

Universidade de Lisboa

Faculdade de Farmácia



Anticoagulation management for postoperative atrial fibrillation after cardiothoracic surgery

Maria Miguel Pinto da Silva

Mestrado Integrado em Ciências Farmacêuticas

2017

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**Monografia de Mestrado Integrado em Ciências Farmacêuticas
apresentada à Universidade de Lisboa através da Faculdade de Farmácia**

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2017



Barts Health
NHS Trust

O projeto apresentado na presente monografia resulta do acordo bilateral estabelecido entre a Faculdade de Farmácia da Universidade de Lisboa e o Hospital St. Bartolomew sediado em Londres, ao abrigo do Programa Erasmus+. Este projeto teve a supervisão e orientação do Professor Sotiris Antoniou e Jagjot Chahal.

Resumo

Introdução: A fibrilhação auricular (FA) é a arritmia sustentada mais comum na prática clínica e está associada ao aumento da mortalidade e morbidade, assim como a hospitalizações frequentes e à redução da qualidade de vida. A fibrilhação auricular pós-operatória (FAPO) é uma variante da FA clássica que se caracteriza pelo diagnóstico de um novo caso de FA, habitualmente auto-limitada, após realização de cirurgia-major (tipicamente cardíaca) em doentes que se encontravam em ritmo sinusal previamente ao procedimento cirurgico e sem historial clínico prévio desta arritmia. Estima-se que a FAPO ocorra em cerca de 30% das cirurgias-major.

Neste sentido, a terapêutica anticoagulante é essencial como profilaxia para o acidente vascular cerebral, sendo que tanto os anticoagulantes orais não antagonistas da vitamina K (NACOs) (apixabano; dabigatrano; edoxabano; rivaroxabano) como os antagonistas da vitamina K (AVK) (varfarina; acenocumarol) se revelam eficazes na prevenção do acidente vascular cerebral na fibrilhação auricular.

Embora a varfarina seja amplamente usada na prática clínica, a sua eficácia está dependente da manutenção da percentagem de tempo no intervalo terapêutico a um nível superior a 65%. Por sua vez, os NACOs revelam-se como uma alternativa à varfarina, sendo referidos como opção preferencial nos normativos das mais reconhecidas sociedades de cardiologia. No entanto, o tempo ideal para iniciar a terapêutica com estes agentes no período pós-operatório carece de investigação, devido à exclusão desta população dos ensaios clínicos randomizados de fase III.

Desta forma, no âmbito do programa Erasmus, este projeto foi desenvolvido durante os três meses em que tive a oportunidade de integrar o Departamento de Farmácia do Hospital St. Bartholomew sediado em Londres, Reino Unido. Tendo sido proposto pelo responsável deste departamento, este estudo teve como objetivo aprofundar o conhecimento relativamente ao tratamento ótimo e efetivo com anticoagulantes orais e, em última análise, permitir a otimização, eficácia e segurança destes agentes. Além disso, refletindo o importante papel do farmacêutico enquanto membro integrado numa equipa multidisciplinar de profissionais de saúde, este projeto permitiu de igual forma, a promoção da discussão com cirurgiões, médicos e enfermeiros acerca do potencial de possíveis mudanças a adotar futuramente na prática clínica de modo a garantir uma melhor gestão da FAPO, e consequentemente proporcionar os melhores cuidados em saúde a estes utentes.

Objetivos: Este estudo teve como propósito comparar a gestão da terapêutica anticoagulante oral na fibrilhação auricular pós-cirurgia cardiotorácica.

Deste modo, foram formuladas quatro questões de investigação:

1. Qual percentagem de pacientes prescritos com varfarina que demonstrou um tempo no intervalo terapêutico superior a 65%, seis semanas após a alta hospitalar?
2. Qual é a dosagem adequada de NACOs no período pós-operatório?
3. Qual é o momento ideal para iniciar terapêutica com NACOs no período pós-operatório?
4. Os anticoagulantes orais foram descontinuados nos doentes que revelaram reversão para ritmo sinusal seis semanas após a alta hospitalar?

Assim, tendo como ponto de partida as questões supracitadas, foram definidos os seguintes objetivos específicos para este estudo:

- i) Avaliar a eficácia da varfarina no período pós-operatório;
- ii) Investigar as tendências e padrões na prática clínica em relação à NACOs (*i.e.*, escolha do NACO prescrito, dosagem, período pós-operatório de iniciação terapêutica);
- iii) Esclarecer as características envolvidas na hipótese de considerar a redução da dose de NACOs, bem como o prazo ideal para iniciar a terapêutica com estes fármacos no período pós-operatório;
- iv) Identificar o número de doentes que revertem para ritmo sinusal (RS) seis semanas após a cirurgia cardiotorácica;
- v) Analisar as taxas de descontinuação de anticoagulantes orais, quando é verificada a reversão para RS.

Métodos: Foi conduzido um estudo ambiespectivo em doentes que desenvolveram fibrilhação auricular pós operatória entre janeiro de 2016 e janeiro de 2017.

O estudo compreendeu duas fases distintas; Uma retrospectiva e uma prospectiva (desenho ambiespectivo). As informações presentes nos registos médicos dos utentes submetidos a cirurgia entre os dias 1 de janeiro de 2016 e 31 de janeiro de 2017 foram avaliadas retrospectivamente para determinar a amostra de interesse para estudo com base nos critérios de elegibilidade definidos. Foram igualmente consultados retrospectivamente os

registos de distribuição da farmácia e os relatórios de controlo de stocks para identificar todos os doentes com prescrições de varfarina ou novos anticoagulantes orais nas alas cardiotorácicas durante o período de coleção de dados. Foram assim constituídos dois coortes de exposição, de acordo com o subgrupo farmacoterapêutico adotado (AVK vs NACO).

Foram analisados os registos de prescrição de fármacos e notas médicas eletrónicas, a fim de seleccionar de entre os pacientes prescritos com estes anticoagulantes orais, os que foram dispensados do hospital com um diagnóstico confirmado de fibrilhação auricular pós-operatória. Dados demográficos, historial médico e estudos laboratoriais foram analisados.

Foram definidas como variáveis de interesse, os valores de tempo no intervalo terapêutico especificamente para o grupo-varfarina; o NACO prescrito, respetiva dose e dia de início da terapêutica no período pós-operatório para o grupo-NACO; CHA₂DS₂-VASc score, tendo sido realizada a estratificação de risco para tromboembolismo e acidente vascular cerebral para ambas as coortes através da análise dos fatores de risco individuais.

A fase prospetiva decorreu desde 31 de Janeiro até 28 de abril de 2017 e serviu para recolher os dados das consultas de follow-up, realizadas em média cerca de seis semanas após cirurgia no Hospital St. Bartolomew. Através da consulta deste dados obteve-se assim informação sobre a reversão para ritmo sinusal (ou não), a consequente descontinuação dos anticoagulantes orais.

Os valores de *International Normalized Ratio* (INR) que estão na origem do cálculo do tempo no intervalo terapêutico foram obtidos através de contactos estabelecidos com as clínicas de anticoagulação onde estes utentes realizavam as mediações do INR. Estes valores foram obtidos prospetivamente para os doentes que continuaram a terapia com varfarina e consequente monitorização de INR coincidente com a fase prospetiva do estudo.

Os dados recolhidos foram analisados recorrendo a estatística descritiva univariada e bivariada. Os dados discretos são apresentados como frequências absolutas e relativas, enquanto que os dados contínuos são apresentados através da tendência central e medidas de dispersão, incluindo média, mediana e desvio padrão. A análise bivariada serviu para comparar as características dos utentes das duas coortes de doentes expostas aos dois diferentes tratamentos e verificar se as características dos doentes, nomeadamente o seu perfil de risco de AVC ou risco hemorrágico, poderiam justificar a sua inclusão num ou noutro grupo farmacoterapêutico. Dado o tamanho amostral e a distribuição não-normal dos dados, foram seleccionados testes não-paramétricos; o chi-quadrado e a sua extensão pelo teste Exacto de Fisher foram utilizados para analisar dados categóricos e o teste Wilcoxon

Mann-Whitney para analisar dados contínuos. O intervalo de confiança considerado foi de 95%. Todos os dados foram analisados usando o IBM Statistical Software Package for Social Sciences (SPSS, versão 24).

O protocolo deste estudo foi aprovado pela Comissão de Ética do Hospital St. Bartolomew, sob o número 8021.

Resultados: Sessenta e quatro utentes desenvolveram fibrilhação pós-operatória, dos quais 39 (60.9%) e 25 (39.1%) foram medicados com varfarina e NACOs, respetivamente.

Foram obtidos 27 dados de valores de tempo no intervalo terapêutico (69% dos medicados com varfarina), sendo que 14 doentes (52%) demonstraram valores de tempo no intervalo terapêutico inferiores a 65%, refletindo fraco controlo e pouca eficácia da terapêutica anticoagulante com varfarina.

No que concerne à iniciação de NACOs no período pós-operatório, foi revelado que a terapêutica com estes anticoagulantes teve início, em média, 8.36 ± 3.74 dias após realização do procedimento cirúrgico.

Relativamente à reversão para RS, 22 doentes (62.9%) do grupo da varfarina e 13 doentes (65.0%) do grupo dos NACOs tinham revertido para RS seis semanas após a alta hospitalar. De entre estes doentes, um total de 14 (40.0)% descontinuou os anticoagulantes orais após confirmação de ritmo sinusal.

Conclusões: Alcançar um tempo no intervalo terapêutico superior a 65% revela-se desafiante e difícil de alcançar no que diz respeito à terapêutica com varfarina, sendo tal facto demonstrado pela proporção de pacientes que demonstraram valores que expressam a baixa eficácia deste agente, ainda que eventualmente resultante da sua utilização em contexto real onde questões associadas ao estilo de vida, inclusivamente alimentares e de adesão à terapêutica, poderão influenciar profundamente a capacidade de autogestão do doente.

Deste modo, os anticoagulantes orais não antagonistas da vitamina K, iniciados oito dias após cirurgia cardiorácica, podem constituir uma alternativa mais efetiva na trombopprofilaxia associada à fibrilhação auricular. No entanto, será prudente confirmar estes dados em amostras de maior dimensão dadas as limitações deste exercício académico.

Estudos adicionais devem igualmente ser realizados de modo a estabelecer a dose ideal, bem como o período apropriado para iniciar a terapêutica anticoagulante com estes agentes na fase aguda do pós-operatório.

Palavras-chave: Fibrilhação auricular pós-operatória, cirurgia cardiotorácica, anticoagulantes orais, varfarina, anticoagulantes orais não antagonistas da vitamina K.

Abstract

Background: Oral anticoagulation is essential following post-operative atrial fibrillation. Although warfarin is commonly used, its efficacy is dependent on the achievement of a time in therapeutic range above 65%. Non-vitamin K oral anticoagulants are an alternative option, however the optimal time to initiate post-operatively is unknown, due to 'recent surgery' often being cited as an exclusion criteria within phase III clinical trials.

Purpose: To compare the management of oral anticoagulation for stroke prevention in postoperative atrial fibrillation after cardiothoracic surgery.

Methods: An ambispective study was conducted at large tertiary centre analysing patients that developed postoperative atrial fibrillation after cardiothoracic surgery from January 2016 to January 2017 reviewing both patient and surgical data.

Results: Sixty-four patients developed postoperative atrial fibrillation, of which 39 (60.9%) and 25 (39.1%) were prescribed warfarin and non-vitamin K oral anticoagulants (NOACs), respectively. 14 (51.9%) patients had a confirmed time in therapeutic range below 65%, reflecting poor anticoagulant control with warfarin. NOACs were initiated on an average of 8.36 ± 3.74 days post-operatively. 22 (62.9%) patients in the warfarin group and 13 (65.9%) patients in the NOAC group were confirmed to be in sinus rhythm six weeks after discharge. Among these patients, 14 (40.0%) stopped the anticoagulation after restoration of sinus rhythm, of which were more likely to continue if were receiving a NOAC.

Conclusion: Whilst warfarin is commonly initiated for post-operative atrial fibrillation, a time in therapeutic range below 65% for warfarin shows that acute optimal anticoagulation management is difficult to achieve, especially for the short term patients that revert back in to sinus rhythm. NOACs may possibly be a more effective alternative, initiating eight days post operatively. However further studies need to be conducted to ensure optimal dose of these agents as well as the ideal timeframe to initiate anticoagulation in the acute post-operative phase.

Keywords: Cardiothoracic surgery, stroke prevention, post-operative atrial fibrillation, non-vitamin K oral anticoagulants (NOAC), warfarin, oral anticoagulants

Acknowledgements

I would first like to express my gratitude to Professor Sotiris Antoniou for giving me the opportunity of doing my research work at St. Barts Hospital. His vast knowledge, expertise, support and understanding, added considerably value to my academic experience.

Very special thanks to Jagjot Chahal who accompanied my work very closely and worked actively to provide me with the time and the support to pursue our goals in this project.

I must also acknowledge all of the team from the Pharmacy Department with whom I have had the pleasure to work during my stay in London. Their support, kindness and advices gave me the will to work harder and made me enjoy to the most my Erasmus+ period. Further, their role as Pharmacists and Pharmacy Technicians and the way all of them work together toward a common vision is truly an inspiration that I will remember as such an amazing example during my working days as a future Pharmacist.

I would like to thank Professor Filipa Alves da Costa and Professor Ana Paula Martins for supporting me since the beginning of this journey and for establishing the contacts that allowed this programme to happen. It was through their encouragement, understanding and kindness that I had the opportunity to do the Erasmus Programme in such a respectable and highly regarded place. Their assistance at all levels of this research project and their guidance in the redaction of this report were crucial to complete this thesis.

Finally, I must express my very profound gratitude to my parents and to my sister for providing me with unfailing support and continuous encouragement throughout my years of study. They are my ultimate role models. Thank you. *Obrigada*.

Abbreviations and Acronyms

AF	Atrial fibrillation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
BID	bis in die
BNF	British National Formulary
CABG	Coronary artery bypass graft
CHA ₂ DS ₂ -VASc	Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)
CHADS ₂	Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)
CI	Confidence interval
CrCl	Creatinine clearance
CT	Cardiothoracic
ECG	Electrocardiogram/electrocardiography
EHRA	European Heart Rhythm Association
ENGAGE AF	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation
ESC	European Society of Cardiology
GFR	Glomerular filtration rate
HAS-BLED	Hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (65 years), drugs/alcohol concomitantly (1 point each)
HEMORR ₂ HAGES	Hepatic or renal disease, ethanol abuse, malignancy history, older age 75, reduced platelet count/function/antiplatelet, rebleeding risk (scores double), hypertension (uncontrolled), anaemia, genetic factors, excessive fall risk, stroke history
INR	International normalized ratio
LVEF	Left ventricular ejection fraction
MV Repair	Mitral valve repair
NHS	National Health Service
NICE	National Institute for Care and Health Excellence
NOAC	Non-vitamin K antagonist oral anticoagulant

OAC	Oral anticoagulation/oral anticoagulant
ORBIT AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
POAF	Postoperative atrial fibrillation
QD	quaque die
RELY AF	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
SR	Sinus rhythm
tAVR	Tissue aortic valve repair
TIA	Transient ischaemic attack
tMVR	Tissue mitral valve repair
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

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Introduction

Postoperative atrial fibrillation (POAF) is defined as new onset of atrial fibrillation (AF) (usually self-terminating) after major surgery, typically cardiac, in patients who were in sinus rhythm before surgery and had no prior history of AF⁽¹⁾. It develops in approximately 30% of cardiothoracic surgical patients and it is associated with an increased risk of mortality and morbidity, predisposes patients to a higher risk of stroke, requires additional treatment, and increases the costs of the post-operative care.⁽²⁾

Thromboembolic events represent one of the most catastrophic complications of AF and without anticoagulation the annual stroke risk is estimated to be between 1.9% and 18.2% depending on comorbidities.⁽³⁾ Based on this, anticoagulation is indicated to reduce the risk of stroke and while deciding on the optimal anticoagulation strategy, the risk of bleeding in these patients must be weighed against the potential benefit derived from decreasing the stroke risk, and the usually self-limited nature of POAF.⁽³⁾

In this context, warfarin continues to be widely used in clinical practice and although it has shown to reduce the risk of stroke by 60%⁽⁴⁾, its efficacy is dependent on achieving a time in therapeutic range (TTR) above 65%⁽⁵⁾, which it is proven to be challenging to attain. Further, warfarin has multiple limitations related to its narrow therapeutic window combined with many drug–drug and drug–food interactions, necessitating regular coagulation monitoring and dose adjustments.⁽⁶⁾

In order to overcome some of these limitations, four non-vitamin K antagonists (NOACs) – dabigatran, rivaroxaban, apixaban and edoxaban – have been approved as options for the prevention of stroke and systemic embolism in patients with non-valvular AF.^(7–10) These agents have been demonstrated to be as safe and effective as warfarin⁽¹¹⁾ being now the preferred option in european guidelines.⁽¹²⁾

When compared to warfarin, NOACs offer several advantages with their rapid onset of action, short half-life, less drug interactions, no dietary interaction, and fixed dose response without the need for monitoring.⁽¹³⁾ However, the phase III clinical trials assessing their use in AF excluded patients with recent surgery within 30 days.^(14–17) Consequently, the existing guidelines on POAF management and stroke prevention for cardiac surgical patients are still primarily extrapolated from studies involving nonsurgical atrial fibrillation patients.⁽¹⁸⁾ As a result, besides considerable variation among AF guidelines there is also a large gap regarding practical guidance on an anticoagulation strategy for specific patients who develop atrial fibrillation during the post-operative period. Notably, several questions remain

unanswered and uncertainty exists on several aspects, such as: the minimal duration of POAF required to trigger initiation of OAC in the cardiac surgical population and more specifically the ideal timeframe to initiate anticoagulant therapy with NOACs; the adequate dose of NOACs in the postoperative period and if it is required dose adjustments in the acute period after surgery, as well as the optimal duration for which anticoagulation must be continued after cessation of POAF. Thus, precise practical guidelines in the early postoperative period are imperative in order to take maximal advantage of these drugs, ensuring optimal efficacy and safety.

Given the background, the present study, conducted at St. Barts Hospital in London, United Kingdom, aims to address some of these key management questions for cardiac surgical patients with POAF.

In this thesis some aspects of the state of the art of atrial fibrillation are stated in **Chapter 1**. The context, objectives and research questions of this study are described in **Chapter 2**. The methods used in this study are described in **Chapter 3**. The main results are presented in **Chapter 4**. The discussion of the findings is presented in **Chapter 5** and, finally, the main conclusions are highlighted in **Chapter 6**.

1. Atrial Fibrillation

1.1. Clinical types of atrial fibrillation

Based on presentation, duration and termination of the arrhythmia, AF can be divided into five different patterns: First diagnosed, Paroxysmal, Persistent, Long-standing persistent and permanent AF.⁽¹⁹⁾

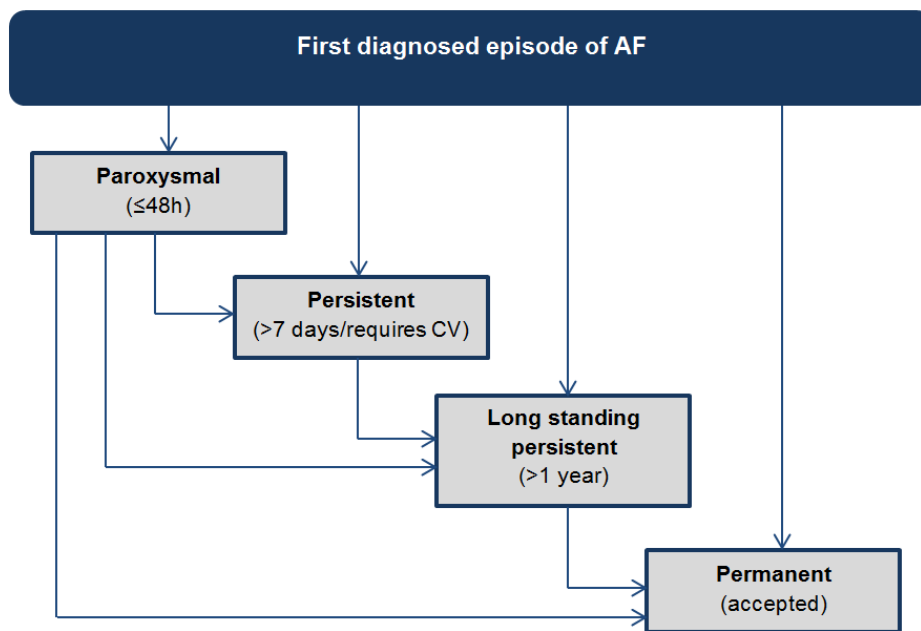


Figure 1.1 - Clinical patterns of atrial fibrillation

There are multiple potential mechanisms behind AF that can vary between patients showing the same AF pattern, resulting in different clinical types of this arrhythmia. Hence, considering some of the major drivers of AF, such as lifestyle factors, genetics or cardiac and systemic comorbidities, as a result of different and not completely understood pathophysiological mechanisms, it is possible to distinguish some of the clinical types of AF⁽¹⁹⁾ (Table 1).

Table 1 – Clinical types and presentation of atrial fibrillation ⁽¹⁹⁾

AF Type	Clinical Presentation
AF secondary to structural heart disease	AF in patients with LV systolic or diastolic dysfunction, long-standing hypertension with LVH, and/or other structural heart disease. The onset of AF in these patients is a common cause of hospitalization and a predictor of poor outcome.
Focal AF	Patients with repetitive atrial runs and frequent, short episodes of paroxysmal atrial fibrillation. Often highly symptomatic, younger patients with distinguishable atrial waves (coarse AF), atrial ectopy, and/or atrial tachycardia deteriorating in AF.
Polygenic AF	AF in carriers of common gene variants that have been associated with early onset AF.
Post-operative AF	New onset of AF (usually self-terminating) after major surgery (typically cardiac) in patients who were in sinus rhythm before surgery and had no prior history of AF.
AF in patients with mitral stenosis or prosthetic heart valves	AF in patients with mitral stenosis, after mitral valve surgery and in some cases other valvular disease.
AF in athletes	Usually paroxysmal, related to duration and intensity of training.
Monogenic AF	AF in patients with inherited cardiomyopathies, including channelopathies.

AF denotes atrial fibrillation; LV, left ventricle, LVH left ventricular hypertrophy

1.2. Diagnosis and detection of atrial fibrillation

To date, there are many hundreds of thousands of patients with AF who are currently unaware, untreated and at substantially elevated risk of suffering a stroke. The early diagnosis of AF performs a vital role and is associated with an increased range of treatment options, some of which have been demonstrated to eliminate AF permanently.⁽²⁰⁾

The current gold standard test used to detect AF is a 12-lead ECG interpreted by a cardiologist. Other tests that can be used may involve alternative types of ECGs read by a general practitioner (GP) in combination with preliminary pulse palpation carried out by a healthcare professional.⁽²¹⁾

Guidelines suggest that the first step in AF detection should be pulse palpation, since the presence of an irregular pulse is a clinical sign that can be quickly, simply and reliably elicited in any healthcare situation.⁽²²⁾

Moreover, pulse palpation is a vital opportunity to detect AF in general practice. Hence, one way to improve the detection of AF is to identify opportunities in clinical practice to be proactive in screening for AF, for example, by adding a simple pulse check to existing protocols for established clinics such as hypertension, weight management, asthma, chronic obstructive pulmonary disease (COPD), spirometry, cardiovascular and diabetes clinics.⁽²³⁾

In fact, Screening for Atrial Fibrillation in the aged (SAFE) study, reported that opportunistic screening using pulse palpation in high-risk patients including the elderly, followed by recording an electrocardiogram is as effective as systematic screening using ECG interpretation.⁽²⁴⁾ Identification of those with undiagnosed atrial fibrillation is important, as these patients can receive treatment sooner if opportunistic case finding is undertaken using manual pulse palpation in those presenting with symptoms commonly associated with atrial fibrillation.⁽²²⁾ In this context, NICE guidelines recommend performing manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying atrial fibrillation in people presenting with any of the following symptoms: breathlessness/dyspnea, palpitations, syncope/dizziness, chest discomfort, stroke/transient ischemic attack.⁽²⁵⁾

When an irregular pulse has been detected, an ECG must be performed in all people, whether symptomatic or not. Definitive diagnosis of AF thus requires rhythm documentation using an electrocardiogram (ECG) showing the typical pattern of AF: Absolutely irregular RR intervals and no discernible, distinct P waves⁽¹²⁾.

Paroxysmal AF may not be detectable unless an event is occurring at the time of the pulse check or ECG. Therefore, detecting Paroxysmal AF is as important as detecting persistent AF, but more challenging.⁽²⁶⁾ Based on this fact, in people with suspected paroxysmal atrial fibrillation undetected by standard ECG recording, recommendations rely on the use of 24-hour ambulatory ECG monitor in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart and on the use of an event recorder ECG in those with symptomatic episodes more than 24 hours apart.⁽²⁵⁾

Echocardiography has also an important role in the assessment of atrial fibrillation. Transthoracic echocardiography (TTE) allows rapid, safe, relatively comprehensive assessment of cardiac structure and function that can help to define the underlying aetiology of AF and the risk of complications⁽²⁷⁾. Therefore it is recommended to perform a TTE when a rhythm-control strategy that includes cardioversion is being considered; when there is a high risk or a suspicion of underlying structural/functional heart disease that influences their subsequent management or in whom refinement of clinical risk stratification for antithrombotic therapy is needed.⁽²⁵⁾

A more accurate evaluation of valvar lesions, especially prosthetic dysfunction, is possible by Transoesophageal echocardiography (TOE) and alternative thromboembolic sources can be readily identified, including complex atheroma of the ascending thoracic aorta and arch.⁽²⁷⁾

Although this is a safe procedure, it is not indicated for all patients in AF, being generally performed when TTE demonstrates an abnormality that warrants further specific assessment; in whom TTE is technically difficult or of questionable quality and where there is a need to exclude cardiac abnormalities for whom TOE cardioversion is being considered⁽²⁵⁾

Figure 1 summarizes the basic steps referred in current guidelines as the standard care for AF detection.

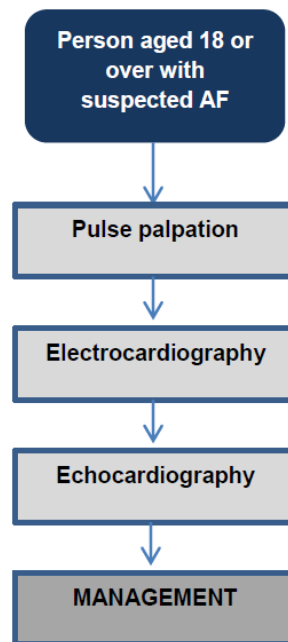


Figure 1 – Pathway for the detection and diagnosis of atrial fibrillation

1.3. Stroke and bleeding risk in atrial fibrillation

1.3.1. Clinical scores for stroke risk assessment: CHADS₂ and CHA₂DS₂-VASc

Several recognized risk factors such as congestive heart failure, hypertension, advanced age, diabetes, and previous stroke have been used to develop stroke risk stratification schemes for AF, with CHAD₂ and CHA₂DS₂-VASc being the most commonly used to quantify the risk of stroke in AF patients.⁽²⁸⁾

The CHADS₂ Score was published in 2001 and it was formed by combining two other preexisting stroke-risk schemes, Atrial Fibrillation Investigators (AFI)⁽²⁹⁾ and Stroke Prevention in AF (SPAF)⁽³⁰⁾ schemes⁽¹⁷⁾. Including independent risk factors that were proven to increase the risk of stroke, CHADS₂ was formed by assigning 1 point each for the

presence of congestive heart failure, hypertension, age 75 or older and diabetes mellitus and by scoring 2 points for previous stroke or transient ischemic attack.⁽³¹⁾

Although the CHADS₂ scoring system provided a sensitive and easy way to predict the risk of stroke in AF patients, the system placed a large number of patients in the low (score 0) and intermediate (score 1) categories.⁽³²⁾

Therefore, in 2010, CHA₂DS₂-VASc Score was published with the rationale that other risk assessment schema omit important risk factors, have low predictive ability, and categorize too many patients as intermediate risk, leaving the choice of anticoagulant or antiplatelet therapy to the discretion of the clinician.⁽³³⁾ By reclassifying and incorporating additional new risk factors not previously identified in CHADS₂, CHA₂DS₂-VASc includes vascular disease (prior MI, peripheral arterial disease, or aortic plaque), age 65–74 and gender category (female) in its scoring system.⁽³⁴⁾

This score has showed an improvement in predictive value for thromboembolism over the CHADS₂ schema, with low event rates in low-risk subjects and the classification of only a small proportion of subjects into the intermediate-risk category.⁽³⁴⁾

International guidelines recommend the use of CHA₂DS₂-VASc score to estimate the stroke risk in AF patients. Furthermore, according to the guidance present in ESC guidelines a CHA₂DS₂-VASc score of 1 or more for men, and 2 or more for women are a predictor for the benefit of anticoagulation for these patients.⁽³⁵⁾ The 2014 American Heart Association/ American College of Cardiology/ Heart Rhythm Society (AHA/ACC/HRS) guidelines also endorse the use of this score to assess the risk of stroke and in this guidance OAC prophylaxis is recommended for patients with a score of 1, whereas OAC use is a definite recommendation for patients with a score of 2 or greater and for those with a history of stroke or transient ischemic attack.⁽³⁶⁾

Risk factor	CHADS ₂ Score	CHA ₂ DS ₂ -VASc Score
Congestive heart failure/ left ventricular dysfunction	1	1
Hypertension	1	1
Age ≥ 75 years	1	2
Diabetes mellitus	1	1
Stroke/transient ischemic attack/thromboembolism	2	2
Vascular disease (previous myocardial infarction, peripheral artery disease, aortic plaque)	NA	1
Age 65-74 years	NA	1
Sex category (female)	NA	1

Figure 2 - Clinical scores for stroke risk assessment: CHADS₂ and CHA₂DS₂-VASc

1.3.2. Clinical scores for bleeding risk assessment: HEMORR₂HAGES and HAS-BLED

In the management of POAF and chronic AF, the risk of stroke must be balanced against the risk of bleeding when considering anticoagulation strategies. ⁽³²⁾

With the aim of support clinical decision making regarding antithrombotic therapy for stroke prevention and reduce the bleeding events in patients with AF, predictive models for bleeding have been developed. These include HAS-BLED and HEMORR₂HAGES scoring systems.

In 2006, HEMORR₂HAGES was proposed and combined several bleeding risk factors previously identified: hepatic or renal disease, ethanol abuse, malignancy, older (age > 75 years), reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors (CYP 2C9 single nucleotide polymorphisms), excessive fall risk (including neuropsychiatric disease) and stroke. Based on the relative risks and the predictable value of each factor, all bleeding risk factors weight 1 point, except for a prior bleed that scores 2 points. ⁽³⁷⁾

Risk factor	HEMORR ₂ HAGES Score
Hepatic or renal disease (1 point each)	1 or 2
Ethanol Abuse	1
Malignancy	1
Older age (>75 years)	1
Reduced platelet number or function	1
<u>Rebleeding</u>	2
Hypertension	1
Anemia	1
Genetic factors	1
Excessive fall risk	1
Stroke	1

Figure 3 – HEMORR₂HAGES Score for bleeding risk assessment

In 2010, a new practical risk score to estimate the 1-year risk for major bleeding was developed and validated in a cohort of real-world 3450 patients with AF.⁽³⁸⁾

HAS-BLED score is a simple bleeding risk tool representing each of the following common bleeding risk factors and assigning 1 point for the presence of each: hypertension (uncontrolled systolic blood pressure >160 mm Hg), abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile INRs, elderly, and concomitant drugs and/or alcohol excess. This score ranges from 0 to 9, with scores of ≥3 indicating high risk of bleeding, for which caution and regular review of the patient are recommended.

Risk factor	HAS-BLED Score
Hypertension	1
Abnormal liver or renal function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Elderly (> 65 years)	1
Drugs or Alcohol (1 point each)	1 or 2

Figure 4- HAS-BLED Score for bleeding risk assessment

This score has been validated in several cohort studies and has shown to perform better in predicting bleeding complications than other risk scores, also suggesting its powerful predictive value for major bleeding risk prediction in high-risk AF.^(39–41)

In addition, HAS-BLED is more user friendly in comparison with other bleeding scores and is made up of clinical information that is routinely available before therapy is initiated (with the exception of INR values), thereby making it more clinically applicable.⁽⁴²⁾

The use of HAS-BLED score is recommended in the ESC guidelines as well as the Canadian Cardiovascular Society guidelines and the 2014 NICE guidelines. The AHA/ACC/HRS guidelines and the JCS guidelines 2014 have also introduced the specific contents of the HAS-BLED score and implied the importance of the score.⁽⁴³⁾

Overall, bleeding risk schema offer a starting point for physicians to consider bleeding when initiating or continuing long-term OAC in AF patients, and to think about potentially correctable risk factors, for example, in the case of the HAS-BLED score, by treating

uncontrolled blood pressure, improving anticoagulation control labile INRs (if on VKAs) or stopping concomitant aspirin use.⁽⁴⁴⁾

1.4. Oral Anticoagulants for stroke prevention in Post-operative AF

1.4.1. Vitamin K Antagonist: Warfarin

For many decades, the vitamin K antagonists (VKAs) have been the only oral anticoagulant drugs available for clinical use for the primary and secondary prevention of venous and arterial thromboembolic events. VKAs may include warfarin, acenocoumarol, or phenprocoumon, but warfarin is the most common oral vitamin K antagonist utilized worldwide.⁽⁴⁵⁾

Warfarin is indicated for prophylaxis and treatment of venous thrombosis; prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation as well as for the reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.⁽⁴⁶⁾

Currently, the level of anticoagulation with warfarin is expressed as the International Normalised Ratio (INR), which is derived from the ratio between the actual prothrombin time and that of a standardized control serum.⁽¹⁾ Indeed, the efficacy of warfarin depends on maintenance of the INR within the designated therapeutic range. For instance, the available evidence indicates a higher incidence of ischemic stroke in patients with nonvalvular AF with insufficient anticoagulation (INR<2), and a higher incidence of bleeding events in overanticoagulated patients with nonvalvular AF (INR>3).⁽⁴⁷⁾ Therefore, based on achieving a balance between stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2.0–3.0 is the likely optimal range for prevention of stroke and systemic embolism in patients with non-valvular AF⁽¹⁾.

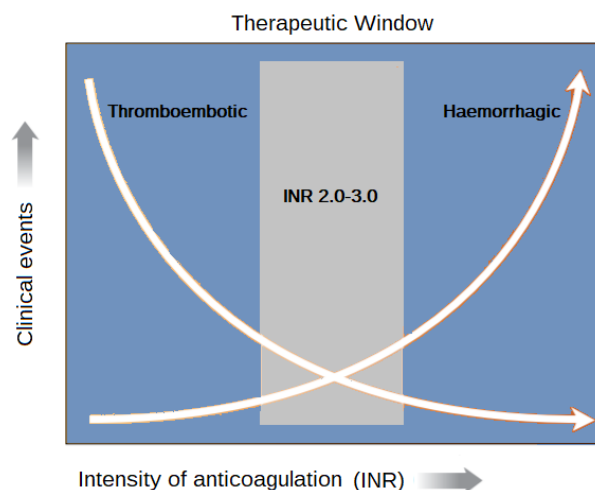


Figure 5- Balancing the risk of VKAs therapy

Time in Therapeutic Range (TTR) is also commonly used to evaluate the quality of warfarin therapy and is an important tool for assessing the risks versus benefits of warfarin therapy. TTR estimates the percentage of time a patient's INR is within the desired treatment range or goal and is widely-used as an indicator of anticoagulation control.⁽⁴⁸⁾ Therefore, according to NICE guidelines, a TTR below 65% is a reflection of poor anticoagulation control with warfarin.⁽⁵⁾ Additionally, based on evidence, once TTR falls below 40% there is no significant difference in terms of overall mortality when comparing treatment with warfarin versus treatment without warfarin (**Figure 6**).⁽⁴⁹⁾

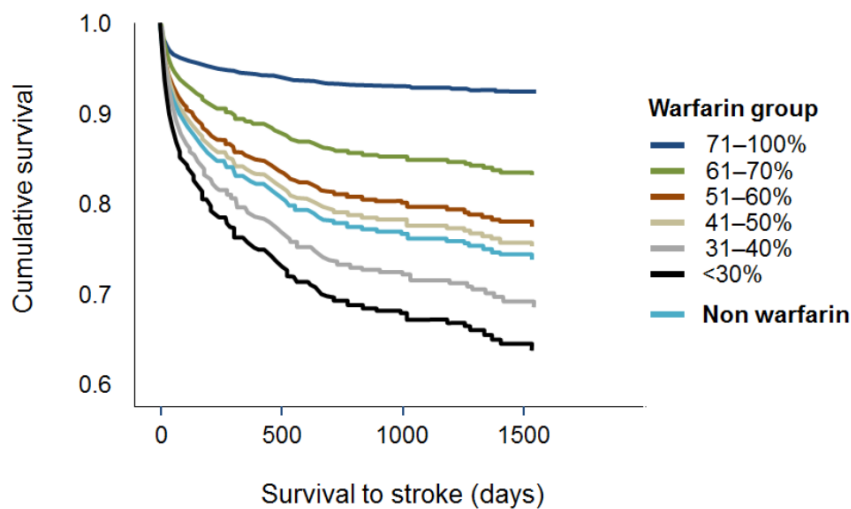


Figure 6- Survival to post atrial-fibrillation stroke by level of INR control expressed in TTR.
Findings from Morgan CL et al. study assessing the outcomes associated with INR control in a cohort of AF patients anticoagulated with warfarin.

Multiple meta-analyses of randomized and real-world studies have been performed in order to estimate the quality of INR control in AF populations receiving VKAs.^(47,50,51) These meta-analyses have demonstrated poor INR control with TTRs and proportion of INR measurement in range typically below 60% and nearly twice the amount of time being spent below versus above the therapeutic INR range.⁽⁵²⁾ Moreover, TTR had a significant relationship with adverse outcomes, including major haemorrhage and thromboembolic rates, supporting the reporting of TTR as the optimal measure of INR control.⁽⁵¹⁾

Based on its narrow therapeutic range and on the difficulty to attain a TTR above 65%, warfarin requires regular coagulation monitoring and consequent dose adjustments in some patients to keep the anticoagulation intensity within the therapeutic range. Furthermore, control of INR is affected by a large number of problems inherent to vitamin K antagonists that are heavily influenced by drug-drug and food-drug interactions, alcohol consumption, hepatic dysfunction, genetic variation in enzyme activity, and dietary intake of vitamin K.⁽⁵³⁾ The combination of all these factors can have a significant impact on patients' daily lives,

such as considerable time spent in the clinic for coagulation monitoring and dietary restrictions, all of which may reduce patients' quality of life.⁽⁶⁾

1.4.2. Non-vitamin K Antagonist: NOACs

Although the efficacy of warfarin and other VKAs has been proven, the low and suboptimal use has led to the development of NOACs⁽⁵⁴⁾, overcoming some of the limitations with VKA therapy and expanding the therapeutic options for primary and secondary stroke prevention in patients with nonvalvular AF (NVAf)⁽⁵⁵⁾.

In simplified terms the NOACs act at either of two specific levels of the clotting cascade. Dabigatran is a direct thrombin inhibitor, whereas apixaban, rivaroxaban and edoxaban are direct factor X (Xa) inhibitors.⁽⁵⁶⁾ Therefore, direct targeting of factor Xa or thrombin allows for a rapid onset of anticoagulation effect, expected to begin two hours following the first dose; as well as a fast onset of action with the loss of anticoagulant effect within 24 hours after discontinuation of these drugs.⁽⁵⁷⁾

NOACs have predictable pharmacokinetics and pharmacodynamics and a lower potential for food and drug interactions. These agents can, therefore, be given at fixed dosing schedules without the need for dietary restrictions or routine coagulation monitoring.⁽⁶⁾

All NOACs are partially eliminated via the kidney. Therefore, the assessment of kidney function is important to estimate their clearance from the body.⁽⁵⁸⁾ Based on these properties, apixaban, edoxaban and rivaroxaban^(7,8,10) are not recommended in patients with AF who have CrCl <15 mL/min and dabigatran⁽⁹⁾ is contraindicated in patients with CrCl <30 mL/min. However, there are no effectiveness and safety outcome data for NOACs in patients with advanced CKD (CrCL<30 mL/min), and the current ESC Guidelines recommend against their use in such patients.⁽⁵⁸⁾

NOACs are also contraindicated in patients with mechanical heart valves. The outcomes of the RE-ALIGN trial that assessed dabigatran vs. warfarin in patients with mechanical valves reinforced the recommendations of the current guidelines against the use of NOACs in these patients, since this trial had to be terminated prematurely due to an excess of thromboembolic and bleeding events among patients receiving dabigatran (150, 220 or 300 mg twice daily).

NOACs are all substrates of P-glycoprotein (Pgp), a transport protein present in enterocytes and the liver which reduces the bioavailability of its substrates.⁽⁵⁷⁾ Hence, even if the potential for drug–drug interactions is less with NOACs compared to VKA, there is still a significant potential for interactions and caution is required when they are coadministered with drugs such as verapamil, amiodarone and dronedarone.⁽⁵⁹⁾ By contrast, drug–food interactions are

not expected with the new anti-Xa anticoagulants as vitamin K intake does not influence their mechanism of action.⁽⁵⁷⁾

Unlike VKAs, the main limitation of NOACs is the lack of available specific reversal agents. Thus, specific reversal agents for NOACs are urgently needed especially in cases of emergency surgery or life-threatening bleeding.⁽⁶⁰⁾

1.4.3. Current guidelines on the management of post-operative AF

In order to support clinicians in the management of atrial fibrillation, a multitude of evidence-based guidelines has been created by major cardiovascular societies such as the Canadian Cardiovascular Society (CCS), the European Society of Cardiology (ESC) and Heart Rhythm Society (HRS) as well as the American College of Cardiology (ACC) and American Heart Association (AHA)⁽⁶¹⁾.

Although, these societies have continued to publish updated recommendations regularly, reflecting the rapid progress in AF understanding and therapeutic options, there is still a gap regarding the use of OAC in POAF proving that more specific recommendations concerning type, timing and duration of early postoperative anticoagulation deserve study and need to be determined.

In fact, to date, a limited number of studies assessed anticoagulation in patients with POAF and most of them were retrospective and had short-term follow up⁽⁶²⁾. Moreover, NOACs have not been specifically tested in patients with POAF, as patients with recent cardiac surgery were excluded in the large randomised trials of NOACs versus warfarin.⁽⁶³⁾

Although many of the recommendations of the various societies are similar, there are important differences in the methodologies underlying their development and the specific content.

Previous AHA/ACC guidelines stated that POAF lasting longer than 48 hours warranted anticoagulation, but this recommendation was removed from the newest update.⁽⁶⁴⁾ Interestingly, the AHA/ACC/HRS guidelines published in 2014, only refer that it is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients.⁽⁶⁵⁾

In contrast, in 2011, comprehensive CCS guidelines on the management of POAF were published, stating that anticoagulation is recommended for patients with AF prolonged for more than 72h, and also, once initiated, anticoagulation should be continued for six weeks.⁽⁶⁶⁾ CCS justifies this guidance, mentioning that this recommendation places a higher value on minimizing the risk of thromboembolic events and a lower value on the potential for postoperative bleeding. Because the risk of postoperative bleeding decreases with time, the

benefit-to-risk ratio favours a longer period without anticoagulation in the postoperative setting than that suggested in other settings.

In 2014, AATS published new guidelines providing a range of on the prevention and treatment of AF for thoracic surgical procedures. This evidence-based guideline has more specific recommendations regarding anticoagulation in the postoperative period, not only referring that anticoagulation should be considered if POAF last for more than 48h, but having also in consideration the features involved in the choice of the oral anticoagulant in this setting.⁽⁶⁷⁾

The ESC guidelines for the management of atrial fibrillation published in 2010 recommend that anticoagulation medication for POAF should be considered when the duration of AF is superior to 48 hours. This guidance also refers that if sinus rhythm is restored successfully, duration of anticoagulation should be for a minimum of 4 weeks but more prolonged in the presence of stroke risk factors.⁽¹⁹⁾

In 2016, ESC released the updated guidelines and differently from the previous guidance, the recommendation on anticoagulation therapy for POAF present in this document only refer that long term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk.⁽³⁵⁾

Moreover, since there are no randomized, controlled clinical trials that specifically address the problem of anticoagulation therapy for the POAF, recommendations in regard to preference for VKA or NOACs and criteria for anticoagulation are based on the established therapy for nonsurgical situations modified by the potential risk of bleeding in the postoperative patient.⁽⁶⁸⁾

In this context, based on the absence of specific guidelines from professional societies, Hospitals and healthcare professionals can play an important role in the development of institutional-level policies for the management of POAF in surgical patients.

Table 2 – Guidelines for the management of AF: Recommendations for post-operative atrial fibrillation

Issuing Organization	Year	Recommendations for POAF	Class	Level
American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS)	2014	It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as advised for nonsurgical patients	IIA	B
European Society of Cardiology (ESC)	2010	Unless contraindicated, antithrombotic/ anticoagulation medication for post-operative AF should be considered when the duration of AF is >48 h.	IIA	A
		If sinus rhythm is restored successfully, duration of anticoagulation should be for a minimum of 4 weeks but more prolonged in the presence of stroke risk factors.	IIA	B
	2016	Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk.	IIA	B
Canadian Cardiovascular Society (CCS)	2011	We suggest that consideration be given to anticoagulation therapy if postoperative continuous AF persists for > 72 hours. This consideration will include individualized assessment of the risks of a thromboembolic event and the risk of postoperative bleeding.	Conditional recommendation	Low-quality evidence
American Association for Thoracic Surgery (AATS)	2014	Anticoagulation within the first 48-hrs of POAF should be considered based on the CHA ₂ DS ₂ -VASc risk score of the patient for stroke weighed against the risk of postoperative bleeding.	I	C
		For effective anticoagulation, an INR range of 2–3, with a target of 2.5, for warfarin is recommended unless otherwise contraindicated.	I	C
		New oral anticoagulants (Dabigatran, Rivaroxiban, Apixiban) are reasonable as an alternative to warfarin for patients who do not have a prosthetic heart valve, hemodynamically significant valve disease, and/or severe renal impairment or risk of GI bleeding.	IIA	B
		New oral anticoagulants should be avoided for patients at risk for serious bleeding (including gastrointestinal bleeding) as they cannot be readily reversed. However, their use may be recommended in situations where achievement of a therapeutic INR with warfarin has proved to be difficult.	III	C
		It is reasonable to continue anticoagulation therapy for 4 weeks after the return of sinus rhythm because of the possibility of slowly resolving impairment of atrial contraction with an associated ongoing risk for thrombus formation and for delayed embolic events.	IIA	C

AF denotes atrial fibrillation; CHA₂DS₂-VASc, Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female); INR, International Normalized Ratio.

1.5. Pharmaceutical Intervention: The Role of the Clinical Pharmacist

The Department of Health report included oral anticoagulants as high risk medicines, based on repeated serious errors that occur with these drugs, emphasising the particular effort that needs to be made in order to improve medication safety.⁽⁶⁹⁾

In fact, in primary care, anticoagulants are one of the classes of medicines most commonly associated with fatal medication errors. A study conducted in Denmark with the purpose to describe the severity of adverse medication incidents caused by oral anticoagulants in hospitals showed that all fatal and almost all serious adverse medication incidents were associated with the prescribing phase of the medication process. In addition, this study also showed that during admission and surgery, prescribing excess anticoagulant was the most frequent problem and, on the other side, during discharge, prescribing insufficient anticoagulant was the most frequent problem.⁽⁷⁰⁾

Every day in the hospital setting, pharmacists are involved in several aspects of patient care from providing dose recommendations and adjustments, interpreting laboratory results, checking for drug interactions, and providing education to patients and caregivers.⁽⁷¹⁾

In the context of anticoagulant therapy, pharmacists play an integral role as members of a multidisciplinary team, not only by ensuring that patients receive the correct drug and dose in a timely manner, but also by considering patient factors such as renal and hepatic dysfunction.⁽⁷²⁾ Assessing drugs that can predispose the patient to a greater risk of adverse effects as well as screening for drug-drug interactions is also essential, as many medications used in the treatment of AF have narrow therapeutic indexes and the potential to cause serious adverse events.⁽⁷³⁾

In the UK, when commenced on anticoagulants, all patients are given a pack called Oral Anticoagulant Therapy: Important information for patients, which include general information and practical advice. Patient counselling is provided by the clinical pharmacist before anticoagulant therapy is commenced and prior to hospital discharge as well as on their first visit to the anticoagulant clinic.⁽⁷⁴⁾ During patient counselling, the pharmacist discusses with the patient the contents and purpose of the anticoagulant therapy information pack and drawing attention to the following points^(71,74,75):

- The indication for which the anticoagulant has been started and the expected duration of treatment;
- The dose of anticoagulant to take on discharge;
- What to do in case of missed dose;

- The importance of adherence;
- When to seek medical attention;
- Potential drug interactions and adverse effects;
- For patients prescribed warfarin: The need for regular blood tests as well as dietary advice.

A study conducted with the aim to investigate the effect of pharmacists counselling on the warfarin knowledge revealed that it improves following pharmacist verbal counselling.⁽⁷⁶⁾ Notably, warfarin is proven to be safely used more likely by patients who are aware of the potential for drug interactions, understand the rationale for monitoring, and can identify the symptoms of warfarin toxicity. Patient counselling is thus one of the most important fields of action performed by clinical pharmacists since they are uniquely trained to discuss medications with patients.

Additionally, pharmacists also have a role in outpatient anticoagulation clinics, including ⁽⁷⁷⁾:

- Consulting with individual patients after the measurement of their INR;
- Adjusting doses of anticoagulants in response to INR and changes in the patient's drug regimen or state of health;
- Promoting concordance with treatment and a healthy lifestyle while taking therapy;
- Communicating with other healthcare professionals and referring difficult cases to a member of the medical team.

In this context, several studies assessed the impact of pharmacist-managed anticoagulation clinics, showing that pharmacists impact positively warfarin management leading to better INR control and reduced rates of thromboembolic complications compared with standard care.^(78–80)

Multiple factors are pointed out in order to explain the positive impact of pharmacist in anticoagulation clinics, such as: their higher knowledge of pharmacokinetics and drug - interactions with anticoagulants; a wider appreciation of non-prescribed treatments, such as over-the-counter and herbal remedies, effective link between inpatient and outpatient care provided by the clinical pharmacy team⁽⁷⁷⁾

In the case of NOACs, a study published in 2015 suggests that although monitoring is not required, pharmacists have a critical role to play in NOACs adherence. This study showed that the percentage of adherent patients was higher at sites that performed appropriate patient selection, pharmacist-driven patient education and pharmacist-led adverse event and adherence monitoring.⁽⁸¹⁾

According to World Health Organization (WHO) and International Federation of Pharmacy (FIP), *“keeping up to date both scientifically and professionally is probably the most important demand throughout the career of a pharmacist. As the role of the pharmacist evolves and becomes more focused on pharmaceutical care, there is a need for greater involvement by the pharmacist in the outcome of drug therapy and the management of the individual patient’s medicines. In addition, the pharmacist is also facing new opportunities in all fields of pharmacy as well as an explosion in the amount of new medicine information that is available”*.⁽⁸²⁾ In this sense, this statement reiterates and reinforces the truly importance of pharmacists to keep up to date in what concerns the evolution of anticoagulant strategies in the context of atrial fibrillation as well as to be aware of their important role that is proven to positively impact patient outcomes, not only in the hospital setting but also in community pharmacy.

2. Context, objectives and research questions

This study took place at St. Bartholomew's Hospital in London, United Kingdom. This tertiary care Hospital is one of the five hospitals integrating Barts Health NHS which provides care to 2.5 million patients in this city.⁽⁸³⁾

St Bartholomew's Hospital is a leading, internationally renowned teaching hospital and since 2015, is home to the Barts Heart Centre, the largest cardiac centre in the UK and Europe's largest arrhythmia service. According to the available data, this Centre is currently treating over 5,000 patients a month and performs about 150 intervention procedures, 50 cardiothoracic surgical procedures and 3,500 outpatient appointments and diagnostics per week.⁽⁸⁴⁾

By performing such a high number of cardiothoracic surgeries, postoperative atrial fibrillation is a constant condition among St. Barts' patients for whom oral anticoagulation therapy performs a vital role for stroke prophylaxis. Although warfarin has been the preferred therapy, the emerging NOACs require reconsideration of current treatment practices. This also leads to a need of a better understanding on how to combine a patient's stroke risk with the prescription of the optimal anticoagulant treatment. Moreover, the inconsistency and diversified recommendations observed in current guidelines on the management of postoperative atrial fibrillation as well as the exclusion of patients undergoing surgery within 30 days from the phase III clinical trials⁽¹⁴⁻¹⁷⁾ assessing the use of NOACs in atrial fibrillation, supports the need of clarifying the factors that should be considered in the decision-making process of OAC prescription in the postoperative period.

Therefore, the purpose of this study is to compare the management of the oral anticoagulants and to assess the control of International Normalized Ratio for stroke prevention in postoperative atrial fibrillation after cardiothoracic surgery.

On this basis, four research questions were formulated:

1. What percentage of patients prescribed warfarin reached a Time in Therapeutic Range above 65%, six weeks post discharge?
2. What is the appropriate dosing of NOACs post-operatively?
3. What is the ideal time to initiate therapy with NOACs post-operatively?
4. For patients who have shown restoration of sinus rhythm at follow-up appointment, was the oral anticoagulation therapy discontinued?

These research questions will be answered sequentially as data is analysed (section 4 of the monograph).

The specific objectives of this research are to:

- i) Assess warfarin management in the postoperative period;
- ii) Investigate the tendencies and patterns in clinical practice regarding the prescription of Non-vitamin K Antagonist Oral Anticoagulants (i.e. choice of NOAC prescribed, dosage, postoperative period of therapy initiation);
- iii) Clarify the features involved in the hypothesis of considering dose reduction of non-vitamin K oral anticoagulants as well as the ideal timeframe to initiate the therapy with these medicines in the postoperative period;
- iv) Identify the number of patients that revert back to sinus rhythm (SR) 6 weeks following cardiothoracic surgery;
- v) Analyse discontinuation rates of oral anticoagulants, when restoration of sinus rhythm is attained.

In the framework of Erasmus Programme, this project was developed during the three months in which I had the opportunity to integrate the Department of Pharmacy of St. Bartholomew's Hospital. This research was suggested to me by this department's head, with the aim of enhancing knowledge regarding optimal anticoagulant treatment. Ultimately, the project's aim was to optimize effectiveness and safety of these drugs. Moreover, reflecting the important role of pharmacists as part of a multidisciplinary team of healthcare professionals, this project intended to promote the discussion with surgeons, general practitioners and nurses concerning the potential of future practice changes to ensure the management of atrial fibrillation after surgery, by providing these patients the best possible care.

3. Methods

3.1. Study design

This study was conducted at the large tertiary centre, Barts Heart Centre in London, United Kingdom between January 2017 and April 2017.

An ambispective study design was used in order to compare warfarin to non-vitamin K oral anticoagulants in what concerns optimal stroke prevention management in patients that developed postoperative atrial fibrillation after undergoing cardiothoracic surgery.

The study comprises two different phases; one retrospective and one prospective (ambispective design). Information from medical records related to the patients who underwent surgery between the 1st of January 2016 and the 31st of January 2017 were assessed retrospectively. The prospective phase included dates beyond this period as contacts were made with patients still being followed-up, until the end of the internship period, ie, 28th of April 2017 (**Figure 7**).

This study was approved by the Ethic Committee of the Hospital, under the protocol number 8021.

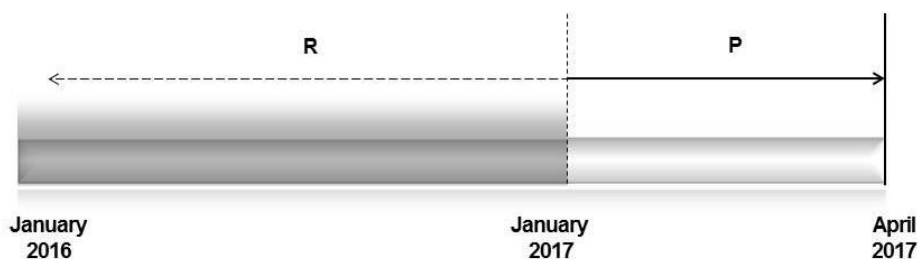


Figure 7- Study design. R denotes Retrospective phase; P Prospective phase

3.2. Participants

We identified all cardiothoracic surgery patients who developed postoperative atrial fibrillation and initiated anticoagulant therapy with either warfarin or a NOAC between the 1st of January, 2016 and the 31st of January, 2017.

Eligible patients were required to be at least 18 years of age with documented diagnosis of postoperative atrial fibrillation and oral anticoagulation treatment prescribed at discharge. Patients were excluded if they had any mechanical heart valve replacement procedure

performed; if they discontinued treatment; if the follow-up information could not be assessed or if the data documenting the medicines prescribed at the time of discharge were not available.

A priori sample size estimation was not performed as we were unable to include more patients than those physically existing in this centre. We have considered more appropriate instead to determine a posteriori the power associated with the sample obtained.

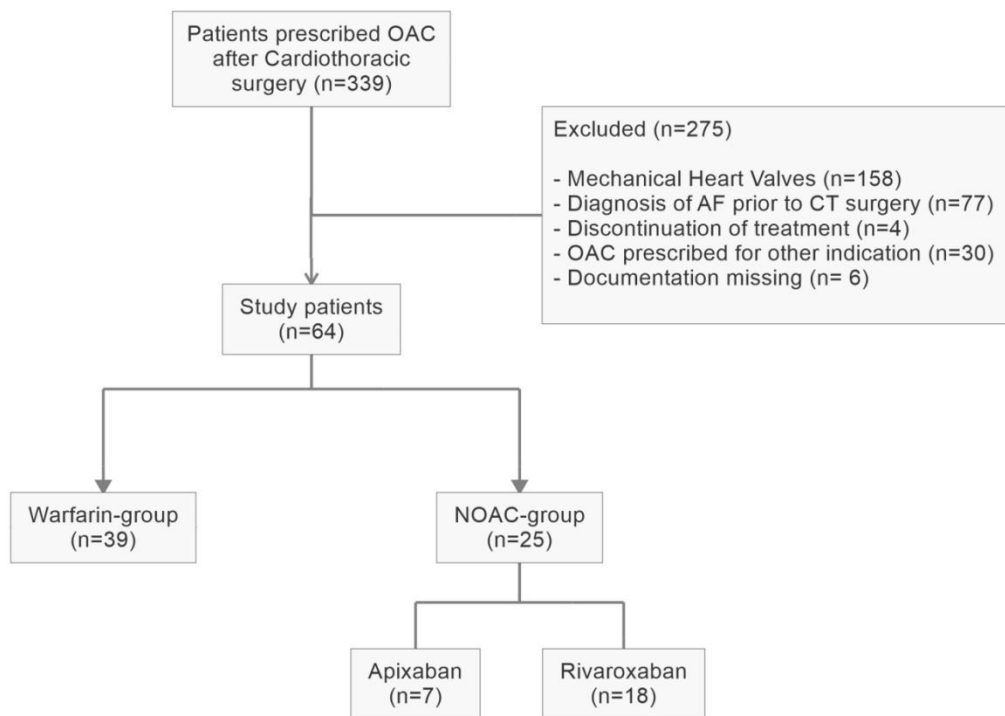


Figure 8-Patient Flow Chart.

64 patients were included in this study, including 39 patients in the warfarin-group and 25 patients in the NOAC-group.

3.3. Data collection

3.3.1. Data sources

Pharmacy dispensing records and stock control reports were used to identify all patients prescribed warfarin or NOACs on the cardiothoracic wards during the period of data collection.

Medication prescription charts and electronic medical notes were accessed in order to select among patients prescribed these medicines, and discharged from hospital with a confirmed

diagnosis of postoperative atrial fibrillation. Patients' demographics, medical history and laboratory studies were collected and analyzed.

3.3.2. Variables of interest

CHA₂DS₂-VASc score was determined for all patients, considering the individual risk factors for this score, based on the information available in medical records and prescription charts. Specifically for patients prescribed warfarin, International Normalized Ratio (INR) values were obtained by contacting the Anticoagulation Clinics where these patients had been followed and monitored. In view of assessing anticoagulation control with warfarin, the percentage of time a patient spent within the therapeutic range (TTR) was estimated, assuming that the difference in INR values between two consecutive measurements was linear, according to the Rosendaal Method⁽⁸⁵⁾.

For both cohorts, we assessed follow-up details, based on the cardiothoracic follow-up appointment arranged approximately six weeks after surgery, in order to determine the percentage of patients that had reverted back to sinus rhythm (SR) as well as the percentage of patients in this situation that had instructions to stop the oral anticoagulant.

3.3.3. Data collection tools

For the purpose of data collection we developed the Audit Tool presented in the **appendix A**, in which data on age, sex, date and type of surgery was collected. Considering the potential of each parameter to contribute to the purpose of this study, we calculated creatinine clearance (ClCr), estimated by the Cockcroft-Gault formula⁽⁸⁶⁾; we collected data on the concomitant use of other medications and also patients' weight, since all of the four NOACs have recommendations on dose reduction considering these factors.⁽⁵⁸⁾

Although this study is not looking directly for safety outcomes, we considered relevant to register significant events observed after initiating therapy, hence we also collected information of eventual bleedings or thromboembolic events, in the cases where this information was signaled in medical records or patients' charts.

Specifically for patients prescribed a NOAC, we collected the information on the NOAC prescribed, day of initiation post-surgery and the dosage regimen.

Finally, we assessed cardiothoracic follow up details, by collecting data on the time after surgery that the cardiothoracic follow-up appointment takes place; if in this appointment it is shown the maintenance of atrial fibrillation or the reversion to sinus rhythm and, when sinus

rhythm is shown in the ECG, if the indication for the patient is to stop the oral anticoagulant or to continue the medicine.

3.3.4. Data analysis

The collected data were analyzed using descriptive statistics. Discrete data are presented as absolute and relative frequencies, whereas continuous data are presented using central tendency and dispersion measures including mean, median and standard deviation. Bivariate analyses were also considered to compare the characteristics of patients in the two cohorts and ascertain if there were differences that could justify their inclusion in one or the other prescribing group. Given the sample size and non-normality data distribution, non-parametric tests were chosen; the chi-squared and the Fisher's Exact test were used to treat categorical data and the Wilcoxon Mann-Whitney test to treat continuous data. The confidence interval considered was 95%. All data was analysed using the IBM Statistical Software Package for Social Sciences (SPSS, version 24).

4. Results

4.1. Patient Baseline Characteristics

This study included 64 patients that developed atrial fibrillation after cardiothoracic surgery. Overall, 52 patients were male (81.3%) and the mean age of patients was 71.0 ± 10.3 years. The mean CHA₂DS₂-VASc score was 3.2 ± 1.5 . The highest proportion of the study population, corresponding to 15 patients (23.4%), has shown a CHA₂DS₂-VASc score of 3. Three patients (4.7%) have shown a score of 0; six patients (9.4%) had a score of 1; 12 patients (18.8%) have shown a score of 2; whereas 14 patients (21.9%) had a score of 4 and also 14 patients (21.9%) patients have shown a score equal or above 5

Risk factors were analysed with vascular disease and hypertension being the predominant comorbidities with 44 (68.1%) and 43 patients (67.2%), respectively, exhibiting these conditions. Nine patients (14.1%) had diabetes mellitus and three patients (4.7%) have had a previous Stroke/ TIA/ thrombo-embolism.

Among these patients, 39 (60.9%) were prescribed warfarin and 25 (39.1%) were prescribed a NOAC for stroke prophylaxis. In terms of concurrent antiplatelet therapy, half of the patients (n=32) were taking aspirin; seven (10.9%) were taking clopidogrel and two patients (3.1%) were taking both aspirin and clopidogrel simultaneously with the prescribed anticoagulant.

The most common surgical operation was CABG, with 24 patients (37.5%) undergoing this cardiothoracic procedure and fourteen patients (21.9%) being submitted to CABG in association with another procedure (**Table 3**).

Table 3- Demographics, Medical History and Laboratory studies

	Overall (n=64)	Warfarin (n=39)	NOAC (n=25)
Age, yr ‡			
Mean ± SD	70.98 ± 10.27	72.62 ± 8.08	68.44 ± 12.74
Median	72	76	71
Interquartile Range	42-89	52-85	42-89
Sex, n (%) ‡			
Female	12 (18.8)	8 (20.5)	4 (16.0)
Male	52 (81.3)	31 (79.5)	21 (84.0)
Type of surgery, n (%)			
CABG	24 (37.5)	17 (43.6)	7 (28.0)
Tavr	10 (15.6)	8 (20.5)	2 (8.0)
Tmvr	2 (3.1)	1 (2.6)	1 (4.0)
MV Repair	2 (3.1)	0 (0.0)	2 (8.0)
CABG + other (combination)	14 (21.9)	7 (17.9)	7 (28.0)
Other	12 (18.8)	6 (15.4)	6 (24.0)
CHA₂DS₂-VASc Score, n (%) ‡			
0	3 (4.7)	1 (2.6)	2 (8.0)
1	6 (9.4)	2 (5.1)	4 (16.0)
2	12 (18.8)	8 (20.5)	4 (16.0)
3	15 (23.4)	8 (20.5)	7 (28.0)
4	14 (21.9)	10 (25.6)	4 (16.0)
≥5	14 (21.9)	10 (25.6)	4 (16.0)
Mean ± SD	3.19 ± 1.53	3.42 ± 1.48	2.79 ± 1.54
Median	3	4	3
Comorbidities/ Risk factors, n (%)			
Vascular disease	44 (68.8)	28 (71.8)	16 (64.0)
Hypertension	43 (67.2)	27 (69.2)	16 (64.0)
Diabetes mellitus	9 (14.1)	9 (23.1)	0 (0.0)
Previous stroke/ TIA/ thrombo-embolism	3 (4.7)	2 (5.1)	1 (4.0)
Renal Function, eGFR (ml/min) ‡			
Mean ± SD	69.22 ± 23.47	68.03 ± 22.21	71.08 ± 25.66
Median	74.5	72.0	79.0
Concomitant Antithrombotic medication, n (%)‡			
Aspirin	32 (50.0)	22 (56.4)	10 (40.0)
Clopidogrel	7 (10.9)	5 (12.8)	2 (8.0)
Aspirin + Clopidogrel	2 (3.1)	1 (2.6)	1 (4.0)
Left Ventricular Ejection Fraction, n (%)⁺ ‡			
Preserved (≥50%)	32	17 (45.9)	15 (60.0)
Mid-range (40-49%)	23	16 (43.2)	7 (28.0)
Reduced (<40%)	7	4 (10.8)	3 (12.0)

CABG denotes coronary artery bypass graft; tAVR, tissue aortic valve replacement; tMVR, tissue mitral valve replacement; MV Repair, mitral valve repair; TIA, transient ischaemic attack; CHA₂DS₂-VASc, Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female); eGFR, estimated glomerular filtration rate.

⁺ Left ventricular ejection fraction was classified based on 2016 European Society of Cardiology (ESC) guidelines for Heart Failure⁽¹²⁾

‡ p ≥ 0.05 for the between-group comparison.

4.2. KEY QUESTION 1: What percentage of patients prescribed warfarin has shown a Time in Therapeutic Range above 65%?

For patients prescribed warfarin, the time they spent in the target INR range (i.e. 2.0-3.0) was measured by the percentage of time in therapeutic range (TTR) at six weeks post discharge. Patients were stratified according to their time in range: equal or above 65%; between 64-41% and equal or below 40%.

TTR values were obtained for 27 patients, corresponding to 69.2% of the total of patients of warfarin-group. In this study, 51.9% of patients taking warfarin have shown a TTR below 65%, reflecting poor anticoagulation control and 25.9% had values below 40% (**Figure 9**). The median TTR was 60% and the mean time in range was 61.6% during the first six weeks of treatment.

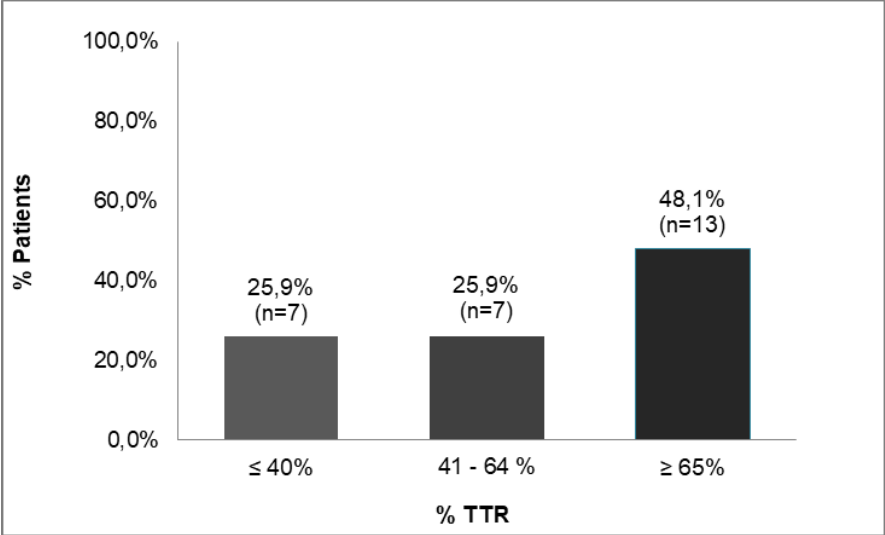


Figure 9- Percentage of Time in Therapeutic Range in patients on warfarin therapy.

Proportion of patients who have shown therapeutic and subtherapeutic percentages of time in therapeutic range, considering a target INR range of 2.0 to 3.0.

Figure 10 compares the mean TTR obtained in this study with the mean TTR published in the four phase III clinical trials assessing the use of NOACs in AF⁽¹⁴⁻¹⁷⁾. This graph shows no discrepancy between the mean TTR obtained in these trials and the mean TTR obtained in this study, suggesting that poor anticoagulation control with warfarin constitutes a common factor in several studies comparing the use of warfarin with NOACs in atrial fibrillation.

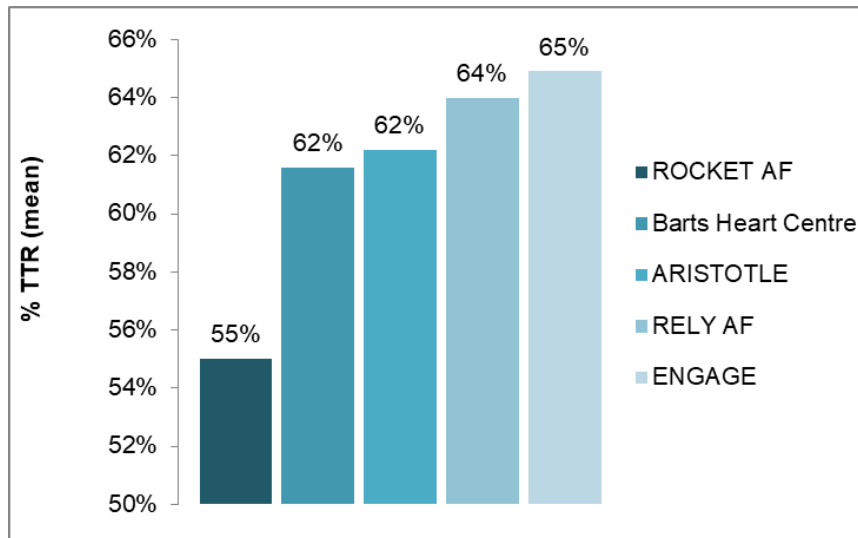


Figure 10- Comparison of the mean time in therapeutic range between Barts Heart Centre and phase III clinical trials assessing the use of NOACs in Atrial Fibrillation.

4.3. KEY QUESTION 2: What is the appropriate dosing of NOACs post-operatively?

Among 25 patients receiving therapy with a NOAC, 18 were prescribed rivaroxaban whereas seven were prescribed apixaban. There were no records of patients prescribed with either Dabigatran or Edoxaban, although both of them integrate the British National Formulary (BNF) as well as the local hospital formulary⁽⁸⁷⁾. **Figure 11** shows the overall NOACs dose regimens. The standard dose regimens are 20mg once daily for rivaroxaban and 5mg twice daily for apixaban. Low dose regimens are 15mg once daily of rivaroxaban and 2.5 mg twice daily for apixaban. Of the 18 patients prescribed rivaroxaban, 15 (83.3%) were prescribed the standard dose of 20 mg once daily, while 3 (16.7%) were receiving the lower dose. A much lower proportion of patients prescribed apixaban were recommended the standard dose regimen (42.9%) and the remaining 57.1% were prescribed the lower dose of 2.5 mg twice daily.

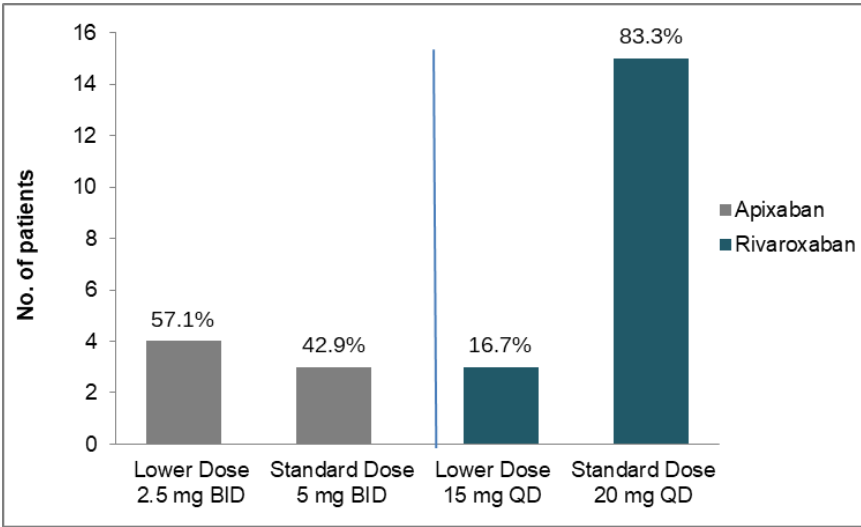


Figure 11- Dosing regimens of NOACs.

BID denotes twice-daily regimen; NOAC non-vitamin K oral anticoagulants; QD once-daily regimen.

4.4. KEY QUESTION 3: What is the ideal time to initiate therapy with NOACs post-operatively?

Fourteen patients (56%) initiated therapy between 96h and 1 week post-surgery, whereas ten patients (40%) started therapy at least one week after surgery and one patient (4%) was started on a NOAC on day 2 post operatively. Overall, NOACs were initiated on average 8.36 ± 3.74 days post-operatively, with a minimum of two days and a maximum of 17 days between surgery and the initiation of therapy (**Figure 12**).

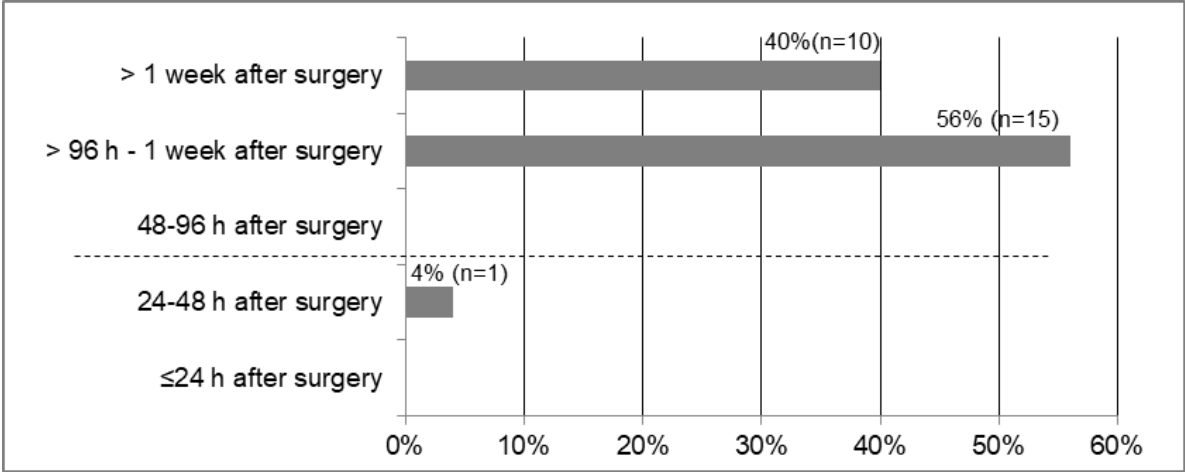


Figure 12- Initiation time of therapy with NOACs after cardiothoracic surgery.
Adapted from European Heart Rhythm Association (EHRA) Survey, 2016.

4.5. KEY QUESTION 4: For patients who have shown restoration of sinus rhythm at follow-up appointment, was the oral anticoagulation therapy discontinued?

Follow up details of cardiac rhythm were unknown for four patients from the warfarin-group and five patients from the NOAC-group.

In the warfarin-group, sinus rhythm had been restored in 22 patients (63%), whereas, in the NOAC-group 13 patients (65%) have shown to be back in to SR at the cardiothoracic appointment (**Figure 13A**). This difference, was however non-significant ($p \geq 0.05$).

Overall, 40% of patients were advised to stop oral anticoagulation when sinus rhythm was restored. Among patients taking warfarin, 11 (50%) have stopped the oral anticoagulant when back to sinus rhythm. A higher percentage of patients from the NOAC-group remained on anticoagulation therapy, with three patients (23%) of patients discontinuing the therapy after restoration of sinus rhythm (**Figure 13B**). Although the difference observed was statistically non-significant ($p \geq 0.05$), there is an apparent tendency of a higher discontinuation rate among warfarin-users when sinus rhythm is restored.

In patients in whom oral anticoagulation was discontinued, the mean CHA₂DS₂-VASc Score was 3.5 ± 1.6 for the warfarin-group and 2.7 ± 1.4 for the NOAC-group.

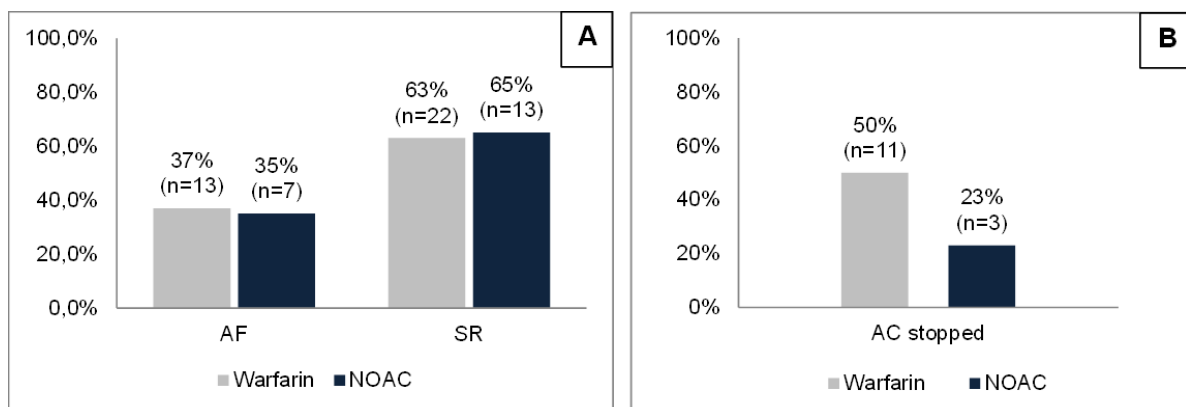


Figure 13- Restoration of sinus rhythm and discontinuation of anticoagulant therapy.
(A) Proportion of patients who have shown to be in sinus rhythm and in atrial fibrillation at the cardiothoracic follow up appointment;
(B) Percentage of patients advised to discontinue oral anticoagulant therapy after restoration of sinus rhythm. AC anticoagulant therapy; AF atrial fibrillation; SR sinus rhythm.

5. Discussion

Although warfarin remains the most prescribed oral anticoagulant in clinical practice, the achievement of a TTR above 65% and the maintenance of an appropriate level of anticoagulation continue to be one of the biggest challenges when prescribing this drug.

The quality of anticoagulation control with warfarin is commonly expressed as the average TTR, i.e. maintaining an international normalized ratio (INR) between 2.0 and 3.0⁽⁸⁸⁾. As a consequence, the time a patient spends within the target range has a profound impact on the effectiveness of warfarin to prevent stroke and a poor warfarin management can be harmful to the patient, being associated with adverse outcomes, such as major haemorrhage and thromboembolic events.⁽⁵¹⁾ In this study, 51.9% of patients taking warfarin have shown a TTR below 65% 6 weeks post-operative, reflecting poor anticoagulation control. Another 25.9% of patients had values below 40% for whom, based on evidence, there is no significant difference in terms of overall mortality when comparing treatment with warfarin versus treatment without warfarin⁽⁴⁹⁾

The mean time spent in range among warfarin users observed in this study is consistent with the findings of the phase III trials assessing the use of the four NOACs in AF, with all of them showing TTR values below 65% for the comparison group on warfarin.^(15–17,89) Indeed, the finding of relatively poor anticoagulation control among warfarin users has been reported in several studies. A systematic review which included a total of 38 articles assessing anticoagulation control has shown that only 15% of the reviewed articles had reported both TTR and INRs in range.⁽⁵¹⁾ Another study looking at patients with a diagnosis of AF in the UK was also consistent with the correlation between TTR, the risk of stroke and mortality rates, demonstrating that warfarin users who spent at least 70% of time within range had the largest reduction in the risk of stroke and had shown lower mortality rates.⁽⁹⁰⁾

Other relevant question is whether patients in the trials on NOACs had an increased risk of stroke when warfarin was initiated after randomization in warfarin-naive patients. In the ARISTOTLE trial, the stroke rate per 100 patient-years among warfarin-treated patients in the first 30 days was higher in the warfarin-naive (5.41) than the warfarin-experienced (1.42) groups [hazard ratio (HR) 3.8]. The stroke rates were similar in the apixaban treated population regardless of prior warfarin status. In RE-LY, the risk of stroke in the first 30 days was 0.12% for the pooled dabigatran groups and 0.26% for warfarin (odds ratio 2.23, 95% confidence interval 0.81–6.15) in the warfarin-naive population, a pattern was not seen in the warfarin-experienced group. In ROCKET-AF, the stroke rate per 100 patient-years in patients treated with warfarin compared with rivaroxaban in the first 30 days after

randomization was 2.84 for rivaroxaban and 4.40 for warfarin (HR 1.6) in the warfarin-naive group. In warfarin-experienced patients, the rates were 1.92 for rivaroxaban and 2.86 for warfarin.⁽⁹¹⁾

Theoretically, warfarin at initiation could lead to a hypercoagulable state with an increased risk of thrombo-embolic events. Azoulay et al. have performed a post-hoc nested-control analysis using the UK Clinical Practice Research Datalink in a cohort of 70 766 patients with AF. The hypothesis of an increased early stroke risk after the initiation of warfarin in patients with AF was based on the early effect of warfarin preventing production of the natural anticoagulants protein C and S, and the suspicion that the early labile nature of warfarin's effect could result in thrombotic events. Azoulay et al. observed a 71% increase of stroke in the first 30 days of warfarin use, while a decreased stroke risk was observed afterwards.⁽⁹²⁾

Therefore, in light of such a high number of patients with labile INR control, anticoagulant therapy with NOACs may represent a safer option for these individuals and the potential risks and benefits of switching to a NOAC should be considered as a TTR below 65% constitutes agreed criteria for NOAC initiation, according to NICE guidelines⁽⁵⁾.

Despite the emergence of NOACs, there is still a gap in knowledge regarding the use of NOACs in early post-operative scenario, which can lead to lack of confidence in the prescription of NOACs by some clinicians. In this study, 39% of patients were prescribed NOACs, with rivaroxaban showing to be the most frequently prescribed, followed by apixaban, which is consistent with overall market data. The higher percentage of patients being prescribed rivaroxaban is consistent with the worldwide market trends, since in 2015 this medicine was among the Top 20 of pharmaceutical products marketed around the world⁽⁹³⁾, being the only NOAC integrating this ranking.

Dabigatran and edoxaban were not prescribed in this study population, although both of them are currently included in the local hospital formulary. The possible explanations for this finding include the once daily dose regimen of rivaroxaban, which can potentially support the adherence to therapy and represent a more attractive alternative for AF patients; edoxaban would be an alternative also prescribed once daily, but was the last NOAC approved by the European Medicines Agency, with marketing authorization only in 2015⁽⁹⁴⁾, in comparison with apixaban licensing in 2011⁽⁹⁵⁾ and both rivaroxaban and dabigatran in 2008^(96,97). Although apixaban had a later timing of market entry when compared to dabigatran, there are some pharmacologic differences that can relate to the higher rates of apixaban prescription. One example is the contraindication of dabigatran in patients with severely reduced kidney function (CrCl under 30 mL/min)⁽⁹⁸⁾, while rivaroxaban and apixaban can be used in a lower dose^(99,100). Moreover, in guidance documents from the Prescribing

Committee of UK's NHS, rivaroxaban and apixaban are referred as the suitable options for most patients with non-valvular AF, whereas in some situations, dabigatran is not preferred or even contraindicated.⁽¹⁰¹⁾

To date, there is still a need for evidence in terms of optimal doses as well as time to initiate post-operatively.

The previously published European Heart Rhythm Association Survey supports the need for more precise practice guidelines regarding the use of these agents in the early post-operative period by showing a vast heterogeneity within the medical community. The results of this survey show that one quarter of the participant centres did not use NOACs in the post-operative scenario, while among the centres prescribing NOACs, 50% initiated therapy within 48 h post-surgery and in 16.7% of centres, therapy was even started within 24 h post-cardiac surgery.⁽¹⁰²⁾

According to the collected data, we observed that NOACs were initiated on an average of 8.36 ± 3.74 days post-operatively, with a minimum of two days and a maximum of 17 days between surgery and the initiation of therapy. Whilst acknowledging that this study did not focus on safety outcomes, hence any recommendation for the optimal timeframe for NOACs initiation in the post-operative setting is not fully supported by the evidence gathered, we believe the ideal time to initiate therapy safely should be immediately before discharge, having in consideration that the median length of stay for these patients is 8 days.⁽¹⁰³⁾ This hypothesis is supported by evidence that safe discharge correlates with patient's overall clinical status and higher stability.

The European Society of Cardiology guidelines indicate that the choice of a NOAC and its dosing should consider several factors, such as: concurrent medication, patient age, weight, renal function and comorbidities.⁽⁵⁸⁾ Nonetheless, there are no specific recommendations regarding the appropriate dosing in the first months after surgery for which both hypercoagulability and haemorrhagic risk are known to be high.⁽¹⁰⁴⁾ Therefore, based on the higher susceptibility for the occurrence of adverse effects, dose adjustments should be considered in the early post-operative setting, and a lower dose (i.e. 15 mg once daily for rivaroxaban and 2.5 mg twice daily for apixaban) can represent a safer option for these patients, potentially for the first 30 days post-surgery as this was the exclusion period in phase III randomized clinical trials conducted to date.

The discontinuation of oral anticoagulation when long-term SR is achieved is also controversial. In this study, we have found that 37% of patients were advised to stop the oral anticoagulant when SR was restored, with a higher percentage of patients from the NOAC-

group remaining on anticoagulation therapy, in comparison with 11 patients (50%) from the warfarin-group who stopped this agent.

POAF can be a reversible condition with 90% of patients restoring SR spontaneously six to eight weeks post-surgery.⁽¹⁰⁵⁾ Although the optimal duration of anticoagulant therapy has not been established, in general, if normal sinus rhythm returns, it is imperative to determine the risk-benefit of discontinuing anticoagulation therapy. Moreover, as AF can be asymptomatic, the permanent appearance of SR should not be, by itself, criteria to stop anticoagulation. Additionally, ESC guidelines for the management of AF, recommend that, for patients at risk for stroke, therapy should be continued long term after cardioversion, irrespective of the method or the apparent maintenance of SR. While for patients without stroke risk factors, therapy should continue for 4 weeks after cardioversion.⁽³⁵⁾

In concordance with these findings, a previous study assessing the discontinuation of warfarin and NOACs in patients with AF reported that 29.7% of patients had discontinued the anticoagulant agent, pointing the permanent return to sinus rhythm as the main reason for the discontinuation of the treatment.⁽¹⁰⁶⁾

Indeed, returning to SR does not remove the risk of stroke and the decision of discontinuing anticoagulation when SR is restored should be made based on the individual patient thromboembolic risk profile, assessed by the CHA₂DS₂-VASC score.

These facts highlight the importance of regular follow up appointments for patients at high risk of stroke as well as an individual evaluation of the benefits of anticoagulation therapy in patients at low risk of stroke.

6. Conclusion

Postoperative atrial fibrillation is common and contributes to a worse outcome of surgical patient, predisposing them to a higher risk of stroke. Therefore, anticoagulant therapy is a crucial strategy on the basis of a comprehensive assessment of stroke and bleeding risk and also having in consideration the self-terminating nature of this condition.

Although warfarin was the first choice for many years, there are several obstacles and limitations inherent to this drug. More specifically, attaining a time in therapeutic range superior to 65% is proven to be challenging, as we have seen across the warfarin-users represented in this study, reflecting poor warfarin's management. Indeed, based on the profound impact that time in therapeutic range has upon the effectiveness of warfarin to prevent stroke, for the 26% of patients who have shown a time in therapeutic range below or equal to 40%, the outcomes can be worse while in warfarin than with no treatment. Given this facts, NOACs can potentially represent a safer and more effective option for this patients. Additionally, in terms of the outcomes concerning the reversion to sinus rhythm, there was no significant difference observed in both cohorts, which emphasises the effectiveness of both NOACs and warfarin.

On the other hand, the heterogeneity observed in the current clinical practice regarding the use of NOACs in the postoperative period reiterate the importance of specific practical guidance for POAF, in order to take maximal advantage of these drugs, ensuring optimal efficacy and safety. Indeed, the decision criteria for NOACs dose adjustments and timeframe of initiation as well as overall discontinuation of oral anticoagulants when sinus rhythm is restored are notably different.

Therefore, further research is mandatory to clarify the features involved in the anticoagulant therapy with NOACs in the postoperative setting as well as the outcomes for surgical patients.

7. References

1. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;31(19):2369–429.
2. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery. *J Am Coll Cardiol*. 2008;51(8):793–801.
3. Yadava M, Hughey AB, Crawford TC. Postoperative atrial fibrillation: Incidence, mechanisms, and clinical correlates. *Cardiol Clin* [Internet]. 2014;32(4):627–36. Available from: <http://dx.doi.org/10.1016/j.ccl.2014.07.002>
4. Hart RG, Pearce LA, Aguilar MI. *Annals of Internal Medicine Review Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation*. 2014;
5. NICE. *Atrial fibrillation: management*. 2014;
6. Zirlik A, Bode C. Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. *J Thromb Thrombolysis*. 2017;43(3):365–79.
7. EMA. Assessment report Xarelto. 2013;44(EMA/CHMP/115246/2014):1–107. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500201726.pdf
8. EMA. Assessment report Lixiana. 2015;44(April).
9. EMA. Assessment Report Pradaxa. 2008;1–36.
10. EMA. Assessment report Eliquis. 2011;44(EMEA/H/C/002148 Assessment).
11. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955–62.
12. Task A, Members F, Ponikowski P, Poland C, Voors AA, Germany SDA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution . 2016;2129–200.
13. Shameem R, Ansell J. Disadvantages of VKA and requirements for novel anticoagulants. *Best Pract Res Clin Haematol*. 2013;26(2):103–14.
14. Granger, CB.; Alexander JH, McMurray JJ; Lope RD; Hylek EM; Hanna M et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2008;339–54.
15. Patel, MR.; Mahaffey KW; Garg J; Pan G; Singer DE; Hacke W et al; RA investigators. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med*. 2011;883–91.
16. Giugliano RP, Ruff CT, Braunwald E, Murphy S a, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* [Internet]. 2013;369(22):2093–104. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24251359>
17. Connolly, SJ.; Ezekowitz, MD.; Yusuf S.; Eikelboom J; Oldgren J; Parekh A et al; R-LSC and I. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2009;557–68.
18. Ha ACT, David C, Verma S. Management of postoperative atrial fibrillation after cardiac surgery. 2016;183–90.
19. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the

- management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* [Internet]. 2010 Oct 1 [cited 2017 Nov 2];31(19):2369–429. Available from: <https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehq278>
20. Call to action - Atrial Fibrillation Preventing A Stroke Crisis [Internet]. [cited 2017 Oct 29]. Available from: <http://www.preventaf-strokecrisis.org/report/call-to-action>
 21. Ps M, Teljeur C, Ryan M, Sm S. Systematic screening for the detection of atrial fibrillation (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. 2016;(6).
 22. Dewar RI, Lip GYH. Identification, diagnosis and assessment of atrial fibrillation. *Heart*. 2007;93(September):25–8.
 23. Christine Cottrell. Atrial fibrillation 2: assessment and diagnosis. *Pract Nurs* [Internet]. 2012 [cited 2017 Oct 29];23(2). Available from: https://www.educationforhealth.org/wp-content/uploads/2015/03/PN_23_2_77_AF2_NEW.pdf
 24. Swancutt D, Hobbs R, Fitzmaurice D, Mant J, Murray E, Jowett S, et al. A randomised controlled trial and cost effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in the over 65s: (SAFE) [ISRCTN19633732]. *BMC Cardiovasc Disord*. 2004;4:12.
 25. NICE. Assessing atrial fibrillation - NICE Pathways. *Atr Fibrillation Manag* [Internet]. 2014;1–6. Available from: <https://pathways.nice.org.uk/pathways/atrial-fibrillation/assessing-atrial-fibrillation#content=view-node%3Anodes-electrocardiography>
 26. Uittenbogaart SB, Verbiest-van Gorp N, Erkens PMG, Lucassen WAM, Knottnerus JA, Winkens B, et al. Detecting and Diagnosing Atrial Fibrillation (D2AF): study protocol for a cluster randomised controlled trial. *Trials* [Internet]. 2015 Oct 23 [cited 2017 Sep 23];16:478. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26499449>
 27. Troughton RW, Asher CR, Klein AL. the Role of Echocardiography in Atrial Fibrillation and Cardioversion. *Heart*. 2003;89:1447–54.
 28. Larsen TB, Potpara T, Dagres N, Pison L, Estner H, Blomström-Lundqvist C. Stroke and bleeding risk evaluation in atrial fibrillation: results of the European Heart Rhythm Association survey. *Europace* [Internet]. 2014;16(5):698–702. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24798958>
 29. Atrial Fibrillation Investigators. Risk Factors for stroke and Efficacy of Antithrombotic Therapy in Atrial Fibrillation: Analysis of Pooled Data From Five Randomized Controlled Trials. 1994;
 30. Investigators TSP in AF. Predictors of Thromboembolism in Atrial Fibrillation: I. Clinical Features of Patients at Risk. *Ann Intern Med* [Internet]. 1992 Jan 1 [cited 2017 Oct 29];116(1):1. Available from: <http://annals.org/article.aspx?doi=10.7326/0003-4819-116-1-1>
 31. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes Results From the National Registry of Atrial Fibrillation. *Jama*. 2001;285(22):2864–70.
 32. Anderson E, Dyke C, Levy JH. Anticoagulation strategies for the management of postoperative atrial fibrillation. *Clin Lab Med* [Internet]. 2014;34(3):537–61. Available from: <http://dx.doi.org/10.1016/j.cll.2014.06.012>
 33. Odum LE, Cochran KA, Aistrophe DS, Snella KA. The CHADS(2) versus the New CHA(2)DS(2)-VASc Scoring Systems for Guiding Antithrombotic Treatment of Patients with Atrial Fibrillation: Review of the Literature and Recommendations for Use. *Pharmacotherapy*. 2012;32(3):285–96.
 34. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based

- approach: The Euro Heart Survey on atrial fibrillation. *Chest* [Internet]. 2010;137(2):263–72. Available from: <http://dx.doi.org/10.1378/chest.09-1584>
35. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. *Rev Esp Cardiol (Engl Ed)*. 2017;70(1):50.
 36. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol* [Internet]. 2014 Dec [cited 2017 Sep 18];64(21):2246–80. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0735109714017392>
 37. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151(3):713–9.
 38. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. *Chest* [Internet]. 2010;138(5):1093–100. Available from: <http://dx.doi.org/10.1378/chest.10-0134>
 39. Zhu W, He W, Guo L, Wang X, Hong K. The HAS-BLED score for predicting major bleeding risk in anticoagulated patients with atrial fibrillation: A systematic review and meta-analysis. *Clin Cardiol*. 2015;38(9):555–61.
 40. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GYH. Performance of the HEMORR 2HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: The AMADEUS (Evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial. *J Am Coll Cardiol* [Internet]. 2012;60(9):861–7. Available from: <http://dx.doi.org/10.1016/j.jacc.2012.06.019>
 41. Lip GYH, Banerjee A, Lagrenade I, Lane DA, Taillandier S, Fauchier L. Assessing the risk of bleeding in patients with atrial fibrillation: The loire valley atrial fibrillation project. *Circ Arrhythmia Electrophysiol*. 2012;5(5):941–8.
 42. Lane DA, Lip GYH. Use of the CHA2DS2-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation*. 2012;126(7):860–5.
 43. Senoo K, Lane D, Lip GY. Stroke and bleeding risk in atrial fibrillation. *Korean Circ J* [Internet]. 2014 Sep [cited 2017 Oct 29];44(5):281–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25278980>
 44. Lip GYH, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace* [Internet]. 2011;13(5):723–46. Available from: <https://academic.oup.com/europace/article-lookup/doi/10.1093/europace/eur126>
 45. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy - Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 SUPPL.).
 46. Bristol-Myers-Squibb. Warfarin Full Prescribing Information. FDA drug labeling [Internet]. 2011;1–36. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf
 47. Reynolds MW, Fahrbach K, Hauch O, Wygant G, Estok R, Cella C, et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: A systematic review and meta-analysis. *Chest* [Internet]. 2004;126(6):1938–45. Available from: <http://dx.doi.org/10.1378/chest.126.6.1938>
 48. Abbasinazari M, Farsad BF, Dabagh A, Bakshandeh H. Evaluation of time in therapeutic range

- (TTR) in patients with non-valvular atrial fibrillation receiving treatment with warfarin in Tehran, Iran: A cross-sectional study. *J Clin Diagnostic Res*. 2016;10(9):FC04-FC06.
49. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. *Thromb Res [Internet]*. 2009;124(1):37–41. Available from: <http://dx.doi.org/10.1016/j.thromres.2008.09.016>
 50. Mearns ES, White CM, Kohn CG, Hawthorne J, Song J, Meng J, et al. Quality of vitamin K antagonist control and outcomes in atrial fibrillation patients: a meta-analysis and meta-regression. 2014;12(1):1–20.
 51. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: A systematic review. *Circ Cardiovasc Qual Outcomes*. 2008;1(2):84–91.
 52. Schein JR, White CM, Nelson WW, Kluger J, Mearns ES, Coleman CI. Vitamin K antagonist use: evidence of the difficulty of achieving and maintaining target INR range and subsequent consequences. *Thromb J [Internet]*. 2016;14(1):14. Available from: <http://thrombosisjournal.biomedcentral.com/articles/10.1186/s12959-016-0088-y>
 53. Lane DA, Lip GYH. Maintaining therapeutic anticoagulation: The importance of keeping “within range.” *Chest*. 2007;131(5):1277–9.
 54. Umut K, Esra K, Gokhan A. Novel oral anticoagulants in non-valvular atrial fibrillation: Pharmacological properties, clinical trials, guideline recommendations, new antidote drugs and real-world data. *Int J Cardiovasc Acad*. 2016;
 55. Biase L Di. Use of direct oral anticoagulants in patients with atrial fibrillation and valvular heart lesions. *J Am Heart Assoc*. 2016;5(2):1–10.
 56. Khoo CW, Tay K-H, Shantsila E, Lip GYH. Novel oral anticoagulants. *Int J Clin Pract*. 2009;63(4):535–7.
 57. Salem J-EJ, Sabouret P, Funck-Brentano C, Hulot J-S. Pharmacology and mechanisms of action of new oral anticoagulants. *Fundam Clin Pharmacol [Internet]*. 2015;29(1):10–20. Available from: http://www.readcube.com/articles/10.1111%2Ffcp.12091?r3_referer=wol&tracking_action=preview_click&show_checkout=1&purchase_referrer=onlinelibrary.wiley.com&purchase_site_license=LICENSE_DENIED%5Cnhttp://onlinelibrary.wiley.com/doi/10.1111/fcp.12091/full
 58. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-Vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17(10):1467–507.
 59. Katritsis DG, Gersh BJ, Camm AJ. Anticoagulation in Atrial Fibrillation - Current Concepts. *Arrhythmia Electrophysiol Rev*. 2015;4(2):100–7.
 60. Almegren M. Reversal of direct oral anticoagulants. *Vasc Health Risk Manag*. 2017;13:287–92.
 61. Andrade JG, Macle L, Nattel S, Verma A, Cairns J. Contemporary Atrial Fibrillation Management: A Comparison of the Current AHA/ACC/HRS, CCS, and ESC Guidelines. *Can J Cardiol [Internet]*. 2017;33(8):965–76. Available from: <http://dx.doi.org/10.1016/j.cjca.2017.06.002>
 62. Thijs V, Lemmens R, Farouque O, Donnan G, Heidbuchel H. Postoperative atrial fibrillation: Target for stroke prevention? *Eur Stroke J [Internet]*. 2017;2(3):239698731771936. Available from: <http://journals.sagepub.com/doi/10.1177/2396987317719363>
 63. Yoon CH, Park YK, Kim SJ, Lee M, Ryoo S, Kim G-M, et al. Eligibility and preference of new oral anticoagulants in patients with atrial fibrillation: comparison between patients with versus without stroke. *Stroke [Internet]*. 2014;45(10):2983–8. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/25147329>

64. Carrie Evavold, MD Juan Lessing, MD Wendy Tzou, MD Frank Merritt M. Should Patients Who Develop Postoperative Atrial Fibrillation Start Anticoagulation? *Hospitalist*. 2016;0–4.
65. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol* [Internet]. 2014 Dec [cited 2017 Oct 15];64(21):2246–80. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0735109714017392>
66. Mitchell LB. Canadian Cardiovascular Society atrial fibrillation Guidelines 2010: Prevention and treatment of atrial fibrillation following cardiac surgery. *Can J Cardiol*. 2011;27(1):91–7.
67. Gyorgy Frendl, MD, PhD, Alissa C. Sodickson, MD, Mina K Chung, MD&, Albert L. Waldo, MD, PhD(Hon), Bernard J Gersh, MB, ChB, DPhi, James E Tisdale, Pharm.D, Hugh Calkins, MD^, Sary Aranki, MD, Tsuyoshi Kaneko, MD, Stephen Cassivi, MD, Sidney C. Smith Jr, TKW, MD, MSc, PhD, David Amar, MD, and Dale Adler M. 2014 AATS Guidelines for the Prevention and Management of Peri-Operative Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures Gyorgy. *J Thorac Cardiovasc Surg*. 2014;148(3):1–80.
68. Hogue CW, Creswell LL, Gutterman DD, Fleisher L a. Epidemiology, mechanisms, and risks: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. *Chest* [Internet]. 2005;128(2 Suppl):9S–16S. Available from: http://dx.doi.org/10.1378/chest.128.2_suppl.61S
69. Smith J. Building a safer NHS for patients: improving medication safety. *Dep Heal*. 2004;180.
70. Henriksen JN, Nielsen LP, Hellebek A, Poulsen BK. Medication errors involving anticoagulants: Data from the Danish patient safety database. *Pharmacol Res Perspect*. 2017;5(3):1–8.
71. Rose AE. Anticoagulation Management [Internet]. Vol. 1. 2015. 151-177 p. Available from: <http://link.springer.com/10.1007/978-3-319-22602-6>
72. The British Journal of Cardiology. Anticoagulation module 5: the role of the pharmacist | The British Journal of Cardiology [Internet]. [cited 2017 Nov 7]. Available from: <https://bjcardio.co.uk/2013/04/anticoagulation-module-5-the-role-of-the-pharmacist-2/>
73. Hoie E, Karen O, Katie N, Susana C, Begley K. Direct Oral Anticoagulants for the Prevention of Stroke in Nonvalvular Atrial Fibrillation. *Pharmacist* [Internet]. 2017; Available from: <http://www.who.int/iris/handle/10665/69399>
74. Edition S, Of M, Patients A, With T, Anticoagulants O, Guidelines C. Guideline on the management of adult patients treated with oral anticoagulants in Suffolk. 2010;(May):1–31.
75. Warfarin and Beyond: An Update On Oral Anticoagulation Therapy [Internet]. [cited 2017 Nov 7]. Available from: <https://www.uspharmacist.com/article/warfarin-and-beyond-an-update-on-oral-anticoagulation-therapy>
76. Collins S, Barber A, Sahm L. Pharmacist’s Counselling Improves Patient Knowledge Regarding Warfarin, Irrespective of Health Literacy Level. *Pharmacy* [Internet]. 2014;2(1):114–23. Available from: <http://www.mdpi.com/2226-4787/2/1/114/>
77. Semple S. Outpatient management of anticoagulation therapy | Hospital Pharmacy Europe [Internet]. 2001 [cited 2017 Nov 7]. Available from: <http://www.hospitalpharmacyeurope.com/featured-articles/outpatient-management-anticoagulation-therapy>
78. Bungard TJ, Gardner L, Archer SL, Hamilton P, Ritchie B, Tymchak W, et al. Evaluation of a pharmacist-managed anticoagulation clinic: Improving patient care. *Open Med*. 2009;3(1):16–21.
79. Shah KJ, Pharm D, Mansukhani R, Pharm D, Bloomstein D, Pharm D, et al. Outcomes of a

- Pharmacist Managed Anticoagulation Service. 2010;6:62–7.
80. Young S, Bishop L, Twells L, Dillon C, Hawboldt J, O’Shea P. Comparison of pharmacist managed anticoagulation with usual medical care in a family medicine clinic. *BMC Fam Pract* [Internet]. 2011;12(1):88. Available from: <http://bmcfampract.biomedcentral.com/articles/10.1186/1471-2296-12-88>
 81. Shore S, Ho PM, Lambert-Kerzner A, Glorioso TJ, Carey EP, Cunningham F, et al. Site-Level Variation in and Practices Associated With Dabigatran Adherence. *JAMA* [Internet]. 2015 Apr 14 [cited 2017 Sep 18];313(14):1443. Available from: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2015.2761>
 82. Wiedenmayer K, Summers; RS, Mackie C a., Gous AGS, Everard M, Tromp D, et al. Developing pharmacy practice A focus on patient care. 2006;87. Available from: <http://www.who.int/iris/handle/10665/69399>
 83. Our background and history - Barts Health NHS Trust [Internet]. [cited 2017 Jul 5]. Available from: <https://www.bartshealth.nhs.uk/our-background-and-history>
 84. St Bartholomew’s Hospital - Barts Health NHS Trust [Internet]. [cited 2017 Jul 5]. Available from: <https://www.bartshealth.nhs.uk/st-bartholomews>
 85. Rosendaal FR, Cannegieter SC, Van Der Meer FJM, Briet E. A Method to Determine the Optimal Intensity of Oral Anticoagulant Therapy. *Schattaucr Vcrlagsgesellschaft mbH*. 1993;69(3):236–9.
 86. Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. *Nephron*. 1976;16:31–41.
 87. FormularyComplete BHB provided by. Barts Health Formulary on BNF. 2015.
 88. Lip GYH, Hart RG, Conway DSG. Antithrombotic therapy for atrial fibrillation. *BMJ* [Internet]. 2002 Nov 2 [cited 2017 Oct 22];325(7371):1022–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12411366>
 89. Keating GM. Apixaban: A review of its use for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Vol. 73, *Drugs*. 2013. p. 825–43.
 90. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost*. 2011;106(5):968–77.
 91. Diener HC, Granger CB, Patel MR. Is there a period of liability with initiation of warfarin in patients with atrial fibrillation? *Eur Heart J*. 2014;35(28):1834–5.
 92. Azoulay L, Dell’aniello S, Simon TA, Renoux C, Suissa S. Initiation of warfarin in patients with atrial fibrillation: Early effects on ischaemic strokes. *Eur Heart J*. 2014;35(28):1881–7.
 93. Health I. TOP 20 GLOBAL PRODUCTS 2015 [Internet]. 2015 [cited 2017 Sep 11]. Available from: [http://www.imshealth.com/files/web/Corporate/News/Top-Line Market Data/Top_20_Global_Products_2015.pdf](http://www.imshealth.com/files/web/Corporate/News/Top-Line%20Market%20Data/Top_20_Global_Products_2015.pdf)
 94. European Medicines Agency. Lixiana (Edoxaban): EPAR summary for the public [Internet]. 2017 [cited 2017 Sep 10]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002629/WC500189048.pdf
 95. European Medicines Agency. Eliquis (Apixaban): EPAR summary for the public [Internet]. 2014 [cited 2017 Sep 10]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002148/WC500107773.pdf
 96. European Medicines Agency. Xarelto (Rivaroxaban): EPAR summary for the public [Internet].

- 2013 [cited 2017 Sep 10]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000944/WC500057109.pdf
97. European Medicines Agency. Pradaxa (Dabigatran etexilate): EPAR summary for the public. 2015;
 98. Electronic Medicines Compendium. Pradaxa 110 mg hard capsules - Summary of Product Characteristics (SPC) - (eMC) [Internet]. [cited 2017 Sep 12]. Available from: <http://www.medicines.org.uk/emc/medicine/20760>
 99. Electronic Medicines Compendium. Xarelto 10 mg film-coated tablets - Summary of Product Characteristics (SPC) - (eMC) [Internet]. [cited 2017 Sep 12]. Available from: <http://www.medicines.org.uk/emc/medicine/21265>
 100. Electronic Medicines Compendium. Eliquis 2.5 mg film-coated tablets - Summary of Product Characteristics (SPC) - (eMC) [Internet]. [cited 2017 Sep 12]. Available from: <http://www.medicines.org.uk/emc/medicine/24988>
 101. Nottinghamshire Area Prescribing Committee. Atrial Fibrillation (Non-valvular): prescriber decision support on anticoagulation Contents Assessing patients for anticoagulation in AF Patient factors and anticoagulant choice Checklist for initiation Warfarin monitoring and reviewing DOAC monitoring. 2014;(Reviewed December 2016).
 102. Vranckx P, Potpara T, Dagres N, Heidbuchel H, Maisel W, Rawn J, et al. Non-vitamin K oral anticoagulants in patients with atrial fibrillation after cardiac surgery: the results of the European Heart Rhythm Association Survey. *Europace* [Internet]. 2016;18(7):1113–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27358360>
 103. Kalavrouziotis D, Buth KJ, Ali IS. The impact of new-onset atrial fibrillation on in-hospital mortality following cardiac surgery. *Chest* [Internet]. 2007;131(3):833–9. Available from: <http://dx.doi.org/10.1378/chest.06-0735>
 104. HK Chopra, GS Wander, Praveen Chandra VK. Atrial Fibrillation Update: A Textbook of Cardiology. JP Medical Ltd, 2017; 2017.
 105. Peter R. Kowey, Adam Mohmand-Borkowski JFB. Clinical Management of Atrial Fibrillation. Professional Communications; 2011. 338 p.
 106. Königsbrügge O, Simon A, Domanovits H, Pabinger I, Ay C. Thromboembolic events, bleeding, and drug discontinuation in patients with atrial fibrillation on anticoagulation: a prospective hospital-based registry. *BMC Cardiovasc Disord* [Internet]. 2016;16(1):254. Available from: <http://bmccardiovascdisord.biomedcentral.com/articles/10.1186/s12872-016-0438-5>

Appendices

Appendix A: POAF Audit Tool

Patient Initials: _____	Patient MRN: _____	Date of Surgery _____
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<u>Patient Details:</u>
Gender: F/ M Age: _____ Weight: _____ Creatinine Clearance: _____ mL/min
Concomitant medication: _____ _____
<u>NOAC Details:</u>
NOAC prescribed: Apixaban/ Dabigatran/ Edoxaban/ Rivaroxaban
Date NOAC initiated: _____
Prescribed dose: _____
Clinical Notes (significant bleeding, thromboembolic events): _____ _____ _____

<u>Warfarin Details:</u>
Anticoagulation Clinic: _____
TTR at six weeks post discharge: _____ %

<u>LMWH Details</u>
LMWH Dose: _____
Date LMWH initiated: _____

<u>Cardiothoracic follow up details:</u>
Date of cardiothoracic follow up appointment: _____
SR/ AF
If back into SR, was Anticoagulant stopped? Yes / No

Discharge date: _____

Appendix B: Abstract submission for European Society of Clinical Pharmacy: International Symposium in Heidelberg, Germany, from the 9th to the 11th October 2017.

Abstract Submission for ESCP 2017 Symposium

Hospital Pharmacy - Pharmaceutical Care

ESCP17SY-1127

Anticoagulation management for post-operative atrial fibrillation after cardiac surgery

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Please specify your abstract type: Descriptive abstract (for projects)

Background and Objective: Oral anticoagulation is essential following post-operative atrial fibrillation (POAF). Although warfarin is commonly used, its efficacy is dependent on time in therapeutic range (TTR) >65%. Direct oral anticoagulants (DOACs) are an alternative option, however the optimal time to initiate post-operatively is unknown, due to exclusion of 'recent surgery' within phase 3 clinical trials.

Design: To identify the number of patients that revert back to sinus rhythm (SR) 6 weeks following POAF following cardiac surgery and assess which class provides optimal stroke prevention for this period. A retrospective study was conducted at large tertiary centre analysing patients that developed POAF after cardiothoracic surgery from January 2016 to January 2017 reviewing both patient and surgical data.

Results: Sixty-four patients had developed POAF, of which 39 (60.9%) and 25 (39.1%) were prescribed warfarin and DOAC respectively. 13 (33.3%) patients had a confirmed TTR <65%, reflecting poor anticoagulant control with warfarin. DOACs were initiated on an average of 8.36 ± 3.74 days post-operatively. 21 (53.8%) patients in the warfarin group and 11 (44%) patients in the DOAC group were confirmed to be in sinus rhythm 6 weeks after discharge. Among these patients, 37.5% stopped the anticoagulation when in SR.

Conclusion: A TTR <65% for warfarin shows that acute optimal anticoagulation management is difficult to achieve, especially for the short term patients that revert back in to SR. DOACs may possibly be a more effective alternative, initiating 8 days post operatively. However further studies need to be conducted to ensure optimal dose of each DOACs in the acute post-operative phase.

Disclosure of Interest: None Declared