ELECTRONIC RECORD LINKAGE COHORT STUDY OF EVIDENCE-BASED MANAGEMENT AND OUTCOMES IN PATIENTS WITH ISCHAEMIC HEART DISEASE AND ATRIAL FIBRILLATION

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ABSTRACT

BACKGROUND

Implementation of evidence-based medicine is often suboptimal. The objectives of this thesis are to explore the delivery of evidence-based medicine and outcomes in patients with ischaemic heart disease (IHD) and atrial fibrillation (AF).

METHODS

Retrospective observational cohort studies were conducted using linked anonymised data from the secure anonymised information linkage (SAIL) databank. Patients included (i) those undergoing percutaneous coronary intervention, (ii) patients prescribed vitamin K antagonist (VKA) for AF, and (iii) patients with AF who had undergone successful PCI.

RESULTS

Amongst patients directed to take clopidogrel for one-year post-PCI, discontinuation was far lower (~6%) than in previous studies where the treatment duration was not known. Despite this, early discontinuation and/or bleeding was associated with an increased risk of adverse events.

In a national cohort of PCI patients, we observed a low rate of achievement of international guideline target lipid levels (<25%) and low prescribing of intensive lipid lowering therapy amongst those not at target. Females and patients who had undergone elective PCI were least likely to have their lipid levels documented and be at target.

In patients prescribed VKA for AF guideline defined poor anticoagulation control was common and associated with significantly higher bleeding event rates, independent of common comorbidities that are recognised as risk factors for stroke and bleeding.

In patients with AF who had undergone PCI outcomes were poor: approximately 1 in 5 had either a stroke, acute coronary syndrome (ACS) or died in the year follow-up. Bleeding events were also common and associated with a five, three and four-fold increased risk of stroke, ACS, and death.

CONCLUSION

This thesis has characterised the nature of multiple therapeutic gaps and associated adverse outcomes with common clinical conditions. Thus, identifying opportunities to improve outcomes in individual patients and at population level.

DECLARATIONS

I declare that the work presented in this thesis has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any other degree.

Daniel Harris 5th August 2021

This thesis is the result of my own investigations, except where otherwise stated and that other sources are acknowledged by footnotes giving explicit references and that a bibliography is appended.

Daniel Harris 5th August 2021

I give consent for this thesis, if accepted to be made available online in the University's Open Access Repository and for inter-library loan, and for the title and summary to be made available to outside organisations.

Daniel Harris 5th August 2021

I declare that that the University's ethical procedures have been followed and, where appropriate, that ethical approval has been granted.

Daniel Harris 5th August 2021

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PUBLICATIONS AND ABSTRACTS PRESENTED DURING THE PERIOD OF THIS PH.D.

At the time of submission of this thesis, papers from chapters 2,3 & 4 were published, chapter 5 was in review and chapter 6 was in the process of submission. The references to the published manuscripts are as follows:

1. Harris DE, Lacey A, Akbari A, et al. Early Discontinuation of P2Y12 antagonists and Adverse Clinical Events Post–Percutaneous Coronary Intervention: A Hospital and Primary Care Linked Cohort. *J Am Heart Assoc* 2019; 8: e012812. 2019/10/29. DOI: 10.1161/JAHA.119.012812.

2. Harris DE, Thayer D, Wang T, et al. An observational study of INR control according to NICE criteria in patients with non-valvular atrial fibrillation-The SAIL Warfarin Out of Range Descriptors Study (SWORDS). *Eur Heart J Cardiovasc Pharmacother* 2019 2019/11/27. DOI: 10.1093/ehjcvp/pvz071.

3. Harris DE, Lacey A, Akbari A, et al. Achievement of European guideline-recommended lipid levels post-percutaneous coronary intervention: A population-level observational cohort study. *Eur J Prev Cardiol* 2020/03/31. DOI: 10.1177/2047487320914115.

The following abstracts have also been presented at international conferences:

- Early discontinuation of $P2Y_{12}$ antagonists and adverse outcomes post percutaneous coronary intervention. Presented at American College of Cardiology Conference 2018, Orlando. JAAC (March 2018); 71, 11
- Early discontinuation of $P2Y_{12}$ antagonists and adverse outcomes post percutaneous coronary intervention. Presented at Europrevent 2018, Ljubljana. European Journal of Preventive Cardiology (May 2018); 25, suppl_1
- Discontinuation of statins and adverse clinical outcomes post percutaneous coronary intervention. Presented at American Heart association conference 2018, Chicago. Circulation. 2018; 138, suppl_1:14994
- Evaluation of the Effectiveness of Warfarin Anticoagulation in Welsh Patients with Non-Valvular Atrial Fibrillation: The Sail Warfarin Out of Range Descriptors Study (SWORDS). Presented at American Heart association conference 2018, Chicago. Circulation. 2018; 138, suppl_1:14903
- Bleeding events associated with NICE defined poor INR control. An observational study of patients prescribed warfarin for non-valvular atrial fibrillation in the Welsh population. Presented at European Heart & Stroke Conference 2020, Barcelona.
- An observational Study of INR Control and Bleeding Events, According to European Society of cardiology (ESC) Guidelines, in Non-Valvular Atrial Fibrillation (NVAF) patients stratified by Male and Female Sex. Presented at the International Society on Thrombosis and Haemostasis Congress 2020 Milan. Res Pract Thromb Haemost. 2020;4 (Suppl 1): PB2086

In addition the following publication and abstracts has arisen from this Ph.D:

- Thayer D, Rees A, Kennedy J, et al. Measuring follow-up time in routinely-collected health datasets: Challenges and solutions. *PLoS One* 2020; 15: e0228545. 2020/02/11. DOI: 10.1371/journal.pone.0228545
- Machine learning approaches for prediction of 1-year risk of major bleeding events in anticoagulated atrial fibrillation patients in Wales. Presented at European Heart & Stroke Conference 2020, Barcelona.
- A longitudinal study of anticoagulant prescribing in patients with Atrial Fibrillation in Wales. Stroke Conference Wales, Cardiff 2019
-

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GLOSSARY

Acute coronary syndromes (ACS)	This encompasses a range of conditions including unstable angina, non-ST-segment-elevation myocardial infarction (NSTEMI) and ST-segment-elevation myocardial infarction (STEMI) that are due to a sudden reduction of blood flow to the heart, usually due to rupture of an atherosclerotic plaque that promotes formation of a clot in one of the coronary arteries.
Anticoagulants	A group of drugs that reduce the activity of one or more factors involved in the coagulation of blood and prolong the clotting time. Oral anticoagulants include Vitamin K antagonists (VKA) and the direct oral anticoagulants (DOACS). These are commonly prescribed to reduce the risk of clots developing in atrial fibrillation and also following deep vein thrombosis and pulmonary embolism.
Antiplatelet	A group of drugs including aspirin and $P2Y_{12}$ antagonists that decrease platelet aggregation and thrombus formation.
Atrial fibrillation (AF)	Atrial fibrillation is an irregular and often rapid heart rate that can increase the risk of strokes, heart failure and other heart-related complications. During atrial fibrillation, the heart's two upper chambers (the atria) beat chaotically and without contractile function, out of coordination with the two lower chambers (the ventricles) of the heart which beat irregularly.
Cardiovascular disease (CVD)	A group of disorders of the heart and vasculature, including hypertension; ischaemic heart disease (IHD); cerebrovascular disease (stroke); peripheral vascular disease (PVD); arrhythmias; rheumatic and congenital heart disease, and cardiomyopathies.
Coronary artery bypass grafting (CABG)	Coronary artery bypass grafting is a surgical procedure to restore normal blood flow to the heart, by connecting venous or arterial grafts from the aorta or internal mammary artery to the native coronary arteries beyond their region(s) of blockage.

Cox-regression	Cox regression is a statistical method for investigating the effect of several variables upon the time a specified event takes to happen, in order to identify those variables that are independently associated with the occurrence of these events.
Direct oral anticoagulants (DOACS)	A generic term for a group of oral anticoagulants that inhibit coagulation factor Xa or thrombin activity. In the United Kingdom the following are available: apixaban, edoxaban and rivaroxaban (anti-factor Xa) and dabigatran (a direct thrombin inhibitor).
Dual antiplatelet therapy (DAPT)	A combination of antiplatelet agents including aspirin and a $P2Y_{12}$ inhibitor/antagonist prescribed to reduce the risk or recurrent coronary ischaemic events post ACS. Also initiated at the time of coronary stent deployment to reduce the risk stent thrombosis and restenosis.
Ischaemic heart disease (IHD)	A pathological process characterised by development +/- destabilisation of atherosclerotic plaque in the coronary arteries. Also referred to as coronary heart disease.
In stent restenosis (ISR)	This occurs when part of an artery in which a stent has been placed becomes blocked.
Multivariable analyses	A statistical tool for determining the relative contributions of different variables (causes) to a single outcome or event.
Non-ST-elevation acute coronary syndrome (NSTE-ACS)	Also referred to as non-ST-elevation myocardial infarction (NSTEMI). This is characterised by episodes of chest pain at rest or with minimal exertion, which increase in frequency or severity, often with dynamic ECG changes and release of biomarkers reflecting myocardial injury. This is usually caused by destabilisation or rupture of an atherosclerotic plaque.
$P2Y_{12}$ inhibitors	$P2Y_{12}$ inhibitors (also referred to $P2Y_{12}$ antagonists) are antiplatelet agents including clopidogrel, prasugrel and ticagrelor. These are commonly prescribed to reduce the risk of thrombosis following acute coronary syndromes, coronary stent implantation and stroke.
Percutaneous coronary intervention (PCI)	This is a non-surgical procedure that uses a catheter (a thin flexible tube) to place and inflate a thin balloon, usually followed by placement of a small tubular structure called a stent, to open up blood vessels in the heart that have been narrowed by a coronary plaque.

Peripheral vascular disease (PVD)	Peripheral vascular disease is a common term used to refer to atherosclerotic peripheral arterial disease. This is a condition where a build-up of fatty deposits in the arteries restricts blood supply. This may occur in any artery outside of the heart and brain but most commonly occurs in the arteries in the legs.
ST elevation myocardial infarction (STEMI)	STEMI results from complete and prolonged occlusion of an epicardial coronary blood vessel, usually due to destabilisation of an atherosclerotic plaque, triggering the development of a clot which completely blocks the vessel. This rapidly shuts off the blood supply to the heart muscle supplied by the artery, which starts to die unless blood flow can be restored promptly. STEMI is defined based on ECG criteria, characterised by acute, regional elevation of the ST-segments or development of a new left bundle branch block pattern on the 12 lead ECG.
Stent thrombosis	Stent thrombosis is defined as a thrombotic (clot-related) occlusion of a coronary stent. Stent thrombosis is a major complication associated with stent placement in percutaneous coronary intervention (PCI).
Univariable analysis	Univariable analysis is a simple statistical technique for analysing the strength of the relationship between a single variable (predictor) to an individual outcome or event.
Unstable angina (UA)	Sometimes referred to as acute coronary syndromes ‘ACS’. UA is defined as myocardial ischaemia at rest or minimal exertion in the absence of cardiomyocyte necrosis.

CHAPTER 1.

THESIS INTRODUCTION

This thesis examines the evidence-based management of two areas of cardiovascular disease (CVD); the management of ischaemic heart disease (IHD) focussing on the period post-percutaneous coronary intervention (PCI), and secondly the antithrombotic management for the prevention of stroke in patients with atrial fibrillation (AF).

CARDIOVASCULAR DISEASE

CVD is a group of disorders of the heart and vasculature, including hypertension; IHD; cerebrovascular disease; peripheral vascular disease (PVD); arrhythmias; rheumatic and congenital heart disease, and cardiomyopathies. CVD is the single most common cause of death in the UK and worldwide, and in countries of all income groups.[1, 2] In the UK, mortality from CVD has been decreasing (1980-2013), despite an increase in hospital admission and little change in prevalence.[3] The decrease in mortality has largely been attributed to improvement in the management of individuals (including secondary prevention, heart failure treatment, management of the acute myocardial infarction, and hypertension), and improvement at a population level by reduction in smoking, improvement in blood pressure and cholesterol.[4]

ISCHAEMIC HEART DISEASE

IHD is a pathological process characterised by the accumulation of atherosclerotic plaque in the epicardial coronary arteries (figure 1.1). This chronic disease may have stable periods and can be modified by changes to lifestyle, pharmacotherapy, and invasive interventions. However, most often this disease is progressive and plaque growth can obstruct and occlude coronary arteries leading to myocardial ischaemia presenting clinically as angina.[5, 6] Abrupt

thrombotic occlusion of a high-risk coronary plaque can result in the most serious clinical manifestations of coronary artery disease, i.e. unstable angina (UA), acute myocardial infarction (AMI) (either as a non-ST-elevation acute coronary syndrome [NSTE-ACS] or ST-elevation-[STEMI]) and sudden death.[5]

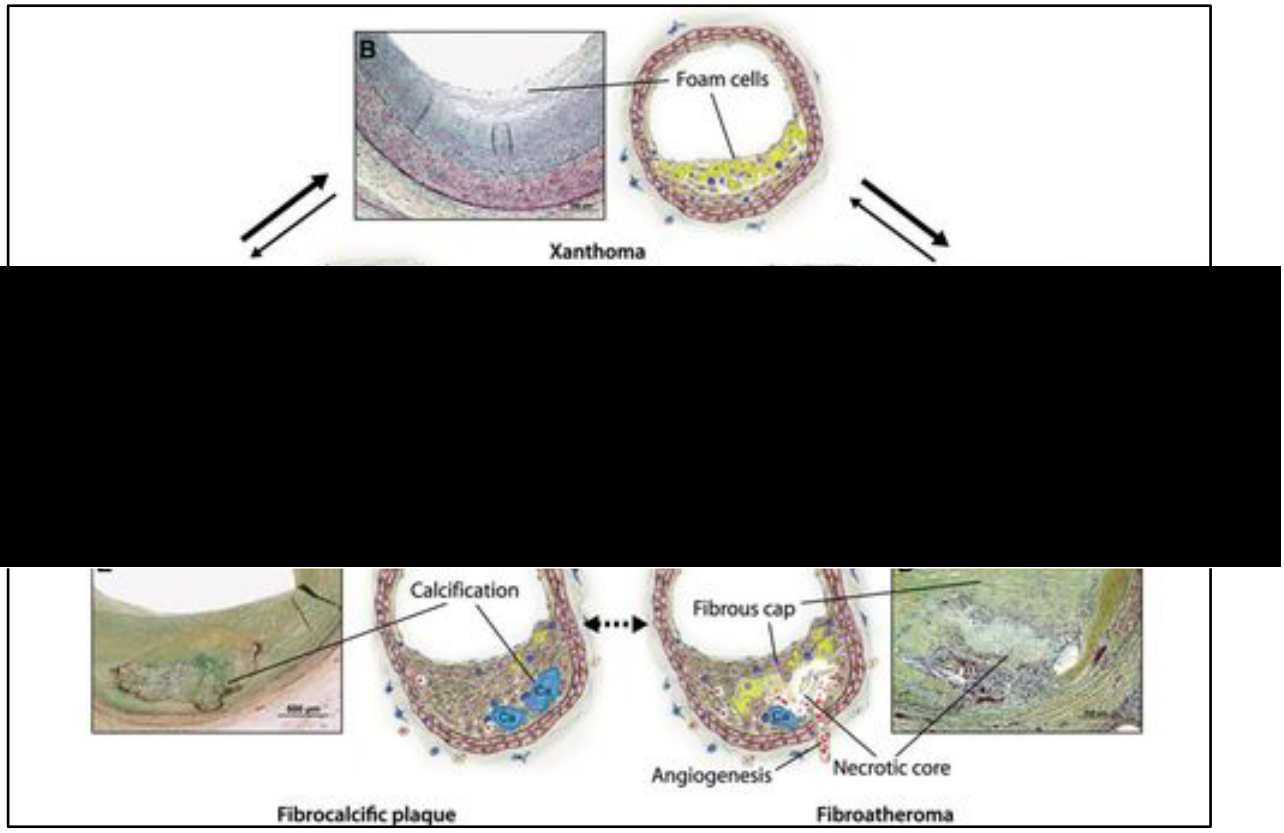

Figure 1.1 Lesion types of atherosclerosis and a proposed sequence of their development.

A, thickening characterized by smooth muscle cell accumulation within the intima. **B**, Intimal xanthoma corresponding to the accumulation of foam cell macrophages within the intima. Pathological intimal thickening in **C** denotes the accumulation of extracellular lipid pools in the absence of apparent necrosis. **D**, Fibroatheroma indicating the presence of a necrotic core. The necrotic core and surrounding tissue may eventually be calcified, which forms fibrocalcific plaque shown in **E**.

From Bentzon JF. *et al* Mechanisms of plaque formation and rupture. *Circ Res* 2014; 114: 1852-1866.[7]

Atherosclerotic lesions develop from a complex interplay between circulating factors, cell types and repeated exposure to systemic and local injury.[8] High blood concentration of

apolipoprotein B (ApoB) containing lipoproteins, of which low-density lipoprotein (LDL) usually is the most prevalent form, is the most common cause of atherosclerosis. However, the disease is multifactorial and atherosclerotic plaques can develop at even modest levels of circulating LDL. Smoking, diabetes, hypertension, male-sex, and genetic susceptibility also contribute to the disease.

In the initial stages of atherosclerosis, LDL particles accumulates in the arterial intima and are then modified by processes of oxidation and aggregation. These modified lipoproteins act as stimulators of the immune system inducing endothelial cells and smooth muscle cells to express adhesion molecules that interact with receptors on monocytes and stimulate their homing, migration, and differentiation into macrophages and dendritic cells (figure 1.1a).[7]

Macrophages and dendritic cells take up lipids from the insudating lipoproteins and become foam cells (figure 1.1b).[7, 9] Xanthomas or 'fatty streaks' then develop from accumulating several layers of foam cells. While many xanthomas do not progress any further, some develop lipid pools below the layer of foam cells (figure 1.1c). Ongoing invasion of macrophages with progressive lipid accumulation and inflammation leads to cellular necrosis (figure1.1d). This results in pools of free cholesterol, cellular debris, along with lipid accumulation and inflammatory cells known as necrotic cores (also referred to as 'lipid rich cores'). Angiogenesis provides oxygen and nutrients for the expanding plaque but leads to further infiltration of immune and atherogenic lipoproteins. The plaque neovessels are fragile and may rupture leading to extravasation of erythrocytes and plasma protein. Intraplaque bleeds expands the plaque core and causes inflammation and is a common trigger for plaque rupture. Continued plaque growth results in a formation of a thin fibrous plaque susceptible to rupture (figure 1.1e and 1.2).

The development of atherosclerotic plaques and the resulting progressive obstruction may lead to stable angina. However, an ACS is nearly always the result of plaque rupture and thrombus formation.

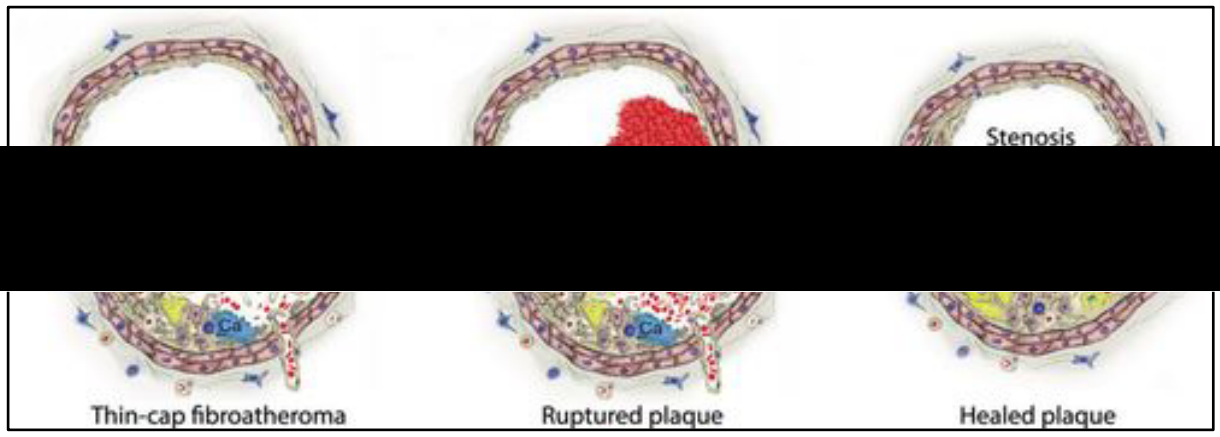

Figure 1.2 Plaque rupture and healing.

Rupture of a thin-cap fibroatheroma with nonfatal thrombus and subsequent healing with fibrous tissue formation and constrictive remodelling.

From Bentzon JF. *et al* Mechanisms of plaque formation and rupture. *Circ Res* 2014; 114: 1852-1866.[7]

MECHANISMS OF PLATELET ACTIVATION AND SITES OF ACTION FOR ANTIPLATELET THERAPY

Although platelets can adhere to intact endothelium, and participate in the progression of atherosclerosis, plaque rupture and exposure of the thrombogenic substrates to circulating platelets stimulates platelet attachment to the exposed subendothelium and platelet activation leading to aggregates and local thrombus formation. Activated platelets cause a positive feedback loop amplifying the response to the original stimulus and activation of the coagulation cascade leading to the formation of fibrin and a solid clot.[8]

Platelet adherence to the ruptured endothelium is rapidly enabled by the platelet specific adhesion-signalling system, consisting of glycoprotein (GP)Ib-IX-V that binds von Willerbrand factor (vWF) and collagen. Engagement of this signalling system leads to rapid

platelet activation and morphological changes in platelet shape and plasma membrane as well as degranulation that promotes coagulation including activation of factor Xa and thrombin.

In activated platelets, release of the agonist, adenosine diphosphate (ADP), and activation of the cyclooxygenase pathway leads to production and release of thromboxane A2 (TxA2). This reinforces platelet activation by autocrine stimulation of G-protein–coupled receptors for ADP (P2Y1 and P2Y12) or TxA2.[10] Thus, activation via primary platelet receptors, GPIb-IX-V/GPVI, or secondary receptors for ADP, TxA2 or, thrombin leads to activation of the platelet integrin, αIIbβ3 (GPIIb/IIIa) that binds fibrinogen or vWF and mediates platelet aggregation.

Understanding of the processes involved in platelet activation, platelet aggregation and activation of the coagulation cascade leading to the development of thrombi has allowed us to exploit this system, using multiple antithrombotic agents binding at key receptors to reduce the normal thrombotic response, aid revascularisation and reduce further thrombotic episodes (figure 1.3).

Aspirin inhibits prostaglandin(PG) -endoperoxidase synthase (PTGS1; also known as cyclooxygenase 1), preventing the production of PGs, particularly in platelets, inhibiting the TxA2 production.[10] The P2Y12 receptor antagonists (clopidogrel, prasugrel and ticagrelor) prevents the binding ADP and subsequent platelet activation. Abciximab, tirofiban and eptifibatide bind directly to the GPIIb/IIIa receptors on activated platelets preventing the binding of fibrinogen and von Willebrand factor.[11]

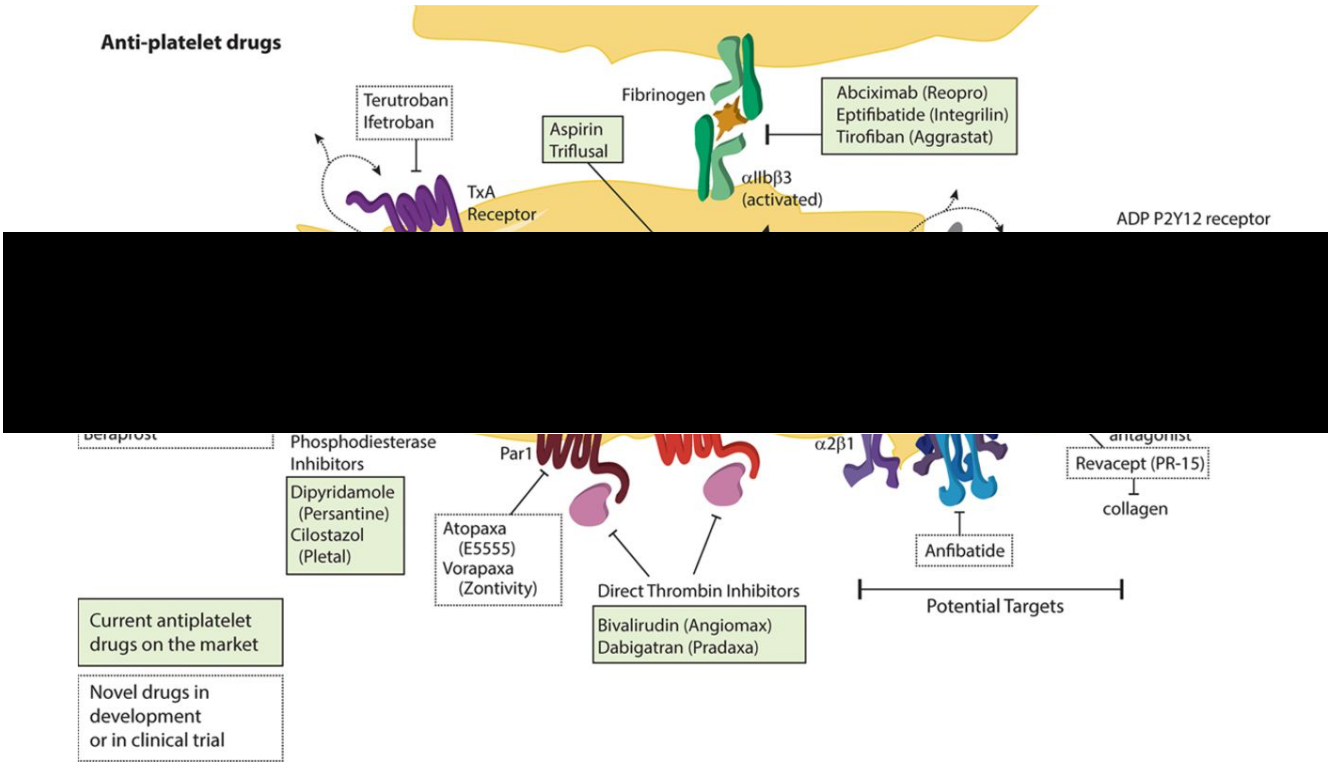

Figure 1.3 Platelet targets of antiplatelet therapy.

Schematic showing platelet surface receptors and signalling pathways leading to platelet activation and activation of the integrin, αIIbβ3, which binds fibrinogen or Von Willebrand factor and mediates platelet aggregation. Targets of currently available (shaded boxes) and novel drugs in development or in clinical trial (white boxes) are indicated. COX indicates cyclooxygenase; GP, glycoprotein; and TxA2, thromboxane A2.

From Metharom P *et al*. Current state and novel approaches of antiplatelet therapy. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015; 35:1327–1338.[10]

In patients presenting with an ACS activation of the coagulation system and release of clotting factors produce small amounts of thrombin, that is amplified by activated platelets. Management of patients with an ACS relies on combinations of antithrombotic therapy to arrest platelet activity and thrombin production.[12] Dual antiplatelet therapy (DAPT), consisting of aspirin and a $P2Y_{12}$ antagonist is the cornerstone of treatment. Anticoagulation with a herparinoid is indicated during the acute phase until revascularisation or chest pain has

rescinded. For patients undergoing invasive revascularisation intravenous GPIIb/IIIa inhibitors may also be administered to further inhibit platelet activity in very high-risk patients.

CORONARY ANGIOGRAPHY

Coronary angiography provides the gold standard in defining the degree of severity of atherosclerotic coronary disease. Angiography involves insertion of a catheter into either the femoral or radial artery that is guided to the coronary arteries. Local injection of contrast dye and use of X ray imaging facilitates the visualisation of the coronary arteries allowing characterisation of the nature of the disease which is necessary to inform revascularisation strategies.

While there are no absolute contraindications to coronary angiography, neither is the procedure risk free. Bleeding is estimated to occur in ~2%, although most are minor, haematoma and retroperitoneal bleeds occurs in ~0.2% of cases[13]; the incidence of death is ~ 0.05% for diagnostic procedures[14]; risk of stroke is 0.05-0.1% in those undergoing diagnostic angiography increasing to 0.18% - 0.4% in those proceeding to intervention[15], acute kidney injury occurs in ~1.7% of cases and allergic reactions to contrast media in ~1% of patients. Risk of complications are higher amongst older patients, diabetics, those with renal insufficiency and the morbidly obese. Patients with severe ischaemic heart disease, reduced ejection fraction, recent stroke or MI, or a propensity to bleeding are at particularly increased risk of cardiac and vascular complications.

The transfemoral approach provides easier access, allows repeated puncturing, less radiation time and less contrast media.[16] In comparison transradial catheterisation reduces bleeding, haematoma formation, facilitates earlier discharge, is patient preferred and is also lower cost. Studies amongst ACS patients randomly assigned to either transradial or

transfemoral approach have demonstrated lower bleeding with transradial (1.6 vs 2.3%; relative risk (RR) 0.67, 95% confidence interval (CI) 0.49-0.92, *P*=0.009) and improved mortality (1.6 vs 2.2%; RR 0.72, 95%CI 0.53-0.99, *P*=0.045) compared with transfemoral access.[16]

Revascularisation by percutaneous coronary intervention and antiplatelet therapy

Coronary revascularisation by percutaneous coronary intervention (PCI) is now the dominant revascularisation strategy for patients presenting with STEMI across Europe.[17] It is also an established mode of revascularisation in patients with NSTE-ACS and may also be indicated in flow-limiting coronary stenosis in patients with stable coronary artery disease (SCAD) to reduce myocardial ischaemia, amongst patients who remain symptomatic despite medical therapy.[17] PCI may involve aspiration of a thrombus; administration of thrombolytic drugs direct to the thrombus, balloon angioplasty or most commonly, insertion of a stent.

Balloon angioplasty was the earliest form of PCI but was limited by unpredictable vessel closure and high rate of restenosis at the site of the treated lesion due to vessel recoil, plaque prolapse and constrictive remodelling. The implantation of metal stents overcame many of these early issues with balloon angioplasty. The additional mechanical strength resulting in increased luminal diameter helped prevent vessel recoil and remodelling. However, there were two important limitations with these early stents. The first, stent thrombosis (ST) was reported to have occurred in approximately 25% of cases within 14 days of stent implantation despite judicial use of heparin, thrombolytics and/or anticoagulation.[18]

The second limitation, in-stent restenosis (ISR) is defined as a reduction in lumen diameter after PCI determined by an excessive tissue proliferation in the stented artery

'neointimal proliferation', or by new-occurring atherosclerotic process called 'neoatherosclerosis'.[19] Risk factors for restenosis include diabetes, smoking, reduce left ventricular function, age gender and previous by-pass surgery.[19]

Drug eluting stents and improvements in stents design including thinner struts and more biocompatible polymer coatings as well as stents that are fully bioresorbable have reduced the occurrence of ISR.

Stent thrombosis, although rare (<2% in the first year) has a major clinical impact with mortality as high as 45%.[20] There are a number of mechanisms leading to stent thrombosis including patient, pharmacological, procedural, lesion and device factors, as well as platelet and coagulation factors.

Patients presenting with ACS, diabetics, smokers, those with severely depressed left ventricular function and chronic kidney disease are at increased risk of stent thrombosis.[21] High post-intervention platelet reactivity, thrombocytosis, hypercoagulable state and antiplatelet resistance should also be considered,[22, 23] but early discontinuation of antiplatelet therapy is the leading cause of stent thrombosis.[21]

The use of drug-eluting-stents (DES) has shown to be more effective in reducing stent thrombosis and restenosis over bare metal stents (BMS) and the newer generation of DES may also be more effective at reducing stent thrombosis over the first-generation DES.[24, 25]

Regardless of stent type, the insertion of a stents(s) mandates a period of dual antiplatelet therapy (DAPT), most commonly a combination of aspirin and $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel or ticagrelor). The use of DAPT in the setting of PCI has been an established strategy since the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial published in 1996.[26] In this trial patients were randomised to receive either antiplatelet

therapy (ticlodipine plus aspirin) or anticoagulant therapy (intravenous heparin, phenprocoumon, and aspirin). The primary end point was a composite of cardiovascular death, MI, aortocoronary bypass surgery, or repeat angioplasty occurred in 1.6% of those in the antiplatelet arm and 6.2% in the anticoagulant arm (RR 0.25, 95%CI 0.06-0.77).

Since the ISAR trial, $P2Y_{12}$ inhibitor therapy has been refined; firstly, to safer therapy (from ticlodipine to clopidogrel) and more recently to more potent/consistent and predictable therapy (clopidogrel to prasugrel or ticagrelor),[27-31] particularly amongst patients with ACS. However, improved antiplatelet effect with prasugrel and ticagrelor over clopidogrel, comes with a cost of increased major and fatal bleeding. In the TRITON-TIMI 38 trial (Trial to assess Improvement in Therapeutic Outcomes by optimising platelet inhibition with prasugrel Thrombolysis in Myocardial Infarction 38), 13,608 patients with moderate to high risk ACS undergoing PCI were randomised to prasugrel or clopidogrel.[31] The primary endpoint of CV death, nonfatal MI or nonfatal stroke occurred in 12.1% of patients receiving clopidogrel and 9.9% receiving prasugrel (HR 0.81, 95%CI 0.73-0.90; P<0.001), however, major bleeding occurred in 2.4% receiving prasugrel and 1.8% of patients receiving clopidogrel (HR 1.32, 95%CI 1.03-1.68; P=0.03).

In the PLATO (PLATelet inhibition and patient Outcomes) trial 18,624 patients with an ACS were randomised to clopidogrel or ticagrelor.[32] The primary endpoint of CV death, MI, or stroke occurred in 9.8% receiving ticagrelor compared to 11.7% receiving clopidogrel (HR 0.84, 95%CI 0.77-0.92; P <0.001). In patients not undergoing coronary artery bypass grafting, bleeding events were 4.5% in those receiving ticagrelor and 3.8% in those receiving clopidogrel (P=.03).

Research has also focused on the optimal duration of therapy.[33-37] The necessity to study longer durations (beyond one year) of DAPT first arose due to the risk of late stent

thrombosis occurring after first-generation drug-eluting stent implantation. However, the rate of stent thrombosis amongst the new-generation DES is low at 0.5%, (95%CI 0.3-0.7 per 100 person-years).[38] Therefore, the ongoing risk of bleeding associated with prolonged DAPT does not justify the absolute benefit in preventing stent thrombosis, although there may be additional benefit from reducing development of thrombosis in non-stented arteries as well as providing systemic benefit from reducing stroke and peripheral artery occlusion.

More recent research has focused on the systemic benefits from DAPT on reduction of cerebrovascular and peripheral vascular events and on the use of 'triple therapy' with low dose direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) and without.[39-45] However, the addition of oral anticoagulants to antiplatelet therapy for the longer term prevention of ischaemic events (in patients without other indication for anticoagulation) post ACS has been limited by the excess in bleeding events.[46]

The Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) RCT investigated a range of doses of apixaban (2.5mg twice daily, 10mg once daily, 10mg twice daily and 20mg once daily) in 1715 patients with a recent ACS. Nearly all patients received aspirin and 76% clopidogrel. The primary endpoint was major or clinically relevant bleeding and secondary endpoint was the composite of CV death, MI severe recurrent ischaemia, or stroke. The two higher dose apixaban arms were discontinued early due to excess bleeding. There was a trend towards lower rates of ischaemic events (compared to placebo) in the remaining treatment arms but with a more pronounced increase in bleeding.

In the ATLAS ACS 2-TIMI 51 trial 15,526 patients with a recent ACS were randomised to receive 2.5mg or 5mg twice daily rivaroxaban or placebo.[39] 93% of patients were prescribed a $P2Y_{12}$ inhibitor in addition to aspirin. The lower dose (one quarter of the stroke prevention dose in AF) was associated with a decrease in CV mortality (2.7% vs 4.1%, *P*=0.002) but not the higher dose. Both doses were associated with an increase in non-fatal bleeding.

Current guidelines recommend for a minimum of one year of DAPT for patients presenting with an ACS undergoing stenting at low risk of bleeding, reduced to six months amongst those at higher risk of bleeding (figure 1.4).[47, 48] Amongst those with stable CAD undergoing PCI with stenting at low risk of bleeding the minimum duration of DAPT is 6 months, decreasing to 3 months amongst those at higher risk of bleeding.

In practice, the duration of DAPT may be dependent on a number of clinical characteristics. Duration may be shorter than guidelines to accommodate the need for future surgery; or to take account of risk factors for bleeding or poor adherence; the need to initiate or maintain anticoagulation for AF, valvular disease or thromboembolism; or as a result of limited evidence from RCTs in specific subgroups such as the elderly, or those with advanced kidney or liver disease. Duration of DAPT may also continue beyond the one year 'standard' where patients have had multiple revascularisation events, extensive length of stenting or extensive atherosclerotic disease, or have comorbidities such as diabetes and peripheral vascular disease.

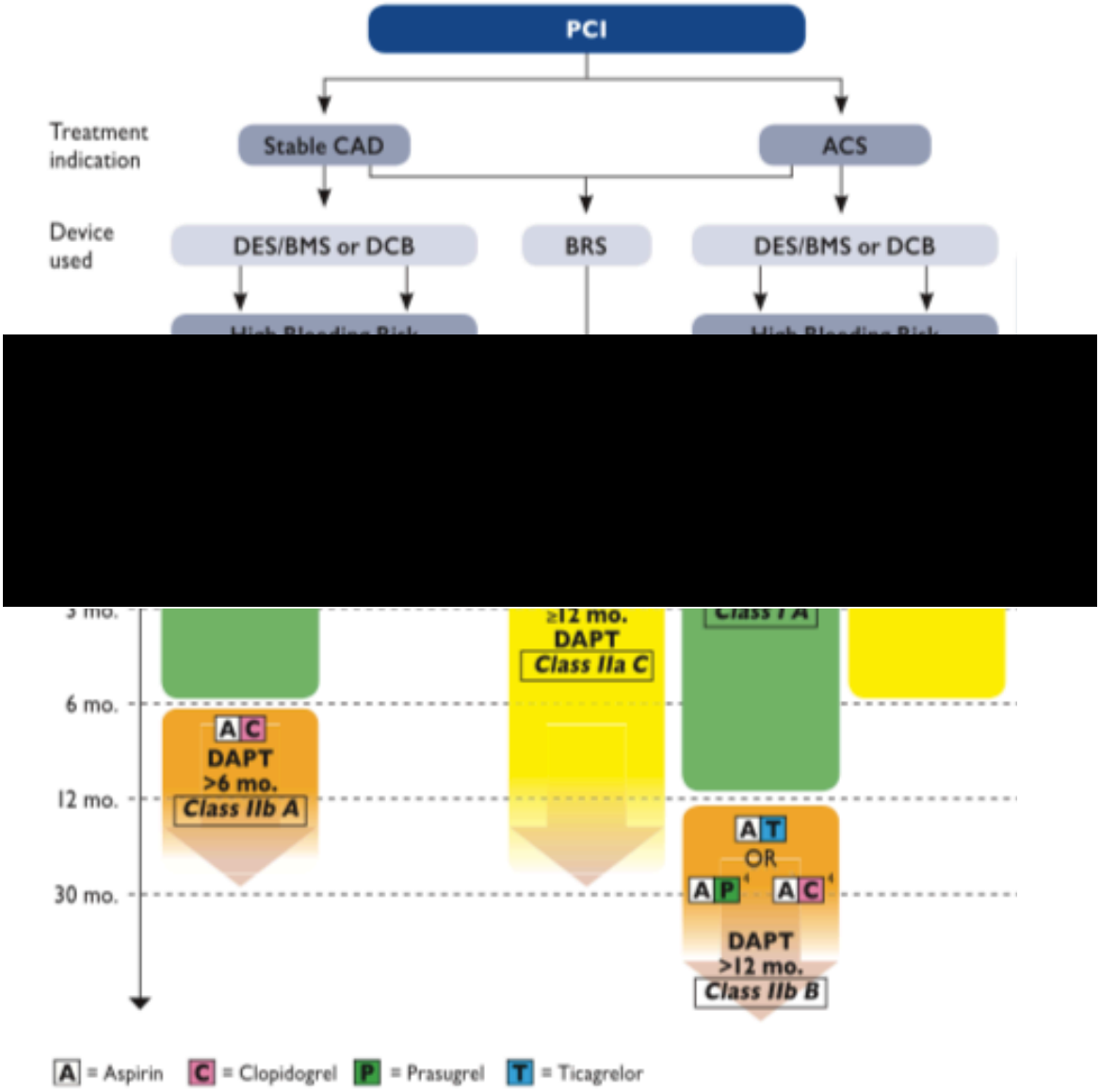

Figure 1.4 Algorithm for DAPT in patients with coronary artery disease.

ACS indicates acute coronary syndrome; BMS: bare-metal stent; BRS: bioresorbable vascular scaffold; DCB: drug-coated balloon; DES: drug-eluting stent; PCI: percutaneous coronary intervention; stable CAD: stable coronary artery disease. Colour-coding refers to the ESC classes of recommendations (green = Class I; yellow = Class IIA; orange = Class IIb).

From Valgimigli et al. *Eur Heart J*. 2018; 39, 213-254.[47]

Revascularisation with coronary artery bypass grafts

While this thesis focusses on the evidenced based management of patients post PCI as opposed to medically managed or those undergoing coronary artery bypass grafting (CABG), for completeness it is worth mentioning a few words on these alternatives.

CABG is a surgical procedure to restore normal blood flow to the heart. The procedure may involve either diverting the left internal mammary artery to the left anterior descending branch of the left coronary artery or harvesting the saphenous vein from the leg and attaching one end to the aorta and the other immediately after the obstruction.

The main advantages of PCI revascularisation compared to CABG include rapid reperfusion, rapid recovery with less post-operative complications, better patient comfort and lower cost. However, CABG may be preferable over PCI in diabetics, patients with reduced LV function (EF<35%), contraindications to DAPT, recurrent diffuse in-stent stenosis and those requiring indication for concomitant cardiac surgery.[49]

Conservative medical management

While PCI is the preferred method of reperfusion for many patients with STEMI or NSTEMI, procedure related complications may limit the feasibility of PCI in the elderly, frail, patients with chronic kidney disease, and left ventricular heart failure. Furthermore, in patients with a tendency to bleed, non-compliant with medicines or require urgent surgery, avoiding PCI with stents and the commitment to a period of DAPT may be preferable. Discontinuing or reducing antiplatelet therapy in patients who are either medically managed or who have undergone CABG is a risk but much less of a risk than in patients who have recently been stented who may experience stent thrombosis.

In the situation where neither PCI or CABG is feasible then an multi-disciplinary team approach consisting of interventional and non-interventional cardiologist may decide the best treatment approach.

In patient with an ACS where medical management is the preferred option, DAPT for one year is recommended in those not at high risk of bleeding, reduced to six months in patients with a high risk of bleeding.[27]

MANAGEMENT OF DYSLIPIDAEMIA IN THE SECONDARY PREVENTION OF CORONARY HEART DISEASE

As previous discussed, ApoB containing lipoproteins play an important role in atherosclerosis. A concordance of information from RCTs, epidemiological studies and Mendelian randomisation studies have consistently demonstrated a log-linear relationship between LDL-C plasma concentration, prolonged exposure to higher LDL-C overtime and increased risk of atherosclerotic CVD.[50-53]

The reduction in LDL-C and other ApoB lipoproteins including very low density (VLDL), intermediate density (IDL), lipoprotein (a) Lp(a) and triglyceride (TG) is a recognised clinical target for both primary and secondary CVD risk management. Again, the concordance of information from RCTs, basic science and observational studies confirms that the greater the absolute reduction in LDL-C the greater the CV risk reduction.[54,55, 56]

Statins are the first line treatment for both the primary and secondary management of CVD risk.[57] The predominant effect of statins is through reduction in LDL-C, with a lesser effect on TG. Statins have also a number of suggested pleiotropic effects including anti-inflammatory and antioxidant effects that may be beneficial in the prevention of CVD. The

degree of LDL-C reduction differs between statins and dose. A high-intensity statin regimen is defined by the European Society of Cardiology/European atherosclerosis Society (ESC/EAS) as the dose of statin that, on average, reduces LDL-C by ≥50%. This includes doses for atorvastatin ≥40mg and rosuvastatin≥20mg per day.

Statins are amongst the most extensively studied medical treatments of all time. The majority of the land-mark statin trials compared either statin vs control or intensive vs less intensive statin treatment rather than a treat to target approach.[58-61] This gave rise to the proposition of a "fire and forget" approach as a strategy of prescribing lipid lowering treatment.[62] However, when the mean achieved LDL-C from these trials are mapped against cardiovascular outcomes, there is a clear trend to lowering CV events with lower LDL-C. A meta-analysis that included >170,000 patients from 26 RCTs of a statin vs control or more intensive vs less intensive regimen, concluded that for each 1mmol/L reduction in LDL-C there was ~ 22% reduction in the major vascular events (a combined endpoint of MI, death from IHD, or stroke or coronary revascularisation) over 5 years.[56]

Despite the impressive benefits of statin therapy, in practice the response to treatment can be variable,[63] and intolerance is reported in 10-20% of patients (largely due to reported muscle pain and myalgia) although in contrast, in RCTs of statin vs placebo there has been little difference, if any in the reporting in muscle symptoms between statin and control groups.[64]

The benefits of lipid lowering on CV outcomes is not limited to statin therapy. Ezetimibe inhibits cholesterol uptake from the intestine which reduces the amount of cholesterol delivered to the liver. In response, the liver reacts by upgrading LDL-recptor expression, leading to reduction in circulating LDL-C in the blood. Clinical trials with ezetimibe have shown a moderate reduction in LDL-C (~15-22%),[65] when added to statin

therapy there is an additional ~15% greater reduction in LDL-C.[66] Clinical trials testing this approach have reported only a moderate 2% absolute risk reduction in clinical outcomes (HR=0,94, 95%CI 0.89-0.99, *P*=0.016) over seven years, commensurate with the moderate additional lowering of LDL-C.[67]

The more recently introduced anti-proprotein convertase substilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) have been shown to provide much more substantial lowering of LDL-C. The PCSK9 protein plays an important role in cholesterol homeostasis, mainly by reducing recycling of LDL receptors to the surface of hepatocytes. The mAbs evolocumab and alirocumab target the PCSK9 protein resulting in an increase surface expression of LDL receptors that subsequently results in decreased circulating LDL-C levels.

Clinical studies of the PCSK9 antagonists, either alone or in combination with statins, and/or other lipid lowering agents results in a substantial reduction in LDL-C (~60%). Two clinical trials have examined cardiovascular outcomes with these agents: the Further Cardiovascular Outcomes Research with PCSK9 inhibition in subjects with Elevated Risk (FOURIER)[68] and the Evaluations of cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY outcomes).[69] Both these trials recruited patients with a history of a ASCVD (ODYSSEY also included recent ACS within 1 to 12 months), prescribed maximally-tolerated statin therapy with an LDL-C ≥1.8mmol/L. Patients in both trials were randomised to the respective PCSK9 or placebo with follow up of 2.2 (FOURIER) and 2.8 (ODYSSEY)years. The benefits ranged from 15-20% reduction in the primary endpoints of adverse CV outcomes.

Fibrates have only a marginal, <20% reduction in LDL-C but are estimated to reduce TG levels by ~50%. The overall benefit on CV mortality is much less robust than statins, except

in subsets of the population with atherogenic dyslipidaemia (high TG levels and low HDL-C).[70]

The further lowering of LDL-C and improved CV outcomes with these non-statin agents has enforced the message of the importance of LDL-C lowering to treatment goals over a fire and forget approach. The latest (2019) ESC/EAS guidelines now recommended that LDL-C reduction of ≥50% from baseline and a LDL-C goal of <1.4mmol/L [<55mg/dL] in very high CVD risk patients, (reduced from <1.8mmol/L [70g/dL], in the 2016 guidelines) and <1.0mmol/L [<40mg/dL] in patients with recurrent atherosclerotic cardiovascular events within the previous 2 years.[57, 71]

Guidelines have also incorporated ezetimibe and PCSK9 inhibitors to be used in a step wise approach for patients at high risk (or above) of CV events who are not at target (or intolerant) with statin therapy.[57]

Additional therapeutic targets have been identified in recent years. The REDUCE-IT trial tested icosapent ethyl in patients established cardiovascular disease or with diabetes and other risk factors, prescribed statin therapy with a fasting TG level of 1.5-5.6mmol/L.[72] Over a median 4.9 year follow up the primary endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularisation, or unstable angina occurred in 17.2% of patients in the icosapent ethyl group, compared with 22.0% in the placebo group.

Furthermore, recent real-world studies in patients with known ASCVD and controlled LDL-C, have observed that patients with even moderately raised TG levels are at an increased risk of ASCVD, affirming hypertriglyceridaemia as an additional therapeutic risk factor.[73]

ESC guidelines now recommend considering prescribing N-3 fatty acids (N-3) in patients at high risk (or above) with TG levels between 1.5 and 5.6mmol/L despite statin therapy. [57]

ATRIAL FIBRILLATION

In a normal sinus rhythm electrical impulse originating in the sinoatrial node (SA node) of the right atrium sends an electrical impulse through the right and left atria, causing them to contract and force blood through to the respective ventricles (figure 1.5). The electrical impulse travels to the atrioventricular (AV node) which provides an electrical bridge to the ventricles allowing them to contract and pump blood out of the heart in a synchronised manner.[74]

In AF electrical impulses are disorderly, with many impulses beginning and spreading at the same time through the atria, competing to travel through the AV node. The AV node limits these impulses traveling through the ventricles, but many get through resulting in irregular and rapid ventricular contractility and heartbeat.

Dysregulation in heart rhythm from SA control can result in the heart rate being unable to adjust its rate effectively to normal stresses and demands of the body. Increase in resting heart rate and exaggerated heart rate response to exercise can result in shorter diastolic filling time, reducing cardiac output. This is further affected by irregular ventricular response. Loss of atrial contractile function can lead to diastolic dysfunction and atrial remodelling.[75]

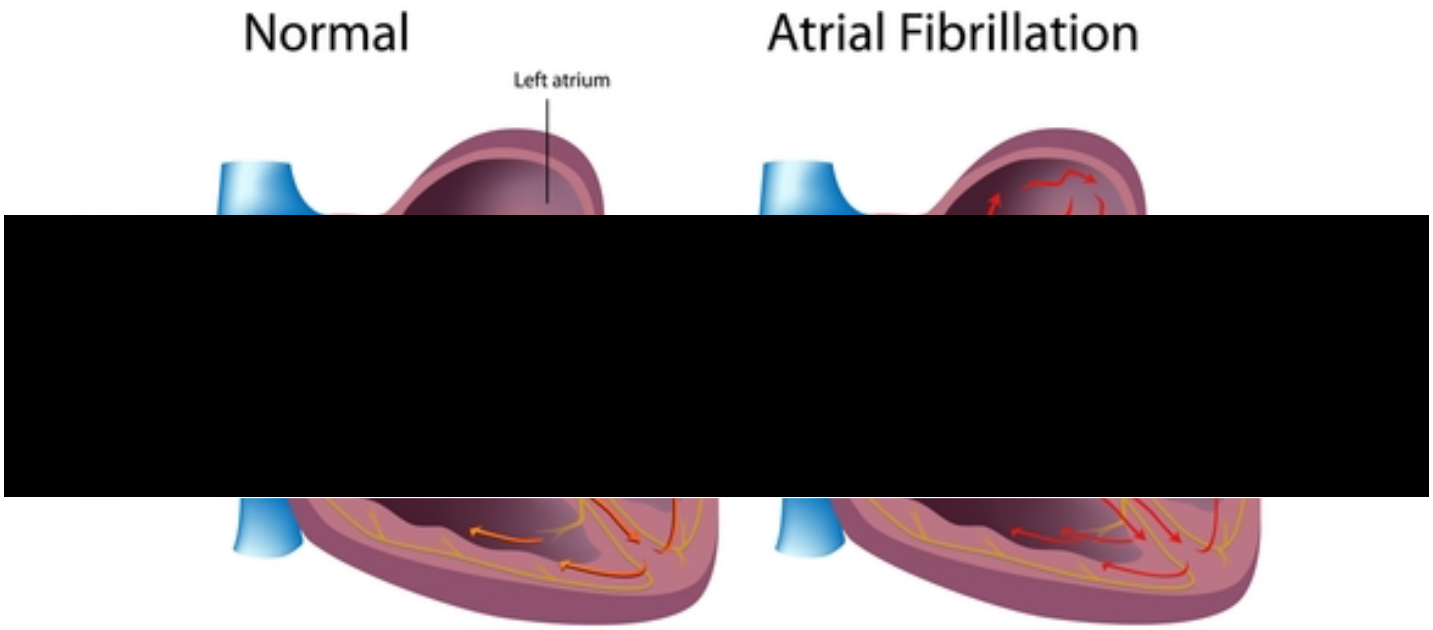

Figure 1.5 Electrical impulses in 'normal' sinus rhythm and in atrial fibrillation.

From http://www.secondscount.org/heart-condition-centers/info-detail-2/what-is-atrial-fibrillation-afib-af#.YKJ9aC1Q3GI

The prevalence of AF is estimated to be between 2-3%.[76, 77] Prevalence increases with age and in patients with hypertension, diabetes, heart failure, IHD, valvular heart disease, obesity or chronic kidney disease.[78, 79] AF is independently associated with an increase in all-cause mortality,[80-82] quintuples the risk of stroke[83] and accounts for approximately 20% of all ischaemic strokes. Strokes due to AF tend to be more severe and associated with a higher mortality.[80, 81, 84, 85]

AF also increases the risk of systemic embolic events (SEE). The frequency of these extracranial events is less well documented in both real-world studies and RCTs of anticoagulant in AF. Pooled data from four large RCTs of anticoagulation in AF estimate the risk of SEE at 0.24 per 100 patient years compared with 1.92/100 patient years for cerebral embolism.[86] The majority of these SEE occurred in the lower extremities (54%), 31%

mesenteric and 10% in the upper extremities. Despite these relatively rarer events, morbidity and mortality is high with 60% requiring endovascular or surgical intervention and 25% mortality within 30days.

MANAGEMENT STRATEGY FOR ATRIAL FIBRILLATION

Outside of the management of patients who present acutely and haemodynamically unstable the management of AF involves (i) identification and correction of precipitating risk factors such as hypertension, thyrotoxicosis or hyperthyroidism, infection, excess alcohol consumption or amphetamine and other illicit drug use; (ii) assessing and managing the risk of stroke; (iii) assessing heart rate and considering rate control therapy and (iv) considering rhythm management for symptomatic improvement.[87]

MECHANISM OF THROMBOSIS IN ATRIAL FIBRILLATION

Thrombogenesis in AF is multifactorial: blood stasis, endothelial dysfunction and clotting activation (figure 1.6) are factors thought to contribute to thromobosis.[88, 89] The most common site of intra-atrial thrombus formation is the left atrial appendage (LAA) (a long narrow pocket) is predisposed to blood stasis. Dilated atria, impaired contractility, and changes in the left atrial appendage occur as a result of AF give rise to abnormalities in blood flow and stasis in the left atria. Damage to the endothelium increases production of von Willebrand factor (a glycoprotein that act as a bridging molecule at sites of vascular damage and promotes platelet aggregation). Abnormal haemostasis and coagulation are also noted in patients with AF.

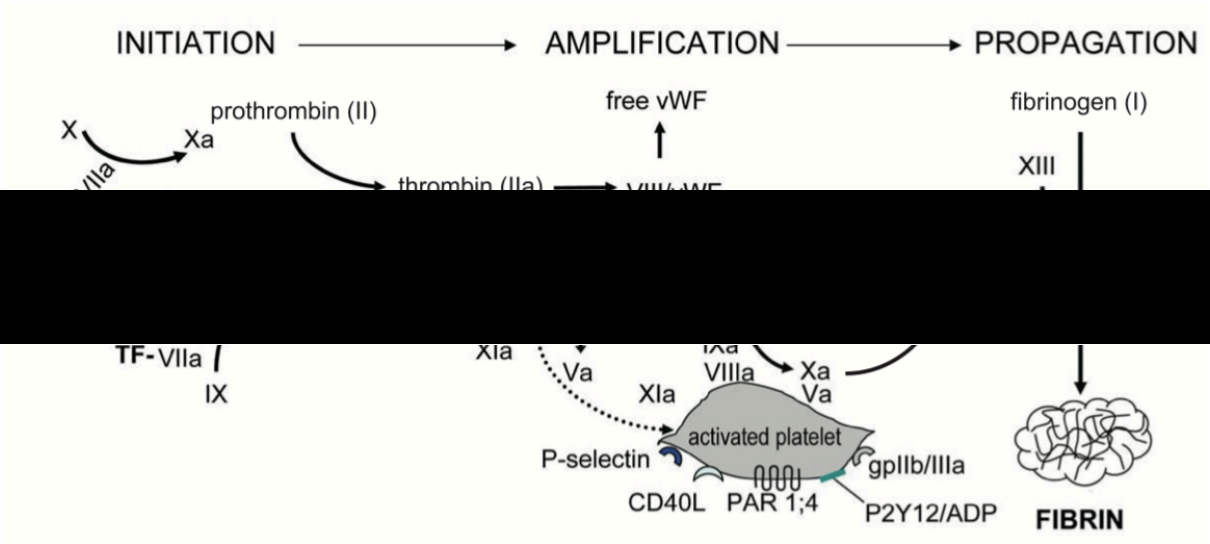

Figure 1.6 Phases of coagulation processes leading to formation of fibrin clot.

Three overlapping phases are involved in the cell surface-based coagulation. The initiation phase starts with vascular injury, tissue factor (TF)-expressing cells are exposed to coagulation factors in the vessel lumen, initiating thrombosis. Platelets are activated and recruited to the site of injury. TF/FVIIA complexes activates coagulation factors IX, IXa, X and Xa generating small amounts of thrombin. The amplification phase results in signalling further platelet activation and aggregation, Thrombin on the surface of platelets activates FV, FVIII and FXI. In the propagation phase, binding of FVIIIa with FIXa, and FVa with FXa on platelet surfaces accelerates the production of FXa and thrombin. During propagation sufficient thrombin is generated for the clotting of soluble fibrinogen to form a fibrin meshwork.

From De Caterina R et al. General mechanisms of coagulation and targets of anticoagulants. Thrombosis and Haemostasis. 2013; 109: 569-579.[90]

The oral anticoagulants (OAC) include the vitamin-K antagonists (VKA) (most commonly warfarin) and direct oral anticoagulants (DOAC). Both groups are highly effective at preventing ischaemic strokes in AF [91-96], but differ significantly in their mechanism of inhibition within the clotting cascade (figure 1.7), prescribing and monitoring requirements.

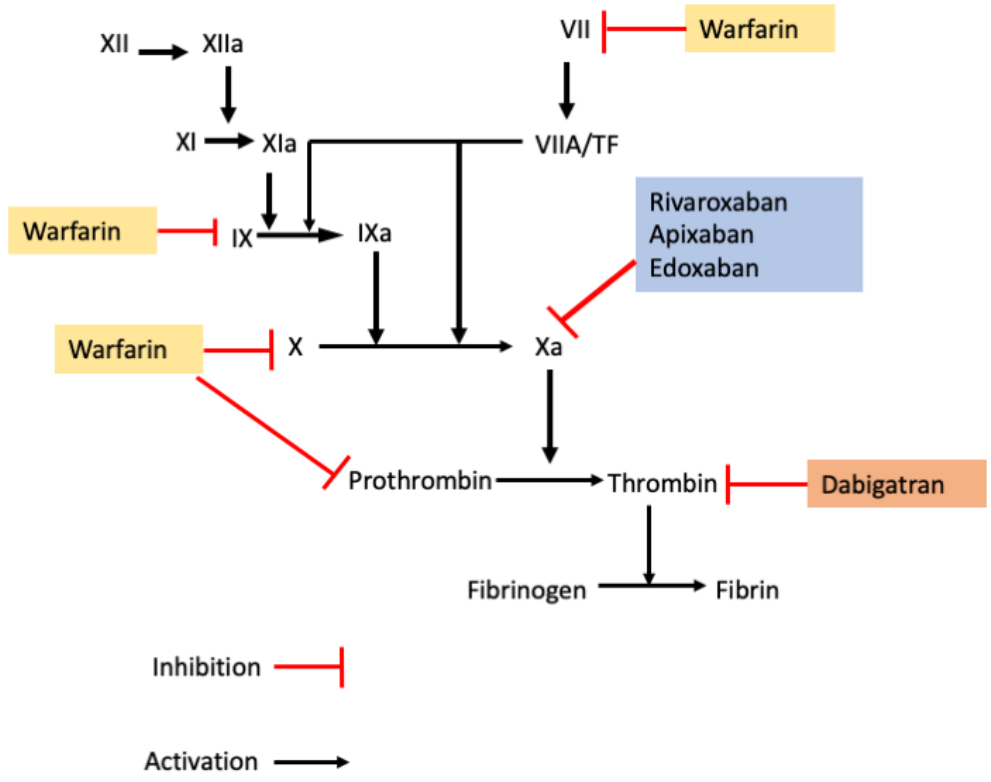

Figure 1.7 Coagulation cascade and site of inhibition for warfarin and DOAC.

Vitamin K is essential to the production of several coagulation factors including factors II, VII, IX and X, as well as regulatory factors protein S and C. VKAs competitively inhibits vitamin K epoxide reductase complex 1, an essential enzyme for activating Vitamin K.

VKAs have been successful in reducing the risk of stroke[97], with a meta-analysis of 29 trials including 28,044 patients concluding dose adjusted warfarin conferred an approximate two-thirds reduction in stroke.[91] Despite their effectiveness, there are a number of practical limitations to the use of VKAs including the high intra and inter-patient variability in response and the requirement to monitor and dose adjust according to the International Normalised Ratio (INR). Guidelines recommend maintaining an INR between 2 to 3.[87, 98, 99] Increased INR is associated with increasing risk of bleeding while subtherapeutic INR increases the risk of stroke and systemic embolism. The net clinical benefit of warfarin is associated with the proportion of time that INR values are maintained within the therapeutic range, referred to as the time in therapeutic range (TTR).[100, 101] TTR> 70% is associated with the greatest reduction in stroke and least bleeding events[102] while TTR<50% offers no greater stroke protection than no therapy.[100]

In earlier placebo controlled trials, aspirin was reported to offer a 42% reduction in stroke and systemic embolism events (6.3% vs 3.6% per year).[103] However, further studies and a meta-analysis of seven trials comparing aspirin and placebo in patients with AF with additional risk factors for stroke concluded that the stroke risk reduction with aspirin was a more modest and non-significant 20% reduction.[91]

In comparison with VKAs, aspirin provides far less reduction in stroke but confers as high a bleeding risk as OAC.[104] The Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA) randomised patients ≥75 years with AF to either warfarin (target INR 2-3) or aspirin 75mg once daily (published 2007). Mean follow up was 2.7years, the yearly risk of the primary-endpoint of fatal or disabling stroke, intracranial haemorrhage, or clinically significant arterial embolism in warfarin group occurred in 1.8% vs 3.8% for the aspirin group; absolute yearly risk reduction 2%, 95% CI 0·7–3·2. The yearly risk of extracranial haemorrhage was 1.4% warfarin vs 1.6% (aspirin); absolute risk reduction 0.2%, 95%CI -0.7 - 1.2%.

The ACTIVE-W trial tested combination antiplatelet therapy (aspirin plus clopidogrel versus warfarin in patients with AF. However, this trial was stopped early because of clear evidence of superiority of OAC in reducing vascular events (stroke, SEE, MI or vascular death) and a lower risk of major bleeding with OAC.[105]

Despite the above trials showing superiority of VKAs, aspirin continued to be prescribed in AF, in part due to the recognition of the unsuitability of warfarin for many patients, intensive monitoring requirements, extensive interactions with other medicines and food and, importantly patient refusal of this treatment.[106]

The DOACs include the factor Xa inhibitors apixaban, edoxaban and rivaroxaban and the direct thrombin inhibitor dabigatran. In comparison to VKAs, the DOACs are prescribed at fixed doses, require infrequent monitoring and dose adjustment based only on weight, age and renal function.

In 2011 the AVERROES RCT tested apixaban vs aspirin in 5599 patients in whom VKA therapy was unsuitable.[104] The trial was stopped early due to superiority of apixaban; the primary outcome of stroke or systemic embolism was 1.6% per year in the apixaban group and 2.7% per year in the aspirin arm (HR with apixaban, 0.45; 95%CI, 0.32-0.62, $P<0.001$). There was no significant difference in major bleeding events (1.4 vs 1.2%, $P=0.57$).

In 2012 the ESC updated their AF guidance with the withdrawal of aspirin for stroke prevention in AF[107], followed by the National Institute for Health and Care Excellence (NICE) doing so in 2014.[108] International guidelines now recommend OAC in all patients with AF except those as the lowest risk of ischaemic stroke where the risk of bleeding may exceed the net benefit from reduction in stroke.[87, 109]

Trials comparing each of the DOACs vs warfarin showed a decrease in overall bleeding events with DOACs[93, 95, 96, 110] with some also showing a reduction in stroke or systemic embolism[93, 96] and a reduction in mortality.[93]

Clinical risk scores for stroke and bleeding risk in patients with Atrial fibrillation

The risk of stroke or systemic embolism amongst patients with AF is dependent on various clinical and echocardiographic features. Understanding the individual's stroke risk is necessary to inform decisions on anticoagulation, which can be a delicate balance between decreasing stroke risk and increasing the risk of bleeding.

Several risk stratification tools based on small population observational studies have been available[111, 112], however, the CHA_2DS_2-VASc score developed using data from large registries and surveys, provides a simple and validated method of calculating annual stroke risk for which decisions on prescribing anticoagulation can be based.[113]

The risk of stroke in patients with AF using the CHA_2DS_2-VASc score is calculated as: (Congestive heart failure, 1point; hypertension, 1 point; age 65-74, 1 point, age≥75, 2 points, diabetes, 1 point; prior stroke or TIA, 2 points and vascular disease [prior MI, peripheral vascular disease or aortic plaque], 1point). As the CHA_2DS_2-VASc score increases so does the adjusted annual risk of stroke (table1.1). International guidelines recommend considering prescribing OAC in patients with a risk score of ≥1 in males and ≥2 in females.[87, 109]

Table 1.1 Adjusted stroke rate based in CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Adjusted stroke rate (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.9
7*	9.6
8*	6.7
9*	15.2

*for CHA_2DS_2-VASc score ≥7 there was insufficient power to accurately calculate the stroke rate.

Adapted from Lip GY, Nieuwlaat R, Pisters R, et al. 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: 263-272.

The benefits of stroke prevention with OAC needs to be carefully balanced with the increase risk of bleeding. Risk factor scores have been predominantly developed based in patients prescribed VKA including the HAS-BLED (hypertension [uncontrolled, >160mmHg systolic], 1 point; abnormal renal/liver function, 1 point each; history of stroke, 1point; bleeding history or predisposition, 1point; labile INR, 1 point; 1 Age >65years, 1 point; drugs/alcohol (antiplatelet agents, non-steroidal anti-inflammatory agents) 1 point each (table 1.2).[114] The HAS-BLED score was developed from the data from a cohort of 3,978 patients prescribed VKA and enrolled in the Euro Heart Survey on AF (a European registry). The predictive accuracy in the cohort (C statistic 0.72) was consistent when applied across multiple subgroups. The HAS-BLED score has since been incorporated into international guidelines on AF management.[87, 109]

Stroke and bleeding risk factors can overlap. However, where the stroke risk calculated from the CHA_2DS_2-VASc can only increase, the bleeding risk calculated with the HAS-BLED score is partially modifiable and is intended to be used to identify and manage risk factors for bleeding. In patients with a high bleeding risk, it is recommended that bleeding risk factors be identified and managed, rather than withholding OAC where possible.[87]

Table 1.2 Adjusted bleed rate in HAS-BLED score

HAS-BLED score	Adjusted bleed rate (%/year)
1	1.3
2	1.88
3	3.74
4	8.7
5	12.5

Adapted from Lip GY, Nieuwlaat R, Pisters R, et al. 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: 263-272.

ATRIAL FIBRILLATION IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

IHD is a risk factor for developing AF and similarly hypertension, increasing age and left ventricular dysfunction are shared risk factors for both IHD and AF. Approximately 10% of patients undergoing PCI have AF, although estimates vary from 6-12%.[115-117] Furthermore, new-onset AF has been reported to occur in ~6-8% of patients within 7days of PCI.[118, 119]

The presence of AF in patients undergoing PCI represents a clinical challenge. DAPT is recommended to prevent in-stent thrombosis and coronary artery occlusion in patients undergoing PCI for both ACS and elective stenting.[27, 48] In patients with AF, OAC been shown to be superior to the combination of aspirin and clopidogrel in preventing vascular events (stroke, systemic embolism, myocardial infarction(MI) and death).[120] The combination of DAPT plus OAC, referred to as triple antithrombotic therapy (TAT) may provide both coronary and cerebral protection but increases the risk of bleeding.[121-123]

Despite this relatively common clinical dilemma, prospective trials, real-world observational studies and registry data investigating optimal antithrombotic therapy in AF patients undergoing PCI have been sparse. The What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial was the first prospective randomised trial to test the use of clopidogrel alone with OAC versus TAT in patients undergoing PCI where there was an additional indication for OAC.[123] In this small trial of 573 patient with follow up for one year there were fewer bleeds in the OAC+AP group 19.4% vs 44.4% in the TAT group (HR 0.36, 95% CI 0.26-0.50, P<0.0001), although the reduction in bleeding was particularly confined to minimal and minor bleeding events, with a non-statically significant reduction in major bleeding. There was no increase in thrombotic events, including MI, target vessel revascularisation and stroke. However, this

small open label study had a number of limitations, including low numbers to assess differences in thrombotic outcomes, procedural antithrombotic therapy was not described, and the trial included patients with indication for OAC other than AF. Despite these limitations this study was the first prospective study to assess TAT vs OAC+AP antithrombotic therapy in patients undergoing PCI with indications for OAC.

Studies utilising Danish registry data have analysed the risk of MI/coronary death, ischaemic stroke, and bleeding according to multiple antithrombotic therapy regimens in patients with AF hospitalised with MI and /or undergoing PCI between 2001-2009.[124] Compared to TAT, bleeding risk was non-significantly lower for OAC+clopidogrel (HR 0.78, 95% CI: 0.55 to 1.12) and significantly lower for OAC+aspirin and aspirin+clopidogrel. There was no increased risk of recurrent coronary events with either OAC+clopidogrel (HR 0.69, 95%CI 0.48-1.00), OAC+aspirin (HR 0.96, 95%CI 0.77-1.10) or aspirin+clopidogrel (HR 1.17, 95%CI 0.96-1.42), but aspirin+clopidogrel was associated with increased risk of stroke (HR1.50, 95%CI 1.03-2.20) vs TAT. The low rate of PCI (<50%) amongst the population, lack of prospective randomisation, and potential for cofounding limits the generalisability of these data to contemporary PCI population.

Recent RCT have investigated DOAC vs VKA based TAT and OAC+AP strategies in patients with AF undergoing PCI or with recent ACS.[40, 42-44] These studies have demonstrated lower bleeding events with DOAC based strategies and lower bleeding events with OAC+AP compared to TAT with the exception of the edoxaban based trial which was non inferior to VKA.

These trials demonstrated lowering bleeding events amongst patients receiving DOAC (bleeding event rate ranged from 10.5% to 17% depending on trial) compared to 14.7% to 26.7% amongst patients receiving VKA. These trials were underpowered to examine ischaemic outcomes and therefore the optimal antithrombotic strategy that minimises bleeding events

while also preventing stroke and recurrent coronary ischaemic events is still unknown. Furthermore, these trials included patients that were primarily undergoing elective PCI for stable angina or medically managed ACS patients. Therefore, these results may not be applicable to the contemporary PCI population which predominantly undergo PCI for an ACS.

Despite the limitations in the data, these prospective trials provide the best evidence to guide practice in managing this clinical situation. Current European and North American guidelines recommend a tailored approach to prescribing antithrombotic therapy in this population based on thrombotic and bleeding risk, and thus limiting overall exposure to TAT (figure 1.8).[125, 126]

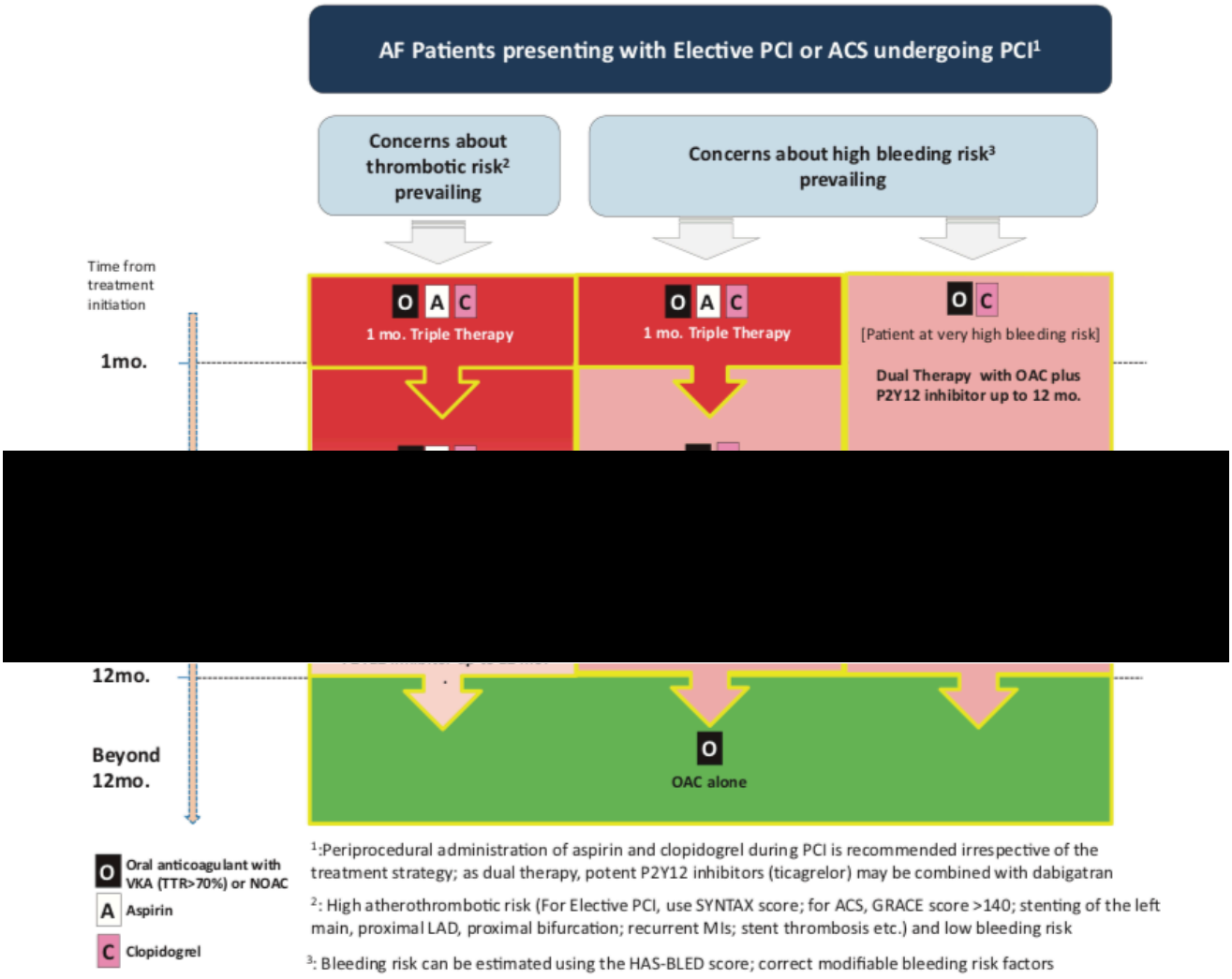

Figure 1.8 Management algorithm for AF patients presenting with elective PCI or ACS undergoing PCI.

From Lip et al. *Eur Heart J.* 2018; 39: 2847-2850.[125]

USING REAL-WORLD DATA TO IDENTIFY AND DESCRIBE GAPS IN THE DELIVERY OF THE EVIDENCED BASED MEDICINE

Despite an extensive evidence base into the management of IHD and AF, the delivery of evidence-based medicine is frequently suboptimal. Identifying and characterising gaps in the management of patients has the potential to improve clinical outcomes and reduce the burden of disease at both an individual and population level. The following provides a brief outline of the objectives of each of the results chapters presented in this thesis:

OBJECTIVES OF CHAPTER 2

Real-world data on antiplatelet use post-PCI suggests that delay in access or premature discontinuation of $P2Y_{12}$ antagonist treatment is associated with an increase in adverse outcomes.[127, 128] However, these studies have not taken account of the intended duration of therapy or bleeding events that may occur, resulting in cessation of antiplatelet treatment.

Our objectives were (i) to analyse the early discontinuation rate of $P2Y_{12}$ antagonists post PCI, (ii) explore factors associated with early discontinuation and (iii) analyse the risk of major adverse cardiovascular events (MACE: death, acute coronary syndrome, revascularisation or stroke) associated with discontinuation from a pre-specified prescribing instruction of one year.[129]

OBJECTIVES OF CHAPTER 3

In September 2019 the European Society of Cardiology & European Atherosclerosis Society updated their guidelines for the management of dyslipidaemia, recommending more intensive lowering of lipids in patients with known or at high risk (or above) of CVD. It is unknown

what proportions of patients at very high CVD risk achieve, or do not achieve, recommended levels of LDL-C (non-HDL-C) and/or TGs; and how these respective patient groups are treated. The objectives of this study were to document (i) lipid lowering treatment (LLT) and (ii) achievement of prior and current ESC/EAS lipid targets in a contemporary national cohort of patients post-percutaneous coronary intervention (PCI), who would be considered to be at very high CVD risk according to the ESC/EAS classification.[130]

Objectives of Chapter 4

In patients with non-valvular atrial fibrillation (NVAF) prescribed warfarin, the UK National Institute for Health and Care Excellence (NICE) defines poor INR control as a TTR of <65%, any 2 INRs within a 6-month period of ≤1.5 ("low"), 2 INRs ≥5 within 6months, or any INR ≥ 8 ("high").

Variability in INR control described by frequency of very low or very high INRs (as defined by NICE), as distinct from TTR, has not been previously described. The objectives of this study were (i) to quantify the number of patients with NVAF prescribed warfarin who exhibit NICE-defined poor INR control and (ii) describe the demographic and clinical characteristics of these patients, as well as the relationship between these characteristics and poor INR control.[131]

Objectives of Chapter 5

In patients with NVAF prescribed warfarin, the association between guideline defined 'poor' INR control and bleeding outcomes has not been fully characterised. The objectives of this

study were to (i) quantify bleeding rates, and (ii) evaluate associations between bleeding, comorbidities, and poor INR control.

Objectives of Chapter 6

Real world data examining outcomes in patients with AF who have undergone PCI are limited and the association between bleeding and ischaemic outcomes has not been fully evaluated. Our objectives were to analyse the rate of hospitalisation for major cardiovascular events, haemorrhage and mortality in patients with AF in the first year after successful PCI, accounting for risk factors and antithrombotic regimen.

Objectives of Chapter 7

In this conclusion chapter we bring together the key themes from this thesis; summarise the gaps identified in the provision of evidenced based medicine, discuss the strengths, and importance of the novel elements of the presented studies as well as the limitations of real-world data.

METHODS

This section provides detail on how I collected, processed, and analysed the data used in this Ph.D. Acquiring and processing the cardiac intervention and discharge prescribing datasets, as well as the identification of the extensive list of codes used for the classification of cardiovascular disease, haemorrhagic events, comorbidities, risk factors, and medicines represented a substantial proportion of the time taken to complete this Ph.D. Therefore, I have given additional emphasis on those processes here. In addition, the methodology specific to each of the studies is contained within the respective outcome chapters.

SECURE ANONYMISED INFORMATION LINKAGE DATABANK

The data used in this Ph.D. was predominantly accessed and processed using the Secure Anonymised Information Linkage (SAIL) Databank.[132-134] SAIL is part of the national electronic-health records research infrastructure for Wales and contains anonymised data that is routinely collected from health and social care systems. The following core datasets held within SAIL were used for this PhD: the Patient Episode Database for Wales (PEDW),[135] which records hospital admission and discharge dates, diagnoses and operational procedures, demographic data, and date of death where applicable, for patients attending hospital in Wales; the Welsh Longitudinal General Practice (WLGP) dataset[136] containing demographic, clinical and prescribing data for approximately 80% of primary care practices across Wales; the Welsh Demographic (WDS) dataset,[137] which contains basic demographic information and history of individuals' residence in Wales and registration with GP practices; and the Welsh Index of Multiple Deprivation (WIMD) 2011,[138] an area-based deprivation measure. Further detail on some of these core datasets is provided later in this chapter.

GOVERNANCE, ETHICS AND APPROVALS

SAIL provides a secure environment for the processing of person-based data and does not receive or handle identifiable data. The anonymised data is only made available for research projects that offer a potential for benefit and those that have been approved by an information governance review panel (IGRP). The IGRP contains independent members from the National Research Ethics Committee (NREC) and British Medical Association (BMA), as well as lay members of the public.

Each of the studies presented within this Ph.D. used anonymised patient data that is routinely collected for clinical and administrative purposes; therefore, a separate ethics approval was not required, however, each study was approved by the SAIL IGRP.

In line with standard operating procedures for both SAIL and Swansea Bay University Health Board (SBUHB), permission was granted from the data holder of the Cardiac intervention dataset, Dr Geraint Jenkins for the use of that data within this Ph.D. The SBUHB Caldicott guardian approved accessing and transfer of both the cardiac intervention and discharge medication dataset to SAIL.

PROCESSING OF DATA WITHIN THIS THESIS

In this chapter, I have detailed sections of pertinent methodology that I believe will help explain and justify each of the steps taken from identifying and accessing data to analysing and presenting. I have provided examples of the structured query language (SQL) I used for data linkage and data processing with examples of the outputs from my SQL queries; these examples are provided to highlight relevant steps, and I have endeavoured to provide these in a chronological order.

I have concentrated on detailing the methodology from chapter two; this was the first study that I undertook within this thesis, it is where I developed much of the methodology and created lists of diagnostic, comorbidity, risk factor and prescribing codes that were utilised in subsequent chapters. It also describes the additional process of managing a dataset external to the SAIL databank and transporting that data into SAIL.

CORONARY INTERVENTION DATASET

In addition to the core datasets held within SAIL, for chapter two it was necessary to identify patients undergoing percutaneous coronary intervention (PCI) from the Regional Cardiac Centre at Morriston Hospital and record their discharge prescribing data relevant to the admission. These patients were identified from the coronary intervention dataset held at the centre. This dataset contains demographic, procedural (form of PCI undertaken; stent type, number and position, and antithrombotic strategy) and clinical data (presenting electrocardiogram (ECG), indication for PCI, comorbidities, and risk factors). Data held within this dataset is entered at the time of the procedure by the medical team performing the intervention.

DISCHARGE PRESCRIBING DATA

For patients discharged home following PCI from the regional centre, their discharge medication list was identified from the SBUHB electronic transfer of care (ETOC) or discharge system. The ETOC system provides a summary of information for the patients GP regarding their admission to hospital. The medication section of the ETOC details changes to the patient's medicines including those that were stopped, dose changes and new medicines that were started and intended durations.

Initially the individual patient discharge medication regimen was identified by manually searching the ETOC system for records correlating to the admission period for the PCI. However, this process was laborious and extremely time consuming. With thanks to Mr John Fitzgerald from the SBUHB information technology department we were able to link the demographic data and date of intervention from the cardiac intervention dataset to the ETOC system to automate the download of prescription data for the corresponding hospital admission. Where there was either no medication entered on the ETOC or no ETOC for the hospital admission the patient's medical notes were screened for a paper record of the discharge prescription, these data was then entered into a spreadsheet and checked by a second person for transcription errors.

ANONYMISATION OF PERSON DATA

Datasets transferred to SAIL such as the coronary intervention dataset and prescribing dataset require an anonymisation process to protect personal identifiable data (figure 1.9). Firstly, demographic data is split from any clinical or event component. Both of these files have a unique identifier applied. The demographic data is transferred to the NHS Wales Informatics Service (NWIS) and the clinical information with unique identifier is transferred to SAIL.

NWIS anonymises and encrypts the demographic data. Each individual record is assigned an Anonymous Linking Field (ALF). This anonymised demographic data is then sent to SAIL to be recombined with the clinical data. As a final safeguard SAIL further encrypts the ALF to a project encrypted ALF (ALF_PE) before the data is made available. The ALF_PE is a unique identifier, assigned to each individual. Within each project, the same individual can be identified from each of the core datasets using the ALF_PE.

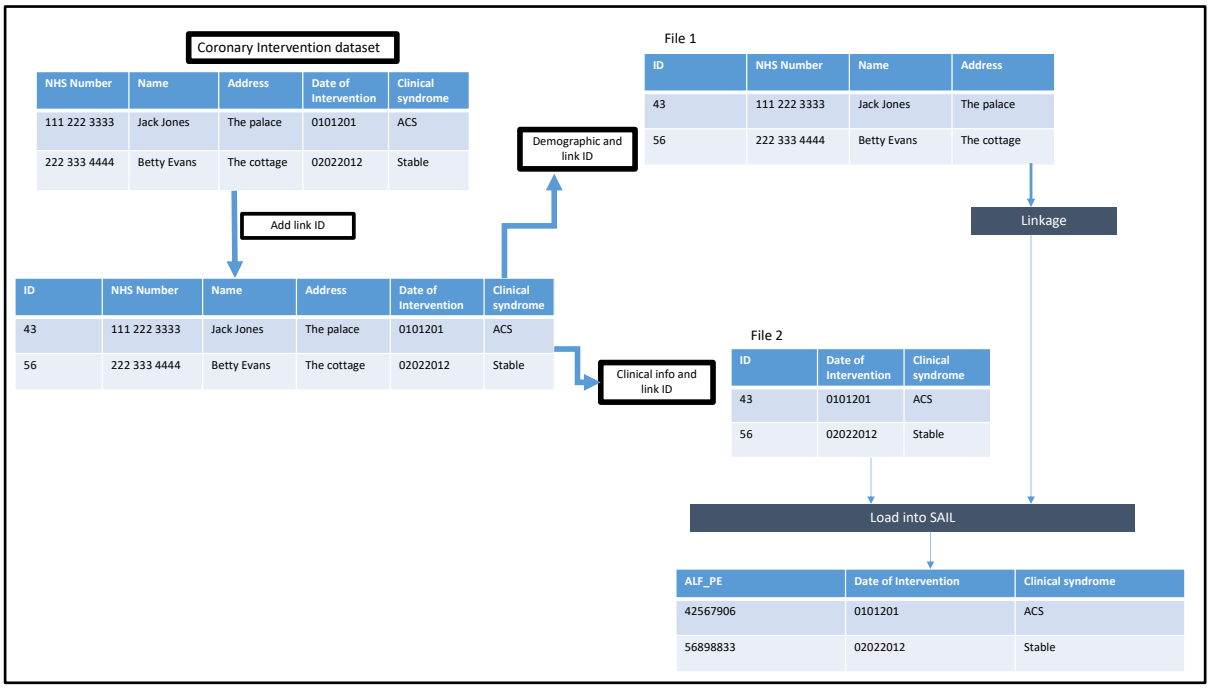

Figure 1.9 Example of anonymisation of datasets for transfer and use within SAIL.

PROCESSING DISCHARGE PRESCRIBING DATASET WITHIN SAIL

The discharge prescribing dataset contained the following columns: ALF_PE; date of intervention; drug name, strength, direction, and duration. Data within the drug name and strength columns contained a mixture of structured and unstructured data, while all the data within the direction and duration columns were unstructured due to it being manually entered into the ETOC system. The drug name column contained both capitalised and lowercase forms for the same drug and the misspelled names (figure 1.10); strength may be presented as 'milligrams', 'MG' or 'mg' or '75mg' and '75 mg', and there were numerous ways of expressing the same duration (figure 1.11). Searching or selecting data in this unstructured format would be liable to error and inefficient so it was necessary to format or 'clean' the data into a structure that could easily be processed (figure 1.12).

```
select count (drug), drug from sail0441v.saildrug
group by drug
 4530 ASPIRIN
 3424 CLOPIDOGREL
 2167 ATORVASTATIN
 1879 SIMVASTATIN
 1485 LANSOPRAZOLE
 1099 RAMIPRIL
  946 GLYCERYL TRINITRATE
  922 CLODPIDOGREL
  //
   19 clopidogrel
```

Figure 1.10 SQL query displaying the frequency of drug names and highlighting the spelling & misspelling of clopidogrel.

```
select count (duration),duration from sail0441v.saildrug d
where  d.drug like '%CLO%'
group by duration
841    1 YEAR
746    1YEAR
518    12 Months
419    12 MONTHS
331    1 Year(s)
302    12 Month(s)
225    1 MONTH
110    Ongoing
92     1 Month(s)
84     1 year
66     12MONTHS
64     1month
53     LIFELONG
47     1year
42     UNSPECIFIED
30     1 month
28     1 Months
28     6 Months
26     3 Months
24     3 Month(s)
20     30 Day(s)
17     ONGOING
17     3 MONTHS
16     3MONTH
15     L
13     U
13     28 Day(s)
12     6 MONTHS
```

Figure 1.11 SQL showing different durations for clopidogrel

```
create  table sailw441v.saildrug_ammend as(
select d.*,
d.duration as duration_orig,  case when duration in ('12MONTHS','12 months','1 YEAR-
','1YEAR','1year','12 Month(s)','1 MONTH FOLLOWED BY 75MG OD FOR ONE YEAR','1 YEAR','12
MONTHS','12 months','12 MONTHS FOR GP TO REVIEW','1 Year(s)','12 MonthS','12 MONTHD','1
year','1YEAR','12 Months') then '1 year'            -- 1 year
 when duration in ('30 days','12 months','ONE MONTH','1 Month','1 Months','30
Day(s)','28 Day(s)','30 Days','4 Week(s)','31 Days','28days',
     '4 Weeks','28 Days','1 MO0NTH','1 MO0NTH','28 DAYS','1 month','4 WEEKS','28
Day(s)','1 Month','1 Month(s)','1MONTH','1month','4 Weeks','28 DAYS','30 Days','31
Days','1 Months','1 MONTH') then '1 month'            -- 1 month
     when duration in ('1 Week(s)','14 Day(s)','4 Day(s)','5 Day(s)','15 Day(s)','2
weeks','12 Days','7 Day(s)','3 Days','1 week','1 WEEK',
     '2 Week(s)','20 Day(s)','7 Days','22 Day(s)','3 Day(s)','3 Days','13 Day(s)','18
Day(s)','18 Days','2 WEEKS DUE TO RAPID ENDOTHELIASATION OF GENOUS STENT',
     '24 Day(s)','5 Days','4 Days','21 DAYS','22 DAYS','25  DAYS','26 DAYS','stop on
discharge','18 days','3 Days','less than 1 month','14 DAYS','25 days')
      then 'less than 1 month'
     when duration in
('ONGOING','INDEFINITELY','INDEFINTELY','life','l','lifelong','lIFELONG','liFELONG','LON
G TERM','Ongoing','INDEFINITELY','INDEFINTELY','ongoing','Life
Long','LIFELONG','lifeLONG','ONGOING','L','life','LONGTERM','LiFELONG') then 'life'
     when duration in('6 Months','6 MONTHS','6MONTH','6 months','6
Month(s)','6months','6 MONTHS THEN REPLACED WITH WARFARIN') then '6 months'
     when duration in('3 Months','3 Month(s)','3MONTH','3months','3
months','3MONTHS','90 Day(s)','3 MONTHs') then '3 months'
     when duration in('U','u','UNSPECIFED','unspecified','uNSPECIFIED','UNSPECIFIED')
then 'unspecified'
else duration end as duration_ammended,
       d.drug as drug_orig, case  when drug in
('CLOPIDOGREL','CLODPIDOGREL','clopidogrel') then 'clopidogrel'
       when drug in('aspirin','ASPIRIN','ASPIRIN E/C','ASPIRIN EC','ASPIRIN M/R') then
'aspirin'
       when drug in ('warfarin','WARFARIN','WARFARIN SODIUM') then 'warfarin'
       when drug in ( 'ATORVASTATIN','ATORVASTAIN','ATORVASASTATIN','ATORVSTATIN') then
'atorvastatin'
       when drug in
('simvastain','simvastatin','SIMVASTATIN','simvastatn','SIMWASTATIN') then 'simvastatin'
       when drug in ('prasugrel','PRASUGREL','PRASUGREL 10MG TABLETS','PRASUGREL 5MG
FILM COATED TABLETS') then 'prasugrel'
       else drug end as drug_ammended,
       d.strength as strength_orig,  case when strength in ('80mg','80MG','80
mg','80','80 MG') then '80'
       when strength in ('40mg od','40mg','40MG','40 mg','40 MG') then '40'
       when strength in ('20mg','20MG','20 mg','20 MG') then '20'
       when strength in ('10MG','10mg','10 mg','10 MG') then '10'
       when strength in ('60 MG','60MG','60mg') then '60'
       when strength in ('30MG') then '30'
       when strength in ('25mg') then '25'
       when strength in ('50MG') then '50'

       else strength end as strength_ammended

from sail0441v.saildrug d)with no data;
```

Figure 1.12 SQL used to ‘clean’ and structure the prescribing data

At this point we had obtained a list of patients (anonymised to an ALF_PE) who had undergone a PCI at Morriston hospital, the date of PCI and a list of medications prescribed at discharge. The next step was to create datasets of hospital admissions, discharges and diagnoses to identify admission dates and discharge dates relevant to the PCI and use this dataset to describe comorbidities and patient outcomes of interest.

PATIENT EPISODE DATABASE FOR WALES AND HOSPITAL CODING STANDARDS

Before describing the process in creating hospital datasets, I will take the opportunity to explain how data from a patient hospital admission is collected and processed.

For each patient hospitalised in Wales, the Patient Episode Database for Wales (PEDW) records the admission and discharge dates, diagnoses and operational procedures and demographic data.[135] Date of death is also recorded when the patient dies within hospital. These records are completed at 'finished consultant episode' (FCE). Within each FCE, one primary and one or more secondary diagnosis using the International Classification of Disease, 10th Revision (ICD-10) is recorded.

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision 4th Edition (ICD-10), is a standardised coding system for both mortality (cause of death) and morbidity (diagnoses). The classification of mortality and morbidity using the ICD-10 system is a mandatory national requirement for NHS. This includes both day cases, scheduled and unscheduled hospital care. The ICD-10 system translates diagnoses and cause of death to alpha-numeric codes. The use of these codes allows for the easy storage and retrieval of information. These data are collected and stored in datasets such as the Hospital Episodes Statistics (HES) in England, Patient Episode Data for Wales (PEDW), Scottish Morbidity

Records (SMR), Cancer Registries, National Service Frameworks, Care Pathways, Performance Indicators, Commissioning Data Sets and other Central Returns.

Clinical coders apply the ICD-10 codes according to an established criterion, providing consistent information for statistical purposes. Clinical coders use the medical record to assign the ICD-10 codes. The medical record may contain handwritten or computerised record, correspondence, discharge letters, clinical work sheets, care pathways and diagnostic test reports.

For example, Patient X is admitted to Princess of Wales Hospital in Bridgend for an Acute Myocardial Infarction (AMI) on the 1st of February 2016. Patient X remains solely under the care of Consultant A for the next seven days and is then discharged home. Within the medical notes it is written that Patient X had a MI. In this case there is one FCE and the ICD-10 code I21.9 (Unspecified MI) is applied by the clinical coder. In this same example, if ST-Elevation Myocardial Infarction or STEMI had been written in the notes then I21.3 (Acute transmural myocardial infarction of unspecified site) would be applied. Similarly, if Non-ST Elevation Myocardial Infarction or NSTEMI had been written then I21.4 (Acute subendocardial myocardial infarction) would be applied.

If this episode had occurred before the 1st April 2015 then I21.9 would have been applied for either MI, STEMI or NSTEMI before this date. If the patient had a documented 'STEMI of the inferior wall' then the code I21.1 (Acute transmural myocardial infarction of inferior wall) would be applied regardless if this episode was before or after the 1st April 2015. Hence the code applied is dependent on the detail of the diagnoses written in the medical record and whether it occurred before or after a change in the criteria for coding was applied on the 1st April 2015.

ICD-10 codes are applied per FCE. For patients transferred between hospitals ≥ 1 FCE will be recorded and if a patient is transferred between consultants within a single hospital, then an FCE will apply to each consultant episode.

Clinical coding for patients who present with acute coronary syndromes (ACS) is particularly challenging as the care may be transferred between multiple consultants at different hospitals and between separate organisations or health boards. Within SAIL, consecutive FCE within a single hospital admission are grouped as patient 'spells' and where patients are transferred between hospitals during a single period of care spells are grouped into 'superspells' (figure 1.13).

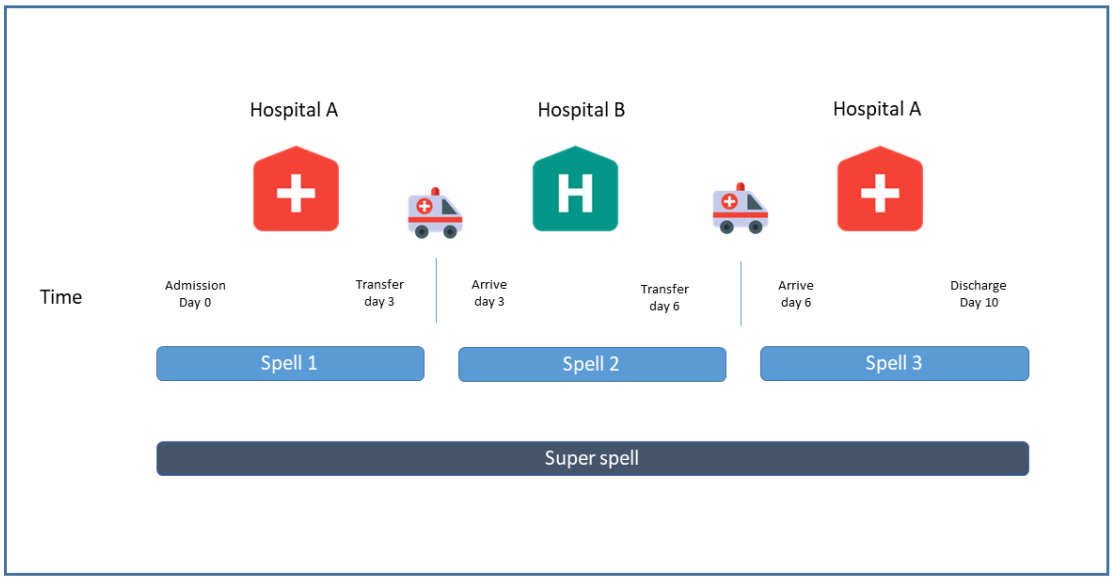

Figure 1.13 Schematic of classifications of spells and superspells during a single period of care at multiple hospitals

Clinical coders apply ICD-10 codes to co-morbidities that a patient may present with but only if it is documented in a patient's notes. For example, in a patient presenting with an MI who also has hypertension written in the notes then ICD-10 codes I21.9 (unspecified MI) and I10.x (Essential (primary) Hypertension) would be recorded in a secondary position. If the patient

was known to be hypertensive either from blood pressure recording documented on the observation chart or previously diagnosed prior to the admission but not recorded in the medical notes the diagnosis of hypertension cannot be inferred by the coder and therefore cannot have the relevant ICD-10 code applied. Likewise, atrial fibrillation observed on an electrocardiograph (ECG) but not written in the medical notes will not be documented by a clinical coder.

Classification of Interventions and Procedures

Operational and procedural codes are also applied for each FCE following the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4). Clinical coders apply OPCS-4 codes to the procedures recorded in the medical record for each consultant episode within the hospital provider spell.

Following expert advice from Miss Tracy Francis, Lead Clinical Coding Auditor for SBUHB and then scrutiny and agreement between Prof. Halcox, Dr Dave Smith and myself we collated a list of OPCS-4 codes to identify patients who have undergone PCI (and also revascularisation by CABG) (see chapter two supplementary table 3).

Creating hospital datasets

Within SAIL hospital datasets were created by linking together the individual tables containing details of spells (including start and end date, route of admission, individual hospital code), superspells, diagnostic and/or operational codes for the relevant patients (ALF_PE) (figure 1.14). Following this it was necessary to group and chronologically order the spells within each

superspell and identify the date of the first spell (true admission date) and the date of the last spell (true discharge date) (figure 1.15).

```
create table sailw441v.aspice_hosp_OPCS_data as(
--insert into sailw441v.aspice_hosp_OPCS_data
select distinct ops.*,aspice.system_ID_PE
from sail0441v.apice_alf aspice
inner join

(SELECT DISTINCT spell.ALF_PE,AGE_EPI_STR_YR, SPELL.admis_dt AS SPELL_START,
admis_mthd_cd, SPELL.DISCH_DT, SPELL.DISCH_DESTINATION_CD, SPELL.SPELL_DUR,
EPI.spell_num_pe, SPELL.REF_ORG_CD, EPI.EPI_STR_DT,
EPI.epi_end_dt, EPI.epi_dur,EPI.epi_num, x.oper_cd_123, X.OPER_DESC_123,
z.oper_cd,z.oper_desc_4, OPER.OPER_num,SPELL.DUR_ELECT_WAIT,
EPI.CON_SPEC_CD_OF_TREAT,
EPI.prov_unit_cd,EPI.CURR_PROV_UNIT_CD, super.person_spell_num_PE, dense_rank()
over (partition by spell.alf_pe, super.person_spell_num_pe order by
spell.admis_dt)
as spell_seq FROM SAIL0441V.PEDW_SPELL_20160420 SPELL

INNER JOIN SAIL0441v.PEDW_EPISODE_20160420 EPI
ON SPELL.PROV_UNIT_CD = EPI.PROV_UNIT_CD
AND SPELL.SPELL_NUM_PE = EPI.SPELL_NUM_PE
left JOIN SAIL0441v.PEDW_DIAG_20160420 DIAG
ON SPELL.PROV_UNIT_CD = DIAG.PROV_UNIT_CD
AND SPELL.SPELL_NUM_PE = DIAG.SPELL_NUM_PE
and EPI.epi_num = DIAG.epi_num
left JOIN SAIL0441V.PEDW_OPER_20160420 OPER
ON SPELL.PROV_UNIT_CD = OPER.PROV_UNIT_CD
AND SPELL.SPELL_NUM_PE = OPER.SPELL_NUM_PE
and EPI.epi_num = OPER.epi_num
left JOIN SAILREFRV.ICD10_DIAG_CD y
ON y.DIAG_CD = DIAG.DIAG_CD
left JOIN SAILREFRV.OPCS4_OPER_CD_123 x
on X.OPER_CD_123 = OPER.OPER_CD_123
left JOIN SAILREFRV.OPCS4_OPER_CD z
on z.OPER_CD = OPER.OPER_CD
left join sail0441v.PEDW_SUPERSPELL_20160920 super
on super.spell_num_PE = SPELL.spell_NUM_PE) ops

on aspice.alf_pe = ops.alf_pe;
)with no data ;
```

Figure 1.14 SQL for creating hospital tables

```
create table sailw441v.OPCSmaster as (
--insert into sailw441v.OPCSmaster
select distinct a.*, b.min_spell_start,b.max_disch_dt from
(select * from sailw441v.aspice_hosp_OPCS_data) a
inner join
(select distinct
h.system_id_pe,h.person_spell_num_pe,i.min_spell_start,i.max_disch_dt from
(select * from sailw441v.aspice_hosp_OPCS_data) h
inner join
(select distinct system_id_pe, person_spell_num_pe, min(spell_start) as
min_spell_start, max(disch_dt) as max_disch_dt from
sailw441v.aspice_hosp_OPCS_data
group by system_id_pe, person_spell_num_pe) i
on h.system_id_pe = i.system_id_pe
and h.person_spell_num_pe = i.person_spell_num_pe
and (h.disch_dt = i.max_disch_dt or h.spell_start = i.min_spell_start)
) b
on a.system_id_pe = b.system_id_pe
and a.person_spell_num_pe = b.person_spell_num_pe
order by a.system_id_pe, a.person_spell_num_pe,a.spell_seq
)
with no data;
```

Figure 1.15 SQL code to identify start date and end date of each hospital admission

Once each superspell had an identified start and end date it was necessary to identify the first hospital admission during the study period that corresponded with the index PCI. Hospital admissions occurring prior to the first admission during the study period for a PCI would then help inform previous diagnoses, comorbidities and prior revascularisation events. Hospital admissions post discharge for the index PCI would then inform the outcome events.

WELSH LONGITUDINAL GENERAL PRACTICE DATASET

The Welsh Longitudinal General Practice (WLGP) dataset[136] contains demographic, clinical and prescribing data for approximately 80% of primary care practices across Wales. This dataset was joined to the patients of interest (ALF_PE), with the date of admission and discharge for the primary PCI. Events recorded in the WLGP were denoted as occurring before

or after the index admission. Events entered in the WLGP are recorded using Read codes which is a thesaurus of clinical terms and provide the standard vocabulary by which clinicians can record patient findings, procedures and prescription.

PATIENT OUTCOMES, CO-MORBIDITIES AND PRESCRIPTIONS

In order to create a list or 'dictionary' of relevant comorbidities, adverse events and prescribed drugs a number of methods were undertaken for identifying the Read, ICD-10 and OPCS-4 codes of interest.

Firstly, the NHS Read code browser was searched to identify the relevant codes documented in primary care. The Read code system is structured into sections containing history/symptoms; diagnostic procedures; laboratory procedures; infectious diseases; diseases by organ system, and drugs by organ system. Similarly, ICD-10 and OPCS-4 codes can be searched from the relevant online browsers.

Using the hospital datasets, it was possible to rank the frequency of ICD-10 codes applied to patients identified as undergoing PCI (figure 1.16). I also searched for relevant key words such as 'failure' (figure 1.17) to identify patients with heart failure or 'diabet' for diabetes, within the hospital and GP datasets.

NHS commissioning groups publish online list of Read codes for common conditions for the purpose of supporting the Quality Operating Framework (QoF). These were used to cross check the lists of Read codes we had identified using the above methods.

Using these range of methods, it was eventually possible to triangulate the codes and agree a final list between Prof Halcox and myself.

Once lists of the relative diagnoses, risk factors and prescriptions had been created and joined to the respective hospital and GP datasets It was then possible to assign these as happening before (or during the index admissions) and classify as comorbidities/pre-existing treatment or after the admission and therefore could be used to identify outcomes of interest or prescriptions issued post index event.

The list of diagnostic codes assembled for this thesis is extensive (~100 pages). To avoid unnecessary documentation and printing within this written thesis I have provided these online:

https://github.com/DHARRISSWAN/diagnostic_codes/blob/master/Suppl_table1_05022019.docx

The SQL used to assemble the final chapter of this thesis (and representative of all the chapters) is also online:

https://github.com/DHARRISSWAN/sql

INTERNAL VALIDATION

To ensure the veracity of the data a number of checks were made. During each stage of data processing, simple counts of patients and lines of data were made to ensure there was no unintended loss or gain of data. All coding was checked by a data analyst with experience of cardiac datasets, Dr Arron Lacey. All outputs and statistical analyses were reviewed by Prof Gravenor and Prof Halcox prior to submission to journals and this thesis.

```
select count (distinct alf_pe),pref_term_30, event_cd from
sailw441v.GP_before_first
where pref_term_30 like '%failure%'
group by pref_term_30,event_cd
126;Left ventricular failure;G581.
73;Heart failure;G58..
49;Congestive heart failure;G580.
29;Chronic renal failure;K05..
21;Seen in heart failure clinic;9N0k.
18;Acute renal failure;K04..
9;Referral heart failure clinic;8HTL.
8;Heart failure annual review;662W.
8;Heart failure confirmed;1O1..
6;Compensation for renal failure;7L1A.
6;Renal failure unspecified;K06..
5;Congestive heart failure monit;662T.
<5;Heart failure norm eject frac;G583.
<5;[D]Respiratory failure;R2y1.
<5;End stage renal failure;K050.
<5;Respiratory failure;H59..
<5;Secondary ovarian failure;C1631
<5;[D]Respiratory failure NOS;R2y1z
<5;Admit heart failure emergency;8H2S.
<5;DNA heart failure clinic;9N4w.
<5;Heart failure follow-up;8HBE.
<5;Heart failure monit 2nd letter;9Or4.
<5;Heart failure monitoring admin;9Or..
<5;[X] Hepatic failure;J625.
<5;Acute hepatic failure;J6000
<5;Acute left ventricular failure;G5810
<5;Alcoholic hepatic failure;J6130
<5;Chroncongestive heart failure;G5801
<5;Chronic type 2 respir failure;H593.
<5;Decompensated cardiac failure;G5802
<5;Heart failure 6 month review;662p.
<5;Heart failure info given to pt;67D4.
<5;Heart failure NOS;G58z.
<5;Heart failure resolved;21264
<5;Other acute renal failure;K04y.
<5;Other ovarian failure;C163.
<5;Renal failure after care;SP154
```

Figure 1.16 SQL code and results of searching hospital datasets for the word ‘failure’

```
SELECT DIAG_CD_1234,  count (DISTINCT alf_pe ), diag_desc_4 FROM
sailw441v.aw_Hosp_master  WHERE bafta = 'during'AND diag_num  = '1' GROUP BY
DIAG_CD_1234,diag_desc_4  ORDER BY DIAG_CD_1234

I251   13697  Atherosclerotic heart disease
I219   4114   Acute myocardial infarction, unspecified
I211   3871   Acute transmural myocardial infarction of inferior wall
I210   2851   Acute transmural myocardial infarction of anterior wall
I214   2607   Acute subendocardial myocardial infarction
I200   1750   Unstable angina
I249   1004   Acute ischaemic heart disease, unspecified
R074   701    Chest pain, unspecified
I248   532    Other forms of acute ischaemic heart disease
I209   480    Angina pectoris, unspecified
I212   409    Acute transmural myocardial infarction of other sites
I213   349    Acute transmural myocardial infarction of unspecified site
R072   297    Precordial pain
I229   216    Subsequent myocardial infarction of unspecified site
K831   180    Obstruction of bile duct
C250   164    Malignant neoplasm of head of pancreas
C155   118    Malignant neoplasm of lower third of oesophagus
R073   117    Other chest pain
T828   107    Oth comps of cardic & vasc prosthet devs implants & grafts
C221   99     Malignant neoplasm, intrahep bile duct carcinoma
I501   89     Left ventricular failure
I258   82     Other forms of chronic ischaemic heart disease
I48X   77     Atrial fibrillation and flutter
I259   75     Chronic ischaemic heart disease, unspecified
I472   70     Ventricular tachycardia
C259   69     Malignant neoplasm of pancreas, unspecified
T855   65     Mech comp gastrointestinal prosth devs implants & grafts
I500   60     Congestive heart failure
C159   59     Malignant neoplasm of oesophagus unspecified
I460   58     Cardiac arrest with successful resuscitation
J181   56     Lobar pneumonia, unspecified
R17X   55     Unspecified jaundice
K830   51     Cholangitis
I350   49     Aortic (valve) stenosis
R55X   49     Syncope and collapse
K805   43     Calculus of bile duct without cholangitis or cholecystitis
I490   41     Ventricular fibrillation and flutter
I221   38     Subsequent myocardial infarction of inferior wall
R060   38     Dyspnoea
I208   36     Other forms of angina pectoris
I442   35     Atrioventricular block, complete
C160   34     Malignant neoplasm of cardia of stomach
C240   34     Malignant neoplasm of extrahepatic bile duct
I220   33     Subsequent myocardial infarction of anterior wall
T825   32     Mech compl of other cardiac & vascular devices and implants
C154   31     Malignant neoplasm of middle third of oesophagus
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Figure 1.17 SQL code and results showing the frequency of ICD-10 codes during a hospital admission for a PCI

CONTRIBUTIONS

The results chapters within this thesis are presented as submitted to the journals. Each of these chapters were drafted by myself and reviewed and amended following comments from the co-authors. The datasets in chapters 2, 3 and 5 were created by myself with input and validation from Dr Arron Lacey, Ashley Akbari and Fatemeh Torabi. The SAIL team assembled the datasets for chapters 4 and 5 using SQL code that I provided for the TTR calculation and using the list of clinical codes that I developed earlier in this thesis. All statistical analyses were conducted by myself with the exception of the following: (i) in chapter 4, I specified all tests to be conducted, however, the R code for the lasso test was written by the SAIL team and the output was reviewed by myself, (ii) in chapter 5, I specified all analyses to be carried out, however, Fatemeh Torabi wrote and implemented the code for the regression analyses. I provided the list of and justification for the covariates to be included in the analyses as well as review of data and interpretation for all outputs.

The results chapters within this thesis have been in the active voice with the pronoun 'we' throughout for consistency with published manuscripts.

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CHAPTER 2.

EARLY DISCONTINUATION OF P2Y12 ANTAGONISTS AND ADVERSE CLINICAL EVENTS POST PERCUTANEOUS CORONARY INTERVENTION – A HOSPITAL & PRIMARY CARE LINKED COHORT

Abstract

Background

Early discontinuation of $P2Y_{12}$ antagonists post percutaneous coronary intervention (PCI) may increase risk of stent thrombosis or non-stent recurrent myocardial infarction.

Our aims were (i) to analyse the early discontinuation rate of $P2Y_{12}$ antagonists post PCI, (ii) explore factors associated with early discontinuation and (iii) analyse the risk of major adverse cardiovascular events (MACE: death, acute coronary syndrome, revascularisation or stroke) associated with discontinuation from a pre-specified prescribing instruction of one year.

Method and Results

We studied 2,090 patients (2011-15) who were recommended for clopidogrel for 12m (+aspirin) post-PCI within a retrospective observational population cohort. Relationships between clopidogrel discontinuation and MACE were evaluated over 18m follow up.

Discontinuation of clopidogrel in the first four quarters was low at 1.1%, 2.6%, 3.7% and 6.1% respectively. Prior revascularisation, prior ischaemic stroke and age >80years (y) were independent predictors of early discontinuation. In a time-dependent multiple regression model, clopidogrel discontinuation and bleeding (HR=1.82[1.01-3.30] and HR=5.32[3.14-8.94] respectively) were independent predictors of MACE as were age <49y and ≥60y (vs those aged 50-59y), hypertension, CKD stage 4+, prior revascularisation, ischaemic stroke and thromboembolism. Furthermore, in those with both bleeding and clopidogrel discontinuation HR for MACE was 9.34[3.39-25.70].

Conclusions

Discontinuation of clopidogrel is low in the first year post-PCI, where a clear discharge instruction to treat for 1 year is provided. While this is reassuring from the population level, at an individual level discontinuation earlier than the intended duration is associated with an increased rate of adverse events, most notably in those with both bleeding and discontinuation.

BACKGROUND

Poor medication adherence is often associated with adverse patient events across multiple disease outcomes. This is of particular concern in the setting of modern cardiac intervention with stent implantation for acute coronary syndromes (ACS) where discontinuation of antiplatelet therapy risks both stent stenosis and non-stent related myocardial infarction. As such the use of dual antiplatelet therapy (DAPT), aspirin plus a $P2Y_{12}$ inhibitor, in patients undergoing coronary revascularization is an established treatment strategy in the prevention of short- and long-term thrombotic complications.[1-3]

Current guidelines recommend a minimum of 12 months DAPT for patients presenting with ACS undergoing coronary PCI with stent implantation, reduced to at least 6 months in the presence of risk factors for bleeding.[4, 5] In patients with stable coronary artery disease, a minimum of 6 months is recommended following drug eluting stents (DES) implantation and at least one month following a bare metal stent (BMS) or in those with a high risk of bleeding. The presence of comorbidities such as atrial fibrillation (AF) may necessitate the need for concomitant anticoagulation and therefore shorter durations of DAPT may be warranted. Likewise, the need to undergo surgery in the future may also mandate shorter durations of DAPT.

A number of observational studies have shown that an increase in major adverse cardiac events (MACE) is associated with a delay in access to prescriptions for $P2Y_{12}$ inhibitors following coronary PCI,[6, 7] or premature discontinuation following a myocardial infarction (MI) or stent implantation.[8-13] Rates of discontinuation vary between studies with some reporting 13% discontinuation within 30 days,[10] and others up to 40 to 50% within one year. [8, 9] However, these studies have not identified the intended duration of therapy post discharge or taken account of comorbidities that may warrant shorter durations of DAPT. Furthermore, the

study populations were predominantly medically treated ACS,[8, 14] or in case of the PARIS registry, predominantly stable angina patients undergoing PCI.[15]

Our objectives were to (i) analyse the rate of early discontinuation of clopidogrel following discharge from hospital in a post PCI population where the duration of DAPT was specified for one year (ii) explore potential factors associated with discontinuation in prescribing (iii) analyse the risk of death and major cardiovascular events associated with discontinuation.

METHODS

We undertook a retrospective observational cohort study using linked anonymised healthcare data from the Secure Anonymised Information Linkage (SAIL) Databank,[16, 17] for patients undergoing PCI at a tertiary cardiac centre in Wales. The study population was identified from the cardiac intervention database and included patients who were discharged from hospital (between January 2011 and November 2015) following PCI for either stable or acute coronary artery disease. Follow up was for eighteen months. Patients who underwent coronary artery bypass grafting (CABG) during the index admission or had a prior or contemporary diagnosis of AF were excluded from the study.

This study makes use of anonymised patient data, therefore informed consent was not required. Approval for the study was granted by the SAIL Information Governance Review Panel (IGRP). All data can be made available to researchers via standard SAIL IGRP protocols.

DATASETS AND LINKAGE

The cardiac intervention dataset contains procedural, clinical and demographic data on patients undergoing PCI. Information on the prescribing of antithrombotic therapy was obtained from

the hospital discharge summaries. These datasets were linked to the Welsh Longitudinal General Practice (WLGP) dataset to record the continuity of antithrombotic therapy and presence of co-morbidities, risk factors and demographics[18]. Date of death, where relevant, was identified form the Annual District Death Extract (ADDE)[19] containing mortality records from the Office of National Statistics (ONS) and deprivation quintile was assigned using the Welsh Index of Multiple Deprivation (WIMD), an area-based deprivation measure.[20]

For each patient hospitalised in Wales, the Patient Episode Database for Wales (PEDW) records the admission and discharge dates, diagnoses and operational procedures and demographic data. Date of death is also recorded when the patient dies within hospital. These records are completed at 'finished consultant episode' (FCE). Within each FCE, one primary and one or more secondary diagnosis using the International Classification of Disease, 10th Revision (ICD-10) is recorded. Operational and procedural codes are also applied for each FCE following the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4). PEDW was used to describe cardiac revascularization (either PCI or CABG) and major bleeding events prior to the index admission (see supplementary table 2.1 for ICD-10 Codes used to identify bleeding events). Major bleeding events included gastrointestinal bleeds, intracranial bleeds, urinary tract bleeds and airway bleeds.

Both PEDW and WLGP datasets were searched for prior history or contemporary diagnosis of vascular disease (peripheral artery disease or aortic plaque), AF/flutter, MI, ischemic stroke, thromboembolism and heart failure.

INDEX EVENT DATA

For each patient, the first entry in the cardiac intervention database occurring during the study period was identified as the index intervention. The date of admission and discharge were identified either side of the index intervention using the PEDW dataset. Prescribing data

corresponding to the index intervention was extracted from the electronic discharge summaries. Where an electronic discharge summary was not available, paper copies of the discharge summary, where available were searched and the prescribing data was recorded.

$P2Y_{12}$ ANTAGONIST PRESCRIBING AND DISCONTINUATION

Prescribing of $P2Y_{12}$ antagonists post discharge was recorded within consecutive three-month periods following the date of discharge from hospital. Discontinuation was deemed to have occurred when there was a three-month period without a $P2Y_{12}$ antagonist prescription prior to the intended date of treatment cessation. The precise time to discontinuation is unknown but was approximated as the centre point within the first three-month period where no $P2Y_{12}$ antagonist had been prescribed i.e. 46 days for the first three-month period, 137 days for the second three-month period; 228 days, 319 days, 411 and 501 days for the third to sixth-three-month period respectively.

STATISTICAL ANALYSES

Baseline variables and patient characteristics including demographics, lifestyle behaviours and medical history were presented as percentages and means with standard deviations. Differences between those prescribed $P2Y_{12}$ therapy for one year and all other regimes were compared using the χ^2 test for categorical variables and the two-sample t-test for continuous variables. A Cox proportional-hazards model was used to determine the baseline characteristics associated with 'time to discontinuation' from the prescribing instruction at the point of discharge from hospital. Bleeding subsequent to PCI, occurring during the period of intended prescription duration was included as a time dependent covariate. Hazard ratios (HRs) and 95% Confidence

Intervals (CI) were calculated for the respective clinical variables. In analysing time to discontinuation, death during the follow up was treated as a censoring event and hence we assumed that the time to death (or other loss to follow-up) was not related to the time-to-attrition distribution.

The primary clinical end point was a combination of death of any cause, subsequent readmission to hospital for an MI, unstable angina (UA), acute ischemic heart disease, ischemic stroke or transient ischemic attack (TIA) or readmission after 30 days from the index discharge date for either CABG, or recurrent coronary PCI (See supplementary tables 2.2 and 2.3 for ICD-10 and OPCS codes used to establish these endpoints). A Cox proportional hazards model was used to determine characteristics of the cohort associated with this adverse composite outcome, specifically the effect of discontinuation was modelled as a time-dependent covariate. In estimating the effect of discontinuation, we attempted to control for expected risk factors by including the key baseline characteristics in the Cox model. In addition, we had to control for effects of bleeding, again as a time-dependent covariate. We created a covariate with 4 levels representing the overall time dependent classification: no discontinuation and no bleed, discontinuation occurred but no bleed, bleed occurred but no discontinuation and finally, both events have occurred. For those patients with an adverse outcome only discontinuation and/or bleeding events occurring prior to the endpoint were included in the analysis. All models were run in SPSS software (version 22.0; SPSS, Inc., Chicago, IL). Variables were initially considered separately in univariable analyses; the final multivariable cox model was selected by minimising the Akaike information criterion (AIC) (with a comparison to model selection using Bayesian information criteria (BIC)).

RESULTS

STUDY POPULATION

Of the 5,532 patients undergoing PCI during the study period, 3,066 (55.4%) were discharged and had a complete linked healthcare dataset available (figure 2.1). A further 397 (7.2%) were excluded who had AF or underwent a CABG procedure during the index admission. Of the final 2,770 patients meeting the inclusion criteria 2,090 (75.5%) were prescribed clopidogrel for one year (plus aspirin 75mg once daily for life). Of this cohort the mean age was 63.2 years, 73.5% were male and 86.5% underwent PCI for an ACS (table 2.1).

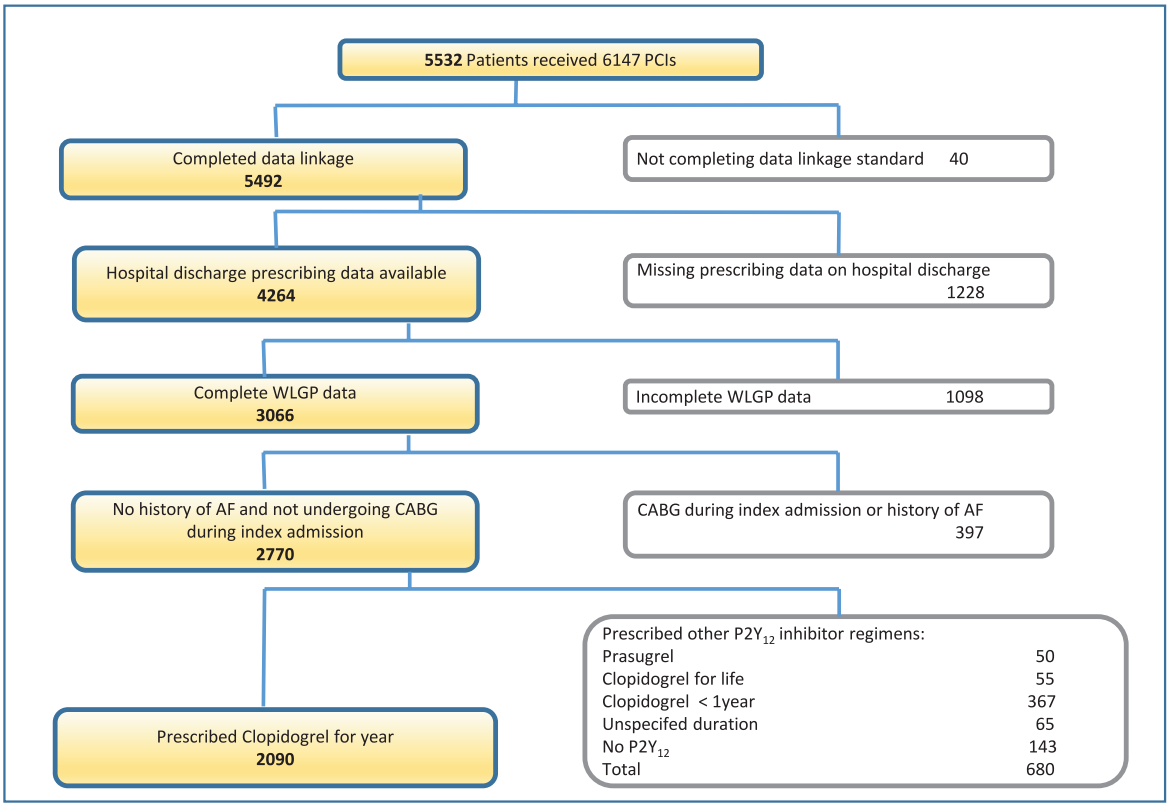

Figure 2.1 Study population cohort selection

Table 2.1 Demographics and medical history of patients by discharge prescribing intention of $P2Y_{12}$ Inhibitors.

	Clopidogrel for 1 year	Other regimens	*P* value
	n=2,090	*n*=680	
Percentage of total group	75.5%	24.5%	
Mean age, (SD)	63.2 (11.8)	66.6 (12.3)	<0.001
Characteristic, *n*(%)			
Male	1537 (73.5)	450 (66.2)	0.001
Obese	511 (24.4)	181 (26.6)	0.097
Smoker	784 (37.5)	237 (34.9)	0.579
Deprivation index			0.08
1 (most deprived)	337 (16.1)	129 (18.9)	
2	411 (19.7)	129 (18.9)	
3	489 (23.4)	166 (24.4)	
4	415 (19.9)	106 (15.9)	
5 (least deprived)	398 (19.0)	138 (20.2)	
Unknown	40 (1.9)	12 (1.8)	
Prior medical history, *n*(%)			
Hypertension	851 (40.7)	303 (44.6)	0.074
Ischemic heart disease	612 (29.3)	242 (35.6)	0.002
Myocardial infarction	351 (16.8)	144 (21.2)	0.01
Coronary revascularization	203 (9.7)	98 (14.4)	0.001
Ischemic stroke	115 (5.5)	46 (6.8)	0.22
Heart failure	259 (12.4)	67 (9.9)	<0.001
Peripheral vascular disease	81 (3.9)	46 (6.8)	0.002
Thromboembolism	14(0.7)	9 (1.3)	0.10
Diabetes	382 (18.3)	156 (23.0)	0.007
Chronic kidney disease stage 4+	16 (0.8)	10 (1.5)	0.097
Chronic liver disease	24 (1.1)	7 (1.0)	0.80
Dyslipidemia	380 (18.2)	149 (21.9)	0.031

Continued on next page.

Table 2.1 continued.

	Clopidogrel for 1 year	Other regimens	*P* value
Prior medical history, *n*(%)			
Dementia	9 (0.4)	4 (0.6)	0.60
Prior bleeding events	205 (9.8)	89 (13.1)	0.16
Medication prescribed within 1 year prior to admission, *n*(%)			
Aspirin	711 (34.0)	282 (41.5)	<0.001
$P2Y_{12}$ antagonist	230 (11.0)	107 (15.8)	0.001
Statins	924 (44.2)	347 (51.0)	0.002
Clinical syndrome, *n*(%)			0.045
Acute coronary syndrome	1,808 (86.5)	563 (82.8)	
Stable coronary disease	282 (13.5)	117 (17.2)	

In comparison with those prescribed any other regimen on discharges, these patients had a lower mean age, lower rate of previous diagnoses for ischemic heart disease; MI, prior coronary revascularization, heart failure or dyslipidaemia, and were less likely to have been prescribed in the year prior to the index event either aspirin, $P2Y_{12}$ inhibitors or statins (further comparisons between those included and those excluded [with or without discharge prescribing data available] is contained in supplementary table 2.4).

CLOPIDOGREL DISCONTINUATION

The rate of discontinuation during the periods 0 to 3 months, 3 to 6 months, 6 to 9 months and 9 to 12 months post discharge was approximately 1.1%, 2.6%, 3.7% and 6.1% respectively (figure 2.2). Between 12 to 15 months 47% had discontinued clopidogrel, and 76.2%. by 15 to 18 months.

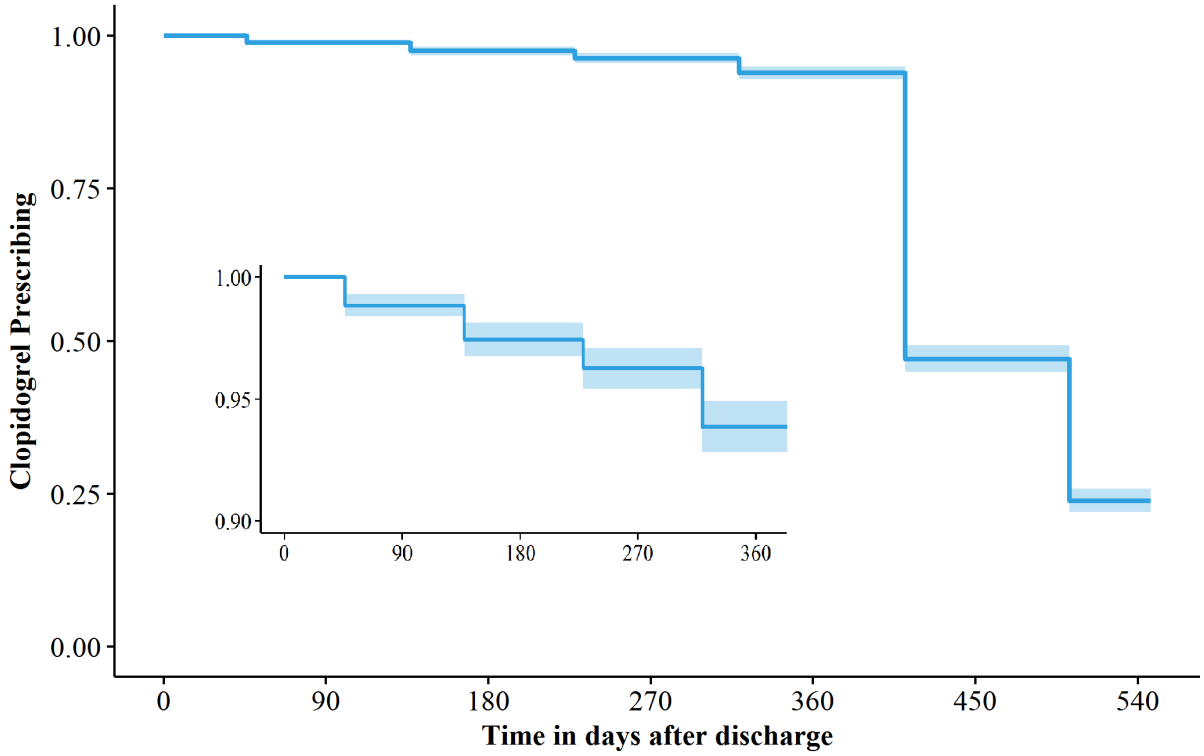

Figure 2.2 Discontinuation of clopidogrel post PCI in those recommended to continue for one year

Factors associated with clopidogrel discontinuation during the first 12 months included: increasing age, hypertension, ischemic heart disease (IHD), prior MI, prior coronary revascularization, ischemic stroke, heart failure, vascular disease, prior bleeding events and bleeding during the follow up period (figure 2.3). After adjusting for all baseline characteristics, previous revascularization, previous ischemic stroke and age groups 80 or older were independently associated with discontinuation (table 2.2).

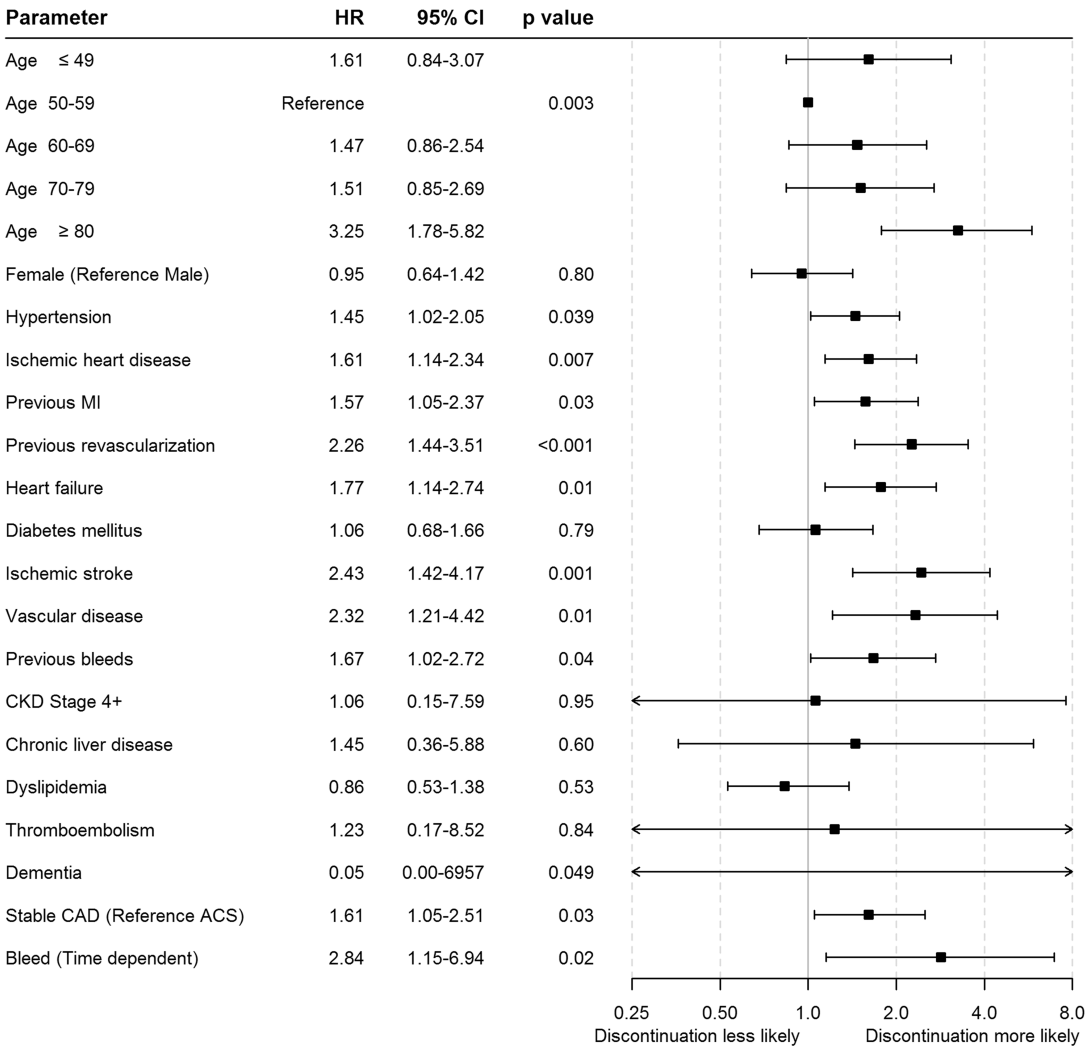

Figure 2.3. Characteristics associated with clopidogrel discontinuation within one year of discharge during follow up using univariable cox proportional hazards model

DEATH AND MAJOR CARDIOVASCULAR EVENTS

The incidence of death or major cardiovascular events in those who had no discontinuation or bleeding events post discharge was 9.5 per 100 person year (95% CI, 8.39-10.74); in patients who had discontinued clopidogrel but had no bleeding events the incidence was 15.2 (95% CI, 6.72-24.24); in patients who had a bleeding event but no discontinuation it was 41.9 (95% CI, 21.38-60.10); and in patients who had both bleeding and discontinuation it was 64.6 per 100 person years (95% CI, 1.29-127.96).

Table 2.2 Multivariable Cox proportional hazard model of characteristics associated with clopidogrel discontinuation

Covariate*	Hazard ratio	Lower CI	Upper CI	*P* value
Age				
≤ 49	1.61	0.84	3.08	
50-59	Reference			0.005
60-69	1.47	0.86	2.53	
70-79	1.51	0.84	2.69	
≥ 80	3.25	1.79	5.88	
Previous revascularization	2.09	1.32	3.33	0.002
Previous ischemic stroke	1.95	1.12	3.39	0.018

*The following variables were included in the mutually adjusted model: age; gender; presenting clinical syndrome; hypertension; prior coronary revascularization; prior bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes; chronic kidney disease stage 4+; chronic liver disease, dyslipidemia; and dementia. Lower CI and upper CI indicates the lower and upper 95% confidence intervals.

Patient characteristics associated with death or major cardiovascular events included: age 49 or less or 60 and above compared to those aged 50 to 59, hypertension, prior MI, prior coronary revascularization, ischemic stroke, heart failure, vascular disease, thromboembolism, diabetes, CKD, chronic liver disease, clopidogrel discontinuation and bleeding during follow up (figure 2.4).

Characteristics independently associated with death or major cardiovascular events in a multivariable Cox proportional hazards model included age less than 49 and 70 and above compared to those aged 50-59; previous coronary revascularization; a history of thromboembolism, CKD stage 4 or 5 and ischemic stroke (table 2.3). After adjustment for these factors, the time dependent effects of discontinuation and bleeding were significantly associated with death or major cardiovascular events. For discontinuation alone, there was an estimated hazard ratio of 1.82 [95%CI (1.01-3.30)] compared to patients with no

discontinuation and no bleeding events. Similarly, the occurrence of bleeding alone in those without discontinuation was associated with an increased risk of death or major cardiovascular events [HR= 5.30, 95%CI (3.14-8.94)]. Notably, the combined effect of having both discontinuation and bleeding was associated the greatest likelihood of adverse events [HR = 9.34, 95%CI (3.39-25.70)].

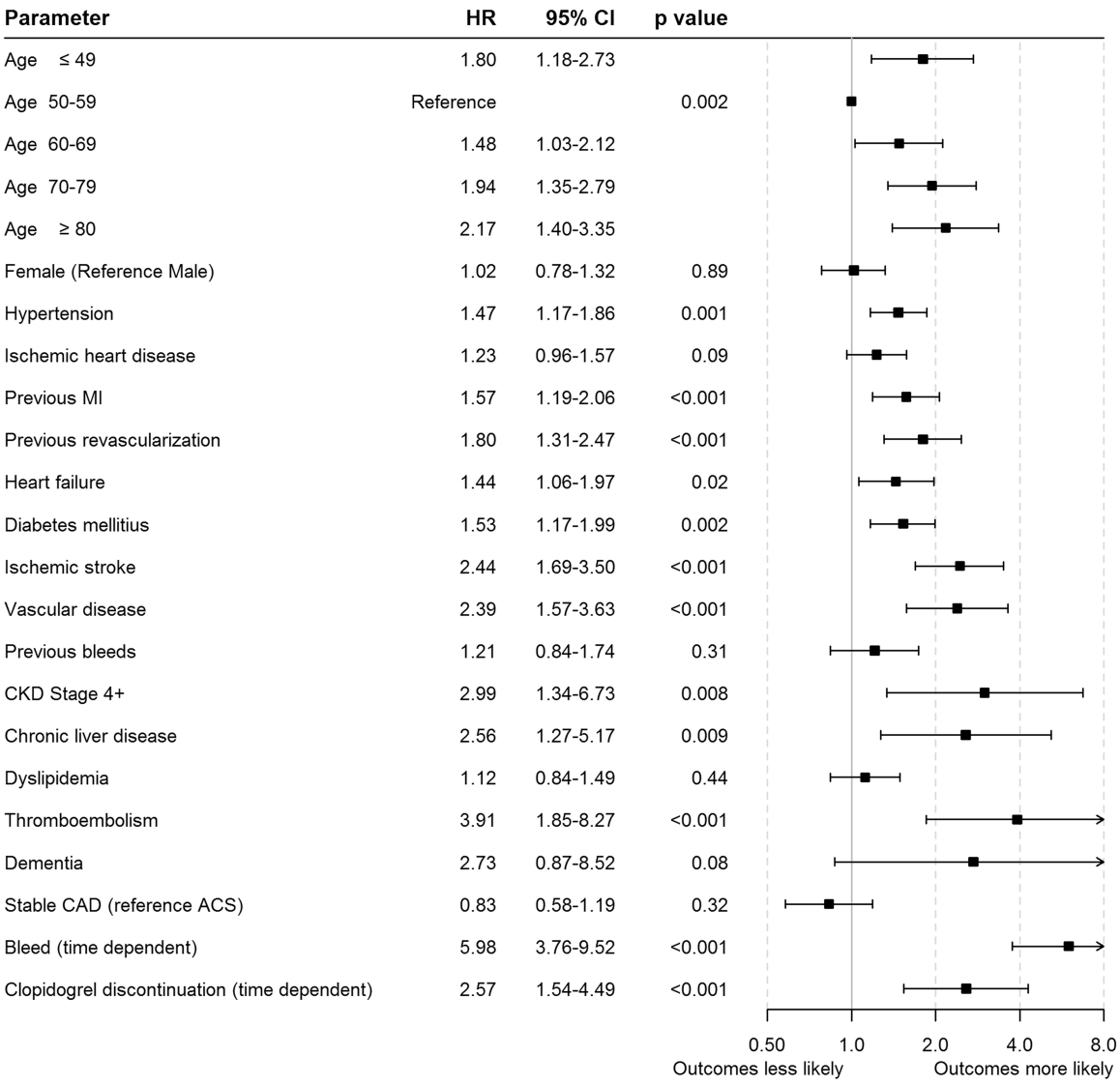

Figure 2.4. Characteristics associated with death or major cardiovascular adverse events

Table 2.3 Multivariable Cox proportional hazard model of characteristics associated with adverse clinical outcomes

Covariate*	HR	Lower CI	Upper CI	*P* value
Age decile				0.019
≤49	1.94	1.27	2.96	
50- 59	Reference			
60-69	1.36	0.95	1.94	
70-79	1.57	1.09	2.29	
≥80	1.72	1.10	2.68	
Hypertension	1.30	1.02	1.66	0.03
Chronic kidney disease stage 4+	2.30	1.01	5.22	0.048
Previous revascularization	1.47	1.06	2.03	0.021
Previous ischemic stroke	1.96	1.34	2.86	<0.001
Previous thromboembolism	3.18	1.48	6.83	0.003
Time dependent variable of clopidogrel discontinuation and/or bleed				<0.001
(1) Discontinuation only	1.82	1.01	3.30	
(2) Bleed only	5.30	3.14	8.94	
(3) Discontinuation and bleed	9.34	3.39	25.70	

*The following variables were used in the model selection procedure: age; gender; presenting clinical syndrome; hypertension; prior coronary revascularization; prior bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes; chronic kidney disease stage 4+; chronic liver disease, dyslipidemia; dementia and time dependent variables or clopidogrel discontinuation, bleeding and both discontinuation and bleeding. Lower CI and upper CI indicates the lower and upper 95% confidence intervals.

As a comparison, model selection was also explored using BIC. This resulted in selection of fewer patient characteristics, however the effects of bleeding and clopidogrel discontinuation were retained in the final model as statistically significant.

For completeness, the characteristics associated with the individual outcomes of MI, stroke, revascularization, and death are presented in supplementary tables 2.5 and 2.6.

Assessment of risk factors associated with bleeding was not a primary objective of this study, but none the less an important consideration. In a multivariable analysis prior bleeding events [HR=2.82, 95% CI (1.67-4.76)], chronic kidney disease [HR=6.15, 95% CI (2.22-17.08)] and chronic liver disease [HR=3.62 (1.14-11.51)] were independently associated with bleeding events during follow up (supplementary table 2.7). These variables were not independently associated with risk of clopidogrel discontinuation.

DISCUSSION

This is the first real-world outcome study examining the rate of clopidogrel discontinuation following PCI where the intended prescribing duration of DAPT is known. Notably, discontinuation of $P2Y_{12}$ inhibitor therapy is low in this population, where a specified prescribing instruction to continue for 12 months is provided, in contrast to other studies where the prescribing duration was not known. Furthermore, despite the low discontinuation rate, discontinuation was still identified as an important predictor of adverse outcomes in this population, especially in those with concomitant bleeding.

The observed rate of discontinuation is in marked contrast with findings from previous studies where it had been suggested that up to a half of patients post MI discontinue therapy within 12months.[8] We note this was observed in an historical ACS patient group who were predominantly treated medically as opposed to receiving contemporary PCI therapy. Nevertheless, our observed rate of discontinuation was still lower than expected. There are a number of possible explanations for this difference, including greater contemporary recognition of the importance of continued use of $P2Y_{12}$ inhibitors post PCI, improved communication of the prescribing intention from secondary to primary care and possibly the

availability of free prescriptions to all patients in Wales. However, addressing these questions was outside the scope of this study.

Amongst those patients who discontinued clopidogrel earlier than the initial intended period, the hazard of death or major cardiovascular events was greater compared to those who continued therapy, as expected and in keeping with previous studies.[8, 21] Other independent predictors of adverse outcomes included ischemic stroke and previous revascularization; both likely markers of diffuse or severe cardiovascular disease. However, both ischemic stroke and previous revascularization were also predictors of discontinuation. Whether these contrasting findings are a consequence of shared risk factors such as aging, comorbidities or the index PCI being a consequence of poor adherence to medication is unknown.

Other independent predictors of discontinuation included advanced age, which has previously been shown to be a predictor of early discontinuation of clopidogrel post MI. Bleeding events measured as a time dependent variable were not an independent predictor of discontinuation, contrasting with observations from a previous study. [8] It is possible that those patients with prior bleeding events or at higher risk of bleeding may have been instructed for a shorter course of DAPT at discharge and were therefore not included in this analysis. The exclusion of patients undergoing CABG and those with AF, both groups of which are at higher risk of bleeding and subsequent discontinuation of $P2Y_{12}$ treatment, may explain this observation. We found no association between deprivation quintiles and clopidogrel discontinuation, nor deprivation quintiles and major adverse outcomes in univariable analyses. Therefore, deprivation index was not included in the final multivariable analyses.

In this study, we documented gastrointestinal bleeds; intracranial bleeds, urinary tract bleeds and airway bleeds in order to be consistent with previous studies, [22] but bleeding events occurring in other organ systems may have had major clinical outcomes and resulted in

cessation of therapy. However, the lack of an accepted standard for defining relevant bleeding events and defining their severity in real-world datasets is a recognised limitation for studies such as these.

Bleeding events were also highly predictive of adverse outcomes, as expected. Bleeding is a recognised adverse consequence of antiplatelet therapy and is associated with a greater incidence of death and ischemic events.[1, 3, 23, 24] We found that the greatest risk of death or major cardiovascular events occurred in those with both discontinuation and bleeding events in our cohort. Whilst it is not possible to identify the specific cause of adverse outcomes in this group, it is recognised that contributing factors to worse outcomes includes the triggering of pro-thrombotic and pro-inflammatory responses following a bleed, combined with discontinuation of antiplatelet therapy leading to a rebound increased risk of ischemic events.

While discontinuation was reassuringly low in the first 12 months, it is notable that continuation of prescribing beyond 12 months was high with almost a quarter (24% [n=427] of 1,779 patients with follow up data up to 18months post discharge) of patients still receiving a prescription for clopidogrel between 15 to 18 months after discharge from the index event. Possible reasons for continuation of clopidogrel include recurrent ischemic events, however, we noted that only 22.5% (n=96) within this group had a documented readmission for recurrent major cardiovascular event during follow up. It is possible that further clinical events occurred that led to a decision to continue or change therapy, although it is unlikely that this was the case for the majority of patients. As prescriptions are provided free in Wales, there is no financial disincentive to stop treatment, which may explain the relatively high numbers of patients continuing treatment beyond the recommended period.

As the dataset only examined outcomes up to 18 months, there was insufficient power to explore the relationship between extended prescriptions beyond 12 months and the effect on

either cardiovascular events or bleeding due to relatively low numbers and short exposure times.

STRENGTHS AND LIMITATIONS OF THIS STUDY

We believe that this study further refines our understanding of the impact of $P2Y_{12}$ discontinuation on clinical outcomes. By identifying the discharge prescribing intention, we have avoided overestimation by excluding those with shorter durations of DAPT. Thus, although our analysis only evaluates 40% of the entire PCI population, we believe that these patients are representative of the majority of the post PCI population who are recommended to receive one year of DAPT, as our analysis has excluded patients requiring anticoagulation, those undergoing surgery and those without a complete linked dataset. There were also many clinical and demographic differences between those directed to one year of clopidogrel and the remaining group who had greater prevalence of risk factors for both cardiovascular and bleeding events. By keeping those higher risk patients in the analyses, overrepresentation of these important risk factors would likely have led to further overestimation of the actual relationship between discontinuation and adverse cardiovascular events. Furthermore, the exclusion of those with AF and/or undergoing CABG, who are at higher risk of bleeding and subsequent discontinuation of $P2Y_{12}$ inhibitors, has likely further reduced the rate of discontinuation and the effect of bleeding events leading to discontinuation.

There are several limitations to this study. While we have identified the prescribing intention from hospital, we were not able to identify the quantity of medication issued from either hospital or primary care, therefore we were unable to calculate precisely when an individual's prescription would have finished if taken according to instruction. In the WLGP dataset we noted that prescriptions were usually issued every month, but occasionally repeated

every two months. Within a three-month period if no prescription had been issued it was possible to assume that either a one-month or two-month supply made in the previous quarter had been exhausted. Discontinuation was deemed to have occurred when there was a three-month period without a $P2Y_{12}$ antagonist prescribed. Using this method, we were able to detect periods where we had greater certainty that an individual's prescription was likely to have finished but we lacked the precision for identification of shorter periods of discontinuation.

As with any observational studies, we cannot determine whether the association between clopidogrel discontinuation and adverse outcomes was causal or may have been confounded by the influence of unrecorded co-morbidities including unrecorded bleeding events, the under-utilisation of other prognostically relevant medicines or new undocumented behaviours. The prescribing and potential discontinuation from aspirin was not accounted for in this study. In the UK aspirin is widely available without a prescription and is inexpensive therefore the assessment of aspirin discontinuation from the WLGP dataset may have led to classifications of periods of discontinuation when a patient may have self-medicated.

It was not possible to identify the cause of discontinuation in this study. While the recording of prescriptions issued from the WLGP dataset is robust, currently it is not possible to identify the dispensing of those prescriptions. Access to prescription dispensing records in addition to the prescribing records from the WLGP dataset would have improved the sensitivity of capturing periods 'off treatment' and the association between non-adherence as well as discontinuation and adverse outcomes. Furthermore, it is not possible to identify if patients took the medication as intended, as is the case in most clinical studies. Therefore, this study does not confirm whether compliance with medication and periods of discontinuation could be attributed to either intentional or unintentional patient non-compliance or intentional prescriber discontinuation. It is possible that patients recorded as having discontinued clopidogrel received prescriptions either privately or from out-patient hospital appointments, although rare

in Wales, neither of which would have been captured in this study. However, this would likely further increase the true difference in the effect of discontinuation on adverse outcomes.

During the study period international guidelines changed to preferentially recommended the use of the more potent $P2Y_{12}$ antagonists such as ticagrelor or prasugrel. However, due largely to financial restrictions within the Welsh health service clopidogrel remained the mainstay of treatment for ACS during this time. Although this paper addresses the use of clopidogrel post PCI, we believe this paper remains of critical value as it illustrates the importance of knowing the schedule duration of any therapy before drawing conclusions on the impact of early discontinuation. Although not addressed in this study one may expect the adverse impact of poor concordance with newer more effective therapies to be even greater.

Lastly, this observational study was conducted within a health service that is both accessible and free at the point of care, including the free provision of medication. This should be born in mind when comparing the results of this study to those systems where access to health care and affordability may influence therapy and outcomes at a population level.

CONCLUSION

In conclusion, this study has demonstrated that identifying the intended duration of $P2Y_{12}$ antagonist therapy on discharge following a PCI is essential for determination of the correct rate of premature discontinuation in real world outcome studies. The rate of discontinuation was reassuringly low in this patient group and much lower than anticipated in previous studies. While this is reassuring from the population level, at an individual level, discontinuation of $P2Y_{12}$ antagonist therapy earlier than the intended duration is associated with an increased rate of adverse events. Our data emphasise the importance of improving processes to ensure optimal concordance with evidence based preventative therapy post PCI.

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SUPPLEMENTARY MATERIAL

MAJOR BLEEDING EVENTS

Major bleeding events were classified as gastrointestinal bleeds, intracranial bleeds, urinary tract bleeds and airway bleeds resulting in admission to hospital.

Supplementary table 2.1 *ICD-10* Codes for major bleeding events

Bleeding event	Code	Description
Intracranial hemorrhage	I608	Other subarachnoid hemorrhage
Intracranial hemorrhage	I602	Subarachnoid hemorrhage from anterior communicating artery
Intracranial hemorrhage	I604	Subarachnoid hemorrhage from basilar artery
Intracranial hemorrhage	I600	Subarachnoid hemorrhage from carotid siphon and bifurcation
Intracranial hemorrhage	I607	Subarachnoid hemorrhage from intracranial artery unspecified
Intracranial hemorrhage	I601	Subarachnoid hemorrhage from middle cerebral artery
Intracranial hemorrhage	I606	Subarachnoid hemorrhage from other intracranial arteries
Intracranial hemorrhage	I603	Subarachnoid hemorrhage from posterior communicating artery
Intracranial hemorrhage	I605	Subarachnoid hemorrhage from vertebral artery
Intracranial hemorrhage	I609	Subarachnoid hemorrhage unspecified
Intracranial hemorrhage	I629	Intracranial hemorrhage (non-traumatic) unspecified
Intracranial hemorrhage	I613	Intracerebral hemorrhage in brain stem
Intracranial hemorrhage	I614	Intracerebral hemorrhage in cerebellum
Intracranial hemorrhage	I611	Intracerebral hemorrhage in hemisphere cortical
Intracranial hemorrhage	I610	Intracerebral hemorrhage in hemisphere subcortical
Intracranial hemorrhage	I612	Intracerebral hemorrhage in hemisphere unspecified
Intracranial hemorrhage	I615	Intracerebral hemorrhage intraventricular
Intracranial hemorrhage	I616	Intracerebral hemorrhage multiple localized
Intracranial hemorrhage	I619	Intracerebral hemorrhage unspecified
Intracranial hemorrhage	I618	Other intracerebral hemorrhage
Intracranial hemorrhage	I691	Sequelae of intracerebral hemorrhage
Intracranial hemorrhage	I692	Sequelae of other non-traumatic intracranial hemorrhage
Intracranial hemorrhage	S064	Epidural hemorrhage
Intracranial hemorrhage	S065	Traumatic subdural hemorrhage
Intracranial hemorrhage	S066	Traumatic subarachnoid hemorrhage
Gastrointestinal hemorrhage	K250	Gastric ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K254	Gastric ulcer chronic or unspecified with hemorrhage
Gastrointestinal hemorrhage	K260	Duodenal ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K264	Duodenal ulcer chronic or unspecified with hemorrhage
Gastrointestinal hemorrhage	K270	Peptic ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K280	Gastrojejunal ulcer acute with hemorrhage
Gastrointestinal hemorrhage	K920	Hematemesis
Gastrointestinal hemorrhage	K921	Melaena
Gastrointestinal hemorrhage	K922	Gastrointestinal hemorrhage unspecified
Airway hemorrhage	J942	Hemothorax
Airway hemorrhage	R042	Hemoptysis
Airway hemorrhage	R048	Hemorrhage from other sites in respiratory passages
Urinary tract hemorrhage	R31X	Unspecified hematuria
Urinary tract hemorrhage	N028	Recurrent and persistent hematuria
Urinary tract hemorrhage	N029	Recurrent and persistent hematuria unspecified

PRIMARY END POINT CODES

The primary end point was death due to any cause, subsequent readmission to hospital for an MI, unstable angina, acute ischemic heart disease, ischemic stroke or transient ischemic attack (TIA) or readmission after 30 days from the index discharge date for either CABG, or recurrent coronary PCI.

Supplementary table 2.2 *ICD10* codes for major adverse outcomes

Diagnosis	Code	Description of code
MI	I219	Acute myocardial infarction unspecified
MI	I214	Acute subendocardial myocardial infarction
MI	I210	Acute transmural myocardial infarction of anterior wall
MI	I211	Acute transmural myocardial infarction of inferior wall
MI	I212	Acute transmural myocardial infarction of other sites
MI	I213	Acute transmural myocardial infarction of unspecified site
MI	I220	Subsequent myocardial infarction of anterior wall
MI	I221	Subsequent myocardial infarction of inferior wall
MI	I228	Subsequent myocardial infarction of other sites
Acute ischemic heart disease	I249	Acute ischemic heart disease
Unstable angina	I200	Unstable angina
Ischemic Stroke / TIA	I661	Occlusion and stenosis of anterior cerebral artery
Ischemic Stroke / TIA	I663	Occlusion and stenosis of cerebellar arteries
Ischemic Stroke / TIA	I660	Occlusion and stenosis of middle cerebral artery
Ischemic Stroke / TIA	I664	Occlusion and stenosis of multiple and bilateral cerebral arteries
Ischemic Stroke / TIA	I668	Occlusion and stenosis of other cerebral artery
Ischemic Stroke / TIA	I662	Occlusion and stenosis of posterior cerebral artery
Ischemic Stroke / TIA	I669	Occlusion and stenosis of unspecified cerebral artery
Ischemic Stroke / TIA	I64X	Stroke not specified as hemorrhage or infarction
Ischemic Stroke / TIA	I651	Occlusion and stenosis of basilar artery
Ischemic Stroke / TIA	I652	Occlusion and stenosis of carotid artery
Ischemic Stroke / TIA	I653	Occlusion and stenosis of multiple and bilateral pre cerebral arts
Ischemic Stroke / TIA	I658	Occlusion and stenosis of other precerebral artery
Ischemic Stroke / TIA	I659	Occlusion and stenosis of unspecified precerebral artery
Ischemic Stroke / TIA	I650	Occlusion and stenosis of vertebral artery
Ischemic Stroke / TIA	G458	Other transient cerebral ischemic attacks and related syndrome
Ischemic Stroke / TIA	G459	Transient cerebral ischemic attack unspecified
Ischemic Stroke / TIA	I636	Cerebral infarct due cerebral venous thrombosis nonpyogenic
Ischemic Stroke / TIA	I632	Cerebral infarct due unspecifed occlusion or stenos precerebral arteries
Ischemic Stroke / TIA	I630	Cerebral infarct due to thrombosis of precerebral arteries
Ischemic Stroke / TIA	I634	Cerebral infarction due to embolism of cerebral arteries
Ischemic Stroke / TIA	I631	Cerebral infarction due to embolism of precerebral arteries
Ischemic Stroke / TIA	I633	Cerebral infarction due to thrombosis of cerebral arteries
Ischemic Stroke / TIA	I639	Cerebral infarction unspecified
Ischemic Stroke / TIA	I635	Cerebral infarct due unspecified occlusion or stenos cerebral arts
Ischemic Stroke / TIA	I638	Other cerebral infarction
Ischemic Stroke / TIA	I693	Sequelae of cerebral infarction
Ischemic Stroke / TIA	I694	Sequelae of stroke not specified as hemorrhage or infarction

Supplementary table 2.3 OPCS codes (versions 4.5 to 4.8) for major adverse outcomes		
Procedure	Code	Description
CABG	K401	Saphenous vein graft replacement of one coronary artery
CABG	K402	Saphenous vein graft replacement of two coronary arteries
CABG	K403	Saphenous vein graft replacement of three coronary arteries
CABG	K404	Saphenous vein graft replacement of four or more coronary arteries
CABG	K408	Other specified saphenous vein graft replacement of coronary artery
CABG	K409	Unspecified saphenous vein graft replacement of coronary artery
CABG	K411	Autograft replacement of one coronary artery
CABG	K412	Autograft replacement of two coronary arteries
CABG	K413	Autograft replacement of three coronary arteries
CABG	K414	Autograft replacement of four or more coronary arteries
CABG	K418	Other specified other autograft replacement of coronary artery
CABG	K419	Unspecified other autograft replacement of coronary artery
CABG	K421	Allograft replacement of one coronary artery
CABG	K422	Allograft replacement of two coronary arteries
CABG	K423	Allograft replacement of three coronary arteries
CABG	K424	Allograft replacement of four coronary arteries
CABG	K428	Other specified allograft replacement of coronary artery
CABG	K431	Prosthetic replacement of one coronary artery
CABG	K442	Revision of replacement of coronary artery
CABG	K451	Double anastomosis of mammary arteries to coronary arteries
CABG	K453	Anastomosis of mammary artery to left anterior descending coronary artery
CABG	K454	Anastomosis of mammary artery to coronary artery NEC
CABG	K471	Endarterectomy of coronary artery
Coronary PCI	K49	Transluminal balloon angioplasty of coronary artery
Coronary PCI	K491	Percutaneous transluminal balloon angioplasty of one coronary artery
Coronary PCI	K492	Percutaneous transluminal balloon angioplasty of multiple coronary arteries
Coronary PCI	K493	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery
Coronary PCI	K494	Percutaneous transluminal cutting balloon angioplasty of coronary artery
Coronary PCI	K498	Other specified transluminal balloon angioplasty of coronary artery
Coronary PCI	K499	Unspecified transluminal balloon angioplasty of coronary artery
Coronary PCI	K503	Percutaneous transluminal injection of therapeutic substance into coronary artery
Coronary PCI	K504	Percutaneous transluminal atherectomy of coronary artery
Coronary PCI	K75	Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
Coronary PCI	K751	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery
Coronary PCI	K752	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery
Coronary PCI	K753	Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery
Coronary PCI	K754	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC
Coronary PCI	K758	Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
Coronary PCI	K759	Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
Coronary PCI	Y141	Insertion of expanding covered metal stent into organ NOC
Coronary PCI	Y142	Insertion of expanding metal stent into organ NOC
Coronary PCI	Y143	Insertion of metal stent into organ NOC

Supplementary table 2.4. Demographics and medical history of patients included and excluded in the analysis

* N=3,459

	Included	Excluded	P
Percentage of overall	*n*=2,090 60.4	*n* = 1,369 39.6	
Mean age, (SD)	63.2 (11.8)	65.9 (12.2)	<0.001
Characteristic, *n*(%)			
Male	1537 (73.5)	942 (68.8)	0.003
Obese	511 (24.4)	345 (25.2)	0.62
Smoker	784 (37.5)	496 (36.2)	0.45
Deprivation index			0.12
1	337 (16.4)	250 (18.2)	
2	411 (20.0)	260 (18.9)	
3	489 (23.9)	337 (24.6)	
4	415 (20.2)	229 (16.7)	
5	398 (19.4)	264 (19.3)	
Unknown	40 (1.9)	29 (2.1)	
Prior medical history, *n*(%)			
Hypertension	851 (40.7)	608 (44.4)	0.03
Ischemic Heart Disease	612 (29.3)	525 (38.3)	<0.001
Myocardial Infarction	351 (16.8)	280 (20.5)	0.006
Coronary revascularization	203 (9.7)	209 (15.3)	<0.001
Ischemic Stroke	115 (5.5)	97 (7.1)	0.06
Heart Failure	259 (12.4)	237 (17.3)	<0.001
Vascular Disease	81 (3.9)	81 (5.9)	<0.001
Thromboembolism	14(0.7)	17 (0.7)	0.36
Diabetes	382 (18.3)	297 (21.7)	0.01
CKD Stage 4+	16 (0.8)	16 (1.2)	0.22
Chronic liver Disease	24 (1.1)	13 (0.9)	0.58
Dyslipidemia	380 (18.2)	288 (21.0)	0.04
Dementia	9 (0.4)	9 (0.7)	0.36
Prior bleeding events	205 (9.8)	164 (12.0)	0.04
Aspirin	711 (34.0)	610 (44.6)	<0.001
$P2Y_{12}$ antagonist	230 (11.0)	265 (19.6)	<0.001
Statins	924 (44.2)	733 (53.5)	<0.001
Clinical syndrome, *n*(%)			<0.001
ACS	1,808 (86.5)	1,030 (75.2)	
Stable	282 (13.5)	339 (24.8)	

*Comparisons made here are between those meeting the inclusion criteria and prescribed clopidogrel for one year (n=2090) and those not meeting the inclusion criteria but had linked data available before the index admission, survived at least one day after discharge but did not have AF or received CABG during the index admission. Comparisons are made using the χ^2 test for categorical variables and the independent T test for continuous variables

Individual outcomes of MI, ischemic stroke, coronary revascularization and death

The primary outcome measure (the composite of MI, ischemic stroke, coronary revascularization 30 days' post discharge and death) occurred in 286 (13.7%) of the cohort. The number of patients having an MI during follow up was 167 (8.0%), ischemic stroke 31 (1.5%), coronary revascularization 100 (4.8%) and death 46 (2.2%). For completeness we modelled baseline characteristics and the time dependent effects of discontinuation and /or bleeding against these individual outcome measures in a multivariable Cox-proportional hazard model (supplementary table 2.5). In these models we found no significant association between discontinuation and/or bleeding on coronary revascularization. We also calculated the event rate per 100 patient years (supplementary table 2.6). In the case of MI, revascularization, and stroke there were no patients who had both clopidogrel discontinuation and bleeding events prior to the adverse outcome.

Supplementary table 2.5. Multivariable Cox proportional hazard model of characteristics associated with the independent adverse outcomes of MI, ischemic stroke, coronary revascularization or death

	MI HR (95% CI), p value	Ischemic Stroke HR (95% CI), p value	Revascularization HR (95% CI), p value	Death HR (95% CI), p value
Covariate		-	-	-
Age decile		-	-	-
≤49	2.44 (1.42-4.2),	-	-	-
50- 59	Reference, p=0.21	-	-	-
60-69	1.71 (1.05-2.78)	-	-	-
70-79	1.96 (1.19-3.22)	-	-	-
≥80	1.99 (1.08-3.67)	-	-	-
Hypertension	-	2.29 (1.06-4.97), p=0.035	-	-
Liver disease	2.74 (1.21-6.22), p=0.016	-	-	-
CKD stage 4+	-	-	6.43 (2.35-17.45), <0.001	-
Previous revascularization	2.42 (1.64-3.59), p<0.001	-	1.83 (1.09-3.07), p=0.02	-
Previous ischemic stroke	-	5.71 (2.58-12.66), p<0.001	2.21 (1.19-4.09), p=0.01	-
Previous thromboembolism	-	-	3.33 (1.03-10.73), p=0.04	-
Heart failure	-	4.03 (1.95-8.30), p<0.001	-	-
Clinical Syndrome		-	-	-
Stable CAD	Reference			
ACS	2.09 (1.20-3.66), p=0.009			
Previous Thromboembolism	4.68 (2.15-10.19), P<0.001	-	-	-
Time dependent variable of discontinuation and/or bleed				
No discontinuation and no bleed	Reference, p<0.001	Reference, p<0.001	-	Reference, p<0.001
(1) Discontinuation only	1.76 (0.76-4.05)	-	-	6.00 (2.44-14.76)
(2) Bleed only	5,78 (2.88-11.60)	9.78 (3.30-28.95)	-	5.94 (1.79-19.72)
(3) Discontinuation and bleed	-	-	-	61.47 (21.18-178.39)

*The following variables were included in the model: age; gender; presenting clinical syndrome; hypertension; prior coronary revascularization; prior bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes; CKD stage 4+; chronic liver disease, dyslipidemia; dementia and time dependent variables or clopidogrel discontinuation, bleeding and both discontinuation and bleeding. Only variables associated with one or more outcomes are presented. The final variables were selected in a multivariable co model by minimizing the Akaike information criterion.

Supplementary table 2.6. Individual event rate* for Stroke, MI, coronary revascularization and death according to presence of clopidogrel discontinuation and/or bleed

	MI	Ischemic stroke	Coronary revascularization	Death
No discontinuation and no bleed	5.34	0.08	3.02	1.22
Discontinuation only	17.43	0.07	12.43	6.06
Bleed only	18.75	10.5	8.38	6.06
Discontinuation and bleed	-	-	-	64.6

*Event rate calculated in events per 100 patient years.

Supplementary table 2.7. Multivariable Cox proportional hazard model of characteristics associated with bleeding events during follow up

Covariate	HR	CI lower	CI upper	p
Prior bleeding	2.82	1.67	4.76	<0.001
CKD stage 4+	6.15	2.22	17.08	<0.001
Chronic liver disease	3.62	1.14	11.51	<0.001

*The following variables were included in the model: age; gender; presenting clinical syndrome; hypertension; prior coronary revascularization; prior bleeding events; ischemic stroke; heart failure; vascular disease; thromboembolism; diabetes; CKD stage 4+; chronic liver disease and dyslipidemia.

CHAPTER 3

ACHIEVEMENT OF EUROPEAN GUIDELINE-RECOMMENDED LIPID LEVELS POST-PERCUTANEOUS CORONARY INTERVENTION: A POPULATION-LEVEL OBSERVATIONAL STUDY

ABSTRACT

AIMS

2019 ESC/EAS guidelines recommend more aggressive lipid targets in high and very high-risk patients and addition of adjuvant treatments to statins in uncontrolled patients. We aimed to assess (i) achievement of prior and new ESC/EAS lipid targets and (ii) lipid lowering therapy (LLT) prescribing in a nationwide cohort of very high-risk patients.

METHODS

We conducted a retrospective observational population study using linked health-data in patients undergoing percutaneous coronary intervention (PCI) (2011-17). Follow-up was one-year post discharge.

RESULTS

10,071 patients had a documented LDL-C level, of whom 48% had an LDL-C <1.8mmol/L (2016 target) and (23%) <1.4mmol/L (2019 target). 5,340 had non-HDL-C documented with 57% <2.6mmol/L (2016) and 37% <2.2mmol/L (2019). In patients with recurrent vascular events, fewer than 6% of the patients achieved the 2019 LDL-C target of <1.0mmol/L. 10,592 had triglyceride (TG) levels documented, of whom 14% were ≥2.3mmol/L and 41% ≥1.5mmol/L (2019).

High intensity (HI-statins) were prescribed in 56.4% of the cohort, only 3% were prescribed ezetimibe, fibrates or prescription-grade N-3 fatty acids. Prescribing of these agents was lower amongst patients above target LDL-C, non-HDL-C and TG. Females were more likely to have LDL-C, non-HDL-C and TG levels above target.

CONCLUSION

There was a low rate of achievement of new ESC/EAS lipid targets in this large post-PCI population and relatively low rates of intensive LLT prescribing in those with uncontrolled lipids. There is considerable potential to optimise LLT further through statin intensification and appropriate use of novel LLT, especially in women.

BACKGROUND

Cardiovascular disease (CVD) carries a high burden of morbidity and mortality.[1] Patients with established CVD are at higher risk of recurrent events, however, the progressive implementation of evidence-based therapies has improved survival and reduced recurrence of major adverse cardiovascular events (MACE).[2] Randomised controlled trials (RCTs) have consistently shown that the use of statins improves clinical outcomes in patients with, and at increased risk of, CVD. Furthermore, use of higher intensity statins leads to better outcomes than less intensive statin therapy.[3] The impact of statin therapy on clinical outcomes is directly related to the achieved reduction of Low-density lipoprotein cholesterol (LDL-C) levels. However, patients with increasing LDL-C still have progressively worse outcomes, despite statin therapy.[3]

The addition of ezetimibe to statin therapy confers a modest improvement in patient outcomes in keeping with its modest reduction in LDL-C.[4] Recent RCTs have demonstrated that more intensive lipid lowering therapy with the addition of Proprotein convertase subtiliskin/kexin type 9 (PCSK9) inhibitors to statins, leads to further improvement in clinical outcomes.[5, 6] The REDUCE-IT study has also shown that the addition of high-dose omega-3 fatty acid treatment (icosapent-ethyl 2g twice/day) improves outcomes in high risk patients with moderate hypertriglyceridemia (1.7-5.6mmol/L, [150-499mg/dL]) on statin therapy.[7]

The European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) have recently updated their guidelines for management of dyslipidaemia in which they recognise the implications of these new clinical trial data.[8] It is now recommended that LDL-C reduction of ≥50% from baseline and a LDL-C goal of <1.4mmol/L [<55mg/dL] in very high CVD risk patients, (reduced from <1.8mmol/L [70g/dL], in the 2016 guidelines) and <1.0mmol/L [<40mg/dL] in patients with recurrent atherosclerotic cardiovascular events

within the previous 2 years.[8, 9] These guidelines recommend the addition of ezetimibe to statin therapy and PCSK9 inhibitors in patients who are not at goal despite taking maximally tolerated statin dose +/- ezetimibe. There is also an emphasis on the importance of considering non-HDL-C levels as secondary treatment targets, especially in those individuals with elevated triglycerides (TG). Furthermore, in patients at high risk (or above) with triglyceride levels between 1.5 and 5.6mmol/L despite statin therapy, N-3 fatty acids (N-3) should be considered.

It is unknown what proportions of patients at very high CVD risk achieve, or do not achieve, these recommended levels of LDL-C, non-HDL-C and/or TGs; and how these respective patient groups are treated. A better understanding of these relationships will identify not only the therapeutic gap, but also the potential opportunity to optimise CVD risk management at an individual and population level. The objectives of this study were to document (i) lipid lowering treatment (LLT) and (ii) achievement of prior and current ESC/EAS lipid targets in a contemporary national cohort of patients post-percutaneous coronary intervention (PCI), who would be considered to be at very high CVD risk according to the ESC/EAS classification.

METHODS

We undertook a retrospective observational cohort study using linked anonymised electronic health record (EHR) data for patients undergoing PCI in Wales, UK between January 2012 and December 2017. Access to data and linkage was performed using the Secure Anonymised Information Linkage (SAIL) Databank.[10, 11] SAIL is part of the national e-health records research infrastructure for Wales; the following linked data sources are held within SAIL: secondary care hospital admission data within the Patient Episode Database for Wales (PEDW),[12] primary care General Practitioner (GP) data within the Welsh Longitudinal General

Practice (WLGP)[13], demographic data and GP registration history within the Welsh Demographic Service Dataset(WDSD) (see supplement for further details).[14]

Study subjects included those ≥18 years of age at the time of first PCI, who were discharged and had at least 90 days of follow-up data available in the WLGP data. An index date was assigned to the date of the first PCI during the study period for each patient. Follow-up was for one-year from the discharge date of the index hospital admission. The WLGP data was used to describe the presence of hypertension, ischemic heart disease, chronic kidney disease (CKD) stage 4+, chronic liver disease (including cirrhosis, fibrosis, chronic hepatitis and chronic active hepatitis, fatty liver, sclerosis of the liver, unspecified alcoholic liver damage, hepatic failure), dementia, prescriptions for lipid lowering therapy and recorded lipid levels. Both PEDW and WLGP data were used to describe a prior history of myocardial infarction and a prior or contemporary (at time of index admission) diagnosis of peripheral vascular disease (PVD), heart failure, atrial fibrillation (AF), diabetes mellitus and ischaemic stroke. PEDW was also used to identify if the index admission was for an acute coronary syndrome (ACS) and identify patients with hospital admission for a non-embolic stroke/transient ischaemic attack (TIA) or ACS within two years prior to the index hospital admission.

LIPID LEVELS AND PRESCRIPTIONS FOR LIPID MODIFYING THERAPY

The time to the first lipid profile and the lowest LDL-C, non-HDL-C and TG between 28 days and one-year post discharge was documented for each patient. Prescriptions for lipid lowering therapy (LLT) including statins, ezetimibe, fibrates and prescription-grade N-3 were identified during the follow up period.

LLT prescribed in the 90 days immediately post discharge and within 90 days prior to the lowest LDL-C and non-HDL-C were classified as high intensity statin (HI-statin; atorvastatin ≥40mg/d and rosuvastatin ≥20mg/d), non-high intensity (NI-statin; any other statin prescription), combination of ezetimibe and/or fibrate with either HI- or NI-statin (combination statin) and other treatments including ezetimibe and/or fibrate (other treatment) without a co-prescription of statin or no treatment.

LLT prescribed within the 90 days prior to the lowest TG level were classified as statin (either HI- or NI-statin); combination fibrate and/or N-3 with statin (combination statin), fibrate and/or N-3 (other) or no treatment.

We identified the number (and proportion) of patients achieving (i) LDL-C < or ≥: 1.4 and 1.8mmol/L; (ii) non-HDL-C < or ≥: 2.2 and 2.6mmol/L [< or ≥:65 and 100mg/dL]; (iii) TG < or ≥ 1.5 and 2.3mmol/L [135 and 200mg/dL] and their respective LLT regimen.

We also evaluated the number (and proportion) of patients with recurrent events within 2 years achieving LDL-C <or ≥ 1.0mmol/L and non-HDL-C < or ≥ 1.8mmol/L and their respective LLT regimens.

STATISTICAL ANALYSIS

Baseline variables including patient characteristics, medical history and LLT are presented as mean and standard deviation for continuous variables, and as frequency and percentage for categorical variables. Comparisons between groups with and without lipid profiles documented during follow up were performed using 2-sample *t*- test for normally distributed continuous variables and χ^2 for categorical variables, as appropriate. A multivariable binary logistic regression analysis was then conducted to identify independent variables associated with the

absence of a lipid profile. Variables included in this analysis included age, sex, hypertension, diabetes mellitus, CKD stage 4+, chronic liver disease, dementia, heart failure, ischaemic stroke, PVD, AF, ACS during the index admission and LLT prescribed in the first 90 days post-discharge.

Next, we investigated the association between achieved lipid levels (LDL-C> >1.4mmol/L, non-HDL-C>2.2mmol/L and TG>1.5mmol/L) as the dependent variable in a binary logistic regression model. Variables in this model included age, sex, hypertension, diabetes mellitus, CKD stage 4+, chronic liver disease, dementia, heart failure, ischaemic stroke, PVD, AF, ACS during the index admission and LLT prescribed in the first 90 days post-discharge. Model selection for all multivariable analyses was conducted using forward stepwise approach in SPSS version 22.0.

RESULTS

We identified 22,164 patients who had undergone a PCI during the study period, of whom 15,203 met the study inclusion criteria with a total of 14,577 years of follow up data (supplementary figure 3.1). The mean follow-up was 349 days (SD= 46.7days), mean age was 64.9years (SD= 11.9) and 10,933 (71.9%) were male (table 3.1). Of these, 11,048 (72.7%) had a lipid profile documented in their record during the year post discharge, of whom 1,154 (10.4%) had their first lipid profile within 28 days of discharge (figure 3.1). Overall, 8,573 (56.4%) of patients were prescribed high intensity statins and the prescribing rate was considerably higher amongst those who presented with an ACS during the index admission [7,269 (68.5%) v 1,304 (28.4%), p<0.001].

Patients who were female, had a history of CKD stage 4+, dementia, ischaemic stroke, AF and PVD were independently less likely to have a documented lipid in the year post discharge (supplementary table 3.1). Patients with diabetes mellitus, prescribed LLT and had an ACS during the index admission were independently more likely to have a lipid profile.

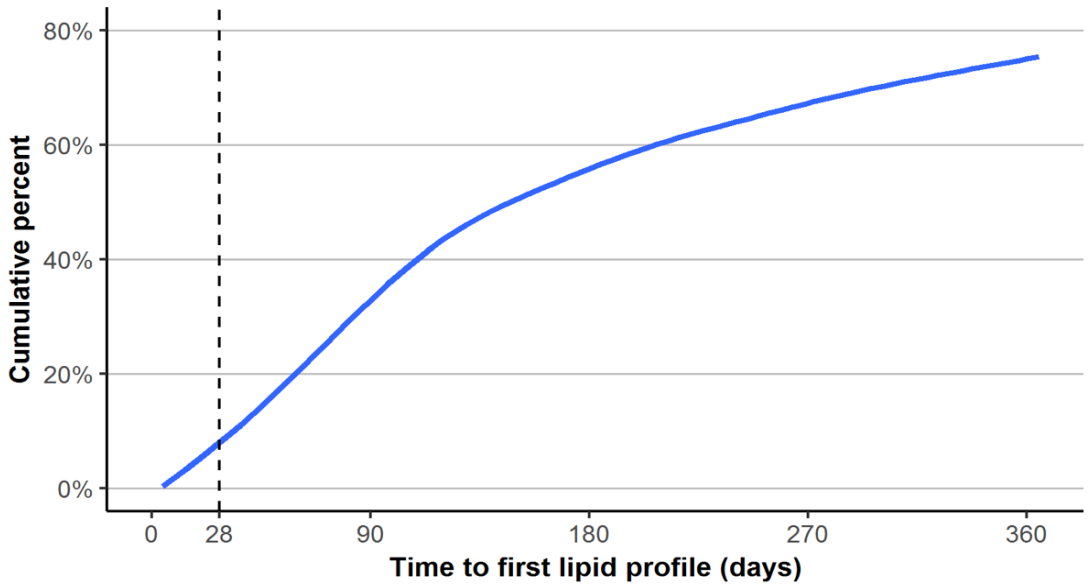

Figure 3.1 Time to first post-discharge lipid profile

Table 3.1. Cohort characteristic and comparison between those with and without a documented lipid profile in the first-year post-discharge -post-PCI

	Total cohort N = 15,203	With lipid profile N = 11,048	Without lipid profile N= 4,155	*P* Value*
Percent of total cohort	100%	72.7%	27.3%	
Mean Age (SD)	64.9 (11.9)	64.6 (11.4)	66.6 (13.0)	<0.001
Male N (%)	10,933 (71.9)	8,077 (73.1)	2,856 (68.7)	<0.001
Past medical history, N(%)				
Hypertension	6,331 (41.6)	4,581 (41.5)	1,750 (42.1)	0.46
Ischemic heart disease	4,029 (26.5)	2,934 (26.6)	1,095(26.4)	0.80
Previous MI	2,489 (16.4)	1,809 (16.4)	680 (16.4)	0.99
Previous revascularisation	1,414 (9.3)	1,013 (9.2)	401 (9.7)	0.36
Diabetes	3,516 (23.1)	2,769 (25.1)	747 (18.0)	<0.001
CKD stage 4+	182 (1.2)	96 (0.9)	86 (2.1)	<0.001
Liver disease	182 (1.2)	131 (1.2)	51 (1.2)	0.83
Dementia	91 (0.6)	47 (0.4)	44 (1.1)	<0.001
Heart failure	2,203 (14.5)	1,583 (14.3)	620 (14.9)	0.35
Ischemic stroke	1,011 (6.7)	690 (6.2)	321 (7.7)	0.001
Peripheral vascular disease	939 (6.2)	626 (5.7)	313 (7.5)	0.001
Atrial Fibrillation	1,634 (10.7)	1,105 (10.0)	529 (12.7)	<0.001
ACS during index admission	10,617 (69.8)	7,978 (72.2)	2,639 (63.5)	<0.001
Recurrent cardiac atherosclerotic event or non-embolic ischaemic stroke within two years	1,020 (6.7)	715 (8.0)	305 (8.6)	0.26
Stroke with two years	347 (2.3)	235 (2.6)	112 (3.2)	0.10
MI within two years	682 (4.5)	480 (5.4)	202 (5.7)	0.46
Cardiac revascularisation within two years	73 (0.5)	54 (0.6)	19 (0.6)	0.63

Continued on next page.

Table 3.1 continued.

	Total cohort N = 15,203	With lipid profile N = 11,048	Without lipid profile N= 4,155	*P* Value*
LLT prescribed within 90 days post discharge				<0.001
No lipid lowering therapy	993 (6.5)	379 (3.4)	614 (14.8)	
High Statin	8,573 (56.4)	6,399 (57.9)	2,174 (52.3)	
Non-high intensity statin	5,179 (34.1)	3,914 (35.4)	1,265 (30.4)	
Statin & other†	311 (2.0)	242 (2.2)	69 (1.7)	
Other LLT	147 (1.0)	114 (1.0)	33 (0.8)	

*P value for comparison between those with and without a lipid profile; CKD indicates Chronic Kidney Disease; ACS indicates Acute Coronary Syndrome; LLT indicates lipid lowering therapy, Other LLT indicates ezetimibe and/or fibrate.
† Other LLT includes prescriptions for ezetimibe and/or fibrate.

LDL- C LEVELS

Of the 11,048 with any lipid profile, 10,071 patients had an LDL-C documented between 28 days and one year (mean lowest LDL-C= 1.90mmol/L, SD=0.79) (figure 3.2a). Of these, 4,812 (47.8%) had an LDL-C below the 2016 EAS/ESC target of 1.8mmol/L, but only 2,353 (23.4%) were below the 2019 target of 1.4mmol/L.

A total of 1,020 (6.7%) of patients had experienced an atherosclerotic event within two years prior to the index PCI (including 347 (2.4%) with a stroke, 682 (4.5%) with a MI and 73 (0.5%) who had undergone a coronary revascularisation) of whom 627 had documented LDL-C. Of these 627, Only 33 (5.3%) had LDL-C levels below the new 2019 ESC/EAS target of 1.0mmol/L (Figure 3.2c).

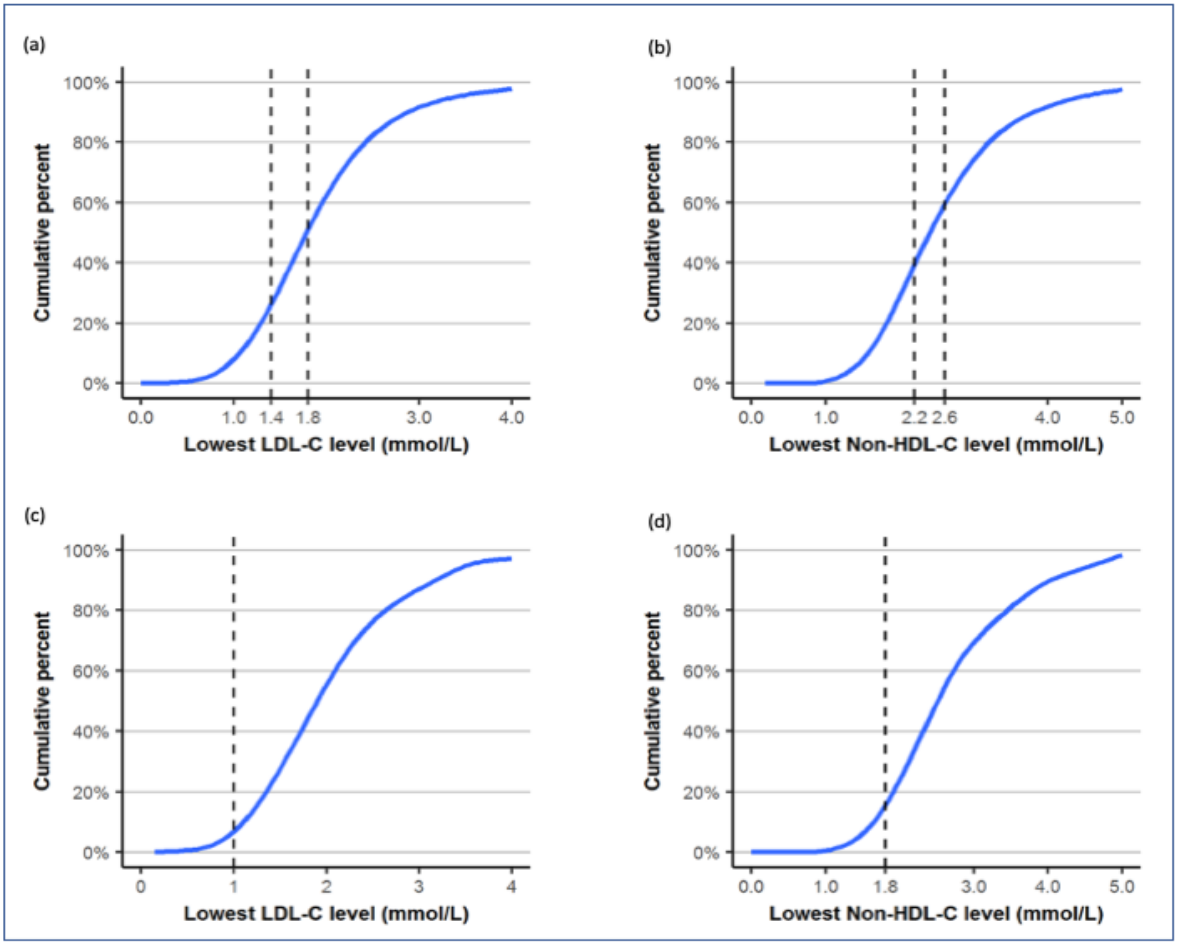

Figure 3.2 Post discharge lipid results

(a) Lowest LDL-C recorded between 28 and 365 days in 10,071 patients, (b) lowest non-HDL-C recorded between 28 and 365days in 5,340 patients, (c) lowest LDL-C recorded between 28 and 365 days in 627 patients with recurrent events and (d) lowest non-HDL-C recorded in 314 patients with recurrent events.

Considering patients with documented LDL-C levels greater than 1.8 and 1.4mmol/L, 2,437 (46%) and 4,082 (53%) respectively were prescribed high intensity statins; 117 (2.2%) and 146 (1.9%) were prescribed a combination of ezetimibe and/or fibrate plus a statin, and 103 (2.0%) and 109 (1.4%) prescribed ezetimibe and/or fibrate without a statin (figure 3.3).

Of the 594 of patients with recurrent events within 2 years and LDL-C ≥1.0mmol, 312 (52.5%) were prescribed high intensity statins; 214 (36.0%) were prescribed standard intensity statins, 19 (3.1%) were prescribed ezetimibe and/or a fibrate in addition to a statin, 12 (2.0%)

were prescribed either ezetimibe and/or fibrate without a statin and 37 (6.2%) patients were not prescribed any LLT.

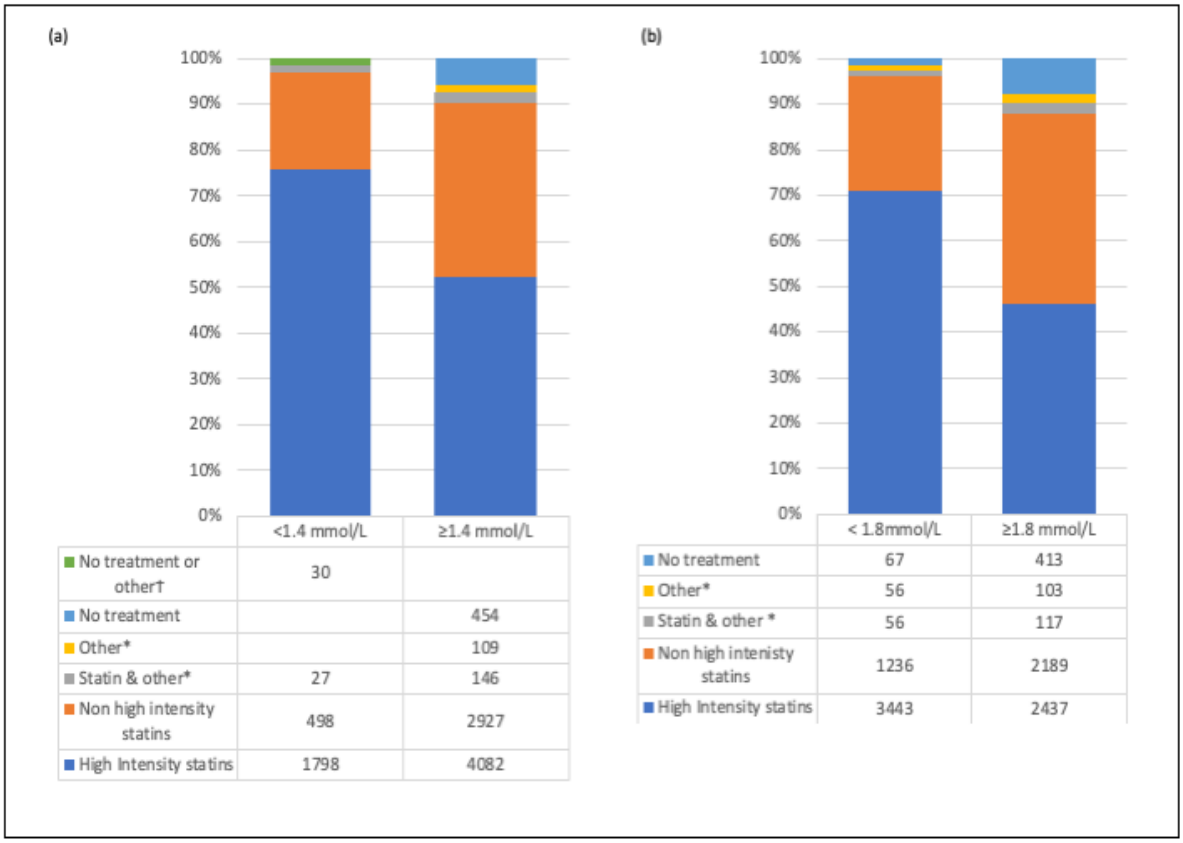

Figure 3.3 Prescribed lipid lowering therapy in patients at or above (a) 2019 & (b) 2016 ESC/EAS guideline LDL-C targets.

Other treatment indicates prescription for ezetimibe or fibrates; statin and other indicates prescription for either high intensity or standard intensity statin plus either ezetimibe or fibrate. † Governance restrictions within SAIL prohibit the reporting of numbers <5. Due to the low number of patients prescribed 'other' lipid lowering treatment with a LDL-C <1.4 we have grouped these patients with no treatment.

Characteristics independently associated with LDL-C ≥1.4mmol/L in a binary logistic regression analyses include female sex and PVD. Diabetes mellitus, increasing age and the presence of an ACS during the index admission were independently associated with achieving the 2019 target LDL-C <1.4mmol/L (supplementary table 3.2).

NON-HDL-C LEVELS

Non-HDL-C levels were documented 5,340 patients (mean lowest non-HDL-C =2.6mmol/L, SD= 0.97) of which 2,286 (42.8%) had a non-HDL-C ≥2.6mmol/L and 3,366 (63.0%) ≥ 2.2mmol/L (figure 3.2b). Amongst those with recurrent atherosclerotic events, 314 patient had non-HDL-C results documented of which only 40 (12.7%) were below the threshold of 1.8mmol/L (figure 3.2d).

The distribution of LLT regimens was similar in patients below or above target non-HDL-C to those observed in those at and not at LDL-C targets (supplementary figure 3.2).

Characteristics independently associated with non-HDL-C >2.2mmol/L included female sex, hypertension and PVD (supplementary table 3.3). ACS during the index admission, increasing age and LLT but not diabetes were predictive of a non-HDL-C < 2.2mmol/L

TG Levels

A total of 10,592 patients had TG levels recorded between 28 days and one year (mean lowest TG= 1.54mmol/L, SD=1.01), of whom 1,524 (14.4%) had TG≥2.3mmol/L and 4,314 (40.7%) had TG≥1.5mmol/L (figure 3.4).

Of those patients with TG ≥2.3mmol/L and ≥1.5, 1,313 (86.2%) and 3,847 (89.2%) were prescribed statins respectively, 62 (4.1%) and 122 (2.0%) prescribed fibrates and/or N-3 and 133 (8.7%) and 312 (7.2%) were not prescribed any LLT (figure 3.5).

In a multivariable analysis, variables independently associated with TG>1.5mmol/L included female sex, hypertension, CKD stage 4+, ischaemic stroke, PVD, and diabetes mellitus (supplementary table 3.4).

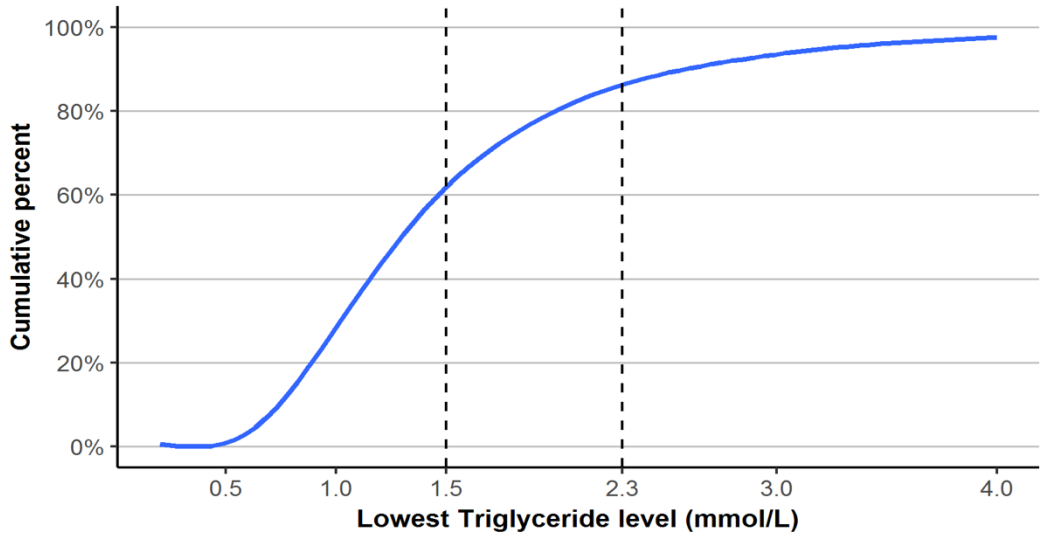

Figure 3.4 Lowest Triglyceride recorded between 28 and 365 days in 10,592 patients

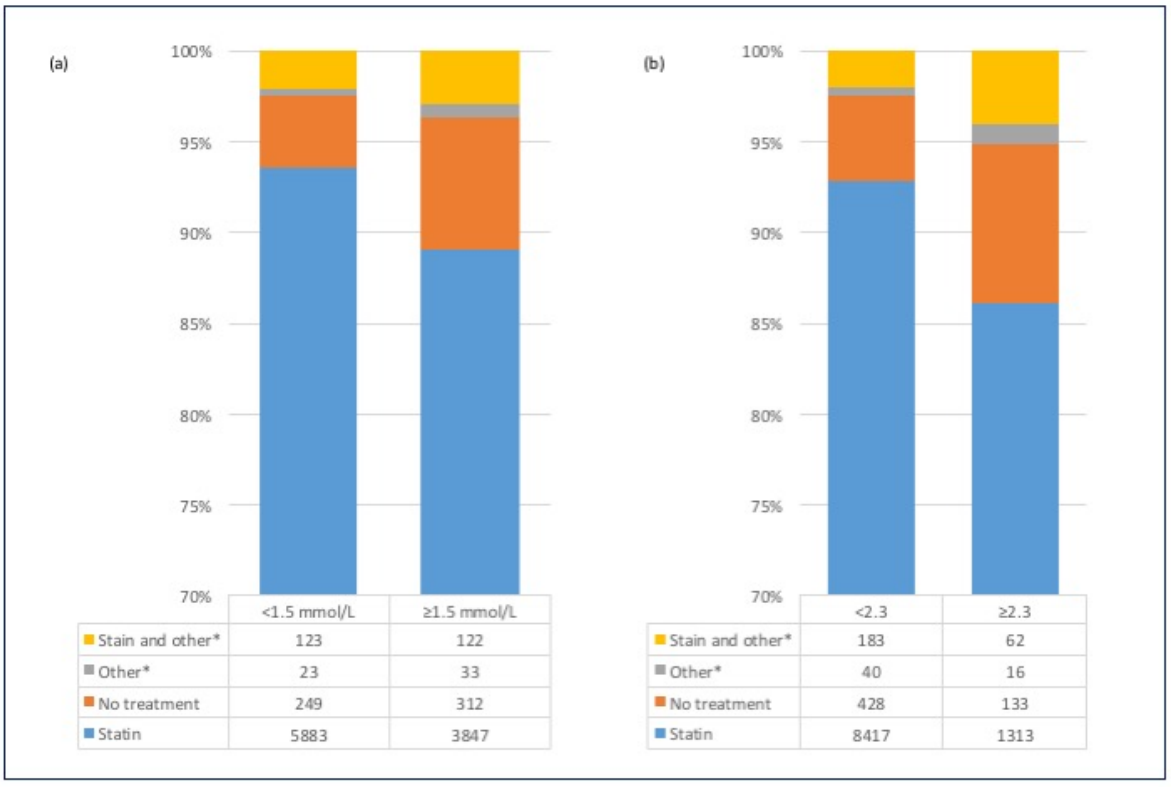

Figure 3.5 Number of patients and lipid lowering therapy according to Triglyceride levels.

*Other treatment indicates either fibrate or N-3 fatty acid.

DISCUSSION

This is the first real world study examining the prescribing of lipid lowering therapy and achieved lipid levels against the recently published ESC/EAS guideline targets in a national cohort of patients' post-PCI. This analysis was conducted in order to examine the potential implications for changes in management strategy at a system level in this important patient population. Notably, just under half (47.8%) of very high-risk patients had LDL-C below the 2016 ESC/EAS target of 1.8mmol/L in the year post-PCI, but fewer than a quarter (23.4%) were below the 2019 target of 1.4mmol/L. Furthermore, fewer than 6% of patients with recurrent atherosclerotic events achieved the new target of 1.0mmol/L where the index PCI was within 2 years of a prior admission for an ACS or non-embolic ischaemic stroke.

We also found that over 40% of patients had TG levels at or above 1.5mmol/L, the threshold for the new recommendation for consideration of high-dose N-3 prescription. In keeping with our findings, a recent Canadian real-world study has shown that approximately 25% of patients with atherosclerotic cardiovascular disease had moderately elevated TG with controlled LDL-C, with an increased event rate seen in these patients compared to those with TG of 1.0mmol/L.[15]

We found the prescribing of HI-statins to be considerably lower amongst patients with LDL-C levels not at target. Whilst it is possible that a proportion of these patients were intolerant of HI-statins, it is likely that a high proportion of patients prescribed NI-statins with LDL-C above the 1.4 and 1.8mmol/L respective targets, would be tolerant of HI-statins, given prior reported levels of statin intolerance in 10-20% of statin treated patients.[16-18] Furthermore, the (co-)prescribing of other LLTs, such as ezetimibe or fibrate, was also low.

Similarly, amongst those patients with recorded TG levels ≥2.3mmol/L and ≥1.5mmol/L, the prescribing of fibrate or N-3s were also low with < 3% of patients prescribed

these treatments alone or with statin therapy. However, these therapies are not endorsed by the UK National Institute for Health and Care Excellence (NICE).[19]

Although HI-statin prescription is recommended by NICE, only 56.4% of the patients in this study were receiving this treatment. However, our observed HI-statin prescribing rate was considerably higher than documented in previous observational studies of patients with MI, which have reported high intensity statin use in between only 4 and 31% of MI patients.[16, 20, 21] Although, those studies were in different health care systems to the UK, [16, 21] and in historical MI populations,[16] rather than a recent post PCI population, ACS was the indication for PCI in the majority of patients in our cohort (69.8%).

To allow assessment of response to treatment and consideration that LDL-C levels tend to fall transiently after an ACS, ESC guidelines recommend that lipid levels should be consequently (re-)evaluated 4-6 weeks after an ACS. Therefore, in this study we only analysed lipid profiles recorded beyond 28 days post-PCI. For patients with ≥1 result we identified the lowest lipid levels recorded between 28 days and one-year and documented the LLT prescription in the period preceding the lowest relevant result. Thus, the results of this study do not represent long term lipid prescribing or lipid control beyond 1-year. However, LLT prescribing, treatment concordance and lipid control has previously been shown to decrease significantly over time.[22, 23]

Just under three quarters (73.1%) of our cohort had a lipid profile recorded during the first-year post discharge. Females and those with a history of CKD stage 4+, ischaemic stroke, AF and/or PVD were less likely to have lipid levels and have lipid levels not at target. Importantly, these are clinical characteristics associated with worse outcomes and provide further evidence of gender disparity in the management of CVD risk.[24]

Notably patients with an ACS during the index admission were almost 2.5 times more likely to be prescribed HI-Statin than those undergoing PCI for stable disease and more likely to have lipids checked in the year post discharge. These observations are possibly due to the differences in clinical pathways between ACS and elective patients undergoing PCI for stable coronary artery disease who are less likely to have changes made to longer term CVD prevention regimens at that point in time.

The 2016 non-HDL-C and LDL-C targets were achieved in 57% and 48% of patients, whereas the 2019 respective targets were achieved in 37% and 23% of patients. Importantly, whilst diabetic patients were more likely to achieve LDL-C targets this was not the case for non-HDL-C, emphasising the importance of considering this measure in this very high-risk population.

Two recent registry studies looked at the effectiveness of LDL-C control in populations with coronary artery disease (CAD).[25, 26] In both these registries approximately 42% of ACS patients had LDL-C levels below the 2016 ESC/EAS target of < 1.8mmol/L, but only 28% of stable CAD achieved this.

Both of these studies emphasise the difficulty faced in achieving adequate LDL-C control across high-risk populations, even considering the less stringent 2016 targets. These registry findings are consistent with ours which also reflects the challenges in achieving the even more stringent 2019 targets. It is likely that increased use of novel therapies will be required, where appropriate in order to close this therapeutic gap.

STRENGTHS AND LIMITATIONS

We believe that by identifying important gaps in the achievement of ESC/EAS guideline target lipid levels, this study has demonstrated the potential opportunity for improved secondary prevention of CVD through optimisation of evidence-based lipid lowering therapy. Although the data in this study represent practice prior to the publication of the 2019 guidelines, this is a recent, representative cohort of very high-risk patients who would now qualify for more aggressive LDL-C, non-HDL-C and TG targets according to the new guidelines.

There are a number of potential limitations to this study. While we identified the prescribing of LLT from primary care GP data, we were not able to identify the quantity of medication prescribed, whether it was dispensed, or if the patient complied with therapy. This study makes no assumptions on medication compliance which is often low in chronic conditions, particularly with statins.[27, 28] Therefore, the prescribing of LLT reported in this study likely describes a best-case management scenario.

We did not identify any patients post PCI who were prescribed PCSK9 inhibitors in our dataset. These agents were only approved for use within the UK National Health Service (NHS) in June 2016.[29, 30] Although the prescribing of these treatments is mainly provided though specialist hospital outpatient clinics, whose data was not available for this study, the uptake of PCSK 9 inhibitors within Wales has been very low. Therefore, it is unlikely that the absence of the prescribing data for these treatments would have significantly changed these results.

It was not possible to characterise the reasons why over a quarter of our patients did not have a lipid profile documented in their primary care EHR data during the year post discharge. It is unlikely that this was due to 'loss to follow-up' as we only included patients with ≥90days follow-up (mean follow-up =349 days), which should have allowed sufficient time post-PCI to record lipid profiles. Patients without lipid levels typically had higher risk characteristics. It is

unknown whether this difference observed in lipid monitoring is explained by confounding factors or a risk-treatment paradox. It is possible that some patients had lipid profiles documented post-discharge within secondary care pathology datasets that were not available for this study, however longer-term risk factor management is undertaken in primary care for the vast majority of patients in Wales in both the primary and secondary prevention settings.

Lipid profiles recorded during the index admission were also not available for this study. While we categorised patients at or above target levels, we were not able to calculate the percentage LDL-C reduction from baseline. It is therefore likely that an even greater number of patients would not have achieved both a ≥50% reduction in LDL-C and a target level.

In this study, 6.7% of patients were classified as having recurrent atherosclerotic events, including a previous hospital admission for an ACS, coronary revascularisation, non-embolic stroke or TIA within 2 years before the index PCI. Due to ambiguity of clinical coding of peripheral vascular disease within the secondary care hospital admissions PEDW data, we were unable to accurately detect acute peripheral vascular events and therefore these were not included. We noted that a far greater number of our patient cohort had experienced clinical atherosclerotic events over 2years before the index PCI (table 3.1).

It was beyond the scope of this study to evaluate the relationships between early post-PCI lipid levels, LLT strategy and clinical outcomes in the first year post-PCI. The purpose of this short report was to characterise the nature of LLT and achievement of lipid targets according to contemporary ESC/EAS[9] guidance at the time of PCI and to document the potential for further optimisation of lipid management in this very high-risk cohort with reference to the new guideline targets and recommended treatments. Therefore, future

prospective evaluation will be required to evaluate the nature of any changes in lipid management and impact on lipid levels and clinical outcomes at a population level.

A last, but important consideration is that the data for this study were obtained from patients treated in the Welsh NHS, where the cost of health care, including prescription drugs, is entirely free at the point of delivery. This mitigates against potential barriers of affordability of follow-up consultation, lipid monitoring and medication purchasing. These would be important considerations when comparing the findings of our study to other healthcare systems, where greater discrepancies in quality of care might be expected in more economically disadvantaged individuals and populations.[31]

CONCLUSION

We have identified a relatively low rate of prescribing of high intensity statins with or without additional evidence-based LLT agents in a large post-PCI patient population, as well as a relatively low proportion of these patients achieving the new EAS/ESC lipid targets. Our data suggest that there is considerable potential to optimise LLT through statin intensification and appropriate use of novel LLT. This would be expected to increase the proportion of very high-risk patients achieving target lipid levels and improve clinical outcomes at an individual and population level. However, the budgetary impact of novel management strategies and thus potential value to health care providers and funders will need to be carefully planned and evaluated.

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SUPPLEMENTARY MATERIAL

Supplementary table 3.1 Multivariable binary regression analysis of variables associated with the absence of a documented lipid profile during follow up**.**

Covariate	OR	Lower CI	Upper CI	*P*
Female	1.18	1.09	1.28	<0.001
CKD stage 4+	2.26	1.65	3.09	<0.001
Dementia	2.35	1.52	3.63	<0.001
Ischaemic stroke	1.19	1.03	1.38	.018
AF	1.20	1.07	1.35	0.002
PVD	1.41	1.22	1.64	<0.001
ACS during index admission	0.77	0.71	0.84	<0.001
Diabetes mellitus	0.56	0.50	0.62	<0.001
LLT				
No LLT	Reference			<0.001
HI statin	0.25	0.22	0.29	<0.001
NI stain	0.22	0.18	0.25	<0.001
Other LLT*	0.21	0.14	0.31	<0.001
Statin & other LLT*	0.63	0.46	0.85	<0.001

*Other LLT indicates the prescribing of ezetimibe and/or fibrate.

The following variables were included in the model: age, sex, hypertension, diabetes mellitus, CKD stage 4+, chronic liver disease, dementia, heart failure, ischaemic stroke, PVD, AF, ACS during the index admission and LLT prescribed in the first 90 days post discharge

Supplementary table 3.2. Multivariable binary regression analysis of variables associated with LDL-C ≥1.4mmol/L

Covariate	OR	Lower CI	Upper CI	*P*
Age	0.98	0.98	0.99	<0.001
Female	1.83	1.63	2.06	<0.001
PVD	1.43	1.13	1.80	<0.001
ACS during index admission	0.62	0.55	0.71	<0.001
Diabetes mellitus	0.59	0.53	0.66	<0.001
LLT				
No LLT	Reference			<0.001
HI Statin	0.13	0.08	0.19	
NI statin	0.32	0.21	0.49	
Other LLT	1.74	0.59	5.11	
Statin other LLT	0.31	0.17	0.55	

*Other LLT indicates the prescribing of ezetimibe and/or fibrate.
The following variables were included in the model: age, sex, hypertension, diabetes mellitus, CKD stage 4+, chronic liver disease, dementia, heart failure, ischaemic stroke, PVD, AF, ACS during the index admission and LLT

Supplementary table 3.3 Multivariable binary regression analysis of variables associated with non-HDL-C ≥2.2mmol/L

Covariate	OR	Lower CI	Upper CI	*P*
Age	0.97	0.96	0.97	<0.001
Female	1.82	1.58	2.09	<0.001
PVD	1.65	1.22	2.22	0.001
ACS during index admission	0.57	0.49	0.67	<0.001
Hypertension	1.14	1.01	1.29	0.038
LLT				
No LLT	Reference			<0.001
HI Statin	0.09	0.06	0.15	
NI statin	0.24	0.15	0.39	
Other LLT	2.47	0.56	10.94	
Statin other LLT	0.42	0.20	0.89	

*Other LLT indicates the prescribing of ezetimibe and/or fibrate.

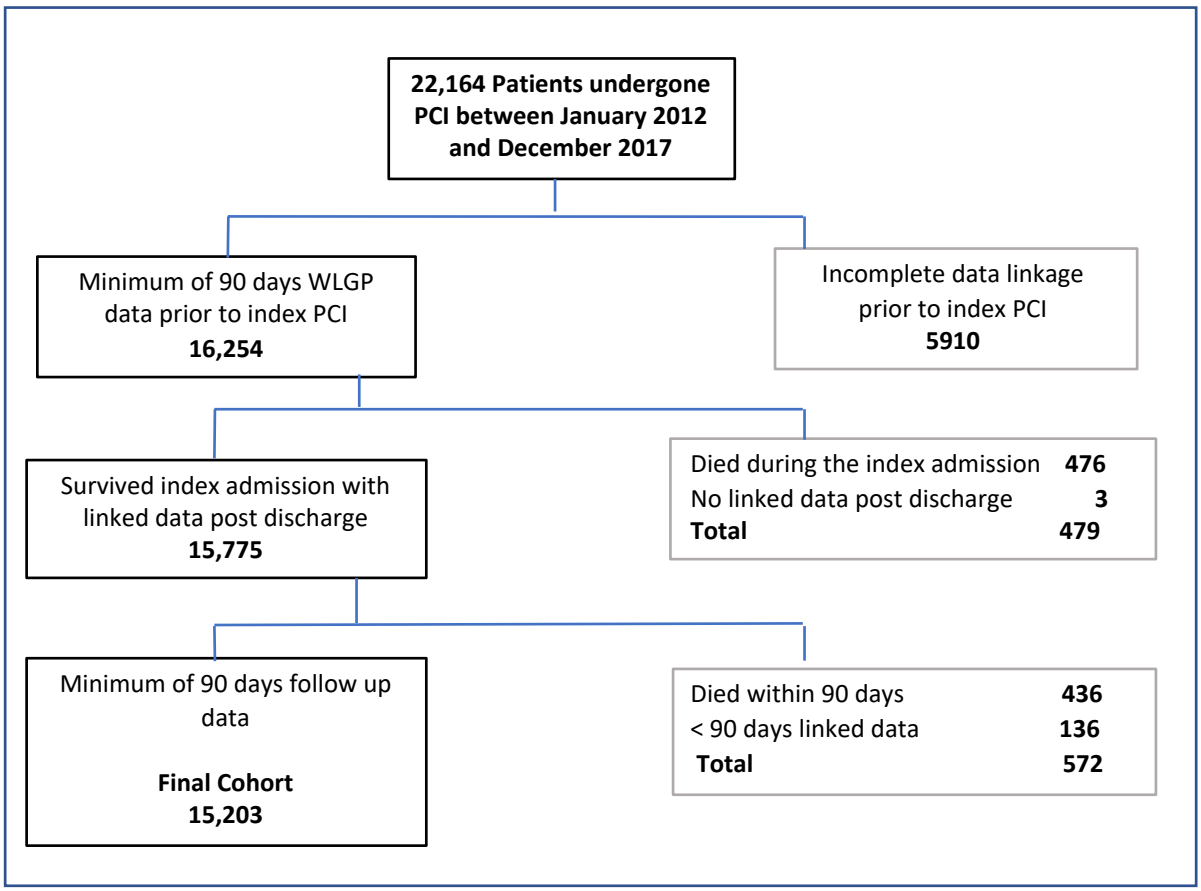
The following variables were included in the model: age, sex, hypertension, diabetes mellitus, CKD stage 4+, chronic liver disease, dementia, heart failure, ischaemic stroke, PVD, AF, ACS during the index admission and LLT

Supplementary table 3.4 Multivariable binary regression analysis of variables associated with triglycerides ≥1.5mmol/L

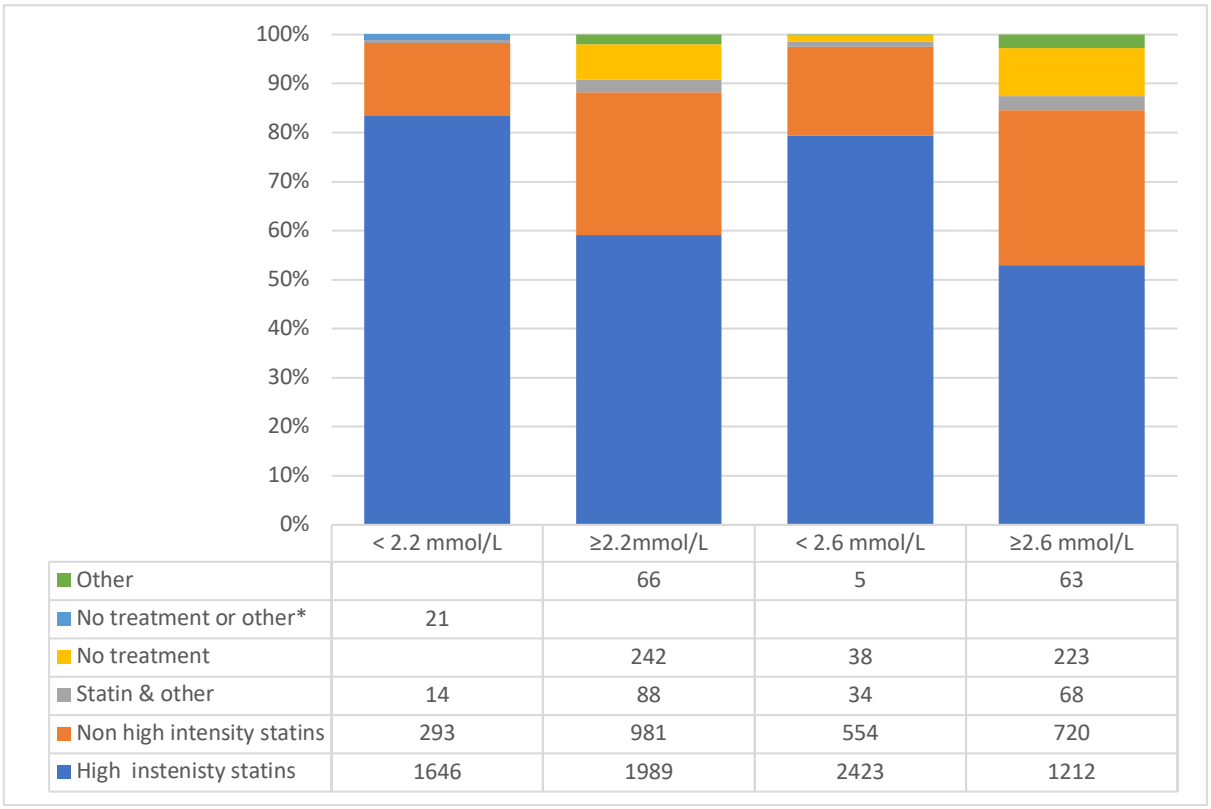
Covariate	OR	Lower CI	Upper CI	*P*
Age	0.98	0.97	0.98	<0.001
Female	1.26	1.14	1.38	<0.001
Hypertension	1.21	1.11	1.32	<0.001
CKD stage 4+	1.83	1.16	2.88	0.009
Ischaemic stroke	1.33	1.12	1.59	0.001
Atrial fibrillation	0.85	0.73	0.98	0.025
PVD	1.48	1.24	1.77	<0.001
ACS during index admission	0.77	0.71	0.85	<0.001
Diabetes mellitus	1.91	1.74	2.11	<0.001
LLT				
No LLT	Reference			<0.001
Other LLT*	0.91	0.49	1.68	
Statin	0.55	0.45	0.66	
Statin other LLT	0.68	0.49	0.94	

*Other LLT indicates the prescribing of a fibrate and/or N-3.

The following variables were included in the model: age, sex, hypertension, diabetes mellitus, CKD stage 4+, chronic liver disease, dementia, heart failure, ischaemic stroke, PVD, AF, ACS during the index admission and LLT



Supplementary figure 3.1 Study population cohort selection.



	< 2.2 mmol/L	≥2.2mmol/L	< 2.6 mmol/L	≥2.6 mmol/L
Other		66	5	63
No treatment or other*	21			
No treatment		242	38	223
Statin & other	14	88	34	68
Non high intensity statins	293	981	554	720
High instenisty statins	1646	1989	2423	1212

Supplementary Figure 3.2 Number of patients and lipid lowering therapy according to non-HDL-C level.

*Governance restrictions within SAIL prohibit the reporting of numbers <5. Due to the low number of patients prescribed 'other' lipid lowering treatment with a non-HDL-C < 2.2, we have grouped these patients with no treatment.

CHAPTER 4.

AN OBSERVATIONAL STUDY OF INR CONTROL ACCORDING TO NICE CRITERIA IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION. THE SAIL WARFARIN OUT OF RANGE DESCRIPTORS STUDY (SWORDS)

ABSTRACT

AIMS

In patients with non-valvular atrial fibrillation (NVAF) prescribed warfarin, the UK National Institute of Health and Care Excellence (NICE) defines poor anticoagulation as a TTR of <65%, any 2 INRs within a 6-month period of ≤1.5 ("low"), 2 INRs ≥5 within 6-months, or any INR ≥ 8 ("high").

Our objectives were to (i) quantify the number of patients with poor INR control and (ii) describe the demographic and clinical characteristics associated with poor INR control.

METHOD AND RESULTS

Linked anonymised health record data for Wales (2006-2017) was used to evaluate patients prescribed warfarin who had at least 6 months of INR data.

32,380 patients were included. In total, 13,913 (43.0%) patients had at least one of the NICE markers of poor INR control. Importantly, in the 24,123 (74.6%) of the cohort with an acceptable TTR (≥65%), 5,676 (23.5%) had either low or high INR readings at some point in their history. In a multivariable regression female gender, age (≥75), excess alcohol, diabetes heart failure, ischaemic heart disease and respiratory disease were independently associated with all markers of poor INR control.

CONCLUSION

Acceptable INR control according to NICE standards is poor. Of those with an acceptable TTR (>65%) one quarter still had unacceptably low or high INR levels according to NICE criteria. Thus, only using TTR to assess effectiveness with warfarin has the potential to miss a large number of patients with non-therapeutic INRs who are likely to be at risk of stroke, systemic embolism and bleeding.

BACKGROUND

Warfarin is the most common oral anticoagulant prescribed to reduce the risk of stroke in patients with atrial fibrillation (AF). Warfarin, like other Vitamin K antagonists (VKAs), has several limitations, including many drug-drug and drug-food interactions.[1] Furthermore, patient characteristics and comorbidities can lead to high intra-and inter-patient variability in response.[2, 3] In patients with non-valvular AF (NVAF) without any other indication for anticoagulation, current guidelines recommend an International Normalised Ratio (INR) range of 2.0 – 3.0.[4-6] The net clinical benefit of warfarin is associated with the proportion of time that INR values are maintained within the therapeutic range, referred to as the time in therapeutic range (TTR).[7, 8] Subtherapeutic INR results are associated with an increase in thromboembolism[9], while supertherapeutic INR results are associated with increased risk of bleeding including haemorrhagic stroke.[10-12]

In the UK, the National Institute for Health and Care Excellence (NICE) recommends that, in patients prescribed warfarin for AF to, "Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following: two INR values higher than 5 or one INR value higher than 8 within the past 6 months; two INR values less than 1.5 within the past 6 months; [and/or] TTR less than 65%."[13] NICE advises that "If anticoagulation control cannot be improved, then the risks and benefits of alternative stroke prevention strategies should be discussed with the patient." For patients with non-valvular atrial fibrillation (NVAF) alternative anticoagulation with direct oral anticoagulants (DOACs) can now be provided. [14, 15]

A number of observational studies and clinical trials have reported the TTR of patients prescribed VKAs for AF,[3, 10, 16-21] with the average TTR in these studies ranging from 53.7-68.4%, highlighting the increased risk of stroke and systemic embolism with subtherapeutic INRs, as well as the excess bleeding risk with supertherapeutic INRs. However, the wider

variability in INR control described by frequency of very low or very high INRs (as defined by NICE), as distinct from TTR, has not been previously described. This is of particular importance as it would characterise important therapeutic gaps at both an individual and population level, which are not captured by TTR alone.

The objectives of this study were (i) to quantify the number of patients with NVAF prescribed warfarin who exhibit NICE-defined poor INR control and (ii) describe the demographic and clinical characteristics of these patients, as well as the relationship between these characteristics and poor INR control.

METHOD

STUDY DESIGN AND DATA SOURCES

A retrospective observational cohort study was conducted using linked anonymised healthcare data for patients prescribed warfarin for NVAF between January 2006 and April 2017 in Wales, United Kingdom, using the Secure Anonymised Information Linkage (SAIL) Databank.[22-24] SAIL is part of the national e-health records research infrastructure. The following datasets held within SAIL were linked: the Patient Episode Database for Wales (PEDW),[25] which records hospital admission and discharge dates, diagnoses and operational procedures, demographic data, and date of death where applicable for the population of Wales; the Welsh Longitudinal General Practice (WLGP) dataset[26] containing demographic, clinical and prescribing data for approximately 76% of primary care practices across Wales; the Welsh Demographic (WDS) dataset,[27] which contains basic demographic information and history of individuals' residence in Wales and registration with GP practices; and the Welsh Index of Multiple Deprivation (WIMD) 2011,[28] an area-based deprivation measure.

Study subjects included those who had a diagnosis of AF/atrial flutter recorded in the WLGP dataset at any point prior to or during the study period and who were at least 18 years old at time of diagnosis. Patients were excluded if they had valvular AF (defined as AF in the presence of mitral stenosis, rheumatic mitral valve disease, prior mitral valve surgery and any metallic prosthetic heart valve), were pregnant during the study period, or had a history of Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE). This AF cohort was then restricted to patients who were prescribed warfarin during the study period and had at least 6 months of recurrent INR tests recorded in the WLGP dataset during the study period (excluding the first 6 weeks after start of treatment; a period when the warfarin dose is typically still being tailored to the patient's needs).

Medical history, demographic information and prescriptions

A census date was assigned to each patient from when they met all of the inclusion criteria. Demographic data, prior diagnoses, and comorbidities (chosen to reflect standard stroke and bleeding risk classification, and comorbidities of major organ systems) prior to the census date for each patient were identified. Individual age was calculated at the census date. The presence of heart failure, hypertension, vascular disease (defined as prior myocardial infarction (MI) or peripheral vascular disease (PVD) including peripheral artery disease and aortic plaque), prior stroke (including TIA), gender and age were used to calculate the individual CHA_2DS_2-VASc score. In addition, the presence of the following were also identified prior to the census date for each patient (see supplementary table 1 for list codes): chronic kidney disease (CKD) stage 4+, chronic liver disease (including cirrhosis, fibrosis, chronic hepatitis and chronic active hepatitis, fatty liver, sclerosis of the liver, unspecified alcoholic liver damage, hepatic failure), dementia, thyroid disease (both hyper and hypothyroidism), epilepsy and respiratory disease, ischaemic heart disease (including stable, unstable and MI), haemorrhagic stroke, major bleeding events (including respiratory bleeds, urinary tract bleeds, intracranial bleeds and gastrointestinal bleeds) and excess alcohol consumption

Calculation of individual Time in Therapeutic Range (TTR) and identification of low and high INRs

NICE recommends using the Rosendaal method for calculating TTR; this method assumes a linear change in INR between consecutive tests (for example, if two consecutive INR tests are 2.5 and 3.5 with 30 days between tests, the method estimates that 15 days were in range, and 15 days were out of range.[29] Thus, the estimated TTR is 50% during that 30 days period).

In this study, a modified Rosendaal method was used to calculate individual TTR. Following the census date for each patient, the first 6 weeks of INR results were excluded, to account for any initiation period. Individual INR results were identified, as well as the time span between them; when the interval between INR results was greater than 84 days, the INR test results were excluded from the overall calculation of individual TTR. The calculation began again when there were two INR results within 84 days carried out because long gaps between INR tests most likely represented periods where treatment was discontinued. An INR value of less than 2.0 was considered subtherapeutic and an INR value greater than 3.0 was considered supertherapeutic.

Patients were categorised as having: (i) "unacceptable" or "acceptable" individual TTR control (< 65% or ≥ 65% respectively); (ii) "low" INRs (two INR results <1.5 in any 6-month period), or (iii) "high" INRs defined by two INR results greater than 5 in any 6 month period or one result greater than 8. In addition, these three markers were combined into an overall "poor" INR control category, which included all patients with at least one of these NICE-defined indicators of poor control. Patients without any NICE criteria of poor INR control were categorised as "adequate" INR control.

STATISTICAL METHODS

Baseline variables and characteristics of patients included in the analysis were presented as percentages or means with standard deviations. Characteristics of patients with each of the three markers of poor control, as well as the overall poor control category, were compared to those with "acceptable" INR control (defined as the absence of any marker of poor control). Differences in these characteristics between groups were summarised using chi-squared tests for categorical variables and independent t-tests for continuous variables. Next, we investigated

two sets of multivariable models for the adverse outcomes. First, a binary logistic regression model was constructed with CHA_2DS_2-VASc score and deprivation index (using WIMD quintiles) as the predictors, and "poor" control vs "adequate" as the primary (binary) dependent outcome. This model was repeated with "unacceptable" TTR, "low" INR, and "high" INR as the dependent outcome (in each case in a binary comparison with "adequate" INR control).

The second set of models attempted to identify all independent risk factors, by testing all available predictors from the baseline co-morbidities and risk factors (including those components within the CHA_2DS_2-VASc score), age, gender and WIMD quintile. Binary dependent variables were the same as above (each of the three individual markers of poor control, as well as the overall poor control category, in comparison with a baseline good control). For this exploratory analysis, a large number of independent variables were considered, and the final set of predictors was chosen based on a search of all models (without interactions) and minimising the Bayesian Information Criterion (BIC).[30] Model selection was also carried out using the lasso regularisation method,[31] to check for consistency in the variables found in the final models. Analysis was carried out using SPSS version 22.0 and the package glmnet in R.[32]

MISSING DATA

Comparisons were made between those included in the final cohort for analysis and (i) those with NVAF prescribed warfarin but with less than 6 months of INR test results for analysis, and (ii) those where there was no INR recorded in the WLGP dataset (see supplementary table 4.2). Finally, within the final cohort for analysis, comparisons were made between those with and without deprivation index data available (see supplementary table 4.3).

RESULTS

Over 4 million patient records were identified in the SAIL Databank during the study period; 110,592 had a diagnosis of AF and were aged over 18 at the time of diagnosis, of whom a total of 32,380 met the final inclusion criteria for this study (figure 4.1). During a mean follow-up time of 4.3 years per patient, the mean TTR was 72.6%; 42.5% of the cohort was female; the mean age was 73.5 years (standard deviation = 9.7 years); and the median CHA_2DS_2-VASc score was 3 (table 4.1).

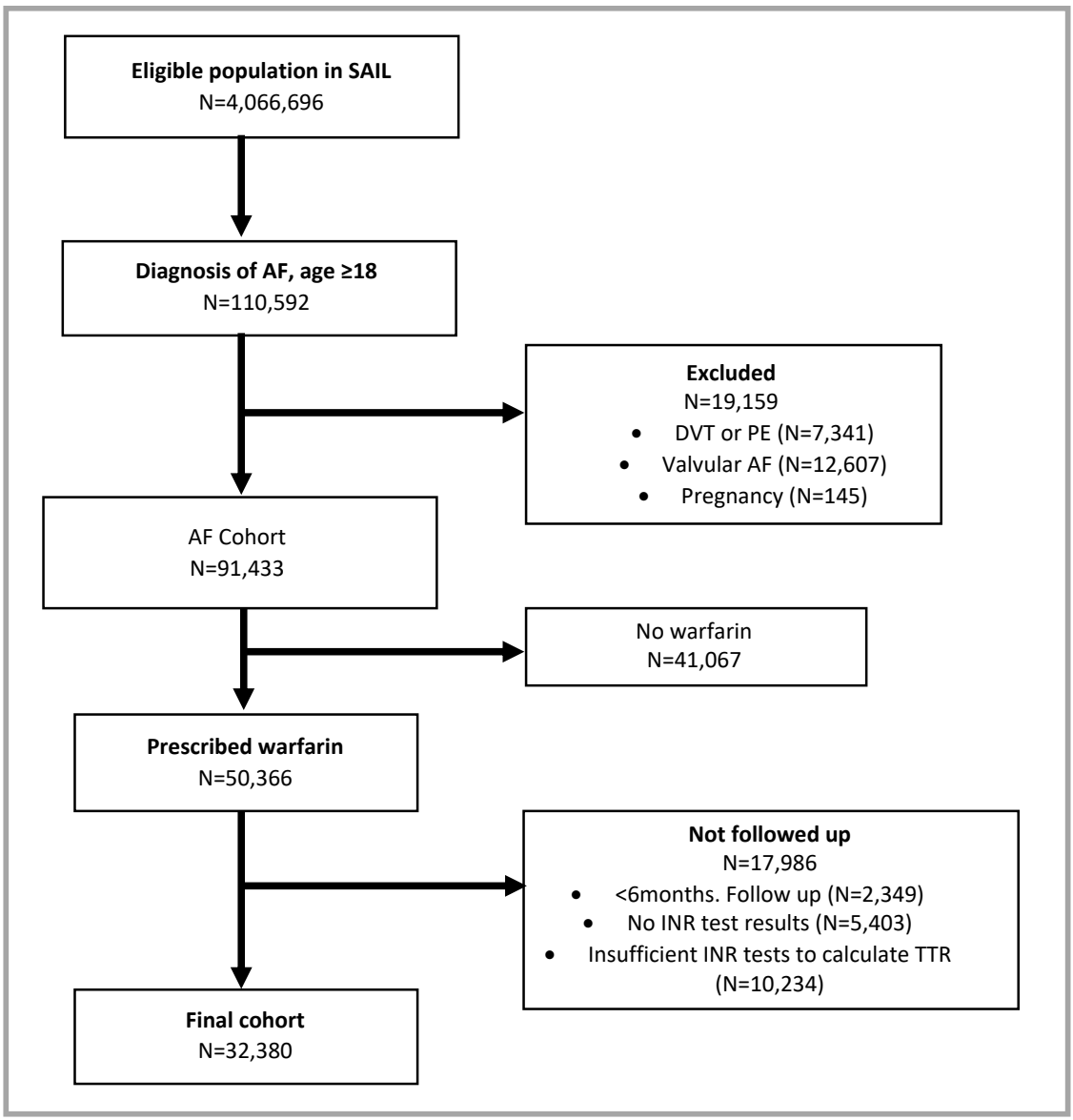


Figure 4.1 Inclusion criteria for study cohort

Table 4.1 Cohort demographics and medical history.

	N = 32,380
	N (%)
Age <65	5,412 (16.7)
65-74	10,875 (33.6)
>=75	16,093 (49.7)
Female	13,751 (42.5)
Deprivation index (quintile)	
1 (most deprived)	5,309 (17.5)
2	5,875 (19.3)
3	6,728 (22.1)
4	5,862 (19.3)
5	6,645 (21.8)
CHA_2DS_2-Vasc score	
0 and 1	4,356 (13.5)
2	5,949 (18.4)
3	7,242 (22.4)
4	6,814 (21.0)
5	4,281 (13.2)
6	2,495 (7.7)
>=7	1,243 (3.8)
Excessive alcohol intake	850 (2.6)
Cancer	6,134 (18.9)
CKD stage 4+	375 (1.2)
Dementia	364 (1.1)
Diabetes	6,876 (21.2)
Epilepsy	206 (0.6)
Haemorrhagic stroke	204 (0.6)
Heart failure	7,264 (22.4)
Hypertension	21,234 (65.6)
Ischaemic heart disease	9,641 (29.8)
Ischaemic stroke	6,661 (20.6)
Liver disease	611 (1.9)
Major bleeding event	4,536 (14.0)
Peripheral vascular disease	1,883 (5.8)
Respiratory disease	6,305 (19.5)
Thromboembolism	426 (1.3)
Thyroid disease	4079 (12.6)

In total, 13,913 (43.0%) patients had at least one of the NICE markers of poor INR control (figure 4.2). Of this group, 8,237 (25.4%) had an unacceptable TTR (<65%) and 9,781 (30.2%) had two low INR readings within a six-month period. Overall, 3,148 (9.7%) had high INRs during the study period, including 2,649 (8.2%) that had two or more INR results greater than 5 in a 6-month period, and 961 (3.0%) had an INR of greater than 8.

In the 24,143 (74.6%) cohort with an acceptable TTR (≥65%), many had other signs of poor INR control: 5,090 (21.1%) had low INRs and 1,217 (5.0%) had high INRs. Overall, of those with acceptable TTR, 5,676 (23.5%) had either low or high INR readings at some point in their history.

When considering European Society of Cardiology guidelines, which recommend a TTR ≥70%; 11, 876 (36.7%) of patients' TTR fell below this threshold.[6] Furthermore, of the 20,504 patients with recommended TTR ≥70%, 3,990 (19.5%) patients met the NICE criteria for low or high INRs (supplementary figure 4.2).

Patient characteristics associated with one or more signs of poor INR control include female sex, increasing social deprivation, increasing CHA_2DS_2-VASc score, heart failure, prior bleeding events, cancer, ischaemic heart disease, PVD, ischaemic stroke, thromboembolism, thyroid disease, respiratory disease, diabetes, epilepsy, dementia, excessive alcohol intake, liver disease, and CKD stage 4+(figure 4.3). Increasing CHA_2DS_2-VASc score from 2 was associated with an increasing likelihood of each marker of poor INR control, including the overall combined marker of poor INR control (figure 4.4).

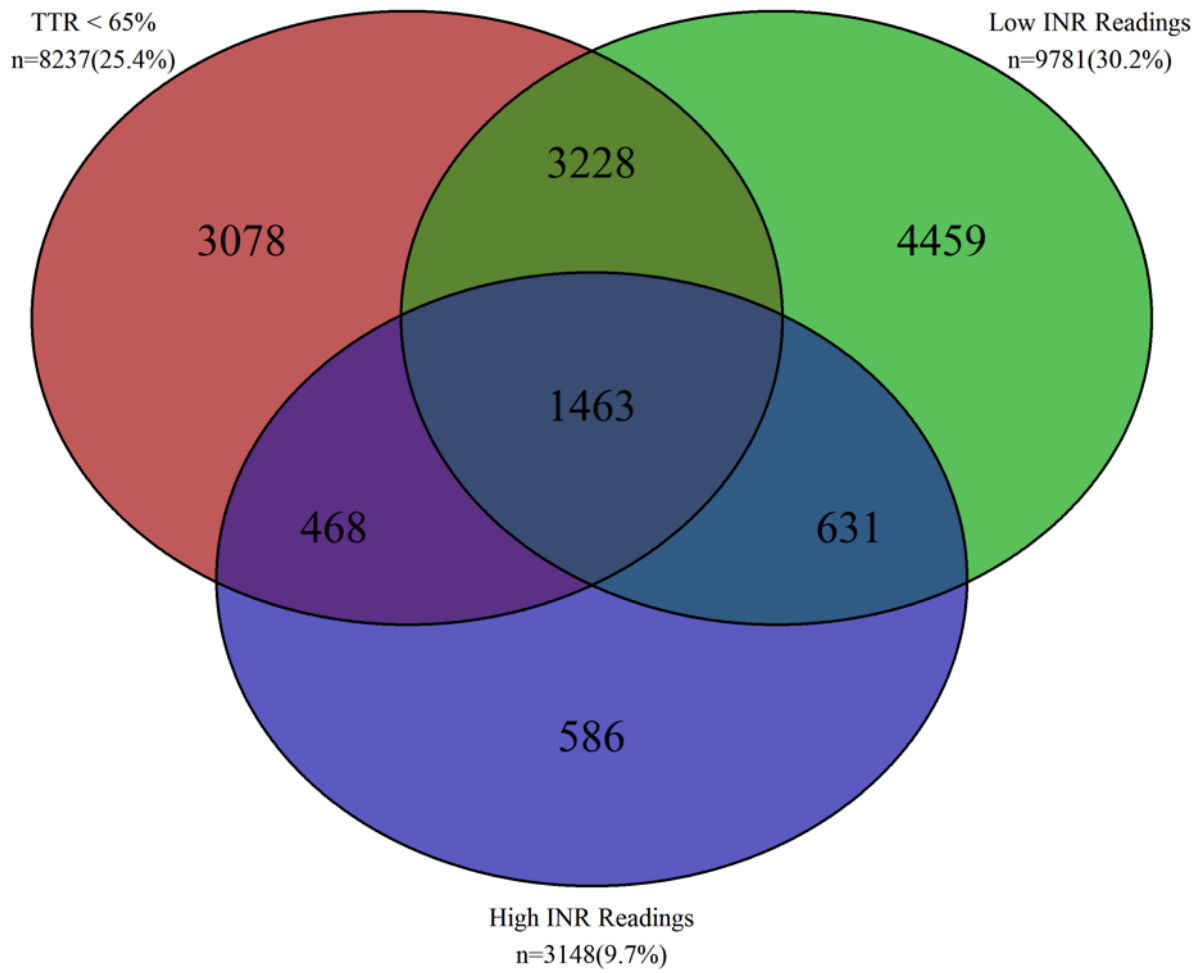


Figure 4.2 Number of patients with poor INR control according to NICE criteria.

MULTIVARIABLE MODELLING

In the first set of models, a CHA_2DS_2-VASc score of 3 or more was significantly associated with all markers of poor INR control (table 4.2). A similar relationship was observed between higher levels of deprivation and the risk of poor INR control.

In the second set of models, exploring all possible independent variables, after BIC model selection, age, female gender, excess alcohol consumption, heart failure, ischaemic heart disease, respiratory disease and diabetes were independently associated with all measures of poor INR control (table 4.3). Peripheral vascular disease was associated with 'poor control', 'high INRs' and 'TTR < 65%' while prior major bleeding and dementia were associated with

'poor control' and 'TTR < 65%'. Ischaemic stroke was only associated with 'high INRs' and deprivation index was only associated with 'TTR < 65%'. Highest adjusted odds ratios, across all markers or poor control, were detected for excess alcohol consumption, which is also predictive of bleeding.

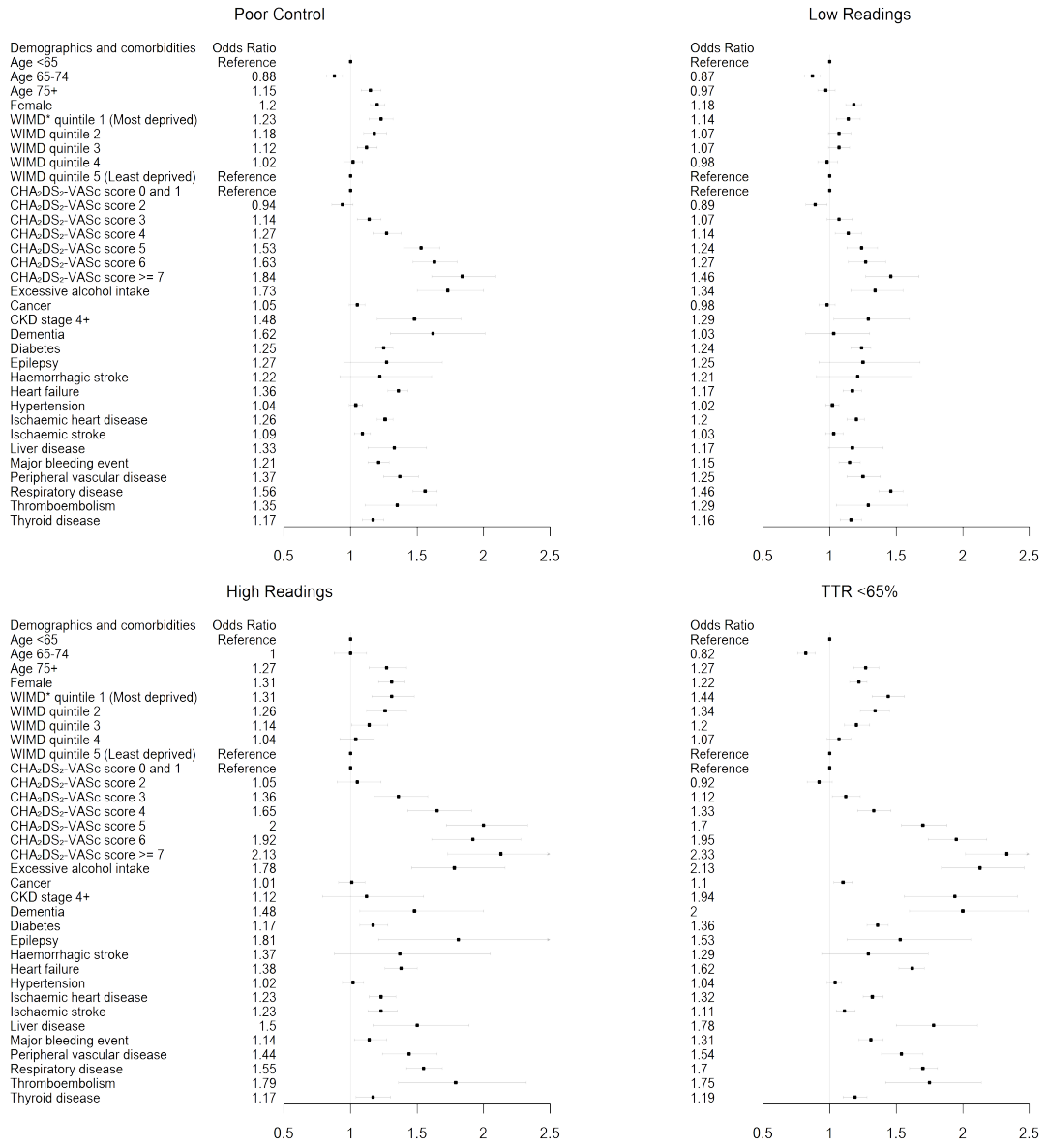


Figure 4.3 Characteristics associated with poor INR control.

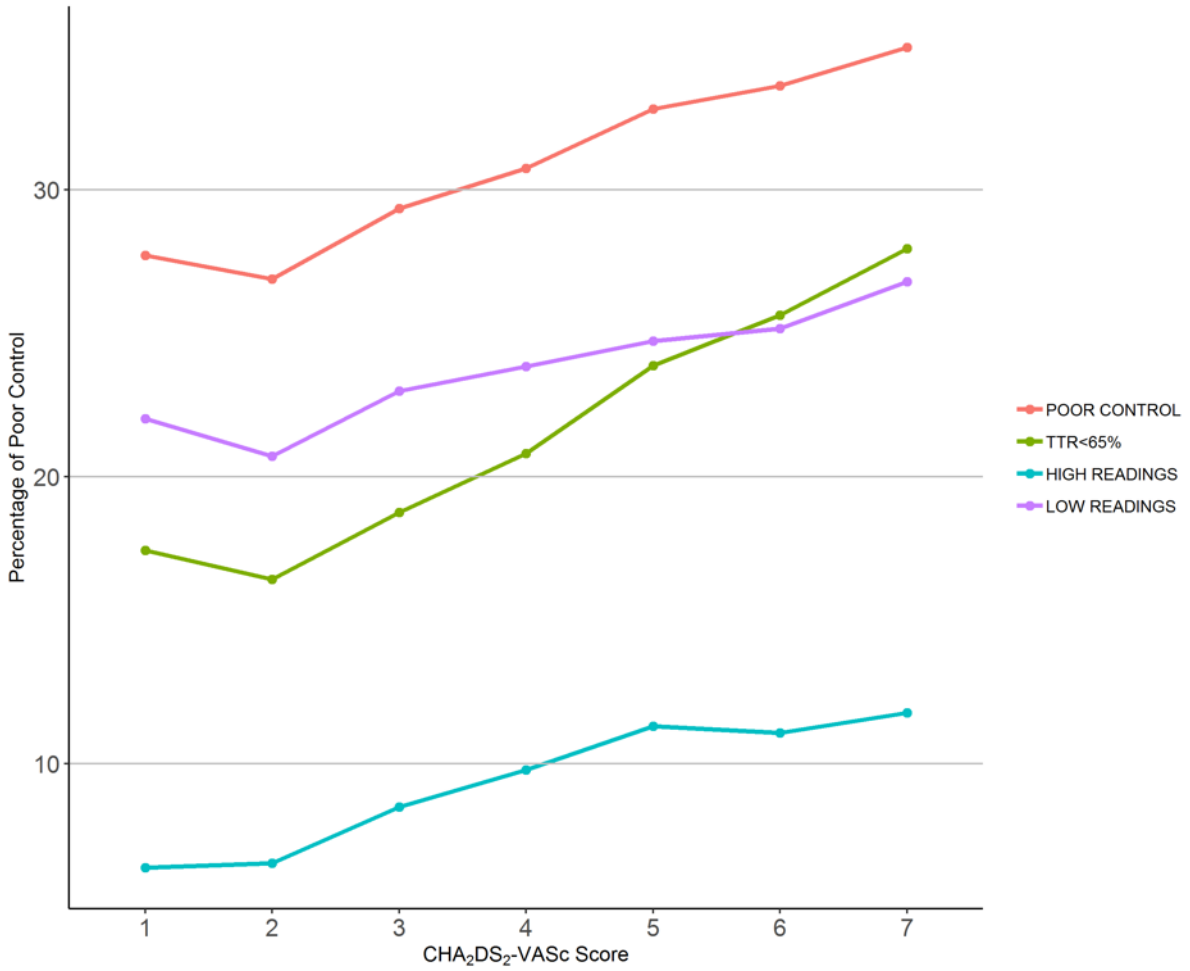


Figure 4.4 INR control verses thromboembolic risk

Table 4.2 Multivariable logistic regression model of INR control verses deprivation index and CHA_2DS_2-VASc score

Predictor	Poor Control	Low INRs	High INRs	TTR <65%
Deprivation index* (quintiles). Adjusted odds ratio (95% CI)				
5 (Least deprived)	Reference, overall p value <0.001	Reference, overall p value <0.001	Reference, overall p value <0.001	Reference, overall p value <0.001
4	1.02 (0.95-1.10)	0.99 (0.92-1.08)	1.05 (0.93-1.20)	1.07 (0.98-1.17)
3	1.12 (1.05-1.21)	1.11 (1.02-1.19)	1.18 (1.05-1.33)	1.21 (1.12-1.32)
2	1.17 (1.09-1.26)	1.12 (1.03-1.21)	1.31 (1.16-1.48)	1.32 (1.22-1.44)
1 (most deprived)	1.21 (1.13-1.31)	1.18 (1.09-1.28)	1.36 (1.20-1.54)	1.41 (1.30-1.54)
CHA_2DS_2-VASc Score. Adjusted odds ratio (95% CI)				
0 or 1	Reference, overall p value <0.001	Reference, overall p value <0.001	Reference, overall p value <0.001	Reference, overall p value <0.001
2	0.94 (0.86-1.02)	0.90 (0.82-0.98)	1.02 (0.87-1.19)	0.91 (0.82-1.01)
3	1.13 (1.05-1.23)	1.11 (1.01-1.21)	1.39 (1.19-1.61)	1.14 (1.04-1.26)
4	1.27 (1.17-1.37)	1.20 (1.10-1.32)	1.72 (1.49-2.01)	1.36 (1.23-1.50)
5	1.53 (1.39-1.67)	1.39 (1.26-1.53)	2.21 (1.85-2.65)	1.76 (1.58-1.95)
6	1.62 (1.46-1.79)	1.46 (1.30-1.63)	2.22 (1.90-2.59)	1.99 (1.77-2.25)
≥7	1.82 (1.60-2.07)	1.69 (1.46-1.96)	2.57 (2.07-3.20)	2.37 (2.04-2.75)

*Deprivation index used is the WIMD quintile.[28]

Table 4.3 Multivariable regression models of patient characteristics verses INR control.

	Poor Control Adjusted odds ratio, (95% CI), p	Low INRs Adjusted odds ratio, (95% CI), p	High INRs Adjusted odds ratio, (95% CI), p	TTR <65% Adjusted odds ratio, (95% CI), p
Age ≤64	Reference, <0.001	Reference, <0.001	Reference, <0.001	Reference, <0.001
65-74	0.84 (0.78-0.90)	0.82 (0.76-0.88)	0.88 (0.78-1.01)	0.76 (0.70-0.84)
≥75	1.07 (1.00-1.15)	0.99 (0.92-1.06)	1.19 (1.06-1.35)	1.19 (1.09-1.28)
Female	1.23 (1.17-1.29), <0.001	1.25 (1.19-1.32), <0.001	1.45 (1.33-1.57), <0.001	1.29 (1.21-1.36), <0.001
Excess alcohol	1.79 (1.55-2.08), <0.001	1.62 (1.38-1.90), <0.001	2.45 (1.97-3.03), <0.001	2.32 (1.97-2.72), 0.001
Major bleeding events	1.15 (1.08-1.23), 0.001			1.23 (1.14-1.32), <0.001
Cancer				
CKD stage 4+				
Dementia	1.51 (1.22-1.89), 0.001			1.83 (1.44-2.33), <0.001
Diabetes	1.20 (1.14-1.28), <0.001	1.24 (1.17-1.32), <0.001	1.21 (1.10-1.33), <0.001	1.29 (1.21-1.38), 0.001
Epilepsy				
Heart failure	1.24 (1.17-1.31), <0.001	1.17 (1.11-1.25), <0.001	1.39 (1.27-1.53), <0.001	1.42 (1.33-1.52), <0.001
Hypertension				
Ischaemic heart disease	1.17 (1.11-1.23), <0.001	1.20 (1.14-1.27), <0.001	1.22 (1.11-1.32), <.001	1.20 (1.13-1.27), <.001
Ischaemic stroke			1.24 (1.13-1.36), 0.001	
Liver disease				
PVD	1.25 (1.13-1.38), <0.001		1.42 (1.22-1.65), <0.001	1.35 (1.20-1.51), <0.001
Respiratory disease	1.51 (1.43-1.60), <0.001	1.54 (1.45-1.64), <0.001	1.75 (1.59-1.92), <0.001	1.69 (1.59-1.82), <0.001
Thromboembolism				
Thyroid disease				
Deprivation index[a] (quintiles)				
5 (Least deprived)				Reference, <0.001
4				1.03 (0.95-1.13)
3				1.15 (1.06-1.26)
2				1.23 (1.13-1.35)
1 (most deprived)				1.28 (1.17-1.40)

All patient characteristics shown in table 4.1 were modelled, only characteristics that were significant in any of models are shown in the table.

[a] Deprivation index used is the WIMD quintile.[28]

We found very good match between the variables selected by the BIC and Lasso model selection procedures (classifying by inclusion/exclusion the match was 78.9% for 'poor control', 89.4% for 'Low', 89.4% for 'High', 89.4% for 'TTR < 65%'; see supplementary table 4.4). All predictors highlighted above were consistently selected by both procedures. BIC selection tended to be more conservative, with slightly fewer variables selected in the final models.

DISCUSSION

This is the first population study examining the effectiveness of warfarin therapy according to the NICE clinical guideline criteria for INR indicators of poor anticoagulation control, across a population with NVAF. In this study, only 57.0% of patients had adequate INR control according to NICE criteria. Increasing stroke risk, as assessed by the CHA_2DS_2-VASc score, was associated with a greater risk of poor INR control, as were many individual clinical characteristics that are also associated with increased risk of stroke or bleeding. Unlike previous studies, not only was TTR evaluated but also the NICE criteria for unacceptably low and high INR levels. Importantly, we found that almost a quarter of those patients with acceptable TTR (>65%) demonstrated evidence of unacceptably low or high INR levels according to NICE criteria during the study period. These findings suggest that the risk of stroke, systemic embolism and/or bleeding, at both an individual patient and a population level, may be under-appreciated if TTR is followed as the sole measure of effectiveness of anticoagulation. Whilst it is important to recognize that the specific relationships between NICE low and high criteria and risks of major bleeding and stroke have not been definitively characterized, these are pragmatic values identifying very low and high INR readings in chronically treated patients, defined by an expert consensus panel that should mandate clinical attention in UK practice.

This study evaluated the impact of multiple clinical and demographic factors in one of the largest real-world studies of INR control in patients with NVAF. Increasing CHA_2DS_2-VASc score (above 3), and hence increasing stroke risk, was strongly associated with poor INR control. As these patients are at the greatest thromboembolic risk and therefore likely to derive the greatest absolute benefits from effective anticoagulation, our data emphasise the particular importance of close monitoring and appropriate treatment selection in these vulnerable individuals. Individual risk factors for stroke including diabetes, heart failure, PVD, ischaemic heart disease and female gender were independently associated with markers of poor INR control. Prior major bleeding events and excess alcohol consumption, both risk factors for bleeding, were also associated with poor INR control. This is likely to reflect that patients with increasing comorbidity have an increasing number of potential influences on warfarin bioavailability and coagulation factor synthesis.

Previous studies have demonstrated that increasing CHA_2DS_2-VASc score, as well as comorbidities including heart failure, diabetes, CKD, chronic obstructive pulmonary disease, female sex, and lower income, are associated with lower TTR. [2, 3, 21]. The models presented in our study confirm this finding, and also show that both CHA_2DS_2-VASc score and multiple individual comorbidities are associated with low and high INRs. It is not known whether it is the direct physiological effect of these comorbidities, or medications prescribed for them, that are responsible for poor INR control; however, the observed association between increasing stroke risk and risk factors for bleeding associated with poor INR control warrants increased vigilance in those patients with increasing risk of stroke or bleeding.

The mean TTR of our cohort was higher than recorded in many previous studies, and the number of patients achieving adequate TTR had improved each year during the study (supplementary figure 4.1). Previous studies have suggested that INR management within anticoagulation clinics is associated with better TTR control.[3, 33] This study does not make

comparisons between individual anticoagulation services or models of service delivery. There are several ways of delivering anticoagulation services in Wales, with many anticoagulation services being provided within primary care GP services. This may have contributed to the high TTR observed in this study, because it is also possible that patients who are difficult to control are managed within specialist anticoagulation services within secondary care, and their data were not included in this study. Furthermore, those with troublesome INR control may have been switched to direct oral anticoagulants (DOACs), a newer class of medications that were introduced in the latter period of this study.

The observation that the number of patients with adequate TTR increased across the study period, yet the number with low or high INRs remained relatively constant, is of interest but unexplained. It may be possible to improve TTR across the population through improved monitoring, interventions or patient selection, but less easy to prevent low or high INRs in response to acute events or changes to medication, especially in patients with multiple comorbidities that impact on INR variability.[34-36]

We excluded AF patients with "valvular AF" (mitral stenosis, rheumatic mitral valve disease, prior mitral valve surgery or any metallic prosthetic heart valve), those with a history of DVT or PE and those pregnant during the study period. These patients may have had "individualised" INR targets, which would not necessarily have been identifiable in the SAIL databank and may potentially have biased the study towards a greater number of patients with 'poor INR control' when applying specific NICE and/or ESC criteria for AF. Thus, we decided to take a conservative approach by excluding them from the analyses. Furthermore, our clinical experience suggests that these more complex patients are more often managed via specialist secondary care haematology led anticoagulation services and their INR results would not have been available for analysis in this study.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This is the first study that has investigated not just TTR, but also low and high INR events, as markers of poor therapeutic control with warfarin therapy, allowing us to highlight that there is a substantial cohort of patients likely to be at risk of poor outcomes who may be missed if TTR is the sole focus.

The use of a large, data-rich, linked population data source is a particular strength of this study. The linked primary and secondary care data held by SAIL enable the investigation of a very large cohort of individuals longitudinally over a period of years and across multiple data sources, giving a much more complete picture of patient treatment, health, and characteristics than previous studies.

In calculating the TTR, NICE guidance recommends excluding the first six weeks of INR results and calculating the TTR over a maintenance period of six months. This recommendation was incorporated into the methodology of this study. During the study period it is possible that there were temporary discontinuations of warfarin therapy due to acute illness, in response to elevated INR results or admissions to hospital. In order to address this, periods where there was a gap of greater than 84 days between INR readings were excluded, but this is an imperfect measure, and it is not possible to definitively identify gaps in treatment.

Although it may be argued that periods of temporary discontinuation should be excluded from assessing INR control according to NICE criteria, unless patients receive alternative treatment to reduce the risk of stroke, they are exposed to an increased risk of thromboembolic events. The destabilisation of INR control during acute illnesses and the prolonged subtherapeutic or supertherapeutic coagulation during gaps in anticoagulation is a recognised limitation in the use of warfarin.

In total there were 17,986 patients identified with NVAF and prescribed warfarin that were excluded from the study, of which 5,403 did not have any INR readings available, and a further 10,234 that had insufficient INR readings (less than 6 months) to analyse. It is not known why 5,403 patients did not have INR readings recorded but it is possible that these patients were managed via coagulation clinics outside of the primary care setting and their results are not incorporated into the WLGP dataset. It is not known what effect the incorporation of their results into this study would have made; however, these patients had a significantly higher rate of nearly all comorbidities and higher prevalence of excess alcohol consumption that were associated with greater likelihood of poor INR control in the models presented in this study.

In the final cohort 1,961 (6.1%) had a missing deprivation index and were therefore excluded from the multivariable analyses. This group had slightly lower prevalence of comorbidities (other than excess alcohol consumption), suggesting an overall lower risk group than those included in the multivariable analyses. Regardless, all major comorbidities were well represented in the multivariable models and the inclusion of this group would not be expected to have a significant impact on the observed associations.

Some patients may have had different, individualized INR targets, which would not be evaluable in this study. By identifying and excluding patients with valvular AF and those with other indications for anticoagulation, both groups with potentially higher INR targets, we have limited overestimates of poor INR control. The linkage of hospital and GP datasets has further improved the identification and exclusion of patients. However, it remains possible that undocumented valvular disease, multiple DVTs or PEs, or individually adjusted INR targets, may have resulted in the inclusion of patients with a targeted INR range outside of 2 to 3, who would then potentially be misclassified as having poor INR control.

Due to the nature of the study, it was not possible to detect whether excess alcohol consumption has an interacting effect on warfarin, directly affected the INR, or was a marker of poor compliance.

CONCLUSION

In this study, forty three percent of Welsh patients had at least one marker of poor INR control. Of those with an acceptable TTR (>65%) one quarter still had unacceptably low or high INR levels according to NICE criteria. Paradoxically, patients at the highest risk of stroke and with risk factors for bleeding were most likely to have poor INR control and may benefit from closer attention to therapeutic effectiveness and alternative anticoagulation strategies where appropriate. If TTR is used as the sole measure of warfarin's therapeutic effectiveness, the risk of stroke, systemic embolism and bleeding may well be under-estimated. Further work is required to define the specific level of risk associated with NICE and other guidelines' criteria for poor INR control and seek to identify novel measures of INR control for optimal risk stratification.

While the results of this study suggest there is considerable opportunity to improve both embolic and bleeding risk, the relationship between poor INR control and these clinical outcomes remains to be determined. Nevertheless, in accordance with NICE guidelines, almost a half of NVAF patients prescribed warfarin for thromboembolic risk reduction warrant review to optimise INR control or consider alternative anticoagulation strategies where appropriate.

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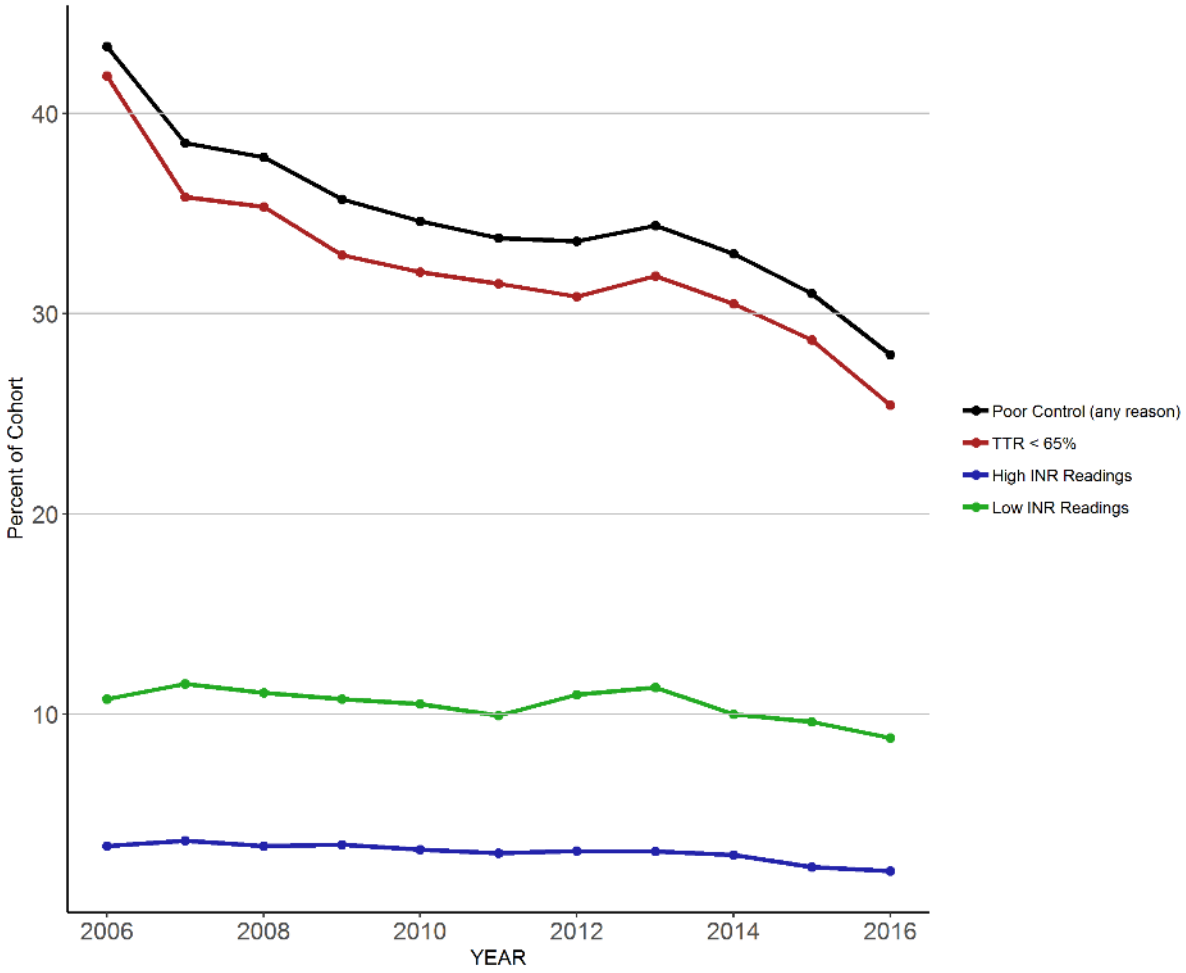
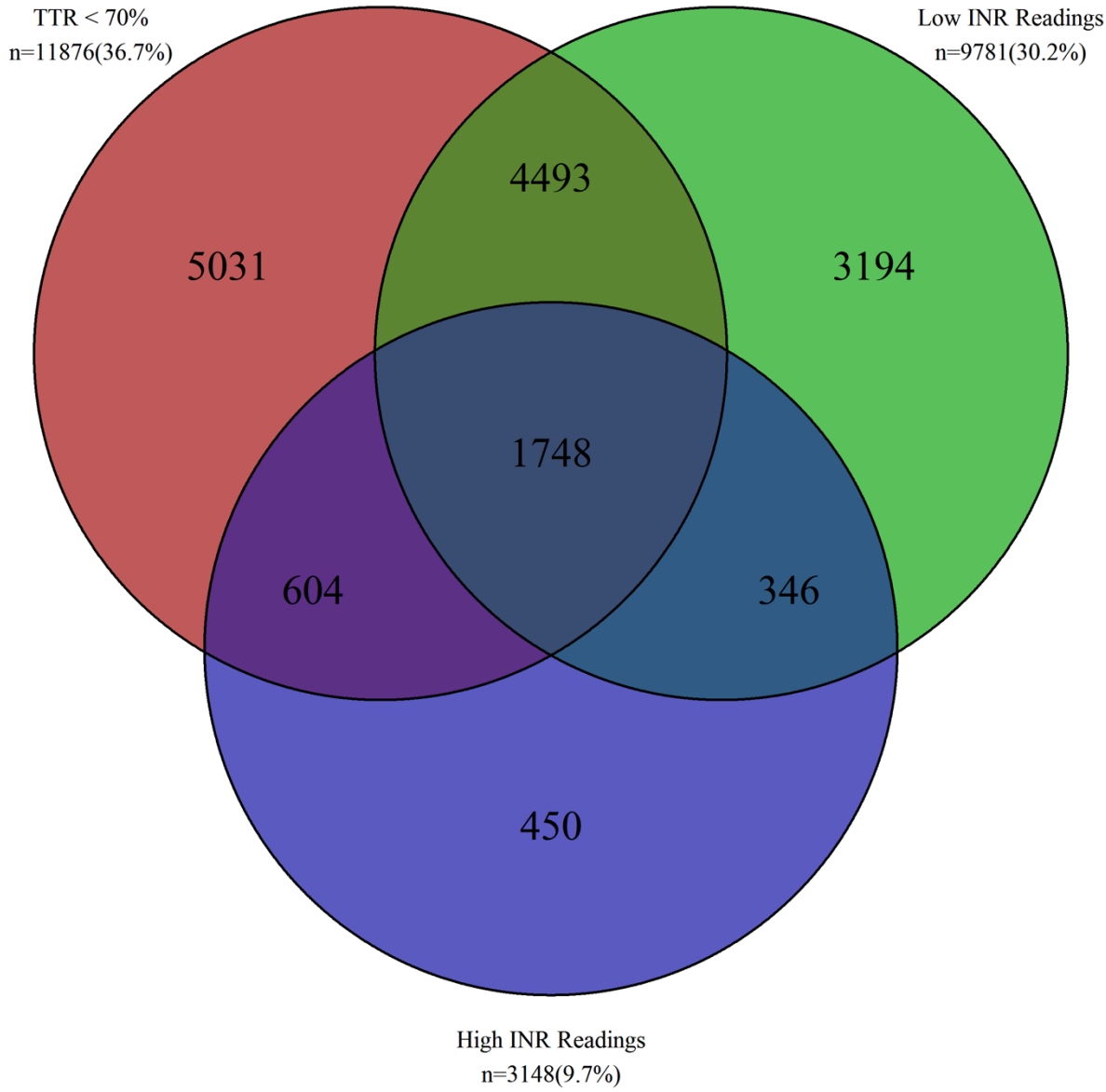


Supplementary Figure 4.1 Change in INR control across the study period



Supplementary Figure 4.2 Number of patients with TTR<70% or have low or high INRs using the NICE low and high criteria.

Supplementary table 4.1 Diagnostic codes

The list of diagnostic codes is extensive and therefore has been provided online:

https://github.com/DHARRISSWAN/diagnostic_codes/blob/master/Suppl_table1_05022019.docx

Supplementary table 4.2 Cohort characteristics and comparisons to patients with INR readings that were not available and those with insufficient INR readings for inclusion

	Cohort analysed N=32380	INR not available N=5403	Insufficient INR readings[a] N=10234
	Mean (SD)	Mean (SD), *P*[b]	Mean (SD), *P*[c]
Age	70.40 (10.61)	70.14 (11.75), 0.098	71.13 (11.89), <0.001
CHA_2DS_2Vasc score	3.38 (1.70)	3.70 (1.93), <0.001	3.58 (1.87), <0.001
	N (%)	N (%), *P*[b]	N (%), *P*[c]
Female	13751 (42.5)	2179 (40.3), 0.003	4302 (42.0), 0.448
Deprivation index (quintile)			
1 (most deprived)	5309 (17.5)	927 (17.9), <0.001	1769 (18.5), 0.118
2	5875 (19.3)	926 (17.9)	1848 (19.3)
3	6728 (22.1)	1056 (20.4)	2142 (22.4)
4	5862 (19.3)	819 (15.9)	1778 (18.6)
5 (least deprived)	6645 (21.8)	1437 (27.8)	2040 (21.3)
Excess alcohol intake	850 (2.6)	194 (3.6), <0.001	346 (3.4), <0.001
Cancer	6134 (18.9)	1677 (31.0), <0.001	2312 (22.6), <0.001
CKD stage 4+	375 (1.2)	195 (3.6), <0.001	263 (2.6), <0.001
Dementia	364 (1.1)	346 (6.4), <0.001	309 (3.0), <0.001
Diabetes	6876 (21.2)	1417 (26.2), <0.001	2476 (24.2), <0.001
Epilepsy	206 (0.6)	53 (1.0), 0.006	88 (0.9), 0.021
Haemorrhagic stroke	204 (0.6)	137 (2.5), <0.001	72 (0.7), 0.461
Heart failure	7264 (22.4)	1991 (36.8), <0.001	2921 (28.5), <0.001
Hypertension	21234 (65.6)	3351 (62.0), <0.001	6471 (63.2), <0.001
Ischaemic heart disease	9641 (29.8)	1892 (35.0), <0.001	3383 (33.1), <0.001
Ischaemic stroke	6661 (20.6)	1298 (24.0), <0.001	2223 (21.7), 0.013
Liver disease	611 (1.9)	263 (4.9), <0.001	299 (2.9), <0.001
Major bleeding event	4536 (14.0)	1533 (28.4), <0.001	1864 (18.2), <0.001
Peripheral vascular disease	1883 (5.8)	481 (8.9), <0.001	778 (7.6), <0.001
Respiratory disease	6305 (19.5)	1238 (22.9), <0.001	2308 (22.6), <0.001
Thromboembolism	426 (1.3)	109 (2.0), <0.001	180 (1.8), 0.001
Thyroid disease	4079 (12.6)	723 (13.4), 0.114	1344 (13.1), 0.162

[a] This group contains patients with a diagnosis of NVAF, prescribed warfarin but with less than 6months of INR available for analysis. [b] P value for comparison between INR not available group and the cohort group analysed. [c] P value for comparison between INR insufficient group.

Supplementary table 4.3 Comparisons between those with deprivation index data present and missing from the final cohort

N=32,380

	Deprivation index present N=30419	Deprivation index missing N=1961
	Mean (SD)	Mean (SD), *P*[a]
Age	70.48 (10.53)	69.05 (11.74), <0.001
CHA_2DS_2Vasc score	3.39 (1.69)	3.24 (1.76), <0.001
	N (%)	N (%), *P*[a]
Female	12987 (42.7)	764 (39.0), 0.001
Excess alcohol intake	784 (2.6)	66 (3.4), 0.041
Cancer	5788 (19.0)	346 (17.6), 0.137
CKD stage 4+	351 (1.2)	24 (1.2), 0.864
Dementia	335 (1.1)	29 (1.5), 0.154
Diabetes	6471 (21.3)	405 (20.7), 0.534
Epilepsy	190 (0.6)	16 (0.8), 0.376
Haemorrhagic stroke	194 (0.6)	10 (0.5), 0.585
Heart failure	6818 (22.4)	446 (22.7), 0.755
Hypertension	20029 (65.8)	1205 (61.4), <0.001
Ischaemic heart disease	9086 (29.9)	555 (28.3), 0.148
Ischaemic stroke	6236 (20.5)	425 (21.7), 0.224
Liver disease	577 (1.9)	34 (1.7), 0.668
Major bleeding event	4343 (14.3)	193 (9.8), <0.001
Peripheral vascular disease	1789 (5.9)	94 (4.8), 0.052
Respiratory disease	5938 (19.5)	367 (18.7), 0.399
Thromboembolism	404 (1.3)	22 (1.1), 0.5
Thyroid disease	3840 (12.6)	239 (12.2), 0.597

[a] *P* value for comparison between those with and without deprivation index.

Supplementary table 4.4 Multivariable regression models of patient characteristics verses INR control using BIC and Lasso models.

	Poor Control		Low INRs		High INRs		TTR <65%	
	BIC	Lasso	BIC	Lasso	BIC	Lasso	BIC	Lasso
Age	√	√	√		√		√	√
Female	√	√	√	√	√	√	√	√
Excess alcohol	√	√	√	√	√	√	√	√
Major bleeding events	√	√	√	√			√	√
Cancer								
CKD stage 4+		√						√
Dementia	√	√					√	√
Diabetes	√	√	√	√	√		√	√
Epilepsy								
Heart Failure	√	√	√	√	√	√	√	√
Hypertension								
Ischaemic heart disease	√	√	√	√	√	√	√	√
Ischaemic Stroke		√			√			
Liver disease								√
PVD	√	√		√	√	√	√	√
Respiratory disease	√	√	√	√	√	√	√	√
Thromboembolism								
Thyroid disease		√						
Deprivation index[b] (quintiles)		√					√	√
Match between BIC and Lasso model selection[c]	78.9%		89.5%		89.5%		89.5%	

[a] All patient characteristics shown in table 1 were modelled, only characteristics that were significant in any of models are shown in the table.
[b] Deprivation index used is the WIMD quintile.[28]
[c] The match between BIC and Lasso model selection was calculated by the sum of variables that were selected by both models and not selected by both variables divided by the total number of variable in the models.

CHAPTER 5

BLEEDING EVENTS ASSOCIATED WITH POOR INR CONTROL IN A NATIONAL COHORT PRESCRIBED WARFARIN FOR NON-VALVULAR ATRIAL FIBRILLATION. THE SAIL AF BLEEDING RISK EVALUATION (SABRE) STUDY

ABSTRACT

AIMS

In patients with non-valvular atrial fibrillation (NVAF) prescribed warfarin, the association between 'poor' International Normalized Ratio (INR) control and bleeding outcomes has not been fully characterised. This study set out to (i) quantify bleeding rates, and (ii) evaluate associations between bleeding, comorbidities, and poor INR control (ESC and NICE criteria).

METHODS AND RESULTS

Linked, anonymised, population-scale, patient-level data for Wales from the SAIL Databank (2006-17) were used to evaluate individual patients' INR control. 35,035 patients were included, mean follow-up 4.3y, mean TTR 71.9%, mean CHA_2DS_2-VASc score 3.5 (SD=1.7). The percentage of time spent in poor INR control using the ESC criteria [TTR<70%] was 40.9% and NICE criteria [TTR<65% or 2 INRs <1.5 within 6 months or 2 INRS >5 within 6-months, or any INR>8] was 34.0%.

Across the study period, 5,766 bleeds occurred in 5,039 patients (during periods of INR calculation). The event rates during periods of adequate and poor INR control were 3.3 and 4.8 per 100 patient years respectively (similar between NICE and ESC criteria). Using a time-varying Cox model, poor INR control according to ESC (HR=1.42 [1.34-1.50], <0.001) and NICE (HR=1.38 [1.31-1.46], <0.001) criteria were independently associated with bleeding risk as were increasing age, prior bleeding events, and chronic kidney disease.

CONCLUSION

Periods of guideline-defined poor INR control are associated with significantly higher bleeding event rates, independently of common comorbidities that are recognised as risk factors for stroke and bleeding.

INTRODUCTION

Successful therapeutic use of warfarin has several important practical limitations, including high intra and inter-patient variability requiring regular monitoring of the International Normalised Ratio (INR).[1, 2] In patients with non-valvular atrial fibrillation (NVAF), and without any other indication for anticoagulation, the target INR is in the range 2-3.[3-7] The net clinical benefit is associated with the proportion of time that INRs are maintained in this range (time in therapeutic range [TTR]).[8 9] Subtherapeutic INRs are associated with an increased risk of stroke and thromboembolism, while supratherapeutic INRs are associated with an increased risk of bleeding.[8, 10, 11]

Guidelines stress the importance of assessing INR control, achieving adequate TTR, and reassessing ongoing anticoagulation with warfarin if high TTR cannot be achieved. European Society of Cardiology (ESC) [4] and Unites States (US) [5] guidelines recommend a TTR of ≥ 70%, while the United Kingdom National Institute of Health and Care Excellence (NICE) defines 'poor' anticoagulation as any of the following: (i) TTR of <65%; (ii)2 INR values less than 1.5 within the past 6 months ('low') or 2 INR values higher than 5 within the past 6 months ('high') or 1 INR value higher than 8.[6]

We have previously demonstrated that a large proportion of patients exhibited suboptimal INR control according to the NICE guideline criteria in a large population based study [12]. However, the likelihood of bleeding associated with suboptimal control, according to guideline criteria has not been fully addressed in a large-scale, real-world population.

The objectives of this study were to (i) quantify bleeding events in patients prescribed warfarin for non-valvular atrial fibrillation (NVAF), and (ii) evaluate the association between bleeding events, patient clinical/demographic characteristics, and poor INR control (defined using NICE and European/American guideline criteria).

METHODS

A retrospective, observational, cohort study was conducted using linked, anonymised, population-scale, electronic health record (EHR) data for 35,035 patients prescribed warfarin for NVAF between January 2006 and December 2017 in Wales, United Kingdom, using the Secure Anonymised Information Linkage (SAIL) Databank.[13-15] SAIL is part of the national e-health records research infrastructure for Wales (holding > 4million linked patient records across primary and secondary care along with other administrative and specialist data). The following data sources held within SAIL were linked at individual patient level: the Patient Episode Database for Wales (PEDW),[16] which records hospital admission and discharge dates, diagnoses and operational procedures, demographic data, and date of death (where applicable) for the population of Wales; the Welsh Longitudinal General Practice (WLGP) dataset[17] containing demographic, clinical, and prescribing data for approximately 80% of primary care practices across Wales; the Welsh Demographic Dataset (WDSD)[18], which contains basic demographic information and history of individuals' residence in Wales, their registration history with General Practices (GP); and Lower layer Super Output Area (LSOA) 2001 which is used to identify the Welsh Index of Multiple Deprivation (WIMD) 2011,[19] an area-based deprivation measure.

COHORT SELECTION

Patients eligible for the study comprised of those who had a diagnosis of AF/atrial flutter recorded in the WLGP data,[12] at any point prior to or during the study period (2006-17) and who were at least 18-years old at time of diagnosis. Patients were excluded if they had valvular AF (defined as AF in the presence of mitral stenosis, rheumatic mitral valve disease, prior mitral valve surgery and any metallic prosthetic heart valve) or had a history of Deep Vein

Thrombosis (DVT) or Pulmonary Embolism (PE) prior to, or within 6-months, of being eligible to enter the study. Those who had a diagnosis of DVT, PE, or valvular AF appearing more than 6-months after baseline were censored at the point of new diagnosis but not excluded from the study. In addition, any patient who was pregnant during the study was excluded.

TEMPORAL CALCULATION OF INR CONTROL

In addition to the exclusion criteria, the cohort was then restricted to patients who had at least 6-months of recurrent INR tests recorded in the WLGP (excluding the first 6-weeks after start of treatment, a period when the warfarin dose is typically still being tailored to the patient's needs), a minimum of 4 INRs in a rolling 6-month period (suppl. material 'temporal INR control, figure 5.1 & 5.2a-5.2d) with no gap greater than 84 days between any two consecutive INR results and a gap of between 90 to 183 days between the first and last reading within a 6-month period. In addition, there needed to be a warfarin prescription in any 84-day window. Individual TTR was calculated at each INR results using the modified Rosendaal method.[20]

Based on these criteria, an algorithm was developed to allow the temporal calculation of INR control, and assign patients to 'adequate' or 'poor' INR control cohorts at each INR reading. Three criteria of poor INR control were assessed: (1) NICE poor INR control, categorised as having one (or more) of the following (i) TTR <65%, (ii) "low" INRs (two INR results <1.5 in any 6-month period) (iii) "high" INRs, defined as two INR results greater than 5 in any 6-month period or one result greater than 8; (2) ESC/US criteria of poor INR control, defined as periods of TTR <70%; and (3) a modified ESC/US criteria for poor INR control, defined as TTR < 70% or any "low" or "high" INRs as per NICE criteria. Periods outside of 'poor' criteria were classed as 'adequate' INR control.

Patients could move between adequate or poor control, leave for any period during which there were insufficient or no INR results or no warfarin prescription available, and re-

enter when there was another 6-month window with sufficient INR results and warfarin prescriptions to evaluate.

An index date was assigned to each patient from when they met all of the inclusion criteria. The number of days a patient was in good and/or poor control was calculated to the end of 2017. Patients were censored at death, when a bleeding event occurred (including bleeds occurring during a period when INR control was not calculated), or when lost to follow-up (end of the primary care record which includes where data is no longer recorded, a patient moves to a practice where data is not supplied to SAIL, a patient moves out of Wales or dies).

Bleeding events

Bleeding events were categorised as gastrointestinal (GI), urinary, respiratory, intracranial, gynaecological, ocular, or miscellaneous bleeds in other organ systems recorded in either the PEDW or WLGP data (see supplementary tables 5.1a & 5.1b for diagnostic codes to define bleeding events). Bleeding events that occurred during periods of INR calculation and within 84 days of the last warfarin prescription were included, and patients were classified as having poor or adequate INR control based on the preceding 6-months of INR data.

Medical history, demographic information, and prescriptions

Demographic and clinical data (chosen to reflect standard stroke and bleeding risk classification,[21, 22] and comorbidities of major organ systems) prior to the index date for each patient were identified. Individual age and deprivation quintile were assigned at the index date. The presence of heart failure, hypertension, vascular disease (defined as prior myocardial infarction (MI) or peripheral vascular disease (PVD) including peripheral artery disease and aortic plaque), prior stroke (including transient ischaemic attack [TIA]), gender, and age were used to calculate the individual CHA_2DS_2-VASc score at index date.[21]

STATISTICAL METHODS

Baseline variables and characteristics of patients included in the analysis were presented as percentages. Characteristics of patients who bled during periods of INR calculation were compared to those without bleeding events using chi-squared tests.

We investigated the association between bleeding event outcome and INR control, using the NICE, ESC/US and the modified ESC/US definition of adequate or poor INR control. Since our data allow us to estimate periods of time for which a patient moves between periods of poor and adequate control, it was necessary to treat INR control as a time-dependent variable and estimate hazard ratios representing the risk for an individual at any specific time point. In the first multivariable-model, we used a Cox regression to estimate the risk of bleed according to INR control status, adjusting for the baseline individual CHA_2DS_2-VASc score and deprivation quintile. A second Cox regression model was used to investigate the effect of INR control (time-dependent), adjusting for all potential risk factors known to be associated with stroke and bleeding, including the individual components of CHA_2DS_2-VASc score. Analyses were performed using IBM SPSS v26 and R version 3.5.3 survival package.

We calculated the bleeding event rate during the periods of adequate or poor INR control using each of the guideline thresholds for INR control. The analyses were repeated using secondary outcomes: the most common bleeding events by organ system.

MISSING DATA

Comparisons were made between those included in the final cohort for analysis and (i) those with NVAF prescribed warfarin but with inadequate or no INR test results for analysis, and (ii) those with insufficient INR tests recorded in the WLGP to classify INR control prior to a bleed (supplementary table 5.2). Finally, within the final cohort for analysis, comparisons were made

between those with and without deprivation quintile data available (supplementary table 5.3). Differences in these characteristics between groups were again summarised using chi-squared tests for categorical variables and independent t-tests for continuous variables.

RESULTS

Over 4 million patient records were identified in the SAIL Databank during the study period; 124,324 had a diagnosis of AF and were aged over 18 at the time of diagnosis, of whom a total of 35,035 met the final inclusion criteria (figure 5.1). During a mean follow-up time of 4.3 years per patient, the mean TTR was 71.9; 42.9% of the cohort was female; the mean age was 73.7 years (standard deviation [SD] = 9.7 years); and the mean CHA_2DS_2-VASc score was 3.5 (SD=1.7) (table 5.1). The percentage of time spent in poor INR control using the NICE criteria was 34.0%, 40.9% using ESC criteria, and 41.4% using modified ESC criteria.

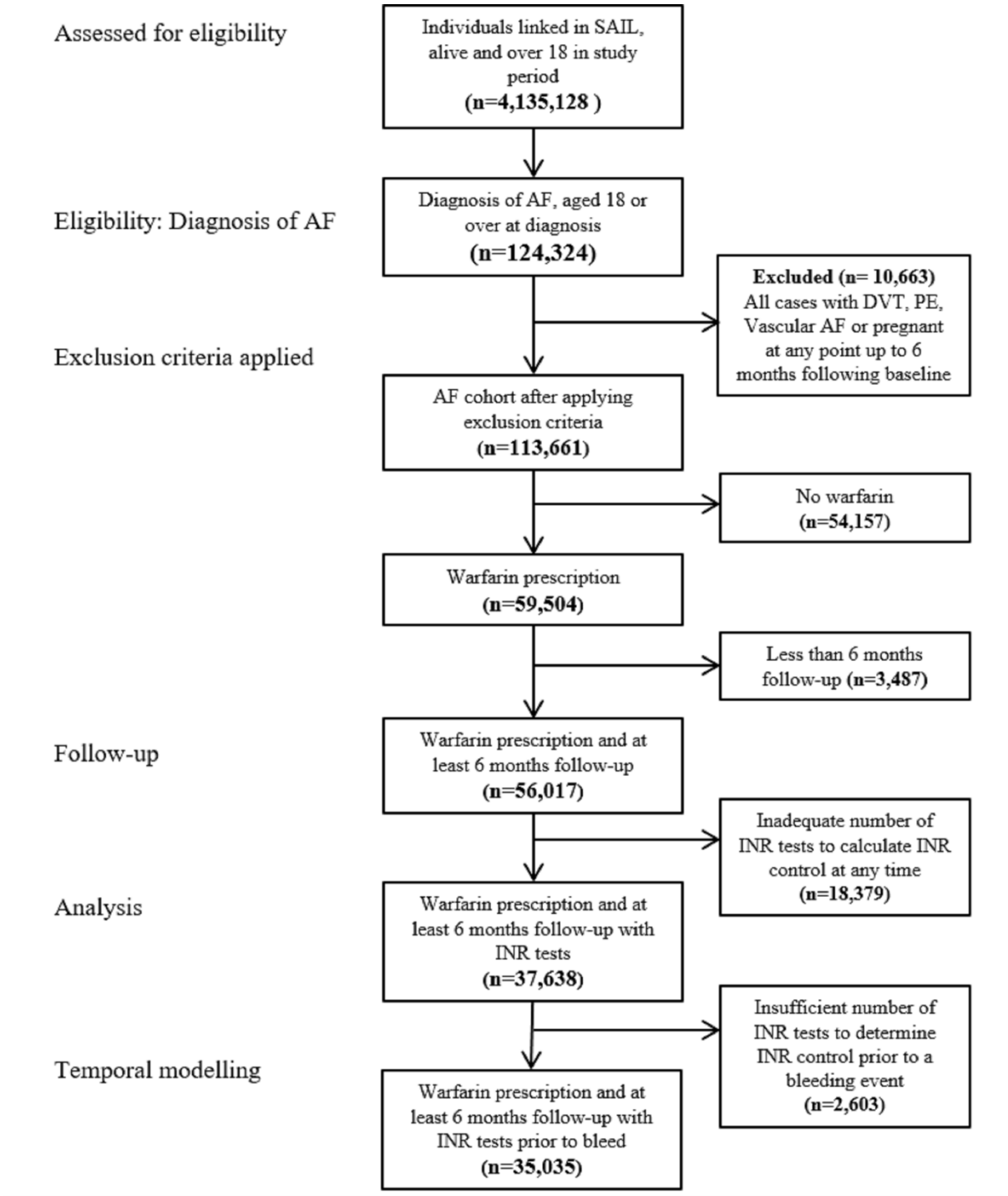


Figure 5.1 Inclusion criteria for study cohort

Table 5.1 Cohort baseline characteristics; including pair-wise comparisons of baseline characteristics of subgroups with and without bleeding events during follow up.

	Final Cohort N (%)	Patients with bleeding events N (%)	Patients without bleeding events N (%)	*P* value
	N= 35,035	N= 5,039	N=29,996	
Age				0.001
18-64	5,679 (16.2)	725 (14.4)	4,954 (16.5)	
65-74	11,610 (33.1)	1,703 (33.8)	9,907 (33.0)	
75+	17,746 (50.7)	2,611 (51.8)	15,135 (50.5)	
Female	15,041 (42.9)	2,011 (39.9)	13,030 (43.5)	<0.001
Deprivation index (quintile)				0.009
1 (most deprived)	5,732 (17.0)	832 (17.1)	4,900 (17.0)	
2	6,573 (19.5)	945 (19.4)	5,628 (19.5)	
3	7,450 (22.1)	1,027 (21.1)	6,423 (22.3)	
4	6,611 (19.6)	915 (18.8)	5,696 (19.8)	
5 (least deprived)	7,296 (21.7)	1,143 (23.5)	6,153 (21.4)	
CHA_2DS_2-VASc score				0.001
0 and 1	3,971 (11.3)	485 (9.6)	3,486 (11.6)	
2	6,018 (17.2)	815 (16.2)	5,203 (17.3)	
3	7,859 (22.4)	1,170 (23.2)	6,689 (22.3)	
4	7,692 (22.0)	1,128 (22.4)	6,564 (21.9)	
5	4,999 (14.3)	764 (15.2)	4,235 (14.1)	
6	2,962 (8.5)	470 (8.9)	2,492 (8.4)	
≥7	1,534 (4.4)	240 (4.5)	1,294 (4.4)	
Heart failure	8,283 (23.6)	1,223 (24.3)	7,060 (23.5)	0.256
Hypertension	23,049 (65.8)	3,558 (67.1)	19,492 (65.6)	0.025
Diabetes	7,476 (21.3)	1,182 (22.3)	6,294 (21.2)	0.07
Ischemic stroke	7,291 (20.8)	1,163 (23.1)	6,128 (20.4)	<0.001
Thromboembolism	486 (1.4)	67 (1.3)	419 (1.4)	0.44
Ischemic heart disease	10,608 (30.3)	1,721 (34.2)	8,887 (29.6)	<0.001
Peripheral Vascular Disease	2139 (6.1)	326 (6.5)	1,813 (6.0)	0.24
Liver disease	670 (1.9)	97 (1.9)	573 (1.9)	0.944
Chronic Kidney disease (stage 4+)	417 (1.2)	65 (1.3)	352 (1.2)	0.48
Excessive alcohol intake	935 (2.7)	117 (2.3)	818 (2.7)	0.099
Any prior bleeding	4657 (13.3)	870 (17.3)	3787 (12.6)	<0.001

*Deprivation index was calculated using the Welsh Index of Multiple Deprivation 2011 quintiles.

Table 5.2 Multivariable Cox-regression model for hazard of major bleeding events determined by poor INR control (according to NICE, ESC/US and a modified-ESC/US criteria).

Results are adjusted for CHA_2DS_2-VASc score and deprivation quintiles. Any changes in INR control status for individuals over time were included in the model as a time dependent variable.

	NICE	ESC/US	Modified ESC/US
	HR (95%CI), *P* value	HR (95%CI), *P* value	HR (95%CI), *P* value
Poor INR control	1.40 (1.33-1.48), <0.001	1.43 (1.35-1.51), <0.001	1.44 (1.36-1.52), <0.001
CHA_2DS_2-VASc score			
0 &1	Reference	Reference	Reference
2	1.22 (1.09-1.37), <0.001	1.22 (1.09-1.37), <0.001	1.22 (1.09-1.37), <0.001
3	1.45 (1.30-1.61), <0.001	1.45 (1.29-1.61), <0.001	1.45 (1.30-1.61), <0.001
4	1.54 (1.38-1.72), <0.001	1.54 (1.38-1.72), <0.001	1.54 (1.38-1.72), <0.001
5	1.67 (1.48-1.87), <0.001	1.66 (1.48-1.87), <0.001	1.66 (1.48-1.87), <0.001
6	1.68 (1.47-1.92), <0.001	1.68 (1.47-1.92), <0.001	1.68 (1.47-1.92), <0.001
7	1.99 (1.70-2.34), <0.001	1.98 (1.69-2.33), <0.001	1.98 (1.69-2.33), <0.001
Deprivation index (quintiles)*			
1 (most deprived)	Reference	Reference	Reference
2	0.99 (0.91-1.10), 0.99	0.99 (0.91-1.10), 0.99	1.01 (0.91-1.10), 0.99
3	0.96 (0.87-1.05), 0.36	0.96 (0.87-1.05), 0.36	0.96 (0.87-1.05), 0.36
4	0.96 (0.88-1.06), 0.45	0.96 (0.88-1.06), 0.45	0.96 (0.88-1.06), 0.45
5 (least deprived)	1.00 (0.92-1.10), 0.97	1.00 (0.92-1.09), 0.97	1.00 (0.92-1.10), 0.97

*Deprivation index was calculated using the Welsh Index of Multiple Deprivation 2011 quintiles.

Across the entire study period, including periods where there were insufficient INR data to calculate INR control, a total of 7,220 bleeds occurred in 6,304 patients (supplementary figure 5.3). During periods of INR calculation, 5,766 bleeds occurred in 5,039 patients (figure 5.2). Patients who bled tended to be older, male, have higher CHA_2DS_2-VASc score, had a higher prevalence of hypertension, prior ischemic stroke, ischemic heart disease, and prior bleeding events compared to those without a recorded bleeding event (table 5.1). Censoring at the first bleed, gastrointestinal bleeding events were the most common, N=2,042 (39.3%), followed by

urinary, N=1,344 (25.8%); intracranial, N=527 (10.2%); respiratory, N=488 (9.4%); miscellaneous, N=371 (7.2%), gynaecological, N=301 (5.8%), and ocular 119 (2.3%) bleeding events. A total of 153 patients had a bleed within multiple organ systems on the same day as the first bleed.

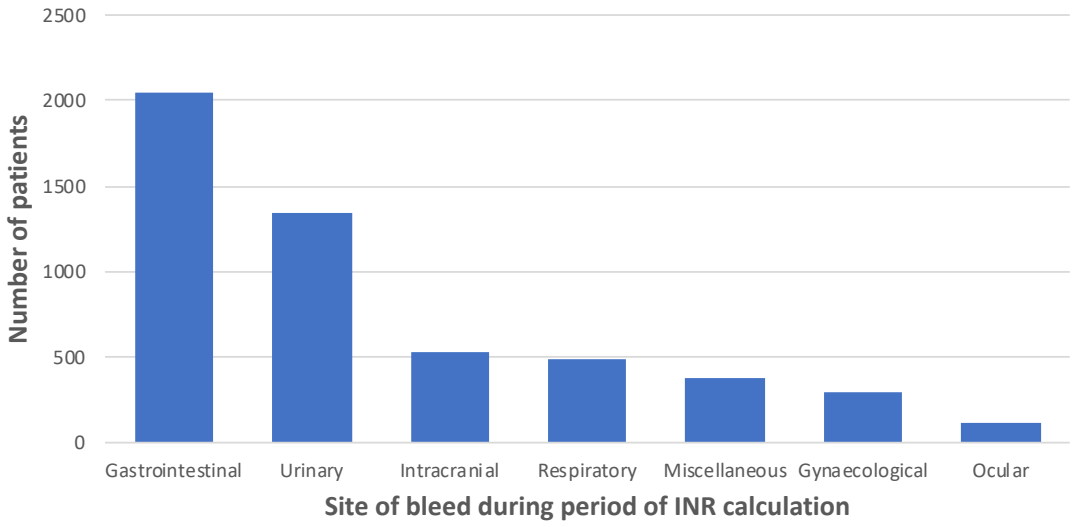


Figure 5.2 Number of bleeds by organ system during periods of INR calculation.

Numbers represent the first documented bleed in patients who had >1 bleed. 153 patients had bleeds in multiple organ systems on the day of the first identified bleeding event.

Table 5.3 Multivariable Cox-regression model for hazard of major bleeding events determined by poor INR control (according to NICE, ESC/US and a modified-ESC/US criteria).

Results are adjusted for individual components of CHA_2DS_2-VASc score, plus baseline characteristics. Any changes in INR control status for individuals over time were included in the model as a time dependent variable.

	NICE	ESC/US	Modified ESC/US
	HR (95%CI), *P* value	HR (95%CI), *P* value	HR (95%CI), *P* value
Poor INR control	1.38 (1.31-1.46), <0.001	1.42 (1.34-1.50), <0.001	1.43 (1.35-1.51), <0.001
Female	0.85 (0.80-0.90), <0.001	0.85 (0.80-0.90), <0.001	0.85 (0.80-0.90), <0.001
Age			
<65	Reference	Reference	Reference
65-74	1.26 (1.16-1.38), <0.001	1.27 (1.16-1.38), <0.001	1.27 (1.16-1.38), <0.001
≥75	1.62 (1.48-1.77), <0.001	1.62 (1.49-1.77), <0.001	1.62 (1.49-1.77), <0.001
Excessive alcohol consumption	0.96 (0.79-1.17), 0.71	0.96 (0.80-1.16), 0.69	0.96 (0.80 -1.16), 0.69
Prior bleeding events	1.55 (1.44-1.67), <0.001	1.55 (1.44-1.67), <0.001	1.55 (1.44-1.67), <0.001
Hypertension	1.05 (0.99-1.12), 0.07	1.05 (0.99-1.12), 0.07	1.05 (0.99-1.12), 0.07
Liver disease	1.15 (0.94-1.41), 0.19	1.15 (0.93-1.41), 0.19	1.15 (0.93-1.41), 0.19
Diabetes	1.12 (1.05-1.20), <0.001	1.12 (1.05-1.20), <0.001	1.12 (1.05-1.20), <0.001
Heart failure	1.08 (1.01-1.15), 0.03	1.08 (1.01-1.15), 0.03	1.08 (1.01-1.15), 0.03
Ischemic heart disease	1.16 (1.10-1.24), <0.001	1.16 (1.10-1.23), <0.001	1.16 (1.09-1.23), <0.001
Ischemic stroke	1.10 (1.03-1.17), 0.005	1.10 (1.03-1.17), 0.006	1.10 (1.03-1.17), 0.006
PVD*	1.11 (0.98-1.24), 0.09	1.11 (0.98-1.24), 0.09	1.11 (0.98-1.24), 0.09
Thromboembolism	0.93 (0.73-1.20), 0.59	0.93 (0.73-1.20), 0.59	0.93 (0.73-1.20), 0.58
CKD (stage 4+)	1.45 (1.13-1.85), 0.003	1.44 (1.13-1.85), 0.003	1.44 (1.13-1.85), 0.003

*PVD indicates Peripheral vascular Disease; CKD indicates Chronic Kidney disease.

ESTIMATES OF THE EFFECT OF INR CONTROL ON RISK OF BLEED

Considering poor INR control as a univariable the hazard ratio (HR) for bleeding using the NICE criteria was 1.43 [(95% CI 1.35-1.51), $p<0.001$], using the ESC/US criteria [HR=1.45 (95%CI 1.38-1.54), $p< 0.001$] and the modified ESC/US criteria [HR=1.47 (95%CI 1.39-1.55), $p<0.001$].

In the first set of multivariable models, poor INR (defined using either NICE, ESC/US, and modified ESC/US criteria for poor INR control) was associated with an increased risk of bleeding (table 5.2) after adjustment for CHA_2DS_2-VASc score and deprivation quintile. CHA_2DS_2-VASc score was also independently associated with bleeding events, after mutual adjustment, within each of the three measures of INR control, while there was no significant association with deprivation level.

In the second set of multivariable models, adjustment was made for the full range of baseline characteristics. Poor INR control according to NICE, ESC/US and modified ESC/US criteria was again associated with bleeding events (table 5.3), independent of other risk factors. After mutual adjustment, increasing age was also associated with bleeding events, as was liver disease, CKD (stage 4+), heart failure, ischemic heart disease, ischemic stroke, PVD, and diabetes. Prior bleeding events were most strongly associated with subsequent bleeding during follow-up. Female sex was associated with fewer bleeds.

Notably, the HR for poor INR control was very stable across all models, for all guideline criteria and was very similar in the models containing all available covariates. Indeed, the adjusted hazard ratios all remained close to the estimate from the univariable model with only poor INR control.

BLEEDING EVENT RATE

The event rate (per 100 patient-years) during periods of INR calculation was 3.9 (95%CI 3.8-4.0) in the overall population; 3.4 (95% CI, 3.3-3.5) in patients with adequate INR control compared to 4.8 (95% CI 4.6-5.0) in those with poor INR control according to NICE criteria (supplementary table 5.4). Considering the ESC/US criteria, the event rate was 3.3 (95% CI, 3.2-3.4) in those with adequate control and 4.7 (95% CI, 4.5-4.9) in those with poor control. Finally, the event rate for the modified ESC/US criteria was 3.3 (95% CI, 3.2-3.4) in those with adequate control and 4.7 (95% CI, 4.5-4.9) in those with poor control.

BLEEDING RELATED TO INDIVIDUAL ORGAN SYSTEMS

According to the NICE criteria (table 5.4), poor INR control was associated with gastrointestinal, urinary, respiratory, and intracranial bleeds (supplementary tables 5.5-5.6 for ESC/US and modified criteria). The strength of association between baseline clinical characteristics and bleeding events within these organ systems were similar to those in the primary analyses of bleeding at any site. (See supplementary tables 5.7-5.9) for bleeding event rate at the individual organ sites).

Table 5.4. Multivariable Cox-regression model for hazard of major bleeding events determined by poor INR control (according to NICE definition).

Results are adjusted for individual components of CHA_2DS_2-VASc score, plus baseline characteristics. Any changes in INR control status for individuals over time were included in the model as a time dependent variable.

	GI	Urinary	Respiratory	Intracranial
Poor control	1.37 (1.26-1.49), <0.001	1.30 (1.18-1.45), <.001	2.06 (1.75-2.43), <0.001	1.49 (1.26-1.76), <0.001
Female	0.91 (0.83-0.99), 0.05	0.42 (0.37-0.47), <0.001	0.71 (0.60-0.85), <0.001	0.93 (0.78-1.10), 0.38
Age				
<65	Reference	Reference	Reference	Reference
65-74	1.17 (1.02-1.32), 0.05	1.36 (1.16-1.59), <0.001	1.26 (0.96-1.64), 0.09	2.27 (1.62-3.17), <0.001
≥75	1.58 (1.39-1.80), <0.001	1.73 (1.48-2.03), <0.001	2.00 (1.54-1.64), <0.001	4.25 (3.06-5.91), <0.001
Excessive alcohol consumption	1.01 (0.76-1.34), 0.93	0.77 (0.54-1.09), 0.14	1.67 (1.09-2.54), <0.001	1.11 (0.62-2.00), 0.72
Prior bleeding events	1.35 (1.21-1.52), <0.001	2.09 (1.85-2.37), <0.001	1.71 (1.39-2.11), <0.001	1.06 (0.84-1.35), 0.62
Hypertension	1.06 (0.97-1.16), 0.20	1.05 (0.94-1.17), 0.42	0.98 (0.82-1.17), 0.84	1.18 (0.99-1.42), 0.06
Liver disease	1.03 (0.75-1.44), 0.84	1.14 (0.78-1.66), 0.49	1.74 (1.09-2.78), 0.02	1.00 (0.51-1.96), 0.99
Diabetes	1.10 (0.99-1.22), 0.08	1.05 (0.93-1.19), 0.43	1.09 (0.89-1.34), 0.37	1.19 (0.97-1.45), 0.09
Heart failure	1.11 (1.00-1.22), 0.04	1.01 (0.89-1.14), 0.88	1.26 (1.04-1.51), 0.23	1.04 (0.86-1.27), 0.66
Ischemic heart disease	1.22 (1.12-1.34), <0.001	1.14 (1.02-1.28), 0.02	1.17 (0.98-1.39), 0.08	1.02 (0.86-1.22), 0.80
Ischemic stroke	1.12 (1.01-1.24), 0.03	1.04 (0.92-1.17), 0.54	1.16 (0.96-1.40), 0.13	1.37 (1.14-1.64), <0.001
PVD*	1.17 (0.99-1.39), 0.07	0.88 (0.70-1.11), 0.30	1.16 (0.84-1.60), 0.36	0.95 (.067-1.36), 0.80
Thromboembolism	0.97 (0.67-1.41), 0.88	1.14 (0.72-1.80), 0.56	1.47 (0.81-2.65), 0.20	1.06 (0.52-2.16), 0.87
CKD (stage 4+)	1.23 (0.82-1.84), 0.32	1.34 (0.83-2.17), 0.23	2.60 (1.52-4.46), <0.001	1.14 (0.51-2.55), 0.76

DISCUSSION

This is the first population-level, real-world study that has assessed the association between bleeding events and temporal poor INR control in patients prescribed warfarin for NVAF, according to clinical guideline criteria produced by NICE and ESC. Evidence of poor INR control was present in more than a third of patients when applying these criteria. Bleeding events were also common in this cohort, and, although the risk of bleeding was greater during periods of poor INR control, most bleeds occurred during periods of therapeutic INR control. Importantly, poor INR control by any of the criteria was strongly associated with bleeding risk.

Increasing stroke risk, assessed by the CHA_2DS_2-VASc score, was also associated with an increased risk of bleeding, as were many individual characteristics commonly associated with stroke or bleeding. Increasing age (> 75 years) and prior bleeding events were associated with the highest risk of bleeding; both of which have been previously demonstrated to be associated with bleeding whilst prescribed warfarin in previous studies.[23, 24]

We found that females had a lower likelihood of bleeds, in keeping with previous studies.[25, 26] Paradoxically, females have a higher risk of poor INR control, as we found in an earlier study of this cohort.[12] The potential differential in bleeding events by sex could be even greater if INR control could be improved in women.

The overall bleeding event rate in this study was 3.9 bleeds per 100 patient-years. This was similar to that recently reported in another real-world study of INR control[10], but higher than reported in other real-world studies (range 2.5-3.5 bleeds per 100-patients years)[27] and randomized controlled studies where warfarin was included as a comparator against the DOACs (range 3.1-3.4%).[28-30]

While the mean TTR in this study was 72% compared to 55-64% in RCTs, the lower bleeding event rate observed in the RCTs may be explained by selective patient enrolment and enhanced observation of patients compared to real-world studies. Differences in methods of

calculating TTR, and the absence of reporting INR control assessed by very low or very high individual INRs, limits the comparisons that can be made between studies, and health care systems. Lastly, the comparison in bleeding event rate between studies is further limited by the lack of consistent reporting of bleeding events and severity.

Despite a greater proportion of time spent in 'poor' INR control with the ESC and modified ESC criteria (40.9 and 41.4% respectively) compared to the NICE criteria (34.0%), the bleeding event rate and associations between poor INR control and bleeding events were very similar between these measures of poor INR control.

In total there were 20,982 patients prescribed warfarin with NVAF and at least six month's follow-up excluded from the final analyses, of which 18,379 had inadequate numbers of INR results to calculate INR control, and a further 2,603 patients that bled during the study period but had inadequate number of INR results to assign to either adequate or poor INR control (supplementary table 5.2). It cannot be determined why these patients had insufficient INR readings recorded. It is likely that these patients were managed in secondary care. Notably, these patients had a significantly higher rate of most comorbidities associated with greater risk of bleeding.

In the final cohort, 1,373 patients had a missing deprivation quintile and were therefore excluded from the first multivariable analyses (supplementary table 5.3). This group had slightly lower prevalence of hypertension and a slightly higher prevalence of heart failure, otherwise they had very similar characteristics to the overall cohort. Regardless, all major comorbidities were well represented in the multivariable models and the inclusion of this group would not be expected to have a significant impact on the observed associations. Surprisingly we observed no association between deprivation quintile and INR control (observed in a previous study[12]) or with bleeding in this study. The data for both these studies was obtained from patients within the Welsh NHS, where prescriptions and INR monitoring are free to

patients at the point of delivery. This potentially mitigates important barriers to healthcare, especially in more economically-disadvantaged individuals or populations. This should be an important consideration when comparing the findings of our study to other healthcare systems.

We excluded patients with valvular AF and those with a history of DVT or PE. These patients may have had "individualised" INR targets, which would not necessarily have been identifiable in the SAIL Databank and may potentially have biased the study towards a greater number of patients with 'poor INR control'. Furthermore, our clinical experience suggests that these more complex patients are more often managed via specialist, secondary care haematology-led anticoagulation services and their INR results may not have been available for analysis in this study.

In this study we identified the individual components of the CHA_2DS_2-VASc score as well as risk factors associated with bleeding at the index date of admission into the study. It was beyond the scope of this study to recalculate the CHA_2DS_2-VASc score or identify new risk factors/comorbidities dynamically throughout the follow up period. It is unknown whether this may have added some incremental benefit or improved the accuracy in the associations between these variables and bleeding events. Regardless, the results in this large real-world population study are compelling; poor INR control and increasing stroke risk are independent markers of increased risk of bleeding events.

The HASBLED score was not calculated in this study for several reasons; poor INR control (a component of the HASBLED score) was measured independently; pathology results, alcohol and illicit drug use are less robustly documented in the WLGP datasets and aspirin and non-steroidal anti-inflammatory are frequently purchased without a prescription in the UK.

Finally, the HASBLED score, unlike CHA_2DS_2-VASc, is at least partially modifiable and likely to change throughout the study period.

This study evaluated the impact of multiple clinical and demographic factors as well as temporal INR control according to multiple criteria in one of the largest real-world studies of INR control in patients with NVAF. The use of a large, data-rich, linked population data source is a particular strength. The linked primary and secondary care data held by SAIL enable the investigation of a very large cohort of individuals longitudinally over a period of years and across multiple data sources, giving a much more complete picture of patient treatment, health, and characteristics than previous studies.

The temporal calculation of INR control allowed us to assign patients to adequate or poor INR control at each INR result based on the previous 6-months of INR data; periods where there were insufficient INR results were excluded from INR calculation but allowed determination of outcomes during all periods of exposure when there were sufficient INR results to (re)calculate INR control. While this conservative approach had the potential to exclude periods of INR calculation in patients who had planned extended periods between INR tests, fewer than 1.4% of INR tests had an interval of greater than 84-days. This approach provided greater surety that only periods of warfarin administration and monitoring were included in the calculation of INR control. Furthermore, the recalculation of INR control and assignment to adequate or poor INR control at each INR test allowed us to test the association between bleeding events and INR control in the immediate period before the bleed, providing an improvement over previous studies that have reported the association between bleeding events and mean TTR calculated up to years before an event.[8]

CONCLUSION

Periods of poor INR control, according to each of the criteria assessed, as well as increasing stroke risk and specific comorbidities for stroke and bleeding, were highly associated with bleeding events. Reducing bleeding through improvement in INR control at a population level is of importance across healthcare systems. At a patient level, detailed individual risk assessment, consideration of factors that lead to poor INR control and comorbidities that increase bleeding risk remain essential. However, it is clear that improved efforts to optimise INR control are likely to be of value in decreasing bleeding events, as are considerations to alternative anticoagulation with direct oral anticoagulants (DOACs) when appropriate when optimal INR control cannot be achieved.

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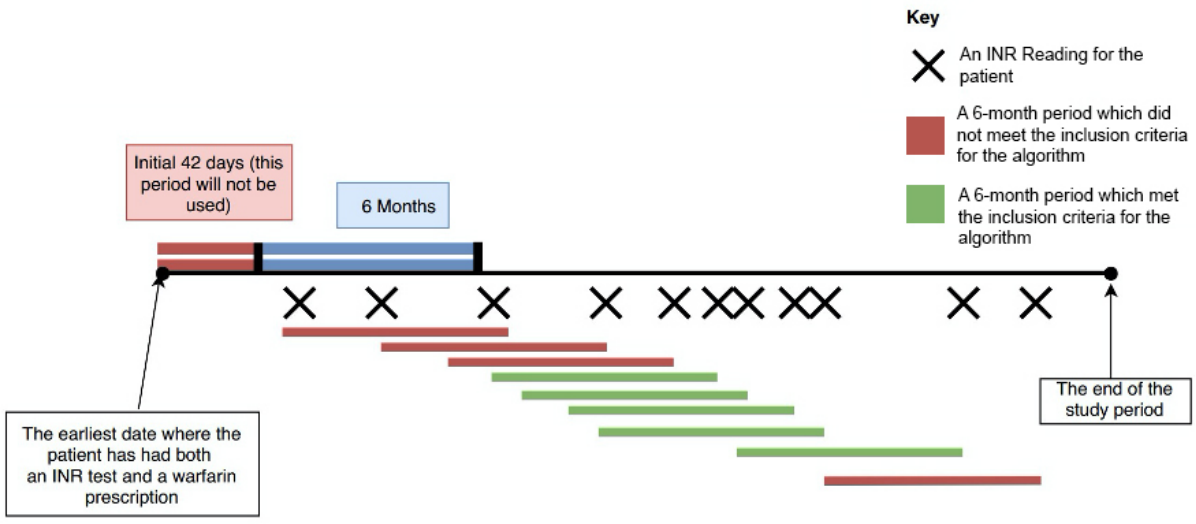
SUPPLEMENTARY INFORMATION

TEMPORAL INR CONTROL

Our algorithm identifies valid temporal windows to identify sufficient readings to allow us to perform TTR calculations. As illustrated in supplementary Figure 1, temporal windows for each patient starts from 42-days after the date which marks the earliest point at which a patient has both had an INR test and received a prescription for warfarin (this is defined as the study start date for the patient). The initial 42-day period is not analysed because the patient's INR is stabilising for this initial period. The existence of records in 6-monthly rolling windows will then be checked and we require at least 4 INR readings in each window to then contribute toward calculation of TTR for the patient. The final result of this algorithm is then used for further analysis to evaluate the bleeding outcomes while taking into the account any changes which might happened in the level of controls during the study period.



Supplementary figure 5.1 TTR Temporal Window Identification Algorithm

The algorithm starts by identifying all of the INR tests the patient received during the study period. If there are 6-months of data present prior to the date of an INR test, the algorithm will identify a potential window to analyse the patient's level of TTR control in the 6-month

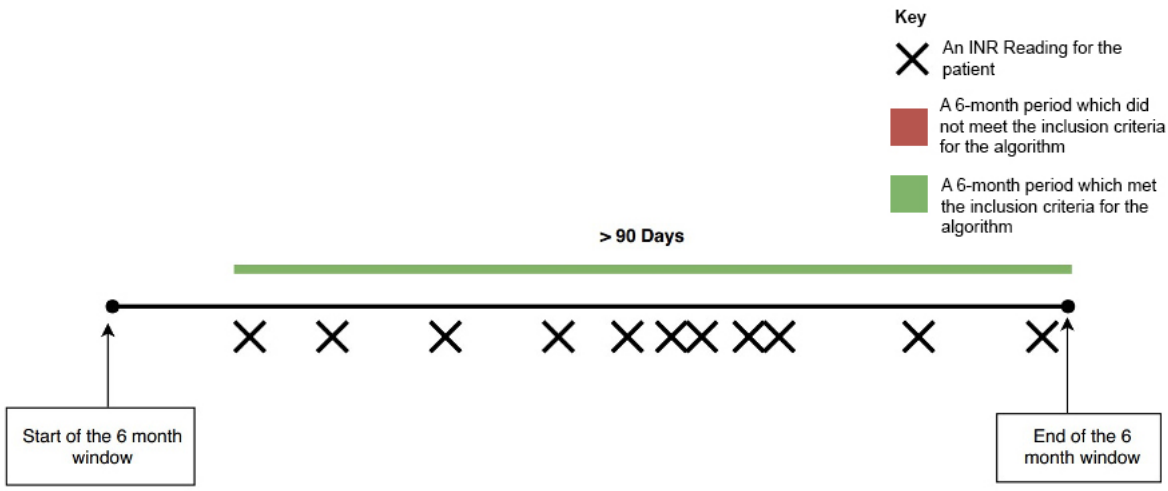
window. The earliest point at which a window can begin is 42-days after the study start date for the patient. The algorithm will then perform a series of checks in order to check that the 6-month window meets the minimum requirements to calculate TTR, which are as follows:

- The patient must have had at least 4 INR readings in the window.
- There must be a gap of between 90 to 183 days from the first to the last reading within the 6-month period. This ensures we have a sufficient time period to calculate a TTR.
- There must be a gap of no more than 84-days between each reading and the subsequent reading in the sequence.

A window is excluded if it does not meet these minimum requirements. A window will always be exactly 6-months (183-days) long. If a patient does not have at least one valid window of data that we can analyse, they are excluded from our analysis. This will produce a series of rolling windows which we can use to analyse the patient's level of control over time.

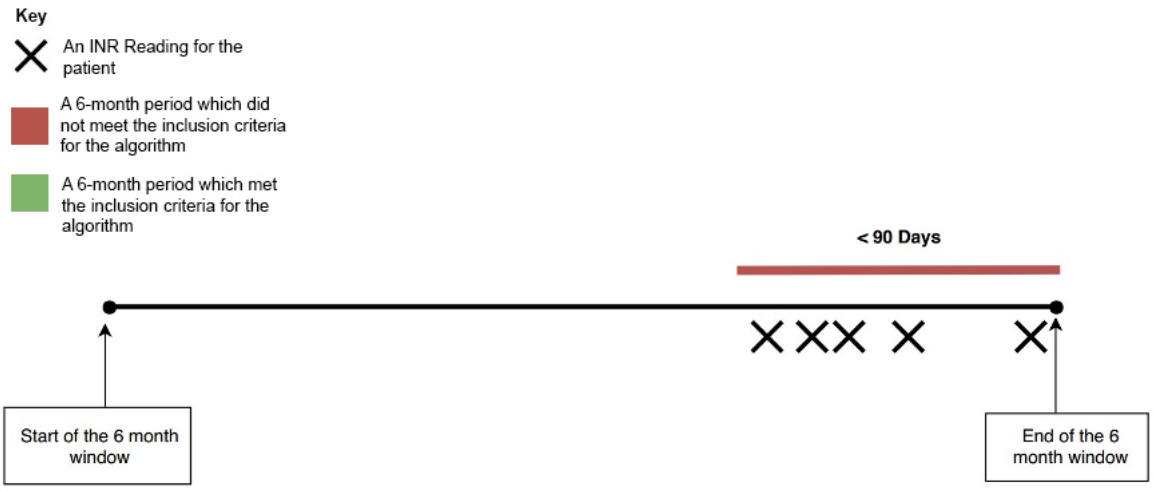
Examples of Exclusion Criteria

Below are a series of examples of valid and invalid temporal windows in the TTR temporal window algorithm.



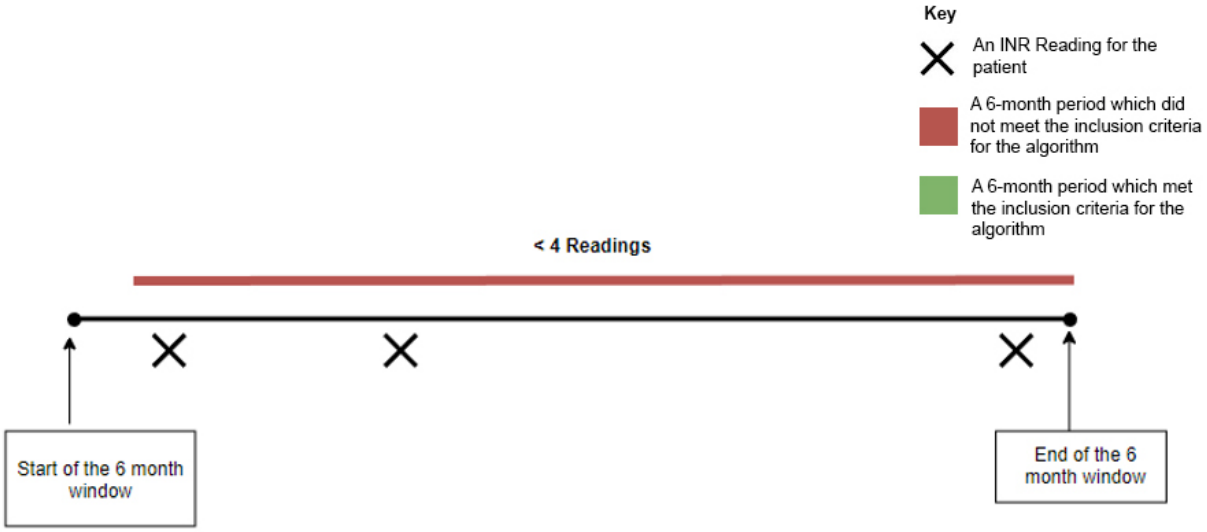
Supplementary figure 5.2a INR inclusion criteria

This is a valid window of analysis, because the patient has had more than 4 INR tests within the period, and there is a gap of more than 90-days from first to last reading:



Supplementary figure 5.2b INR exclusion criteria

This window would be excluded because although there are more than 4 readings within the period, the gap between first and last reading is not sufficient to meet our minimum criteria:

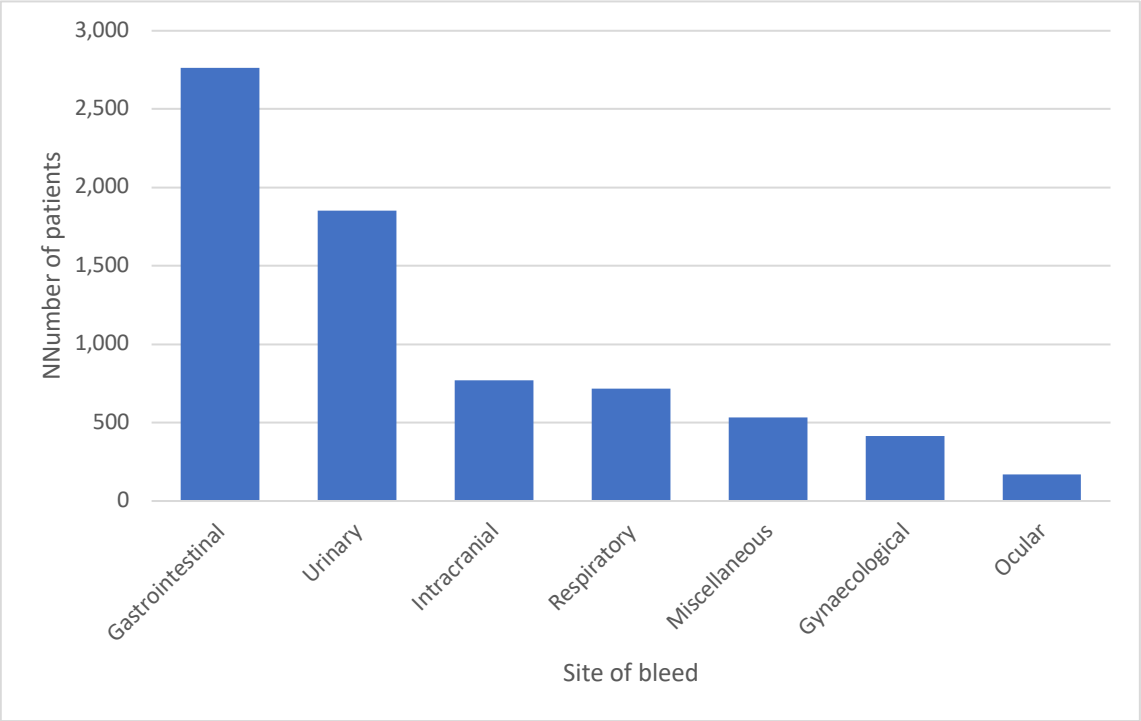


Supplementary figure 5.2c INR exclusion criteria continued

This window would be excluded because there are not 4 readings within the period.

Supplementary figure 5.2d INR exclusion criteria continued

This period would be excluded because there are less than 4 readings, and the gap between each reading and the subsequent reading is greater than 84-days.



Supplementary figure 5.3 Number of bleeds* across the entire study period, including periods outside of INR calculation.

*7,220 bleeds occurred in 6,304 patients across the entire study period.

Supplementary table 5.1a Read codes for bleeding events from WLGP data.

Bleeding event	Read Code	Description
Gastrointestinal	196B.	Painful rectal bleeding
Gastrointestinal	196C.	Painless rectal bleeding
Gastrointestinal	76191	Gastrot ligate bleed
Gastrointestinal	77341	Pt int sphincterot for haemorr
Gastrointestinal	77362	Manual reduct prolapse haemorr
Gastrointestinal	8512	Rectal packing-haemorr.control
Gastrointestinal	G850.	Oesophageal varices + bleeding
Gastrointestinal	G8520	Oesoph.varic.+dis.EC+bleeding
Gastrointestinal	J10y0	Haemorrhage of oesophagus
Gastrointestinal	J1101	Acute GU + haemorrhage
Gastrointestinal	J1111	Chronic GU + haemorrhage
Gastrointestinal	J11y1	Unspec. GU + haemorrhage
Gastrointestinal	J1201	Acute DU + haemorrhage
Gastrointestinal	J1211	Chronic DU + haemorrhage
Gastrointestinal	J12y1	Unspec. DU + haemorrhage
Gastrointestinal	J1301	Acute PU + haemorrhage
Gastrointestinal	J1311	Chronic PU + haemorrhage
Gastrointestinal	J13y1	Unspec. PU + haemorrhage
Gastrointestinal	J1401	Acute GJU + haemorrhage
Gastrointestinal	J1411	Chronic GJU + haemorrhage
Gastrointestinal	J14y1	Unspec. GJU + haemorrhage
Gastrointestinal	J1500	Acute haemorrhagic gastritis
Gastrointestinal	J5109	Bleeding diverticulosis
Gastrointestinal	J573.	Haemorrhage of rectum and anus
Gastrointestinal	J5730	Rectal haemorrhage
Gastrointestinal	J5731	Anal haemorrhage
Gastrointestinal	J573z	Haemorrhage of rectum/anus NOS
Gastrointestinal	J636.	Central haemorrhag necr liver
Gastrointestinal	J6702	Acute haemorrhag.pancreatitis
Gastrointestinal	J68..	Gastrointestinal haemorrhage
Gastrointestinal	J68z.	GIT haemorrhage unspecified
Gastrointestinal	J68z0	Gastric haemorrhage NOS
Gastrointestinal	J68z1	Intestinal haemorrhage NOS
Gastrointestinal	J68z2	Upper GI haemorrhage
Gastrointestinal	J68zz	GIT haemorrhage NOS
Gynecological	7F227	Pack to control P/N vag bleed
Gynecological	8513	Pack non-obst.uterine bleeding
Gynecological	K5311	Corpus luteum cyst haemorrhage
Gynecological	K55y3	Haemorrhage of cervix
Gynecological	K59y3	Intermenstrual bleeding
Gynecological	K5A1.	Postmenopausal bleeding
Gynecological	K5E..	Oth abnorm uterine vagin bleed
Gynecological	K5E0.	Abn uter bleed unrel menst cyc
Gynecological	K5E1.	Abnorm uterine bleeding, unsp
Gynecological	K5E2.	Abnor vagin bleed, unsp
Gynecological	K5Ez.	Abnor uterine vagin bleed unsp
Gynecological	Kyu9D	[X]O spc abnrm uterin+vg bleed
Respiratory	R0630	[D]Cough with haemorrhage
Respiratory	R0631	[D]Pulmonary haemorrhage NOS
Respiratory	Ryu02	[X]Haemor oth site resp
Respiratory	Ryu07	[X]Haemor from resp uns

Supplementary table 5.1a continued. Read codes for bleeding events from WLGP data.		
Bleeding event	**Read Code**	**Description**
Ocular	2BB5.	O/E – retinal haemorrhages
Ocular	2BB8.	O/E – vitreous haemorrhages
Ocular	F4045	Intra-ocular haemorrhage
Ocular	F4243	Ret.pigm.epith.haemorrh.detach
Ocular	F42y1	Superficial retinal haemorrh.
Ocular	F42y3	Deep retinal haemorrhage
Ocular	F42y4	Subretinal haemorrhage
Ocular	F42y5	Retinal haemorrhage NOS
Ocular	F436.	Choroidal haemorrhage/rupture
Ocular	F4360	Choroidal haemorrhage unspec.
Ocular	F4361	Expulsive choroidal haemorrh.
Ocular	F436z	Choroidal haemorr./rupture NOS
Ocular	F4372	Haemorrhagic choroidal detach.
Ocular	F4G32	Orbital haemorrhage
Ocular	F4H41	Optic nerve sheath haemorrhage
Ocular	F4K28	Vitreous haemorrhage
Ocular	F4K7.	Retrobulbar haemorrhage
Ocular	FyuH4	[X]Vitreous haemorrhage/dis CE
Urinary	K1381	Renal artery haemorrhage
Urinary	K13F.	Ureteric haemorrhage
Urinary	K167.	Haemorrhage into bladder wall
Urinary	K16y2	Bladder haemorrhage
Urinary	K19y4	Bleeding from urethra
Urinary	K221.	Prostatic congestion/haemorrh.
Urinary	K2211	Prostatic haemorrhage
Urinary	K221z	Prostatic congest/haemorrh NOS
Urinary	K2752	Corpus cavernosum haemorrhage
Urinary	K2861	Scrotal haemorrhage
Urinary	K2864	Testicular haemorrhage
Urinary	K286w	Male genital haemorrhage NOS
Miscellaneous	7404	Surg arrest bleeding int nose
Miscellaneous	7404y	Surg arrest bleed int nose OS
Miscellaneous	7404z	Surg arrest bleed int nose NOS
Miscellaneous	74213	Surg arr postop bleed adenoid
Miscellaneous	75175	Surg arr PO bleed tooth socket
Miscellaneous	75314	Surg arr PO bleed tonsil bed
Miscellaneous	77352	Inj sclerosing subst haemorrh
Miscellaneous	7H022	Reop chest arr PO bleed abd op
Miscellaneous	7H226	Reop abdo arrest post op bleed
Miscellaneous	7J013	Reopen cran arrest PO bleeding
Miscellaneous	7M0U4	Reexplor & arrest PO bleed NOC
Miscellaneous	851..	Haemorrhage control by packing
Miscellaneous	C063.	Thyroid haemorrhage/infarction
Miscellaneous	C0630	Thyroid haemorrhage
Miscellaneous	C063z	Thyroid haemorrh/infarct NOS
Miscellaneous	C12y1	Haemorrhage of parathyroid
Miscellaneous	C1542	Adrenal haemorrhage
Miscellaneous	D31X.	Haemorrhag condition, unsp
Miscellaneous	D31y.	Other haemorrhagic conditions
Miscellaneous	D31yz	Other haemorrhagic condit.NOS
Miscellaneous	D31z.	Haemorrhagic condition NOS

Supplementary table 5.1a continued. Read codes for bleeding events from WLGP data.		
Bleeding event	**Read Code**	**Description**
Miscellaneous	Dyu34	[X]Haemorrhag condition, unsp
Miscellaneous	J08zD	Angina bullosa haemorrhagica
Miscellaneous	R048.	[D]Throat haemorrhage
Miscellaneous	Ryu73	[X]Haemorrhage, NEC
Intracranial	662o.	Haemorrhagic stroke monitoring
Intracranial	G60..	Subarachnoid haemorrhage
Intracranial	G60..	Subarachnoid haemorrhage
Intracranial	G600.	Ruptured berry aneurysm
Intracranial	G601.	Subarac haem/carotd siph+bifur
Intracranial	G602.	Subarachd haem/mid cerebrl art
Intracranial	G603.	Subarachnd haem/ant commun art
Intracranial	G604.	Subarachn haem/post commun art
Intracranial	G605.	Subarachnd haem/basilar artery
Intracranial	G606.	Subarach haem/vertebral artery
Intracranial	G60X.	Subar haem,intracr art,unsp
Intracranial	G60z.	Subarachnoid haemorrhage NOS
Intracranial	G60z.	Subarachnoid haemorrhage NOS
Intracranial	G61..	Intracerebral haemorrhage
Intracranial	G61..	Intracerebral haemorrhage
Intracranial	G610.	Cortical haemorrhage
Intracranial	G610.	Cortical haemorrhage
Intracranial	G611.	Internal capsule haemorrhage
Intracranial	G611.	Internal capsule haemorrhage
Intracranial	G612.	Basal nucleus haemorrhage
Intracranial	G612.	Basal nucleus haemorrhage
Intracranial	G613.	Cerebellar haemorrhage
Intracranial	G613.	Cerebellar haemorrhage
Intracranial	G614.	Pontine haemorrhage
Intracranial	G614.	Pontine haemorrhage
Intracranial	G615.	Bulbar haemorrhage
Intracranial	G615.	Bulbar haemorrhage
Intracranial	G616.	External capsule haemorrhage
Intracranial	G616.	External capsule haemorrhage
Intracranial	G617.	Intrcereb haem,intraventriculr
Intracranial	G618.	Intracerebrl haem,multip local
Intracranial	G619.	Lobar cerebral haemorrhage
Intracranial	G619.	Lobar cerebral haemorrhage
Intracranial	G61X.	Intracer haem hemisph, unsp
Intracranial	G61X0	Left side intracereb haem unsp
Intracranial	G61X1	Right side intracer haem unsp
Intracranial	G61z.	Intracerebral haemorrhage NOS
Intracranial	G61z.	Intracerebral haemorrhage NOS
Intracranial	G62..	Oth/unspec intracranial bleed
Intracranial	G620.	Extradural haemorrh.-nontraum.

Supplementary table 5.1a continued. Read codes for bleeding events from WLGP data.		
Bleeding event	**Read Code**	**Description**
Intracranial	G621.	Subdural haemorrhage-nontraum.
Intracranial	G623.	Subdural haemorrhage NOS
Intracranial	G62z.	Intracranial haemorrhage NOS
Intracranial	G680.	Sequel/subarachnoid haemorrhag
Intracranial	G681.	Seq/intracerebral haemorrhage
Intracranial	S620.	Cls trm subarach haemorrhage
Intracranial	S621.	Opn trm subarach haemorrhage
Intracranial	S622.	Cls trm subdural haemorrhage
Intracranial	S623.	Opn trm subdural haemorrhage
Intracranial	S624.	Cls trm extradural haemorrhage
Intracranial	S625.	Opn trm extradural haemorrhage
Intracranial	S626.	Epidural haemorrhage
Intracranial	S627.	Traum subarachnoid haemorrhage
Intracranial	S628.	Traumatic subdural haemorrhage

Supplementary table 5.1b *ICD-10* codes for bleeding events from PEDW.		
Bleeding event	**Read Code**	**Description**
Gastrointestinal	I850	Oesophageal varices with bleeding
Gastrointestinal	I983	Oesophageal varices with bleeding in diseases classified elsewhere
Gastrointestinal	K226	Gastro-oesophageal laceration-haemorrhage syndrome
Gastrointestinal	K290	Acute haemorrhagic gastritis
Gastrointestinal	K762	Central haemorrhagic necrosis of liver
Gastrointestinal	K922	Gastrointestinal haemorrhage, unspecified
Gastrointestinal	R041	Haemorrhage from throat
Gastrointestinal	R048	Haemorrhage from other sites in respiratory passages
Gastrointestinal	R049	Haemorrhage from respiratory passages, unspecified
Gastrointestinal	R58X	Haemorrhage, not elsewhere classified
Gastrointestinal	K921	Melaena
Gastrointestinal	K250	Gastric ulceracute with haemorrhage
Gastrointestinal	K254	Gastric ulcerchronic or unspecified with haemorrhage
Gastrointestinal	K260	Duodenal ulceracute with haemorrhage
Gastrointestinal	K264	Duodenal ulcerchronic or unspecified with haemorrhage
Gastrointestinal	K270	Peptic ulceracute with haemorrhage
Gastrointestinal	K280	Gastrojejunal ulceracute with haemorrhage
Gastrointestinal	K921	Melaena
Gastrointestinal	K922	Gastrointestinal haemorrhageunspecified
Gastrointestinal	K921	Melaena
Gastrointestinal	K922	Gastrointestinal haemorrhageunspecified
Gastrointestinal	K922	Gastrointestinal haemorrhageunspecified
Gynecological	N923	Ovulation bleeding
Gynecological	N924	Excessive bleeding in the premenopausal period
Gynecological	N93	Other abnormal uterine and vaginal bleeding
Gynecological	N930	Postcoital and contact bleeding
Gynecological	N938	Other specified abnormal uterine and vaginal bleeding
Gynecological	N939	Abnormal uterine and vaginal bleeding, unspecified
Gynecological	N950	Postmenopausal bleeding
Gynecological	N923	Ovulation bleeding

Supplementary table 5.1b continued. *ICD-10* codes for bleeding events from PEDW.		
Bleeding event	**Bleeding event**	**Bleeding event**
Respiratory	R04	Haemorrhage from respiratory passages
Respiratory	J942	Haemothorax
Respiratory	K920	Haematemesis
Respiratory	R042	Haemoptysis
Respiratory	R048	Haemorrhage from other sites in respiratory passages
Ocular	H356	Retinal haemorrhage
Ocular	H313	Choroidal haemorrhage and rupture
Ocular	H356	Retinal haemorrhage
Ocular	H431	Vitreous haemorrhage
Ocular	H450	Vitreous haemorrhage in diseases classified elsewhere
Miscellaneous	D683	Haemorrhagic disorder due to circulating anticoagulants
Miscellaneous	D698	Other specified haemorrhagic conditions
Miscellaneous	D699	Haemorrhagic condition, unspecified
Miscellaneous	S064	Epidural haemorrhage
Miscellaneous	T792	Traumatic secondary and recurrent haemorrhage
Miscellaneous	T810	Haemorrhage and haematoma complicating a procedure, not elsewhere classified
Miscellaneous	Y60	Unintentional cut, puncture, perforation or haemorrhage during surgical and medical care
Urinary	N421	Congestion and haemorrhage of prostate
Urinary	N028	Recurrent and persistent haematuriaother
Urinary	N029	Recurrent and persistent haematuriaunspecified
Urinary	R31X	Unspecified haematuria
Intracranial	I60	Subarachnoid haemorrhage
Intracranial	I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
Intracranial	I601	Subarachnoid haemorrhage from middle cerebral artery
Intracranial	I602	Subarachnoid haemorrhage from anterior communicating artery
Intracranial	I603	Subarachnoid haemorrhage from posterior communicating artery
Intracranial	I604	Subarachnoid haemorrhage from basilar artery
Intracranial	I605	Subarachnoid haemorrhage from vertebral artery
Intracranial	I606	Subarachnoid haemorrhage from other intracranial arteries

Supplementary table 5.1b continued. *ICD-10* codes for bleeding events from PEDW.		
Bleeding event	**Bleeding event**	**Bleeding event**
Intracranial	I609	Subarachnoid haemorrhage, unspecified
Intracranial	I61	Intracerebral haemorrhage
Intracranial	I610	Intracerebral haemorrhage in hemisphere, subcortical
Intracranial	I611	Intracerebral haemorrhage in hemisphere, cortical
Intracranial	I612	Intracerebral haemorrhage in hemisphere, unspecified
Intracranial	I613	Intracerebral haemorrhage in brain stem
Intracranial	I614	Intracerebral haemorrhage in cerebellum
Intracranial	I615	Intracerebral haemorrhage, intraventricular
Intracranial	I616	Intracerebral haemorrhage, multiple localized
Intracranial	I618	Other intracerebral haemorrhage
Intracranial	I619	Intracerebral haemorrhage, unspecified
Intracranial	I62	Other nontraumatic intracranial haemorrhage
Intracranial	I620	Subdural haemorrhage (acute)(nontraumatic)
Intracranial	I621	Nontraumatic extradural haemorrhage
Intracranial	I629	Intracranial haemorrhage (nontraumatic), unspecified
Intracranial	S065	Traumatic subdural haemorrhage
Intracranial	S066	Traumatic subarachnoid haemorrhage

Supplementary table 5.2 Cohort characteristics and comparisons to patients with inadequate number of INR readings to calculate INR control prior to a bleed and those with inadequate number of INR results to calculate INR control across any period during the study.

	Cohort analysed	Inadequate number of INR results prior to bleed	Inadequate number of INR results to calculate INR control at any point
	N= 35,035	N=2,603	N=18,379
Mean age at entry into study	73.4 (SD=9.4)	73.7 (SD=9.6), P=0.21	*
Mean age diagnosis	70.6 (SD=10.6)	71·7 (SD=10·2), P<0·001	70.8 (SD=11.7), P=0.09
	N (%)	N (%)	N (%)
Age category at entry into study		P=0.36	*
18-64	5,679 (16.2)	410 (15.8)	*
65-74	11,610 (33.1)	898 (34.5)	*
75+	17,746 (50.7)	1295 (49.8)	*
Female	15,041 (42.9)	1041 (40.0), P=0.003	7858 (42.8), P=0.70
Deprivation quintile		P=0.005	P<0.001
1 (most deprived)	5,732 (17.0)	452 (18.0)	2180 (18.5)
2	6,573 (19.5)	510 (20.3)	2195 (18.7)
3	7,450 (22.1)	607 (24.2)	2570 (21.8)
4	6,611 (19.6)	459)18.3)	2187 (18.6)
5 (least deprived)	7,296 (21.7)	484 (19.3)	2636(22.4)
CHA_2DS_2-VASc (mean)	3.5 (SD=1.69)	3.5 (SD=1.7), P=0.10	3.7 (SD= 1.8), P <0.001
	N (%)	N (%)	N (%)
CHA_2DS_2-VASc		P= 0.004	P <0.001
0 &1	3,971 (11.3)	262 (10.1)	1477 (12.1)
2	6,018 (17.2)	495 (19.0)	1702 (13.9)
3	7,859 (22.4)	634 (24.4)	2487 (20.3)
4	7,692 (22.0)	564 (21.7)	2632 (21.5)
5	4,999 (14.3)	352 (13.5)	1907 (15.6)
≥6	4,496 (12.8)	296 (11.4)	2042 (16.7)
Heart failure	8,283 (23.6)	557 (21.4), P=0.009	6366 (34.6), P<0.001
Hypertension	23,049 (65.8)	1704 (65.5), P=0.74	11590 (63.1), P <0.001
Diabetes	7,476 (21.3)	573 (22.0), P=0.42	4643 (25.3), P<0.001
Ischaemic stroke	7,291 (20.8)	520 (20.0), P=0.31	4220 (23.0), P<0.001
Ischaemic heart disease	486 (1.4)	872 (33.5), P=0.001	6627 (36.1), P<0.001
Thromboembolism	10,608 (30.3)	42 (1.6), P=0.34	334 (1.8), P<0.001
PVD	2139 (6.1)	175 (6.7), P=0.21	1584 (8.6), P<0.001
Liver disease	670 (1.9)	59 (2.3), P=0.20	727 (4.0), P<0.001
Chronic kidney disease (stage 4+)	417 (1.2)	42 (1.6), P=0.06	551 (3.0), P<0.001
Excessive alcohol intake	935 (2.7)	63 (2.4), P=0.45	627 (3.4), P<0.001
Any prior bleeding	4657 (13.3)	551 (21.2), P<0.001	4188 (22.8), P <0.001

*Information not entered as this group were not included in the analysis.

Supplementary table 5.3. Comparisons between those with deprivation index present and missing from the final cohort.

N= 35,035.

	Deprivation index present	Deprivation index missing
	N= 33,662	N=1,373
	Mean (SD)	Mean (SD), p
Mean age	73.6 (9.6)	74.3 (10.2), 0.028
CHA_2DS_2-VASc (mean)	3.52 (1.68)	3.53(1.76), 0.71
	N (%)	N (%), p
Age		P = 0.57
18-64	5,466 (16.2)	213 (15.5)
65-74	11,164 (16.2)	446 (32.5)
75+	17,032 (50.6)	714 (52.0)
Female	14,473 (43.0)	568(41.4), 0.23
CHA_2DS_2-VASc		P= 0.30
0 &1	3806 (11.3)	165 (12.0)
2	5777 (17.2)	241 (17.6)
3	7558 (22.5)	301 (21.9)
4	7413 (22.0)	279 (20.3)
5	4811 (14.3)	188 (13.7)
≥6	4297 (12.8)	199 (14.5)
Heart failure	7918 (23.5)	365 (26.6), 0.009
Hypertension	22191 (65.9)	858 (62.5), 0.009
Diabetes	7195 (21.4)	281 (20.5), 0.42
Ischaemic stroke	6999 (20.8)	291 (21.3), 0.67
Ischaemic heart disease	10190 (30.3)	418 (30.4), 0.89
Thromboembolism	463 (1.4)	23 (1.7), 0.35
PVD	2058 (6.1)	81 (5.9), 0.75
Liver disease	640 (1.9)	30 (2.2), 0.45
Chronic kidney disease (stage 4+)	398 (1.2)	19 (1.4), 0.50
Excessive alcohol intake	891 (2.6)	44 (3.2), 0.21
Any prior bleeding	4490 (13.3)	167 (12.2), 0.21

Supplementary table 5.4 Bleeding event rate according to INR guideline criteria.				
Guideline criteria	INR control	Number of bleeds	Number of patient years	Event rate per 100 patient years
NICE				
	Adequate	2926	85445.3	3.4
	Poor	2113	44273.7	4.8
	N/A*	1265	2965.5	42.7
ESC/US				
	Adequate	2538	765805	3.3
	Poor	2501	531386	4.7
	N/A*	1265	2965.5	42.7
Modified ESC/US				
	Adequate	2503	75993.	3.3
	Poor	2536	53725.3	4.7
	N/A*	1265	2965.5	42.7
*NA indicates bleeds occurring during periods where it was not possible to calculate INR control.				

SECONDARY ANALYSES: BREAKDOWN BY TYPE OF BLEED

Supplementary table 5.5 Multivariable Cox-regression model for hazard of bleeding events determined by poor INR control (according ESC/US definition of poor INR control (TTR<70%)).

	GI	Urinary	Respiratory	Intracranial
Poor control (TTR <70%)	1.41 (.30-1.53), <0.001	1.29 (1.17-1.43), <0.001	2.00 (1.6-2.36), <0.001	1.58 (1.34-1.86), <0.001
Female	0.91 (0.83-0.99), 0.03	0.42 (0.37-0.47), <0.01	0.71 (0.60-0.85), <0.001	0.92 (0.78-1.09), 0.36
Age				
<65	Reference	Reference	Reference	Reference
65-74	1.17 (1.03-1.33), 0.02	1.36 (1.16-1.59), <0.001	1.26 (0.96-1.64), 0.05	2.27 (1.62-3.17), <0.001
≥75	1.58 (1.39-1.80), <0.001	1.74 (1.48-2.03), <0.001	2.00 (1.54-2.59), <0.001	4.24 (3.06-5.90), <0.001
Excessive alcohol consumption	1.01 (0.76-1.79), <0.001	0.77 (0.53-1.10), 0.14	1.68 (1.10-2.56), 0.02	1.11 (0.62-1.99), 0.73
Prior bleeding events	1.35 (1.21-1.52),<0.001	2.09 (1.85-2.37), <0.001	1.72 (1.40-2.11), <0.001	1.06 (0.83-1.35), 0.63
Hypertension	1.06 (0.97-1.16), 0.21	1.04 (0.94-1.17), 0.42	0.98 (0.82-1.17), 0.83	1.19 (0.99-1.42), 0.07
Liver disease	1.03 (0.74-1.43), 0.85	1.14 (0.78-1.66), 0.49	1.74 (1.09-2.78), 0.02	0.99 (0.51-1.95), 0.99
Diabetes	1.10 (0.99-1.21), 0.08	1.05 (0.93-1.19), 0.43	1.09 (0.89-1.34), 0.36	1.18 (0.97-1.44), 0.09
Heart failure	1.11 (1.00-1.22), 0.04	1.01 (0.89-1.14), 0.87	1.26 (1.04-1.52), 0.02	1.04 (0.86-1.27), 0.67
Ischemic heart disease	1.22 (1.12-1.34), <0.001	1.14 (1.02-1.28), 0.02	1.17 (0.98-1.39), 0.08	1.02 (0.85-1.22), 0.82
Ischemic stroke	1.12 (1.01-1.24), 0.03	1.04 (0.92-1.17), 0.54	1.16 (0.96-1.40), 0.13	1.37 (1.14-1.64), <0.001
PVD*	1.16 (0.98-1.39), 0.07	0.89 (0.71-1.12), 0.31	1.16 (0.84-1.60), 0.35	0.95 (0.67-1.36), 0.79
Thromboembolism	0.97 (0.66-1.41), 0.88	1.14 (0.73-1.79), 0.57	1.47 (0.81-2.65), 0.20	1.06 (0.52-2.16), 0.87
CKD (stage 4+)	1.23 (0.82-1.84), 0.32	1.35 (0.73-1.79), 0.22	2.63 (1.54-4.50), <0.001	1.14 (0.51-2.55), 0.76

Results are adjusted for individual components of CHA_2DS_2-VASc score, plus baseline characteristics. Any changes in INR control status for individuals over time were included in the model as a time dependent variable.

Supplementary table 5.6 Multivariable Cox-regression model for hazard of major bleeding events determined by poor INR control (according to the modified ESC/US definition of poor INR control (TTR<70% or low or high INRs)).

	GI	Urinary	Respiratory	Intracranial
Poor control (TTR <70%or low or high INRs)	1.41 (1.29-1.53), <0.001	1.31 (0.18-1.45), <0.001	2.08 (1.75-2.46), <0.001	1.60 (1.36-1.88), <0.001
Female	0.91 (0.83-0.99), 0.05	0.42 (0.37-0.47), <0.001	0.71 (0.60-0.85), <0..01	0.92 (0.78-1.09), 0.35
Age				
<65	Reference	Reference	Reference	Reference
65-74	1.17 (1.02-1.33), 0.02	1.36 (1.16-1.59), <0..01	1.26 (0.96-1.64), 0.09	2.27 (1.63-3.17), <0.001
≥75	1.58 (1.39-1.79), <0.001	1.74 (1.48-2.03), <0.001	2.00 (1.54-2.59), <0.001	4.25 (3.06-5.90), <0.001
Excessive alcohol consumption	1.01 (0.76-1.34), 0.95	0.77 (0.53-1.10), 0.14	1.67 (1.09-2.55), 0.02	1.11 (0.62-1.99), 0.73
Prior bleeding events	1.35 (1.21-1.52), <0.001	2.09 (1.85-2.37), <0.001	1.71 (1.39-2.11), <0.001	1.06 (0.83-1.35), 0.63
Hypertension	1.06 (0.97-1.16), 0.21	1.05 (0.94-1.17), 0.43	0.98 (0.82-1.17), 0.82	1.18 (0.99-1.42), 0.07
Liver disease	1.03 (0.74-1.43), 0.84	1.14 (0.78-1.67), 0.49	1.74 (1.09-2.78), 0.02	0.99 (0.51-1.95), 0.99
Diabetes	1.10 (0.99-1.21), 0.08	1.05 (0.93-1.19), 0.43	1.10 (0.90-1.34), 0.37	1.18 (0.97-1.44), 0.09
Heart failure	1.11 (1.00-1.22), 0.04	1.01 (0.89-1.14), 0.88	1.26 (0.90-1.34), 0.02	1.04 (0.86-1.27), 0.68
Ischemic heart disease	1.22 (1.12-1.34), <0.001	1.14 (1.02-1.28), 0.02	1.17 (0.98-1.39), 0.09	1.02 (0.85-1.22), 0.82
Ischemic stroke	1.12 (1.01-1.24), 0.03	1.04 (0.92-1.18), 0.55	1.16 (0.96-1.40), 0.13	1.37 (1.14-1.64), <0.001
PVD*	1.17 (0.99-1.39), 0.07	0.89 (0.71-1.12), 0.31	1.16 (0.84-1.60), 0.36	0.95 (0.67-1.36), 0.79
Thromboembolism	0.97 (0.67-1.41), 0.88	1.14 (0.73-1.79), 0.57	1.46 (0.81-2.64), 0.20	1.06 (0.52-2.15), 0.88
CKD (stage 4+)	1.23 (0.82-1.84). 0.32	1.35 (0.83-2.28), 0.22	2.62 (1.53-4.49), <0.001	1.13 (0.51-2.55), 0.76

Results are adjusted for individual components of CHA_2DS_2-VASc score, plus baseline characteristics. Any changes in INR control status for individuals over time were included in the model as a time dependent variable.

Supplementary table 5.7 Bleeding event rate within organ systems according to periods of NICE guideline criteria for INR control.

Organ system	INR control	Number of bleeds	Number of patient years	Event rate per 100 patient years
Gastrointestinal				
	Adequate	1288	89787	1.4
	Poor	931	44273	2.0
	N/A*	545	2279	23.9
Urinary				
	Adequate	888	90434	0.98
	Poor	597	47404	1.26
	N/A*	369	2250	16.4
Intracranial				
	Adequate	327	93106	0.35
	Poor	262	48883	0.54
	N/A*	182	2081	8.75
Respiratory				
	Adequate	270	92766	0.29
	poor	303	48589	0.62
	N/A*	142	2033	6.99

*NA indicates bleeds occurring during periods where it was not possible to calculate INR control.

Supplementary table 5.8 Bleeding event rate within organ systems according to periods of ESC/US guideline criteria for INR control.

Organ system	INR control	Number of bleeds	Number of patient years	Event rate per 100 patient years
Gastrointestinal				
	Adequate	1113	80460	1.38
	Poor	1106	56246	1.97
	N/A*	545	2280	23.9
Urinary				
	Adequate	787	81044	0.97
	Poor	698	56794	1.23
	N/A*	369	2250	16.4
Intracranial				
	Adequate	276	83437	0.33
	Poor	313	58550	0.53
	N/A*	182	2081	8.75
Respiratory				
	Adequate	234	83150	0.28
	Poor	339	58204	0.58
	N/A*	142	2033	6.99

*NA indicates bleeds occurring during periods where it was not possible to calculate INR control.

Supplementary table 5.9 Bleeding event rate within organ systems according to periods of a modified ESC/US guideline criteria INR control.

Organ system	INR control	Number of bleeds	Number of patient years	Event rate per 100 patient years
Gastrointestinal				
	Adequate	1104	79826	1.38
	Poor	1115	56878	1.96
	N/A*	545	2280	23.9
Urinary				
	Adequate	774	80401	0.96
	Poor	711	57438	1.24
	N/A*	369	2250	16.4
Intracranial				
	Adequate	272	82768	0.33
	Poor	317	59219	0.54
	N/A*	182	2081	8.75
Respiratory				
	Adequate	226	82484	0.27
	Poor	347	58870	0.9
	N/A*	142	2032	6.99

*NA indicates bleeds occurring during periods where it was not possible to calculate INR control.

CHAPTER 6

WALES ATRIAL FIBRILLATION AND RECURRENT EVENTS AFTER PCI (WARP)

A REAL-WORLD ANALYSIS OF BLEEDING AND THROMBOTIC OUTCOMES POST-PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH ATRIAL FIBRILLATION

INTRODUCTION

Antithrombotic prescribing in patients undergoing percutaneous coronary intervention (PCI) complicated by atrial fibrillation (AF) represents a clinical dilemma. Dual antiplatelet therapy (DAPT), a combination of aspirin and $P2Y_{12}$ antagonist is recommended to prevent in stent thrombosis and coronary artery occlusion in patients undergoing PCI for both acute coronary syndrome (ACS) and elective stenting.[1-3] In patients with AF, oral anticoagulation (OAC) has been shown to be superior to the combination of aspirin and clopidogrel in preventing vascular events (stroke, systemic embolism, myocardial infarction(MI) and death). [4]

In patients undergoing PCI who also have AF, guidelines recommend a tailored approach based on stroke risk, bleeding risk and concerns regarding ischaemic risk.[1, 5, 6] The use of the combination DAPT+OAC, triple antithrombotic therapy (TAT) is an option for patients at high risk of coronary events also at high risk of stroke, however, this approach is often limited by concerns over excess bleeding risks.[7] As such, the optimal antithrombotic regimen remains uncertain in this population; the need to protect coronary arteries from thrombosis, prevent stroke and minimise bleeding events that may trigger prothrombotic processes or result in the cessation of antithrombotic therapy represents competing risks.

Recent medium sized randomised control trials (RCTs) have examined bleeding outcomes for a range of Direct Oral Anticoagulants (DOACs) and Vitamin-K antagonists (VKA) based antithrombotic strategies.[8-11] However, real world data are limited, have focused on short-term outcomes[12] and the association between bleeding and ischaemic outcomes has not been fully evaluated.

Our objectives were to analyse the rate of hospitalisation for major cardiovascular events, haemorrhage and mortality in patients with AF in the first year after successful PCI, accounting for risk factors and antithrombotic regimen.

METHOD

We undertook a retrospective observational cohort study using linked anonymised healthcare data for patients undergoing PCI in Wales from January 2011 to December 2018 using the Secure Anonymised Information Linkage (SAIL) Databank.[13, 14] SAIL is part of the National e-health records research infrastructure for Wales (holding > 4million linked patient records across primary and secondary care). The study population included patients discharged from hospital following PCI with a prior or new diagnosis of AF. Follow up was for twelve months post discharge. Patients who also underwent Coronary artery bypass graft surgery during the index admission were excluded.

The following datasets held within SAIL were linked at patient level: the Patient Episode Database for Wales (PEDW),[15] which records hospital admission and discharge dates, diagnoses and operational procedures, demographic data, and date of death where applicable for the population of Wales; the Welsh Longitudinal General Practice (WLGP) dataset[16] containing demographic, clinical and prescribing data for approximately 80% of primary care practices across Wales; the Welsh Demographic (WDS) dataset,[17] which contains basic demographic information and history of individuals' residence in Wales and registration with GP practices; and the Welsh Index of Multiple Deprivation (WIMD) 2011[18], an area-based deprivation measure and the date of death, where relevant, was identified from the Annual District Death Extract (ADDE).[17]

MEDICAL HISTORY, DEMOGRAPHIC INFORMATION AND PRESCRIPTIONS

The PEDW data was used to identify patients undergoing PCI during the study period. The first PCI during the study period was classified as the index admission with the date of admission and discharge identified either side of the index PCI. PEDW was also used to identify whether the index PCI was for an acute coronary syndrome (ACS) or stable disease, prior hospital admissions for major bleeding events, prior coronary revascularisation (either

PCI or coronary artery bypass graph [CABG]) and exclude patients who had undergone CABG during the index admission.

Both PEDW and WLGP data were searched for prior history or contemporary diagnosis of vascular disease (peripheral artery disease or aortic plaque), AF/flutter, MI, Ischemic stroke, arterial thromboembolism, heart failure and diabetes.

Hypertension, ischemic heart disease (IHD), chronic kidney disease CKD (stage 4+), chronic liver disease (including cirrhosis, fibrosis, chronic hepatitis and chronic active hepatitis, fatty liver, sclerosis of the liver, unspecified alcoholic liver damage, hepatic failure), age and sex was identified from the WLGP. Prescriptions for antithrombotic therapy issued within 90 days prior to the index admission date were also documented.

The presence of heart failure, hypertension, vascular disease (defined as prior myocardial infarction (MI) or peripheral vascular disease (PVD) including peripheral artery disease and aortic plaque), prior stroke (including TIA), gender and age were used to calculate the individual CHA_2DS_2-VASc score at the time of the index PCI.[19]

ANTITHROMBOTIC PRESCRIBING AND CLASSIFICATION

Prescriptions for antithrombotic therapy including aspirin, $P2Y_{12}$ inhibitors (including clopidogrel, prasugrel or ticagrelor), and anticoagulants: either warfarin or DOAC (including apixaban, dabigatran, edoxaban or rivaroxaban) recorded in the WLGP during the first 90 days post discharge were documented. Antithrombotic prescriptions were then classified as DAPT (aspirin plus $P2Y_{12}$ antagonist), TAT (DAPT + anticoagulant) or OAC plus single AP (aspirin or $P2Y_{12}$) [OAC+AP]. Other combinations of an antithrombotic therapy were excluded from the final analyses.

STATISTICAL ANALYSES

Baseline variables and patient characteristics including demographics, lifestyle behaviours and medical history were presented as percentages and means with standard deviations. Differences in the baseline characteristics between those prescribed DAPT, OAC+AP and TAT (and those prescribed other antithrombotic regimens not included in the final analysis) were compared using ANOVA.

PRIMARY END POINTS

The Kaplan-Meier method was used to estimate the rate of hospitalisation during follow up for (i) ischaemic stroke (including transient ischemic attacks (TIA); (ii) ACS (including unstable angina, acute ischaemic heart disease and myocardial infarction); and (iii) death (by any cause), (iv) the combination of death or hospital admission for stroke or ACS, and (v) hospitalisations for bleeding events (including respiratory tract, intracranial, gastrointestinal, and urinary tract bleeds) (*see supplementary table 6.1 for ICD-10 codes for all outcomes*). All models were presented by stroke risk according to CHA_2DS_2-VASc score (grouped as CHA_2DS_2-VASc score 1-3 and ≥4) and antithrombotic regimen. The log rank test was used to report difference in survival functions (Kaplan-Meier) between groups.

Cox-proportional hazard models were used to determine predictors associated with the endpoints measured in the Kaplan-Meier analyses, with bleeding during follow up modelled as a time dependent covariate in the first 4 models. In the fifth model (major bleeding event during follow up) and prior hospitalisation for bleeding was included as an independent variable.

All models were run in SPSS version 26.0. The final multivariable Cox model was selected by minimising the Bayesian Information Criterion (BIC).

RESULTS

A total of 25,690 patients were identified who had undergone PCI during the study period (figure 6.1). After excluding those without linked health data (prior to PCI) and/or those who underwent CABG during the index admission, 2,097 (11.2%) had a new or pre-existing diagnosis of AF. 18,674 patients survived the index admission and had post discharge linked data of which 1960 (10.8%) had a diagnosis of AF, of these 1,613 patients were identified as being prescribed DAPT, TAT or OAC +AP (figure 6.1) (*see supplementary table 6.2 for details of antithrombotic regimens*). Of these patients 1,111 (69%) underwent PCI for ACS and 1,170 had a diagnosis of AF prior to the index admission (table 6.1).

Patients prescribed TAT or OAC+AP compared to those prescribed DAPT were older, had a higher CHA_2DS_2-VASc score, higher rates of obesity, diabetes, hypertension, heart failure and prior ischaemic strokes and more likely to have been prescribed oral anticoagulation prior to the index admission. Those prescribed DAPT were more likely to have presented with an ACS during the index admission and had a higher rate of new AF diagnosis compared to other regimens.

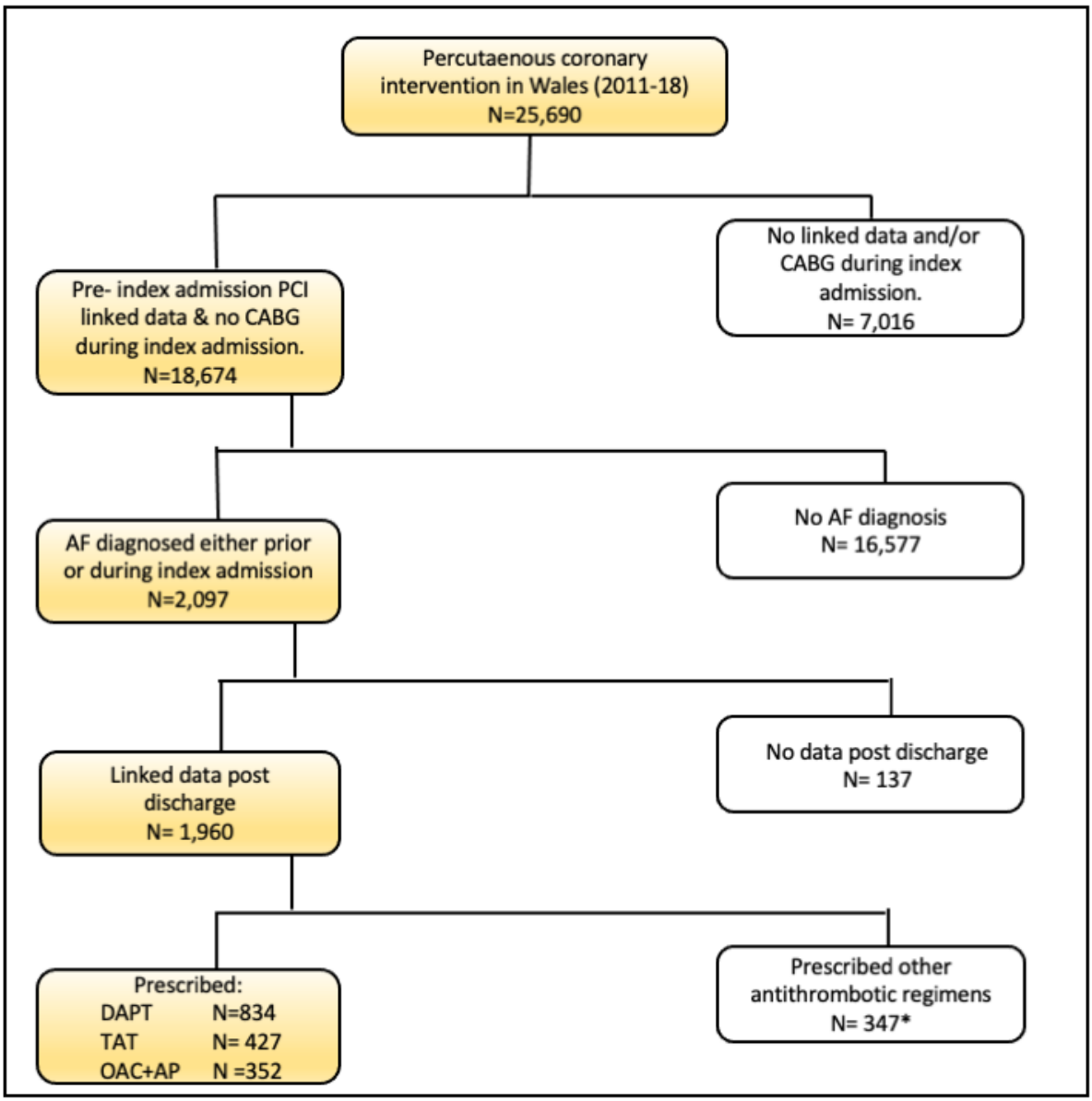


Figure 6.1 Study population cohort selection.

*See supplement for detail of antithrombotic regimens.

Table 6.1 Baseline characteristics of cohort by antithrombotic regimen

	DAPT N= 834	OAC+AP N=352	TAT N=427	*P* value (between subject effects)
Mean age, y (SD)	71.8 (10.2)	74.4 (8.2)	72.9 (8.5)	<0.001
Characteristic, n(%)				
Male	591 (70.9)	244 (69.3)	334 (78.2)	0.007
Deprivation index				0.91
1	151 (18.1)	71 (20.2)	79 (18.5)	
2	163 (19.5)	65 (18.5)	84 (19.7)	
3	167 (20.2)	77 (21.8)	88 (20.6)	
4	163 (19.5)	50 (14.2)	71 (16.6)	
5	169 (20.2)	81 (23.0)	88 (20.6)	
Medical history, n(%)				
Hypertension	427 (51.2)	215 (61.1)	241 (56.4)	0.005
Diabetes	225 (27.0)	106 (30.1)	157 (36.8)	0.002
CKD stage 4+	28 (3.4)	6 (1.7)	13 (3.0)	0.30
Chronic liver disease	9 (1.1)	0 (0)	<5* (<1.2)	0.14
Prior IHD	498 (59.7)	199 (56.5)	263 (61.6)	0.35
Prior MI	236 (28.3)	92 (26.1)	115 (26.9)	0.93
Prior revascularisation	173 (20.7)	76 (21.6)	69 (16.2)	0.006
ACS during index admission	612 (73.4)	224 (63.6)	275 (64.4)	<0.001
Diagnosis of AF before the index admission	533 (63.9)	297 (84.4)	340 (79.6)	<0.001
Prior bleeding event	121 (14.5)	62 (17.6)	81 (19.0)	0.099
Heart Failure	259 (31.1)	145 (41.2)	189 (43.6)	<0.001
Thromboembolism	20 (2.4)	11(3.1)	7 (1.6)	0.39
Ischaemic stroke	93 (11.2)	70 (19.9)	77 (18.0)	<0.001
PVD	93 (11.2)	54 (15.3)	42 (9.8)	0.045
CHA_2DS_2-VASc score, n (%)				<0.001
1-3	362 (43.4)	99 (28.1)	147 (34.4)	
4+	472 (56.6)	253 (71.9)	280 (65.6)	
Mean CHA_2DS_2-VASc score (SD)	3.8 (1.6)	4.5 (1.6)	4.3 (1.7)	<0.001
Prior prescriptions, n(%)				
Antiplatelet (aspirin and/or $P2Y_{12}$ antagonist)	489 (58.6)	115 (32.7)	140 (32.7)	<0.001
Aspirin	448 (53.7)	81 (23.0)	121 (28.3)	<0.001
$P2Y_{12}$ antagonist	148 (17.7)	43 (12.2)	32 (7.5)	<0.001
Oral AC	81 (9.7)	254 (72.1)	278 (65.1)	<0.001
VKA	72 (8.6)	225 (63.9)	233 (54.6)	<0.001
DOAC	9(1.1)	31 (8.8)	45 (10.5)	<0.001

ACS indicates acute coronary syndrome; IHD: Ischaemic heart disease; CKD: Chronic kidney disease; MI: myocardial infarction; PVD: peripheral vascular disease; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; AC: anticoagulant (VKA and/or DOAC); DAPT: dual antiplatelet therapy (combination of aspirin + $P2Y_{12}$ antagonist); OAC+AP: combination of oral anticoagulant (either warfarin or DOAC) + antiplatelet therapy (aspirin or $P2Y_{12}$ antagonist); TAT: combination of oral anticoagulant (either VKA or DOAC) + DAPT; AF: atrial fibrillation.. * Numbers <5 are suppressed due to governance restrictions with the SAIL databank.

During the one year follow up period, 48 (3.0%) patients had been readmitted for an ischaemic stroke, 189 (11.7%) for an ACS, and 124 (7.7%) had died. A total of 315 (19.5%) patients had either been readmitted for an ischaemic stroke or ACS or had died (supplementary table 6.3). During the same period 142 (8.8%) patients had been readmitted for a bleed. The event rate (per 100 patient years) for ischaemic stroke, ACS and death was 3.21 (95%CI 2.75-3.67), 13.47 (95%CI 12.50-14.46) and 8.16 (95%CI 7.43-8.90), respectively (combined outcome rate 22.71 (95%CI 21.4-23.99). The event rate for bleeding was 9.82 (95%CI, 8.99-10.64).

Nine patients experienced both a bleed and a stroke, of whom six had that bleed during the hospital admission for the stroke; in two patients the bleed occurred in a hospital admission prior to that of the stroke, and one patient the bleed occurred in an admission after the stroke. Twenty-four patients bled and had a hospital admission for an ACS, of whom eleven suffered both events during the same hospital admission; in three the bleed was documented during a prior hospital admission to that of the ACS and in ten the bleed was documented in an admission after the ACS. Twenty-three patients bled then died, 2 on the same date. The event rates (per 100 patient years) for stroke, ACS, death and the combination of these events were substantially higher amongst patients that bled (table 6.2).

Table 6.2 Adverse event rates during the first year follow up post-PCI			
	Event rate per 100 patient-years (95% confidence Interval)		
	Overall	Event rate amongst patients who did not bleed*	Event rate amongst patients who bled
Stroke	3.21 (2.75-3.67)	2.72 (2.29-3.16)	13.45 (8.96-17.93)
ACS	13.47 (12.50-14.46)	12.30 (11.34-13.26)	39.34 (31.31-47.37)
Death	8.16 (7.43-8.90)	7.25 (6.53-7.97)	32.78 (25.95-39.62)
Combined stroke, ACS or death	22.71 (21.4-23.99)	20.09 (18.86-21.32)	83.76 (71.67-95.86)
Bleeding	9.82 (8.99-10.64)	NA	NA
*Censoring occurred at time of stroke/ACS/death.			

Relationships between thromboembolic risk and adverse outcomes

Kaplan-Meier analyses showed that patients with a CHA_2DS_2-VASc score ≥4 (compared to those ≤3) were more likely to have a stroke ($p<0.001$), die ($p<0.001$) or bleed (<0.001), but the difference in the rate of ACS was not statistically different (p=0.055).

Relationships between antithrombotic regimen, thromboembolic risk and adverse outcomes

In the Kaplan-Meier analyses, antithrombotic strategy had no association with stroke (p=0.99), ACS (p=0.26), death (p=0.65), or the combination of these events (p=0.38) in those with a CHA_2DS_2-VASc ≤3 and ≥4 (supplementary figure 6.1a-e shows Kaplan-Meier analyses according to antithrombotic strategy in those with a CHA_2DS_2-VASc score ≤3 and ≥4). However antithrombotic regimen was associated with hospitalisation for bleeding events (p=0.002) with lowest bleeding risk seen in those on DAPT in both groups with CHA_2DS_2-VASc ≤3 and ≥4 (figures 6.1a-6e and supplementary figures 6.1a-i & supplementary table 6.3).

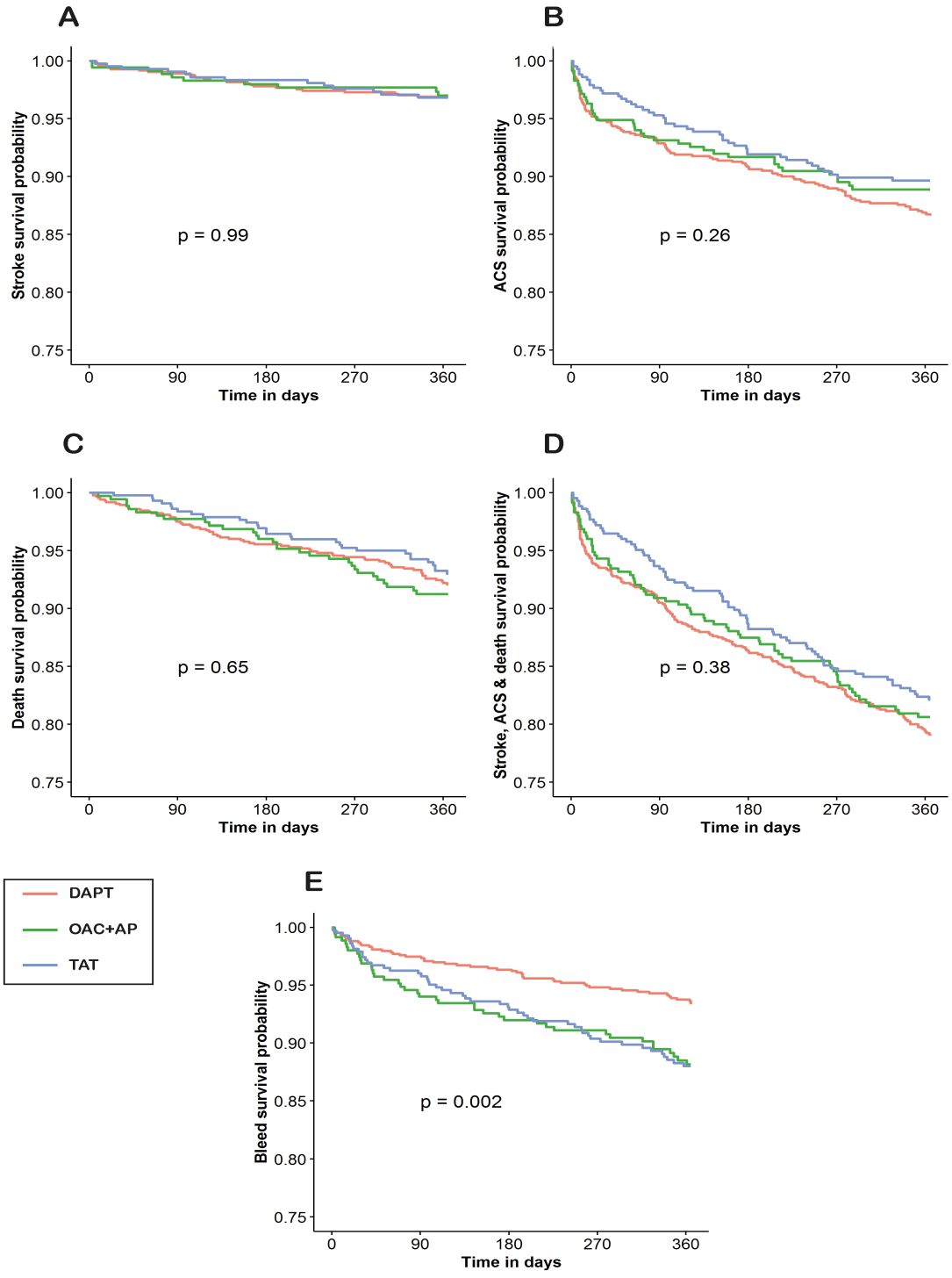


Figure 6.2 Kaplan-Meier estimate of the risk of (a) stroke, (b) ACS, (c) death and (d) combined outcome of stroke, ACS or death, and (e) bleeding event during the first 365 days post discharge, stratified by antithrombotic regimen.

Table 6.3 Multivariable Cox-proportional hazard models of characteristics associated with adverse outcomes

Variable*	Stroke HR (95%CI), *P*	ACS HR (95%CI), *P*	Death HR (95%CI), *P*	Stroke/ACS/ Death HR (95%CI), *P*	Bleed during follow up HR (95%CI), *P*
Bleed during follow up (time dependent)	4.40 (2.01-9.64), <0.001	2.73 (1.57-4.77),<0.001	3.43 (2.16-5.46), <0.001	3.22 (2.26-4.59), <0.001	NA
Antithrombotic regimen	-	-	-	-	-
Dapt	-	-	-	-	Reference, 0.011
OAC+AP	-	-	-	-	1.71 (1.13-2.59)
TAT	-	-	-	-	1.68 (1.14-2.49)
Age	-	-	1.07 (1.05-1.10), <0.001	1.04 (1.02-1.05), <0.001	1.04 (1.02-1.06), 0.001
Gender	-	-	-	-	-
Hypertension	-	-	-	-	-
Diabetes mellitus	-	-	-	-	1.66 (1.19-2.32), 0.003
CKD stage 4+	-	-	-	-	3.16 (1.76-5.67), <0.001
Chronic liver disease	-	-	-	-	-
Heart failure	2.30 (1.28-4.13), 0.005	-	2.40 (1.66-3.48), <0.001	1.59 (1.27-1.99), <0.001	1.45 (1.04-2.03), 0.03
PVD	-	-	-	1.61 (1.21-2.15), 0.01	-
Prior ischaemic stroke	5.48 (3.10-9.68), <0.001	-	-	-	-
Systemic thromboembolism	-	-	-	-	-
Presenting with ACS	-	1.79 (1.26-2.53), 0.001	-	-	-
Previous revascularisation	-	-	-	-	-
Prior bleeding events	NA	NA	NA	NA	1.52 (1.04-2.22), 0.03

*Only variables selected in the final model are presented.
ACS indicates acute coronary syndrome; PVD: peripheral vascular disease; CKD :Chronic kidney disease; DAPT: dual antiplatelet therapy (combination of aspirin + $P2Y_{12}$ antagonist); OAC+AP: combination of oral anticoagulant (either warfarin or DOAC) + antiplatelet therapy (aspirin or $P2Y_{12}$ antagonist); TAT: combination of oral anticoagulant (either VKA or DOAC) + DAPT

MULTIVARIABLE MODELLING

In multivariable Cox-proportional hazard models, bleeding during follow up was significantly associated with death [HR= 3.43, 95%CI (2.16-5.46), *P*<0.001], hospitalisations for stroke [HR=4.40 (2.01-9.64), <0.001] and ACS [HR= 2.73 (1.57-4.77), <0.001], and the combined outcome of stroke, ACS or death [HR=3.22 (2.26-4.59), <0.001] (table 6.3). After mutual adjustment antithrombotic therapy had no association with these outcomes. However, compared to DAPT, both OAC+AP [HR= 1.71 (1.13-2.59), 0.01] and TAT [1.68 (1.14-2.49), 0.01] were associated with bleeding risk.

AIC model selection resulted in selecting only one more variable for stroke and death, three more variable for ACS and the combined outcome of stroke, ACS and death and an exact match for bleeding. (supplementary tables 6.4 and 6.5).

DISCUSSION

In this real-world population-level study of patients with AF undergoing PCI, ischaemic events, hospitalisation for bleeding and all-cause mortality were common. Approximately one in five patients experienced a stroke, ACS or died during the first-year post-discharge. Bleeding events were also common. Notably, the rate of hospitalisation for stroke was almost five times greater, the rate of ACS over three times greater and death was more than four times greater amongst those who bled compared to those who didn't.

Hospitalisation for bleeding events during follow-up, modelled as a time dependent variable was strongly associated with stroke, ACS and death. In patients who had a combination of bleed and stroke or bleed and ACS, we note the bleeding event frequently occurred during that hospital admission for stroke and/or ACS. Bleeding is a recognised adverse consequence of antithrombotic therapy and is associated with a greater incidence of death and ischaemic events. [20, 21] Due to the nature of this real-world data it was not possible to determine the exact sequence of these haemorrhagic and ischemic events during follow up. The triggering of pro-thrombotic and pro-inflammatory responses following a bleed, with or without discontinuation of antithrombotic therapy, in addition to anaemia and/or shock in the case of more severe bleeds, may have led to a rebound increased risk of ischaemic events. Likewise, it is possible that administration of thrombolytic and/or antithrombotic therapy for the management of the stroke and/or ACS may have triggered the haemorrhagic event during that admission.

Patients prescribed OAC+AP or TAT were more likely to experience a bleed compared to those prescribed DAPT as were those with CKD stage 4+ and those with a history of prior bleeding events. Notably, adverse outcomes were predominantly driven by ACS and death with comparatively far fewer strokes, particularly in those with a CHA_2DS_2-VASc score of 1-3.

While there was a numerical decrease in ACS and death amongst those prescribed OAC+AP or TAT compared to DAPT there was no significant association.

Surprisingly we found no association between antithrombotic regimen and risk of stroke. However, this may be explained by differences in patient characteristics between antithrombotic treatment groups. Patients prescribed OAC+AP or TAT had higher CHA_2DS_2-VASc score including greater prevalence of the individual risk factors than DAPT; markers not just for increased stroke risk but also for increased risk of bleeding.[22] Notably, stroke outcomes were still similar on Kaplan-Meier analysis even when analyses were restricted to those with highest stroke risk (CHA_2DS_2-VASc ≥4, supplementary figure 6.1b).

Patients prescribed DAPT were marginally younger, were more likely to have presented with an ACS for the index PCI and were marginally less likely to have had a diagnosis of AF prior to the index admission. It is therefore possible that they had lower AF burden, but this is not possible to assess in this study.

In conducting the Cox-regressions we adjusted for antithrombotic regimen, risk factors and comorbidities. However, due to the nature of this type of analysis, unknown/unrecorded variables may influence these associations between treatment groups, stroke risk and outcomes.

During this study period we identified 25,690 patient who had undergone PCI from a population of Wales of ~3.1M, equating to a PCI rate of ~ 1,023/Million population, consistent with UK practice.[23] The proportion of patients undergoing PCI for an ACS indication (69%) is also consistent with contemporary UK practice. The prevalence of AF in the cohort undergoing PCI (11.2 % during the index admission and 10.8% of those discharged) is consistent with other reports.[24-26] The high prescription rate for DAPT is also consistent with previous reports[25] but not with guidelines; possibly reflecting the lack of definitive evidence on antithrombotic approach to this high risk cohort.

There are a number of limitations with the assigning of patients to antithrombotic regimens. It was not possible to determine the intended discharge antithrombotic regimen from hospital, therefore, antithrombotic regimens were therefore identified from prescriptions issued in the first 90 days post discharge from the index PCI (a period long enough to account for hospital discharge supply to have expired and a new prescription to be issued from primary care). As we did not apply a censoring period, adverse events occurring in the first 90 days may have resulted in amendment of the initial antithrombotic regimen. It was not possible to account for changes to the antithrombotic regimen or patient compliance during the follow-up period. Lastly, there was insufficient data to categorise by DOAC or Vitamin-K antagonist strategy or by aspirin/P2Y12 antagonist combination.

We excluded 347 patients from the final analysis who we could not identify being prescribed DAPT, OAC+AP or TAT. The majority of these patients were prescribed single OAC or AP and 96 where we couldn't identify any antithrombotic therapy (of which almost half had died within 90 days, therefore lacking follow data to assign antithrombotic therapy). Notably this group was less likely to have undergone prior revascularisation and less likely to have undergone the index PCI for an ACS (supplementary table 6.6). Inclusion of small individual treatment groups with heterogenous clinical factors would have likely of had limited validity and wider applicability to the general population.

Patients were grouped according to a CHA_2DS_2-VASc score of 1-3 and ≥4 to provide a balance between those with lower to intermediate risk of stroke to those with higher risk. Due to governance restrictions with the SAIL databank on reporting patient numbers <5, it would have not been possible to report outcomes in smaller groups, particularly where both death and stroke events were already low in CHA_2DS_2-VASc score<3 group and most notably in the small group with a CHA_2DS_2-VASc <2.

The HASBLED score was not calculated in this study for several reasons; INR results were not available (and INR control would not have applied to those prescribed DAPT only or DOAC based regimens); pathology results, alcohol and illicit drug use are less robustly documented in the WLGP datasets and non-steroidal anti-inflammatory are frequently purchased without a prescription in the UK. Finally, the HASBLED score, unlike CHA_2DS_2-VASc, is at least partially modifiable and likely to change throughout the study period. However, risk factors associated with increased risk of bleeding (present at or before the index PCI) were adjusted for in the multivariable analyses.

We documented hospitalisation for gastrointestinal bleeds; intracranial bleeds, urinary tract bleeds and airway bleeds in order to be consistent with previous studies,[27] but bleeding events occurring in other organ systems or bleeding events not resulting in hospitalisation may have had major clinical outcomes. The lack of an accepted standard for defining relevant bleeding events and defining their severity in real-world studies is a recognised limitation.

Similarly, there has been a lack of standardisation of bleeding definitions amongst the major RCTs that have investigated DOAC versus Vitamin K antagonist based TAT and OAC+AP strategies in patients with AF undergoing PCI or with a recent ACS.[8-11] The primary end-point in the AUGUSTUS trial[8] included major or 'clinically relevant bleeds'; in the PIONEER AF-PCI trial primary end point was a composite of major or minor bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria or 'bleeding requiring medical attention'[10], and in the RE-DUAL PCI trial and ENTRUST-AF PCI trials the endpoint was major or 'clinically nonmajor bleeding'. [9, 11]

The rate of bleeding events in these trials ranged from 10.5% to 17% with DOACs, and 14.7% to 26.7% with vitamin K antagonist treatment. In our study we observed a much lower overall bleed rate (8.8%) although we only considered hospitalisation for bleeding in order to focus on more clinically severe bleeds which would not have been possible with the further

inclusion of primary care documented bleeding outcomes. It is therefore uncertain how the addition of potentially less severe bleeding events to the analysis would have influenced the association between bleeding and stroke/ACS events or mortality, and beyond the scope of this study.

Despite the large numbers recruited to RCT's and included in previous real-word studies[28] they have remained underpowered to detect differences in ischaemic or thromboembolic outcomes or mortality between treatment strategies, as is the case with this study. Indeed, it was our main intention to review how these patients were being treated and document their clinical outcomes in relation to treatment strategy and key risk factors in order to understand the key determinants of adverse outcomes in routine clinical practice and to raise the profile of these issues and stimulate debate amongst the clinical community.

It is critical to note that a significant proportion of these patients bled, which was associated with a very high rate of cardiovascular events and death. Our data emphasises the critical importance of considering the expected incremental prognostic impact of PCI on ischaemic outcomes over conservative medical management in patients with AF, before committing them to an antithrombotic regimen that is not only associated with a high bleeding risk but with greatly increased risk of ischaemic events (eg stent thrombosis) if needing to be discontinued due to bleeding, which we observe is not uncommon and an important outcome.

In this study just under a third of patients underwent the index PCI for stable disease, which does not improve clinical outcomes for the majority of clinical indications.[29, 30] Furthermore, trials investigating PCI versus optimal medical therapy have not stratified results by AF or have actively excluded patients with indications for OAC.[31] In contemporary interventional practice, clinicians therefore have to consider the relative safety and efficacy of combination anti-platelet and anticoagulant regimens on the basis of ischaemic and bleeding

risk without definitive RCT evidence for guidance in both the acute and elective. PCI setting for each individual patient

To the best of our knowledge this is the first study that has looked at event rates stratified by stroke risk, antithrombotic therapy and evaluating the impact of bleeding events on stroke, ACS and death. The use of a large, data-rich, linked population data source is a particular strength. The linked primary and secondary care data held by SAIL enabled the investigation of a large cohort if individuals across multiple data sources giving a much more complete picture of patient treatment, risk factors and events over a 1-year period after PCI.

CONCLUSION

In this real-world study of a national cohort of patients with AF who had undergone PCI, adverse events in the year post discharge were common. Approximately one in five patients experienced a stroke, ACS or died during the first-year post-discharge. Bleeding events were also common and were associated with a five, three and four-fold increase risk of stroke, ACS and death. These data emphasise the importance of careful consideration of ischaemic and potential for bleeding complications prior to proceeding to PCI in patients with AF.

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Supplementary table 6.1 *ICD10* codes for major adverse outcomes

Diagnosis	Code	Description
ACS	I210	Acute transmural myocardial infarction of anterior wall
ACS	I211	Acute transmural myocardial infarction of inferior wall
ACS	I214	Acute subendocardial myocardial infarction
ACS	I213	Acute transmural myocardial infarction of unspecified site
ACS	I219	Acute myocardial infarctionunspecified
ACS	I212	Acute transmural myocardial infarction of other sites
ACS	I221	Subsequent myocardial infarction of inferior wall
ACS	I228	Subsequent myocardial infarction of other sites
ACS	I220	Subsequent myocardial infarction of anterior wall
ACS	I229	Subsequent myocardial infarction of unspecified site
ACS	I249	Acute ischaemic heart diseaseunspecified
ACS	I200	Unstable angina
Stroke	I630	Cerebral infarct due to thrombosis of precerebral arteries
Stroke	I633	Cerebral infarction due to thrombosis of cerebral arteries
Stroke	I638	Other cerebral infarction
Stroke	I634	Cerebral infarction due to embolism of cerebral arteries
Stroke	I632	Cereb infarct due unsp occlusion or stenos precerebrl arts
Stroke	I636	Cereb infarct due cerebral venous thrombosisnonpyogenic
Stroke	G458	Other transient cerebral ischaemic attacks and related synd
Stroke	G459	Transient cerebral ischaemic attackunspecified
Stroke	I635	Cerebrl infarct due unspec occlusion or stenos cerebrl arts
Stroke	I639	Cerebral infarctionunspecified
Stroke	I631	Cerebral infarction due to embolism of precerebral arteries
Stroke	I653	Occlusion and stenosis of multip and bilat precerebrl arts
Stroke	I652	Occlusion and stenosis of carotid artery
Stroke	I658	Occlusion and stenosis of other precerebral artery
Stroke	I651	Occlusion and stenosis of basilar artery
Stroke	I650	Occlusion and stenosis of vertebral artery
Stroke	I659	Occlusion and stenosis of unspecified precerebral artery
Stroke	I64X	Strokenot specified as haemorrhage or infarction
Stroke	I661	Occlusion and stenosis of anterior cerebral artery
Stroke	I660	Occlusion and stenosis of middle cerebral artery
Stroke	I668	Occlusion and stenosis of other cerebral artery
Stroke	I662	Occlusion and stenosis of posterior cerebral artery
Stroke	I669	Occlusion and stenosis of unspecified cerebral artery
Stroke	I663	Occlusion and stenosis of cerebellar arteries
Stroke	I664	Occlusion and stenosis of multiple and bilat cerebrl arts
Haemorrhage	R31X	Unspecified haematuria
Haemorrhage	K270	Peptic ulceracute with haemorrhage
Haemorrhage	K254	Gastric ulcerchronic or unspecified with haemorrhage
Haemorrhage	K280	Gastrojejunal ulceracute with haemorrhage
Haemorrhage	K250	Gastric ulceracute with haemorrhage
Haemorrhage	R049	Haemorrhage from respiratory passagesunspecified
Haemorrhage	N028	Recurrent and persistent haematuriaother
Haemorrhage	R042	Haemoptysis
Haemorrhage	R040	Epistaxis
Haemorrhage	R041	Haemorrhage from throat
Haemorrhage	J942	Haemothorax
Haemorrhage	N029	Recurrent and persistent haematuriaunspecified
Haemorrhage	R048	Haemorrhage from other sites in respiratory passages

Haemorrhage	K264	Duodenal ulcerchronic or unspecified with haemorrhage
Haemorrhage	K260	Duodenal ulceracute with haemorrhage
Haemorrhage	K920	Haematemesis
Haemorrhage	K922	Gastrointestinal haemorrhageunspecified
Haemorrhage	K921	Melaena
Haemorrhage	I690	Sequelae of subarachnoid haemorrhage
Haemorrhage	I691	Sequelae of intracerebral haemorrhage
Haemorrhage	I692	Sequelae of other nontraumatic intracranial haemorrhage
Haemorrhage	I602	Subarachnoid haemorrhage from anterior communicating artery
Haemorrhage	I604	Subarachnoid haemorrhage from basilar artery
Haemorrhage	I603	Subarachnoid haemorrhage from posterior communicating artery
Haemorrhage	I608	Other subarachnoid haemorrhage
Haemorrhage	I605	Subarachnoid haemorrhage from vertebral artery
Haemorrhage	I629	Intracranial haemorrhage (nontraumatic)unspecified
Haemorrhage	I607	Subarachnoid haemorrhage from intracranial arteryunspec
Haemorrhage	I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
Haemorrhage	I609	Subarachnoid haemorrhage unspecified
Haemorrhage	I606	Subarachnoid haemorrhage from other intracranial arteries
Haemorrhage	I601	Subarachnoid haemorrhage from middle cerebral artery
Haemorrhage	I611	Intracerebral haemorrhage in hemispherecortical
Haemorrhage	I616	Intracerebral haemorrhagemultiple localized
Haemorrhage	I612	Intracerebral haemorrhage in hemisphereunspecified
Haemorrhage	I610	Intracerebral haemorrhage in hemispheresubcortical
Haemorrhage	I619	Intracerebral haemorrhageunspecified
Haemorrhage	I613	Intracerebral haemorrhage in brain stem
Haemorrhage	I615	Intracerebral haemorrhageintraventricular
Haemorrhage	I618	Other intracerebral haemorrhage
Haemorrhage	I614	Intracerebral haemorrhage in cerebellum

Supplementary table 6.2 Combinations of antithrombotic therapy.	
DAPT , N=834	Aspirin + Clopidogrel N= 704 Aspirin + Prasugrel N=52 Aspirin + Ticagrelor M= 78
OAC+AP, N = 353	VKA+ Aspirin N= 88 VKA + Clopidogrel N=199 VKA + Ticagrelor N=5 DOAC+ Aspirin N=16 DOAC+$P2Y_{12}$ antagonist* N=44
TAT, N=427	VKA+Aspirin+Clopidogrel= 321 VKA+Aspirin+Prasugrel= 7 VKA+Aspirin+Ticagrelor=10 DOAC+Aspirin+ $P2Y_{12}$ antagonist*=89
Other antithrombotic regimens that were excluded N= 347	DOAC only= 20 VKA only=65 Aspirin only = 106 $P2Y_{12}$ antagonist only* = 59 No antithrombotic therapy = 96
*Clopidogrel and ticagrelor numbers have been grouped due to restrictions in SAIL that suppress numbers <5.	

Supplementary table 6.3 Kaplan Meier estimates of patient outcome in the year post discharge

CHA_2DS_2-VASc score	Drug therapy	Number of patients	Patient outcomes				
			Stroke N **(%)**	ACS N **(%)**	Death N **(%)**	Stroke/ACS /Death N **(%)**	Bleed N **(%)**
1-3	DAPT	362	5 **(1.4)**	40 **(11.0)**	*	51 **(14.1)**	11 **(3.0)**
1-3	OAC+AP	99	0 **(0)**	7 **(7.1)**	*	10 **(10.1)**	7 **(7.1)**
1-3	TAT	147	0 **(0)**	13 **(8.8)**	*	16 **(10.9)**	10 **(6.8)**
1-3	Overall	608	5**(1.4)**	60 **(9.9)**	18 **(3.0)**	77 **(12.7)**	28 **(4.6)**
≥4	DAPT	472	20 **(4.2)**	68 **(14.4)**	55 **(11.7)**	122 **(25.8)**	42 **(8.9)**
≥4	OAC+AP	253	10 **(4.0)**	31 **(12.3)**	26 **(10.3)**	57 **(22.5)**	33 **(13.0)**
≥4	TAT	280	13 **(4.6)**	30 **(10.7)**	25 **(8.9)**	59 **(21.1)**	39 **(13.9)**
≥4	Overall	1005	43 **(4.3)**	129 **(12.8)**	106 **(10.5)**	238 **(23.7)**	114 **(11.3)**
All patients	Total	1613	48 **(3.0)**	189 **(11.7)**	124 **(7.7)**	315 **(19.5)**	142 **(8.8)**
*Number <5 are suppressed due to governance restrictions with the SAIL data providers.							

Supplementary table 6.4 Multivariable Cox-proportional hazard models of characteristics associated with adverse outcomes. Models selected using AIC.

Variable*	Stroke HR (95%CI), *P*	ACS HR (95%CI), *P*	Death HR (95%CI), *P*	Stroke/ACS/ Death HR (95%CI), *P*	Bleed during follow up HR (95%CI), *P*
Bleed during follow up (time dependent)	4.02 (1.83-8.84), 0.001	2.36 (1.34-4.15), 0.003	3.40 (2.14-5.41), <0.001	3.29 (2.31-4.70), <0.001	NA
Antithrombotic regimen	-	-	-	-	-
Dapt	-	-	-	Reference, 0.033	Reference, 0.011
OAC+AP	-	-	-	0.76 (0.57-1.00), 0.055	1.71 (1.13-2.59), 0.01
TAT	-	-	-	0.73 (0.55-0.96). 0.023	1.68 (1.14-2.49), 0.01
Age	1.04 (1.01-1.08), 0.02	1.02 (1.00-1.04), 0.01	1.07 (1.05-1.10), <0.001	1.04 (1.02-1.05), <0.001	1.04 (1.02-1.06), 0.001
Gender	-	-	-	-	-
Hypertension	-	-	-	-	-
Diabetes mellitus	-	-	-	-	1.66 (1.19-2.32), 0.003
CKD stage 4+	-	1.81 (0.97-3.36), 0.06	-	-	3.16 (1.76-5.67), <0.001
Chronic liver disease	-	-	-	-	-
Heart failure	2.09 (1.16-3.77), 0.015	-	2.36 (1.63-3.42), <0.001	1.64 (1.31-2.06), <0.001	1.45 (1.04-2.03), 0.03
PVD			1.77 (1.15-2.74), 0.09	1.61 (1.21-2.15), 0.01	-
Prior ischaemic stroke	4.96 (2.80-8.81, <0.001	-	-	1.33 (1.00-1.75), 0.047	-
Systemic thromboembolism	-	-	-	-	-
Presenting with ACS	-	1.83 (1.28-2.60), 0.001	-	1.33 (1.03-1.72), 0.037	-
Previous revascularisation		1.49 (1.07-2.07), 0.018			
Prior bleeding events	NA	NA	NA	NA	1.52 (1.04-2.22), 0.03

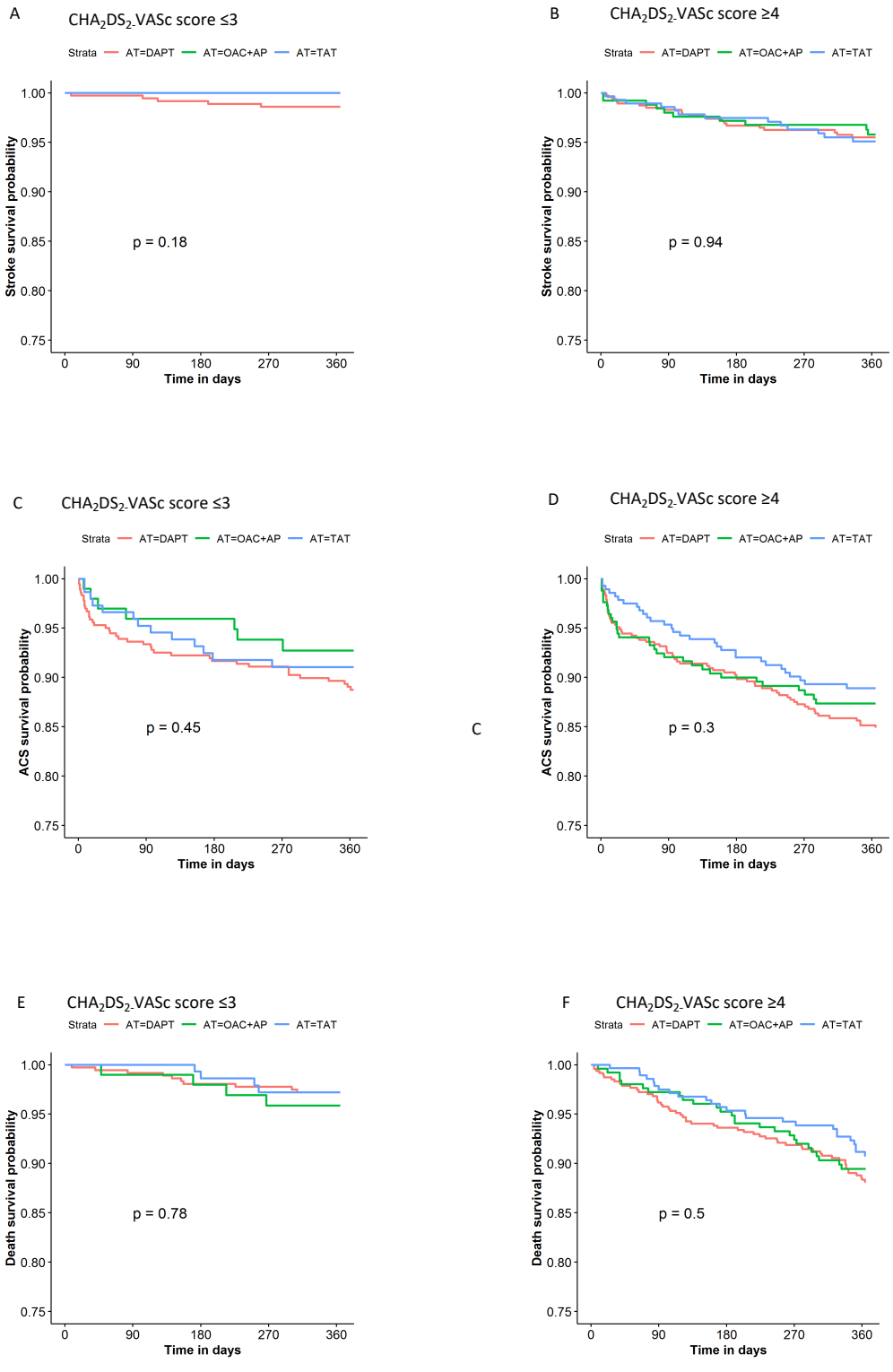
*Only variables selected in the final model using the AIC are presented.

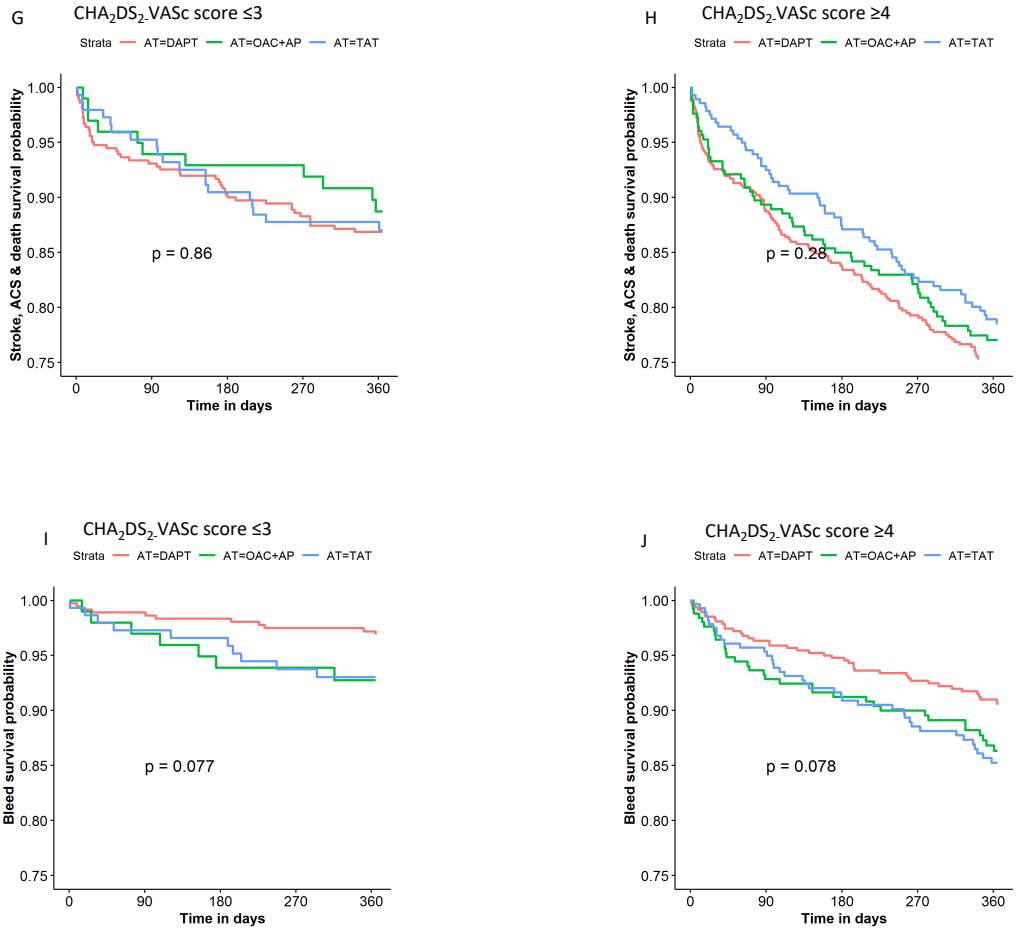
Supplementary table 6.5 Comparison of BIC and AIC selection criteria for multivariable Cox regression models for adverse outcomes

	Stroke		ACS		Death		Stroke/ACS/ Death		Bleed during follow up	
	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC
Bleed during follow up (time dependent)	√	√	√	√	√	√	√	√	NA	NA
Antithrombotic regimen								√	√	√
Age		√		√	√	√	√	√	√	√
Gender										
Hypertension										
Diabetes mellitus									√	√
CKD stage 4+	√	√		√					√	√
Chronic liver disease										
Heart failure					√	√	√	√	√	√
PVD						√	√	√		
Prior ischaemic stroke	√	√						√		
Systemic thromboembolism										
Presenting with ACS			√	√				√		
Previous revascularisation				√						
Prior bleeding events	NA	NA	NA	NA	NA	NA	NA	NA	√	√
Match between BIC and AIC	93%		79%		93%		79%		100%	

Supplementary table 6.6 Cohort characteristics between those included prescribed DAPT, OAC+AP or TAT and those not included prescribed other antithrombotic regimens

	Cohort analysed N= 1614			*Cohort excluded*	
Variable	DAPT N= 834	OAC+AP N=352	TAT N=427	*Other treatment N= 347*	*P* value (between subject effects)
Age. Mean (SD), p	71.8 (10.2)	74.4 (8.2)	72.9 (8.5)	75 (10.0)	<0.001
Gender (M)	591 (70.9)	244 (69.3)	334 (78.2)	234 (67.4)	0.004
Deprivation index					0.849
1	151 (18.6)	71 (20.6)	79 (19.3)	62 (17.9)	
2	163 (20.0)	65 (18.9)	84 (20.5)	59 (17.0)	
3	167 (20.5)	77 (22.4)	88 (21.5)	69 (19.9)	
4	163 (20.0)	50 914.5)	71 (17.3)	67 (19.3)	
5	169 (20.8)	81 (23.5)	88 (21.5)	74 (21.3)	
Obese	230 (27.6)	121 (34.4)	156 (36.5)	90 (25.9)	<0.001
Hypertension	427 (51.2)	215 (61.1)	241 (56.4)	178 (51.3)	0.008
Diabetes	225 (27.0)	106 (30.1)	157 (36.8)	106 (30.5)	0.005
CKD stage 4+	28 (3.4)	6 (1.7)	13 (3.0)	15 (4.3)	0.252
Prior IHD	498 (59.7)	199 (56.5)	263 (61.6)	115 (33.1)	0.036
Prior MI	236 (28.3)	92 (26.1)	115 (26.9)	56 (16.1)	0.002
Prior revascularisation	173 (20.7)	76 (21.6)	69 (16.2)	46 (13.3)	0.005
ACS during index admission	612 (73.4)	224 (63.6)	275 (64.4)	130 (37.5)	<0.001
Diagnosis of AF before index admission	533 (63.9)	297 (84.4)	340 (79.6)	274 (79.0)	<0.001
Prior bleeding event	121 (14.5)	62 (17.6)	81 (19.0)	81 (23.3)	0.003
Heart Failure	259 (31.1)	145 (41.2)	189 (43.6)	129 (37.2)	<0.001
Thromboembolism	20 (2.4)	11(3.1)	7 (1.6)	5 (1.4)	0.375
Ischaemic stroke	93 (11.2)	70 (19.9)	77 (18.0)	60 (17.3)	<0.001
Vascular disease	93 (11.2)	54 (15.3)	42 (9.8)	40 (11.5)	0.102
CHA_2DS_2-VASc score mean (SD)	3.8 (1.6)	4.5 (1.6)	4.3 (1.7)	4.3 (1.6)	<0.001
CHA_2DS_2-VASc score					<0.001
1-3	362 (43.4)	99 (28.1)	147 (34.4)	104 (30.0)	
4+	472 (56.6)	253 (71.9)	280 (65.6)	243 (70.0)	
Prior prescriptions					
Aspirin	448 (53.7)	81 (23.0)	121 (28.3)	117 (33.7)	<0.001
P2Y12	148 (17.7)	43 (12.2)	32 (7.5)	43 (12.4)	<0.001
Antiplatelet	489 (58.6)	115 (32.7)	140 (32.7)	144 (41.5)	<0.001
VKA	72 (8.6)	225 (63.9)	233 (54.6)	98 (28.2)	<0.001
Oral AC	81 (9.7)	254 (72.1)	278 (65.1)	6 (1.7)	<0.001
DOAC	9 (1.1)	31 (8.8)	45 (10.5)	20 (5.8)	<0.001


A
CHA2DS2-VASc score ≤3
Strata AT=DAPT AT=OAC+AP AT=TAT
Stroke survival probability
p = 0.18
Time in days
B
CHA2DS2-VASc score ≥4
Strata AT=DAPT AT=OAC+AP AT=TAT
Stroke survival probability
p = 0.94
Time in days
C
CHA2DS2-VASc score ≤3
Strata AT=DAPT AT=OAC+AP AT=TAT
ACS survival probability
p = 0.45
Time in days
C
D
CHA2DS2-VASc score ≥4
Strata AT=DAPT AT=OAC+AP AT=TAT
ACS survival probability
p = 0.3
Time in days
E
CHA2DS2-VASc score ≤3
Strata AT=DAPT AT=OAC+AP AT=TAT
Death survival probability
p = 0.78
Time in days
F
CHA2DS2-VASc score ≥4
Strata AT=DAPT AT=OAC+AP AT=TAT
Death survival probability
p = 0.5
Time in days



Supplementary figure 6.1 Kaplan-Meier estimates of the risk of (a&b) stroke, (c&d) ACS, (e&f) death and (g&h) combnined outcome of stroke, ACS or death, and (i&j) bleeding event during the first 365 days post discharge, stratified by antithrombotic regimen and CHA_2DS_2-VASc score

CHAPTER 7.

CONCLUDING REMARKS

Within this thesis I have identified gaps in the provision of evidenced based medicine and described the adverse outcomes amongst patients with IHD and AF. The use of large, data-rich, individually linked datasets, spanning multiple data sources, has provided a detailed and more complete picture of patient characteristics and treatment than many previous studies.

In this thesis I described the rate and adverse consequences of discontinuation of $P2Y_{12}$ antagonists in a post PCI population. The incorporation of the cardiac intervention dataset and discharge prescribing datasets into the core SAIL datasets allowed us to identify intended duration of treatment. The ~ 6% rate of discontinuation was much lower than previously presented in the literature (~50%) where intended treatment duration was not known. This study refines our understanding of post PCI antiplatelet discontinuation. Identifying the intended duration of treatment at discharge allowed me to identify patients who had truly discontinued therapy, and accurately describe both patient characteristics and the adverse consequences of early discontinuation.

The inclusion of bleeding as a time dependent variable in the investigation of adverse outcomes with discontinuation $P2Y_{12}$ antagonists post-PCI and amongst patients with AF who had undergone PCI was an important and novel element to these studies. In both studies, bleeding was independently and highly associated with adverse CV outcomes and death.

Assessing the prescribing of LLT and achievement of 2016 and the updated 2019 ESC/EAS guideline lipid targets provided a useful 'barometer' of post-PCI CVD risk management and described the implications at a population level in meeting updated targets. With just under half of patients meeting the 2016 guideline target LDL-C levels and fewer than

a quarter were below 2019 targets, we have demonstrated the gap between guideline recommendations and real-world management.

The SAIL Warfarin Out of Range Descriptors Study (SWORDS) study was the first publication to assess INR control according to NICE consensus defined poor INR control at a population level. This study showed that poor INR control was common with 43% of patients having at least one marker of poor INR control, and amongst those with an acceptable TTR (>65%) one quarter still had unacceptably low or high INR levels according to NICE criteria. This highlighted both the importance of identifying variability of INR control as well as TTR control when using the NICE guideline definition of poor INR control and the extent of poor INR control in the population.

The SAIL AF Bleeding Risk Evaluation (SABRE) study improved our understanding of the association between poor INR control and bleeding events. In this study assessing the temporal presence of poor INR control on bleeding events using NICE and ESC definitions of poor INR control, the percentage of time spent in poor control was 34.0% and 40.9% respectively. Periods of poor INR control according to NICE (HR=1.38 [1.31-1.46], <0.001) and ESC (HR=1.42 [1.34-1.50], <0.001) were independently associated with an increased bleeding risk.

Both SWORDS and SABRE were developed from a large national cohort with extensive longitudinal follow up and are amongst the largest studies of INR control. However, the robustness of these studies and the novel addition to the existing literature lies in both the methodology as well as the population size. The testing of temporal INR control and allowing patients to “move between” poor and adequate INR control during the prospective analysis, coupled with a conservative approach to excluding periods where there was insufficient INR data allowed us to test the association between INR control immediately before a bleed. This

provided an important improvement over previous studies that reported associations between bleeding events and historic INR control, often calculated years before an event.

At the time of submission of this Ph.D. thesis, the analyses within the SABRE study were being updated to include the investigation of the association between INR control and stroke and systemic embolism. Pending reviewer's response to SABRE these data may be combined into one publication.

The published data from both SWORDS (full manuscript) and SABRE (presented as an abstract at time of thesis submission) have been used to support the work of the Welsh 'Stop a Stroke Campaign', and work undertaken by the Welsh the Cardiac Network on stroke prevention. This work has also informed the cross-party coalition on stroke prevention within Welsh Government. For the issue of posterity, it is worth noting that SWORDS was published in November 2019 and SABRE was first presented in abstract form to the European Society of Cardiology Heart and Stroke conference in January 2020. Shortly after this the COVID-19 pandemic was upon us. In the last few months (time of writing July 2020) we have seen large numbers of patients who were previously prescribed warfarin being switched to DOACs in order to reduce patient contact and opportunity for transmission of the virus. At a local level at least, data from these publications has supported clinical pathway development for identification and prioritising of patients who should be considered for alternative therapy.

The final results chapter in this thesis addressed the question of clinical outcomes in relation to antithrombotic management in patients with AF undergoing PCI for treatment of both acute and chronic coronary syndromes. With limited publications and the focus of research and discussion limited to the use of DOAC vs VKA based antithrombotic regimens, our data provides a valuable addition to this field. This study highlighted the far higher rate of adverse outcomes in this group and in particular the higher rate amongst patients who bled.

This emphasises the importance of assessing bleeding risk and careful balance of bleeding risk vs potential therapeutic benefit before undertaking PCI and committing patients to an antithrombotic regimen that is not only associated with a high risk of bleeding but with an increased risk of ischaemic events if needing to be discontinued due to bleeding.

I have endeavoured to present the relevant limitations with the respective chapters. However, an issue not addressed so far is that of veracity of clinical coding and data linkage within SAIL. As mentioned in the introduction, ICD-10 and OPCS-4 codes are entered by clinical coders from information contained in the medical record. Less than 1% of medical records are externally audited, although there is a high rate of internal audit and validation. This is a universal limitation for all real-world research that relies on the use of data that has been collected for clinical and administrative purposes. While it was not possible to validate hospital clinical coding, it was reassuring that all patients who we identified in the cardiac intervention database were coded as having undergone PCI during the same admission within the SAIL PEDW datasets. Fewer than 1% of patients did not have a matched record within SAIL and these were largely accounted for due to a lack of NHS registered number, and/or were domicile outside of Wales.

Throughout this thesis I have detailed the patient characteristics of those most likely to experience adverse events and those least likely to be adhering to guidelines or targets. These data presented within this thesis can potentially be used to aid improvement at both individual and population level. For example, in the post PCI cohort (chapter two), adverse events were highest amongst those who discontinued antithrombotic therapy and/or bled. Notably those most likely to discontinue were those individuals who had previously undergone revascularisation; possibly describing a ‘revolving door’ of poor adherence and repeated revascularisation and worse overall outcomes.

Post-PCI prescribing of high intensity statin and adjuvant lipid lowering therapy was poor, as were achievement of guideline lipid targets. Female patients and those who had undergone elective PCI were less likely to have lipids checked and when checked were less likely be at target. Furthermore, while diabetics were more likely to have achieved guideline LDL-C they were less likely to achieve non-HDL-C targets, highlighting the importance of this measure amongst the diabetic population.

SWORDS and SABRE demonstrated the paradox of those at the highest risk of stroke a priori being most likely to have poor INR control and were also the most likely to bleed.

These data presented within this thesis can be used to identify individuals or groups that may benefit from closer monitoring or consideration of alternative treatment strategies. At a population level our data demonstrates the potential for improvement of patient care and outcomes. These findings have identified the potential to improve patient outcomes and are already being used to that effect.