions;

a: significant difference between eGFR≥90 and eGFR 60-89, $p<0.05$
b: significant difference between eGFR≥90 and eGFR ≤59; $p<0.05$
c: significant difference between eGFR 60-89, and eGFR ≤59; $p<0.05$

3.4.2 Measures of anticoagulation control

3.4.2.1 By ethnicity

In this cohort, 96% of patients were VKA naïve. **Table 3.6** presents the measures of anticoagulation control in the overall population and by ethnic group. Overall mean (SD) TTR and PINRR values were 66.6% (13.3) and 57.6% (11.2) respectively. TTR significantly correlated with PINRR ($r=0.773$, $p<0.001$). White patients had significantly higher mean TTR values compared to Afro-Caribbean and South-Asian patients, based on both mean TTR (by Rosendaal method; $p<0.05$ group comparison) and PINRR ($p<0.05$ for group comparison) **(Figure 3.2).** When TTR and PINRR was dichotomised (<70% vs. ≥70%) the same trend was observed (**Figure 3.3**). The mean (SD) number of INR tests used to calculate TTR was 58.7 (25.5) and was similar across ethnic groups. The proportion of sub-therapeutic INRs (<2.0) was significantly greater among South-Asians and Afro-Caribbeans, with no differences in the proportion of supra-therapeutic INRs by ethnicity (**Figure 3.4**). Overall, 29.6% and 4.1% of the population had at least one INR value above 5.0 and 8.0, respectively (**Figure 3.5**).

Table 3.6: Measures of anticoagulation control overall and by ethnic group

Measures of anticoagulation control, N (%)	Total, N=991	White, N=807	South-Asian, N=102	Afro-Caribbean, N=82	F-value	X^2 value	p-value
Mean (SD) TTR Rosendaal	66.6 (13.2)	67.9 (12.8)	60.5 (12.8)[a]	61.3 (14.2)[b]	22.7	-	**<0.001**
TTR<70%	550 (55.5)	417 (51.7)	75 (73.5)	58 (70.7)		25.9	**<0.001**
TTR≥70%	441 (44.5)	390 (48.3)	27 (26.5)[a]	24 (29.3)[b]			
TTR<65%	400 (40.4)	294 (36.4)	59 (57.8)	47 (57.3)		27.9	**<0.001**
TTR≥65%	591 (59.6)	513 (63.6)	43 (42.2)[a]	35 (42.7)[b]			
Mean (SD) PINRR	57.6 (11.2)	58.8 (10.8)	51.6 (10.9)[a]	53.1 (11.6)[b]	27.3	-	**<0.001**
PINRR<70%	851 (85.9)	677 (83.9)	99 (97.1)	75 (91.5)			**<0.001**
PINRR ≥70%	140 (14.1)	130 (16.1)	3 (2.9)[a, c]	7 (8.5)[b,c]	15.3		
PINRR <65%	736 (74.3)	576 (71.4)	91 (89.2)	69 (84.1)		19.6	**<0.001**
PINRR ≥65%	255 (25.7)	231 (28.6)	11 (10.8)[a]	13 (15.9)[b]			
Mean (SD) number of INR tests	58.7 (25.5)	59.4 (24.6)	55.0 (24.6)	56.5 (33.7)	1.7	-	0.18
Mean (SD) percentage INRs<2	25.7 (10.0)	24.7 (9.5)	30.1 (11.2)[a]	30.2 (10.9)[b]	23.8	-	**<0.001**
Mean (SD) percentage INRs>3	16.6 (7.2)	16.5 (7.3)	17.9 (7.1)	16.5 (6.2)	1.9	-	0.16
INR>5	293 (29.6)	239 (29.6)	31 (30.4)	23 (28.0)	-	0.125	0.94
INR>8	41 (4.1)	36 (4.5)	3 (2.9)	2 (2.4)	-	1.177	0.56
Median (IQR) years of follow-up	5.2 (3.2-7.0)	5.5 (3.4-7.0)	4.3 (2.6-6.7)[a]	4.0 (2.4-6.1)[b]	-	-	**<0.001**

TTR: Time in therapeutic range; PINRR: Percentage of INRs within range; INR: international Normalised Ratio; SD: standard deviation; IQR: interquartile range

[a] significant difference between White and South-Asian groups ($p<0.05$); [b] significant difference between White and Afro-Caribbean groups ($p<0.05$); [c] significant difference between South-Asian and Afro-Caribbean groups ($p<0.05$)

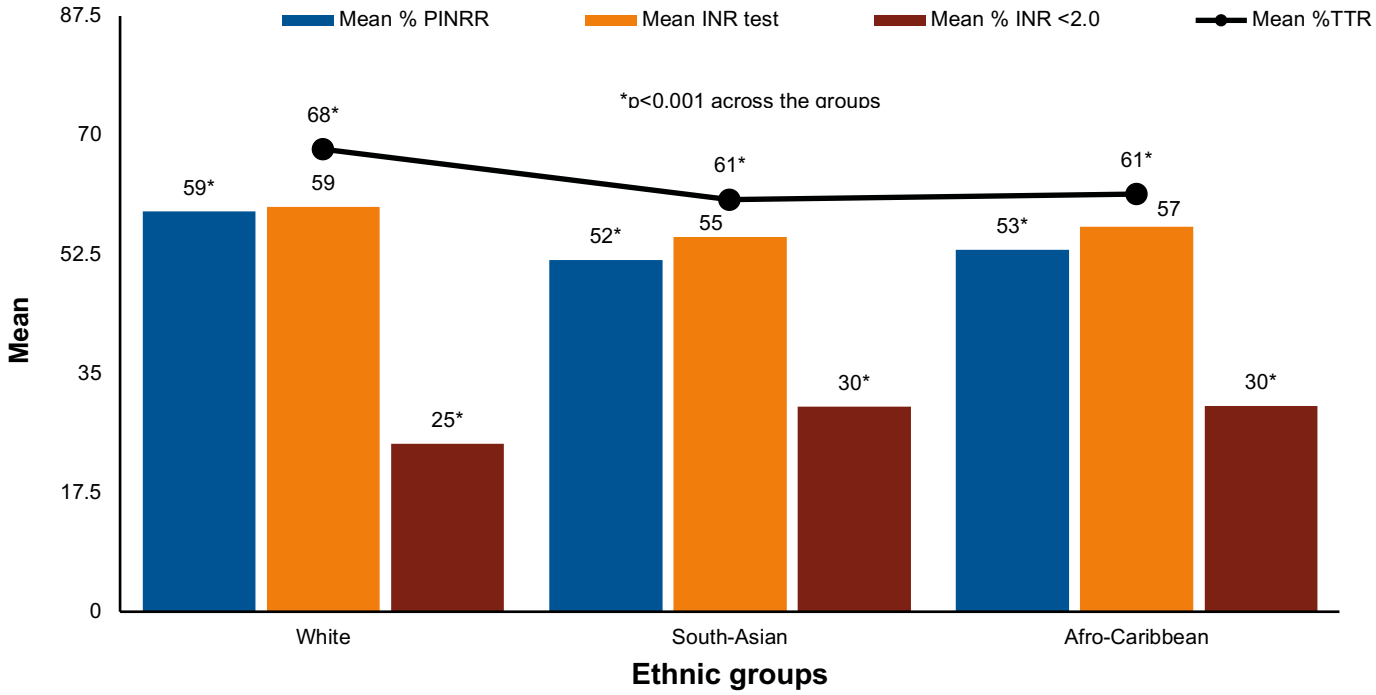


Figure 3.2: Measures of anticoagulation control (including TTR by Rosendaal and PINRR method) by ethnicity

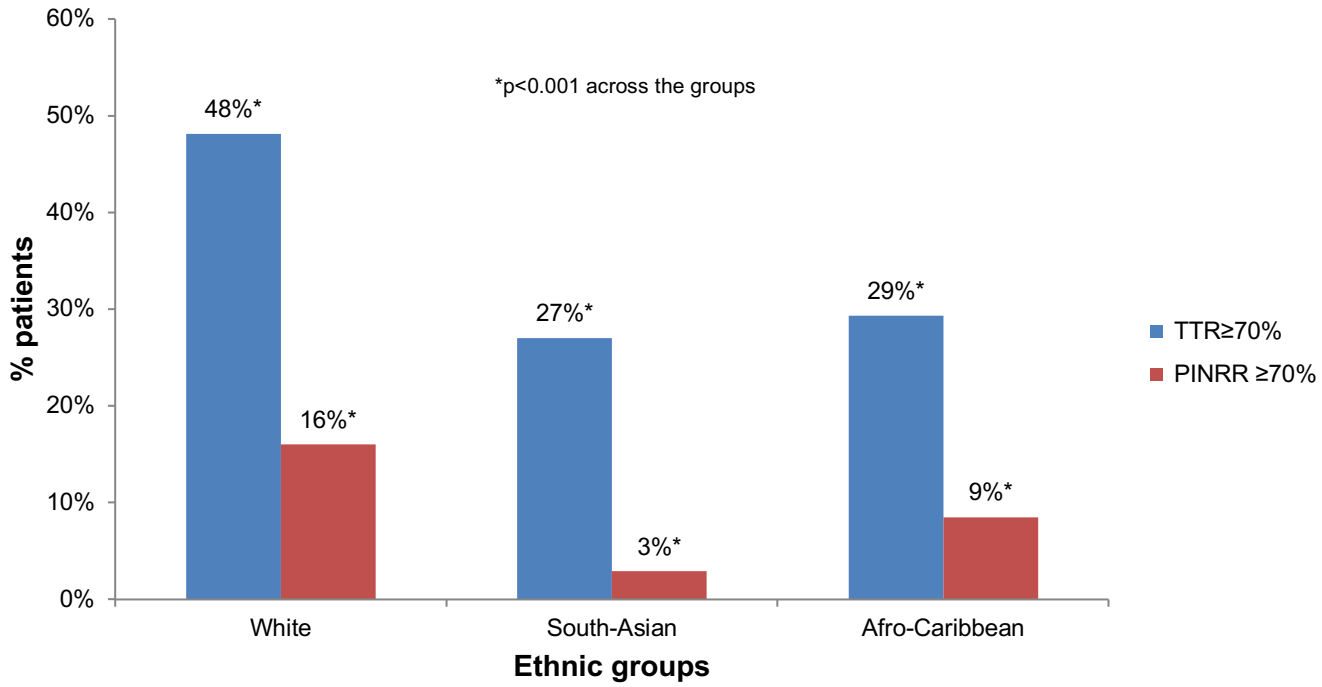


Figure 3.3: Percentage of patients by ethnic group with a therapeutic (TTR≥70%) TTR by the Rosendaal and PINRR method

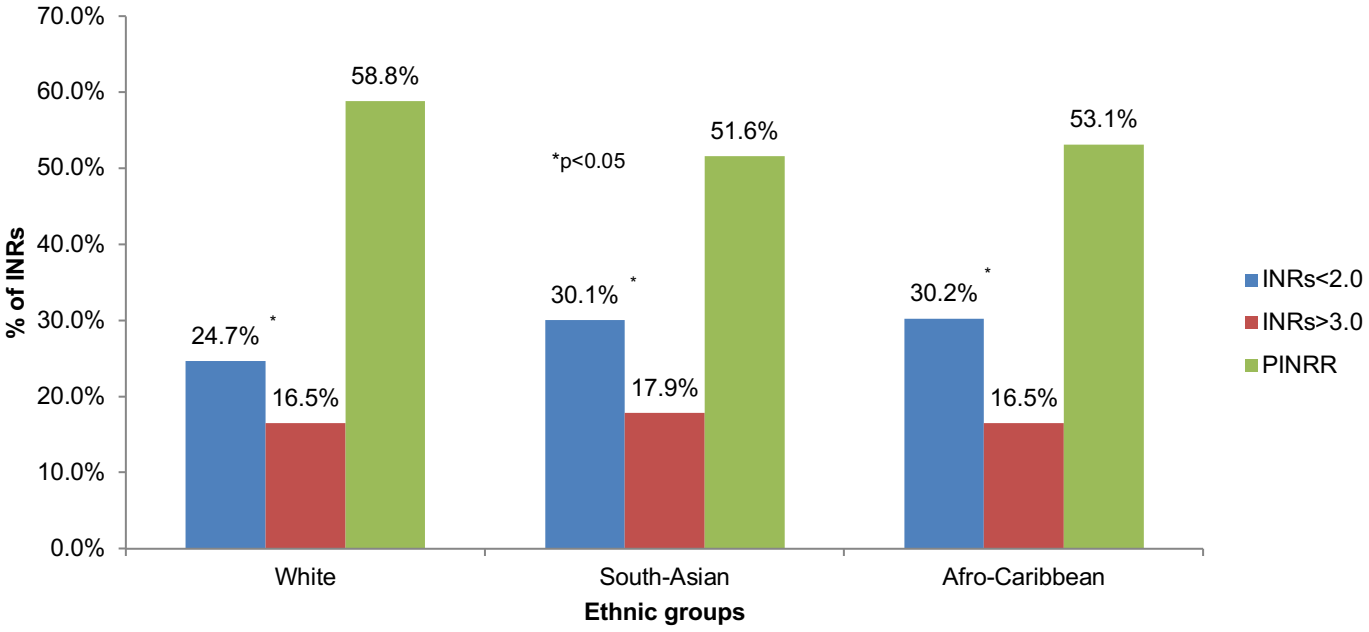


Figure 3.4: Percentage of INRs within therapeutic range (PINRR), and below (INR<2.0) and above (INR >3.0) therapeutic range

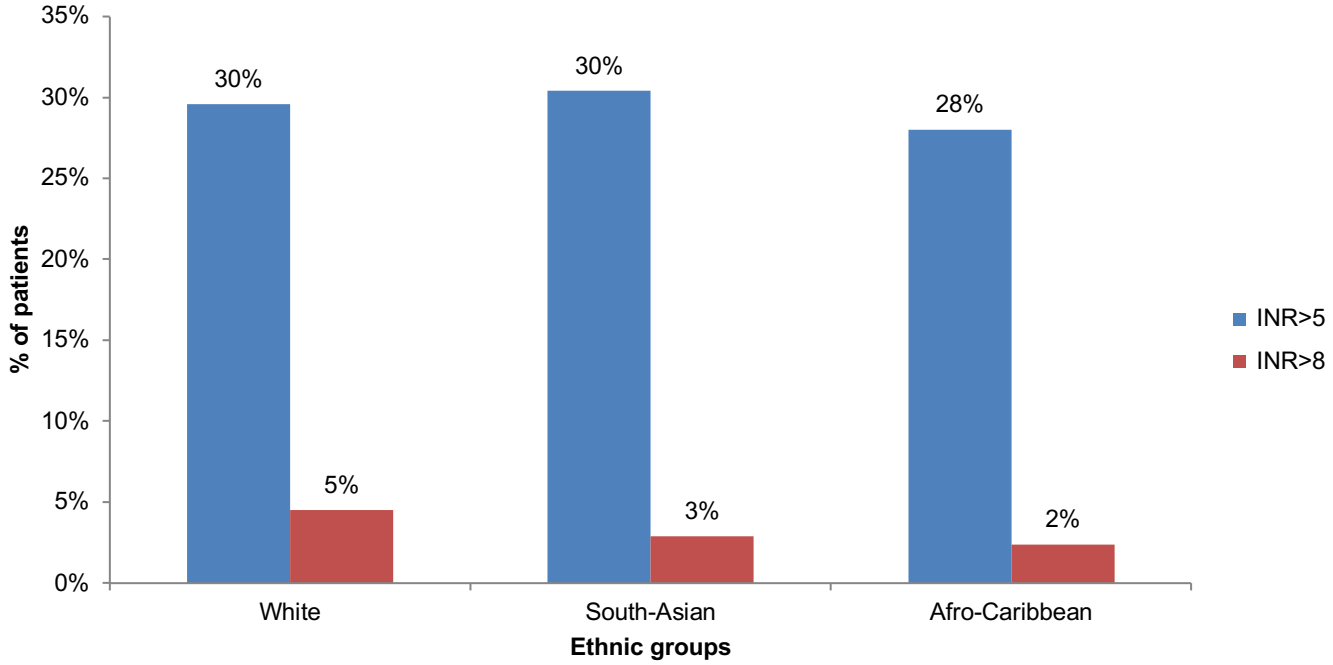


Figure 3.5: Percentage of patients with an INR >5.0 and >8.0

Measures of anticoagulation control continued

3.4.2.2 By age (≥80 and <80 years)

Table 3.7 presents the measures of anticoagulation control when patients were grouped according to age ≥80 and <80 years. The quality of anticoagulation control by both measures, TTR (Rosendaal method) [66.6% in ≥80 and <80 years age group] and PINRR [57.1% in the ≥80 years old vs. 57.7% in <80 years old] were similar between the two age categories. Elderly patients had significantly fewer INR visits (mean 51 vs. 61 visits; p<0.001 for ≥80 vs. <80 years, respectively) and a lower duration of follow up **(Figure 3.6).** Good TTR (defined as TTR and PINRR ≥70%) was 44% and 14% in those aged ≥80 years and <80 years, respectively; over half of the elderly population did not achieve the optimal percentage TTR advocated by clinical guidelines. No significant differences in sub-therapeutic or supra-therapeutic INRs were observed by age (≥80 and <80 years).

Table 3.7: Measures of anticoagulation control among overall population and in patients aged ≥80 and <80 years

N, (%)	Age ≥80, N=205	Age <80, N=786	p-value
Mean TTR (SD)	66.6 (13.8)	66.6 (13.1)	1.00
TTR<70	114 (55.6)	436 (55.5)	1.00
TTR≥70	91 (44.4)	350 (44.5)	
Mean PINRR (SD)	57.1 (11.6)	57.7 (11.1)	0.54
PINRR<70	176 (85.9)	675 (85.9)	1.00
PINRR≥70	29 (14.1)	111 (14.1)	
Mean (SD) number of visits	**51.2 (22.7)**	**60.7 (25.8)**	**<0.001**
Mean (SD) percentage of INRs<2	26.6 (9.8)	25.5 (24.5)	0.17
Mean (SD) percentage of INRs>3	16.4 (15.6)	16.7 (7.1)	0.60
INR>5	70 (34.1)	223 (28.4)	0.13
INR>8	10 (4.9)	31 (3.9)	0.69
Median (IQR) years follow up	**4.4 (2.6-6.2)**	**5.7 (3.3-7.1)**	**<0.001**

TTR: Time in therapeutic range, PINRR: Percentage of INRs within range; INR: international Normalised Ratio; SD: standard deviation; IQR: interquartile range

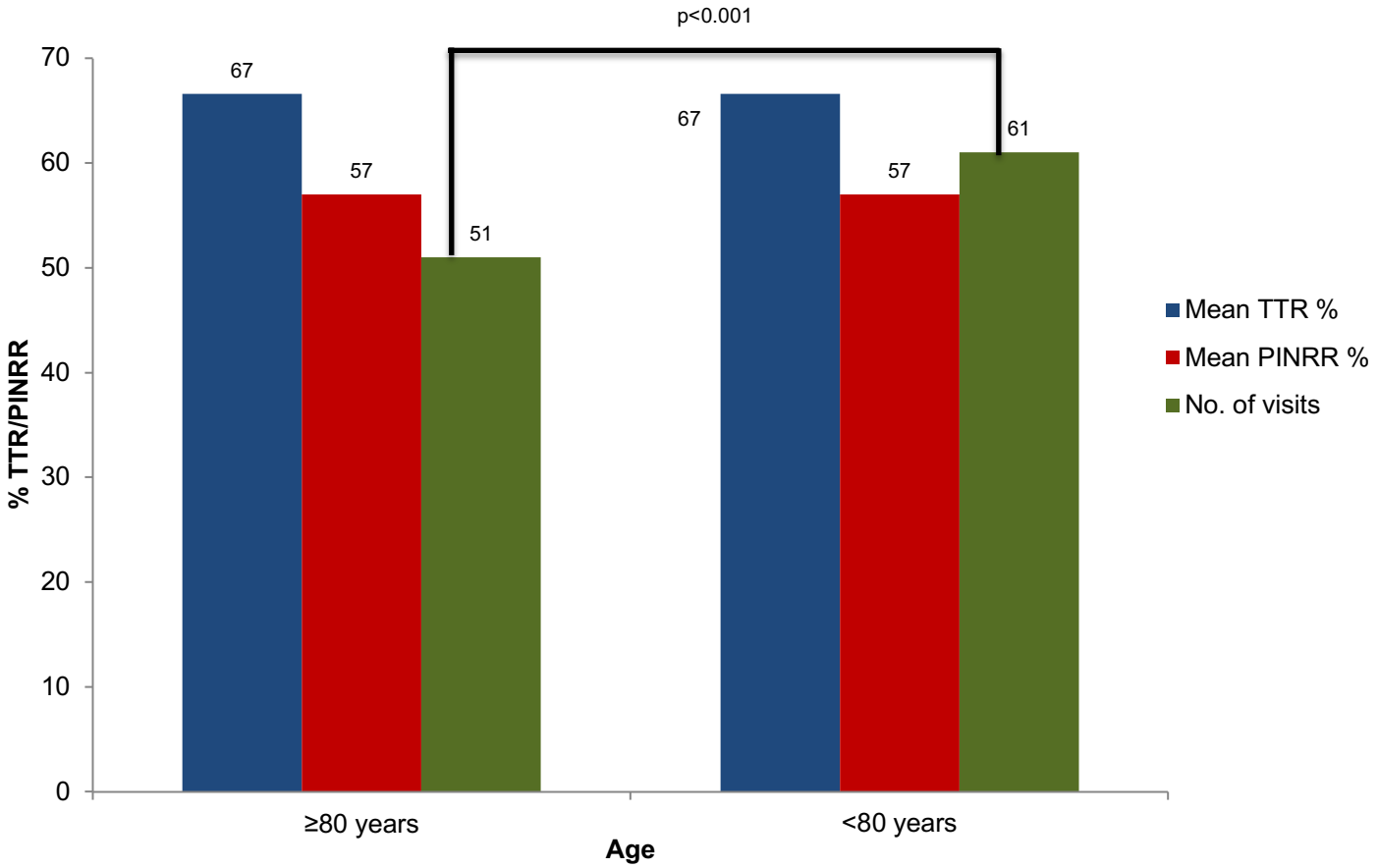


Figure 3.6: Mean percentage TTR and PINRR and number of visits among patients aged ≥ 80 and <80 years

Quality of anticoagulation control continued

3.4.2.3 By categories of kidney disease

Table 3.8 presents the measures of anticoagulation control according to the different categories of kidney disease. Overall, there was no statistically significant difference in the quality of anticoagulation control, measured by TTR (Rosendaal's method), by kidney disease groups, although TTR was higher in patients with eGFR 60-89 and eGFR ≤59 (67% in both groups) compared to those in with eGFR ≥90 (64%; overall p=0.053) **(Figure 3.7).** There was a significant trend in higher PINRR in patients with eGFR 60-89 and eGFR ≤59 (PINRR 58% in both groups) compared to those with eGFR ≥90 (PINRR 55%; all p<0.05 for group comparison) **(Table 3.8 and Figure 3.7).**

Higher proportions of patients with eGFR 60-89 and eGFR ≤59 achieved good TTR compared to eGFR ≥90 (p<0.05 for group comparison). Sub-therapeutic INRs (INR <2.0) **(Table 3.8 and Figure 3.8)** and the proportion of patients with at least one INR >8.0 were significantly more prevalent in patients with eGFR ≥90 compared to eGFR 60-89 (p<0.05 for group comparison). Meanwhile, the proportion of supra-therapeutic INRS >3.0 did not differ by kidney function groups **(Table 3.8 and Figure 3.8).**

Table 3.8: Measures of anticoagulation control among different categories of kidney disease, N=974

N, (%)	All (n=974)	eGFR≥90 ml/min N=133	eGFR 60-89 ml/min N=491	eGFR ≤59 ml/min N=350	Overall p-value
Mean TTR (SD)	66.5 (13.2)	64.0 (14.1)	66.9 (12.7)	67.0 (13.4)	0.053
TTR<70	542 (55.6)	87 (65.4)	263 (53.6)[a]	192 (54.9)[b]	**0.05**
TTR≥70	432 (44.4)	46 (34.6)	228 (46.4) [a]	158 (45.1)[b]	
Mean PINRR (SD)	57.4 (11.1)	55.0 (11.5)	57.8 (10.6)[a]	57.8 (11.7)[b]	**0.02**
PINRR<70	842 (86.4)	120 (90.2)	427 (87.0)	295 (84.3)	0.21
PINRR≥70	132 (13.6)	13 (9.8)	64 (13.0)	55 (15.7)	
Median (IQR) number visits*	59.0 (41.0-74.0)	61.0 (39.5-78.5)	60.0 (42.0-74.0)	57.5 (41.0-72.0)	0.37
Mean (SD) percentage of INRs<2	25.9 (9.9)	27.8 (9.9)	25.4 (9.8)[a]	25.7 (10.2)	**0.05**
Mean (SD) percentage of INRs>3	16.6 (7.2)	17.0 (8.3)	16.6 (7.0)	16.6 (7.1)	0.84
INR>5	287 (29.5)	41 (30.8)	129 (26.3)	117 (33.4)	0.08
INR>8	40 (4.1)	11 (8.3)	14 (2.9)[a]	15 (4.3)[b,c]	**0.02**
Median (IQR) years follow up*	5.2 (3.2-7.0)	5.0 (2.9-7.0)	5.6 (3.3-7.1)	5.0 (3.2-6.9)	0.18

eGFR ≥90ml/min/1.73m^2- normal kidney function; eGFR 60-89 ml/min/1.73m^2 - Mild kidney disease; eGFR ≤59 ml/min/1.73m^2- mild-moderate-severe and kidney failure

eGFR: estimated glomerular filtration rate, ml/min/1.73 m^2; INR: international normalised ratio; IQR: interquartile range; SD: standard deviation; TTR: time in therapeutic range; PINRR: percentage of INRs in range; *Kruskal-Wallis test was utilised to compare median across the groups

a: significant difference between eGFR≥90 and eGFR 60-89; p<0.05
b: significant difference between eGFR≥90 and eGFR ≤59; p<0.05
c: significant difference between eGFR 60-89 and eGFR ≤59, p<0.05

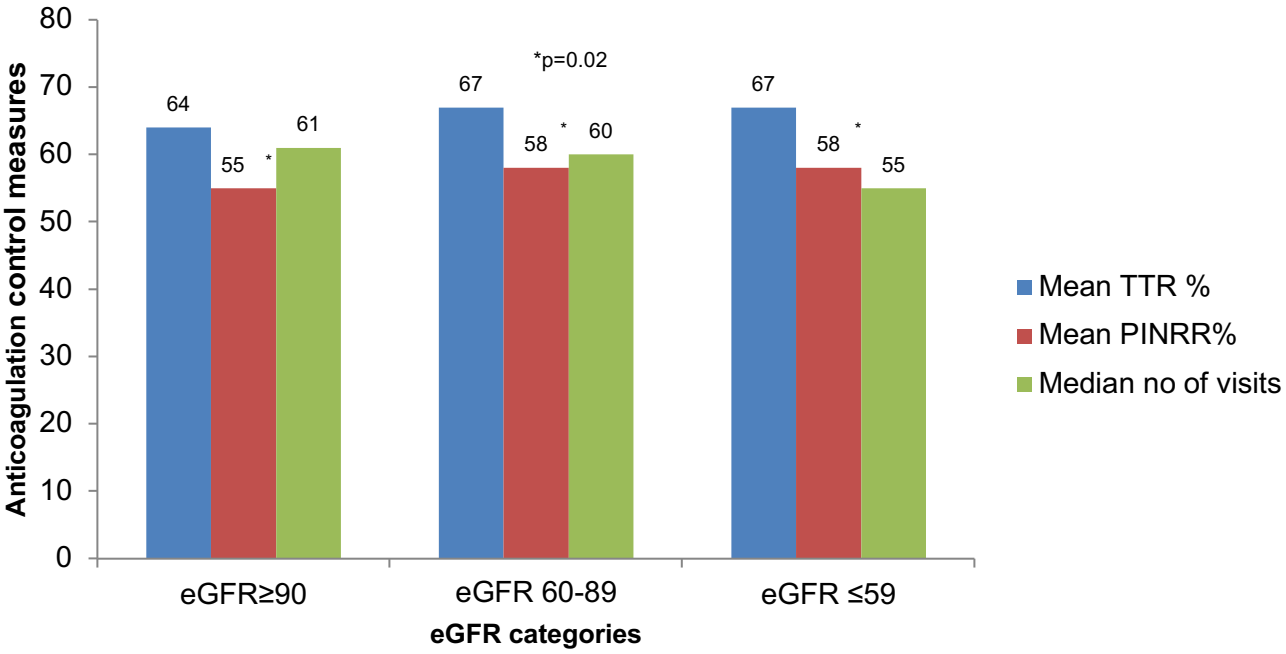


Figure 3.7: Measures of anticoagulation control in different categories of kidney disease

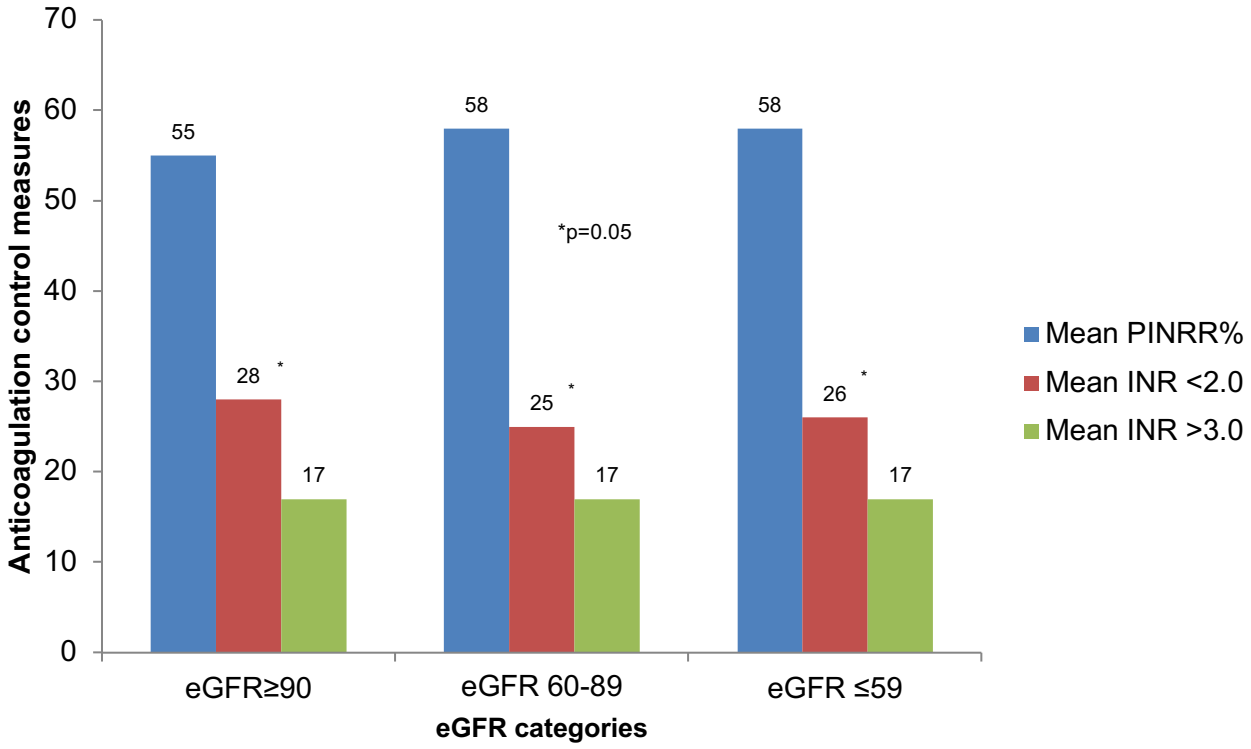


Figure 3.8: The proportion of INRs within, below and above therapeutic range in different categories of kidney disease

3.4.3 Predictors of time in therapeutic range (TTR) by the Rosendaal and PINRR methods

In the unadjusted analyses for predictors of TTR and PINRR (as continuous variables), non-white ethnicity, heart failure, vascular disease, anaemia, and bleeding history, with the addition of diabetes for PINRR, negatively predicted TTR and PINRR **(Table 3.9 and 3.11).**

After adjusting for demographic and clinical variables, smoking history, non-white ethnicity, bleeding history, and heart failure were independent predictors of TTR **(Table 3.10)**, with the addition of vascular disease as an independent predictor of PINRR **(Table 3.12).**

When TTR and PINRR were dichotomised to TTR<70% and PINRR<70%, unadjusted analyses revealed that non-white ethnicity and anaemia significantly predicted poor TTR and PINRR (TTR<70%). Further factors predicting poor TTR (TTR<70%) were vascular disease and heart failure (**Appendix 4, Table A4.2 and A4.3 for full model**). However, after adjusting for demographic and clinical variables, non-white ethnicity and anaemia remained as independent predictors of poor TTR (TTR<70%) and PINRR (PINRR<70%), with vascular disease as an additional factor for predicting poor TTR **(Table 3.13).**

Table 3.9: Unadjusted demographic and clinical predictors of time in therapeutic range (TTR) by the Rosendaal method (linear regression)

Variables	Contribution to R^2	Unstandardized B	Standardized coefficient Beta	95% CI for B	F	Significance p-value
Age at first INR¥	0.002	0.07	0.05	-0.02 to 0.15	2.15	0.14
Female sex	0.00	0.30	0.01	-1.36 to 1.95	0.12	0.73
Smoking history	0.01	-0.93	-0.04	-2.91 to 1.05	0.86	0.36
Ethnicity (non-white)	**0.04**	**-7.09**	**-0.21**	**-9.17 to -5.02**	**45.10**	**<0.001**
Hypertension	0.001	0.84	0.03	-1.19 to 2.87	0.66	0.42
Stroke/TIA	0.001	1.33	0.04	-0.82 to 3.47	1.48	0.23
Heart failure	**0.007**	**-3.29**	**-0.09**	**-5.67 to -0.92**	**7.42**	**0.007**
Diabetes	0.002	-1.43	-0.04	-3.47 to 0.60	1.90	0.17
Vascular disease	**0.004**	**-2.33**	**-0.07**	**-4.55 to -0.11**	**4.24**	**0.040**
Kidney disease	0.00	0.01	0	-1.70 to 1.71	0	0.10
Anaemia	**0.014**	**-4.42**	**-0.12**	**-6.74 to -2.11**	**14.06**	**<0.001**
Bleeding history	**0.008**	**-4.42**	**-0.09**	**-7.45 to -1.39**	**8.19**	**0.004**

¥ Continuous variable

INR: international Normalised Ratio; TIA: transient ischemic attack; TTR: Time in therapeutic range

Table 3.10: Adjusted demographic and clinical predictors of time in therapeutic range (TTR) by the Rosendaal method (linear regression)

Variables	Contribution to R^2	Unstandardized B	Standardized coefficient Beta	95% CI for B	F	Significance p-value
Overall model	0.086	-	-	-	5.51	-
Age at first INR¥		0.06	0.04	-0.05 to 0.17		0.27
Female sex		-0.25	-0.01	-2.30 to 1.79		0.81
Smoking history		**-2.49**	**-0.09**	**-4.55 to -0.42**		**0.02**
Ethnicity (non-white)		**-8.09**	**-0.24**	**-10.69 to -5.49**		**<0.001**
Hypertension		1.94	0.06	-0.52 to 4.37		0.12
Stroke/TIA		0.91	0.03	-1.56 to 3.38		0.47
Heart failure		**-3.18**	**-0.09**	**-5.81 to -0.54**		**0.02**
Diabetes		1.73	0.05	-0.73 to 4.18		0.17
Vascular disease		-1.19	-0.03	-3.87 to 1.49		0.38
Kidney disease		-0.30	-0.01	-2.39 to 1.78		0.78
Anaemia		-2.62	-0.07	-5.56 to 0.32		0.08
Bleeding history		**-3.83**	**-0.08**	**-7.39 to -0.27**		**0.04**

¥ Continuous variable

INR: international Normalised Ratio; TIA: transient ischemic attack TTR: Time in therapeutic range

Table 3.11: Unadjusted demographic and clinical predictors of percentage of INRs in range using the PINRR method (linear regression)

Variables	Contribution to R^2	Unstandardized B	Standardized coefficient Beta	95% CI for B	F	Significance p-value
Age at first INR¥	0.00	0.02	0.01	-0.06 to 0.09	0.15	0.70
Female sex	0.00	0.06	0.00	-1.35 to 1.46	0.01	0.94
Smoking history	0.001	-0.70	-0.03	-2.35 to 0.95	0.69	0.41
Ethnicity (non-white)	**0.05**	**-6.54**	**-0.23**	**-8.29 to -4.79**	**53.75**	**<0.001**
Hypertension	0.001	1.06	0.04	-0.66 to 2.78	1.47	0.23
Stroke/TIA	0.001	0.72	0.03	-1.09 to 2.54	0.61	0.44
Heart failure	**0.006**	**-2.60**	**-0.08**	**-4.61 to -0.59**	**6.42**	**0.011**
Diabetes	**0.008**	**-2.49**	**-0.09**	**-4.21 to -0.77**	**8.06**	**0.005**
Vascular disease	**0.011**	**-3.24**	**-0.11**	**-5.11 to -1.36**	**11.48**	**0.001**
Kidney disease	0.00	-0.15	-0.01	-1.59 to 1.30	0.04	0.84
Anaemia	**0.02**	**-4.12**	**-0.13**	**-6.08 to -2.16**	**17.03**	**<0.001**
Bleeding history	**0.02**	**-5.13**	**-0.12**	**-7.69 to -2.57**	**15.45**	**<0.001**

¥ Continuous variable

INR: international Normalised Ratio; TIA: transient ischemic attack; PINRR: Percentage of INRs within range

Table 3.12: Adjusted demographic and clinical predictors of percentage of INRs in range using the PINRR method (linear regression)

Variables	Contribution to R^2	Unstandardized B	Standardized coefficient Beta	95% CI for B	F	Significance p-value
Overall model	0.10				6.55	
Age at first INR¥		0.01	0.01	-0.08 to 0.10		0.89
Female sex		-0.25	-0.01	-1.94 to 1.44		0.77
Smoking history		**-1.99**	**-0.09**	**-3.70 to -0.28**		**0.02**
Ethnicity (non-white)		**-6.83**	**-0.24**	**-8.98 to -4.67**		**<0.001**
Hypertension		2.48	0.09	0.46 to 4.51		**0.02**
Stroke/TIA		0.91	0.03	-1.14 to 2.95		0.38
Heart failure		**-2.16**	**-0.07**	**-4.34 to 0.02**		**0.05**
Diabetes		-0.18	0.01	-2.21 to 1.86		0.86
Vascular disease		**-2.26**	**-0.08**	**-4.48 to- 0.04**		**0.05**
Kidney disease		0.48	0.02	-1.25 to 2.20		0.59
Anaemia		-1.77	-0.06	-4.20 to 0.66		0.15
Bleeding history		**-4.34**	**-0.11**	**-7.29 to -1.39**		**0.004**

¥ Continuous variable

INR: international Normalised Ratio; TIA: transient ischemic attack; PINRR: Percentage of INRs within range

Table 3.13: Logistic regression for significant predictors of TTR<70% and PINRR <70% (using Rosendaal and PINRR methods)

	Adjusted OR (95% CI) TTR<70% (Rosendaal method)	p-value	Adjusted OR (95% CI) PINRR<70% (PINRR method)	p-value
Ethnicity (non- white)	2.62 (1.67-4.10)	**<0.001**	3.47 (1.44-8.34)	**0.005**
Vascular disease	1.81 (1.16-2.83)	**0.01**	-	
Anaemia	1.65 (1.00-2.70)	**0.05**	6.27 (1.89-20.94)	**0.003**

3.4.4 Major adverse clinical outcomes

During a median follow-up of 5.2 years, 50 (5.0%) patients had thromboembolic events (46 patients with stroke/TIA, 4 systemic embolisms), 78 (7.9%) experienced bleeding events [18 patients with major bleed and 62 patients with CRNMB], 226 (22.8%) were hospitalised for cardiovascular reasons, and 23 (2.3%) patients died. Three hundred and twenty-nine patients (33.2%) presented with ≥1 major adverse clinical event. The overall major adverse clinical outcomes for entire population and by ethnic group are presented in **Table 3.14.**

In terms of the number of events, there were 48 (9.3%) stroke/TIA events, 4 (0.7%) systemic embolism, 91(17.5%) bleeding events [23 (4.4%) major bleed and 68 (13.1%) CRNMB], 353 (68%) CV hospitalisations, and 23 (4.4%) deaths.

3.4.4.1 By ethnicity

There was no significant difference in the rate of major adverse clinical outcomes among the three ethnic groups except for CV hospitalisations, where the rate was significantly higher among South Asians compared to Whites (32.3% vs. 21.3%, respectively; p<0.05 for group difference) and Afro-Caribbeans [32.3% vs. 25.6%, respectively; p<0.05 for group difference] **(Table 3.14).**

When events were stratified by TTR **(Table 3.15)**, patients with CV hospitalisations and ≥1 MACE events were more likely to have poor TTR (TTR<70% and TTR<65%) (CV hospitalisations: 26.5% vs. 18.1%; p=0.002 and 27.3% vs. 19.8%; p=0.008 respectively; and

≥1 MACE events: 37.8% vs. 27.4%; p=0.001 and 37.8% vs. 30.1%; p=0.015 respectively). There were no significant differences in thromboembolic, bleeding events and death when TTR was dichotomised into TTR<70% and TTR<65% by either the Rosendaal or PINNR methods. **(Table 3.15)** CV hospitalisations were also significantly higher when PINRR was <70% (24.4%; p=0.004) but not with PINRR<65%. **(Table 3.16)** Hospitalisations due to non-cardiac causes were significantly higher when TTR<70% or TTR<65% by both the Rosendaal **(Table 3.15)** and PINRR methods. **(Table 3.16)**

Table 3.14: Major adverse clinical outcomes among patients receiving warfarin for stroke prevention for AF overall and by ethnic group

Outcomes, N (%)	Total, N=991	White, N=807	South-Asian, N=102	Afro-Caribbean, N=82	p-value
Stroke/TIA	46 (4.6)	36 (4.5)	5 (4.9)	5 (6.1)	0.79
SE	4 (0.4)	3 (0.4)	0	1 (0.1)	0.41
Stroke/TIA/SE	50 (5.0)	39 (4.8)	5 (4.9)	6 (7.3)	0.62
Bleeding*	78 (7.9)	64 (7.9)	6 (5.9)	8 (9.8)	0.62
Cardiovascular hospitalisation	226 (22.8)	172 (21.3) [a]	33 (32.3) [a]	21 (25.6)	**0.036**
Death	23 (2.3)	20 (2.5)	2 (2.0)	1 (1.2)	0.75
≥1 MACE	329 (33.2)	258 (32.0)	40 (39.2)	31 (37.8)	0.22

Cardiovascular hospitalisation: a hospitalisation with a cardiovascular cause: i) heart failure, MI, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled AF/atrial flutter, supraventricular arrhythmia, ii) valve surgery, CABG surgery, PTCA surgery, pacemaker/ICD insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation AND as recorded in patient's medical documents; DVT – Deep Vein Thrombosis ; Major Bleeding – ISTH Major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding but meet at least one of the 3 criteria: i) leading to hospitalisation or increased level of care, ii) requiring medical intervention by healthcare professional and iii) prompting face to face evaluation.; PE – Pulmonary Embolism; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.* Bleeding ISTH is combination of major bleed ISTH and clinically relevant non-major bleed (CRNMB); MACE: major adverse clinical events.

[a] significant difference between White and South-Asian groups ($p<0.05$)

Table 3.15: Patients experiencing a major adverse clinical event stratified by TTR (<70% vs. ≥70% and <65% and ≥65%)

N (%)	TTR<70%	TTR≥70%	p-value	TTR<65%	TTR≥65%	p-value
CV hospitalisation	146 (26.5)	80 (18.1)	**0.002**	109 (27.3)	117 (19.8)	**0.008**
Stroke/TIA	29 (5.3)	17 (3.9)	0.37	18 (4.5)	28 (4.7)	0.98
SE	3 (0.5)	1 (0.2)	0.78	3 (0.8)	1 (0.2)	0.37
Stroke/TIA/SE	32 (5.8)	18 (4.1)	0.27	21 (5.3)	29 (4.9)	0.93
Bleeding*	50 (9.1)	28 (6.3)	0.14	36 (9.0)	42 (7.1)	0.33
Death	16 (2.9)	7 (1.6)	0.25	14 (3.5)	9 (1.5)	0.07
≥1 MACE	208 (37.8)	121 (27.4)	**0.001**	151 (37.8)	178 (30.1)	**0.015**
Other hospitalisations	247 (44.9)	155 (35.1)	**0.002**	179 (44.8)	223 (37.7)	**0.032**

Cardiovascular hospitalisation: a hospitalisation with a cardiovascular cause: i) heart failure, MI, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled AF/atrial flutter, supraventricular arrhythmia, ii) valve surgery, CABG surgery, PTCA surgery, pacemaker/ICD insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation AND as recorded in patient's medical documents; DVT – Deep Vein Thrombosis ; Major Bleeding – ISTH Major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding but meet at least one of the 3 criteria: i) leading to hospitalisation or increased level of care, ii) requiring medical intervention by healthcare professional and iii) prompting face to face evaluation.; PE – Pulmonary Embolism; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.*Bleeding ISTH is combination of major bleed ISTH and clinically relevant non-major bleed (CRNMB); MACE: major adverse clinical events.

Table 3.16: Patients experiencing a major adverse clinical event stratified by PINRR (<70% vs. ≥70% and <65% and ≥65%)

N (%)	PINRR<70%	PINRR≥70%	p-value	PINRR<65%	PINRR≥65%	p-value
CV hospitalisation	208 (24.4)	18 (12.9)	**0.004**	179 (24.3)	47 (18.4)	0.07
Stroke/TIA	40 (4.7)	6 (4.3)	1.00	35 (4.8)	11 (4.3)	0.91
SE	3 (0.4)	1 (0.7)	1.00	3 (0.4)	1 (0.4)	1.000
Stroke/TIA/SE	43 (5.1)	7 (5.0)	1.00	38 (5.2)	12 (4.7)	0.90
Bleeding*	71 (8.3)	7 (5.0)	0.23	63 (8.6)	15 (5.9)	0.22
Death	20 (2.4)	3 (2.1)	1.00	19 (2.6)	4 (1.6)	0.49
≥1 MACE	298 (35.0)	31 (22.1)	**0.004**	259 (35.2)	70 (27.5)	**0.029**
Other hospitalisations	360 (42.3)	42 (30.0)	**0.008**	320 (43.5)	82 (32.2)	**0.002**

Cardiovascular hospitalisation: a hospitalisation with a cardiovascular cause: i) heart failure, MI, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled AF/atrial flutter, supraventricular arrhythmia, ii) valve surgery, CABG surgery, PTCA surgery, pacemaker/ICD insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation AND as recorded in patient's medical documents; DVT – Deep Vein Thrombosis ; Major Bleeding – ISTH Major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding and that led to hospitalisation, physician medical or surgical treatment, or a change in antithrombotic therapy; PE – Pulmonary Embolism; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.* Bleeding ISTH is combination of major bleed ISTH and clinically relevant non-major bleed (CRNMB).

3.4.4.1.1 Predictors of adverse clinical outcomes

In this exploratory analysis, unadjusted Cox proportional hazard regression analyses revealed that only prior stroke/TIA [HR 2.40 (95% CI 1.33-4.30); p=0.003] and diabetes [HR 2.01 (95% CI 1.11-3.65); p=0.021] predicted thromboembolic (stroke/TIA/ systemic embolism) events (**see Appendix 4, Table A4.4**). However, only prior stroke/TIA history [HR 2.29 (95% CI 1.12-4.68); p=0.02] remained as independent predictor of thromboembolic events, after adjusting for demographic and clinical variables **(Table 3.17).**

For bleeding events (major bleed and CRNMB), increasing age, TTR and PINRR (as continuous variables) predicted bleeding events **(see Appendix 4, Table A4.5)** but after adjustment, only TTR <70%, [HR 1.78 (95% CI 1.01-3.13); p=0.05] independently predicted bleeding events **(Table 3.17).**

In unadjusted Cox proportional hazard regression analyses, non-white ethnicity, heart failure, diabetes, vascular disease, anaemia, TTR and PINRR (both continuous and categorical variable) predicted CV hospitalisation **(see Appendix 4, Table A4.6).** However, after adjustment, only heart failure [HR 1.46 (95% CI 1.02-2.11); p=0.04], vascular disease [HR 1.62 (95% CI 1.11-2.34); p=0.01] and TTR<70% [HR 1.38 (95% CI 1.00-1.89) p=0.05] were independent predictors of CV hospitalisations **(Table 3.17). Figure 3.9** shows the Kaplan-Meier curve illustrating the event free rate for CV hospitalisation by TTR <70% and ≥70%. The rate of CV hospitalisation was significantly higher in patients with poor TTR (6.0/100 pt-yrs) (Log rank test: 11.90; p=0.001) compared to patients with optimal TTR (TTR≥70%; 3.7/100 pt-yrs).

Only increasing age and anaemia predicted all-cause mortality in the unadjusted Cox proportional hazard regression model, however after adjustment, none of the factors were significant predictors of all-cause mortality **(see Appendix 4, Table A4.7).**

When all adverse clinical outcomes were combined as composite events (MACE) in an unadjusted model, non-white ethnic group, hypertension, stroke/TIA, heart failure, diabetes, vascular disease, anaemia and both measures of quality of anticoagulation (TTR and PINNR as continuous and categorical variable) predicted composite events (**see Appendix 4, Table A4.8).** However, after adjusting for demographic and clinical variables, only prior stroke/TIA, vascular disease and TTR<70% predicted ≥1 MACE **(Table 3.17).** Kaplan-Meier analysis **(Figure 3.10)** shows the higher rate of ≥1 MACE in patients with poor TTR (9.1/100 pt-yrs) (Log rank test: 14.25; p<0.001) compared to patients with TTR≥70% (5.9/100 pt-yrs).

Table 3.17: Cox proportional hazard regression analysis for thromboembolic, bleeding events, CV hospitalisations and composite outcomes of thromboembolic events, major bleed and clinically relevant non-major bleeding, cardiovascular hospitalisation and all-cause mortality (≥1 MACE)

Multivariate HR (95% CI)	Thromboembolic events	Bleeding events	CV hospitalisations	≥1 MACE
Stroke/TIA	2.29 (1.12-4.68)	-	-	1.38 (1.03-1.85)
Heart failure	-	-	1.46 (1.02-2.11)	-
Vascular disease	-	-	1.62 (1.11-2.34)	1.67 (1.21-2.30)
TTR <70%	-	1.78 (1.01-3.13)	1.38 (1.00-1.89)	1.45 (1.11-1.89)

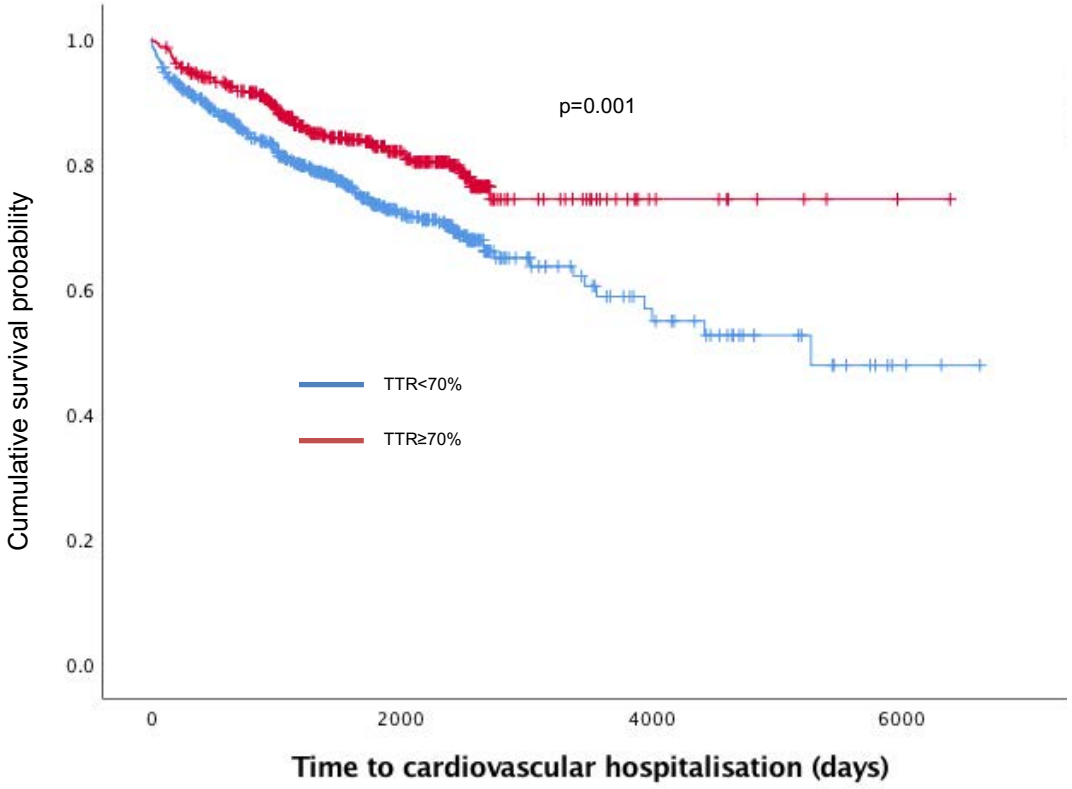


Figure 3.9: Impact of TTR on cardiovascular hospitalization

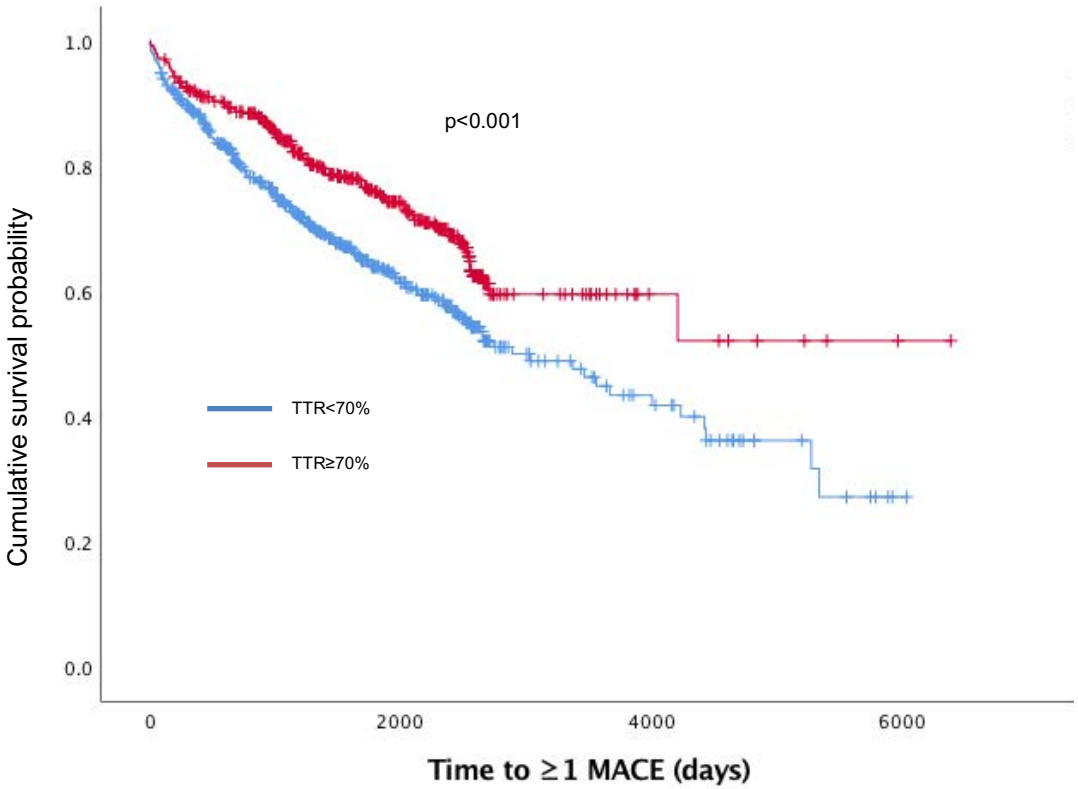


Figure 3.10: Impact of TTR on composite endpoints of thromboembolic events, major and clinically relevant non-major bleeding events, cardiovascular hospitalisation and all-cause mortality (≥1 MACE)

3.4.4.2 Adverse outcomes by age (≥80 years and <80 years)

Only twelve (6%) of the elderly (≥80 years) patients experienced thromboembolic events; 21 (10.2%) had a bleeding event and eight (4.0%) died. The proportion of bleeding (10.2% vs. 7.3% for ≥80 years and <80 years respectively) and fatal (3.9% vs. 1.9% respectively) events were higher among elderly patients. However, cardiovascular hospitalisations (23.9% vs. 18.5%) and the composite of adverse clinical outcome (≥1MACE) (33.7% vs. 31.2%) were proportionally higher in the younger age category (**Table 3.18**).

The Kaplan-Meier curve illustrates the rate of bleeding events which were significantly higher in the elderly group compared to those aged <80 years (2.4% vs. 1.3%, respectively) (Log Rank-test: 6.73; p=0.009 **Figure 3.11**). Univariate Cox regression analysis **(see Appendix 4, Table A4.9 for full model)** showed that only age ≥80 years [HR 1.93 (1.16-3.20); p=0.01] was associated with bleeding risk and this relationship persisted after adjusting for demographic and clinical variables [≥80 years: HR 1.90 (1.01-3.56); p=0.047] **(Table 3.19).** History of stroke/TIA [HR 1.37 (1.02-1.85); p=0.04], vascular disease [HR1.53 (1.10-2.14); p=0.01] and poor TTR (TTR<70%) [HR 1.47 (1.13-1.91); p=0.004] were associated with an increased risk of the composite outcomes (≥1MACE) **(Table 3.19),** however, age ≥80 years was not **(see Appendix 4, Table A4.10 for full model)**.

Table 3.18: Major adverse clinical outcomes among patients receiving warfarin for stroke prevention in AF overall and in patients ≥80 and <80 years

Outcomes, N (%)	Age ≥80, N=205	Event rate/100 pt-yrs	Age <80, N=786	Event rate/100 pt-yrs	P value for proportions
≥1 MACE	64 (31.2)	8.4	265 (33.7)	7.4	0.55
Stroke/TIA/SE	12 (5.9)	1.4	38 (4.8)	0.9	0.68
Bleeding*	21 (10.2)	2.4	57 (7.3)	1.3	0.16
Cardiovascular hospitalisation‡	38 (18.5)	4.7	188 (23.9)	5.0	0.12
Death	8 (3.9)	0.9	15 (1.9)	0.3	0.15

* Bleeding is combination of major bleed according to International Society on Thrombosis and Haemostasis (ISTH) and clinically relevant non-major bleed (CRNMB).

‡Cardiovascular hospitalisation: a hospitalisation with a cardiovascular cause: i) heart failure, myocardial infarction, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled atrial fibrillation/atrial flutter, supraventricular arrhythmia, ii) valve surgery, coronary artery bypass graft surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA) surgery, pacemaker/ICD insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation AND as recorded in patient's medical documents; DVT – Deep Vein Thrombosis; Major Bleeding – ISTH major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding and that led to hospitalisation, physician medical or surgical treatment, or a change in antithrombotic therapy; PE – pulmonary embolism; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.

Table 3.19: Cox proportional hazard regression analysis for the impact of age (≥80 years) on all bleeding events, including major bleeding and clinically relevant non-major bleeding and ≥1 MACE

Multivariate HR (95% CI)	Bleeding events (95% CI)	≥1 MACE (95% CI)
Age ≥80 years	1.90 (1.01-3.56)	1.00 (0.72-1.39)
Stroke/TIA	-	1.37 (1.02-1.85)
Vascular disease	-	1.53 (1.10-2.14)
TTR <70%	-	1.47 (1.13-1.91)

CI: confidence interval; HR: hazard ratio; TIA: transient ischemic attack; TTR: time in therapeutic range

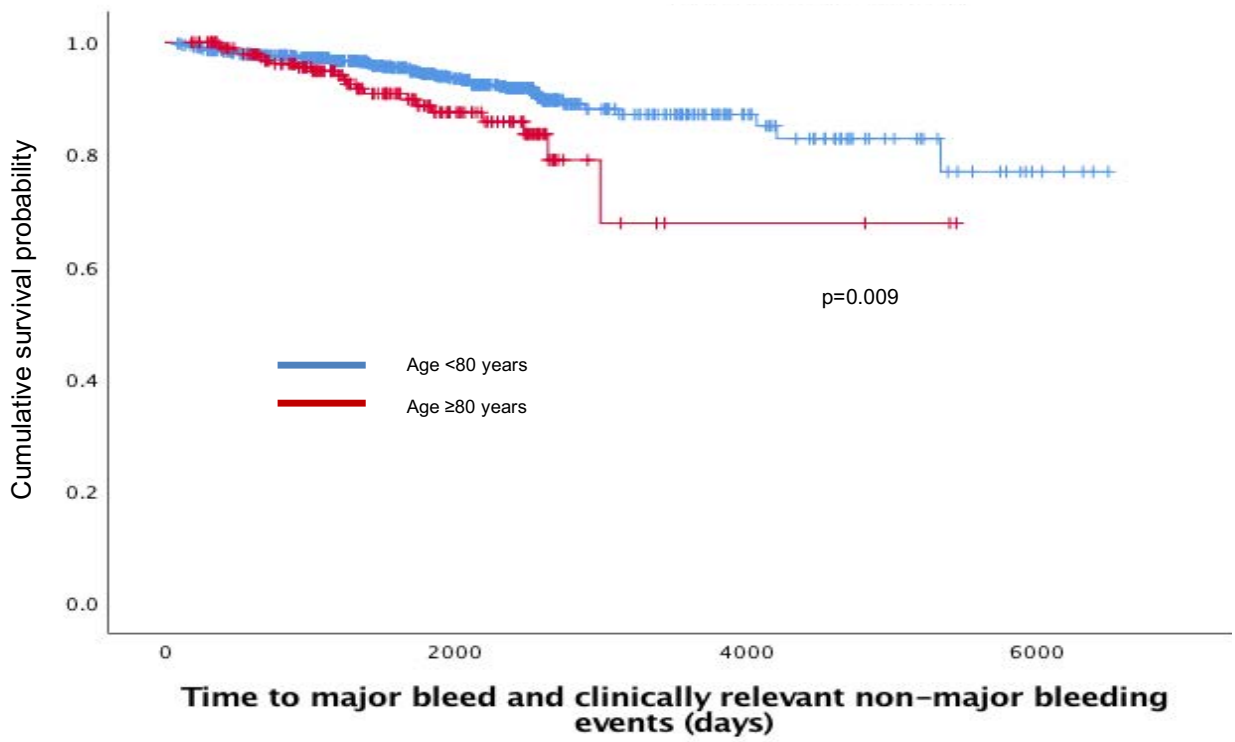


Figure 3.11: Kaplan-Meier curve of bleeding events among patients age ≥80 and <80 years

3.4.4.3 Adverse outcomes by kidney disease

After a median (IQR) of 5.2 (3.2-2.7) years of follow up, 326 patients (33.5%) experienced ≥1 MACE. There is no statistically significant difference in TE, bleeding, CV hospitalisation, death and ≥1 MACE with eGFR ≥90, eGFR 60-89 and eGFR ≤59 ml/min/1.73m^2 respectively **(Table 3.20).**

Table 3.20: Major adverse clinical outcomes among patients receiving warfarin for stroke prevention in AF overall and by different categories of kidney disease

Outcomes	All (N=974)	eGFR≥90 ml/min N=133	eGFR 60-89 ml/min N=491	eGFR ≤59 ml/min N=350	p-value
≥1 MACE	326 (33.5)	52 (39.1)	153 (31.2)	121 (34.6)	0.20
Stroke/TIA/SE	50 (5.1)	7 (5.3)	21 (4.3)	22 (6.3)	0.43
Bleeding*	76 (7.8)	11 (8.3)	39 (7.9)	26 (7.4)	0.94
Cardiovascular hospitalisation	224 (23.0)	37 (27.8)	109 (22.2)	78 (22.3)	0.36
Death	22 (2.3)	3 (2.3)	9 (1.8)	10 (2.9)	0.62

eGFR ≥90ml/min/1.73m^2- normal kidney function; eGFR 60-89 ml/min/1.73m^2- mild kidney disease; eGFR ≤59 ml/min/1.73m^2- mild-moderate-severe and kidney failure

Cardiovascular hospitalisation: a hospitalisation with a cardiovascular cause: i) heart failure, MI, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled AF/atrial flutter, supraventricular arrhythmia, ii) valve surgery, CABG surgery, PTCA surgery, pacemaker/ICD insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation AND as recorded in patient's medical documents; Major Bleeding – ISTH Major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding but meet at least one of the 3 criteria: i) leading to hospitalisation or increased level of care, ii) requiring medical intervention by healthcare professional and iii) prompting face to face evaluation.; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.

* Bleeding ISTH is combination of major bleed ISTH and clinically relevant non-major bleed (CRNMB).

3.5 Discussion

This study found that anticoagulation control, evidenced by TTR and PINRR, was significantly lower in South-Asian and Afro-Caribbean patients compared to White patients, despite similar INR monitoring intensity. In contrast, no significant differences in TTR was evident when the cohort was grouped by age (≥80 vs. <80 years) or kidney disease at baseline. Further, non-white ethnicity was the strongest independent predictor of poor TTR after adjustment for demographic and clinical variables.

3.5.1 Anticoagulation control in the overall cohort

In this study, the overall mean TTR by both methods (Rosendaal and PINRR) and across all ethnic groups was below 70%, which reflects sub-optimal anticoagulation control in this population, according to European guidelines (3). When the PINRR method was used, the overall percentage of time in the therapeutic range was 55.2%, indicating even poorer anticoagulation control. In addition, one third of the patients had at least one INR value above 5, with 4.1% reporting an INR> 8.0, indicative of deranged INR control, associated with higher risk of bleeding (276, 426, 427). These results are in line with the warfarin arms of the recent four landmark NOAC trials [RELY(132), ROCKET-AF (133), ARISTOTLE (134) and ENGAGE-AF (135); mean TTR 64, 58, 66 and 68 respectively] which also showed sub-optimal anticoagulation control despite strict patient inclusion and follow ups. In clinical practice, obtaining a good TTR can be difficult as anticoagulation control is affected by many factors (**see Section 1.5.1 pages 78-100 for more details**). The SAMe-TT_2R_2 score (199) could be used to identify common clinical factors that might predict good/poor anticoagulation and aid physicians to choose the best anticoagulation treatment in this setting.

3.5.1.1 Anticoagulation control in different ethnic groups

Despite similar INR monitoring intensity, it is evident that patients from ethnic minority groups obtained significantly lower quality of anticoagulation control than white patients.

Previous studies by Yong (209) and Golwala et al (210) in the United States have also reported similar findings where Black patients had poorer anticoagulation control compared to Whites, Hispanics, Native Americans and other ethnic minority groups however, no studies to date are available examining anticoagulation control among South-Asian patients. Rao and colleagues (198) investigated patient-level and site-level factors that might influence the differences in anticoagulation control among 9572 Black and 88,481 White patients in the United States. Their findings suggest that greater proportion of the differences may be attributed to non-modifiable factors such as young age, region and poverty level, distance to anticoagulation clinic and presence of co-morbid conditions (198). Although it is not certain, it could be possible that some of these factors (demographics and clinical) might also contribute to ethnic disparities in the quality of anticoagulation control in the current cohort. Younger patients were more commonly seen among South-Asian patients and could perhaps reflect hectic lifestyle resulting in difficulties attending INR appointments. In addition, the presence of vascular disease, diabetes and anaemia were also more commonly seen among patients in the non-white ethnic groups suggesting greater burden of illness among them **(see section 1.5.1.1.4 for more explanation).**

Secondly, although pharmacogenetic factors were not investigated in this study, warfarin metabolism and dose response might differ between ethnic groups. Studies have shown that warfarin dosage requirement is lower in Asians and Whites but higher in Blacks partly due to racial differences in genotype frequencies (428). Patients who inherit one or two copies of CYP2C9*2 or CYP2C9*3 allele are more sensitive to warfarin compared to normal

metabolisers since they impair S-warfarin metabolism by 30-40% and ~80-90% respectively. They are at a higher risk of bleeding during warfarin initiation thus requiring lower doses of warfarin (429-432). The frequencies of the CYP2C9 alleles differ between ethnic groups (433-435). More Caucasians (10-20%) were found to have the *2 allele compared to Asian (1-3%) or African (0-6%) populations (216) and less *3 allele were seen among the African-Americans (209, 216). Moreover, African Americans were also found to have additional CYP2C9 alleles (CYP2C9*5, *6, *8, and *11; the less common ones) which are also associated with reduced function of the CYP2C9 enzyme and contribute to dose variability (436). Thus warfarin dosage can be tailor- made accordingly, if needed, as per guidelines (216, 436).

The role of pharmacogenetics testing and dosing of warfarin patients remains a controversial topic. Two randomized trials examining the impact of genotype dosing towards improving TTR have been contradictory. The EU-PACT trial (437) (N=455) which included participants from European (98.6%), African (0.9%) ancestries and others (0.5%) showed that TTR was significantly higher in the genotype-guided therapy group compared to standard care at 12 weeks (TTR 67.4% vs. 60.3%; $p<0.001$) (437). In contrast, the COAG trial (438) (N=1015) which included more African Americans (27%), 67% European American and 6% Hispanic showed no difference in the mean TTR in patients with genotype-guided dosing compared to clinical-guided dosing of warfarin (TTR 45.2% vs. 45.5% respectively) at 4 weeks. However, TTR improvement by genotype-guided dosing can only be seen among European Americans (2.8%; $p=0.15$) but not among African Americans. Instead worsening TTR was seen among the latter (-8.3%; $p=0.01$). The differences in the results of these two trials could be attributed to heterogeneity in racial diversity, CY2C9*2 and *3, VKORC1 frequency and warfarin indication among the participants. It was also demonstrated (439) that warfarin dosing variability was affected by both clinical and genetic factors in another study (N=1357) comprising of more African Americans (43%). Nevertheless, in African Americans, clinical factors (such as age, CKD, body surface area, and amiodarone) account for higher proportion

of dose variability than genetic factors. Hence, a pharmacogenetic algorithm for warfarin dosing that is race-specific; rather than race-adjusted was suggested.

Third, although this was not investigated in this cohort, previous studies have shown that many AF patients have little knowledge of their condition and lack understanding of the risk and benefit of anticoagulant therapy, in particular among ethnic minority patients (383, 384). This may also contribute to poor adherence to medication and may (or may not) result in poor anticoagulation control. Interventions such as more frequent follow up visits and reviews, educational interventions and counselling are needed (219). For example, discussions about specific food types and health supplements that may interact with warfarin (herbal remedies, vegetarianism, or inconsistent amount of food rich with vitamin K, for example, green leafy vegetables) or specific cultural differences (for example the impact of fasting or excess alcohol on the quality of anticoagulation control) that may affect their understanding are required especially to the ethnic minority groups to ensure that their TTR can be improved in order to achieve the best outcomes and prevent treatment complications (316). Materials for the education intervention should be available in different languages and in different media (booklets, video-clips etc.) so patients who do not speak English but is able to read in their own language can also benefit. Interpreters may also be required so that information shared between the healthcare professional and patient during the counselling session can be effectively understood. Patients should also be encouraged to be actively involved during sessions and to raise any concerns regarding warfarin treatment so that any barriers to adherence can be discussed and overcome. Recently, the TREAT intervention (a one-off educational behavioral session) delivered by a health psychologist demonstrated a significant improvement of TTR compared to patients receiving usual care alone (TTR 76.2% vs. 73.1%, p=0.035) (219). The design of this behavior-change intervention package (consist of DVD delivered by 'expert patient' narratives and consultant cardiologist, educational booklet, diary and patient worksheet) was based on theoretical models (Common Sense Model and Necessity-Concerns Framework), clinical guidelines, relevant literature and AF patient

feedback. This intervention not only resulted in improvement of the quality of anticoagulation control and a greater understanding of AF and its treatment; it also changed patients' belief surrounding their treatment necessity and potential harm (293).

3.5.1.2 Anticoagulation control in in elderly patients

The quality of anticoagulation control was similar among those aged ≥80 and <80 years despite fewer INR visits and shorter follow up among the very elderly patients. Moreover, less than half (44%) of the elderly patients had optimal TTR (TTR≥70%).

These results are consistent with the data obtained from the BAFTA (250) and WASPO (251) trials, with mean TTR comparable to the current elderly cohort (mean TTR 67% and 69% respectively vs. 67% in current elderly cohort). Two other Italian studies (247, 252) reported slightly higher TTR in their cohort (mean TTR 71% in both studies vs. 67% in current elderly cohort) while TTR was lower in another study by Hylek et al (241) among the elderly (≥80 years; mean TTR 58%). This may be explained by the inclusion of an inception cohort by Hylek et al (241), whereas the current study included patients throughout the entire period of treatment (median duration of VKA treatment 5.2 years reflecting long term VKA management). Low TTR (mean TTR 48%) has also been reported in another inception cohort study (200) suggesting the difficulties in achieving good control with VKA therapy especially during the inception period (200).

3.5.1.3 Anticoagulation control in different categories of kidney disease

There was no significant difference in TTR when calculated using the Rosendaal method among AF patients with different categories of kidney disease at baseline. However, when the PINRR method was utilised, a higher percentage of INRs within range was seen among AF patients in with eGFR 60-89 ml/min/1.73m^2 and eGFR ≤59 ml/min/1.73m^2 compared to patients with normal kidney function (eGFR ≥90 ml/min/1.73m^2).

Despite the challenges faced in managing AF patients with CKD, many studies have shown the benefits of VKA therapy in AF and CKD patients in reducing TE, bleeding, cardiovascular hospitalisation and all-cause death (263-265, 269, 440). As mentioned in the literature review, eight (263-270) studies reported TTR data and seven (263-265, 267-270) have shown a significant trend of worsening TTR as the kidney disease worsened (**see section 1.5.1.1.5, pages 81-82 for more information**). For example, in the SPORTIF III and IV trials, the mean TTR among AF patients with eGFR < 60 ml/min was significantly lower than those with eGFR ≥60 ml/min (mean TTR 66.6% vs. 69.6%; p<0.001 respectively) (264). In a retrospective analysis of the Swedish health registers of 307,351 AF patients comprising 13,435 patients with renal disease (diagnosis based on ICD-10 codes), the mean TTR for those with renal disease was also significantly lower than those without renal disease (mean TTR 66.7% vs. 74.6%; p<0.001 respectively) (265).

In contrast, this study did not show a similar trend, instead a non-significant higher TTR was observed in patients with eGFR 60-89 ml/min/1.73m^2 and eGFR ≤59 ml/min/1.73m^2 compared to patients with eGFR ≥90 ml/min/1.73m^2 and this trend was statistically significant when the PINRR method was utilised. Also, sub-therapeutic INRs (INR <2.0) and the presence of at least one INR >8.0 was significantly more prevalent among AF patients with normal kidney function. Similarly, when investigating the influence of kidney disease towards anticoagulation control in linear and logistic regression analyses, the presence of kidney disease (eGFR ≤59

ml/min/1.73m^2) at baseline did not influence sub-optimal anticoagulation control during follow up. This finding is also similar to a study among 724 non-dialysis dependent chronic kidney disease on VKA therapy (266). TTR was significantly higher (75.1%) in patients with moderate kidney disease (eGFR 30-60 ml/min) compared to patients without CKD (eGFR>60 ml/min: TTR 67.0%; p<0.01). There was also a non-significant trend towards higher TTR in the severe CKD group (eGFR <30 ml/min: TTR 70.3%; p=0.41) compared to those without kidney disease. Similar to the current cohort, renal function was assessed at the start of VKA therapy and TTR was calculated throughout the entire treatment period, although the categorisations of kidney disease were different compared to the current cohort. Despite that, one common finding seen was that the quality of VKA therapy seemed to be better in patients with moderate kidney disease than with normal kidney function.

There are several potential explanations for these contradictory findings. First of all, perhaps in this cohort, AF patients with concomitant kidney disease are well managed by a dedicated anticoagulant service thus resulting in similar or better anticoagulation control compared to patients without kidney disease. It could also be that the presence of concomitant 'kidney disease' serves as a 'flag' to the anticoagulant services so that extra care and attention is given throughout the entire monitoring period. This is because patients with concomitant kidney disease are considered to be a 'vulnerable' group of patients and are at higher risk of adverse events including thromboembolism and bleeding. Indeed in the SPORTIF III and IV trials (264), the presence of CKD was significantly associated with an increased risk of stroke and high TTR (TTR ≥70%) was significantly associated with a reduction in the risk of stroke [HR 0.63 (95% CI 0.41-0.98)], major bleeding [HR 0.58 (0.42-0.80)], and mortality [HR 0.63 (0.47-0.84)]. Likewise, a study (266) in The Netherlands of 724 AF patients with VKA therapy and CKD also showed that patients with eGFR <30ml/min were at increased risk of major bleeding and stroke/TIA compared to those with eGFR 30-60 ml/min [HR 1.86 (95% CI 1.08-3.21) and HR 3.93 (95% CI 1.71-9.00) respectively] and this was mediated when the anticoagulation control was sub-optimal. Lastly, better anticoagulation control among patients

with eGFR 60-89 and eGFR ≤59 may be driven by the significantly higher proportion of white patients with eGFR 60-89 and eGFR ≤59. Results from the main analysis have shown that a greater proportion of optimised TTR was seen among white patients compared to non-white patients. Furthermore, logistic regression analysis has shown that non-white ethnicity is an independent predictor of poor TTR. So, this might indirectly influence the TTR results among the CKD patients.

3.5.2 Predictors of anticoagulation control in the whole cohort

This study demonstrates that slightly more than half of the cohort experienced difficulties achieving optimal quality of anticoagulation and therefore further investigation on the predictors of poor anticoagulation control was conducted. Interestingly, non-white ethnicity emerged as the strongest predictor (in both univariate and multivariate linear and logistic regression analyses) of poor quality of anticoagulation control when TTR was calculated via both the Rosendaal and the PINRR methods. Possible explanations towards this finding have been described in **section 3.5.1.2**.

Other significant patient factors related to anticoagulation control evident from this cohort is smoking history, although information on smoking status is only available for 72.4% of patients. It is an independent predictor of poor TTR and PINRR on linear regression analysis and was more prevalent among the Whites compared to South-Asian and Afro-Caribbean patients. This is consistent with three other studies demonstrating smoking as a predictor of poor TTR (199, 205, 208). The relationship of how smoking can influence anticoagulation control is unclear but may reflect less interest in maintaining good health that may translate into poorer adherence to OACs, thus resulting in poor TTR (199).

Clinical factors such as comorbid diseases were shown to have an impact in the quality of anticoagulation control. In linear regression analyses, heart failure and bleeding history negatively predicted both TTR and PINRR, with vascular disease also predicting PINRR.

Meanwhile, in logistic regression analyses, anaemia was an independent predictor of poor anticoagulation control for both TTR<70% and PINRR<70% followed by vascular disease for TTR<70%.

Other studies have also shown an association of poor anticoagulation control with a variety of comorbid conditions such as heart failure (197-202, 253-255), diabetes (197-200, 202, 205, 256), kidney disease (198, 199, 201, 213, 257), liver disease (198, 199, 254, 257), lung disease (199, 201, 204, 205), coronary artery disease (199, 201), peripheral vascular disease (199, 201), stroke (199, 204) and previous bleeding (213). The exact mechanism of this relationship is unclear but perhaps this reflects greater illness burden and complexity including more medications prescribed for each of the conditions thus increasing the potential of drug interaction with warfarin and nonadherence leading to poorer anticoagulation control (201).

3.5.3 Adverse clinical outcomes in the whole cohort

At least 30% of the patients experienced ≥1 MACE and there was no significant difference in terms of the rate of thromboembolic, bleeding events and mortality across the three ethnic groups except for CV hospitalizations, where it was highest among the South-Asians. In this cohort of patients, Afro-Caribbeans had the highest risk of stroke. Although underpowered, there was no significant difference in terms of TE events across different ethnic groups although proportionally, TE and bleeding events were highest among Afro-Caribbeans.

Previous epidemiological studies have shown that black and Hispanic individuals have a two-fold higher annual risk of stroke compared to Whites (441, 442). However, this was not evident in the present study, a finding consistent with the ORBIT-AF registry, that showed no difference in stroke or all-cause mortality among white, black and Hispanic participants where anticoagulation use was high (210). In a subgroup analysis of the AFFIRM trial, there was no

difference in overall survival at 5 year follow up among White, Black and Hispanic participants (443).

Independent predictors of the composite outcome were prior stoke/TIA, vascular disease and poor TTR. Other studies have shown that poor TTR is related to thromboembolic and bleeding events (119, 444) and in this cohort poor TTR (<70%) independently predicted composites of TE, bleeding events, CV hospitalizations and all-cause mortality.

3.5.3.1 Adverse clinical outcomes in elderly

Exploratory analyses of the elderly showed no significant differences in the composite endpoints (≥1 MACE) between the elderly (age ≥80 years) and those aged <80 years. However, age ≥80 years was significantly associated with higher bleeding risk even after adjustment for demographics and clinical variables.

Previous studies have reported conflicting results regarding the increased risk of bleeding among elderly patients on OAC therapy. The absolute rate of major bleeding was 2.5 vs. 0.9 per patient years among ≥80 vs. <80 year old AF patients, respectively receiving warfarin therapy in one Italian study (247). Conversely, a 5-fold increase in incidence rate of bleeding was reported in those aged ≥80 years compared to <80 years (13.1 vs. 4.8 per 100 patients years respectively) in another study (241). Age ≥80 years was associated with increased risk of bleeding events in both studies (241, 247). The difference in bleeding rate between these studies might be explained by the higher proportion of patients experiencing CAD (35% vs. 20%) who were prescribed concomitant aspirin therapy (40% vs. 3.5%) in the latter (241) compared to the former (247) respectively; both of which are factors known to increase risk of bleeding.

In the current cohort, when investigating the factors associated with bleeding events during the entire period of warfarin exposure, age ≥80 years was the only significant factor associated with bleeding events, similar to previous studies (241, 247). Indeed, very close attention needs

to be paid to the very elderly patients who are on OAC therapy to prevent bleeding complications. Various bleeding scores are available to assess bleeding risk in AF patients (3, 176). These scores can be used to guide physicians to 'flag up' factors that may predispose patients to bleeding events. Any modifiable risk factors for bleeding, such as uncontrolled hypertension in the 'H' component of the HAS-BLED score (180) should be addressed by controlling patient's blood pressure. The risk of bleeding is not static thus needs to be evaluated periodically (3, 242).

3.5.3.2 Adverse clinical outcomes in different categories of kidney disease

There were no significant differences in thromboembolic, bleeding, CV hospitalisations, all-cause mortality and ≥1 MACE according to kidney disease though this analysis was purely exploratory. This result must be interpreted with caution as this investigation was not powered to detect any significant difference in any of the adverse clinical outcomes.

Nevertheless, other studies have shown increased risk of thromboembolism, bleeding and mortality in patients with concomitant AF and CKD (264, 445-448). One Swedish AF cohort study from the health registers (265) reported a higher annual rate of stroke (3.9% vs. 2.9% respectively), any bleeding (9.8% vs. 4.1% respectively) and mortality (36.0% vs. 11.5% respectively) in patients with renal failure (definition obtained from the ICD-10 codes N17-19 or by local Swedish procedure codes for haemodialysis, peritoneal dialysis or renal transplantation) compared to those without renal failure (265). In this Swedish cohort, renal failure independently predicted intracranial bleeding [adjusted HR 1.27 (95% CI 1.09-1.49)]. However, despite the high risk of bleeding, the use of warfarin compared to no warfarin therapy was beneficial in renal failure patients in the composite endpoint of ischaemic stroke, intracranial bleed or death [adjusted HR 0.76 (95% CI 0.72-0.80)] (265). Similarly, in the SPAF-III trial, (440) use of warfarin reduced the risk of ischemic stroke and systemic embolism by 76% (95% CI 42%-90%; $p<0.001$) among high risk AF patients with CKD stage 3 (eGFR 30-59 ml/min) compared to the combination of low dose warfarin and aspirin (440).

3.5.4 Strengths and limitations

This is the first study to assess anticoagulation control and adverse clinical outcomes in different ethnic groups in the UK. Other studies looking at the differences in anticoagulation control between ethnic minority groups were conducted in the United States comparing Whites, African-American, Hispanic and Native Americans (198, 210). In addition, two further ancillary analyses were undertaken among elderly and patients with different categories of kidney disease to give insights into the quality of warfarin control in these two sub-groups, managed by one anticoagulation clinic in this Trust.

Furthermore, two methods of calculating TTR were utilised, with both methods correlating with each other and demonstrating similar results. Researchers recommend that ≥2 VKA control measures are reported per study as the quality of anticoagulation control can vary depending on the method of TTR reported (347, 449, 450). Further, TTR was also calculated using a large number of INR results [mean (SD) 58.7 (25.5)] for a median of 5.2 (3.2-7.0) years of follow up reflecting the long-term quality of anticoagulation control in this centre.

The cohort comprised 991 patients but this was only 43 % of the available cohort and thus it is possible that the results are not representative of the whole (N=2478) cohort. Nonetheless, the proportion of patients from each ethnic group included was representative of the total cohort in this Trust. Furthermore, Afro-Caribbean and South-Asian patients constituted about 10% each from the whole population included in the study; similar to the ethnic composition of studies of anticoagulation control by Yong et al and Golwala et al (8.3% and 5% Blacks respectively) (198, 210). However, in general, AF is more prevalent among Whites (8.0%) than Asians (3.9%) and Blacks (3.8%)(35).

In addition, the retrospective review from medical records means that some information was not readily available, including the patient's ethnic group, medical history and medication

history, and thus a small number (3.2%) of patients had to be excluded. Also, recording of adverse clinical events were based on the events occurring in this Trust, thus any events occurring outside this Trust were not captured thus might lead to underestimation of the events of interest.

Finally, this study assessed anticoagulant control by looking at objective measures available on clinical databases. Other variables that could influence anticoagulation control such as distance to anticoagulation clinic, education level, history of employment, quality of life of AF patients (414), magnitude of drug and food interaction, CYP2C9 or VKORC1 genotype (329) were not taken into account in the current analyses.

3.5.5 Clinical implications

The most clinically relevant finding of this study is that achieving optimal quality of anticoagulation control with warfarin is more challenging among non-whites but that being very elderly or having impaired renal function does not independently predict TTR in a setting with a well-managed anticoagulant clinic. This work highlights the importance of good TTR and that there is considerable room for improvement given that less than half the cohort achieved optimal TTR, especially Afro-Caribbean and South-Asian patients. This suggests the need to focus on individual reasons for poor INR control and to develop strategies to improve anticoagulation control where required. For example, more frequent follow up via phone call or face-to-face could be arranged so that more attention can be given to these patients. During the follow ups, factors that can influence anticoagulation control and the importance of being adherent to the anticoagulant should be emphasized. In addition, patients should also be encouraged to inform healthcare professionals if they encounter any problems with VKA therapy so that appropriate remedial action can be taken, and the patient should be reviewed.

3.5.6 Future research

Further prospective, multicenter, observational studies with larger sample sizes (>1000 patients) especially within ethnic minority groups are required to confirm these findings. Perhaps this study can be extended into a multi-national registry including other ethnically diverse countries for example in South-East Asian countries like Malaysia, Thailand, Vietnam, Myanmar, Cambodia and Laos which still uses VKA as the OAC of choice for stroke prevention in AF and in other thrombotic diseases (VTE/PE). It would be of interest to investigate TTR, determinants of TTR (including ethnicity) and its impact on predicting TE and bleeding events in Asian countries. Regional comparison of TTR and adverse clinical outcomes could be undertaken within each country where data in this area is lacking.

Asian populations (451, 452) still rely heavily on herbal preparations for treating medical ailments. For example, 'tongkat ali' (*Eurycoma longifolia*), originating from Malaysia and Indonesia is used as an alternative for testosterone replacement therapy or treatment of impotence (451). Meanwhile, *Withania somnifera,* an Indian ginseng was shown to have potential for cancer-related fatigue and improvement of quality of life in a non-randomised comparative trial of 100 patients (N= 50 chemotherapy + *WH* vs. N=50 chemotherapy alone) with breast cancer (451, 453). Hence, it would be interesting to investigate the impact of herbal products on INR control as VKA-herb interaction have major safety concerns and more data is required in this field.

3.6 Conclusions

Ethnic disparities in the quality of anticoagulation control are evident but not among the very elderly and patients with different categories of kidney disease. South-Asians and Afro-Caribbeans had poorer INR control compared to Whites, despite similar intensity INR-monitoring. After adjustment, non-white ethnicity and anaemia remained the strongest independent predictor of poor TTR and PINRR. Meanwhile, CV hospitalisations were more

prevalent among the South-Asians. Closer attention needs to be given to patients from non-white ethnic groups to understand the reasons of poor anticoagulation control so that effective strategies can be developed and implemented by healthcare providers to improve outcomes.

Chapter 4. Anticoagulation control in operated valvular heart disease patients with and without atrial fibrillation receiving vitamin K antagonist

4.1 Abstract

Introduction: Good quality anticoagulation control among patients with operated valvular heart disease (VHD) is needed to reduce ischaemic complications. There is limited evidence on factors affecting anticoagulation control among this patient population.

Objective: To investigate the quality of VKA control (TTR), predictors of anticoagulation control and the prevalence of adverse clinical outcomes [thromboembolic (stroke/TIA and systemic embolism), bleeding events, cardiovascular hospitalisation and all-cause mortality and ≥1 composite endpoints (MACE)] in operated VHD patients at one acute Trust in the West Midlands, United Kingdom. Exploratory analyses investigated the relationship between INR control and adverse clinical outcomes.

Methods: Retrospective data collection from the electronic medical record database were undertaken to collect all demographics and clinical information. The Rosendaal and percentage INRs in range (PINRR) methods were used to calculate TTR among 456 operated VHD patients of whom 164 (36%) with AF and 292 (64%) without AF. Patient's demographics, comorbidities and other clinical data were used as predictors of TTR and were examined by logistic regression analysis. Chi-squared tests were utilised to explore the relationship between INR control and adverse clinical outcomes.

Results: The mean (SD) age was 51 (14.7), 64.5% were male, 96.1% had a mechanical prosthesis and 64% had aortic valve replacement. Operated VHD patients with AF had lower mean TTR and PINRR [mean (SD) TTR 55.7% (14.2) vs. 60.1% (14.6); p=0.002 respectively; mean PINRR 47.4% (13.5) vs. 51.6% (13.7); p=0.002 respectively], lower proportions with

optimal anticoagulation control (TTR ≥70%) (14.0% vs. 25.7%; p=0.004) and higher proportions with sub-therapeutic INRs (28.4% vs. 23.4%; p<0.001) despite a similar number of INR tests compared to operated VHD patients without AF. Independent factors predicting poor TTR after adjustment for demographic and clinical variables were: female, the presence of AF at baseline, anaemia/bleeding history and HAS-BLED score. Significantly higher proportions of patients with operated VHD and AF died [all-cause mortality (20.7% vs. 5.8%; p<0.001)]. Similarly, more deaths (13.1% vs. 4.1%; p=0.011) and ≥1 MACE (42.7% vs. 27.6%; p=0.006) were seen in patients with TTR <70% compared to TTR≥70% respectively.

Conclusion: Operated VHD patients with AF at baseline have poorer anticoagulation control compared to those without AF at baseline. The presence of concomitant AF, anaemia/bleeding history, as well as female gender, independently predicted poor TTR and the rate of all-cause mortality was significantly higher among operated VHD patients with AF. These findings suggest closer INR monitoring among operated VHD patients especially those with AF to improve anticoagulation control and prevent adverse clinical outcomes.

4.2 Introduction

VKAs are the only anticoagulant of choice in patients undergoing heart valve replacement, especially with mechanical prosthesis (358). The target INR for AF is 2.0-3.0, (349, 351, 358) whereas the INR targets for patients with VHD post-surgery varies depending on factors such as patient risk factors, (example: mitral/tricuspid valve replacement, previous TE, AF, mitral stenosis and LVEF <35%) type of valve, and the thrombogenicity of the prosthesis (349, 351, 358). The 2017 ESC guidelines on the management of valvular heart disease (358) recommend a median INR value be maintained in place of a range to prevent extreme values within the target range. They also recommend a higher median INR value for patients with ≥1 risk factor than those without any of these risk factors (358)(**More details in section 1.7.2.1 page 116**). The newer types of valve used more commonly now, such as Carbomedics, St Jude or Medtronic have low valve thrombogenicity with limited data on the rate of valves thrombogenicity as they are also influenced by patient related risk factor and study design (454); however one review reported HR 1.06 (0.05-0.56) for valve thrombosis among St Jude and Carbomedics valves (455). Patients with risk factors receiving newer types of valves are recommended to achieve a median target INR of 3.0 compared to those without risk factors, where the target INR is lower at 2.5 (349, 351, 358).

4.2.1 Study objectives

To date, only five (377-381) studies, conducted between 2002 and 2018, have investigated anticoagulation control after valve replacement; two (380, 381) used anticoagulation variability while the others (377-380) used TTR. Therefore, the objective of this study was to investigate anticoagulation control measured using TTR (Rosendaal method) and the PINRR method among operated VHD patients, comparing patients with and without AF. Second, to investigate the predictors for poor anticoagulation control, and finally to investigate the prevalence of adverse clinical outcomes including stroke/TIA, bleeding, CV hospitalisations, death and the

composites of ≥1 MACE. Exploratory analyses investigated the relationship between INR control and adverse clinical outcomes.

4.3 Methods

4.3.1 Study design

This is a single centre, retrospective analysis of patients with VHD receiving VKA therapy after valve replacement therapy at one acute Trust in the West Midlands, United Kingdom (SWBH NHS Trust). Data was collected from 1st November 2017 to 31st March 2018. VHD patients receiving VKA therapy were identified from the DAWN AC® anticoagulation management software (**described in section 3.3.1, pages 174-175**).

This study was considered as service evaluation by the SWBH Research and Development department and therefore did not require REC approval. However, local R&D approval was obtained (see email confirmation from SWBH R&D Department, **Appendix 5**).

4.3.1.1 Patient selection

A list of patients with VHD receiving VKA therapy (N=604) was generated from the DAWN AC management software. However, 148 patients were excluded due to: i) VHD but without surgical intervention [N=38; mitral stenosis (N=22), aortic stenosis (N=2), mitral regurgitation (N=2), mitral valve repair (N=4), valvuloplasty (N= 6), and valvulotomy (N= 2)]; ii) incomplete INR results (N=3) and iii) incomplete medical information (N=107). The final cohort consists of 456 VHD patients who had surgical intervention of the affected valve(s) and were prescribed VKA therapy post-surgery. They were stratified into those with and without AF **(Figure 4.1).**

4.3.1.2 Procedure

All baseline characteristics and clinical information including medical history, medication, and laboratory tests were collected from the point that VKA was initiated after surgical replacement

of the valves (i.e., mechanical and tissue valve repair). Information on outcomes i.e., INR results and adverse clinical outcomes occurring after this point were collected using a proforma (**see Appendix 4, Table A4.1**).

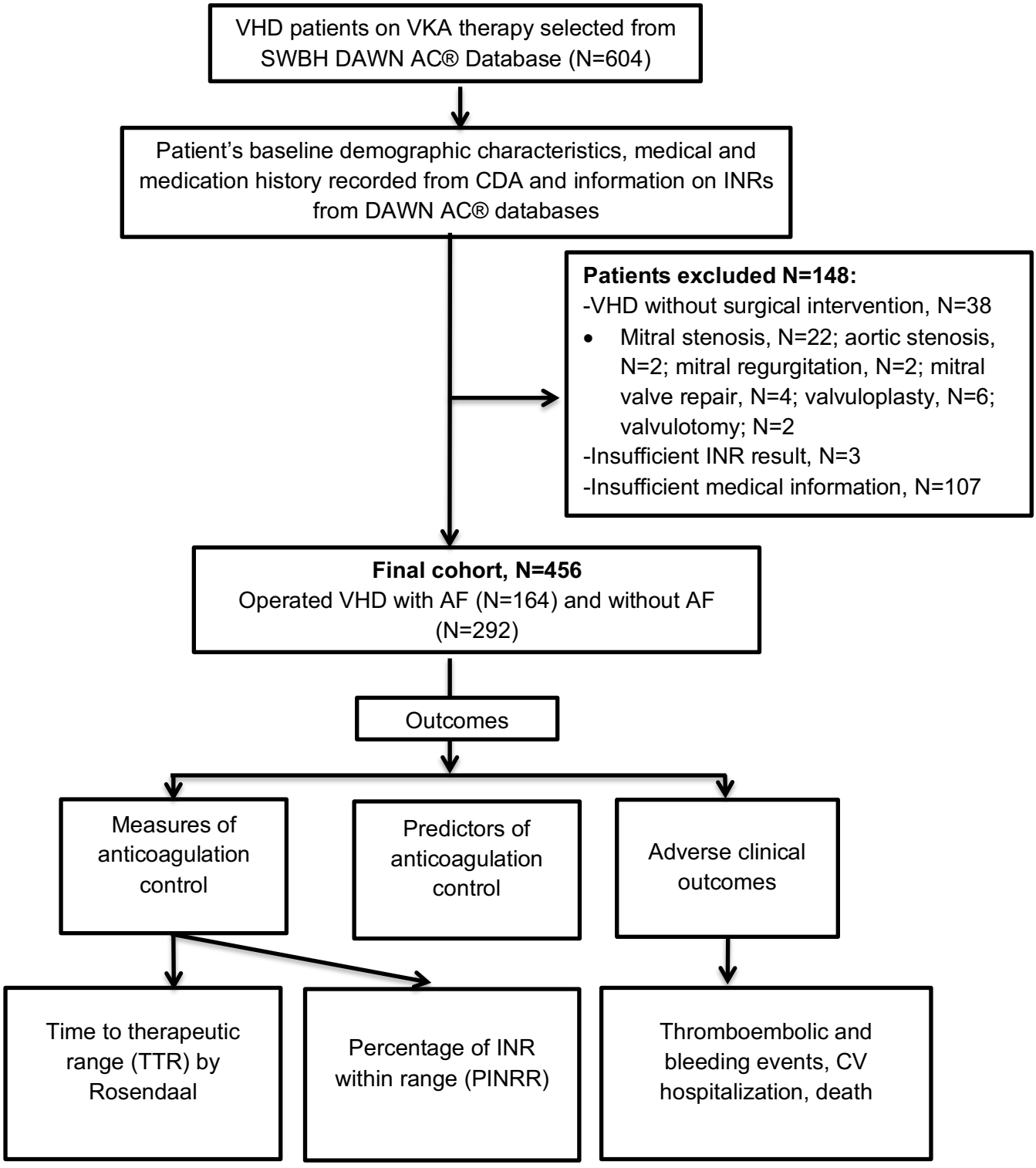


Figure 4.1: Study design and patient selection flow chart

CDA: clinical data archive; CV: cardiovascular; INR: international normalised ratio; TTR: time in therapeutic range; PINRR: percentage of INRs in range; SWBH: Sandwell and West Birmingham Hospitals; VHD: valvular heart disease; VKA: vitamin K antagonist

Dependent/outcome variable

4.3.1.2.1 Time in therapeutic range, TTR

INR values for VKA therapy were collected from CDA and DAWN databases from SWBH NHS Trust for patients with at least three INR values in a year starting from February 2009 until 31 January 2018. The year 2009 is the period where INR readings were consistently available in the hospital databases. Prior to this, another system was utilised and is no longer currently active to allow complete INR data collection resulting in wide gaps between the dates of each INR reading. The quality of anticoagulation control was calculated using the Rosendaal and the PINRR methods (421)(**see section 2.3 for definition and description**). TTR and PINRR were calculated based on each patient's individual target INR range determined by the surgeon; thus, INR ranges differ between patients. TTR and PINRR were further dichotomised into TTR ≥70% and <70% and PINRR ≥70% and <70%, with TTR and PINRR ≥70% reflecting optimal anticoagulation control based on the ESC guideline (3). The proportions of sub-therapeutic INRs (INRs below the target range), supra-therapeutic (INRs above target range) and patients with at least one INR >5.0 or >8.0 were also collected. The follow-up period was defined as the duration of VKA monitoring i.e., from the start date of INR collection until 31st January 2018.

4.3.1.2.2 Definition of Atrial fibrillation

The diagnosis of AF at baseline was obtained directly from the CDA. This was defined as the presence of AF as part of the concomitant diseases at the time of surgery or was diagnosed after the surgery (post-operative). Types of AF including paroxysmal, persistent, long standing and permanent were recorded. If this information was not available, an assumption was made based on the length of time since AF diagnosis and the pattern of ECG recordings available, with confirmation of AF from a medical doctor, according to ESC AF guidelines (3).

4.3.1.3 Predictors: Patient demographics and clinical factors

Patient's age was calculated based on the date of their first valve surgery (ranging from 1972-2017). Other demographic information such as gender, ethnicity, information regarding smoking status and alcohol intake, and other comorbidities, medication history and laboratory parameters were obtained as near to the date (or within one month) of VKA initiation after the first valve surgery, from the CDA. Information on smoking status was available for 372 patients (82%); data on alcohol intake was only available for 353 patients (77%). This information was used to calculate the individual HAS-BLED and SAMe-TT_2R_2 scores. Assumptions were also made for chronic kidney disease, liver disease and anaemia based on the laboratory results (**see page 181 for details**). The calculation of the CHA_2DS_2-VASc, HAS-BLED and SAMe-TT_2R_2 scores were made on the basis of baseline information (**see section 3.3.3, page 177 for more details**).

4.3.1.4 Adverse clinical outcome

Information on adverse clinical outcomes were collected from the CDA covering the same time frame to that of the INR collection i.e., from the point/date where INR was consistently available in the system until 31 January 2018. Adverse clinical outcomes of interest were stroke/TIA/systemic embolism, bleeding (combination of major bleed and CRNMB), CV hospitalisation, death and a composite (≥ 1) of these MACE events. Definitions of each outcome are described in **section 2.3.3.** In this study, the cause of death was specified as CV death when specific information was available. Where cause of death was unavailable, death was classified as all-cause mortality.

4.3.2 Statistical analysis

After performing normality tests, by the histogram plot method and the Kolmogorov-Smirnov test where a bell-shaped distribution in the former and p-values >0.05 in the latter were indicative of normally distributed data, all normally distributed data were expressed as mean (SD), and non-normally distributed data as median (IQR). Demographic and clinical characteristics of patients with categorical data were compared with chi-square or Fisher's exact test when appropriate and are reported as counts and percentage. Independent t-tests were used to compare the means of continuous data for normally distributed data; the Mann-Whitney tests were used for data that was not normally distributed. Univariate and multivariate logistic regression analyses were performed to investigate the predictors of poor TTR (TTR<70%). The relationship between TTR and adverse clinical outcomes were investigated (exploratory) using the chi-squared test and are reported as counts and percentage. A Log-Rank test was performed for AF categories and TTR categories and Kaplan-Meier Curves were used to report the differences in survival and ≥1 MACE between the subgroups. All analyses were conducted using SPSS version 23.0 (406), with p-values <0.05 considered statistically significant.

4.4 Results

4.4.1 Baseline characteristics

Among the 456 patients with operated VHD, only 164 (36.0%) had AF at baseline. The overall mean (SD) age was 51 (14.7), the majority were male (64.5%), of white ethnicity (65.2%), with a mechanical prosthesis (96.1%), and the most common operation was aortic valve replacement (64%) **(Table 4.1).** Patients with operated VHD with AF were significantly older [mean (SD) age 56.6 (13.3); p<0.001], more likely to be female (48.2%; p<0.001), to receive a tissue prosthesis (8.5%; p<0.001), to have had the mitral valve (41.5%; p<0.001) or both mitral and aortic (20.7%; p<0.001) valves replaced. In addition, patients with operated VHD and AF were also more likely to have concomitant heart failure (21.3%; p<0.001), hypertension (72.0%; p=0.007), and pulmonary disease (25.6%; p=0.014) and were likely to be prescribed diuretics (70.1%; p<0.001), amiodarone (22.6%; p<0.001) and digoxin (36.0%; p<0.001), and had higher mean (SD) CHA_2DS_2-VASc [2.6 (1.5); p<0.001] and HAS-BLED scores [1.8 (1.1); p=0.014] compared to patients with operated VHD without AF **(Table 4.1).**

Table 4.1: Baseline characteristics of patients with operated valvular heart disease, with and without AF

		Total, N=456	AF N=164	No AF N=292	p-value
Age at implantation	Mean age (SD)	51.1 (14.7)	56.6 (13.3)	48.0 (15.0)	**<0.001**
Age groups	≤64	382 (83.8)	117 (71.3)	265 (90.8)	**<0.001**
	65-74	59 (12.9)	35 (21.3)	24 (8.2)	
	≥75	15 (3.3)	12 (7.3)	3 (1.0)	
Sex	Female	162 (35.5)	79 (48.2)	83 (28.4)	**<0.001**
	Male	294 (64.5)	85 (51.8)	209 (71.6)	
Ethnic groups‡ (N=454)	White	296 (65.2)	114 (69.9)	182 (62.5)	0.20
	South-Asian	120 (26.4)	35 (29.2)	85 (29.2)	
	Afro-Caribbean	38 (8.4)	14 (8.6)	24 (8.2)	
Alcohol intake	Alcohol >14unit/day (N=353)	32 (9.1)	9 (6.8)	23 (10.4)	0.26
Smoking status	Smoking/ex-smoker (N=372)	83 (22.3)	27 (19.1)	56 (24.2)	0.25
Site(s) of prosthesis	Mitral	110 (24.1)	68 (41.5)	42 (14.4)	**<0.001**
	Aortic	292 (64.0)	62 (37.8)	230 (78.8)	**<0.001**
	Both mitral and aortic	54 (11.8)	34 (20.7)	20 (6.8)	**<0.001**
Types of valve replacement	Mechanical valve	438 (96.1)	150 (91.5)	288 (98.6)	**<0.001**
	Tissue valve	18 (3.9)	14 (8.5)	4 (1.4)	**<0.001**
Past medical history	Heart failure	53 (11.6)	35 (21.3)	18 (6.2)	**<0.001**
	Hypertension	291 (63.8)	118 (72.0)	173 (59.2)	**0.007**
	Diabetes	71 (15.6)	32 (19.5)	39 (13.4)	0.08

Table 4.1 continued

		Total, N=456	AF N=164	No AF N=292	p-value
Past medical history	Stroke/TIA	66 (14.5)	30 (18.3)	36 (12.3)	0.08
	Vascular disease*	118 (25.9)	35 (21.3)	83 (28.4)	0.10
	Lung disease#	89 (19.5)	42 (25.6)	47 (16.1)	**0.014**
	Kidney disease†	17 (3.7)	7 (4.3)	10 (3.4)	0.65
	Anaemia/previous bleeding	189 (41.4)	70 (42.7)	119 (40.8)	0.69
Current medications	Beta-blocker	177 (38.8)	62 (37.8)	115 (39.4)	0.74
	ACEI/ARB	247 (54.2)	94 (57.3)	153 (52.4)	0.31
	Diuretics	233 (51.1)	115 (70.1)	118 (40.4)	**<0.001**
	Amiodarone	50 (11.0)	37 (22.6)	13 (4.5)	**<0.001**
	Concurrent antiplatelet	79 (17.3)	21 (12.8)	58 (19.9)	0.06
	Digoxin	69 (15.1)	59 (36.0)	10 (3.4)	**<0.001**
	Calcium channel blocker	54 (11.8)	20 (12.2)	34 (11.6)	0.86
CHA_2DS_2-VASc score	Mean (SD)	2.0 (1.4)	2.6 (1.5)	1.7 (1.3)	**<0.001**
CHA_2DS_2-VASc score categories	Low risk	102 (22.4)	21 (12.8)	81 (27.7)	**<0.001**
	Intermediate	134 (29.4)	45 (27.4)	89 (30.5)	
	High risk	220 (48.2)	98 (59.8)	122 (41.8)	
HAS-BLED score	Mean	1.6 (1.2)	1.8 (1.1)	1.5 (1.2)	**0.014**
HAS-BLED score categories	Low risk (0-2)	359 (78.7)	127 (77.4)	232 (79.5)	0.61
	High risk (≥3)	97 (21.3)	37 (22.6)	60 (20.5)	

Table 4.1 continued

		Total, N=456	AF N=164	No AF N=292	p-value
SAMe-TT_2R_2 score	Mean	2.7 (1.4)	2.7 (1.4)	2.7 (1.4)	0.53
SAMe-TT_2R_2 score categories	0-2	200 (43.9)	71 (43.3)	129 (44.2)	0.86
	>2	256 (56.1)	93 (56.7)	163 (55.8)	

ACEI/ARB: angiotensin converting enzyme inhibitor/ angiotensin receptor blockade; AF: atrial fibrillation; CHA_2DS_2-VASc score - Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75years [2 points], Diabetes, Stroke [2 points], Vascular disease, Age 65–74 years, and Sex category (female). Total scores range between 0-9; low risk CHA_2DS_2-VASc score: 0 male; 1 female, intermediate: 1male, ≥2 female, high risk CHA_2DS_2-VASc score: ≥2 male; ≥3 female; TIA: transient ischemic attack; eGFR: estimated glomerular filtration rate, ml/min/1.73 m^2; HAS-BLED score – uncontrolled Hypertension: systolic ≥160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR ratio/TTR <60, Drugs/alcohol concomitantly. Total scores range between 0-9; low risk of bleeding range between 0-2 and high risk of bleeding ≥3; SAMe-TT2R2 score – Sex female, Age<60, Medical history (more than two comorbidities), Treatment (interacting drug, e.g. Amiodarone), Tobacco use (doubled) and Race (non-white, doubled). Total scores ranged from 0-8; probable good response to VKA therapy range between 0-2 and probable poor response to VKA therapy ranged from ≥3; SD: standard deviation

* Vascular disease: prior myocardial infarction, peripheral artery disease or aortic plaque; # Lung disease: obstructive and restrictive diagnosed lung conditions; †eGFR <60ml/min or as noted in medical notes; ‡:2 missing information on ethnicity

4.4.2 Quality of anticoagulation control of patients with operated valvular heart disease, with and without AF

As shown in **Table 4.2**, higher INR target ranges [INR 3.0-4.0; 41.4%] were used more often to maintain effectiveness and safety of VKA therapy in the overall population of patients with operated VHD. The overall mean (SD) TTR and PINRR for the cohort was 58.5 (14.6) and 50.1 (13.8) respectively; only 98 patients (21.5%) achieved the optimal TTR target (TTR≥70%) during a median (IQR) of 6.2 (3.3-8.5) years of follow up.

Operated VHD patients with AF had a significantly higher INR target range (3.5, 49.4%; p=0.03), lower mean TTR and PINRR [mean (SD) TTR 55.7 (14.2) vs. 60.1 (14.6); p=0.002 respectively; mean PINRR 47.4 (13.5) vs. 51.6 (13.7); p=0.002 respectively] **(Figure 4.2),** lower proportions with optimal anticoagulation control (TTR ≥70%) (14.0% vs. 25.7%; p=0.004) and higher proportions with sub-therapeutic INRs (28.4% vs. 23.4%; p<0.001) (**Figure 4.3**) despite a similar number of INR tests compared to operated VHD patients without AF. There was no significant difference in INRs above the therapeutic range or the proportions of patients with one or more INR >5.0 or >8.0 **(Table 4.2 and Figure 4.4).**

In exploratory analyses **(Table 4.3),** with measures of anticoagulation control stratified according to the different target INR ranges, patients with a higher TTR target (INR 3.5) had a significantly lower mean (SD) TTR and PINRR [mean (SD) TTR 51.7% (11.8); p<0.001; mean PINRR 42.6% (10.9); p<0.001 respectively], higher mean (SD) number of INR test [122.3 (59.6); p<0.001], higher sub-therapeutic [30.1 (10.2); p<0.001] and supra-therapeutic [26.8 (7.7); p=0.001] INRs and a significantly longer duration of VKA treatment compared to those with target ranges of 2.5 and 3.0. In contrast, a significantly higher proportion of patients with ≥1 INR >5.0 (95.8%; p<0.001) or >8.0 (22.2%; p<0.001) was evident among those with a target INR of 3.0 **(Table 4.3).**

Table 4.2: Measures of anticoagulation control of patients with operated valvular heart disease, with and without AF

Measures of anticoagulation control, N (%)	Total, N=456	AF N=164	No AF N=292	F-value	X^2 value	p-value
Median target INR 2.5‡	110 (24.1)	33 (20.1)	77 (26.4)	-		
3.0	157 (34.4)	50 (30.5)	107 (36.6)	-	6.76	**0.034**
3.5	189 (41.4)	81 (49.4)	108 (37.0)	-		
Mean (SD) TTR Rosendaal*	58.5 (14.6)	55.7 (14.2)	60.1 (14.6)	0.09	-	**0.002**
TTR<70%	358 (78.5)	141 (86.0)	217 (74.3)	-	8.46	**0.004**
TTR≥70%	98 (21.5)	23 (14.0)	75 (25.7)	-		
TTR<65%	310 (68.0)	126 (76.8)	184 (63.0)	-	9.21	**0.002**
TTR≥65%	146 (32.0)	38 (23.2)	108 (37.0)	-		
Mean (SD) PINRR*	50.1 (13.8)	47.4 (13.5)	51.6 (13.7)	0.60	-	**0.002**
PINRR<70%	417 (91.4)	154 (93.9)	263 (90.1)	-	1.97	0.16
PINRR ≥70%	39 (8.6)	10 (6.1)	29 (9.9)	-		
PINRR <65%	398 (87.3)	150 (91.5)	248 (84.9)	-	4.04	**0.05**
PINRR ≥65%	58 (12.7)	14 (8.5)	44 (15.1)			
Mean (SD) number of INR tests	96.2 (55.3)	100.7 (58.8)	93.7 (53.1)	0.60	-	0.19
Mean (SD) percentage INRs below the range	25.2 (12.1)	28.4 (12.5)	23.4 (11.6)	0.85	-	**<0.001**
Mean (SD) percentage above the range	24.9 (9.5)	24.1 (8.6)	25.3 (9.9)	0.64	-	0.22
INR>5	312 (68.4)	118 (72.0)	194 (66.4)	1.48	-	0.22
INR>8	64 (14.0)	26 (15.9)	38 (13.1)	-	0.70	0.40
Median (IQR) years of follow-up	6.24 (3.3-8.5)	5.7 (3.7-8.5)	5.7 (3.1-8.5)	-	-	0.87

AF: atrial fibrillation; INR: international normalized ratio; IQR: interquartile range; PINRR: percentage of INRs within range; SD: standard deviation; TTR: time in therapeutic range; *TTR and PINRR were calculated based on the INR ranges obtained from the anticoagulation clinic; †Median target INR ranges for each patient were different depending on indication and type of surgery and valve used which was set by the operating surgeon.

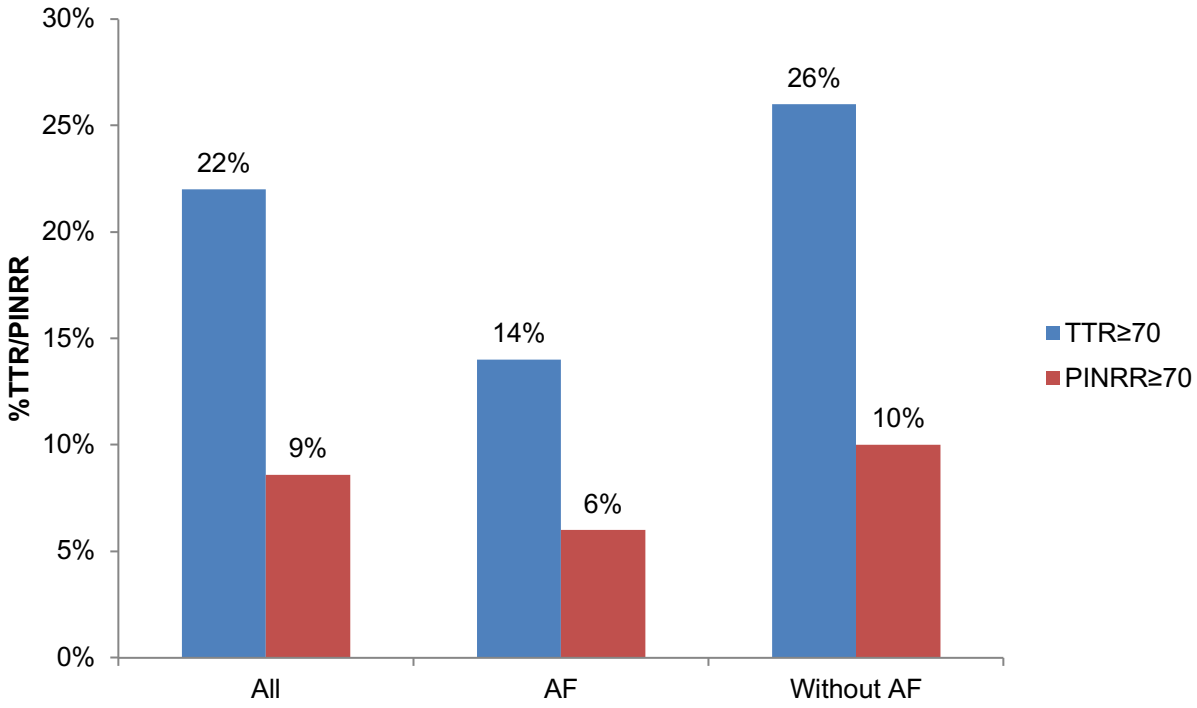


Figure 4.2: Percentage of patients with optimal TTR/PINRR among operated valvular heart disease patients with and without AF

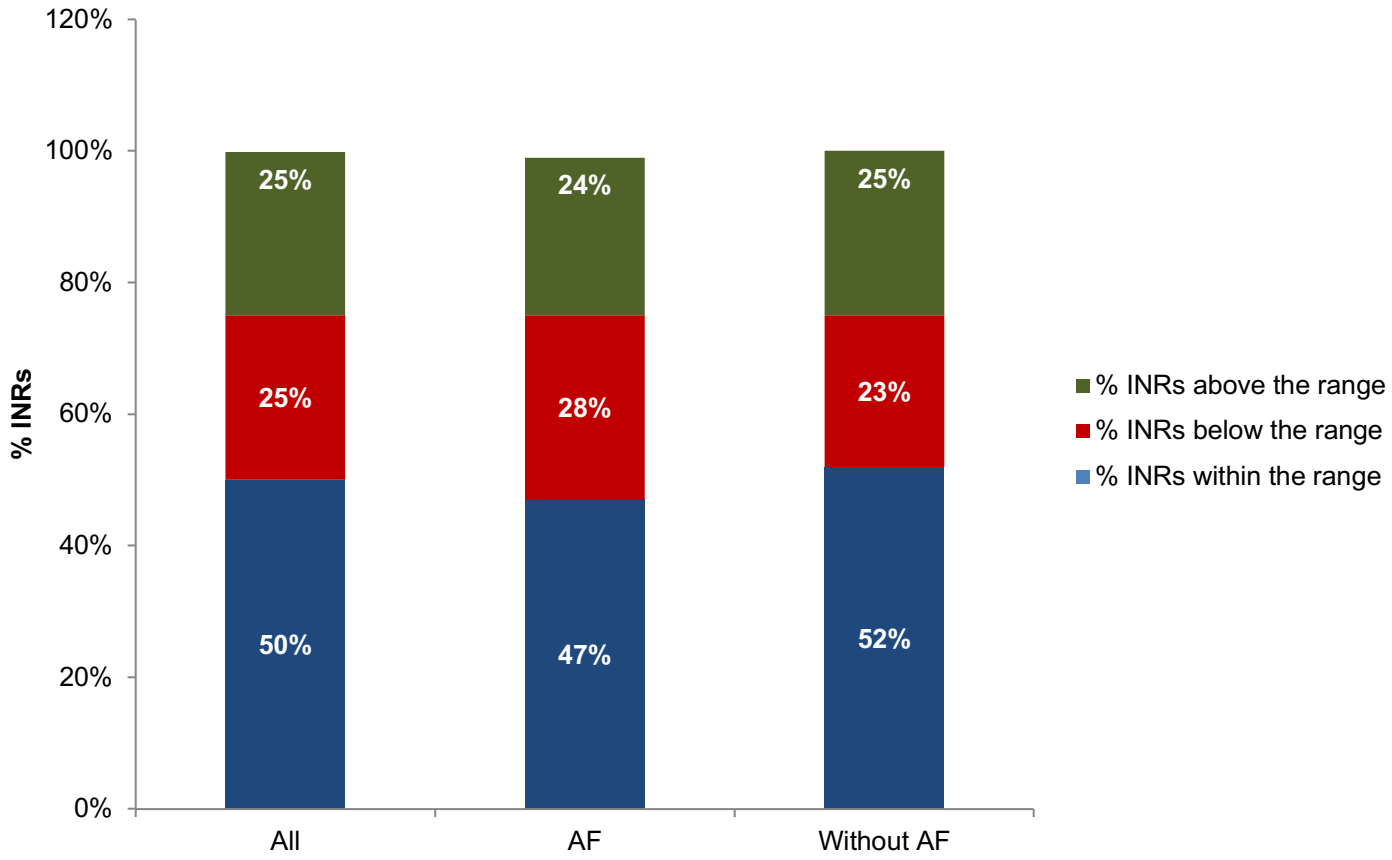


Figure 4.3: **Percentage of INRs within range, below the range and above the range among operated valvular heart disease, with and without AF**

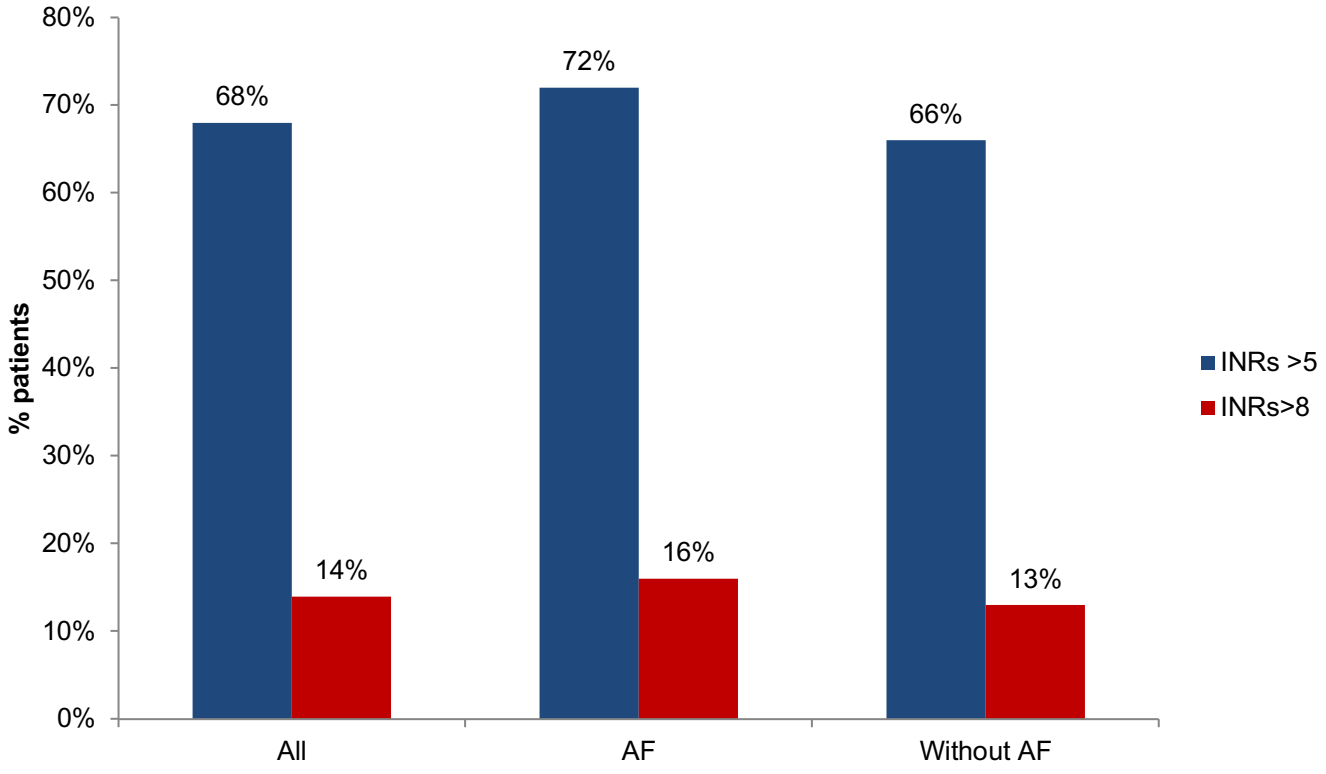


Figure 4.4: Percentage of patients with INRs>5.0 and INRs >8.0 among operated valvular heart disease, with and without AF

Table 4.3: Measures of anticoagulation control of patients according to different target INRs

Measures of anticoagulation control, N (%)	Median INR 2.5 N=110	Median INR 3.0 N=157	Median INR 3.5 N=189	X^2 value	p-value
Mean (SD) TTR Rosendaal*	68.4 (14.4)	59.8 (13.3)[a]	51.7 (11.8)[b, c]	-	**<0.001**
TTR<70%	53 (48.2)	124 (79.0)[a]	181 (95.8)[b, c]	93.3	**<0.001**
TTR≥70%	57 (51.8)	33 (21.0)[a]	8 (4.2)[b, c]		
TTR<65%	37 (33.6)	100 (63.7)[a]	173 (91.5)[b, c]	109.1	**<0.001**
TTR≥65%	73 (66.4)	57 (36.3)[a]	16 (8.5)[b, c]		
Mean (SD) PINRR*	61.4 (12.5)	51.1 (11.8)[a]	42.6 (10.9)[b, c]	-	**<0.001**
PINRR<70%	79 (71.8)	187 (98.9)[a]	151 (96.2)[b]	72.3	**<0.001**
PINRR ≥70%	31 (28.2)	2 (1.1)[a]	6 (3.8)[b]		
PINRR <65%	67 (60.9)	145 (92.4)[a]	186 (98.4)[b, c]	93.7	**<0.001**
PINRR ≥65%	43 (39.1)	12 (7.6)[a]	3 (1.6)[b, c]		
Mean (SD) number of INR tests	71.2 (41.7)	82.3 (44.1)	122.3 (59.6)[b,c]		**<0.001**
Mean (SD) percentage INRs below the range	15.1 (10.1)	26.4 (11.4)[a]	30.1 (10.2)[b, c]	-	**<0.001**
Mean (SD) percentage above the range	24.0 (11.5)	23.1 (9.4)	26.8 (7.7)[b, c]	-	**0.001**
INR>5	35 (31.8)	181 (95.8)[a]	96 (61.1)[b, c]	137.5	**<0.001**
INR>8	3 (2.7)	42 (22.2)[a]	19 (12.1)[b, c]	22.6	**<0.001**
Median (IQR) years of follow-up	5.2 (2.0-8.3)	5.7 (3.0-8.5)	6.5 (5.0-8.6)[b, c]	-	**<0.001**

AF: atrial fibrillation; INR: international normalized ratio; IQR: interquartile range; PINRR: percentage of INRs within range; SD: standard deviation; TTR: time in therapeutic range; *TTR and PINRR were calculated based on the INR ranges obtained from the anticoagulation clinic; †INR ranges for each patient were different depending on indication and type of surgery and this was set by the operating surgeon; a: significant difference between median target INR 2.5 to 3.0; b: significant difference between median target INR 2.5 to 3.5; c: significant difference between median target INR 3.0 to 3.5

4.4.3 Predictors of poor anticoagulation control, TTR <70%

Table 4.4 presents the results obtained from univariate logistic regression analyses investigating the predictors of poor anticoagulation control. Being female [OR 2.2 (95% CI 1.32-3.73)], having an operated mitral valve [OR 1.8 (95% CI 1.02-3.28)] or both mitral and aortic valves [OR 3.0 (95% CI 1.14-7.62)], AF [2.12 (95% CI 1.27-3.54)], anaemia/bleeding history [OR 1.8 (95% CI 1.12-2.92)], digoxin [OR 5.2 (95% CI 1.85-14.69), increasing CHA_2DS_2-VASc [OR 1.2 (95% CI 1.02-1.43) and HAS-BLED [OR 2.7 (95% CI 2.01-3.48)] scores predicted poor TTR among patients with operated VHD with and without AF.

Models 1-6 in **Table 4.5** present the independent factors predicting poor TTR after adjustment for demographic and clinical variables. Being female, the presence of AF at baseline, and anaemia/bleeding history, were consistently present in 4 of the 6 models predicting poor TTR. The HAS-BLED score, which also contains anaemia/bleeding history, also predicted poor TTR in 2 of the 6 models (models 4 and 6).

Table 4.4: Demographics and clinical characteristics associated with predictors of poor TTR (<70%), in univariate analysis among patients with operated valvular heart disease, with and without AF

		Odds ratio (95% CI)	p-value
Age at implantation	Age	1.00 (0.99-1.02)	0.36
Sex	Female	2.22 (1.32-3.73)	**0.003**
Ethnicity‡	White (ref)	-	-
	Non-White	1.22 (0.76-1.96)	0.42
Social history	Alcohol >14unit/day (N=353)	2.41 (0.71-8.15)	0.16
	Smoking/ex-smoker (N=372)	0.72 (0.40-1.30)	0.28
Sites of prosthesis	Mitral only	1.83 (1.02-3.28)	**0.044**
	Aortic only	0.41 (0.24-0.69)	**0.001**
	Mitral and aortic	2.95 (1.14-7.62)	**0.025**
Types of valve replacement	Mechanical valve	0.72 (0.21-2.55)	0.61
	Tissue valve	1.39 (0.39-4.88)	0.61
Past medical history	Atrial fibrillation	2.12 (1.27-3.54)	**0.004**
	Heart failure	1.20 (0.58-2.49)	0.62
	Hypertension	0.97 (0.61-1.55)	0.91
	Diabetes	1.26 (0.66-2.42)	0.48
	Stroke/TIA	1.14 (0.59-2.18)	0.70
	Vascular disease*	1.10 (0.66-1.84)	0.72
	Lung disease#	1.44 (0.79-2.64)	0.24
	Kidney disease†	0.89 (0.28-2.78)	0.84
	Anaemia/bleeding history	1.81 (1.12-2.92)	**0.015**

Table 4.4 continued

		Odds ratio (95% CI)	p-value
	Beta-blocker	0.77 (0.49-1.20)	0.25
	ACEI/ARB	0.66 (0.42-1.04)	0.07
	Diuretics	1.11 (0.71-1.74)	0.64
Current medications	Amiodarone	1.50 (0.68-3.30)	0.32
	Concurrent antiplatelet	1.21 (0.65-2.22)	0.55
	Digoxin	5.21 (1.85-14.69)	**0.002**
	Calcium channel blocker	1.08 (0.53-2.18)	0.83
CHA_2DS_2-VASc score	Mean (SD)	1.21 (1.02-1.43)	**0.028**
HAS-BLED score	Mean	2.65 (2.01-3.48)	**<0.001**
SAMe-TT_2R_2 score	Mean	1.11 (0.94-1.30)	0.21

ACEI/ARB: angiotensin converting enzyme inhibitor/ angiotensin receptor blockade; AF: atrial fibrillation; CI: confidence interval; CHA_2DS_2-VASc score - Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75years [2 points], Diabetes, Stroke [2 points], Vascular disease, Age 65–74 years, and Sex category (female). Total scores range between 0-9; low risk CHA_2DS_2-VASc score: 0 male; 1 female, intermediate: 1male, ≥2 female, high risk CHA_2DS_2-VASc score: ≥2 male; ≥3 female; TIA: transient ischemic attack; eGFR: estimated glomerular filtration rate, ml/min/1.73 m^2; HAS-BLED score – uncontrolled Hypertension: systolic ≥160 mmHg, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR ratio/TTR <60, Drugs/alcohol concomitantly. Total scores range between 0-9; low risk of bleeding range between 0-2 and high risk of bleeding ≥3; SAMe-TT2R2 score – Sex female, Age<60, Medical history (more than two comorbidities), Treatment (interacting drug, e.g. Amiodarone), Tobacco use (doubled) and Race (non-white, doubled). Total scores ranged from 0-8; probable good response to VKA therapy range between 0-2 and probable poor response to VKA therapy ranged from ≥3; SD: standard deviation

* Vascular disease: prior myocardial infarction, peripheral artery disease or aortic plaque; # Lung disease: obstructive and restrictive diagnosed lung conditions; †eGFR <60ml/min or as noted in medical notes; ‡ 2 missing information on ethnicity

Table 4.5: Models of predictors of poor TTR (<70%) in the overall cohort of patients with operated valvular heart disease

Predictors	Model 1[α] (OR 95% CI)	Model 2[†]	Model 3[‡]	Model 4[¥]	Model 5[§]	Model 6[¶]
Age (continuous)	1.00 (0.98-1.02); p=0.98	1.00 (0.98-1.02); p=0.96	1.12 (0.94-1.34); p=0.21 [‡]	-	1.12 (0.93-1.34); p=0.23[§]	-
Female sex	1.93 (1.13-3.30); p=0.016	2.05 (1.21-3.50); p=0.008		2.28 (1.29-4.02); p=0.004		2.51 (1.42-4.44); p=0.002
Site of replacement (2 valves vs. 1 valve)*	2.06 (0.77-5.48); p=0.15	1.15 (0.30-4.35); p=0.84[†]	2.45 (0.93-6.44); p=0.07	2.02 (0.73-5.58); p=0.17	1.16 (0.31-4.36); p=0.83[§]	1.99 (0.50-7.90); p=0.33[¶]
Atrial fibrillation	1.75 (1.01-3.03); p=0.045	1.89 (1.10-3.27); p=0.022	1.74 (1.01-3.00); p=0.047	1.38 (0.78-2.43); p=0.26	1.94 (1.13-3.33); p=0.016	1.51 (0.86-2.65); p=0.16
Anaemia/bleeding history	1.84 (1.13-3.00); p=0.014	1.86 (1.14-3.03); p=0.012	1.72 (1.06-2.80); p=0.028	2.60 (1.98-3.43); p=<0.001[¥]	1.75 (1.08-2.84); p=0.024	2.65 (2.01-3.49); p=<0.001[¶]

*2 valves: aortic **AND** mitral valve vs. 1 valve: aortic **OR** mitral valve
[α] Model 1 includes age, female, site or replacement (2 vs. 1 valve), AF, anaemia/bleeding history
[†] Model 2 includes age; female, type of valve (mechanical vs. tissue), AF, anaemia/bleeding history
[‡] Model 3 includes CHA_2DS_2-VASc score, site or replacement (2 vs. 1 valve), AF, anaemia/bleeding history
[¥] Model 4 includes HAS-BLED score, female, site or replacement (2 vs. 1 valve), AF
[§] Model 5 includes CHA_2DS_2-VASc score, type of valve (mechanical vs. tissue), AF, anaemia/bleeding history
[¶] Model 6 includes female, type of valve (mechanical vs. tissue), AF and HAS-BLED score

4.4.4 Adverse clinical outcome

Table 4.6 shows the proportions of patients with adverse clinical outcomes. Overall there were 31 TE events, 113 bleeding events, 123 CV hospitalisations, 51 deaths and 316 experiences ≥1 MACE. There were no significant differences in TE, bleeding, CV hospitalisation and ≥1 MACE between those with and without AF. However, significantly higher proportions of patients with operated VHD and AF died [all-cause mortality (20.7% vs. 5.8%; p<0.001); CV mortality (7.3% vs. none; p<0.001) and non-CV mortality (13.4% vs. 5.8%; p=0.009)] compared to those operated without AF. In survival analyses, operated VHD patients with AF had a significantly higher risk of all-cause mortality compared to those without AF (Log-Rank: 21.570; p<0.001; **Figure 4.5**)

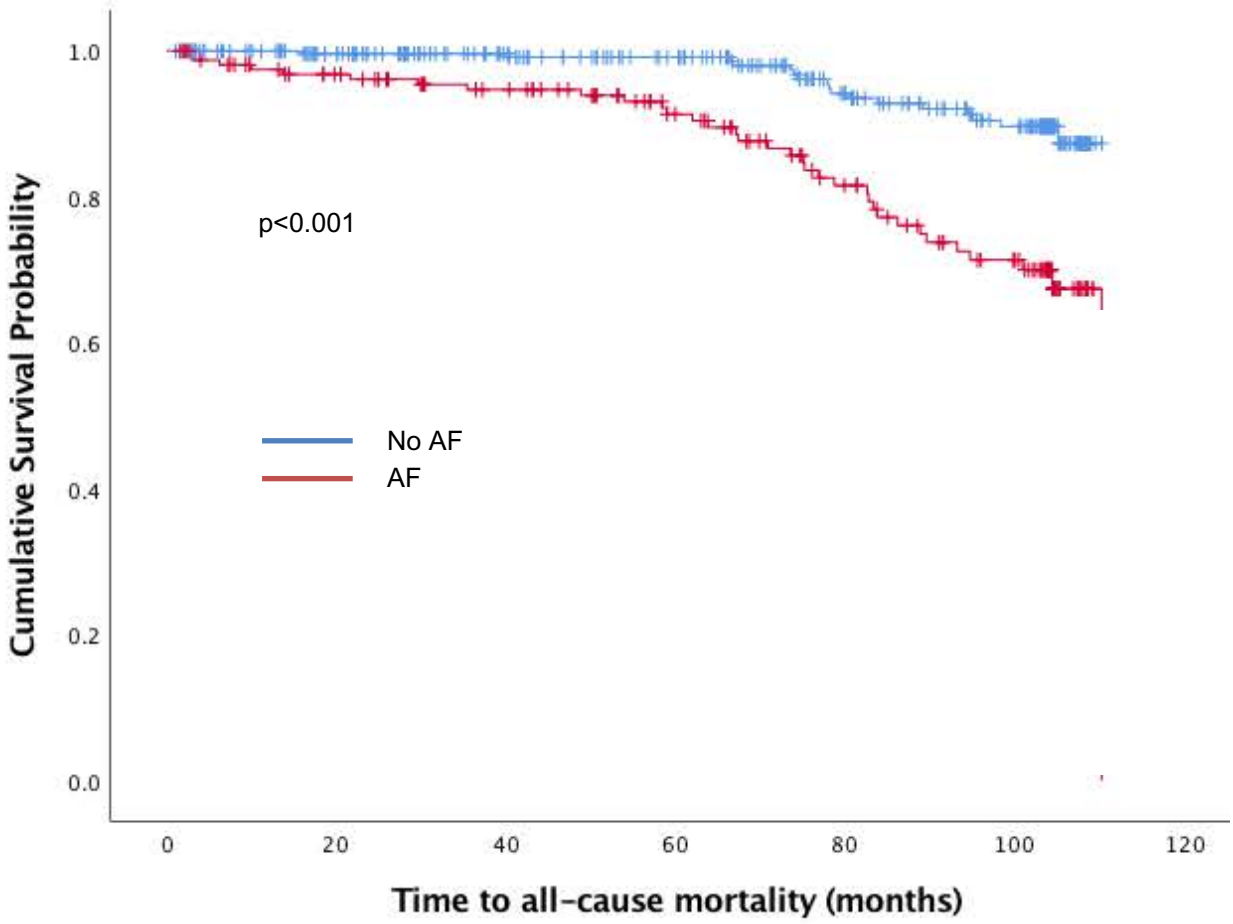
Table 4.7 compares the adverse clinical outcomes by TTR ≥70% and <70% and TTR≥65% and TTR <65%. Higher proportions of patients died (13.1% vs. 4.1%; p=0.011) and experienced ≥1 MACE (42.7% vs. 27.6%; p=0.006) when their TTR was <70% compared to those with TTR≥70%. In survival analyses, patients with TTR <70% had a significantly higher risk of all-cause mortality (Log-Rank: 5.845, p=0.016; **Figure 4.6**) and ≥1 MACE. (Log-Rank: 7.541, p=0.006; **Figure 4.7**) A similar pattern emerged when TTR was stratified as <65%; a significantly higher proportion of patients with TTR <65% died (14.2% vs. 4.8%; p=0.003) or experienced ≥1 MACE (44.5% vs. 28.8%; p=0.001).

Table 4.6: Adverse clinical outcome among patients with operated valvular heart disease, with and without AF

Outcomes, N (%)	Total, N=456	Event rate/100 pt yrs	AF N=164	Event rate/100 pt yrs	No AF N=292	Event rate/100 pt yrs	p-value*
Stroke/TIA/SE	25 (5.5)	1.0	8 (4.9)	0.9	17 (5.8)	1.1	0.67
Bleeding*	85 (18.6)	3.6	30 (18.3)	3.6	55 (18.8)	3.6	0.89
CV hospitalisation	78 (17.1)	3.4	31 (18.9)	3.8	47 (16.1)	3.2	0.45
All-cause death	51 (11.2)	1.9	34 (20.7)	**3.6**	17 (5.8)	**1.0**	**<0.001**
CV death	12 (2.6)	0.5	12 (7.3)	**1.3**	0	**-**	**<0.001**
Non-CV death	39 (8.6)	1.5	22 (13.4)	**2.3**	17 (5.8)	**1.0**	**0.009**
≥1 MACE†	180 (39.5)	8.7	75 (45.7)	10.1	105 (36.0)	7.8	0.051

*p-value for proportion; Cardiovascular hospitalisation: a hospitalisation with a cardiovascular cause: i) heart failure, MI, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled AF/atrial flutter, supraventricular arrhythmia, ii) valve surgery, CABG surgery, PTCA surgery, pacemaker/ICD insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation AND as recorded in patient's medical documents; DVT – Deep Vein Thrombosis ; * Bleeding ISTH is combination of major bleed ISTH and clinically relevant non-major bleed (CRNMB); Major Bleeding – ISTH Major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding but meet at least one of the 3 criteria: i) leading to hospitalisation or increased level of care, ii) requiring medical intervention by healthcare professional and iii) prompting face to face evaluation; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.

† ≥1MACE: major adverse clinical event defined a composite of TE, bleeding, CV hospitalisation and all-cause death



Number at risk	No AF	292	253	214	188	140	107
	AF	164	143	128	103	77	55

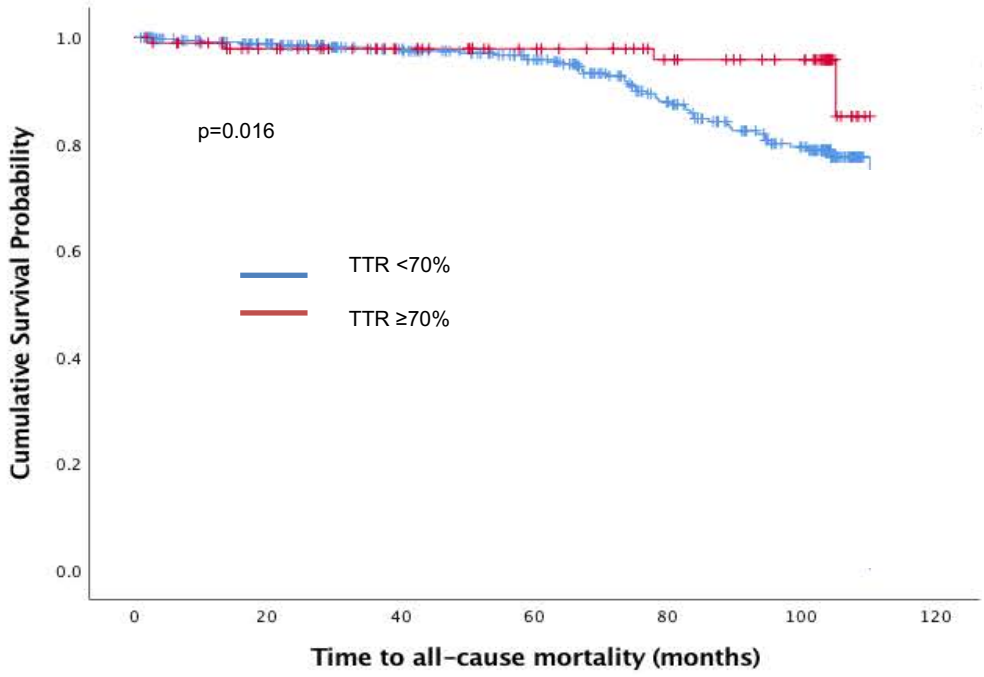
Figure 4.5: Kaplan-Meier curves among operated VHD patients stratified by the presence of AF for all-cause mortality

Table 4.7: Adverse clinical outcome vs. TTR among patients with operated valvular heart disease, with and without AF

N (%)	TTR<70% N=358	TTR≥70% N=98	p-value	TTR<65% N=310	TTR≥65% N=146	p-value
Stroke/TIA/SE	23 (6.4)	2 (2.0)	0.13	20 (6.5)	5 (3.4)	0.19
Bleeding*	72 (20.1)	13 (13.3)	0.12	65 (21.0)	20 (13.7)	0.06
CV hospitalisation	65 (18.2)	13 (13.3)	0.26	58 (18.7)	20 (13.7)	0.19
All-cause death	47 (13.1)	4 (4.1)	**0.011**	44 (14.2)	7 (4.8)	**0.003**
≥1 MACE†	153 (42.7)	27 (27.6)	**0.006**	138 (44.5)	42 (28.8)	**0.001**

Cardiovascular hospitalisation: a hospitalisation with a cardiovascular cause: i) heart failure, MI, new angina, non-fatal cardiac arrest, ventricular arrhythmia, uncontrolled AF/atrial flutter, supraventricular arrhythmia, ii) valve surgery, CABG surgery, PTCA surgery, pacemaker/ICD insertion, carotid endarterectomy, peripheral angioplasty/surgery, limb amputation AND as recorded in patient's medical documents; DVT – Deep Vein Thrombosis; Major Bleeding – ISTH Major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding but meet at least one of the 3 criteria: i) leading to hospitalisation or increased level of care, ii) requiring medical intervention by healthcare professional and iii) prompting face to face evaluation; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.

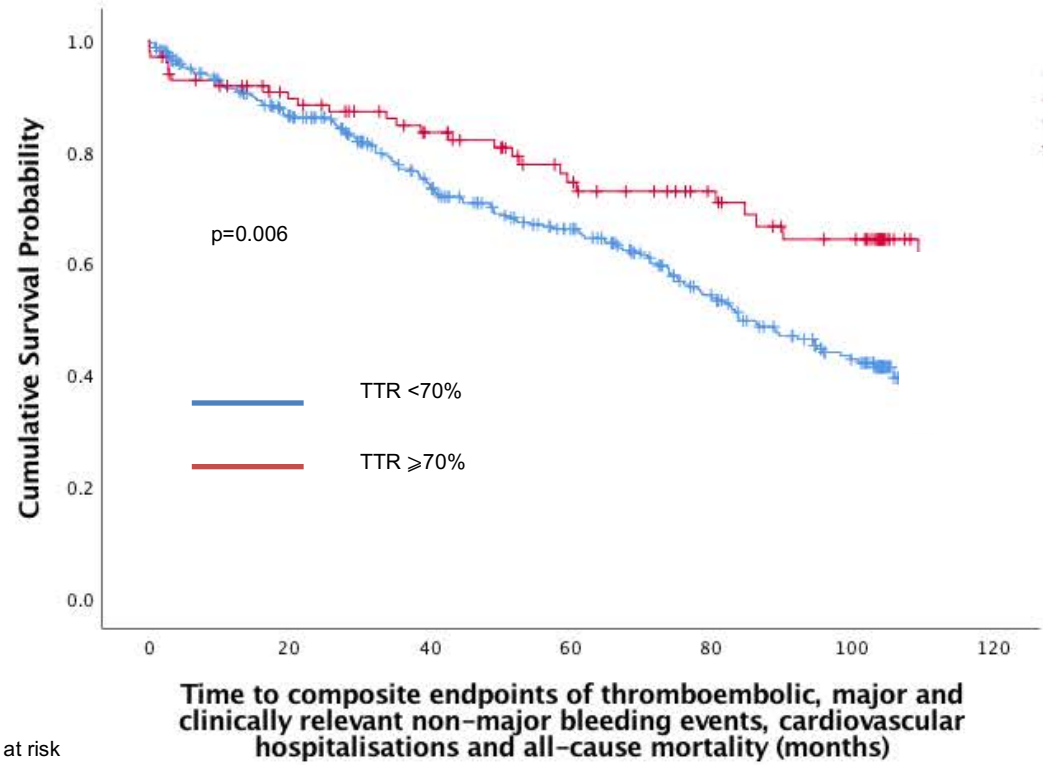
* Bleeding ISTH is combination of major bleed ISTH and clinically relevant non-major bleed (CRNMB); †≥1 MACE: major adverse clinical event defined a composite TE, bleeding, CV hospitalisation and all cause death



Number at risk

TTR <70%	358	317	272	233	171	123
TTR⩾70%	98	84	70	58	46	39

Figure 4.6: Kaplan-Meier curves among operated VHD patients stratified by categories of TTR (TTR <70% vs. TTR≥70%) for all-cause mortality



Number at risk

TTR <70%	358	275	207	160	108	67
TTR⩾70%	98	78	64	47	36	27

Figure 4.7: Kaplan-Meier curves among operated VHD patients stratified by categories of TTR (TTR <70% vs. TTR≥70%) for composites of thromboembolic, bleeding event, cardiovascular hospitalisation and all-cause mortality (≥1 MACE)

4.5 Discussion

This study has three main findings. First, the quality of anticoagulation control was significantly lower in operated VHD patients with AF at baseline compared to those without AF, using both the Rosendaal and PINRR methods. Second, females, the presence of AF, and anaemia/bleeding history significantly predicted poorer anticoagulation control in the overall cohort. Third, the rate of death was significantly higher in those with operated VHD with AF compared to operated VHD patients without AF. To date, this is the first study assessing the quality of anticoagulation control among operated VHD patients stratified by the presence of AF at baseline.

Mechanical heart valves are more thrombogenic but more long-lasting compared to tissue valves (377). Due to this reason, patients with mechanical valve prosthesis require lifelong anticoagulation therapy with a VKA compared to those with tissue valves (without other indication for OAC therapy; for example, AF) who only require anticoagulation therapy for at least the first 3 months following surgery(349, 351, 358). In this cohort of operated VHD patients, 36.0% of the population had concomitant AF, a proportion consistent with two recently published studies (377, 379). In the present cohort, AF patients were also significantly older and more likely to have additional stroke risk factors such as hypertension and heart failure and a greater proportion with AF received mitral or both mitral and aortic valve replacement, compared to patients without AF. Moreover, operated VHD patients with AF have significantly higher mean CHA_2DS_2-VASc and HAS-BLED scores than those without AF at baseline, indicating their higher risk of TE and bleeding events.

In terms of anticoagulation management, the majority of the operated VHD patients with AF had a higher target INR (i.e., INR 3.5) compared to those without AF. In the recent ESC guidelines (358), a target INR of 3.5 is recommended for those patients with ≥1 risk factor (for example AF) and with medium prosthesis thrombogenicity. In this operated VHD cohort, there is insufficient information about the type of valve used thus it was not possible to ascertain the

valves' thrombogenicity and explain the reasons behind the high target range. One possibility is that patients who had their valves replaced from as early as the 1970's were perhaps treated based on recommendations from previous guidelines which suggested a target range of 3.0-4.5 for all patients with prosthetic heart valves (regardless of type) (381). When examining anticoagulation control among patients with different target INRs in an exploratory analysis, TTR and PINRR were significantly lower among patients with a high target INR (INR 3.5) compared to those with target INRs of 2.5 and 3.0, respectively. Furthermore, other markers of poor anticoagulation control (sub-therapeutic INRs, supra-therapeutic INRs, INRs >5.0 and INRS >8.0) were also significantly more prevalent among those with higher INR targets (INR 3.5) compared to those with lower INR targets (INR 2.5 and INR 3.0). The PLECTRUM study (377), a retrospective observational multi-centre study among patients with mechanical heart valves also investigated TTR according to different INR targets and showed consistent results with the current study; lower median TTR among patients with a higher INR target (INR 3.5) [TTR 71.5% vs. 58.6% vs. 46%; p=0.0001 for INR targets of 2.5, 3.0 and 3.5 respectively] (377). Similarly, in the PLECTRUM cohort and the present cohort, TTR was better when the intended INR target was kept at 2.5. These findings may imply the difficulties in achieving INRs within the therapeutic range when a more intense anticoagulation regimen is adopted.

Overall in the present study, the mean (SD) TTR is 58.5% (14.6) and less than a quarter of the cohort achieved optimal TTR (TTR ≥70%), reflecting poor anticoagulation control among operated VHD patients. There is a paucity of literature on the quality of anticoagulation control among operated VHD patients, especially those with AF. Only four studies are available assessing TTR among VHD patients (377-380). The Swedish groups (379) examined TTR among 534 patients (379) and 4687 patients (380) with mechanical heart valves and reported a mean TTR of 71.3% (379) and 72.5% (380) respectively; higher than the mean TTR in the present study. In contrast, two recent studies (377, 378), conducted in Italy (N=2357) (377) and Denmark (N=659) (378), reported a median (IQR) TTR of 60% (47-74%) and 54.9% (39.0-72.9%), respectively; comparable to the TTR in the current study. The findings of the Italian

and Danish studies (377, 378) and the current study show sub-optimal quality of anticoagulation control among operated VHD patients. In contrast, the two Swedish study (379, 380) showed optimal anticoagulation control among operated VHD patients although this could be explained by the fact that generally, Sweden (379) is known to have excellent anticoagulation management resulting in better TTR compared to other countries (206, 456). This again reinforces one important message; the difficulties in maintaining INR levels at the therapeutic range among anticoagulated operated VHD patients. This is more worrying in patients with concomitant AF, as AF patients with VHD carry an even higher risk of TE complications (5-62%)(457) than patients with NVAF (0-18%) (457).

In logistic regression analyses, after adjusting for demographics and clinical variables, being female, the presence of AF and anaemia/bleeding history consistently predicted poor TTR in four of the six models. In addition, the HAS-BLED (which also consist of anaemia/bleeding history) score also predicted poor TTR (<70%) in two of six models. The finding that being female predicts poor TTR is consistent with other non-valvular AF studies (197-203) and is difficult to explain but could be influenced by several factors. The mean age of the overall VHD population was 51 years which is working age. It could be that working women have more hectic lifestyles with household, work and family responsibilities that makes them prone to being non-adherent to medication in general including towards anticoagulation therapy thus leading to poor anticoagulation control. One large American study (458) evaluating medication use and adherence among 16.0 million women and 13.5 million men showed that women were more likely to be non-adherent to their diabetic (35.4% vs. 32.5%; $p<0.0001$) and antihypertensive (25.8% vs. 24.8; $p<0.0001$) medications compared to men respectively and also speculated due to more complex medications regime, more side effects and more responsibilities resulting in self neglect compared to men (458). Furthermore, in this study, the majority of the operated VHD females also had AF at baseline which is also a predictor of poor TTR. Operated VHD patients with AF are older and had multiple comorbidities with complex disease management which might contribute to the lower quality of anticoagulation control

(197, 199, 201, 253). Lastly, history of anaemia/bleeding among operated VHD patients was also an independent predictor of poor TTR consistent with another study among non-valvular AF patients (213). It may be that these patients were managed more cautiously in terms of dosing of VKA. Although information on the dosage of VKAs used was not available, perhaps a lower dosage was used in this group of patients due to the fear of bleeding complications thus leading to the risk of suboptimal anticoagulation control in this population. No other studies have investigated the predictors of TTR specifically among operated VHD patients so comparison with other studies regarding the predictors of poor TTR among operated VHD patients could not be undertaken. However, Poli et al (377) has investigated predictors of TE among mechanical heart valves patients and showed that AF, history of TE and prosthesis at mitral position were associated with TE complications (377).

During a median follow up of 6.2 years, at least two-fifths of all operated VHD patients had ≥1 MACE. The rate of TE was 1.0/100 pt-yrs, which is comparable with that reported by Cannegieter et al (362) (1.0 /100 pt-yrs) but slightly higher than the rate reported by Poli et al (377) (0.67/100 pt-yrs), although the latter acknowledged the low rate of TE events in their cohort despite an overall suboptimal TTR compared to other studies (362). Perhaps the higher TE rate in the current cohort, compared to Poli et al (377), is driven by the higher proportion of patients with history of stroke/TIA prior to valve surgery in the current study compared to Poli et al (377) (14.5% vs. 8.3%).

The rate of bleeding events was 3.7/100 pt-yrs in the current study, higher than Cannegieter et al (362) and Poli et al (377), with 1.4/100 pt-yrs (362) and 1.0/100 patient-years, respectively. (377) The higher bleeding rate in the present cohort might be influenced by the higher target INR rate used (target INR 3.5), although further analyses on predictors of bleeding events (and all the other events) was not undertaken due to lack of power for these analyses.

Additionally, in this cohort, 11% of the patients died which was also higher than that reported from Poli et al (377) (7.4% deaths); this might be explained by differences in the demographic and clinical characteristics of the cohorts. There were more males, patients from ethnic minority groups, smokers/ex-smokers and a higher disease burden (stroke/TIA, diabetes, vascular disease and anaemia) in the present study which could potentially contribute to the differences in the mortality rate.

The proportions of operated VHD patients who had a TE, bleeding event, CV hospitalisation and ≥1 MACE was similar among those with and without AF at baseline. Nevertheless, all-cause mortality (including CV and non-CV related death) was significantly higher among those with AF compared to those without AF indicating that in this cohort, patients with operated VHD and AF have a worse prognosis than those without AF.

When investigating the impact of TTR on adverse clinical outcomes, significantly higher proportions of deaths (all-cause mortality) and patients with ≥1 MACE were seen in the suboptimal TTR category (TTR<70%). This suggests an increased risk of adverse clinical outcomes among operated VHD patients in this cohort when TTR is not optimised. In contrast, two other studies (377, 379) investigating the impact of TTR on TE events among mechanical heart valve patients reported contrasting results. The PLECTRUM (377) study and the Swedish registry (379) showed no relationship between poor TTR and TE events but poor TTR (<61.6%) was associated with bleeding events in the Swedish study (adjusted OR 2.9; p=0.011)(379). However, another study in 2002 (381) showed that mortality was significantly increased in patients with high anticoagulation variability (381). These studies vary in some aspects compared to the present study, especially the target INR used among the patients (high INR target vs. normal INR target vs. patient-specific target), the method of calculating the quality of anticoagulation control (TTR vs. anticoagulation variability), the study design (prospective vs. retrospective), the settings (high TTR setting vs. normal TTR setting), the year of study (2002 vs. 2018) and the sample size included, which could affect the results.

More studies regarding TTR and adverse clinical outcomes among operated VHD patients are needed to confirm these findings.

4.5.1 Strengths and Limitations

This is the first study investigating anticoagulation control in the UK among operated VHD patients stratified by the presence of AF at baseline (obtained from the post-operative notes). Although it is limited by the relatively small sample size, it provides some insights on anticoagulation control among operated VHD patients, with and without AF. Studies investigating anticoagulation control among VHD patients are lacking thus the information gained from this study adds to the limited current literature. In addition, anticoagulation control was assessed for 6.2 years reflecting long term anticoagulation control among VHD patients.

This study is limited by its retrospective, single centre design and the small number of operated VHD patients included, so caution must be applied as the findings might not be transferable to other settings. There is no information on the proportion of pregnancies, the doses of VKAs and type of valve inserted in the patients; if patients were offered PSM or home monitoring service, distance to anticoagulation clinic, level of education, drugs and food interaction and genetic information which could impact the quality of anticoagulation control. Additionally, this study is not powered for adverse clinical outcomes so analyses pertaining to outcomes were exploratory in nature.

4.5.2 Clinical implications

The findings of this study suggest that operated VHD patients with AF at baseline need closer attention and a more robust support system than those without AF. For example, more frequent follow up for closer INR monitoring should be arranged if patients INRs are not within the therapeutic range. During these follow ups, knowledge regarding the need for anticoagulation and the importance of keeping INR within the therapeutic range, the importance of being adherent to medication and avoiding or minimising food and drug

interactions should be reinforced from time to time. Perhaps barriers to medication adherence and persistence should be identified and addressed to improve adherence if this is identified as a cause of poor TTR.

In addition, patient self-monitoring (PSM) of INR could be offered to patients who have difficulties in coming for frequent INR visits provided that appropriate training was given in advance and patients' suitability for PSM has been assessed by the anticoagulant experts. One meta-analysis (459) of eleven trials comparing self-monitoring (self-testing) or self-management (self-testing and self-dosage) versus usual care (dosed by physician or anticoagulation clinic) among anticoagulated patients with VKA therapy for AF, mechanical heart valve and others showed that TE was significantly reduced in patients who were in the PSM group compared to control [HR 0.51; 95% CI 0.31-0.85)] but there was no difference between groups on bleeding and mortality (459). Also, patients with a mechanical heart valve benefited from the PSM with a significant reduction in thrombotic events [HR 0.52; 95% CI 0.35-0.77)] (459).

There may be a role for pharmacogenetic testing in VHD patients with difficulties achieving therapeutic INRs or if they are complicated with multiple strokes or bleeding events after receiving VKA therapy. This could potentially investigate any polymorphism to the CYP2C9 or the VKORCI enzymes which are responsible for warfarin metabolism thus affecting their response to therapy. As NOAC is contraindicated in operated VHD patients with mechanical heart prosthesis, every effort should be made to ensure treatment with VKA is optimal to prevent serious adverse clinical event.

4.5.3 Future work

Future studies with more focus on the quality of anticoagulation in operated VHD patients with AF is recommended as less attention has been paid to this population despite them having higher risk of TE complications than NVAF patients. As more studies are utilising INR variability as another method of measuring quality of anticoagulation control, perhaps future

work could include this method alongside with the TTR via the Rosendaal and PINRR methods and investigate the correlation between these methods. While TTR measures anticoagulation intensity, INR variability measures anticoagulation stability and both methods have been shown to predict warfarin related adverse outcomes (460). However, to date, insufficient evidence exist regarding which method is better in predicting adverse events, thus this would be an area for future research.

Guidelines on antithrombotic management in operated VHD were based on observational studies with small sample sizes and expert opinions. For example, there is as yet no agreement about the optimal level of anticoagulation intensity (INR targets) in different patient populations in order to have the net-clinical benefit of avoiding stroke and bleeding complications. Thus, future work with larger sample sizes (>1000) and prospective study designs is needed to provide greater insights into this population so that better management strategies can be provided to patients.

4.6 Conclusion

Operated VHD patients with AF at baseline have poorer anticoagulation control compared to those without AF at baseline. The presence of concomitant AF, anaemia/bleeding history, as well as female gender, independently predicted poor TTR. The rate of all-cause mortality was significantly higher among operated VHD patients with AF. These findings suggest closer INR monitoring among operated VHD patients, especially those with AF is warranted, to improve anticoagulation and prevent adverse clinical outcomes.

Chapter 5. General discussion and conclusions

Overall, this thesis included prospective (TREAT-2 study) and retrospective (study 2 and 3) studies primarily based on one acute Trust in the West Midlands.

Study 1 (TREAT-2 study) included newly anticoagulated AF patients (warfarin or NOACs) whereas studies 2 and 3 comprised AF and operated VHD patients on long term VKA therapy for the prevention of thromboembolic complications. The TREAT-2 study examined self-reported assessment of psychological measures, knowledge, beliefs and quality of life in AF patients new to OAC therapy. In contrast, studies 2 and 3 investigated objective measures of anticoagulation control (TTR) in AF patients in a multi ethnic population, inclusive of the elderly and patients with different categories of chronic kidney disease and operated VHD patients with and without AF. In addition, the prevalence of adverse clinical outcomes was also explored in studies 2 and 3. These studies were conducted in separate cohorts in order to achieve the objectives stated in section 1.8. However, for Study 1, due to a change in clinical practice regarding the prescription of a NOAC instead of warfarin since 2016, there were insufficient patients initiated on warfarin therapy within the Trust. Therefore, the comparison of the impact of the TREAT-2 intervention on TTR among warfarin-treated patients could not be examined. The main findings of the studies are summarised below:

Study 1 (TREAT-2) main findings:

- Newly anticoagulated AF patients did not appear to be depressed or anxious, had poor knowledge of AF and its treatment and poor quality of life. Despite this, they had a positive perception regarding their medication
- These findings remained unchanged during follow up at six months. However, more patients were aware of the consequences of AF and for some, AF symptoms had improved over time

Study 2 (TTR vs. ethnicity) main findings:

- Differences in the quality of anticoagulation control were evident amongst different ethnic groups but not within elderly populations and patients with different categories of kidney disease
- Despite similar intensity INR-monitoring, South-Asians and Afro-Caribbeans had poorer INR control compared to Whites
- Non-white ethnicity and anaemia remained the strongest independent predictor of poor TTR and PINRR after adjustment of demographic and clinical factors
- CV hospitalisations were more prevalent amongst the South-Asians compared to Afro-Caribbeans and Whites

Study 3 (TTR in VHD) main findings:

- Poorer anticoagulation control was seen in operated VHD patients with AF compared to those without AF
- Independent predictors of poor TTR included AF, anaemia/bleeding history and female gender
- Operated VHD patients with AF had higher rates of death compared to those without AF

Clinical implications

Results from the TREAT-2 study highlighted some positive aspects and identified areas for continued development for newly anticoagulated AF patients. Reassuringly, most patients did not report significant levels of depression or anxiety and most patients understood the importance of taking OAC. However, there was room for improvement in terms of increasing knowledge of AF as a chronic condition and enhancing quality of life.

Findings from Study 2 and 3 suggests that achieving good anticoagulation control is more challenging and the prevalence of adverse clinical outcomes is more commonly seen in AF patients from ethnic minority groups (Afro-Caribbeans and South-Asians) and among operated VHD patients with AF. In Study 2, non-white ethnicity was a significant independent predictor of poor-quality anticoagulation control, while Study 3 identified AF, anaemia/bleeding history and female sex as independent predictors of poor TTR among operated VHD patients. Therefore, in future, more efforts need be made to engage with patients from these populations so that we can fully explore their behaviours and factors contributing to poor INR control and develop strategies to optimise TTR and reduce adverse clinical outcomes.

Future research

To date, many countries still use VKA (rather than NOAC) for stroke prevention in AF especially within Asian countries and therefore the TREAT-2 study could be conducted in these countries. Malaysia, a multi-ethnic country consists of 67.4% Bumiputra (Malays and Indigenous Bumiputra), 24.6% Chinese, 7.3% Indians and 0.7% others (461) still uses warfarin as the main OAC of choice for stroke prevention in AF as well as the treatment of other conditions like venous thromboembolism, pulmonary embolism, mechanical heart valves transplantation.

A further prospective study/registry in a Malaysian cohort (N>1000 including data from the warfarin Medication Therapy Adherence Clinic at regional public hospitals) might further help fill the knowledge gap in understanding the impact of ethnicity on quality of anticoagulation control and adverse clinical outcomes. Adult AF patients who are newly prescribed with OAC therapy (warfarin or NOACs) for: i) stroke prevention in AF ii) prevention of TE complications among operated VHD patients can be included and followed up for 2 years. Demographics and clinical determinants of TTR among the Malaysian population can be investigated. Furthermore, it would be of interest to examine the impact of herbal medications/products on TTR as its usage is extensive among Malaysians due to aggressive promotions by promoters of herbal medicines. As mentioned in **section 1.5.1.2.1 page 91-92,** concomitant use of herbal medicines/products with warfarin therapy has resulted in a major safety concern due to warfarin-herbal interaction which might potentially increase the risk of thrombosis and bleeding complications. Thus, future work in this area is needed. Ancillary analyses might also include validation of the SAMe-TT_2R_2 score in the Malaysian cohort as the score includes non-white ethnicity as one of the predictors of anticoagulation control. Exploratory analysis can additionally investigate TE and bleeding outcomes in relation to TTR cut off values of ≥70% and <70%. Moreover, the incidence of TE, bleeding and mortality between patients prescribed with warfarin vs. NOAC could also be investigated at a population level. These analyses can be investigated separately among AF and operated VHD patients as data on both cohorts are limited in Malaysia.

Studies focusing on patient knowledge, psychological aspects and quality of life in anticoagulated patients in Malaysia are lacking. Thus, it would be of essence to investigate these elements and extend the TREAT-2 study to the Malaysian anticoagulated AF patients managed by the warfarin Medication Therapy Adherence Clinic (**more details can be found in section 2.5.2, pages 169-170)**. A similar study (TREATS-AF study) is also being planned in Thailand with additional aims of investigating the cost-effectiveness of educational-behavioural intervention, cross cultural adaptation, acceptance and satisfaction of this

intervention among Thai AF patients (MRC grant number: MR/ R020892/1 and personal communication with Dr Lane and Professor Lip).

Some patients prescribed long term warfarin therapy may experience worsening or improvements of TTR over time as there are likely to be changes in their comorbidities, drug therapy, anticoagulation management system, etc. that can influence anticoagulation control as stated in **section 1.5.1.** One recent Italian study (462) has shown that about 20% of their NVAF patients (N=1341) showed a worsening in TTR over time (mean follow up 37.7 months) and this was associated with increased risk of cardiovascular events [HR 2.1 (95% CI 1.06-4.14); p=0.03]. Hence, another retrospective longitudinal study could also be designed to examine temporal trends in TTR among NVAF patients receiving long-term warfarin therapy in a Malaysian cohort. It would be of value to build on this area of interest and determine if worsening TTR predicts worse CV outcomes as no study to date has investigated this in a Malaysian population.

The information gained from the proposed future research could then be conveyed to key stakeholders managing patients on anticoagulation therapy so that appropriate actions can be taken to improve their services for the benefits of the patients. Apart from that, these results could add to the current body of knowledge in the field of anticoagulation among Asian patients as this information is currently limited

Conclusions

Among newly anticoagulated AF patients, improvements are needed in AF knowledge. Although quality of life was reduced, most patients were not significantly anxious or depressed and they hold positive beliefs about their medication. Meanwhile, good anticoagulation control is more difficult to achieve in non-white AF patients and operated VHD patients with AF. Predictors of poor TTR include non-white ethnicity and anaemia in the former and the

presence of AF, anaemia and female sex in the latter. Lastly, the prevalence of CV hospitalisation was more common in South-Asian patients while mortality rates were higher among operated VHD patients with AF.

Appendices

Appendix 1

Table A1.1 Proforma

Date of study entry: _____ **The TREAT-2 study**

RXK number:_____	DOB:___/___/____ Age: _____	SEX: ☐ Male ☐ Female
Weight:_____Height:_____	BMI:_____	BP: _____ HR:_____
Group: ☐ 1 AF (warfarin + usual care) ☐ 2 AF (NOAC control) ☐ 3 AF (warfarin + TREAT) ☐ 4 AF (NOAC+ usual care)	AF date diagnosed: ___/____/___OAC type and start date:_____ Paroxysmal ☐ Persistent ☐ Long-standing persistent ☐ Permanent ☐	

1. Ethnic origin:_____
2. Education level

⌗ Primary school ⌗ Secondary school ⌗ College/university

3. Age of leaving formal education_____
4. Marital status

⌗ Married ⌗ Separated ⌗ Widowed
⌗ Single ⌗ Divorced

5. **Past Medical History**

⌗ Hypertension	⌗ Diabetes mellitus (DM)	⌗ Coronary artery disease/myocardial infarction/heart attack
⌗ Peripheral arterial disease (PAD)	⌗ Gastritis	⌗ Previous stroke/transient ischemic attack (TIA)
⌗ Asthma	⌗ Renal disease, eGFR_____	⌗ Hepatic disease
⌗ COPD	⌗ DVT/PE	⌗ Bleeding event
⌗ Congestive heart failure (CHF), NYHA class_____	⌗ *EHRA class* ⌗ *I(no symptoms)* ⌗ *II(mild symptoms-normal activity x affected)* ⌗ *III(severe symptoms-NA affected)* ⌗ *IV(disabling symptoms)*	⌗ Thyroid disease ⌗ Others:

6. Current smoking status

⌗ Yes ⌗ No ⌗ Stopped smoking past 2 yrs

7. Alcohol use:_____
8. **Medications:**

9. HAS-BLEED score: _____

Hypertension	☐
Abnormal liver/renal(1/2)	☐
Stroke	☐
Bleeding	☐
Labile INR	☐
Elderly >65	☐
Drugs/alcohol (1/2)	☐

10. CHA_2DS_2-VASc score:_____

CHF	☐
Hypertension	☐
Age ≥75 (2)	☐
Diabetes	☐
Stroke/TIA/TE (2)	☐
Vascular Disease	☐
Age 65-74	☐
Female	☐

11. **SAMe-TT_2R_2 score**

Sex (female)	
Age (<60y)	
Medical history	
Treatment	
Tobacco use (within 2 yrs) (2)	
Race (not white) (2)	
Total score	

12. **Inclusion criteria**

Adult (>18 years old)	
Women CHA_2DS_2-VASc score of ≥2	
Men CHA_2DS_2-VASc score of ≥1	
NVAF	
OAC-naïve	

13. **Follow up event and dates**

Stroke	
TIA	
Systemic embolism (PE/DVT)	
Major bleeding ISTH	
CRNMB bleeding ISTH	
CV hospitalisation	
Death	

14. **Pill count NOAC at 6 months**

☐ received all boxes ☐ not received all boxes pills left in the box_____

15. **VKA RESULTS**

Anticoagulant used: _____
Start date: _____End date: _____
TTR (Rosendaal): _____PINRR: _____
Days on therapy: _____Total INR: _____
16. INR<2: _____INR>3: _____INR>5: _____INR>8: _____

17. **Lab results**

HB	
Creatinine	
eGFR (ml/min)	
ALT/ALP	

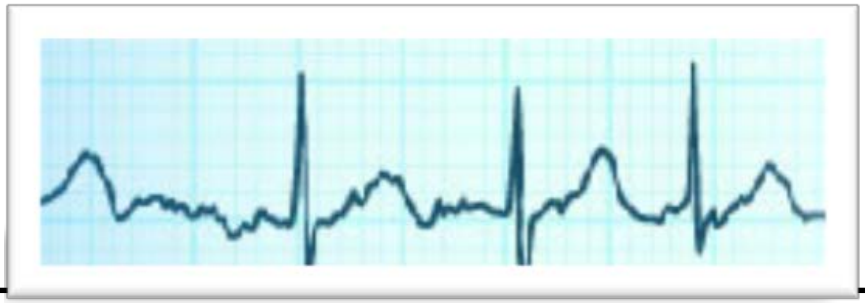
Appendix 2

Baseline and 6 months questionnaire

UNIVERSITY OF BIRMINGHAM

NHS Sandwell and West Birmingham Clinical Commissioning Group

Sandwell and West Birmingham Hospitals NHS Trust



BASELINE QUESTIONNAIRE

TREAT-2: Oral anticoagulation in AF stratified by SAMe-TT_2R_2 score

This questionnaire asks about your personal knowledge of atrial fibrillation, your beliefs about medication, how you feel generally and about your quality of life after being diagnosed with atrial fibrillation.

Please read all the questions or statement carefully. If you are unsure about which response to give to a question or statement, please choose the one that appears most appropriate. This is often your first response. After you have answered ALL questions, please return them in the pre-paid envelope given to you with the questionnaires.

Thank you in advance for your kind cooperation.

Study ID:

Today's date:
Date of birth: **Age:**
Sex: ☐ Male ☐ Female

Part 1: Background

For each of the following questions please tick (√) one response.

1. Ethnic origin (please tick (√) only one box within <u>one</u> ethnic group)

White

- ⌗ White British
- ⌗ Irish
- ⌗ Gypsy or Irish Traveller
- ⌗ Other white

Mixed /multiple ethnic groups

- ⌗ White and Black Caribbean
- ⌗ Others
- ⌗ White and Asians
- ⌗ White and Black African

Asian/Asian British

- ⌗ Indian
- ⌗ Pakistani
- ⌗ Bangladeshi
- ⌗ Chinese
- ⌗ Other Asian

Black/African/Caribbean/Black British

- ⌗ African
- ⌗ Caribbean
- ⌗ Other Black

Other ethnic group

- ⌗ Arab
- ⌗ Other ethnic group

2. Education level

- ⌗ Primary school
- ⌗ Secondary school
- ⌗ College/university
- ⌗ **What age did you leave full-time education? (please write in age)**

_____

3. Marital status: Are you currently (tick (√) one response only)

- ⌗ Married
- ⌗ Single
- ⌗ Separated
- ⌗ Divorced
- ⌗ Widowed

4.Do you currently smoke?

- ⌗ Yes
- ⌗ No

If no, have you stopped smoking in the last 2 years? Yes No

PART 2:

This section asks about how you have felt generally over the last 2 weeks. Please read each of the statements below. Please circle one answer for each statement.

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

If you have experienced any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? Please tick (√) one of the responses below.

Not difficult at all ☐	**Somewhat difficult** ☐	**Very difficult** ☐	**Extremely difficult** ☐

This section asks about how you have felt generally over the last 2 weeks. Please read each of the statements below. Please circle one answer for each statement.

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

If you have experienced any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? Please tick (√) one of the responses below.

Not difficult at all ☐	**Somewhat difficult** ☐	**Very difficult** ☐	**Extremely difficult** ☐

This section asks about your knowledge of atrial fibrillation. Please read each of the questions below. Tick (√) one answer for each question.

1.	**What are the trigger factors for atrial fibrillation?**	
	Allergy to grass, animals or house dust	⌗
	Alcohol, coffee or spicy food	⌗
	Noise or loud sounds	⌗
2.	**Why is it important to take my medication for atrial fibrillation properly?**	
	Because the doctor wants me to	⌗
	To prevent severe consequences of the arrhythmia	⌗
	To prevent the possibility of a heart attack or sudden death	⌗
3.	**If atrial fibrillation is identified without the patient experiencing any complaints, the patient should immediately visit the hospital.**	
	True	⌗
	False	⌗
	Don't know	⌗
4.	**What is atrial fibrillation?**	
	A heart disease in which the heart is not able to pump a sufficient amount of blood through the body	⌗
	A blood disorder causing blood clots in the heart	⌗
	An electric disorder in the atria of the heart which results in the heart contracting too fast and irregularly	⌗
5.	**Why is oral anticoagulation medication prescribed in certain patients with atrial fibrillation?**	
	To prevent the risk of blood clots which can cause a stroke	⌗
	To make the blood flow more easily through the body	⌗
	To prevent fluid retention in the body	⌗
6.	**Why should a person using anticoagulation medication be careful with the use of alcohol?**	
	Alcohol increases the retention of fluid in the body resulting in the blood becoming too thin	⌗
	Alcohol causes a blockage of the blood vessels which in turn, slows blood flow to the heart	⌗
	Alcohol influences the effect of the medication and this effects the clotting ability of the blood	⌗
7.	**Atrial fibrillation is a rare condition.**	

	True	⌗
	False	⌗
	Don't know	⌗
8.	**It is particularly risky if a person does not feel his/her atrial fibrillation.**	
	True	⌗
	False	⌗
	Don't know	⌗
9.	**Which statement with regard to physical exercise is true of patients with atrial fibrillation?**	
	It is important for patients to rest in order to maintain normal heart activity	⌗
	Patients with chronic atrial fibrillation cannot work fulltime	⌗
	It is important to exercise normally within personal limitations	⌗
10.	**Which statement is true?**	
	Atrial fibrillation is life endangering because it can result in a heart attack	⌗
	Atrial fibrillation is completely harmless	⌗
	Atrial fibrillation is harmless if the right medication is taken	⌗
11.	**What is the function of the anticoagulation clinic?**	
	To monitor blood clotting and the number of tablets taken each day	⌗
	To determine if the arrhythmia is present	⌗
	To determine if the patient needs to continue taking oral anticoagulation	⌗

This section asks about your views on medicines prescribed to you. Please read each of the statements and indicate the extent to which you agree or disagree by circling one response.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
1. My health, at present, depends on my medicines	1	2	3	4	5
2. Having to take medicines worries me	1	2	3	4	5
3. My life would be impossible without my medicines	1	2	3	4	5
4. Without my medicines I would be very ill	1	2	3	4	5
5. I sometimes worry about long-term effects of my medicines	1	2	3	4	5
6. My medicines are a mystery to me	1	2	3	4	5
7. My health in the future will depends on my medicines	1	2	3	4	5
8. My medicines disrupt my life	1	2	3	4	5
9. I sometimes worry about becoming too dependent on my medicines	1	2	3	4	5
10. My medicines protect me from becoming worse	1	2	3	4	5
11. Doctors use too many medicines	1	2	3	4	5
12. People who take medicines should stop their treatment for a while every now and again	1	2	3	4	5
13. Most medicines are addictive	1	2	3	4	5
14. Natural remedies are safer than medicines	1	2	3	4	5
15. Medicines do more harm than good	1	2	3	4	5
16. All medicines are poisons	1	2	3	4	5
17. Doctors place too much trust on medicines	1	2	3	4	5
18. If doctors had more time with patients they would prescribe fewer medicines.	1	2	3	4	5

This section refers to how atrial fibrillation affects your quality of life. Please read each of the statements below. Tick (√) one answer for each statement.

Are you currently in atrial fibrillation? ☐ Yes ☐ No

If No, when was the last time you were aware of having had an episode of atrial fibrillation?

Please tick (√) one answer, which best describes your situation:

Earlier today ☐

☐

Within the past week

Within the past month ☐

1 month to 1 year ago ☐

More than 1 year ago ☐

I was never aware of having atrial fibrillation ☐

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered or I did not have this symptoms	**Hardly bothered**	**A little bothered**	**Moderately bothered**	**Quite a bit bothered**	**Very bothered**	**Extremely bothered**
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7
	Not at all limited	**Hardly limited**	**A little limited**	**Moderately limited**	**Quite a bit limited**	**Very limited**	**Extremely limited**
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

	No difficulty at all	**Hardly any difficulty**	**A little difficulty**	**Moderate difficulty**	**Quite a bit of difficulty**	**A lot of difficulty**	**Extreme difficulty**
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7
	Not at all bothered	**Hardly bothered**	**A little bothered**	**Moderately bothered**	**Quite a bit bothered**	**Very bothered**	**Extremely bothered**
13. Feeling worried or anxious that your atrial fibrillation can start anytime	1	2	3	4	5	6	7
14. Feeling worried that atrial fibrillation may worsen other medical conditions in the long run	1	2	3	4	5	6	7

	Not at all bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
15. Worrying about the treatment side effects from medications	1	2	3	4	5	6	7
16. Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy	1	2	3	4	5	6	7
17. Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising.	1	2	3	4	5	6	7
18. Worrying or feeling anxious that your treatment interferes with your daily activities	1	2	3	4	5	6	7
	Extremely satisfied	**Very satisfied**	**Somewhat satisfied**	**Mixed with satisfied and dissatisfied**	**Somewhat dissatisfied**	**Very dissatisfied**	**Extremely dissatisfied**
19. How well your current treatment controls your atrial fibrillation?	1	2	3	4	5	6	7

20. The extent to which treatment has relieved your symptoms of atrial fibrillation?	1	2	3	4	5	6	7

Thank you for completing the questionnaires. Please return them in the stamped-addressed envelope provided.

Appendix 3

Table A3.1: Baseline psychological measures, knowledge and beliefs about medication of AF patients overall and in Group 1, 2, 3 and 4

Baseline measures	Overall, N=139	SAMe-TT_2R_2 0-2		SAMe-TT_2R_2 >2	
		Group 1 N=9	Group 2 N=102	Group 3 N=4	Group 4 N=24
PHQ-9 (9 items; scores range from 0-27)					
Median (IQR) score	4.0 (1.0-8.0)	2.0 (0.5-4.0)	4.0 (1.0-8.0)	2.5 (0-16.3)	5.0 (2-11)
Minimal 0-4, (%)	80 (57.6)	8 (88.9)	59 (57.8)	2 (50.0)	11 (45.8)
Mild 5-9, (%)	31 (22.3)	1 (11.1)	24 (23.5)	1 (25.0)	5 (20.8)
Moderate 10-14, (%)	20 (14.4)	0	13 (12.7)	0	7 (29.2)
Moderately severe 15-19, (%)	5 (3.6)	0	5 (4.9)	0	0
Severe depression 20-27, (%)	3 (2.2)	0	1 (1.0)	1 (25.0)	1 (4.2)
GAD-7 (7 items; scores range from 0-21)					
Median (IQR) score	1.0 (0-5)	0	1.0 (0-2.5)	3.0 (0.3-20.3)	1.0 (0-7.8)
Minimal 0-4, (%)	100 (71.9)	8 (88.9)	74 (72.5)	2 (50.0)	16 (66.7)
Mild 5-9, (%)	23 (16.5)	0	18 (17.6)	1 (25.0)	4 (16.7)
Moderate 10-14, (%)	8 (5.8)	1 (11.1)	5 (4.9)	1 (25.0)	1 (4.2)
Severe anxiety 15-21, (%)	8 (5.8)	0	5 (4.9)	0	3 (12.5)
AF knowledge scale (11 items; scores range from 0-11)					
Total scores, mean (SD) (min-max: 0-11)	5.7 (1.7)	6.8 (1.4)	5.5 (1.7)	6.8 (1.0)	6.0 (1.6)
Total scores, 0-100%	52.0 (15.4)	61.6 (12.7)	50.2 (15.5)	61.4 (8.7)	54.5 (14.9)
AF in general correct score, % **(3 questions)**	24.5 (22.9)	29.6 (33.3)	22.5 (22.6)	41.7 (16.7)	27.8 (23.4)

Baseline measures	**Overall,** N=139	**Group 1** N=9	**Group 2** N=102	**Group 3** N=4	**Group 4** N=24
AF symptoms recognition correct score, % **(3 questions)**	46.5 (32.0)	55.6 (33.3)	43.8 (32.5)	58.3 (31.9)	52.8 (29.4)
AF treatment correct score, % **(5 questions)**	71.8 (20.5)	84.4 (16.7)	70.6 (21.0)	75.0 (25.2)	71.7 (18.6)
Beliefs about medication (BMQ; 18 items)					
BMQ general (scores range from 4-20)					
General overuse (4-20)	10.5 (2.9)	10.1 (3.1)	10.5 (2.9)	11.3 (2.5)	10.9 (3.1)
General harm (4-20)	8.6 (2.9)	6.7 (0.9)	8.6 (2.9)	9.0 (9.5)	9.1 (2.9)
BMQ specific (scores range from 5-25)					
Specific necessity (5-25)	19.0 (3.0)	19.1 (2.8)	18.9 (3.1)	19.3 (1.7)	19.3 (3.0)
Specific concern (5-25)*	13.3 (3.5)	12.4 (2.7)	13.1 (3.5)	11.8 (3.1)	14.5 (3.7)
Necessity-concern differential	5.7 (4.2)	6.7 (4.2)	5.8 (4.2)	7.5 (3.7)	4.9 (4.1)
AFEQT (20 items; scores range from 0-100)					
Symptoms (0-100)*	79.2 (58.3-95.8)	58.3 (41.7-97.9)	83.3 (62.5-96.9)	62.5 (38.5-92.7)	62.5 (50.0-86.5)
Daily activity (0-100)	60.4 (39.6-79.2)	68.8 (31.3-80.2)	60.4 (39.6-81.3)	35.5 (27.6-95.8)	59.4 (37.0-68.2)
Treatment concern (0-100)*	75.0 (52.8-86.1)	77.8 (72.2-84.7)	75.0 (55.6-91.7)	68.1 (50.0-75.7)	65.3 (25.0-83.3)
Satisfaction (N=111) (0-100)*	75.0 (66.7-83.3)	75.0 (60.4-89.6)	75.0 (66.7-83.3)	58.3 (50.0-)	70.8 (50.0-83.3)
Overall global score (0-100)*	66.7 (53.7-77.8)	59.3 (50.9-80.1)	66.7 (54.4-83.3)	65.7 (38.7-87.3)	63.9 (39.1-74.8)

*mean (SD); PHQ-9: Patient Health Questionnaire to measure depression; GAD-7: Generalised Anxiety Disorder to measure anxiety; AF knowledge scale to measure knowledge of atrial fibrillation; BMQ: beliefs about medication questionnaire; AFEQT: Atrial Fibrillation Effect on Quality of Life Questionnaire

Table A3.2: Six month-follow up psychological measures, knowledge and beliefs about medication of AF patients overall and in Group 1, 2, 3 and 4

Follow up measures	Overall, N=105	SAMe-TT_2R_2 0-2		SAMe-TT_2R_2 >2	
		Group 1 N=7	Group 2 N=80	Group 3 N=2	Group 4 N=16
PHQ-9 (9 items; scores range from 0-27)					
Median score (IQR)	4.0 (0.0-9.0)	3.0 (0-8.0)	4.0 (0-9.0)	2.0 (0-0)	5.0 (0.7-9.5)
Minimal 0-4, (%)	56 (54.4)	5 (71.4)	44 (55.0)	2 (50.0)	7 (43.8)
Mild 5-9, (%)	25 (24.3)	1 (14.3)	19 (23.8)	1 (25.0)	5 (31.3)
Moderate 10-14, (%)	15 (14.6)	0	12 (15.0)	0	3 (18.8)
Moderately severe 15-19, (%)	6 (5.8)	1 (14.3)	4 (5.0)	0	1 (6.3)
Severe depression 20-27, (%)	1 (1.0)	0	1 (1.3)	1 (25.0)	0
GAD-7 (7 items; scores range from 0-21)					
Median score (IQR)	1.0 (0-5.0)	0 (0-5)	1.0(0-5.8)	0 (0-5)	1.0 (0-4.8)
Minimal 0-4, (%)	68 (66.0)	4 (57.1)	52 (65.0)	2 (50.0)	12 (75.0)
Mild 5-9, (%)	25 (24.3)	2 (28.6)	21 (26.3)	1 (25.0)	2 (12.5)
Moderate 10-14, (%)	6 (5.8)	0	5 (6.3)	1 (25.0)	1 (6.3)
Severe anxiety 15-21, (%)	1.0 (1.0)	1 (14.3)	2 (2.5)	0	1 (6.3)
AF knowledge scale (11 items; scores range from 1-11)					
Total scores, mean (SD) (min-max: 0-11)	5.9 (1.9)	7.0 (1.3)	5.9 (1.8)	7.0 (1.4)	5.4 (2.1)
Total scores, 0-100%	53.9 (16.9)	63.6 (11.7)	53.6 (16.6)	63.6 (12.9)	49.4 (19.3)
AF in general correct score, % **(3 questions)**	18.4 (22.6)	9.5 (16.3)	18.3 (22.4)	16.7 (23.6)	23.0 (26.4)
AF symptoms recognition correct score, % **(3 questions)**	54.3 (31.4)	71.4 (40.5)	54.2 (31.5)	50.0 (23.6)	47.9 (27.1)

Follow up measures	Overall, N=105	Group 1 N=7	Group 2 N=80	Group 3 N=2	Group 4 N=16
AF treatment correct score, % (5 questions)	74.9 (24.2)	91.4 (15.7)	74.5 (22.5)	100	66.3 (31.6)
BMQ (18 items)					
BMQ general (scores range from 5-25)					
General overuse (4-20)*	10.7 (2.9)	10.7 (1.1)	11.0 (2.9)	11.0 (2.8)	9.3 (3.0)
General harm (4-20)*	8.2 (2.4)	8.4 (1.4)	8.3 (2.4)	8.5 (0.7)	7.8 (2.8)
BMQ specific (scores range from 4-20)					
Specific necessity (5-25)*	19.1 (3.1)	18.6 (1.3)	19.0 (3.0)	19.5 (2.1)	19.5 (4.1)
Specific concern (5-25)*	12.9 (3.8)	14.0 (4.7)	12.8 (3.8)	†	13.2 (3.7)
Necessity-concern differential	6.1 (4.4)	4.6 (4.3)	6.2 (4.2)	8.5 (2.1)	6.3 (5.3)
AFEQT (20 items; scores range from 0-100)					
Symptoms* (0-100)	83.3 (64.6-100)	75.0 (50.0-95.8)	87.5 (66.7-100)	79.2 (58.3-.)	68.8 (53.1-79.2)
Daily activity* (0-100)	54.2 (34.4-77.1)	66.7 (20.8-85.4)	54.2 (35.4-80.7)	46.9 (22.9-.)	49.0 (29.2-69.8)
Treatment concern * (0-100)	72.2 (58.3-88.9)	72.2 (41.7-83.3)	72.2 (59.0-88.2)	81.9 (63.9-.)	69.4 (35.4-97.2)
Satisfaction* (0-100)	83.3 (66.7-91.7)	66.7 (66.7-83.3)	83.3 (66.7-91.7)	91.7 (91.7-91.7)	83.3 (68.8-83.3)
Overall global score* (0-100)	66.7 (49.1-81.9)	77.1 (38.0-83.3)	69.0 (50.9-83.1)	65.7 (56.5-.)	61.6 (43.9-70.0)

*mean (SD); †Patients in Group 3 did not answer; PHQ-9: Patient Health Questionnaire to measure depression; GAD-7: Generalised Anxiety Disorder to measure anxiety; AF knowledge scale to measure knowledge of atrial fibrillation; BMQ: beliefs about medication questionnaire; AFEQT: Atrial Fibrillation Effect on Quality of Life Questionnaire

Appendix 4

Table A4.1: Project proforma: Ethnic differences in anticoagulation control among atrial fibrillation patients receiving warfarin for stroke prevention

Demographics							
RXK number: _____		DOB: ____/___/____Ethnic origin: _____					
Patient number: _____		Age: ____ Sex: M □ F □					
Clinical information							
AF date diagnosed: _____		VKA naïve: yes □ no □					
- Paroxysmal	□						
- Persistent	□						
- Long-standing persistent	□						
- Permanent	□						
Past Medical History	**Details:**						**Date diagnosed**
Valvular heart disease	□	Mitral stenosis	□	Valve replacement	□	Rheumatic □	_____
Stroke	□	Ischaemic	□	Haemorrhagic	□		_____
TIA	□	Total_____					_____
History of TE	□						_____
Coronary artery disease	□	MI	□	CABG	□	PCI □	_____
Heart failure	□	HF-PEF	□	HF-REF	□	EF _____ %	_____
Hypertension	□	Essential	□	Secondary	□		_____
Diabetes	□	Type 1	□	Type 2	□		_____
Lung disease	□	Obstructive	□	Restrictive	□		_____
Vascular disease	□	PAD	□	Aortic Plaque	□	MI □	_____
Cardiomyopathy	□	Dilated	□	Hypertrophic	□		_____
Kidney disease	□	<60 ml/ml	□	<30 ml/min	□	Dialysis □	_____
Hypercholesterolemia	□						_____
Alcohol yes □ no □	**Current smoker** □			**Ex-smoker** □		**Never smoked** □	
Lab results							
Hb							
Egfr							
Creatinine							
Alt							
Alp							

Clinical Outcomes	**Details:**			**Yes** □ Total_____		**No** □	
Stroke	□ Total_____	Ischaemic	□	Haemorrhagic	□		_____
TIA	□ Total_____						_____
VTE / **DVT** / **PE**	□	First	□	Recurrent	□		_____
Bleeding	□	Major ISTH*	□	CR Non-Major **	□	NCR □	_____
Hospitalisation	□						
- CV cause				Total_____			_____
- Bleeding cause	□ _____			Total_____			_____
- Stroke/TIA cause	□ _____			Total_____			_____
Other cause hospitalization	□ _____						
Death	□	Cause: _____		Date: ____/____/____			

Baseline medication list	**Date:**	**Most recent medication list**	**Date:**
1.		1.	
2.		2.	
3.		3.	
4.		4.	
5.		5.	
6.		6.	
7.		7.	
8.		8.	
9.		9.	
10.		10.	

VKA results

Anticoagulant used:_____ Start date: ____/____/____ End date: ____/____/____

Average dose: _____

Target INR range: _____

TTR Rosendaal:_____ %INR range:_____

Days on therapy: _____ Total INRs:_____

INR<2: _____ INR>3: _____ INR>5:_____ INR>8:_____

*Major Bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells; Clinically relevant non-major bleeding (CRNMB): clinically overt bleeding not satisfying the criteria for major bleeding and that led to hospitalisation, physician medical or surgical treatment, or a change in antithrombotic therapy

INR Recordings **Patient number _____** **Hospital number_____**

	DATE	INR	DOSE		DATE	INR	DOSE		DATE	INR	DOSE
1.				35.				69.			
2.				36.				70.			
3.				37.				71.			
4.				38.				72.			
5.				39.				73.			
6.				40.				74.			
7.				41.				75.			
8.				42.				76.			
9.				43.				77.			
10.				44.				78.			
11.				45.				79.			
12.				46.				80.			
13.				47.				81.			
14.				48.				82.			
15.				49.				83.			
16.				50.				84.			
17.				51.				85.			
18.				52.				86.			
19.				53.				87.			
20.				54.				88.			
21.				55.				89.			
22.				56.				90.			
23.				57.				91.			
24.				58.				92.			
25.				59.				93.			
26.				60.				94.			
27.				61.				95.			
28.				62.				96.			
29.				63.				97.			
30.				64.				98.			
31.				65.				99.			
32.				66.				100.			

Table A4.2: Logistic regression for TTR<70% (using Rosendaal method) in relation to demographic and clinical factors

	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age at first INR[¥]	0.99 (0.98-1.0)	0.11	0.99 (0.97-1.0)	0.12
Female sex	1.05 (0.82-1.36)	0.69	1.21 (0.87-1.68)	0.26
Smoking history	1.05 (0.78 -1.42)	0.73	1.27 (0.91-1.77)	0.16
Ethnicity (non- white)	**2.44 (1.72-3.47)**	**<0.001**	**2.62 (1.67-4.10)**	**<0.001**
Hypertension	0.85 (0.62-1.16)	0.29	0.83 (0.56-1.27)	0.35
Stroke/TIA	0.69 (0.50-0.96)	**0.027**	0.82 (0.55-1.22)	0.33
Heart failure	**1.60 (1.10-2.33**)	**0.014**	1.45 (0.94-2.24)	0.09
Diabetes	1.10 (0.81-1.50)	0.55	0.76 (0.51-1.13)	0.17
Vascular disease	**1.83 (1.28-2.61)**	**0.001**	**1.81 (1.16-2.83)**	**0.01**
Kidney disease	1.01 (0.78-1.31)	0.93	0.97 (0.69-1.35)	0.85
Anaemia	**1.96 (1.34-2.85)**	**<0.001**	**1.65 (1.00-2.70)**	**0.05**
Bleeding history	1.51 (0.93- 2.43)	0.09	1.51 (0.83-2.75)	0.17

[¥]continuous variable

INR: international Normalised Ratio**;** TIA: transient ischemic attack TTR: Time in therapeutic range

Table A4.3: Logistic regression for PINRR <70% (using PINRR method) in relation to demographic and clinical factors

	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age at first INR[¥]	1.0 (0.98-1.02)	0.79	0.99 (0.97-1.02)	0.58
Female sex	1.17 (0.81-1.68)	0.40	0.98 (0.62-1.56)	0.95
Smoking history	0.79 (0.52-1.21)	0.28	0.94 (0.60-1.49)	0.80
Ethnicity (non- white)	**3.34 (1.72-6.49)**	**<0.001**	**3.47 (1.44-8.34)**	**0.005**
Hypertension	0.90 (0.57-1.41)	0.64	0.80 (0.45-1.43)	0.45
Stroke/TIA	1.21 (0.75-1.98)	0.44	1.17 (0.66-2.08)	0.59
Heart failure	1.30 (0.75-2.26)	0.36	1.31 (0.70-2.45)	0.40
Diabetes	1.55 (0.95-2.54)	0.08	0.98 (0.55-1.78)	0.96
Vascular disease	1.07 (0.65-1.74)	0.80	0.87 (0.47-1.60)	0.65
Kidney disease	0.79 (0.55-1.14)	0.21	0.66 (0.42-1.05)	0.08
Anaemia	**2.45 (1.26-4.79)**	**0.009**	**6.27 (1.89-20.94)**	**0.003**
Bleeding history	1.50 (0.71-3.19)	0.29	1.0 (0.40-2.54)	0.98

[¥]continuous variable

INR: international Normalised Ratio**;** TIA: transient ischemic attack; PINRR: Percentage of INRs within range

Table A4.4: Cox proportional hazard regression analysis for the outcome of thromboembolic events (including stroke, transient ischaemic attack and pulmonary embolism)

	Univariate HR (95% CI)	p-value	Multivariate	p-value
Age[¥]	0.99 (0.96-1.02)	0.51	0.97 (0.94-1.01)	0.16
Female sex	0.82 (0.46-1.45)	0.50	0.59 (0.28-1.23)	0.16
Smoking history	0.67 (0.33-1.33)	0.17	0.61 (0.28-1.30)	0.20
Ethnicity (non- white)	1.43 (0.73-2.80)	0.29	1.14 (0.49-2.68)	0.76
Hypertension	1.26 (0.61-2.60)	0.53	1.12 (0.44-2.85)	0.81
Stroke/TIA history	**2.40 (1.33-4.30)**	**0.003**	**2.29 (1.12-4.68)**	**0.02**
Heart failure	0.86 (0.37-2.01)	0.73	0.83 (0.31-2.19)	0.70
Diabetes	**2.01 (1.11-3.65)**	**0.021**	1.85 (0.85-4.01)	0.12
Vascular disease	1.08 (0.51-2.30)	0.84	1.33 (0.56-3.19)	0.52
Kidney disease	1.54 (0.88-2.69)	0.13	1.42 (0.69-2.93)	0.34
Anaemia	1.79 (0.89-3.58)	0.10	1.24 (0.47-3.30)	0.67
Bleeding history	1.27 (0.46-3.52)	0.65	0.76 (0.17-3.36)	0.72
TTR (continuous)	0.99 (0.97-1.01)	0.20	0.98 (0.96-1.01)	0.15
TTR <70%	1.56 (0.88-2.79)	0.13	-	
PINRR (continuous)	0.98 (0.96-1.01)	0.19	-	
PINRR <70%	1.17 (0.52-2.60)	0.70	-	

[¥] Continuous variable

Table A4.5: Cox- proportional hazard regression analysis for all bleeding event, including major bleed and clinically relevant non-major bleed

	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI) (Model 1)*	p-value	Multivariate HR (95% CI) (Model 2)#	p-value
Age¥	**1.03 (1.01-1.06)**	**0.016**	1.02 (0.99-1.06)	0.14	1.02 (0.99-1.06)	0.13
Female sex	0.92 (0.58-1.45)	0.71	0.85 (0.48-1.50)	0.58	0.82 (0.47-1.44)	0.49
Smoking history	0.86 (0.51-1.45)	0.57	0.91 (0.52-1.61)	0.74	0.90 (0.51-1.59)	0.71
Ethnicity (non- white)	1.13 (0.64-2.02)	0.67	0.96 (0.47-1.96)	0.90	0.97 (0.48-1.96)	0.93
Hypertension	1.31 (0.73-2.33)	0.37	1.53 (0.71-3.31)	0.28	1.49 (0.69-3.21)	0.31
Stroke/TIA history	1.10 (0.63-1.93)	0.74	1.09 (0.56-2.12)	0.80	1.10 (0.57-2.15)	0.77
Heart failure	1.38 (0.78-2.47)	0.27	1.68 (0.89-3.19)	0.11	1.71 (0.90-3.22)	0.10
Diabetes	1.18 (0.69-2.02)	0.54	0.95 (0.48-1.86)	0.87	0.93 (0.47-1.83)	0.84
Vascular disease	0.97 (0.51-1.83)	0.92	0.83 (0.38-1.81)	0.63	0.78 (0.36-1.71)	0.53
Kidney disease	0.92 (0.57-1.47)	0.72	0.63 (0.35-1.14)	0.12	0.63 (0.35-1.13)	0.12
Anaemia	1.46 (0.80-2.65)	0.22	1.64 (0.77-3.52)	0.20	1.61 (0.75-3.46)	0.22
Bleeding history	1.48 (0.68-3.23)	0.32	1.05 (0.40-2.79)	0.92	1.04 (0.39-2.75)	0.94
TTR (continuous)	**0.98 (0.97-0.998)**	**0.026**	0.98 (0.97-1.00)	0.08	-	
TTR <70%	1.52 (0.95-2.42)	0.08	-		**1.78 (1.01-3.13)**	**0.05**
PINRR (continuous)	**0.97 (0.95-0.99)**	**0.003**	-		-	
PINRR <70%	2.03 (0.93-4.42)	0.07	-		-	

¥continuous variable

*Model 1: excluding PINRR continuous, TTR category and PINRR category, #Model 2: excluding TTR continuous, TTR category, PINRR category

Table A4.6: Cox- proportional hazard regression analysis for cardiovascular hospitalisation

	Univariate HR (95% CI)	p-value	Multivariate* HR (95% CI) (Model 1)	p-value	Multivariate# HR (95% CI) (Model 2)	p-value
Age ¥	0.99 (0.98-1.01)	0.41	0.99 (0.97-1.01)	0.23	0.99 (0.97-1.01)	0.23
Female sex	0.97 (0.74-1.26)	0.81	1.04 (0.76-1.44)	0.80	1.03 (0.75-1.41)	0.87
Smoking history	0.88 (0.66-1.18)	0.40	0.88 (0.64-1.22)	0.45	0.89 (0.64-1.23)	0.48
Ethnicity (non- white)	**1.66 (1.22-2.25)**	**0.001**	1.24 (0.85-1.81)	0.27	1.29 (0.89-1.89)	0.18
Hypertension	1.31 (0.93-1.85)	0.12	0.95 (0.65-1.38)	0.77	0.93 (0.64-1.35)	0.68
Stroke/TIA history	1.12 (0.80-1.55)	0.51	1.13 (0.78-1.63)	0.51	1.13 (0.78-1.63)	0.52
Heart failure	**1.76 (1.27-2.42)**	**0.001**	**1.45 (1.00-2.09)**	**0.05**	**1.46 (1.02-2.11)**	**0.04**
Diabetes	**1.37 (1.01-1.86)**	**0.042**	1.15 (0.80-1.65)	0.45	1.14 (0.79-1.63)	0.49
Vascular disease	**2.17 (1.61-2.93)**	**<0.001**	**1.64 (1.12-2.38)**	**0.01**	**1.62 (1.11-2.34)**	**0.01**
Kidney disease	1.05 (0.80-1.38)	0.71	0.93 (0.67-1.28)	0.64	0.94 (0.68-1.29)	0.68
Anaemia	**1.64 (1.17-2.30)**	**0.004**	1.26 (0.80-1.96)	0.32	1.23 (0.79-1.96)	0.36
Bleeding history	1.09 (0.65-1.81)	0.75	1.17 (0.66-2.06)	0.50	1.18 (0.67-2.09)	0.56
TTR (continuous)	**0.98 (0.97-0.99)**	**<0.001**	**0.99 (0.98-0.99)**	**0.01**	**-**	
TTR <70%	**1.61 (1.23-2.12)**	**0.001**	-		1.38 (1.00-1.89)	**0.05**
PINRR (continuous)	**0.97 (0.96-0.98)**	**<0.001**	-		-	
PINRR <70%	**2.31 (1.42-3.74)**	**0.001**	-		-	

*TTR continuous; # TTR categorical

¥continuous variable

Table A4.7: Cox proportional hazard regression analysis for all-cause mortality

	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age[¥]	1.09 (1.03-1.14)	**0.001**	1.06 (0.99-1.13)	0.07
Female sex	0.66 (0.27-1.61)	0.36	0.86 (0.26-2.86)	0.81
Smoking history	2.13 (0.73-6.24)	0.17	2.87 (0.86-9.52)	0.09
Ethnicity (non- white)	0.78 (0.23-2.63)	0.69	1.19 (0.25- 5.79)	0.83
Hypertension	1.49 (0.51-4.39)	0.47	3.05 (0.39- 24.06)	0.29
Stroke/TIA history	1.65 (0.65-4.18)	0.29	1.72 (0.52-5.69)	0.38
Heart failure	0.94 (0.28-3.18)	0.93	0.99 (0.21-4.59)	0.99
Diabetes	0.94 (0.32-2.76)	0.91	0.65 (0.13-3.21)	0.59
Vascular disease	1.30 (0.44-3.82)	0.64	1.05 (0.26-4.15)	0.95
Kidney disease	1.30 (0.56-3.02)	0.54	1.43 (0.48-4.21)	0.52
Anaemia	**2.86 (1.13-7.27)**	**0.027**	3.39 (0.92-12.52)	0.07
Bleeding history	1.68 (0.39-7.21)	0.48	0.60 (0.07-5.34)	0.65
TTR (continuous)	0.98 (0.95-1.01)	0.13	0.98 (0.94-1.01)	0.20
TTR <70%	1.79 (0.73-4.41)	0.21	-	
PINRR (continuous)	0.97 (0.93-1.01)	0.13	-	
PINRR <70%	1.39 (0.41-4.69)	0.60	-	

[¥]continuous variable

Table A4.8: Cox proportional hazard regression analysis for composite outcome of thromboembolic events, major bleed and clinically relevant non-major bleeding, cardiovascular hospitalisation and all-cause mortality (incorporating TTR as continuous and categorical variables separately)

	Univariate HR (95% CI)	p-value	Multivariate* HR (95% CI) (Model 1)	p-value	Multivariate† HR (95% CI) (Model 2)	p-value
Age¥	1.0 (0.99-1.01)	0.91	0.99 (0.98-1.00)	0.17	0.99 (0.98-1.00)	0.20
Female sex	0.92 (0.74-1.15)	0.48	0.93 (0.71-1.22)	0.62	0.91 (0.70-1.20)	0.51
Smoking history	0.81 (0.63-1.03)	0.09	0.79 (0.60-1.04)	0.09	0.79 (0.60-1.04)	0.09
Ethnicity (non- white)	**1.47 (1.13-1.91)**	**0.004**	1.15 (0.83-1.59)	0.40	1.20 (0.87-1.65)	0.26
Hypertension	**1.36 (1.02-1.81)**	**0.035**	1.09 (0.78-1.52)	0.61	1.06 (0.76-1.48)	0.72
Stroke/TIA history	**1.39 (1.07-1.80)**	**0.014**	**1.39 (1.03-1.86)**	**0.03**	**1.38 (1.03-1.85)**	**0.03**
Heart failure	**1.51 (1.14-1.99)**	**0.004**	1.28 (0.93-1.76)	0.13	1.30 (0.94-1.78)	0.11
Diabetes	**1.41 (1.10-1.82)**	**0.008**	1.24 (0.92-1.67)	0.16	1.22 (0.91-1.65)	0.19
Vascular disease	**1.93 (1.49-2.50)**	**<0.001**	**1.69 (1.23-2.33)**	**0.001**	**1.67 (1.21-2.30)**	**0.002**
Kidney disease	1.18 (0.95-1.48)	0.14	0.99 (0.76-1.30)	0.96	1.00 (0.76-1.31)	0.99
Anaemia	**1.69 (1.27-2.24)**	**<0.001**	1.32 (0.91-1.91)	0.14	1.28 (0.88-1.85)	0.20
Bleeding history	1.32 (0.89-1.96)	0.17	1.25 (0.78-1.99)	0.35	1.26 (0.79-2.01)	0.33
TTR (continuous)	**0.98 (0.98-0.99)**	**<0.001**	**0.99 (0.98-0.99)**	**0.001**	-	
TTR <70%	**1.54 (1.23-1.92)**	**<0.001**	-		**1.45 (1.11-1.89)**	**0.006**
PINRR (continuous)	**0.97 (0.96-0.98)**	**<0.001**	-		-	
PINRR <70%	**1.99 (1.37-2.88)**	**<0.001**	-		-	

*This model considers TTR as continuous variable; † This model considers TTR as categorical variable

¥continuous variable

Table A4.9: Cox proportional hazard regression analysis for all bleeding events, including major bleeding and clinically relevant non-major bleeding including age ≥80 years

	Univariate		Multivariate	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age ≥80 years	**1.93 (1.16-3.20)**	**0.01**	**1.90 (1.01-3.56)**	**0.047**
Female sex	0.92 (0.58-1.45)	0.71	0.82 (0.47-1.44)	0.49
Smoking history	0.86 (0.51-1.45)	0.57	0.91 (0.51-1.61)	0.75
Ethnicity (non- white)	1.13 (0.64-2.02)	0.67	1.01 (0.49-2.05	0.98
Hypertension	1.31 (0.73-2.33)	0.37	1.54 (0.72-3.31)	0.27
Stroke/TIA history	1.10 (0.63-1.93)	0.74	1.09 (0.56-2.13)	0.80
Heart failure	1.38 (0.78-2.47)	0.27	1.71 (0.91-3.24)	0.10
Diabetes	1.18 (0.69-2.02)	0.54	0.93 (0.47-1.84)	0.84
Vascular disease	0.97 (0.51-1.83)	0.92	0.78 (0.35-1.77)	0.56
Kidney disease	0.92 (0.57-1.47)	0.73	0.65 (0.36-1.17)	0.15
Anaemia	1.46 (0.80-2.65)	0.22	1.67 (0.78-3.61)	0.19
Bleeding history	1.48 (0.68-3.23)	0.32	0.99 (0.37-2.64)	0.99
Concomitant antiplatelet therapy	1.47 (0.54-4.03)	0.45	0.92 (0.21-44.06)	0.91
TTR <70%	1.52 (0.95-2.42)	0.08	1.74 (0.99-3.05)	0.055

CI: confidence interval; HR: hazard ratio; TIA: transient ischemic attack; TTR: time in therapeutic range

Table A4.10: Cox- proportional hazard regression analysis for composite endpoints of thromboembolic event, bleeding event, cardiovascular hospitalisation and all-cause mortality including age ≥80 years

	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age ≥80	1.10 (0.84-1.45)	0.50	1.00 (0.72-1.39)	0.99
Female sex	0.92 (0.74-1.15)	0.48	0.90 (0.69-1.18)	0.45
Smoking history	0.81 (0.63-1.03)	0.09	0.82 (0.62-1.07)	0.14
Ethnicity (non- white)	**1.47 (1.13-1.91)**	**0.004**	1.22 (0.89-1.68)	0.22
Hypertension	**1.36 (1.02-1.81)**	**0.04**	1.05 (0.75-1.46)	0.78
Stroke/TIA history	**1.39 (1.07-1.80)**	**0.01**	**1.37 (1.02-1.85)**	**0.04**
Heart failure	**1.51 (1.14-1.99)**	**0.004**	1.32 (0.96-1.82)	0.09
Diabetes	**1.41 (1.10-1.82)**	**0.008**	1.22 (0.91-1.65)	0.19
Vascular disease	**1.93 (1.49-2.50)**	**<0.001**	**1.53 (1.10-2.14)**	**0.01**
Kidney disease	1.18 (0.95-1.48)	0.14	0.96 (0.73-1.25)	0.75
Anaemia	**1.69 (1.27-2.24)**	**<0.001**	1.27 (0.87-1.83)	0.21
Bleeding history	1.32 (0.89-1.96)	0.17	1.25 (0.79-1.99)	0.35
Concomitant antiplatelet therapy	**2.50 (1.67-3.73)**	**<0.001**	1.36 (0.81-2.30)	0.24
TTR <70%	**1.54 (1.22-1.92)**	**<0.001**	**1.47 (1.13-1.91)**	**0.004**

CI: confidence interval; HR: hazard ratio; TIA: transient ischemic attack; TTR: time in therapeutic range

Appendix 5

List of ethical approvals:

Study 1: TREAT-2 study

1. South Birmingham Research Ethics Committee (REC)
2. Health Research Authority (HRA)
3. Confirmation of capacity and capability from Sandwell and West Birmingham Hospitals Research and Development (R&D) department
4. University Hospitals Birmingham (UHB) Research and Development (R&D) department

Study 2 and 3

1. Institutional review from Sandwell and West Birmingham Hospitals Research and Development (R&D) department

References

1. Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. Int J Clin Pract. 2018;72(3):e13070.
2. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11(11):639-54.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-962.
4. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. Circulation. 2013;129(8):837–47.
5. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The Epidemiology of Atrial Fibrillation and Stroke. Cardiol Clin. 2016;34(2):255-68.
6. Stefansdottir H, Aspelund T, Gudnason V, Arnar DO. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. EP Europace. 2011;13(8):1110-7.
7. Lane DA, Skjøth F, Lip GYH, Larsen TB, Kotecha D. Temporal Trends in Incidence, Prevalence, and Mortality of Atrial Fibrillation in Primary Care. J Am Heart Assoc. 2017;6(5).
8. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of Current and Future Incidence and Prevalence of Atrial Fibrillation in the U.S. Adult Population. Am J Cardiol. 2013;112(8):1142-7.
9. Shavadia J, Yonga G, Mwanzi S, Jinah A, Moriasi A, Otieno H. Clinical characteristics and outcomes of atrial fibrillation and flutter at the Aga Khan University Hospital, Nairobi. Cardiovasc J Afr. 2013;24(2):6-9.
10. Bai Y, Wang YL, Shantsila A, Lip GYH. The Global Burden of Atrial Fibrillation and Stroke: A Systematic Review of the Clinical Epidemiology of Atrial Fibrillation in Asia. Chest. 2017;152(4):810–20.
11. Kang S-H, Choi E-K, Han K-D, Lee S-R, Lim W-H, Cha M-J, et al. Underweight is a risk factor for atrial fibrillation: A nationwide population-based study. Int J Cardiol. 2016;215:449-56.
12. Li L-H, Sheng C-S, Hu B-C, Huang Q-F, Zeng W-F, Li G-L, et al. The prevalence, incidence, management and risks of atrial fibrillation in an elderly Chinese population: a prospective study. BMC Cardiovasc Disord. 2015;15:31.

13. Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. Chest. 2015;147(1):109-19.
14. Sano F, Ohira T, Kitamura A, Imano H, Cui R, Kiyama M, et al. Heavy Alcohol Consumption and Risk of Atrial Fibrillation: The Circulatory Risk in Communities Study (CIRCS). Circ J. 2014;78(4):955-61.
15. Chuang SY, Wu CC, Hsu PF, Chia-Yu Chen R, Liu WL, Hsu YY, et al. Hyperuricemia and incident atrial fibrillation in a normotensive elderly population in Taiwan. Nutr Metab Cardiovasc Dis. 2014;24(9):1020-6.
16. Suzuki S, Sagara K, Otsuka T, Kano H, Matsuno S, Takai H, et al. Usefulness of Frequent Supraventricular Extrasystoles and a High CHADS2 Score to Predict First-Time Appearance of Atrial Fibrillation. Am J Cardiol. 2013;111(11):1602-7.
17. Chao T-F, Hung C-L, Chen S-J, Wang K-L, Chen T-J, Lin Y-J, et al. The association between hyperuricemia, left atrial size and new-onset atrial fibrillation. Int J Cardiol. 2013;168(4):4027-32.
18. Rhee CW, Lee J, Oh S, Choi NK, Park BJ. Use of bisphosphonate and risk of atrial fibrillation in older women with osteoporosis. Osteoporos Int. 2012;23(1):247-54.
19. Watanabe H, Tanabe N, Yagihara N, Watanabe T, Aizawa Y, Kodama M. Association Between Lipid Profile and Risk of Atrial FibrillatioN: Niigata Preventive Medicine Study. Circ J. 2011;75(12):2767-74.
20. Iguchi Y, Kimura K, Shibazaki K, Aoki J, Kobayashi K, Sakai K, et al. Annual Incidence of Atrial Fibrillation and Related Factors in Adults. Am J Cardiol. 2010;106(8):1129-33.
21. Sliwa K, Carrington MJ, Klug E, Opie L, Lee G, Ball J, et al. Predisposing factors and incidence of newly diagnosed atrial fibrillation in an urban African community: insights from the Heart of Soweto Study. Heart. 2010;96(23):1878.
22. Kamel H, Kleindorfer DO, Bhave PD, Cushman M, Levitan EB, Howard G, et al. Rates of Atrial Fibrillation in Black Versus White Patients With Pacemakers. J Am Heart Assoc. 2016;5(2).
23. Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. J Electrocardiol. 2008;41(2):94-8.
24. Phrommintikul A, Detnuntarat P, Prasertwitayakij N, Wongcharoen W. Prevalence of atrial fibrillation in Thai elderly. J Geriatr Cardiol. 2016;13(3):270-3.
25. Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. Med J Aust. 2015;202(1):32-5.

26. Sturm JW, Davis SM, O'Sullivan JG, Vedadhaghi ME, Donnan GA. The Avoid Stroke as Soon as Possible (ASAP) general practice stroke audit. Med J Aust. 2002;176(7):312-6.
27. Quality and Outcomes Framework-Prevalence, Achievements and Exceptions Report. 2014-2015. Health & Social Care Information Centre.
28. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing Prevalence of Atrial Fibrillation and Flutter in the United States. Am J Cardiol. 2009;104(11):1534-9.
29. Marcolino MS, Palhares DMF, Benjamin EJ, Ribeiro AL. Atrial fibrillation: prevalence in a large database of primary care patients in Brazil. EP Europace. 2015;17(12):1787-90.
30. Sriharibabu M, Himabindu Y, Kabir Z. Rheumatic heart disease in rural south India: A clinico-observational study. J Cardiovasc Dis Res. 2013;4(1):25-9.
31. White E. Ethnicity and National Identity in England and Wales: 2011. Office for National Statistics.
32. Nybo MS, Skov J. Patient knowledge of anticoagulant treatment does not correlate with treatment quality. Public Health. 2016;141(Supplement C):17-22.
33. Lau C-P, Gbadebo TD, Connolly SJ, Van Gelder IC, Capucci A, Gold MR, et al. Ethnic Differences in Atrial Fibrillation Identified Using Implanted Cardiac Devices. J Cardiovasc Electrophysiol. 2013;24(4):381-7.
34. Lahiri MK, Fang K, Lamerato L, Khan AM, Schuger CD. Effect of Race on the Frequency of Postoperative Atrial Fibrillation Following Coronary Artery Bypass Grafting. Am J Cardiol. 2011;107(3):383-6.
35. Yuh-Jer Shen A, Contreras R, Sobnosky S, Shah AI, Ichiuji AM, Jorgensen MB, et al. Racial/Ethnic Differences in the Prevalence of Atrial Fibrillation Among Older Adults—A Cross-Sectional Study. J Natl Med Assoc. 2010;102(10):906-14.
36. Marcus GM, Alonso A, Peralta CA, Lettre G, Vittinghoff E, Lubitz SA, et al. European ancestry as a risk factor for atrial fibrillation in African Americans. Circulation. 2010;122(20):2009-15.
37. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, et al. Incidence of atrial fibrillation in whites and African-Americans: The Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009;158(1):111-7.
38. Michael Smith J, Soneson EA, Woods SE, Engel AM, Hiratzka LF. Coronary artery bypass graft surgery outcomes among African-Americans and Caucasian patients. Int J Surg. 2006;4(4):212-6.
39. Ruo B, Capra AM, Jensvold NG, Go AS. Racial variation in the prevalence of atrial fibrillation among patients with heart failure. J Am Coll Cardiol. 2004;43(3):429-35.
40. Upshaw CB. Reduced prevalence of atrial fibrillation in black patients compared with white patients attending an urban hospital: an electrocardiographic study. J Natl Med Assoc. 2002;94(4):204-8.

41. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (atria) study. JAMA. 2001;285(18):2370-5.
42. Afzal A, Ananthasubramaniam K, Sharma N, Ai-Malki Q, Ali AS, Jacobsen G, et al. Racial differences in patients with heart failure. Clin Cardiol. 1999;22(12):791-4.
43. Winkelmayer WC, Patrick AR, Liu J, Brookhart MA, Setoguchi S. The increasing prevalence of atrial fibrillation among hemodialysis patients. J Am Soc Nephrol. 2011;22(2):349-57.
44. Hernandez MB, Asher CR, Hernandez AV, Novaro GM. African American Race and Prevalence of Atrial Fibrillation:A Meta-Analysis. Cardiol Res Pract. 2012;2012:275624.
45. Zubaid M, Rashed WA, Alsheikh-Ali AA, AlMahmeed W, Shehab A, Sulaiman K, et al. Gulf Survey of Atrial Fibrillation Events (Gulf SAFE). Circ Cardiovasc Qual Outcomes. 2011;4(4):477.
46. Maru M. Atrial fibrillation and embolic complications. East Afr Med J. 1997;74(1):3-5.
47. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in Cause and Management of Atrial Fibrillation in a Prospective Registry of 15 400 Emergency Department Patients in 46 Countries. The RE-LY Atrial Fibrillation Registry. Circulation. 2014;129(15):1568.
48. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of Atrial Fibrillation to Incidence and Outcome of Ischemic Stroke. Stroke. 2005;36(6):1115.
49. Rizos T, Wagner A, Jenetzky E, Ringleb PA, Becker R, Hacke W, et al. Paroxysmal Atrial Fibrillation Is More Prevalent than Persistent Atrial Fibrillation in Acute Stroke and Transient Ischemic Attack Patients. Cerebrovasc Dis. 2011;32(3):276-82.
50. Hanchate AD, Schwamm LH, Huang W-J, Hylek E. Comparison of Ischemic Stroke Outcomes and, Patient and Hospital Characteristics by Race/Ethnicity and Socioeconomic Status. Stroke. 2013;44(2):469-76.
51. Gattellari M, Goumas C, Aitken R, Worthington JM. Outcomes for patients with ischaemic stroke and atrial fibrillation: the PRISM study (A Program of Research Informing Stroke Management). Cerebrovasc Dis. 2011;32(4):370-82.
52. Gao Q, Fu X, Wei JW, Chen X, Huang Y, Wang J, et al. Use of oral anticoagulation among stroke patients with atrial fibrillation in China: the ChinaQUEST (Quality evaluation of stroke care and treatment) registry study. Int J Stroke. 2013;8(3):150-4.
53. Thakkar S, Bagarhatta R. Detection of paroxysmal atrial fibrillation or flutter in patients with acute ischemic stroke or transient ischemic attack by Holter monitoring. Indian Heart J. 2014;66(2):188-92.
54. Mahajan SK, Kashyap R, Sood BR, Jaret P, Mokta J, Kaushik NK, et al. Stroke at moderate altitude. J Assoc Physicians India. 2004;52:699-702.

55. Tagawa M, Takeuchi S, Chinushi M, Saeki M, Taniguchi Y, Nakamura Y, et al. Evaluating patients with acute ischemic stroke with special reference to newly developed atrial fibrillation in cerebral embolism. Pacing Clin Electrophysiol. 2007;30(9):1121-8.
56. Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2015;14(4):377-87.
57. Mairesse G, Moran P, Van Gelder I, Elsner C, Rosenqvist M, Mant J, et al. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE). Europace. 2017;0:1-35.
58. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. J Am Coll Cardiol. 2006;48(4):e149.
59. Cottrell C. Atrial fibrillation part 1: pathophysiology. Practice Nursing. 2012;23(1):16-21.
60. Di Minno MN, Ambrosino P, Dello Russo A, Casella M, Tremoli E, Tondo C. Prevalence of left atrial thrombus in patients with non-valvular atrial fibrillation. A systematic review and meta-analysis of the literature. Thromb Haemost. 2016;115(3):663-77.
61. Christensen LM, Krieger DW, Hojberg S, Pedersen OD, Karlsen FM, Jacobsen MD, et al. Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. Eur J Neurol. 2014;21(6):884-9.
62. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009;2(5):474-80.
63. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. Eur Heart J. 2014;36(5):281-8.
64. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, et al. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. Eur Heart J. 2014;36(5):288-96.
65. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. Eur Heart J. 2009;31(8):967-75.
66. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. Health Technol Assess. 2005;9(40):iii-iv, ix-x, 1-74.

67. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost. 2013;110(2):213-22.
68. Cooke G, Doust J, Sanders S. Is pulse palpation helpful in detecting atrial fibrillation? A systematic review. J Fam Pract. 2006;55(2):130-4.
69. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, et al. Screening for Atrial Fibrillation. Circulation. 2017;135(19):1851-67.
70. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370(26):2478-86.
71. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. Stroke. 1997;28(2):316-21.
72. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370(26):2467-77.
73. Stollberger C, Chnupa P, Abzieher C, Langer T, Finsterer J, Klem I, et al. Mortality and rate of stroke or embolism in atrial fibrillation during long-term follow-up in the embolism in left atrial thrombi (ELAT) study. Clin Cardiol. 2004;27(1):40-6.
74. Cabin HS, Clubb Ks Fau - Hall C, Hall C Fau - Perlmutter RA, Perlmutter Ra Fau - Feinstein AR, Feinstein AR. Risk for systemic embolization of atrial fibrillation without mitral stenosis. Am J Cardiol. 1990;1(65 (16)):1112-6.
75. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. Eur Heart J. 2016;37(20):1591-602.
76. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: The framingham heart study. JAMA. 1994;271(11):840-4.
77. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. The Lancet. 2015;386(9989):154-62.
78. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. 2012;345:e7895.
79. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J. 2003;21(6):1012-6.
80. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, et al. Association of Chronic Kidney Disease With Atrial Fibrillation Among Adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol. 2011;4(1):26.

81. Chamberlain AM, Agarwal SK, Folsom AR, Duval S, Soliman EZ, Ambrose M, et al. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. Heart Rhythm. 2011;8(8):1160-6.
82. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. J Am Coll Cardiol. 2014;64(3):281-9.
83. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. Ann Intern Med. 2014;160(11):760-73.
84. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate control management. Postgrad Med J. 2009;85(1004):303-12.
85. Tamariz LJ, Bass EB. Pharmacological rate control of atrial fibrillation. Cardiol Clin. 2004;22(1):35-45.
86. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, et al. The evidence regarding the drugs used for ventricular rate control. J Fam Pract. 2000;49(1):47-59.
87. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. Pacing Clin Electrophysiol. 2013;36(1):122-33.
88. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358(25):2667-77.
89. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. Arch Intern Med. 2005;165(3):258-62.
90. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017;14(11):627-8.
91. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GYH. Risk Factors for Stroke and Thromboembolism in Relation to Age Among Patients With Atrial Fibrillation. Chest. 2012;141(1):147-53.
92. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. Arch Intern Med. 1998;158(12):1316-20.
93. Patel D, Mc Conkey ND, Sohaney R, Mc Neil A, Jedrzejczyk A, Armaganijan L. A systematic review of depression and anxiety in patients with atrial fibrillation: the mind-heart link. Cardiovasc Psychiatry Neurol. 2013;2013.
94. Polikandrioti M, Koutelekos I, Vasilopoulos G, Gerogianni G, Gourni M, Zyga S, et al. Anxiety and Depression in Patients with Permanent Atrial Fibrillation: Prevalence and Associated Factors. Cardiol Res Pract. 2018;2018.
95. Dąbrowski R, Smolis-Bąk E, Kowalik I, Kazimierska B, Wójcicka M, Szwed H. Quality of life and depression in patients with different patterns of atrial fibrillation. Kardiol Pol. 2010;68(10):1133-9.

96. Thrall G, Lip GYH, Carroll D, Lane D. Depression, Anxiety, and Quality of Life in Patients With Atrial Fibrillation. Chest. 2007;132(4):1259-64.
97. Frasure-Smith N, Lespérance F, Habra M, Talajic M, Khairy P, Dorian P, et al. Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure. Circulation. 2009;120(2):134-40.
98. Ong L, Irvine J, Nolan R, Cribbie R, Harris L, Newman D, et al. Gender differences and quality of life in atrial fibrillation: the mediating role of depression. J Psychosom Res. 2006;61(6):769-74.
99. Lane DA, Langman CM, Lip GYH, Nouwen A. Illness perceptions, affective response, and health-related quality of life in patients with atrial fibrillation. J Psychosom Res. 2009;66(3):203-10.
100. Wożakowska-Kapłon B, Opolski G, Kosior D, Jaskulska-Niedziela E, Maroszyńska-Dmoch E, Włosowicz M. Cognitive disorders in elderly patients with permanent atrial fibrillation. Kardiol Pol. 2009;67(5):487-93.
101. Chatap G, Giraud K, Vincent J-P. Atrial fibrillation in the elderly. Drugs Aging. 2002;19(11):819-46.
102. Prasun MA. Providing best practice in the management of atrial fibrillation in the United States. J Cardiovasc Nurs. 2012;27(5):445-56.
103. McCabe PJ. What patients want and need to know about atrial fibrillation. J Multidiscip Healthc. 2011;4:413-9.
104. Trovato G, Pace P, Cangemi E, Martines G, Trovato F, Catalano D. Gender, lifestyles, illness perception and stress in stable atrial fibrillation. La Clinica Terapeutica. 2012;163(4):281-6.
105. Tailachidis P, Tsimtsiou Z, Galanis P, Theodorou M, Kouvelas D, Athanasakis K. The Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire: cultural adaptation and validation of the Greek version. Hippokratia. 2016;20(4):264-7.
106. von Eisenhart Rothe A, Hutt F, Baumert J, Breithardt G, Goette A, Kirchhof P, et al. Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation patients: a longitudinal analysis--data from the German Competence Network on Atrial Fibrillation. Europace. 2015;17(9):1354-62.
107. Thompson TS, Barksdale DJ, Sears SF, Mounsey JP, Pursell I, Gehi AK. The effect of anxiety and depression on symptoms attributed to atrial fibrillation. Pacing Clin Electrophysiol. 2014;37(4):439-46.
108. McCabe PJ. Psychological distress in patients diagnosed with atrial fibrillation: the state of the science. J Cardiovasc Nurs. 2010;25(1):40-51.

109. de Queiroz Almeida G, de ACB Noblat L, Passos LCS, do Nascimento HF. Quality of life analysis of patients in chronic use of oral anticoagulant: an observational study. Health Qual Life Outcomes. 2011;9(1):91.
110. Ynsaurriaga FA, Peinado RP, Ormaetxe Merodio JM. Atrial fibrillation and quality of life related to disease and treatment: focus on anticoagulation. Future Cardiol. 2014;10(3):381-93.
111. Diana M-P, Consuelo R-A, Paz A-M, Pia L-J. Analysis of General and Oral Quality of Life and Satisfaction with Treatment among Anticoagulated Patients. Int J Dent Hyg. 2015;1(5):11-7.
112. Corbi IS, Dantas RA, Pelegrino FM, Carvalho AR. Health related quality of life of patients undergoing oral anticoagulation therapy. Rev Lat Am Enfermagem. 2011;19(4):865-73.
113. Casais P, Meschengieser S, Sanchez-Luceros A, Lazzari M. Patients' perceptions regarding oral anticoagulation therapy and its effect on quality of life. Curr Med Res Opin. 2005;21(7):1085-90.
114. Esra Yildiz PhD RN, Nuray Dayapoglu PhD RN. The Satisfaction Levels of Patients Using Anticoagulants. Int J Car Sci. 2017;10(1):568.
115. Matalqah LM, Radaideh K. Health-Related Quality of Life among Atrial fibrillation Patients Undergoing Anticoagulation Therapy. Epidemiol Biostat Public Health. 2018;15(1).
116. Balcı KG, Balcı MM, Canpolat U, Şen F, Akboğa MK, Süleymanoğlu M, et al. Comparison of health-related quality of life among patients using novel oral anticoagulants or warfarin for non-valvular atrial fibrillation. Anatol J Cardiol. 2016;16(7):474.
117. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857-67.
118. Wallentin L, Lopes RD, Hanna M, Thomas L, Hellkamp A, Nepal S, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. Circulation. 2013;127(22):2166-76.
119. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa T-P. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost. 2011;106(5):968.
120. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation Control and Prediction of Adverse Events in Patients With Atrial Fibrillation. Circ Cardiovasc Qual Outcomes. 2008;1(2):84-91.
121. Lip GYH, Al-Saady N, Jin J, Sun M, Melino M, Winters SM, et al. Anticoagulation Control in Warfarin-Treated Patients Undergoing Cardioversion of Atrial Fibrillation (from the

Edoxaban Versus Enoxaparin–Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation Trial). Am J Cardiol. 2017;120(5):792-6.
122. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. Thromb Res. 2009;124(1):37-41.
123. Petersen P, Godtfredsen J, Boysen G, Andersen E, Andersen Br. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. Lancet. 1989;333(8631):175-9.
124. Peterson P, Boysen G. Prevention of stroke in atrial fibrillation. N Engl J Med. 1990;323(482).
125. The Effect of Low-Dose Warfarin on the Risk of Stroke in Patients with Nonrheumatic Atrial Fibrillation. N Engl J Med. 1990;323(22):1505-11.
126. Stroke prevention in atrial fibrillation study: final results. Circulation. 1991;84(2):527-39.
127. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian atrial fibrillation anticoaguiation (CAFA) study. J Am Coll Cardiol. 1991;18(2):349-55.
128. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med. 1992;327(20):1406-12.
129. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993;342(8882):1255-62.
130. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.
131. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: Current status and perspectives (Section III). Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;110(12):1087-107.
132. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2009;361(12):1139-51.
133. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 2011;365(10):883-91.
134. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2011;365(11):981-92.

135. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2013;369(22):2093-104.
136. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GY. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke. 2017;48(9):2494-503.
137. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology. 2007;69(6):546-54.
138. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. Circ J. 2012;76(10):2289-304.
139. Wagstaff A, Overvad TF, Lip G, Lane D. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. QJM. 2014;107(12):955-67.
140. Mikkelsen A, Lindhardsen J, Lip G, Gislason G, Torp-Pedersen C, Olesen J. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. J Thromb Haemost. 2012;10(9):1745-51.
141. Lip GH, Lane DA. Stroke prevention in atrial fibrillation: A systematic review. JAMA. 2015;313(19):1950-62.
142. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female Sex Is a Risk Modifier Rather Than a Risk Factor for Stroke in Atrial Fibrillation. Circulation. 2018;137(8):832.
143. Lehto M, Snapinn S, Dickstein K, Swedberg K, Nieminen MS, investigators O. Prognostic risk of atrial fibrillation in acute myocardial infarction complicated by left ventricular dysfunction: the OPTIMAAL experience. Eur Heart J. 2004;26(4):350-6.
144. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342:d124.
145. Banerjee A, Taillandier S, Olesen Jonas B, Lane Deirdre A, Lallemand B, Lip Gregory YH, et al. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project. Eur J Heart Fail. 2014;14(3):295-301.
146. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.
147. Lip GYH, Frison L, Halperin JL, Lane DA. Identifying Patients at High Risk for Stroke Despite Anticoagulation. Stroke. 2010;41(12):2731.

148. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GYH. A comparison of risk stratification schemes for stroke in 79 884 atrial fibrillation patients in general practice. J Thromb Haemost. 2011;9(1):39-48.
149. Poli D, Lip Gregory YH, Antonucci E, Grifoni E, Lane D. Stroke Risk Stratification in a "Real-World" Elderly Anticoagulated Atrial Fibrillation Population. J Cardiovasc Electrophysiol. 2011;22(1):25-30.
150. Siu C-W, Lip GY, Lam K-F, Tse H-F. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. Heart Rhythm. 2014;11(8):1401-8.
151. Guo Y, Apostolakis S, Blann AD, Wang H, Zhao X, Zhang Y, et al. Validation of contemporary stroke and bleeding risk stratification scores in non-anticoagulated Chinese patients with atrial fibrillation. Int J Cardiol. 2013;168(2):904-9.
152. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449-57.
153. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors Associated With Ischemic Stroke During Aspirin Therapy in Atrial Fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. Stroke. 1999;30(6):1223.
154. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-70.
155. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA. 2003;290(8):1049-56.
156. van Walraven C, Hart RG, Wells GA, Petersen P, Koudstaal PJ, Gullov AL, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. Arch Intern Med. 2003;163(8):936-43.
157. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age> 75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J. 2008;156(1):57-64.
158. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. BMJ. 2013;346:f2573.
159. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Assoc. 2013;2(3):e000250.

160. Japanese Circulation Society Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circ J. 2014;78(8):1997-2021.
161. Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, et al. 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2014;30(10):1114-30.
162. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, et al. Cardiac Biomarkers are Associated with an Increased Risk of Stroke and Death in Patients with Atrial Fibrillation: A RELY Substudy. Circulation. 2012;125(13):1605-16.
163. Conway DSG, Pearce LA, Chin BSP, Hart RG, Lip GYH. Prognostic Value of Plasma von Willebrand Factor and Soluble P-Selectin as Indices of Endothelial Damage and Platelet Activation in 994 Patients With Nonvalvular Atrial Fibrillation. Circulation. 2003;107(25):3141.
164. Lip GYH, Lane D, Van Walraven C, Hart RG. Additive Role of Plasma von Willebrand Factor Levels to Clinical Factors for Risk Stratification of Patients With Atrial Fibrillation. Stroke. 2006;37(9):2294.
165. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. Potentially Preventable Strokes in High-Risk Patients With Atrial Fibrillation Who Are Not Adequately Anticoagulated. Stroke. 2009;40(1):235.
166. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of Oral Anticoagulants in Atrial Fibrillation: A Systematic Review. Am J Med. 2010;123(7):638-45.e4.
167. Zhu W-G, Xiong Q-M, Hong K. Meta-analysis of CHADS2 versus CHA2DS2-VASc for predicting stroke and thromboembolism in atrial fibrillation patients independent of anticoagulation. Tex Heart Inst J. 2015;42(1):6-15.
168. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0–1: a nationwide cohort study. Thromb Haemost. 2012;108(06):1172-9.
169. Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation–friend or foe? Thromb Haemost. 2010;104(01):45-8.
170. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Conti JB, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1-e76.
171. Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T, et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythm. 2017;33(4):345-67.
172. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL, et al. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2016;32(10):1170-85.

173. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC guideline for the management of atrial fibrillation. Eur Heart J. 2012;33(21):2719-47.
174. Ogawa S, Aonuma K, Tse HF, Huang D, Huang JL, Kalman J, et al. The APHRS's 2013 statement on antithrombotic therapy of patients with nonvalvular atrial fibrillation. J Arrhythm. 2013;29(3):190-200.
175. National Institute for Clinical Excellence (2006) Atrial Fibrillation: Management. NICE Guideline
176. Zulkifly H, Lip GYH, Lane DA. Bleeding Risk Scores in Atrial Fibrillation and Venous Thromboembolism. Am J Cardiol. 2017;120(7):1139-45.
177. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet. 2016;387(10035):2302-11.
178. Brien ECO, Simon DN, Singer DE, Thomas LE, Hylek EM, Gersh B, et al. The ORBIT Bleeding Score : A Simple Score to Assess Major Bleeding Risk in Atrial Fibrillation The ORBIT-AF Registry. Eur Heart J. 2015;36(46):3258-64.
179. Fang MC, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A New Risk Scheme to Predict Warfarin-Associated Hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395-401.
180. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.
181. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151(3):713-9.
182. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. DEvelopment of a contemporary bleeding risk model for elderly warfarin recipients*. Chest. 2006;130(5):1390-6.
183. Sanders GD, Lowenstern A, Borre E, Chatterjee R, Goode A, Sharan L, et al. Stroke Prevention in Patients With Atrial Fibrillation: A Systematic Review Update. Comparative Effectiveness Review No. 214. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2015-00004-I for AHRQ and PCORI.) 2018.
184. Lowenstern A, Al-Khatib SM, Sharan L, Chatterjee R, Allen LaPointe NM, Shah B, et al. Interventions for Preventing Thromboembolic Events in Patients With Atrial Fibrillation: A Systematic Review. Ann Intern Med. 2018;169(11):774-87.

185. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, et al. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. Thromb Haemost. 2018;118(12):2171-87.
186. Donzé J, Rodondi N, Waeber G, Monney P. Scores to Predict Major Bleeding Risk During Oral Anticoagulation Therapy : A Prospective Validation Study. Am J Med. 2012;125(11):1095-102.
187. Landefeld CS, Goldman OL. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med. 1989;87(2):144-52.
188. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin ∗. Am J Med. 1998;105(2):91-9.
189. Zhu W, He W, Guo L, Wang X, Hong K. The HAS-BLED Score for Predicting Major Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis. Clin Cardiol. 2015;38(9):555-61.
190. Senoo K, Proietti M, Lane DA, Lip GY. Evaluation of the HAS-BLED, ATRIA, and ORBIT Bleeding Risk Scores in Patients with Atrial Fibrillation Taking Warfarin. Am J Med. 2016;129(6):600-7.
191. Proietti M, Senoo K, Lane DA, Lip GY. Major Bleeding in Patients with Non-Valvular Atrial Fibrillation: Impact of Time in Therapeutic Range on Contemporary Bleeding Risk Scores. Sci Rep. 2016;6:24376.
192. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GYH. Performance of the HEMORR 2 HAGES , ATRIA , and HAS-BLED Bleeding Risk – Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study. JAC. 2012;60(9):861-7.
193. Senoo K, Lip GY. Predictive abilities of the HAS-BLED and ORBIT bleeding risk scores in non-warfarin anticoagulated atrial fibrillation patients: An ancillary analysis from the AMADEUS trial. Int J Cardiol. 2016;221:379-82.
194. Gorman EW, Perkel D, Dennis D, Yates J, Heidel RE, Wortham D. Validation of the HAS-BLED tool in atrial fibrillation patients receiving rivaroxaban. J Atr Fibrillation. 2016;9(2):16-8.
195. White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: Results from sportif iii and v. Arch Intern Med. 2007;167(3):239-45.
196. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation. N Engl J Med. 2003;349(11):1019-26.

197. Nelson WW, Desai S, Damaraju CV, Lu L, Fields LE, Wildgoose P, et al. International Normalized Ratio Stability in Warfarin-Experienced Patients with Nonvalvular Atrial Fibrillation. Am J Cardiovasc Drugs. 2015;15(3):205-11.
198. Rao SR, Reisman JI, Kressin NR, Berlowitz DR, Ash AS, Ozonoff A, et al. Explaining Racial Disparities in Anticoagulation Control. Am J Med Qual. 2014;30(3):214-22.
199. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: The same-tt2r2 score. Chest. 2013;144(5):1555-63.
200. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). J Thromb Haemost. 2010;8(10):2182-91.
201. Rose AJ, Ozonoff A, Henault LE, Hylek EM. Warfarin for atrial fibrillation in community-based practise. J Thromb Haemost. 2008;6(10):1647-54.
202. Melamed OC, Horowitz G, Elhayany A, Vinker S. Quality of anticoagulation control among patients with atrial fibrillation. Am J Manag Care. 2011;17(3):232-7.
203. Boulanger L, Kim J, Friedman M, Hauch O, Foster T, Menzin J. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. Int J Clin Pract. 2006;60(3):258-64.
204. Williams BA, Evans MA, Honushefsky AM, Berger PB. Clinical Prediction Model for Time in Therapeutic Range While on Warfarin in Newly Diagnosed Atrial Fibrillation. J Am Heart Assoc. 2017;6(10):e006669.
205. Macedo AF, Bell J, McCarron C, Conroy R, Richardson J, Scowcroft A, et al. Determinants of oral anticoagulation control in new warfarin patients: analysis using data from Clinical Practice Research Datalink. Thromb Res. 2015;136(2):250-60.
206. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J. 2011;32(18):2282-9.
207. Dlott JS, George RA, Huang X, Odeh M, Kaufman HW, Ansell J, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation. 2014;129(13):1407-14.
208. White RD, Riggs KW, Ege EJ, Petroski GF, Koerber SM, Flaker G. The effect of the amiodarone–warfarin interaction on anticoagulation quality in a single, high-quality anticoagulation center. Blood Coagul Fibrinolysis. 2016;27(2).
209. Yong C, Azarbal F, Abnousi F, Heidenreich PA, Schmitt S, Fan J, et al. Racial Differences in Quality of Anticoagulation Therapy for Atrial Fibrillation (from the TREAT-AF Study). Am J Cardiol. 2016;117(1):61-8.

210. Golwala H, Jackson LR, 2nd, Simon DN, Piccini JP, Gersh B, Go AS, et al. Racial/ethnic differences in atrial fibrillation symptoms, treatment patterns, and outcomes: Insights from Outcomes Registry for Better Informed Treatment for Atrial Fibrillation Registry. Am Heart J. 2016;174:29-36.
211. Okumura K, Komatsu T, Yamashita T, Okuyama Y, Harada M, Konta Y, et al. Time in the therapeutic range during warfarin therapy in Japanese patients with non-valvular atrial fibrillation. - A multicenter study of its status and infuential factors. Circ J. 2011;75(9):2087-94.
212. Witt DM, Delate T, Clark NP, Martell C, Tran T, Crowther MA, et al. Outcomes and predictors of very stable INR control during chronic anticoagulation therapy. Blood. 2009;114(5):952.
213. Lin KJ, Singer DE, Glynn RJ, Blackley S, Zhou L, Liu J, et al. Prediction Score for Anticoagulation Control Quality Among Older Adults. J Am Heart Assoc. 2017;6(10):e006814.
214. Horne BD, Lenzini PA, Wadelius M, Jorgensen AL, Kimmel SE, Ridker PM, et al. Pharmacogenetic Warfarin Dose Refinements Remain Significantly Influenced by Genetic Factors after One Week of Therapy. Thromb Haemost. 2012;107(2):232-40.
215. Ferder NS, Eby CS, Deych E, Harris JK, Ridker PM, Milligan PE, et al. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. J Thromb Haemost. 2010;8(1):95-100.
216. Dean L. Warfarin Therapy and the Genotypes CYP2C9 and VKORC1. 2012 Mar 8 [Updated 2016 Jun 8]. In: Pratt V, McLeod H, Dean L, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
217. Skov J, Bladbjerg E-M, Leppin A, Jespersen J. The influence of VKORC1 and CYP2C9 gene sequence variants on the stability of maintenance phase warfarin treatment. Thromb Res. 2013;131(2):125-9.
218. Polovina M, Djikic D, Vlajkovic A, Vilotijevic M. Patients' knowledge and perspectives on vitamin K antagonists for stroke prevention in atrial fibrillation: implications for treatment quality. Anatolian J Cardiol. 2017;18(3):239-40.
219. Clarkesmith DE, Pattison HM, Lip GYH, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. PLoS One. 2013;8(9):e74037.
220. Wang Y, Kong MC, Lee LH, Ng HJ, Ko Y. Knowledge, satisfaction, and concerns regarding warfarin therapy and their association with warfarin adherence and anticoagulation control. Thromb Res. 2014;133(4):550-4.
221. Tay KH, Lip GYH, Lane DA. Anticoagulation variability: is it the physician, patient or hospital? J Intern Med. 2009;265(3):303-6.

222. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of Study Setting on Anticoagulation Control. Chest. 2006;129(5):1155-66.
223. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. J Manag Care Pharm. 2009;15(3):244-52.
224. Jurcuţ R, Militaru S, Geavlete O, Drăgotoiu N, Sipoş S, Roşulescu R, et al. Predictive factors for obtaining a correct therapeutic range using antivitamin K anticoagulants: a tertiary center experience of patient adherence to anticoagulant therapy. Patient Prefer Adherence. 2015;9:1271-8.
225. Ababneh MA, Al-Azzam SI, Alzoubi KH, Rababa'h AM. Adherence in outpatients taking warfarin and its effect on anticoagulation control in Jordan. Int J Clin Pharm. 2016;38(4):816-21.
226. Obamiro KO, Chalmers L, Bereznicki LRE. A Summary of the Literature Evaluating Adherence and Persistence with Oral Anticoagulants in Atrial Fibrillation. Am J Cardiovasc Drugs. 2016;16(5):349-63.
227. Yao X, Abraham NS, Alexander GC, Crown W, Montori VM, Sangaralingham LR, et al. Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation. J Am Heart Assoc. 2016;5(2).
228. Manzoor BS, Cheng WH, Lee JC, Uppuluri EM, Nutescu EA. Quality of Pharmacist-Managed Anticoagulation Therapy in Long-Term Ambulatory Settings: A Systematic Review. Ann Pharmacother. 2017:1060028017721241.
229. Zhou S, Sheng XY, Xiang Q, Wang ZN, Zhou Y, Cui YM. Comparing the effectiveness of pharmacist-managed warfarin anticoagulation with other models: a systematic review and meta-analysis. J Clin Pharm Ther. 2016;41(6):602-11.
230. Heu MK, Welborn T, Nagykaldi Z. Clinical Question: In adult patients on warfarin, does-home-self-testing of prothrombin time and/or international normalized ratio provide the same outcomes compared to testing by a home health nurse or in a clinical setting? J Okla State Med Assoc. 2016;109(3):99-100.
231. Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. The Lancet. 2012;379(9813):322-34.
232. Bloomfield HE, Krause A, Greer N, et al. Meta-analysis: Effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. Ann Intern Med. 2011;154(7):472-82.
233. Cressman AM, Macdonald EM, Yao Z, Austin PC, Gomes T, Paterson JM, et al. Socioeconomic status and risk of hemorrhage during warfarin therapy for atrial fibrillation: A population-based study. Am Heart J. 2015;170(1):133-40.

234. Violi F, Lip GY, Pignatelli P, Pastori D. Interaction Between Dietary Vitamin K Intake and Anticoagulation by Vitamin K Antagonists: Is It Really True?: A Systematic Review. Medicine (Baltimore). 2016;95(10):e2895.
235. Ge B, Zhang Z, Zuo Z. Updates on the Clinical Evidenced Herb-Warfarin Interactions. Evid Based Complement Alternat Med. 2014;2014:18.
236. Lai YF, Cheen MH, Lim SH, Yeo FH, Nah SC, Kong MC, et al. The effects of fasting in Muslim patients taking warfarin. J Thromb Haemost. 2014;12(3):349-54.
237. Awiwi MO, Yagli ZA, Elbir F, Aglar AA, Guler E, Vural U. The effects of Ramadan fasting on patients with prosthetic heart valve taking warfarin for anticoagulation. J Saudi Heart Assoc. 2017;29(1):1-6.
238. Gomberg-Maitland M, Wenger NK, Feyzi J, Lengyel M, Volgman AS, Petersen P, et al. Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. Eur Heart J. 2006;27(16):1947-53.
239. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-Analysis of Gender Differences in Residual Stroke Risk and Major Bleeding in Patients With Nonvalvular Atrial Fibrillation Treated With Oral Anticoagulants. Am J Cardiol. 2014;113(3):485-90.
240. Sonuga BO, Hellenberg DA, Cupido CS, Jaeger C. Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. Afr J Prim Health Care Fam Med. 2016;8(1):1032.
241. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major Hemorrhage and Tolerability of Warfarin in the First Year of Therapy Among Elderly Patients With Atrial Fibrillation. Circulation. 2007;115(21):2689.
242. Lip GYH, Lane DA. Stroke prevention with oral anticoagulation therapy in patients with atrial fibrillation. Circ J. 2013;77(6):1380-8.
243. Pengo V, Cucchini U, Denas G, Davidson BL, Marzot F, Jose SP, et al. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. Thromb Haemost. 2010;103(02):442-9.
244. Pengo V, Legnani C, Noventa F, Palareti G. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A Multicenter Inception Cohort Study. Thromb Haemost. 2001;85(3):418-22.
245. Wolff A, Shantsila E, Lip GYH, Lane DA. Impact of advanced age on management and prognosis in atrial fibrillation: insights from a population-based study in general practice. Age Ageing. 2015;44(5):874-8.
246. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age Ageing. 2011;40(6):675-83.

247. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Bleeding Risk During Oral Anticoagulation in Atrial Fibrillation Patients Older Than 80 Years. J Am Coll Cardiol. 2009;54(11):999.

248. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004;141(10):745-52.

249. Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged >/=75 years with atrial fibrillation: the Loire Valley atrial fibrillation project. Stroke. 2015;46(1):143-50.

250. Mant J, Hobbs FDR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GYH, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. The Lancet. 2007;370(9586):493-503.

251. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age Ageing. 2007;36(2):151-6.

252. Palareti G, Hirsh J, Legnani C, et al. Oral anticoagulation treatment in the elderly: A nested, prospective, case-control study. Arch Intern Med. 2000;160(4):470-8.

253. Kose E, Arai S, An T, Kikkawa A, Aoyama T, Matsumoto Y, et al. Analysis of factors affecting time in therapeutic range control after warfarin administration. Pharmazie. 2015;70(7):494-8.

254. Kim EJ, Ozonoff A, Hylek EM, Berlowitz DR, Ash AS, Miller DR, et al. Predicting outcomes among patients with atrial fibrillation and heart failure receiving anticoagulation with warfarin. Thromb Haemost. 2015;114(1):70-7.

255. Tomita H, Kadokami T, Momii H, Kawamura N, Yoshida M, Inou T, et al. Patient Factors against Stable Control of Warfarin Therapy for Japanese Non-valvular Atrial Fibrillation Patients. Thromb Res. 2013;132(5):537-42.

256. Pignatelli P, Pastori D, Vicario T, Bucci T, Del Ben M, Russo R, et al. Relationship between Mediterranean diet and time in therapeutic range in atrial fibrillation patients taking vitamin K antagonists. EP Europace. 2015;17(8):1223-8.

257. Efird LM, Mishkin DS, Berlowitz DR, Ash AS, Hylek EM, Ozonoff A, et al. Stratifying the Risks of Oral Anticoagulation in Patients With Liver Disease. Circ Cardiovasc Qual Outcomes. 2014;7(3):461-7.

258. Kooistra HAM, Veeger NJGM, Khorsand N, Kluin-Nelemans HC, Meijer K, Piersma-Wichers M. Long-term quality of VKA treatment and clinical outcome after extreme overanticoagulation in 14,777 AF and VTE patients. Thromb Haemost. 2015;113(4):881-90.

259. Paradise HT, Berlowitz DR, Ozonoff A, Miller DR, Hylek EM, Ash AS, et al. Outcomes of Anticoagulation Therapy in Patients with Mental Health Conditions. J Gen Intern Med. 2014;29(6):855-61.
260. Sood MM, Komenda P, Sood AR, Rigatto C, Bueti J. The intersection of risk and benefit: is warfarin anticoagulation suitable for atrial fibrillation in patients on hemodialysis? Chest. 2009;136(4):1128-33.
261. Holden RM, Booth SL. Vascular calcification in chronic kidney disease: the role of vitamin K. Nat Clin Pract Nephrol. 2007;3(10):522.
262. Elliott MJ, Zimmerman D, Holden RM. Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates. Am J Kidney Dis. 2007;50(3):433-40.
263. Szummer K, Gasparini A, Eliasson S, Ärnlöv J, Qureshi AR, Bárány P, et al. Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction. J Am Heart Assoc. 2017;6(3).
264. Proietti M, Lane DA, Lip GYH. Chronic Kidney Disease, Time in Therapeutic Range and Adverse Clinical Outcomes in Anticoagulated Patients with Non-valvular Atrial Fibrillation: Observations from the SPORTIF Trials. EBioMedicine. 2016;8:309-16.
265. Friberg L, Benson L, Lip GYH. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J. 2015;36(5):297-306.
266. Kooiman J, van Rein N, Spaans B, van Beers KAJ, Bank JR, van de Peppel WR, et al. Efficacy and safety of vitamin K-antagonists (VKA) for atrial fibrillation in non-dialysis dependent chronic kidney disease. PLoS One. 2014;9(5):e94420.
267. Kleinow ME, Garwood CL, Clemente JL, Whittaker P. Effect of chronic kidney disease on warfarin management in a pharmacist-managed anticoagulation clinic. J Manag Care Pharm. 2011;17(7):523-30.
268. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol. 2009;20(4):912-21.
269. Esteve-Pastor MA, Rivera-Caravaca JM, Roldán-Rabadán I, Roldán V, Muñiz J, Raña-Míguez P, et al. Relation of renal dysfunction to quality of anticoagulation control in patients with atrial fibrillation: the FANTASIIA registry. Thromb Haemost. 2018;118(02):279-87.
270. Lobos-Bejarano JM, Castellanos Rodriguez A, Barrios V, Escobar C, Polo-Garcia J, Del Castillo-Rodriguez JC, et al. Influence of renal function on anticoagulation control in patients with non-valvular atrial fibrillation taking vitamin K antagonists. Int J Clin Pract. 2017;71(9).

271. Wittkowsky AK, Devine EB. Frequency and Causes of Overanticoagulation and Underanticoagulation in Patients Treated with Warfarin. Pharmacotherapy. 2004;24(10):1311-6.
272. McMahan DA, Smith DM, Carey MA, Zhou XH. Risk of major hemorrhage for outpatients treated with warfarin. J Gen Intern Med. 1998;13(5):311-6.
273. Gong IY, Schwarz UI, Crown N, Dresser GK, Lazo-Langner A, Zou G, et al. Clinical and genetic determinants of warfarin pharmacokinetics and pharmacodynamics during treatment initiation. PLoS One. 2011;6(11):e27808.
274. Dreisbach AW, Japa S, Gebrekal AB, Mowry SE, Lertora JJ, Kamath BL, et al. Cytochrome P4502C9 activity in end-stage renal disease. Clin Pharmacol Ther. 2003;73(5):475-7.
275. Limdi NA, Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, et al. Warfarin Dosing in Patients With Impaired Kidney Function. Am J Kidney Dis. 2010;56(5):823-31.
276. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e44S-e88S.
277. Joint Formulary Comittee. British National Formulary. 74, editor. London: BMJ Group and Pharmaceutical Press; 2017-2018.
278. Angoulvant D, Villejoubert O, Bejan-Angoulvant T, Ivanes F, Saint Etienne C, Lip GYH, et al. Effect of active smoking on comparative efficacy of antithrombotic therapy in patients with atrial fibrillation: The loire valley atrial fibrillation project. Chest. 2015;148(2):491-8.
279. Nathisuwan S, Dilokthornsakul P, Chaiyakunapruk N, Morarai T, Yodting T, Piriyachananusorn N. Assessing evidence of interaction between smoking and warfarin: a systematic review and meta-analysis. Chest. 2011;139(5):1130-9.
280. Lip GY, Waldo AL, Ip J, Martin DT, Bersohn MM, Choucair WK, et al. Determinants of Time in Therapeutic Range in Patients Receiving Oral Anticoagulants (A Substudy of IMPACT). Am J Cardiol. 2016;118(11):1680-4.
281. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Choucair WK, Lip GY, et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. Eur Heart J. 2015;36(26):1660-8.
282. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005;165(10):1095-106.
283. Lane DA, Barker RV, Lip G. Best Practice for Atrial Fibrillation Patient Education. Curr Pharm Des. 2015;21(5):533-43.

284. Lane DA, Ponsford J, Shelley A, Sirpal A, Lip GYH. Patient knowledge and perceptions of atrial fibrillation and anticoagulant therapy: Effects of an educational intervention programme: The West Birmingham Atrial Fibrillation Project. Int J Cardiol. 2006;110(3):354-8.
285. Lip GY, Kamath S, Jafri M, Mohammed A, Bareford D. Ethnic differences in patient perceptions of atrial fibrillation and anticoagulation therapy: The West Birmingham atrial fibrillation project. Stroke. 2002;33.
286. McCabe PJ, Schad S, Hampton A, Holland DE. Knowledge and self-management behaviors of patients with recently detected atrial fibrillation. Heart Lung. 2008;37(2):79-90.
287. Lip GYH, Agnelli G, Thach AA, Knight E, Rost D, Tangelder MJD. Oral anticoagulation in atrial fibrillation: A pan-European patient survey. Eur J Intern Med. 2007;18(3):202-8.
288. Dantas GC, Thompson BV, Manson JA, Tracy CS, Upshur REG. Patients' perspectives on taking warfarin: qualitative study in family practice. BMC Fam Pract. 2004;5(1):15.
289. Nadar S, Begum N, Kaur B, Sandhu S, Lip G. Patients' understanding of anticoagulant therapy in a multiethnic population. J R Soc Med. 2003;96.
290. Fuller R, Dudley N, Blacktop J. Avoidance hierarchies and preferences for anticoagulation--semi-qualitative analysis of older patients' views about stroke prevention and the use of warfarin. Age Ageing. 2004;33(6):608-11.
291. Fuller R, Dudley N, Blacktop J. Risk communication and older people—understanding of probability and risk information by medical inpatients aged 75 years and older. Age Ageing. 2001;30(6):473-6.
292. Hernández Madrid A, Potpara TS, Dagres N, Chen J, Larsen TB, Estner H, et al. Differences in attitude, education, and knowledge about oral anticoagulation therapy among patients with atrial fibrillation in Europe: result of a self-assessment patient survey conducted by the European Heart Rhythm Association. EP Europace. 2016;18(3):463-7.
293. Clarkesmith DE, Pattison HM, Borg Xuereb C, Lane DA. Developing a Complex Educational-Behavioural Intervention: The TREAT Intervention for Patients with Atrial Fibrillation. Healthcare (Basel). 2016;4(1).
294. Clarkesmith DE, Pattison HM, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation. Cochrane Database Syst Rev. 2013(6):CD008600.
295. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. Ann Intern Med. 2000;133(9):687-95.
296. Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. Br J Haematol. 2004;126(4):557-64.

297. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J. 2012;76(9):2104-11.
298. Schulman S, Shortt B, Robinson M, Eikelboom JW. Adherence to anticoagulant treatment with dabigatran in a real-world setting. J Thromb Haemost. 2013;11(7):1295-9.
299. Gorst-Rasmussen A, Skjøth F, Larsen TB, Rasmussen LH, Lip GYH, Lane DA. Dabigatran adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. J Thromb Haemost. 2015;13(4):495-504.
300. Shore S, Carey EP, Turakhia MP, Jackevicius CA, Cunningham F, Pilote L, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. Am Heart J. 2014;167(6):810-7.
301. Beyer-Westendorf J, Ehlken B, Evers T. Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. EP Europace. 2016;18(8):1150-7.
302. Zhou M, Chang H-Y, Segal JB, Alexander GC, Singh S. Adherence to a Novel Oral Anticoagulant Among Patients with Atrial Fibrillation. J Manag Care Spec Pharm. 2015;21(11):1054-62.
303. McHorney CA, Crivera C, Laliberté F, Nelson WW, Germain G, Bookhart B, et al. Adherence to non-vitamin-K-antagonist oral anticoagulant medications based on the Pharmacy Quality Alliance measure. Curr Med Res Opin. 2015;31(12):2167-73.
304. Crivera C, Nelson WW, Bookhart B, Martin S, Germain G, Laliberté F, et al. Pharmacy quality alliance measure: adherence to non-warfarin oral anticoagulant medications. Curr Med Res Opin. 2015;31(10):1889-95.
305. Cutler TW, Chuang A, Huynh TD, Witt RG, Branch J, Pon T, et al. A Retrospective Descriptive Analysis of Patient Adherence to Dabigatran at a Large Academic Medical Center. J Manag Care Pharm. 2014;20(10):1028-34.
306. Tsai K, Erickson SC, Yang J, Harada AS, Solow BK, Lew HC. Adherence, persistence, and switching patterns of dabigatran etexilate. Am J Manag Care. 2013;19(9):e325-32.
307. Davis NJ, Billett HH, Cohen HW, Arnsten JH. Impact of Adherence, Knowledge, and Quality of Life on Anticoagulation Control. Ann Pharmacother. 2005;39(4):632-6.
308. Castellucci LA, Shaw J, van der Salm K, Erkens P, Le Gal G, Petrcich W, et al. Self-reported adherence to anticoagulation and its determinants using the Morisky medication adherence scale. Thromb Res. 2015;136(4):727-31.
309. Kimmel SE, Chen Z, Price M, et al. The influence of patient adherence on anticoagulation control with warfarin: Results from the international normalized ratio adherence and genetics (in-range) study. Arch Intern Med. 2007;167(3):229-35.

310. Gohil KJ, Patel JA. Herb-drug interactions: A review and study based on assessment of clinical case reports in literature. Indian J Pharmacol. 2007;39(3):129.
311. Rindone JP, Murphy TW. Warfarin-cranberry juice interaction resulting in profound hypoprothrombinemia and bleeding. Am J Ther. 2006;13(3):283-4.
312. Jaspers Focks J, van Vugt SPG, Albers-Akkers MTH, Lamfers EJP, Bloem-de Vries LM, Verheugt FWA, et al. Low performance of bleeding risk models in the very elderly with atrial fibrillation using vitamin K antagonists. J Thromb Haemost. 2016;14(9):1715-24.
313. Friberg L, Rosenqvist M, Lip GYH. Net Clinical Benefit of Warfarin in Patients with Atrial Fibrillation. Circulation. 2012;125(19):2298.
314. Lip GY, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. J Thromb Haemost. 2016;14(9):1711-4.
315. Devereaux PJ, Fahey T, Anderson DR, Gardner MJ, Putnam W, Flowerdew GJ, et al. Differences between perspective of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. BMJ. 2001;323(7323):1218.
316. Freedman B, Potpara TS, Lip GYH. Stroke prevention in atrial fibrillation. Lancet. 2016;388(10046):806-17.
317. Pivatto Júnior F, RS S, I R, RR W, R M, SS B, et al. SAMe-TT2R2 Score in the Outpatient Anticoagulation Clinic to Predict Time in
Therapeutic Range and Adverse Events. Arq Bras Cardiol. 2017;108(4):290-6.
318. Roldan V, Cancio S, Galvez J, Valdes M, Vicente V, Marin F, et al. The SAMe-TTR Score Predicts Poor Anticoagulation Control in AF Patients: A Prospective 'Real-world' Inception Cohort Study. Am J Med. 2015;128(11):1237-43.
319. Abumuaileq RR, Abu-Assi E, Raposeiras-Roubin S, Lopez-Lopez A, Redondo-Dieguez A, Alvarez-Iglesias D, et al. Evaluation of SAMe-TT2R2 risk score for predicting the quality of anticoagulation control in a real-world cohort of patients with non-valvular atrial fibrillation on vitamin-K antagonists. Europace. 2015;17(5):711-7.
320. Skov J, Bladbjerg E-M, Bor MV, Gram J. SAmett2r2 does not predict time in therapeutic range of the international normalized ratio in patients attending a high-quality anticoagulation clinic. Chest. 2014;145(1):187-8.
321. Poli D, Antonucci E, Testa S, Lip GY. A prospective validation of the SAME-TT2R 2 score: how to identify atrial fibrillation patients who will have good anticoagulation control on warfarin. Intern Emerg Med. 2014;9(4):443-7.
322. Gallego P, Roldan V, Marin F, Galvez J, Valdes M, Vicente V, et al. SAMe-TT2R2 score, time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. Am J Med. 2014;127(11):1083-8.

323. Szymanski FM, Lip GYH, Filipiak KJ, Platek AE, Karpinski G. Usefulness of the SAME-TT2R2 score to predict anticoagulation control on VKA in patients with atrial fibrillation and obstructive sleep apnea. Int J Cardiol. 2016;204:200-5.
324. Gorzelak-Pabis P, Zyzak S, Krewko L, Broncel M. Assessment of the mean time in the therapeutic INR range and the SAME-TT2R2 score in patients with atrial fibrillation and cognitive impairment. Pol Arch Med Wewn. 2016;126(7-8):494-501.
325. Chan PH, Hai JJ, Chan EW, Li WH, Tse HF, Wong ICK, et al. Use of the SAMe-TT(2)R(2) Score to Predict Good Anticoagulation Control with Warfarin in Chinese Patients with Atrial Fibrillation: Relationship to Ischemic Stroke Incidence. PLoS One. 2016;11(3):e0150674.
326. Bernaitis N, Ching CK, Chen L, Hon JS, Teo SC, Davey AK, et al. The Sex, Age, Medical History, Treatment, Tobacco Use, Race Risk (SAMe TT2R2) Score Predicts Warfarin Control in a Singaporean Population. J Stroke Cerebrovasc Dis. 2016;26(1):64-9.
327. Proietti M, Lane DA, Lip GYH. Relation of the SAMe-TT2R2 score to quality of anticoagulation control and thromboembolic events in atrial fibrillation patients: Observations from the SPORTIF trials. Int J Cardiol. 2016;216:168-72.
328. Lobos-Bejarano JM, Barrios V, Polo-García J, Escobar C, Vargas-Ortega D, Marín-Montañés N, et al. Evaluation of SAMe-TT2R2 score and other clinical factors influencing the quality of anticoagulation therapy in non-valvular atrial fibrillation: a nationwide study in Spain. Curr Med Res Opin. 2016;32(7):1-7.
329. Ruiz-Ortiz M, Bertomeu V, Cequier A, Marin F, Anguita M. Validation of the SAMe-TT_2R_2 score in a nationwide population of nonvalvular atrial fibrillation patients on vitamin K antagonists. Thromb Haemost. 2015;114(4):695-701.
330. Lip GYH, Haguenoer K, Saint-Etienne C, Fauchier L. RElationship of the same-tt2r2 score to poor-quality anticoagulation, stroke, clinically relevant bleeding, and mortality in patients with atrial fibrillation. Chest. 2014;146(3):719-26.
331. DeSantis G, Hogan-Schlientz J, Liska G, Kipp S, Sallee R, Wurster M, et al. STABLE results: warfarin home monitoring achieves excellent INR control. Am J Manag Care. 2014;20(3):202-9.
332. Samsa GP, Matchar DB. Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management. J Thromb Thrombolysis. 2000;9(3):283-92.
333. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3).

334. Heneghan CJ, Garcia-Alamino JM, Spencer EA, Ward AM, Perera R, Bankhead C, et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev. 2016(7).
335. Gadisseur APA, Kaptein AA, Breukink-Engbers WGM, Van Der Meer FJM, R. Rosendaal F. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. J Thromb Haemost. 2004;2(4):584-91.
336. Zulkifly H, Lip GYH, Lane DA. Use of the SAMe-TT2R2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients receiving vitamin K antagonists: A review. Heart Rhythm. 2018;15(4):615-23.
337. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H-C, Hacke W, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. Eur Heart J. 2017;38(27):2137-49.
338. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag. 2015;11:967-77.
339. Mahaffey KW, Hellkamp AS, Patel MR, Hannan KL, Schwabe K, Nessel CC, et al. End of Study Transition From Study Drug to Open-Label Vitamin K Antagonist Therapy. Circ Cardiovasc Qual Outcomes. 2013;6(4):470.
340. Ruff CT, Giugliano RP, Braunwald E, Mercuri M, Curt V, Betcher J, et al. Transition of Patients From Blinded Study Drug to Open-Label Anticoagulation: The ENGAGE AF–TIMI 48 Trial. J Am Coll Cardiol. 2014;64(6):576-84.
341. Bista D, Chalmers L, Bereznicki L, Peterson G. Potential use of NOACs in developing countries: pros and cons. Eur J Clin Pharmacol. 2014;70(7):817-28.
342. Ling C, Siaw Han M, Len T, Siang Ning S, Ying K, Sing Yee C, et al. Validation of the SAMe-TT2R2 score in atrial fibrillation patients on warfarin therapy: a multicenter, multiethnic Asian cohort. Conference Abstract NHAM Annual Scientific Meeting 8-10 April. 2016.
343. Kataruka A, Kong X, Haymart B, Kline-Rogers E, Almany S, Kozlowski J, et al. SAMe-TT2R2 predicts quality of anticoagulation in patients with acute venous thromboembolism: The MAQI2 experience. Vasc Med. 2017;22(3):197-203.
344. National Institute for Clinical Excellence (2014) Atrial Fibrillation: Management. NICE Guideline (CG180).
345. Gallego P, Roldan V, Marín F, Romera M, Valdés M, Vicente V, et al. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. Thromb Haemost. 2013;110(6):1189-98.

346. Fauchier L, Poli D, Olshansky B. The SAMe-TT_2R_2 score and quality of anticoagulation in AF: Can we predict which patient benefits from anticoagulation? Thromb Haemost. 2015;114(4):657-9.
347. Schmitt L, Speckman J, Ansell J. Quality Assessment of Anticoagulation Dose Management: Comparative Evaluation of Measures of Time-in-Therapeutic Range. J Thromb Thrombolysis. 2003;15(3):213-6.
348. Saksena D, Muralidharan S, Mishra YK, Kanhere V, Mohanty BB, Srivastava CP, et al. Anticoagulation Management in Patients with Valve Replacement. J Assoc Physicians India. 2018;66:59.
349. Lip GYH, Collet JP, de Caterina R, Fauchier L, Lane DA, Larsen TB, et al. Antithrombotic Therapy in Atrial Fibrillation Associated with Valvular Heart Disease: Executive Summary of a Joint Consensus Document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, Endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Thromb Haemost. 2017;117(12):2215-36.
350. Iung B, Vahanian A. Epidemiology of acquired valvular heart disease. Can J Cardiol. 2014;30(9):962-70.
351. Lip GYH, Collet JP, Caterina Rd, Fauchier L, Lane DA, Larsen TB, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace. 2017;0:1-21.
352. Coffey S, Cairns BJ, Iung B. The modern epidemiology of heart valve disease. Heart. 2016;102(1):75.
353. de Dassel JL, Ralph AP, Carapetis JR. Controlling acute rheumatic fever and rheumatic heart disease in developing countries: are we getting closer? Curr Opin Pediatr. 2015;27(1):116-23.
354. Coffey S, Cox B, Williams MJA. Lack of progress in valvular heart disease in the pre–transcatheter aortic valve replacement era: Increasing deaths and minimal change in mortality rate over the past three decades. Am Heart J. 2014;167(4):562-7.
355. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham Study. Neurology. 1978;28(10):973-.

356. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in etiology and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY AF registry. Circulation. 2014;129(15):1568-76.
357. Thomas KL, Jackson LR, Shrader P, Ansell J, Fonarow GC, Gersh B, et al. Prevalence, Characteristics, and Outcomes of Valvular Heart Disease in Patients With Atrial Fibrillation: Insights From the ORBIT-AF (Outcomes Registry for Better Informed Treatment for Atrial Fibrillation). J Am Heart Assoc. 2017;6(12).
358. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
359. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(25):e1159-e95.
360. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2):e576S-e600S.
361. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol. 2011;154(3):311-24.
362. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89(2):635.
363. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. The Cochrane database of Sys Rev. 2013(7):CD003464.
364. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206-14.
365. Heras M, Chesebro JH, Fuster V, Penny WJ, Grill DE, Bailey KR, et al. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. J Am Coll Cardiol. 1995;25(5):1111-9.
366. Cohn LH, Mudge GH, Pratter F, Collins Jr JJ. Five to eight-year follow-up of patients undergoing porcine heart-valve replacement. N Engl J Med. 1981;304(5):258-62.
367. Durães AR, Durães MAO, Correia LCL, Aras R. Antithrombotic strategy in the three first months following bioprosthetic heart valve implantation. Arq Bras Cardiol. 2013;101(5):466-72.

368. El-Husseiny M, Salhiyyah K, Raja SG, Dunning J. Should warfarin be routinely prescribed for the first three months after a bioprosthetic valve replacement? Interact Cardiovasc Thorac Surg. 2006;5(5):616-23.
369. Iung B, Rodes-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. Eur Heart J. 2014;35(42):2942-9.
370. Mérie C, Køber L, Olsen PS, Andersson C, Gislason G, Jensen JS, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. JAMA. 2012;308(20):2118-25.
371. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, et al. Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. J Am Coll Cardiol. 2012;60(11):971-7.
372. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF, et al. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol. 2017;69(11):1372-82.
373. Carnicelli AP, De Caterina R, Halperin JL, Renda G, Ruff CT, Trevisan M, et al. Edoxaban for the Prevention of Thromboembolism in Patients With Atrial Fibrillation and Bioprosthetic Valves. Circulation. 2017;135(13):1273-5.
374. Renda G, De Caterina R, Carnicelli A, Nordio F, Mercuri M, Ruff C, et al. Outcomes in 2824 patients with valvular heart disease treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol. 2016;67(13 Supplement):2194.
375. Duraes AR, de Souza Roriz P, de Almeida Nunes B, Albuquerque FP, de Bulhoes FV, de Souza Fernandes AM, et al. Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively: DAWA Pilot Study. Drugs R D. 2016;16(2):149-54.
376. Pokorney SD, Rao MP, Wojdyla DM, Gersh BJ, Lopes RD, Lewis BS, et al. Apixaban use in patients with atrial fibrillation with bioprosthetic valves: insights from ARISTOTLE. Circulation. 2015;132:A172277.
377. Poli D, Antonucci E, Pengo V, Migliaccio L, Testa S, Lodigiani C, et al. Mechanical prosthetic heart valves: Quality of anticoagulation and thromboembolic risk. The observational multicenter PLECTRUM study. Int J Cardiol. 2018;267:68-73.
378. Havers-Borgersen E, Haider Butt J, Vinding NE, Torp-Pedersen C, Gislason G, Koeber L, et al. P4512Time in therapeutic range and risk of thromboembolism and bleeding in patients with mechanical heart valve prosthesis. Eur Heart J. 2018;39(suppl_1):ehy563.P4512-ehy563.P.

379. Grzymala-Lubanski B, Labaf A, Englund E, Svensson PJ, Själander A. Mechanical heart valve prosthesis and warfarin–Treatment quality and prognosis. Thromb Res. 2014;133(5):795-8.
380. Grzymala-Lubanski B, Svensson PJ, Renlund H, Jeppsson A, Sjalander A. Warfarin treatment quality and prognosis in patients with mechanical heart valve prosthesis. Heart. 2017;103(3):198-203.
381. Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. J Thorac Cardiovasc Surg. 2002;123(4):715-23.
382. Smith DE, Xuereb CB, Pattison HM, Lip GYH, Lane DA. TRial of an Educational intervention on patients' knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin (TREAT). BMC Cardiovasc Disord. 2010;10(1):21.
383. Lip GYH, Kamath S, Jafri M, Mohammed A, Bareford D. Ethnic differences in patient perceptions of atrial fibrillation and anticoagulation therapy the West Birmingham atrial fibrillation project. Stroke. 2002;33(1):238-42.
384. Nadar S, Begum N, Kaur B, Sandhu S, Lip GYH. Patients' understanding of anticoagulant therapy in a multiethnic population. J R Soc Med. 2003;96(4):175-9.
385. Amara W, Larsen TB, Sciaraffia E, Hernández Madrid A, Chen J, Estner H, et al. Patients' attitude and knowledge about oral anticoagulation therapy: results of a self-assessment survey in patients with atrial fibrillation conducted by the European Heart Rhythm Association. Ep Europace. 2015;18(1):151-5.
386. Hendriks JML, Vrijhoef HJM, Crijns HJGM, Brunner-La Rocca HP. The effect of a nurse-led integrated chronic care approach on quality of life in patients with atrial fibrillation. Europace. 2014;16(4):491-9.
387. Clarkesmith DE, Pattison HM, Khaing PH, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation. Cochrane Database Syst Rev. 2017;4:Cd008600.
388. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.
389. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int 2015;2015:217047-.
390. Warren SR, Raisch DW, Campbell HM, Guarino PD, Kaufman JS, Petrokaitis E, et al. Medication adherence assessment in a clinical trial with centralized follow-up and direct-to-patient drug shipments. Clinical Trials. 2011;10(3):441-8.
391. Jayaraman S, Rieder MJ, Matsui DM. Compliance assessment in drug trials: has there been improvement in two decades? Can J Clin Pharmacol. 2005;12(3):e251-3.

392. Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-4.
393. Hohnloser SH, Shestakovska O, Eikelboom J, Franzosi MG, San Tan R, Zhu J, et al. The effects of apixaban on hospitalizations in patients with different types of atrial fibrillation: insights from the AVERROES trial. Eur Heart J. 2013;34(35):2752-9.
394. Ivanovs R, Kivite A, Ziedonis D, Mintale I, Vrublevska J, Rancans E. Association of depression and anxiety with cardiovascular co-morbidity in a primary care population in Latvia: a cross-sectional study. BMC Public Health. 2018;18(1):328-.
395. Haddad M, Walters P, Phillips R, Tsakok J, Williams P, Mann A, et al. Detecting depression in patients with coronary heart disease: a diagnostic evaluation of the PHQ-9 and HADS-D in primary care, findings from the UPBEAT-UK study. PLoS One. 2013;8(10):e78493.
396. Meader N, Mitchell AJ, Chew-Graham C, Goldberg D, Rizzo M, Bird V, et al. Case identification of depression in patients with chronic physical health problems: a diagnostic accuracy meta-analysis of 113 studies. Br J Gen Pract. 2011;61(593):e808-20.
397. Hendriks JML, Crijns HJGM, Tieleman RG, Vrijhoef HJM. The atrial fibrillation knowledge scale: Development, validation and results. Int J Cardiol. 2013;168(2):1422-8.
398. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol & Health. 1999;14(1):1-24.
399. Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB, Lane DA. Patient-reported outcomes for quality of life assessment in atrial fibrillation: a systematic review of measurement properties. PLoS One. 2016;11(11):e0165790.
400. Kroenke K, Spitzer RL, Williams JBW. The Phq-9: Validity of a Brief Depression Severity Measure. J Gen Intern Med. 2001;16(9):606-13.
401. Spitzer RL, Kroenke K, Williams JW, Löwe B. A brief measure for assessing generalized anxiety disorder: The gad-7. Arch Intern Med. 2006;166(10):1092-7.
402. National Institute for Health and Care Excellence (2018) Depression in adults: treatment and management. NICE guideline.
403. National Institute for Health and Care Excellence (2018) Identifying and addressing common mental health disorders. NICE Pathways
404. Conway A, Sheridan J, Maddicks-Law J, Fulbrook P, Ski CF, Thompson DR, et al. Accuracy of anxiety and depression screening tools in heart transplant recipients. Appl Nurs Res. 2016;32:177-81.

405. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, et al. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2011;4(1):15-25.
406. IBM SPSS Statistics for Windows, Version 23. Armonk, NY:IBM Corp.
407. Thrall G, Lane D, Carroll D, Lip GYH. Quality of Life in Patients with Atrial Fibrillation: A Systematic Review. Am J Med. 2006;119(5):448.e1-.e19.
408. Galli F, Borghi L, Carugo S, Cavicchioli M, Faioni EM, Negroni MS, et al. Atrial fibrillation and psychological factors: a systematic review. PeerJ. 2017;5:e3537-e.
409. Perret-Guillaume C, Briancon S, Wahl D, Guillemin F, Empereur F. Quality of life in elderly inpatients with atrial fibrillation as compared with controlled subjects. J Nutr Health Aging. 2010;14(2):161-6.
410. Lioni L, Vlachos K, Letsas KP, Efremidis M, Karlis D, Asvestas D, et al. Differences in Quality of Life, Anxiety and Depression in Patients with Paroxysmal Atrial Fibrillation and Common Forms of Atrioventricular Reentry Supraventricular Tachycardias. Indian Pacing Electrophysiol J. 2014;14(5):250-7.
411. Schnabel RB, Michal M, Wilde S, Wiltink J, Wild PS, Sinning CR, et al. Depression in atrial fibrillation in the general population. PLoS One. 2013;8(12):e79109.
412. Jamous RM, Sweileh WM, El-Deen Abu Taha AS, Zyoud SeH. Beliefs About Medicines and Self-reported Adherence Among Patients with Chronic Illness: A Study in Palestine. J Family Med Prim Care. 2014;3(3):224-9.
413. AlHewiti A. Adherence to Long-Term Therapies and Beliefs about Medications. Int J Family Med. 2014;2014(479596).
414. Piccini JP, Simon DN, Steinberg BA, et al. Differences in clinical and functional outcomes of atrial fibrillation in women and men: Two-year results from the orbit-af registry. JAMA Cardiology. 2016;1(3):282-91.
415. Ferguson C, Inglis SC, Newton PJ, Middleton S, Macdonald PS, Davidson PM. Education and practice gaps on atrial fibrillation and anticoagulation: a survey of cardiovascular nurses. BMC Med Educ. 2016;16(1):9.
416. Mayet AY. Association between oral anticoagulation knowledge, anticoagulation control, and demographic characteristics of patients attending an anticoagulation clinic in Saudi Arabia: a cross-sectional prospective evaluation. Trop J Pharm Res. 2015;14(7):1285-91.
417. Alrasheedy AA, Hassali MA, Wong ZY, Saleem F. Pharmacist-managed medication therapy adherence clinics: The Malaysian experience. Res Social Adm Pharm. 2017;13(4):885-6.

418. Thanimalai S, Shafie AA, Hassali MA, Sinnadurai J. Comparing effectiveness of two anticoagulation management models in a Malaysian tertiary hospital. Int J Clin Pharm. 2013;35(5):736-43.
419. Aidit S, Soh YC, Yap CS, Khan TM, Neoh CF, Shaharuddin S, et al. Effect of Standardized Warfarin Treatment Protocol on Anticoagulant Effect: Comparison of a Warfarin Medication Therapy Adherence Clinic with Usual Medical Care. Front Pharmacol. 2017;8:637-.
420. Kaatz S. Determinants and measures of quality in oral anticoagulation therapy. J Thromb Thrombolysis. 2007;25(1):61-6.
421. Rosendaal FR, Cannegieter SC, Van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69(3):236-9.
422. Poller L, Keown M, Ibrahim S, Lowe G, Moia M, Turpie AG, et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. J Thromb Haemost. 2008;6(6):935-43.
423. Fauchier L, Angoulvant D, Lip GY. The SAMe-TT2R2 score and quality of anticoagulation in atrial fibrillation: a simple aid to decision-making on who is suitable (or not) for vitamin K antagonists. Europace. 2015;17(5):671-3.
424. National Institute for Clinical Excellence (2014) Chronic kidney disease in adults: assessment and management. NICE guideline (CG182).
425. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.
426. Optimal Oral Anticoagulant Therapy in Patients with Nonrheumatic Atrial Fibrillation and Recent Cerebral Ischemia. N Engl J Med. 1995;333(1):5-10.
427. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbroucke JP, Briet E. Optimal Oral Anticoagulant Therapy in Patients with Mechanical Heart Valves. N Engl J Med. 1995;333(1):11-7.
428. Perera MA, Gamazon E, Cavallari LH, Patel SR, Poindexter S, Kittles RA, et al. The missing association: sequencing-based discovery of novel SNPs in VKORC1 and CYP2C9 that affect warfarin dose in African Americans. Clin Pharmacol Ther. 2011;89(3):408-15.
429. Lindh JD, Holm L, Andersson ML, Rane A. Influence of CYP2C9 genotype on warfarin dose requirements—a systematic review and meta-analysis. Eur J Clin Pharmacol. 2009;65(4):365-75.
430. Limdi NA, McGwin G, Goldstein JA, Beasley TM, Arnett DK, Adler BK, et al. Influence of CYP2C9 and VKORC1 1173C/T Genotype on the Risk of Hemorrhagic Complications in African-American and European-American Patients on Warfarin. Clin Pharmacol Ther. 2008;83(2):312-21.

431. Higashi MK, Veenstra DL, Kondo L, et al. Association between cyp2c9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA. 2002;287(13):1690-8.
432. Aithal GP, Day CP, Kesteven PJL, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. The Lancet. 1999;353(9154):717-9.
433. Sistonen J, Fuselli S, Palo JU, Chauhan N, Padh H, Sajantila A. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. Pharmacogenet Genomics. 2009;19(2):170-9.
434. Solus JF, Arietta BJ, Harris JR, Sexton DP, Steward JQ, McMunn C, et al. Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. Pharmacogenomics. 2004;5(7):895-931.
435. Lee CR, Goldstein JA, Pieper JA. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. Pharmacogenet Genomics. 2002;12(3).
436. Johnson J, Caudle K, Gong L, Whirl-Carrillo M, Stein C, Scott S, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update.
437. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A Randomized Trial of Genotype-Guided Dosing of Warfarin. N Engl J Med. 2013;369(24):2294-303.
438. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, et al. A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing. N Engl J Med. 2013;369(24):2283-93.
439. Limdi NA, Brown TM, Yan Q, Thigpen JL, Shendre A, Liu N, et al. Race influences warfarin dose changes associated with genetic factors. Blood. 2015;126(4):539-45.
440. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in Atrial Fibrillation Patients with Moderate Chronic Kidney Disease. Clin J Am Soc Nephrol. 2011.
441. Jones MR, Horner RD, Edwards LJ, Hoff J, Armstrong SB, Smith-Hammond CA, et al. Racial Variation in Initial Stroke Severity. Stroke. 2000;31(3):563.
442. Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, et al. Stroke Incidence among White, Black, and Hispanic Residents of an Urban CommunityThe Northern Manhattan Stroke Study. Am J Epidemiol. 1998;147(3):259-68.
443. Bush D, Martin LW, Leman R, Chandler M, Haywood LJ, Investigators NA. Atrial fibrillation among African Americans, Hispanics and Caucasians: clinical features and outcomes from the AFFIRM trial. J Natl Med Assoc. 2006;98(3):330.
444. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. Am Heart J.170(1):141-8.e1.

445. Apostolakis S, Guo Y, Lane DA, Buller H, Lip GYH. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. Eur Heart J. 2013;34(46):3572-9.
446. Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). Am Heart J. 2010;159(6):1102-7.
447. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation. 2009;119(10):1363-9.
448. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrol Dial Transplant. 2012;27(10):3816-22.
449. Ansell J, Hollowell J, Pengo V, Martinez-Brotons F, Caro J, Drouet L. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: the international study of anticoagulation management (ISAM). J Thromb Thrombolysis. 2007;23(2):83-91.
450. Fitzmaurice DA, Hobbs F, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: A randomized, controlled trial. Arch Intern Med. 2000;160(15):2343-8.
451. Ming LC. Use of herbal products in Southeast Asian countries. Arch Pharm Prac. 2016;7(5):1.
452. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.
453. Biswal BM, Sulaiman SA, Ismail HC, Zakaria H, Musa KI. Effect of Withania somnifera (Ashwagandha) on the Development of Chemotherapy-Induced Fatigue and Quality of Life in Breast Cancer Patients. Integr Cancer Ther. 2012;12(4):312-22.
454. Butchart EG, Gohlke-Bärwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, et al. Recommendations for the management of patients after heart valve surgery. Eur Heart J. 2005;26(22):2463-71.
455. Grunkemeier GL, Wu Y. “Our complication rates are lower than theirs”: Statistical critique of heart valve comparisons. J Thorac Cardiovasc Surg. 2003;125(2):290-300.
456. Vestergaard AS, Skjøth F, Larsen TB, Ehlers LH. The importance of mean time in therapeutic range for complication rates in warfarin therapy of patients with atrial fibrillation: A systematic review and meta-regression analysis. PLoS One. 2017;12(11):e0188482.

457. Blustin JM, McBane RD, Ketha SS, Wysokinski WE. Distribution of thromboembolism in valvular versus non-valvular atrial fibrillation. Expert Rev Cardiovasc Ther. 2014;12(10):1129-32.
458. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. J Womens Health (Larchmt). 2014;23(2):112-9.
459. Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. Lancet. 2012;379(9813):322-34.
460. Razouki Z, Ozonoff A, Zhao S, Jasuja Guneet K, Rose Adam J. Improving Quality Measurement for Anticoagulation. Circ Cardiovasc Qual Outcomes. 2014;7(5):664-9.
461. Population Distribution and Basic Demographics Characteristics Report 2010 (Updated: 05/08/2011). Department of Statistics Malaysia.
462. Pastori D, Farcomeni A, Saliola M, Del Sole F, Pignatelli P, Violi F, et al. Temporal trends of time in therapeutic range and incidence of cardiovascular events in patients with non-valvular atrial fibrillation. Eur J Intern Med. 2018;54:34-9.