# Prediction of new-onset postoperative atrial fibrillation and long-term outcomes. Aspects in relation to cardiac surgery

Rasmussen, Louise Feilberg

*DOI (link to publication from Publisher):*
10.54337/aau527271134

*Publication date:*
2022

*Document Version*
Publisher's PDF, also known as Version of record

# PREDICTION OF NEW-ONSET POSTOPERATIVE ATRIAL FIBRILLATION AND LONG-TERM OUTCOMES

ASPECTS IN RELATION TO CARDIAC SURGERY

BY
LOUISE FEILBERG RASMUSSEN

DISSERTATION SUBMITTED 2022

AALBORG UNIVERSITY
DENMARK

# PREDICTION OF NEW-ONSET POSTOPERATIVE ATRIAL FIBRILLATION AND LONG-TERM OUTCOMES

## ASPECTS IN RELATION TO CARDIAC SURGERY

by

Louise Feilberg Rasmussen

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2022

Dissertation submitted: 11.11.2022

PhD supervisor: Sam Riahi, MD, PhD
Department of Clinical Medicine, Aalborg University &
Department of Cardiology,
Aalborg University Hospital

Assistant PhD supervisors: Professor Emeritus Jan Jesper Andreasen, MD, PhD
Aalborg University

Professor Søren Paaske Johnsen, MD, PhD
Aalborg University

Professor Gregory Lip, MD, PhD
University of Liverpool & Aalborg University

Søren Lundbye-Christensen, PhD,
Aalborg University

PhD committee: Associate Professor Ashkan Eftekhari
Aalborg University, Denmark

Associate Professor Ulrik Dixen
University of Copenhagen, Denmark

Professor Anders Jeppsson
University of Gothenburg, Sweden

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-794-9

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk



Printed in Denmark by Stibo Complete, 2022

# ENGLISH SUMMARY

Postoperative atrial fibrillation (POAF) is a very common complication after cardiac surgery, with an incidence of 15-60 % depending on the definition and type of surgery. The arrythmia usually presents itself two to three days after surgery. Previously, POAF was believed to be a benign and transient phenomenon. However, recent research has shown that patients who develop POAF after cardiac surgery have an increased risk of other complications, such as stroke, and a higher risk of long-term mortality.

Various measures can be taken to provide the patient with optimal prophylaxis and postoperative care in relation to POAF. However, potentially serious adverse events from antiarrhythmic drugs as well as limited hospital budgets necessitate a more targeted strategy. A risk prediction model for POAF would ideally select patients at high risk who could benefit from focused prophylaxis and therapy, but to date, no model has been developed with sufficient accuracy and performance to be implemented in clinical practice. Another aspect of potential complications related to POAF is how to reduce the potential thromboembolic risk associated with atrial fibrillation (AF). To decrease this risk, an assessment of each patient's individual risk of ischemic stroke of cardioembolic origin is needed.

This thesis aims to provide new knowledge about potential new prediction models for POAF after cardiac surgery. Furthermore, to investigate the etiology of strokes as well as long-term outcomes following coronary artery bypass grafting (CABG) with emphasis on POAF as a predictor for ischemic strokes as well as prognosis.

It is based on three studies; in the first study, an investigation of the use of the $C_2$HEST score in predicting POAF was performed. The score consists of readily available variables in the clinic and is simple to use. Although the risk score has been tested in populations with incident AF of nonsurgical characteristics with good results, our study showed that the performance of the risk model in a population of patients undergoing cardiac surgery was limited. In the second study, a prediction model for POAF was developed with the use of postoperative atrial-derived ECG. The highest predictive score was achieved using age, BMI, and two atrial-derived components from the temporary epicardial pace wires, which confirms previously published studies showing that markers of atrial function can serve as good predictors of POAF.

The final study was a large retrospective study drawing on data from five registries in Denmark to investigate the association of POAF with postoperative ischemic stroke. The results showed that patients with POAF had a higher incidence of cardioembolic stroke than non-POAF patients, although the finding was not statistically significant.

This PhD dissertation provides insights into new approaches to developing prediction models for the risk of POAF in patients undergoing cardiac surgery and highlights the importance of establishing the most likely cause of stroke when planning the best stroke prophylaxis postoperatively. Alongside other scientific contributions, the presented studies may support further progress in the risk prediction of POAF and provide valuable knowledge about postoperative cardioembolic stroke risk in patients undergoing CABG.

# DANSK RESUME

Postoperativ atrieflimren (POAF) er en hyppig komplikation efter hjertekirurgi og forekommer hos ca. 20-40 % af patienterne afhængig af definition og operationstype. Typisk opstår hjerterytmeforstyrrelsen på 2. eller 3. dagen efter operationen. Hvor man tidligere opfattede komplikationen som et forbigående og benignt fænomen, tyder større studier nu på, at komplikationen er forbundet med øget risiko for andre komplikationer, heriblandt apopleksi samt øget mortalitet. Selvom hjertekirurgiske indgreb, brug af hjerte-lungemaskine og anæstesi er forbedret betydeligt gennem de sidste årtier, vedbliver POAF at blive en hyppig komplikation.

Der er flere forebyggende foranstaltninger man kan iværksætte i daglig klinisk praksis, for at forebygge og behandle POAF. Dog er mange antiarytmika forbundet med betydelig risiko for bivirkninger og desuden vil administration af medicin til patienter i risiko ikke altid være omkostningseffektiv. For at lette den kliniske beslutningstagning, kan en effektiv klinisk model til risikostratificering for POAF være et godt redskab for målrettet terapi, men indtil videre er der ikke udviklet en model med tilstrækkelig nøjagtighed og validitet til implementering i daglig praksis. Et andet vigtigt aspekt i forhold til komplikationer forbundet med POAF, er reduktionen af potentielle thromboemboliske komplikationer i relation til atrieflimren. For at kunne vurdere den reelle risiko for postoperativ iskæmisk apopleksi, er det nødvendigt med en vurdering af den specifikke risiko for apopleksi af kardioembolisk type.

Denne ph.d.-afhandlings formål er at bibringe ny information om prædiktion af POAF samt at undersøge ætiologien af de apopleksier, som patienter, der har fået foretaget koronar bypassoperation (CABG), rammes af.

Ph.d.-afhandlingen bygger på tre studier. I det første studie undersøgte vi om $C_2$HEST scoren kan anvendes til prædiktion af POAF. Risikoscoren er nem at anvende og består af komponenter, der er let tilgængelige i klinisk praksis. Selvom $C_2$HEST scoren er blevet udviklet til og testet i flere populationer med incident atrieflimren med gode resultater, viste vores studie at den prædiktive evne er begrænset i en population af hjertekirurgiske patienter. I det andet studie, udviklede vi en risikomodel til prædiktion af POAF ud fra postoperative atriale elektrogrammer. Den bedste prædiktive model bestod af alder, BMI og to variable dannet fra de atriale elektrogrammer og bekræfter tidligere publicerede studier, der viser at markører for atrial funktion fungerer som gode prædiktorer. Det sidste og tredje studie var et større retrospektivt registerstudie, der bygger på 10 års data fra hjertekirurgiske patienter, der har fået foretaget isoleret CABG. Her viste vi at forekomsten af iskæmiske apopleksier og risiko for død ikke er associeret med forekomsten af POAF, når der justeres for risikofaktorer. Ydermere at fordelingen af iskæmiske apopleksier var

forskellig i POAF versus non-POAF-patienter, med en højere andel af kardioemboliske apopleksier i POAF-patienter. Dette fund var dog ikke signifikant.

Dette ph.d.-studie bidrager med ny viden om prædiktorer for POAF og tester nye risikomodeller til at prædiktere komplikationen. Ydermere belyser afhandlingen vigtige aspekter i forekomsten og typer af apopleksier som hjertekirurgiske patienter rammes af. Sammen med andre videnskabelige bidrag, kan studierne i denne afhandling bidrage til at optimere prædiktionsmodellerne for POAF og ydermere bidrage med vigtig information om risiko for postoperative iskæmiske apopleksier blandt patienter, der har fået foretaget CABG.

# ACKNOWLEDGEMENTS

The work that forms the basis of this thesis was carried out at the time I was employed as a clinical assistant to the Professor at the Department of Cardiothoracic Surgery, Aalborg University Hospital. My interest in postoperative atrial fibrillation was developed during my time as a junior doctor at the department, and fortunately, I was able to spend three years exploring the subject.

This research and thesis would not have been possible without great help along the way. First and foremost, I owe my greatest gratitude to my principal supervisor Professor Emeritus Jan Jesper Andreasen, for giving me the opportunity to nerd out and explore research as well as developing my presenting and teaching skills. You have always provided constructive feedback and have an excellent ability to know when I was hitting a dead-end and get me back on track.

I would like to say thank you to Søren Lundbye-Christensen for patiently walking me through STATA coding and statistical methods; much to my initial disbelief in my statistical capabilities, I truly enjoyed our sessions together. Søren Paaske Johnsen for invaluable help with methodological challenges and for providing insights to the world of Clinical Epidemiology. Sam Riahi for taking me in as your PhD student during the final year and providing important inputs from a nonsurgical cardiology perspective. It was a great privilege to have Dr Gregory Lip as a cosupervisor on this project, with his tremendous knowledge on atrial fibrillation and risk models.

I would like to express my immense gratitude to all of the persons who have provided their invaluable support and assistance as coauthors and external experts along the way: Claus Graff, Jacob Melgaard, Grethe Andersen & Janne Nørgaard Mortensen.

The research for this thesis was financially supported by AP Møller Fonden and AF Study Group, Aalborg University. Thank you to all of the staff at the Department of Cardiothoracic Surgery and the Cardiothoracic ICU, Aalborg University Hospital, especially my colleagues in the Research Unit: Dorthe Nøhr, Jeanett Sylvan Nielsen, Hanne Skinbjerg and Allan Vestergaard Danielsen.

I am also thankful for my fellow PhD students: Nadja Albertsen, Inaluk Kleist, Jens Nørgaard and Marie Haase Juhl for getting me out of corona-solitude and providing a forum with invaluable feedback, advice, and endless amounts of coffee.

Finally, my warmest thanks go to Alexander and my children for their love and support.

Louise Feilberg Rasmussen, MD

# TABLE OF CONTENTS

# ABBREVIATIONS

aEG: atrial electrogram
AF: atrial fibrillation
AI: artificial intelligence
ATC: anatomical therapeutic chemical classification
AUC: area under the curve
BMI: body mass index
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CAG: coronary angiography
$C_2$HEST score: coronary artery disease or chronic obstructive pulmonary disease (1 point each); hypertension (1 point); elderly (age ≥75 years, 2 points); systolic heart failure (2 points); thyroid disease (hyperthyroidism, 1 point)
CHF: congestive heart failure
CI: confidence interval
COPD: chronic obstructive pulmonary disease
CPR: (Danish) civil registration number
DPR: Danish national patient registry
DNPR: Danish national prescription registry
ECC: extracorporeal circulation
ECG: electrocardiogram
HR: hazard ratio
ICD: internal classification of diseases
IHD: ischemic heart disease
LVEF: left ventricular ejection fraction
MI: myocardial infarct
NOAC: novel oral anticoagulants
NPV: negative predictive value
OAC: oral anticoagulant
OR: odds ratio
PCI: percutaneous coronary intervention
POAF: postoperative atrial fibrillation
PPV: positive predictive value
ROC: receiver operating curve
SR: sinus rhythm
TIA: transient ischemic attack
TOAST: Trial of Org 10172 in Acute stroke Treatment (classification of ischemic stroke)
uFRAC: unipolar fractionation
uLAT: unipolar local activation time
VF: ventricular fibrillation
VT: ventricular tachycardia
WDHR: Western Denmark Heart Registry

# LIST OF PAPERS

This thesis is partly based on the following three papers, which are referred to in the text by Roman numerals.

**Paper I:**

LF Rasmussen, JJ Andreasen, S Lundbye-Christensen, S Riahi, S Paaske Johnsen, G Y.H. Lip, Using the C2HEST score for predicting postoperative atrial fibrillation after cardiac surgery: A report from the Western Denmark Heart Registry, the Danish National Patient Registry, and the Danish National Prescription Registry, Journal of Cardiothoracic and Vascular Anesthesia, 2022.

**Paper II:**

LF Rasmussen, JJ Andreasen, S Riahi, G Y.H. Lip, S Lundbye-Christensen, J Melgaard, C Graff (2022) Prediction of postoperative atrial fibrillation with postoperative epicardial electrograms, Scandinavian Cardiovascular Journal, 56:1, 378-386, DOI: 10.1080/14017431.2022.2130421

**Paper III:**

LF Rasmussen, JJ Andreasen, S Riahi, S Lundbye-Christensen, S Paaske Johnsen, G Andersen, J Mortensen, Risk of subtypes of strokes following new-onset postoperative atrial fibrillation in cardiac surgery. A population-based cohort study, JAHA: Journal of the American Heart Association, 2022, In press.

# CHAPTER 1. INTRODUCTION

Since its development in the 1960s, open cardiac surgery has undergone tremendous advancements with respect to the procedures themselves, the cardiopulmonary bypass system and anesthetic and postoperative intensive care. Surgery is now being offered to a wider range of patients in terms of comorbidities and advanced age. Approximately 2500 adult open chest cardiac surgical procedures are performed in Denmark every year[1]. In comparison, the US performs approximately 300.000 operations annually[2].

Despite overall advancements, new-onset postoperative atrial fibrillation (POAF) remains a very common complication after cardiac surgery. It occurs in approximately one-third of the patients undergoing cardiac surgery, usually within the first week[3]. Although the arrythmia is mostly self-limiting, and the majority of patients are discharged in sinus rhythm, researchers have shown that the rate of subsequent atrial fibrillation (AF) development is higher in the patients with episodes of POAF than in those without[4,5]. Furthermore, patients experiencing POAF after cardiac surgery have a longer hospital stay and greater short- and long-term mortality than with patients without this postoperative complication[6–8].

Prevention of POAF through prophylactic drugs has been shown to be effective in multiple studies[9]. However, indiscriminate use of treatments as part of a routine may cause an unacceptable risk of side effects and added hospital costs for the patients. Identifying patients at high risk of developing POAF would help guide the clinicians in providing targeted prophylaxis and postoperative care in relation to stroke prophylaxis. Furthermore, targeted prevention may most likely be cost-effective.

Research into the prediction of POAF has accelerated in recent years through the identification of key predictors related to patient characteristics and increased knowledge of the pathophysiology of POAF, combined with improved technology for the development of valid prediction models (machine learning, artificial intelligence (AI), etc.). Even though strong efforts have been made to provide clinicians with a valid and easy-to-use prediction model for POAF in cardiac surgery, none thus far been of adequate quality for implementation in daily practice.

Identifying patients at risk of POAF may also benefit patients in the long term in relation to later complications and adverse events.

The evidence about a possible association between POAF and late ischemic stroke and other thromboembolic complications is conflicting, and several larger registry-based studies have not been able to answer whether the risk is reduced or equal to nonsurgical de novo AF[10,11]. Thus, the question of whether long-term anticoagulants are warranted for this group is still unanswered.

This PhD thesis will focus on different aspects of POAF, and the multifaceted approach needed in the risk assessment and care of the cardiac surgical patients with this arrhythmia. It will highlight the different aspects concerning risk prediction models for POAF and touch upon some of the long-term consequences of POAF with emphasis on stroke and death.

This thesis consists of 10 chapters and is divided thematically into two parts: one focuses on predictors and risk prediction models for POAF, and one is concerned with long-term outcomes in relation to POAF and stroke. After this brief introduction in Chapter one, Chapter two presents an overview of the available knowledge about POAF and its implications for patients undergoing cardiac surgery. Chapter three introduces the aims and hypotheses of the thesis. In Chapter four, the data sources and settings for the included papers are described.

In Chapters five and six, the results of the three papers are presented and placed in the context of the current available literature on these subjects. It reviews and critiques highlighted papers on the topic and introduces the applied risk scores studied.

Chapter 8 discusses the main study findings and the studies' limitations and strengths. Before this, Chapter 7 will provide some methodological considerations in relation to the papers included in the thesis. Finally, Chapter 9 will focus on some of the perspectives of the thesis, and the remaining part of the thesis (Chapter 10) will provide the conclusions.

Whenever the abbreviation POAF is used in this thesis, it will refer to the phenomenon of new-onset postoperative atrial fibrillation. Although POAF also occurs in noncardiac surgery patients, this thesis will focus solely on POAF in a cardiac surgery setting.

The next chapter of the thesis will give an overview of postoperative complications following cardiac surgery, with an emphasis on POAF, and touch upon some of the identified pathophysiological mechanisms and predictors of POAF. It examines the implications for the patients and strategies to prevent and treat the complications.

# CHAPTER 2. BACKGROUND

## 2.1. POSTOPERATIVE COMPLICATIONS IN RELATION TO CARDIAC SURGERY.

Today, patients referred for coronary revascularization procedures are older, typically with several comorbidities, and are likely to have more extensive extracardiac vascular disease than patients evaluated for such procedures in the past[12]. Despite more complex procedures on high-risk patients and an ageing patient group, the overall mortality rate for cardiac surgery has continued to decline[13]. Nevertheless, adverse cardiac and neurologic outcomes are still a major concern for the older patients[14].

Coronary artery bypass grafting (CABG) has been a beneficial treatment for coronary artery disease (CAD) since its development in the 1960s and is the most commonly performed cardiac procedure. It is being offered as a symptom-relieving treatment primarily for patients with coronary artery disease in the left main coronary artery, multivessel disease and patients with CAD and diabetes[15]. The second most commonly performed surgical procedure is replacement of the aortic valve, followed by mitral valve repair or substitution. Most patients will have surgery performed with extracorporeal circulation (ECC), which functions as a physiological substitute for the heart and lungs during surgical procedures on the heart. The use of ECC often triggers a significant inflammatory response due to the patient's blood coming into contact with the synthetic surfaces of the tubes and filters of the heart-and-lung machine[16]. Other potential complications associated with the use of ECC involve vasospasm and disturbances of platelet-endothelia cell interactions, as well as potential allergic reactions to the protamine sulphate used for reversing heparin[17]. Off-pump surgery for isolated CAD has been introduced in order to eliminate the risks associated with the use of ECC[18].

In a recent study, Pahwa *et al*. investigated complications after cardiac surgery and their impact on survival in 26221 patients[19]. In this study, postoperative blood product use was considered a complication and was the most common (47.3%), followed by POAF (32%). Other less common complications were prolonged ventilation, renal failure, reoperation for bleeding and the need for an ICD/pacemaker. Stroke, renal failure, and pneumonia were significantly associated with higher mortality. The 30-day mortality following isolated first-time CABG is approximately 3.2% in Denmark, in line with cardiac centres in the US and the UK[20–22]. However, a direct comparison between countries is difficult, as most cardiac centres do not have follow-up data on patients after they are discharged from the surgical ward. In recent decades, postoperative complications, including POAF, have been better handled with improved technology and refined procedures.

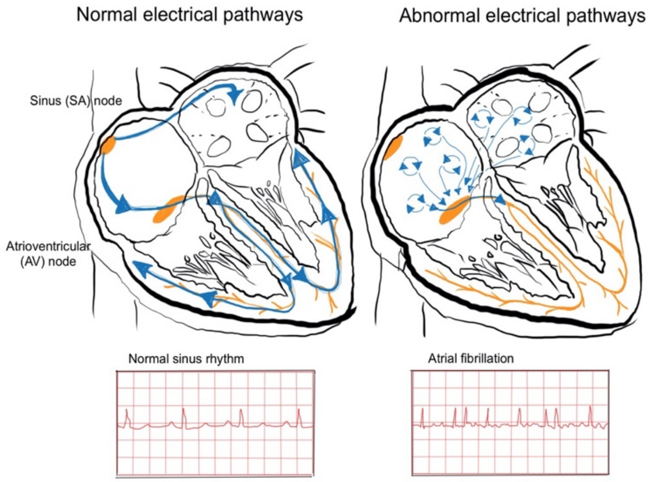
### 2.1.1. ABOUT POAF

POAF is the most common arrythmia and the most common adverse event after cardiac surgery[23]. Consequently, it has been the subject of intensive research over the past decades. Several studies have shown the effect of preventive and treatment strategies, but the incidence remains high. In fact, there has been no decrease in the risk-adjusted incidence of POAF after CABG [24].

POAF was previously believed to be a mostly transitionally and benign phenomenon, but research has provided new insights concerning its frequent complications and their long-term consequences. Several studies investigating the long-term outcomes of POAF contradict the notion that new-onset POAF is merely a benign phenomenon. El-Chami *et al.*[25] found a relative increase in mortality of 21% over a mean follow-up period of six years among POAF patients. Patients undergoing cardiac surgery have a much higher risk of POAF than with patients undergoing noncardiac surgery[7]. Additionally, there is a tendency towards a higher risk of POAF when cardiac surgery becomes more complicated. Most studies report a higher risk of POAF in connection to valve and concomitant revascularization surgery than for isolated CABG. When compared with the much less invasive percutaneous coronary intervention (PCI) procedure, the incidence of POAF has been reported to be much higher after surgery[26]. Furthermore, patients experiencing POAF after surgery carry an up to fivefold risk of later AF recurrences and stroke in the months after the surgery[27].

POAF does not differ from AF in its definition and presentation: it is defined as a supraventricular tachyarrhythmia with consequent neutralized mechanical atrial contractions (Figure 1).

*Figure 1. Electrical pathways in sinus rhythm and atrial fibrillation*



This results in an irregular rhythm on the ECG; the normal P waves are replaced by fibrillatory waves that vary in size and shape. The QRS-complexes are typically irregular and have a rapid rate of 150 to 200 beats/min[28]. This can be accompanied by symptoms such as palpitations, shortness of breath and dizziness, but most patients are asymptomatic.

The pathophysiology underlying the development of POAF still needs to be established; it is most likely caused by multiple factors. Several risk factors and electrophysiologic changes associated with POAF have been identified through ongoing research. They can be divided into factors concerning the patient, risk factors in connection with the operation and finally the postoperative factors.

*Figure 2 gives an overview of the identified risk factors with the best evidence.*

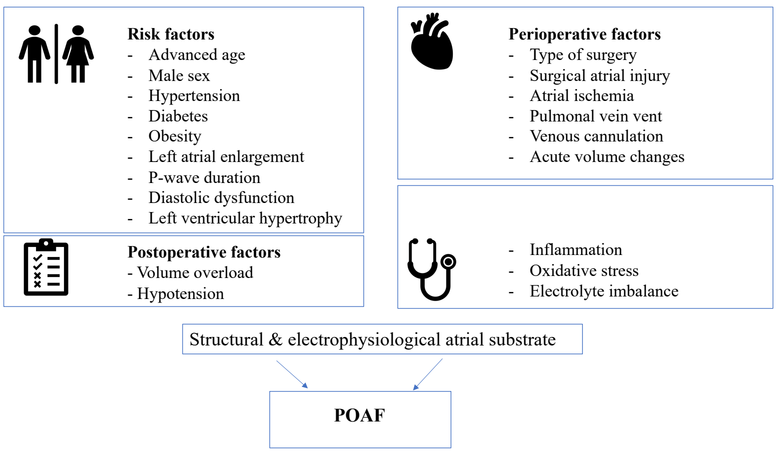



*Figure 2. Patients developing POAF most likely have a preexisting atrial structural substrate that interacts with pre- and postoperative factors. Adapted from Echahidi [29]*

The risk factor with the strongest association with POAF across multiple studies has been increasing age[4,30–32]. Other patient-related risk factors independently associated with POAF are male sex, history of AF, congestive heart failure, hypertension, chronic obstructive pulmonary disease (COPD), and obesity[7,33,34].

Surgical trauma itself may also induce conditions that elevate the risk of POAF. Hypotension or inadequate cardioprotection during the procedure, pericarditis and myocarditis, postoperative decreases in left ventricular function associated with elevated atrial pressures, administering adrenergic and cholinergic drugs that change the chemical balance, hypoglycemia or hypothyroidism, and reflex autonomic activation have all been shown to increase the susceptibility to POAF[33].

When investigating the pathophysiology behind POAF, the necessary factors for disturbances of the normal physiological conduction system of the heart are similar to nonsurgical AF. In 1964, Moe *et al.*[35] proposed the multiple wavelet theory of AF, which still forms the basis of our understanding of AF pathophysiology. Multiple propagating waves in the presence of correspondently short and heterogeneous refractoriness of the atrial myocardium sustain the supraventricular arrhythmia. Later, it was shown that even a single premature atrial beat blocked in the refractory regions of the atrium could cause re-entrant activation, resulting in multiple wavefronts with subsequent fibrillation[36]. Moreover, AF also causes changes in atrial electrical conduction and can maintain or facilitate reinduction of the tachyarrhythmia: "AF causes AF"[37].

The literature distinguishes between electrical and structural remodeling as a prerequisite for the development of AF. Large atria and abnormal intrathoracic pressure are often seen in patients with a high body surface area; this may increase their susceptibility to POAF through altered electrophysiological properties[38]. Proarrhythmic changes are also often seen in congestive heart failure or valve pathology that seem to cause dilated atria. On the biochemical level, the structural changes in the atria involve upregulating gene expression that favors shortening of the refractory period[34].

Thus, the multifactoral mechanism of POAF is likely to be similar to that in patients with nonsurgical AF, although electrophysiologic studies of POAF are sparse. From the presented overview of the etiology of POAF, it is fair to say that in at least some of the patients developing POAF after cardiac surgery, substantially altered atrial function is already present preoperatively.

#### 2.1.1.1 Clinical features and diagnostics

The incidence of POAF varies considerably with the definition of POAF, population and type of surgery. As previously stated, POAF is a very common complication after cardiac surgery; it occurs in approximately 30% of CABG cases, approximately 50% of valve surgery cases and up to 60 % of combined graft and valve surgery cases[39,40]. It is likely that there is a higher incidence of POAF than reported because some centers only record POAF when it requires treatment, as demonstrated by Filardo *et al.*[41]. An investigation of 9268 patients revealed a 6.4% higher incidence of POAF when including the observed incidences on telemetry, and they also found a significantly higher risk of mortality (odds ratio (OR) 2.08, 95% confidence interval (CI), 1.17-3.69) than those captured. Furthermore, the reported increased incidence over the last 20 years is most likely due to an increased focus on the complications, advanced age of the patients and increased complexity of cardiothoracic surgery[28,42].

The onset of POAF is typically occurs on day two or three but can occur at any point during the hospital stay[43,44]. Often, the patients are asymptomatic, but some patients do experience palpitations, chest pain, shortness of breath, or generalized anxiety. Other hemodynamic complications, such as congestive heart failure, renal insufficiency, infections, increased need for pacing or inotropic support, have been shown to be associated with POAF[33,45]. Several studies have shown an association between POAF and an increased risk of thromboembolism, stroke and death[4,30,46,47]. A direct causal relationship between POAF and these complications has not been established; most likely, advanced age and structural damage to the heart in combination with POAF will result in a higher propensity for other complications.

POAF often converts to sinus rhythm spontaneously, regardless of the therapeutic strategy, but persistent episodes of AF and those where the patient is hemodynamically unstable require clinical intervention. Consequently, patients who experience POAF often have with longer hospital stays and undergo additional investigations, resulting in increased health care costs[30,48].

#### 2.1.1.2 Prevention and Treatment of POAF

There are limited approaches available to effectively prevent POAF. Those with the highest levels of evidence are summarized and discussed in the following review.

In the 2020 European Society of Cardiology (ESC) Guidelines for the management of AF developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), it is recommended that patients start treatment with beta-blocker therapy after cardiac surgery (Class I, Level A) [49]. Another recommendation is amiodarone, which can be given as a prophylactic therapy before cardiac surgery (Class I, Level A).

A large meta-analysis from 2006 found that the odds ratio for the effect of beta-blockers on the incidence of POAF was 0.36 (95% CI 0.28-0.47, P <0.001), but after trials confounded by postoperative nonstudy beta-blockers withdrawal were excluded, the OR was 0.69 (95% CI 0.54-0.87, p<0.001)[50]. Similarly, the eighteen trials included evaluating amiodarone for the prevention of POAF showed that amiodarone reduced POAF from an average incidence of 33.2% in the control group to 19.8% (OR 0.48, 95% CI 0.40-0.57). However, the administration of amiodarone was associated with bradycardia and ventricular tachycardia (VT) or ventricular fibrillation (VF).

In the randomized RASCABG trial, 259 patients undergoing elective, isolated CABG were allocated to receive either amiodarone or placebo as prophylaxis for POAF with a follow-up of 30 days[51]. The occurrence of POAF was significantly reduced in the group receiving prophylactic amiodarone compared with the placebo group (11% vs.

26%, $p<0.01$). The postoperative prophylactic treatment did not result in a reduction in the length of stay but was associated with a lower cost (mean total cost per patient was €7639 in the amiodarone group and € 7814 in the placebo group ($p>0.01$))[52].

A number of recent studies have shown beneficial effects of simple or complex overdrive pacing or atrial demand pacing (30-45 bpm) for the prevention of POAF[50]; however, in the European Association for Cardio-thoracic Surgery and the Canadian Cardiovascular Society guidelines[53,54], only biatrial pacing is recommended as an intervention that significantly decreases the occurrence of POAF.

In some studies, decreased levels of the serum electrolytes potassium and magnesium have been associated with POAF. Rectifying these levels can be prophylactic[50,55].

For patients requiring treatment of POAF, the pharmacologic strategies are either rate or rhythm control, and when appropriate, treatment with anticoagulation. The guidelines recommend the use of one or more of the abovementioned medications: beta blockers, amiodarone and calcium channel blockers[28,54]. In daily clinical practice, usually one agent is administered at a time, as all three drugs may lead to bradycardia and hypotension. In a recent prospective clinical study[56] comparing rate versus rhythm control, 523 patients who underwent cardiac surgery and subsequently developed POAF were randomly assigned to either receive medications to slow the heart rate or were treated with amiodarone with or without a rate-slowing agent. If POAF persisted for 24 to 48 hours after randomization, direct-current cardioversion was recommended. The results showed that neither treatment strategy offered a significant clinical benefit over the other in terms of length of stay, bleeding or thromboembolic events, postoperative mortality, or freedom from AF at 60 days.

Although POAF may once have been considered a benign and predominantly benign complication, its associations with increased morbidity, such as renal dysfunction, infections and stroke, and increased mortality, are now well established. Hence, there is a need for more studies on prediction models as well as research into long-term outcomes after POAF.

# CHAPTER 3. AIMS AND HYPOTHESES

The overall aims of this thesis were to develop and evaluate new predictive models of POAF in cardiac surgery as well as to explore the type of strokes and long-term outcomes following POAF after CABG. This thesis is based on three studies that all centre around POAF after cardiac surgery, and these studies are discussed in relation to the literature.

More specifically, the aims of the individual new studies included in the thesis were as follows:

1) To test the $C_2$HESTscore's ability to predict POAF after cardiac surgery in a large Danish population and compare its performance with an age-modified m$C_2$HEST score as well as with the $CHADS_2$ and $CHA_2DS_2$-VASc scores.
   We hypothesized that the $C_2$HEST-score would perform equally well in a cardiac surgical population as it has been shown to perform well in nonsurgical AF populations.
2) To investigate whether it is possible to predict POAF following cardiac surgery with the use of atrial electrograms recorded early postoperatively from temporal pacing wires routinely placed on the epicardial surface of the right atrium.
   We hypothesized that because variables associated with atrial function serve as good predictors of POAF, variables derived directly from the atria would perform well as predictors in a model.
3) To investigate the types of ischemic strokes that patients undergoing CABG suffer from and whether POAF results in an increased risk of later cardioembolic stroke and mortality.
   We hypothesized that patients suffering from ischemic stroke after cardiac surgery and POAF are more likely to suffer from cardioembolic stroke than patients who do not have this complication.

# CHAPTER 4. DATA SOURCES AND SETTING

In this chapter, a summary of the materials and methods for each study included in this thesis is provided. A detailed description can be found in the respective published papers.

**Danish registries in Studies I and III**

The Danish registries provide unique possibilities for etiological understanding and knowledge of the possible prevention of certain diseases. All Danish citizens are registered with a unique personal identification number, their CPR-number, which is used in all national registers, facilitating linkage among all the national registers.

*Western Denmark Heart Registry*

The Western Denmark Heart Registry (WDHR) is a clinical quality database, containing data on all adult patients in Western Denmark referred for coronary angiography (CAG), PCI or cardiac surgery. It serves as a monitor for the quality of cardiac intervention in Central and Western Denmark, comprising approximately three million inhabitants, which is equivalent to 55% of the Danish population[57,58].

*The Danish Civil Registration system*

The Danish Civil Registration system was established in 1968, and every resident in Denmark is provided with a unique civil registration number at birth or immigration. The unique 10-digit number, their CPR-number, consists of 6 digits representing the date of birth, followed by 3 serial digits that represent the century of birth, and the last digit signifies the sex (even for females, odd for males). The registry contains information on name, sex, date of birth, place of birth, citizenship, identity of parents and vital status for each citizen in Denmark[59]. Because registration is required by law, the data quality is very high and is continuously validated by its use in all public institutions[59].

*The Danish National Patient Register*

The Danish National Patient Register (DPR) has registered all hospital admission and discharge diagnoses in Denmark since 1977. Diagnoses are classified according to the International Classification of Diseases (ICD). From 1977 through 1993, the ICD-8 version was used, and the newest ICD10 version was used from 1994 and onwards. Information on emergency room contacts and hospital outpatient clinics has been available since 1995[60]. All contacts with the Danish health care system are registered with a unique record ID, that can be linked to the CPR-number. In addition to administrative data, such as municipality and region of residence, the registry contains information on admission type (acute or elective, etc.), contact type (in- or outpatient), specialty of medicine, department, contact diagnoses and dates of admission and discharge.

*The Danish National Prescription Registry*

The Danish National Prescription Registry (DNPR) contains individual-level information on all prescription drugs, including Anatomical Therapeutic Chemical classification (ATC) codes and units, claimed from Danish pharmacies since 1995[61].

**Clinical setting for study II**

The Department of Cardiothoracic Surgery, Aalborg University Hospital, is one of four cardiac surgical centres in Denmark, providing care for the inhabitants of the Northern Region (approx. 600.000 citizens). Between 350-400 open adult cardiac surgical procedures are performed every year in this hospital.

## 4.1. ETHICAL AND LEGAL ISSUES

In Denmark, no ethical approval is necessary for studies using data based entirely on registries.

Study I and II were approved by the institutional review board at Aalborg University Hospital (id- number 2020-022 and 2020-015).

Study III was approved by the Danish Patient Safety Authority (3-3013-3229/1 and 31-1522-73) and registered in the North Denmark Region research database(id-2019-115).

The chapter that follows will present the theoretical background for the first part of this thesis by reviewing the current literature on the prediction models for POAF after cardiac surgery.

# CHAPTER 5. PREDICTING POAF

As mentioned in the previous paragraphs, 30 to 40% of cardiac surgical patients who experience POAF are at increased risk of renal dysfunction/failure[32,62], stroke[30,63], and congestive heart failure[11]. These complications often necessitate more health care resources with a longer need for intensive care and extended hospital stays. These outcomes translate into a considerable financial impact; one study estimates an annual cost of approximately $2 billion specifically for POAF-related care[29].

The adverse effect of preventive/therapeutic interventions and the costs of longer hospital stays and medical treatments make a more targeted strategy necessary. Hence, research into valid prediction models that can identify patients at high risk of POAF has markedly increased.

## 5.1. PREDICTION MODELS IN GENERAL

Risk prediction models help clinicians customize treatments and provide guidance for patients. In general, prediction models use variables collected prior to the outcome of interest and should contain fairly easily obtainable variables if they are to be implemented on a clinical basis. The performance of a prediction model is measured on two levels: *calibration*, which is a measure of how well the predicted probability agrees with the observed probabilities, and *discrimination*, which refers to the model's ability to separate diseased individuals from the healthy individuals.

The area under the receiver operating characteristic (ROC) curve (AUC) is the most commonly used performance measure to discriminate between those with and without the outcome (ex POAF vs. non-POAF). ROC is equal to the plot of sensitivity (the true positive rate) on the y-axis and 1 minus specificity (the false-positive rate) on the x-axis for all possible classification thresholds. For binary data, the AUC is identical to C-statistics for time-to-event data, and each cut point is associated with a different sensitivity and specificity[64].

Text Box 1.

| |
|---|
| Terms used in prediction studies.[16]<br><br>Sensitivity: defined as the fraction of true positive classification among the total number of patients with the outcome<br><br>Specificity: defined as the fraction of true negative classifications among the total number of patients without the outcome.<br><br>AUC: the probability that a randomly selected subject who experienced the outcome will have a higher risk score of having the outcome occur than a randomly selected subject who did not experience the outcome. The area under the ROC curve is equivalent to the C-statistic or concordance statistic. |

The AUC is the probability that, for two random individuals from the population (one who experiences POAF and one who does not), the model will predict a higher risk for the first patient. The AUC ranges from 0.5 (the model is no better than flipping a coin) to 1 (a perfect model that predicts every case accurately). When presented alone, the AUC lacks direct clinical application and is best viewed as a summary of the discrimination of the model. It is often more informative to present the ROC with all meaningful classification thresholds and a calculated positive predictive value (PPV) and negative predictive value (NPV)[65]. One should bear in mind that even important predictive variables with significant odds ratios may only have a small impact on the AUC.

## 5.2. EXISTING RISK SCORES

The following risk factors for POAF after cardiac surgery have previously been identified: Advanced age is one of the risk factors for POAF that is most widely reported in the literature[31,32,41,66–70]. Other, often mentioned predictors of POAF in patients undergoing cardiac surgery are hypertension, diabetes, race, body mass index (BMI) >30, previous myocardial infarction (MI), COPD, previous stroke, low LVEF, and type of surgery[31,42,44,71]. Several intraoperative risk factors have also been reported: use of ECC, time on ECC, blood transfusion[33].

The sections below cover the literature on existing prediction models on POAF after cardiac surgery. The systematic search was performed using PubMed and Embase (Appendix A for search terms). Only studies where cardiac surgery patients (n≥ 100) comprised the population and where discriminative ability and calibration were included.

Table 1: Selected prediction models for the risk of POAF in relation to cardiac surgery.

| **Study** | **Patients & Design** | **Time of measurement** | **Predictive Variables chosen** | **AUC** | **Limitations/ Strengths** |
|---|---|---|---|---|---|
| Burgos *et al.* (2021) [67] **COM-AF** | 3113 (654 with POAF (21%)) | Prospective | COM-AF: age (≥75: 2 points, 65-74: 1 point), heart failure (2 points), female sex (1 point), hypertension (1 point), diabetes (1 point), previous stroke (2 points) | AUC=0.78 (95% CI 0.76-0.80) | No internal or external validation/Prospectively collected data |
| Pollock *et al.* (2018) [68] **STS Score** | 8976 CABG patients (2141 with POAF (23.9%) | Retrospectively collected data | 15 variables on procedure and comorbidities [https://riskcalc.sts.org/stswebriskcalc/calculate](https://riskcalc.sts.org/stswebriskcalc/calculate) | AUC=0.58 (95% CI: 0.56-0.59) | No internal or external validation/large dataset |
| Mariscalco *et al.* (2014)[72] **POAF Score** | 17262 (4561(26.4%) developed POAF | Prospective registered, retrospectively collected | Age, COPD, eGFR<15 mL/min or dialysis, emergency op, preoperative IABP, LVEF<30%, valve surgery | AUC=0.64 (95% CI 0.63-0.65) | POAF defined as 15 min AF duration, no distinction btw POAF/atrial flutter/large cohort |
| Thorén *et al.* (2012) [69] | 7115 patients (2270 (32%) with POAF) | Prospectively registered | Age, preoperative serum creatinine ≥150 µmol/l, male sex, NYHA class III/IV, current smoking, prior myocardial infarction (MI) and absence of hyperlipidemia, hypertension, ACC-time and CPB-time | AUC=0.62 (95% CI: 0.61-0.64) | /Isolated CABG |

| | | | | | |
|---|---|---|---|---|---|
| Magee *et al.* (2007) [70] **Atrial fibrillation Risk Algorithm** | 19620 (4215 with POAF (21.5%)) | Retrospectively collected | 14 variables: Age, weight, pump status (on), height, prolonged ventilator usage, preop arrhythmia, ACE inhibitor usage, betablocker usage, anticoagulants, previous CABG, CHF, smoker, chronic lung disease, race | AUC=0.72 | Included patients with AF pre-op/Large dataset |
| Mathew *et al.* (2004)[32] **AF Risk Index** | 4657(1503 with POAF (32.3%)) | Prospective | Age, CHF, LV hypertrophy, aortic atherosclerosis, bicaval cannulation, ACE-inhibitor or betablocker treatment preop. | AUC= 0.77 | No ROC/isolated CABG |
| Amar *et al.* (2004) [73] | 1553 (508 (33%) developed POAF) | Prospective | Age, prior history of AF, P-Wave duration, postoperative low cardiac output | AUC=0.69 | Included patients with known AF preop/ |
| Zaman *et al.* (2000)[74] | 328 (92 (28.2%) developed POAF) | Prospective | Signal-averaged P-wave duration (SAPD), age, sex | - | No ROC/only elective CABG |

*Abbreviations: ACC-time: aortic cross-clamp time; ACE inhibitor: angiotensin-converting enzyme inhibitor; AUC: area under the curve, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, CPB: cardiopulmonary bypass time; eGFR: estimated glomerular filtration rate, IABP: intra-aortic balloon pump, LV: left ventricle; NYHA: New York Heart Association classification for the extent of heart failure; POAF: postoperative atrial fibrillation; STS: Society of Thoracic Surgeons*

As outlined above, previous prediction models on POAF have been sparsely tested outside the population of development. Leaving out the existing risk models, developed for other purposes(Society of Thoracic Surgeons (STS) score), few of the risk models meet the defined criteria for independent validation[64]. The discriminative capacities range from AUC 0.58-0.78, and some risk models include variables that are not very easily obtainable.

The search for a valid prediction model that can accurately predict POAF after cardiac surgery has led many researchers to test existing risk scores designed for other purposes in this setting.

The $CHADS_2$ score, HATCH score and STS score generally showed poor discrimination AUC <0.6 or were assessed in small populations[68,75,76]. The $CHA_2DS_2VASc$ score, an updated $CHADS_2$ score (Table 2), is a simple risk score scheme developed for stroke and thromboembolic risk stratification in patients with AF. This risk model is widely used in clinical practice, despite its only moderate discriminative power during development[77]. It serves as a guidance tool in the decision to initiate life-long anticoagulation in AF patients with a certain score (≥2 for women and ≥1 for men). In this context, the risk model stratifies patients according to a certain threshold and helps physicians identify patients at the greatest risk, which provides more clinical value than discriminative power. Several studies have tested the $CHA_2DS_2VASc$ score's ability to predict POAF after cardiac surgery with moderate to good results[68,78–80].

The $C_2HEST$ score has recently been validated for predicting incidental AF in both the general population and patients with ischemic stroke with good results[81,82]. That is why we thought it would be interesting to see if the score had similar good performance in predicting POAF after cardiac surgery.

**Table 2. Risk scores used in this thesis**

| **Acronym** | **Risk Factor** | **Points** |
|---|---|---|
| $C_2HEST$ score | | |
| $C_2$ | CAD/COPD | 1-2 |
| H | Hypertension | 1 |
| E | Elderly (age ≥ 75 y) | 2 |
| S | Systolic HF | 2 |
| T | Thyroid disease(hyperthyroidism) | 1 |
| | Total points | 0-8 |
| $CHADS_2$ risk score | | |
| C | CHF | 1 |
| H | Hypertension | 1 |
| A | Age > 75 | 1 |
| D | Diabetes | 1 |

| | | |
|---|---|---|
| S | Stroke or TIA | 2 |
| $CHA_2DS_2$-VASc | | |
| C | CHF or LVEF ≤ 40% | 1 |
| H | Hypertension | 1 |
| A | Age ≥ 75 | 2 |
| D | Diabetes | 1 |
| S | Stroke/TIA/thromboembolism | 2 |
| V | Vascular disease | 1 |
| A | Age 65–74 | 1 |
| S | Female | 1 |

*Abbreviations: CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; HF: heart failure; CHF: congestive heart failure; TIA: transient ischemic attack; LVEF: left ventricular ejection fraction.*

## 5.3. STUDY I

Study I was conducted in collaboration with Jan Jesper Andreasen, Søren Lundbye-Christensen, Sam Riahi, Søren Paaske Johnsen and Gregory Y.H. Lip[83].

The study aimed to evaluate the performance of the $C_2$HEST score for the prediction of POAF in a cohort of cardiac surgery patients. The performance of the $C_2$HEST score was compared with an age modified $C_2$HEST score, the $CHA_2DS_2$VASc score and the $CHADS_2$ score.

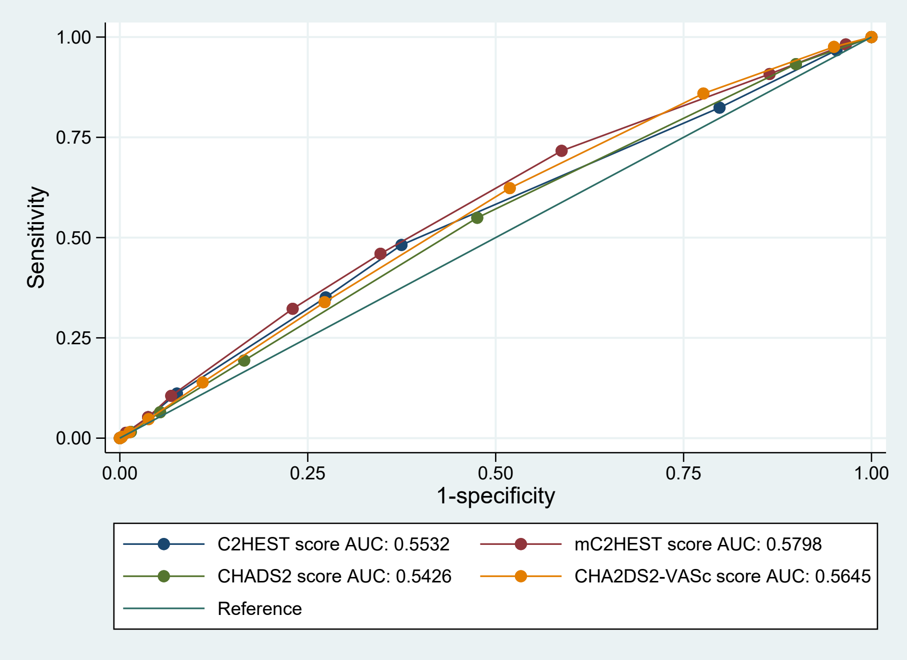
*Methods:*

The study was a registry-based observational study, and the study population was identified in the WDHR. The data were linked with data from nationwide Danish registries to obtain complete data on all of the components of the risk scores. All patients undergoing cardiac surgery ≥18 years were included.

*Results:*

The study population comprised 14279 patients, and 4298 (30.1%) of those developed POAF. In general, the discriminative capacities, as measured by the AUC, were modest.

**Figure 3. Performance of the risk scores for predicting postoperative atrial fibrillation after cardiac surgery.**




*$C_2$HEST indicates coronary artery disease or chronic obstructive pulmonary disease (1 point each), hypertension (1 point), elderly (age ≥75 years, 2 points), systolic heart failure (2 points), thyroid disease (1 point); m$C_2$HEST is a modified version with one additional variable (m= age between 65-74 years, 1 point); $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack; $CHA_2DS_2$-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category.[83]*

*Conclusion:*

The $C_2$HEST score's ability to predict POAF in a population of patients who underwent cardiac surgery was limited. The $C_2$HEST score seems to be of limited value as a screening tool for identifying patients at high risk of POAF, even though higher risk scores were associated with an increased risk of POAF. The predictive abilities of the $C_2$HEST score were similar to those of the $CHADS_2$ and $CHA_2DS_2$-VASc scores in the studied population.

Currently, there is no widely accepted clinical risk model for predicting POAF, and the last section of this chapter highlights some of the pitfalls in developing a valid risk model for POAF. With the exception of advancing age, the reported risk factors and predictors are frequently contradictory. Furthermore, most of the mentioned risk models do not have external validation and lack calibration assessments.

Altogether, this laid the groundwork for the next study, where we developed and tested a new risk score specifically developed for patients undergoing cardiac surgery. First, some thoughts on how to improve the current risk models are discussed.

## 5.4. IMPROVEMENT OF RISK PREDICTION MODELS

The prediction of POAF after cardiac surgery may be difficult using clinical predictors alone. As concluded in the previous section, multiple studies have shown that prediction models for POAF after cardiac surgery are very similar in their performance. Increasing research is now turning to ECG and echocardiographic measurements in attempts to make the risk models more precise.

When stratifying patients at high risk of POAF after cardiac surgery, certain characteristics in the ECG have shown great potential as predictors in risk models. In a recent large study of 180922 patients with 649931 normal sinus rhythm ECGs, it was shown through an AI model that subtle patterns on the normal sinus rhythm ECG can suggest the presence of AF[84]. Similarly, in a large Danish study on incident AF with more than 280.000 in the study population, both short and long P-wave duration in the ECG were associated with an increased risk of AF during a median follow-up of 6.7 years[85]. In contrast, Rader and colleagues[86] evaluated clinical and ECG predictors of POAF in 13356 patients who underwent cardiac surgery and found that only P-wave amplitude in lead aVR and lead V1 were strong predictors of POAF. They found no relationship between the P-wave duration, PR interval, QRS duration and semiquantitative ECG diagnosis of atrial enlargement and an increased risk of POAF.

These findings, in combination with knowledge from a previous study from our research group[87], led us to the following study. Changes in the atria and duration of the P-wave have been associated with POAF in multiple reports[38,88,89], but the potential of incorporating atrial electrogram measures into POAF prediction models has not been explored. The temporary pacing wires placed perioperatively in most cardiac procedures provide a greatly enhanced tracing of atrial activity.

## 5.5. STUDY II

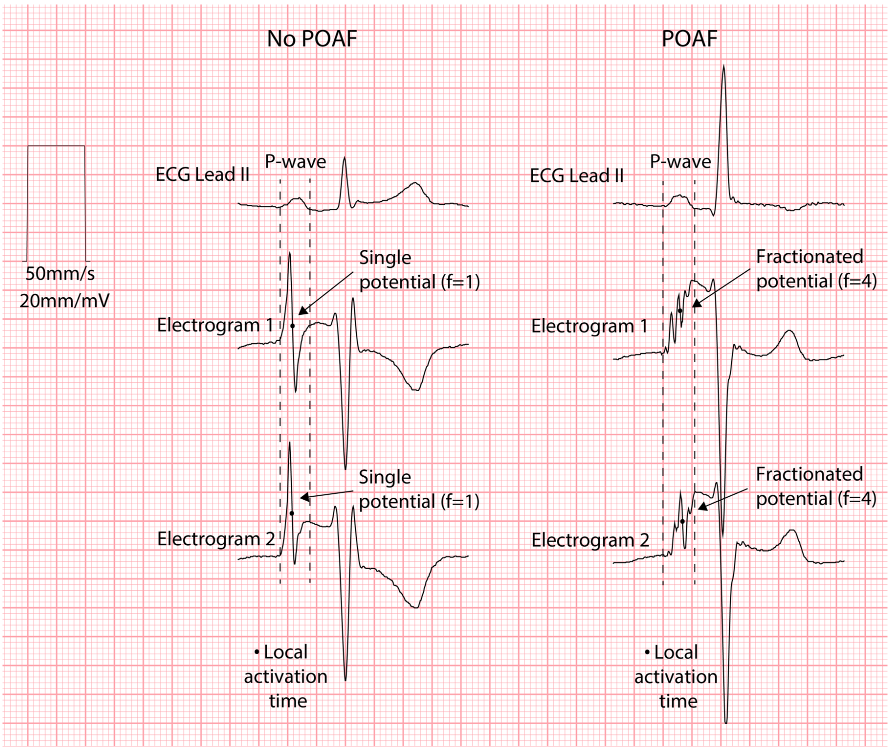
Study II was conducted in collaboration with Jan J. Andreasen, Sam Riahi, Gregory Y.H. Lip, Søren Lundbye-Christensen, Jacob Melgaard and Claus Graff [90].

The study aimed to test whether the addition of atrial electrograms would improve the predictive capabilities of a risk model for POAF after cardiac surgery previously developed in our research group[87].

*Methods:*

The study was a prospective observational study in which all patients undergoing cardiac surgery at Aalborg University Hospital were screened from June 2019 to March 2020. The outcome was the development of POAF within one month postoperatively. As part of the routine, four temporary epicardial pacemaker wires are installed at the end of all cardiac procedures in Aalborg University Hospital. If not in use for pacing, the two wires placed on the right atrium can be used for recording an atrial electrogram. On the first postoperative morning, a 12-lead standard ECG and two atrial unipolar electrograms were recorded for at least one minute. Patients with known AF or who had AF on the recorded ECG were excluded. Hemodynamic parameters detected by the Swan-Ganz catheter were recorded with Vital Recorder, and the obtained ECGs were transferred to the GE MUSE Cardiology Information System (vs. 9.0) and analysed with the 12SL software (vs. 243; GE Healthcare, Wauwatosa, WI, USA).

**Figure 4. The configuration of the ECG and atrial electrograms in patients with and without POAF.**

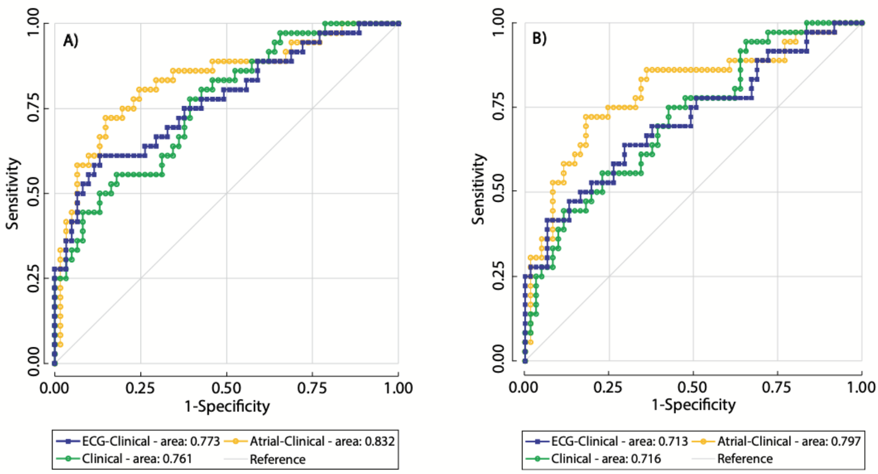


*The figure shows how the variables derived from the atrial electrograms, local activation time (uLAT) and fractionation (uFRAC), were calculated. ECG lead II is shown as a reference.[90]*

*Results:*

Using measurements derived from the ECG, aECG and patient characteristics, three multivariable prediction models for POAF were constructed. The Atrial-Clinical Model, which consists of age, BMI and two unipolar electrogram measurements quantifying the local activation time and fractionation, was strongly associated with the outcome POAF, and when the performance of the model was assessed through ROC with cross-validation, the AUC was improved (AUC 0.796, 95% CI 0.698-0.894) compared with previous ECG-clinical and clinical models (AUC 0.716, 95% CI 0.606-0.826 and AUC 0.718, 95% CI 0.613-0.822, respectively).

**Figure 5. Receiver operating characteristic curves for multivariable POAF prediction models**




*The best prediction model for POAF was the atrial-clinical model. A) Model without cross-validation. B) Model with 10-fold cross validation. The clinical model consisted of age, sex and BMI, and the ECG-clinical model consisted of PR interval, duration of P-wave, left atrial enlargement and QRS duration. The atrial-clinical model consisted of age, BMI, uLAT (unipolar local activation time) and uFRAC (unipolar fractionation).*

*Conclusion:*

This study shows that there was a strong association between the atrial-derived variables, uLAT and uFRAC, and POAF, and as anticipated, these predictors improved the predictive abilities of the risk model. However, because of the small sample size, these promising results, should be validated in future studies with more participants and perhaps impact analyses.

The chapter that follows is the second part of the thesis, which entails a short theoretical background section on outcomes after cardiac surgery with emphasis on postoperative strokes. This serves as a platform for the third study.

# CHAPTER 6. NEUROLOGICAL COMPLICATIONS OF CARDIAC SURGERY

After heart failure, neurologic complications are the most common cause of morbidity and mortality after cardiac surgery. There is a lack of clear understanding of the pathophysiology of postoperative neurologic events, making the development of preventive strategies difficult. For decades, there was a general assumption that adverse neurologic events were specifically related to the use of ECC. This led to the development of off-pump surgery, where CABG is performed without the use of ECC. However, large randomized studies comparing conventional on-pump surgery with off-pump surgery in relation to the risk of adverse neurologic outcomes have not shown a significant reduction associated with off-pump surgery[18,91,92].

Therefore, more surgical centres are now focusing on reducing the risk factors related to the patient. Preoperative and perioperative screening to evaluate, for example, the degree of atherosclerosis of the aorta or carotids may result in further imaging tests or change the surgical approach[15]

Neurologic deficits can be roughly divided into encephalopathy, stroke and neurocognitive dysfunction[93,94]. Some studies have shown that up to 45% of the patients who have undergone cardiac surgery will have new ischemic brain lesions that are clinically undetected[14]. The most reported risk factors for stroke after cardiac surgery are advanced age, prior cerebrovascular disease, prior carotid artery stenosis, prior peripheral vascular disease, prolonged ECC time and POAF[46,95].

Overall, the incidence of stroke in relation to cardiac surgery ranges from 1.5-6% depending on the patient characteristics and type of procedure. It is well known that valve surgery and manipulation of the aorta during surgery puts patients at higher risk of a subsequent stroke. A retrospective report from the Society of Thoracic Surgeons National Cardiac Database of 49264 cardiac surgeries between 2001 and 2012 reported a higher risk-adjusted association among POAF patients and subsequent stroke with increased complexity of the surgery (CABG, OR 2.31 (1.92-2.79), aortic valve replacement, OR 2.70 (1.56-4.67) and mitral valve replacement/plastic OR 4.21 (1.60-11.11)[39].

The neurologic complications in the form of stroke in relation to CABG patients will be reviewed in the following section.

## 6.1. STROKE AFTER CABG

Despite advances in surgical techniques and postoperative care, the incidence of perioperative stroke has remained largely unaffected[20,96]. It is estimated that half of these patients with stroke will have permanent complications, e.g., paresis or aphasia. Half of these will have a need for help or extra care in their daily life. A significant portion of stroke patients suffer from late symptoms after stroke, such as depression, pain, tiredness, and epilepsy[97].

Well-investigated potential causes of perioperative embolic strokes stem from aortic manipulation (e.g., clamping, cannulation) and sudden flow through the aortic cannula against the aortic wall that sends an embolic shower of atheromatous debris or cholesterol through the cerebrovascular system[47,98].

An intraoperative stroke may be diagnosed when the patient recovers from anesthesia and is likely related to the surgical procedure. It may be the result of air or atheromatous emboli during manipulation or cannulation of the aorta. Other strokes present themselves later in the postoperative phase after the patient has fully recovered from anesthesia and is determined to be neurologically intact.

The pathophysiology behind late postoperative stroke has not been well investigated. A wide range of risk factors and pathophysiologic mechanisms can give rise to a stroke following cardiac surgery. Earlier studies on stroke after CABG classify stroke as a dichotomous event, i.e., ischemic, or hemorrhagic. It is worthwhile to distinguish ischemic stroke further to be able to provide optimal prophylaxis and postoperative care for patients.

Patients undergoing cardiac surgery who suffer from perioperative stroke have a worse outcome than those without a stroke[99,100]. In-hospital mortality in relation to stroke appears to be higher than for postoperative strokes. As an example, Dacey *et al.* followed 35733 consecutive patients after CABG; 1.6% had a stroke perioperatively, and their survival at 1, 5, and 10 years was 83%, 58.7%, and 26.9%, respectively. This represented a threefold increase in mortality compared with patients without stroke[101].

In a large prospective cohort study of 35733 patients undergoing isolated CABG, patients who developed stroke had more comorbidities and a significantly increased risk of death (hazard ratio (HR) 3.2; 95% CI, 2.8-3.7; $p<0.001$) compared with those not experiencing stroke[101].

### 6.1.1. ETIOLOC MECHANISMS OF STROKE SECONDARY TO CABG

AF leads to the formation of thrombi in the left atrium with possible embolization into peripheral and cerebral vessels. During thrombus formation, three criteria are necessary: endothelial dysfunction, clotting activation and blood stasis (Wirchow's triad). In AF/POAF patients, the flow velocity in the left atrium and appendage is markedly reduced. However, multiple factors are involved in the increased thrombus formation, and whether the increased risk of stroke is due to a higher risk of cardio embolism or whether POAF is just a marker of complex disease has not been well investigated. Because of the different etiologic origins of stroke, this thesis will focus on stroke after isolated CABG.

To investigate the role of POAF in patients suffering from stroke after a CABG operation, a systematic literature search was performed to find previous studies reporting on the consequences of POAF after isolated CABG for a later ischemic stroke using PubMed and Embase (see Appendix 1A for the search terms).

Table 3: Selected studies on CABG, POAF and stroke

| **Study** | **Design and Population** | **Follow-up** | **Main findings** |
|---|---|---|---|
| Conen *et al.* (2021)[102] | Prospective study. Data from the CORONARY RCT study. 4654 patients undergoing CABG. 778 (16.8%) with POAF | Up to 5 years | The incidence of stroke was 0.75 vs. 0.45 events per 100 patient-years in those with and without POAF, respectively, and the adjusted HR was 1.27 (95% CI, 0.81-2.00; P=0.30) |
| Jawitz *et al.* (2020)[99] | Retrospective registry. 294.533 patients 65 years or older who underwent isolated CABG between 2007-2012 | 7 years | 88.464 (30.0%) patients experienced POAF. 1.9% suffered from a stroke. When adjusted for preoperative covariates and other additional postoperative complications, the aHR for stroke within 90 days of the procedure was 1.36(1.26-1.48) and beyond 90 d postoperatively 1.31(1.21-1.42). |
| Mauero *et al.* (2020)[103] | Two matched groups of CABG patients(total=8324) using either warm or cold cardioplegia | Only in-hospital events and outcomes were assessed | The rate of POAF was 18% (1472 cases). The overall rate of stroke, mortality and neurological mortality were 1.3% (108), 2.9% (240) and 0.9% (78), respectively.<br>Higher likelihood of developing POAF with cold cardioplegia (OR 1.618).<br>POAF patients showed significantly higher rates of stroke and neurological mortality (OR 1.990 and 2.403, respectively). |
| Benedetto *et al.* (2020)[104] | 3023 patients, 734 (24.3%) developed POAF) | 10 years | The cumulative incidence of cerebrovascular accidents (CVA) was 6.3% vs. 3.7% in patients with POAF and sinus rhythm, respectively.<br>The distribution of the 46 CVAs in the POAF group was 23 ischemic, 4 hemorrhagic and 19 unknown causes. A total of 83 CVAs were recorded in the SR group (55 ischemic, 7 hemorrhagic and 21 unknown). |
| Taha *et al.* (2020)[11] | Retrospective registry based. 24.523 patients (7368 (30%) with POAF) | Median follow-up 4.5 years (range 0-9 years) | Adjusted HR for ischemic stroke 1.18 (95% CI, 1.05-1.32), any thromboembolism HR 1.16(1.05-1.28) (ischemic stroke, TIA, peripheral arterial embolism), recurrent AF HR 4.16, 3.76-4.60). POAF not associated with all-cause mortality and early initiation of OAC not associated with reduced risk of ischemic stroke. |

| | | | |
|---|---|---|---|
| Thorén *et al.* (2020)[105] | Observational cohort study. Matched controls. 7145 patients, 31% w POAF. | Median follow-up 9.8 years | POAF was associated with ischemic stroke (HR 1.23; 95% CI 1.06-1.42) and heart failure (HR 1.44; 95% CI 1.27-1.63) during follow-up. Adjusted for AF during follow-up, POAF remained associated with ischemic stroke (HR 1.21; 95% CI 1.04-1.41). POAF was associated with higher overall mortality (HR 1.21; 95% CI 1.11-1-32), cardiac mortality (HR 1.35; 95% CI 1.18-1.54), and cerebrovascular mortality (HR 1.54; 95% CI 1.18-1.54). |
| Almassi *et al.* (2019)[63] | Data from ROOBY-FS RCT. 2103 patients undergoing isolated CABG, 551 (26.2%) with POAF | 5 years | The unadjusted 5-year all-cause mortality rate was 16.3% in patients with POAF vs. 11.9% in patients without POAF. After risk adjustment, there was no significant difference between groups. The absolute incidence of stroke at 5-year follow-up was 3% in both groups with no significant difference in either unadjusted or risk-adjusted outcomes. |
| Schulman *et al.* (2015)[106] | Retrospective registry based 2264 patients, 403 (17.8%) with POAF | 30 days | CT-verified stroke within 30 days postoperatively. Eight patients developed ischemic stroke (stroke rate 2.0%), the majority within 1-3 days postoperatively. |
| Horwich *et al.* (2013)[107] | Retrospective cohort study. 8058 CABG patients. 2214 developed POAF (27.5%) | Median follow-up 5.7 years (SD 3.4) | In-hospital mortality was 2.4% and not significant between groups.<br>Patients with POAF had a relative adjusted increased risk of stroke of 24% at one-year (3.6% vs. 2.9%), 23% at five-year (9.5% vs. 7.7%), and 22% at 10 year follow-up (17.7% vs. 14.5%) compared to patients without POAF. |
| Saxena *et al.* (2012)[62] | Retrospective cohort study. 19497 patients who underwent isolated CABG between 2001-2009. 5547 (28.5%) developed POAF | 44 months (range 0-106) | Adjusted operative and 30-day mortality were similar between the two groups. Long-term survival at 1, 3, 5, and 7 year was significantly lower in patients who developed POAF compared to those who did not (96.4% vs. 97.7%, 92.4% vs. 95.4%, 86.6 vs. 91.4%, and 80.6% vs. 87%). Significant increase in incidence of permanent stroke in patients with POAF (1.3% vs. 0.7%, $p<0.001$) |
| Mariscalco *et al.* (2008) [108] | Prospective observational study. 1832 patients who underwent isolated CABG between 2000-2005. 2 cardiac centres in Italy | 51 months ($25^{th}$ to $75^{th}$ percentile, 41 to 63) | Patients with POFA had a higher incidence of stroke (3% vs. 1%; $P = 0.006$)<br>Long-term mortality rates were significantly worse in POAF patients compared with non-POAF patients, HR 2.26. |

| | | | |
|---|---|---|---|
| Villareal *et al.* (2004)[30] | Retrospective cohort design with case-matched controls. 6475 patients who underwent isolated CABG between 1993 to 1999. 994 (16%) with POAF. | Mean follow-up 5± 2 years | POAF was associated with greater in-hospital mortality (OR 1.7, p=0.0001), stroke (OR 2.02, p=0.001) and prolonged hospital stays (14 vs. 10 days, p>0.0001). In the case-matched population POAF was an independent predictor of long-term mortality (OR 3.4, P= 0.0018). |
| Lahtinen *et al.* (2003)[109] | Retrospective cohort design. 2630 On-pump CABG patients. Analyses of predictors of perioperative strokes. | Only in-hospital events | 52(2.0%) patients with postoperative stroke. Of these, 19 (36.5%) had AF preceding the stroke. Postoperative in-hospital death occurred in 5 patients with POAF. Patients with known AF were also included in the analyses of the postoperative strokes. |
| Stamou *et al.* (2001)[46] | Retrospective cohort design. 16528 CABG patients, | Only in-hospital events | 333 (2%) patients with early postoperative stroke. POAF was significantly associated with stroke (OR 1.7, P<0.001). In-hospital mortality was higher in patients with stroke (n=47, 14.4%) than in patients without stroke (n=436, 2.7%; p<0.001) |

*Abbreviations: CABG: coronary artery bypass grafting; OR: odds ratio; POAF: new-onset postoperative atrial fibrillation.*

Most of the studies report an increased risk of both perioperative and late stroke in patients with POAF. Conen *et al.*[102] prospectively followed 4624 patients and found higher long-term mortality and risk of MI but not stroke. As the data were collected primarily for the CORONARY trial, the study's limitations include selection bias and the study's criteria for POAF, which was defined as POAF lasting > 5 minutes and requiring treatment. Lahtinen *et al.*'s[109] title of their paper ("Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery") indicates a causal relationship, but it is doubtful whether POAF plays a role in the early postoperative strokes in this small population.

Few studies have examined the pathophysiology of the strokes after CABG surgery. Benedetto *et al*.[104] described an overall higher rate of stroke in POAF patients than in patients discharged in sinus rhythm. However, the distribution of ischemic stroke was higher in the group with sinus rhythm than in the group with POAF (50% vs. 66% of the CVAs).

A wide range of vascular diseases can lead to ischemic stroke. It is important to establish the most likely cause of ischemic stroke, as the cause can influence the short- and long-term treatment of patients. One widely used and accepted way of classifying and investigating ischemic stroke was developed from the placebo-controlled multicentre trial called the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[110]. The classification is based on clinical findings in the patient's history and examination, from brain imaging, as well as the findings of ancillary testing, including vascular and cardiac imaging. The system is fairly easy to use and establishes the most likely cause of ischemic stroke.

**Table 4. TOAST classification of subtypes of acute ischemic stroke**

| **Large-artery atherosclerosis** |
|---|
| Cardioembolism |
| Small-vessel occlusion |
| Stroke of other determined etiology |
| Stroke of undetermined etiology<br>Two or more causes identified<br>Negative evaluation<br>Incomplete evaluation |

It is evident that a gap in the literature exists on the characteristics of late strokes following CABG and POAF, which is what led to the hypothesis in the following study.

### 6.1.2. STUDY III

Study III was conducted in collaboration with Jan J. Andreasen, Søren Lundbye-Christensen, Sam Riahi, Søren Paaske Johnsen, Grethe Andersen and Janne Mortensen[111].

The aim of this study was to investigate the ischemic strokes that patients undergoing CABG suffer from and their association to POAF. The secondary objectives were to investigate the mortality, causes of death and whether patients discharged with a prescription for antithrombotic medicine had a lower risk of ischemic stroke.

*Methods:*

Using WDHR, we identified all patients who underwent isolated CABG between 2010 and 2018 and linked the data to their CPR-number, the DPR, the DNPR and the Cause of Death Register. All postoperative strokes were validated in the patient records, and the clinical descriptions, magnetic resonance (MRi) and computed tomography (CT) scans were used to categorize the type of stroke according to TOAST.

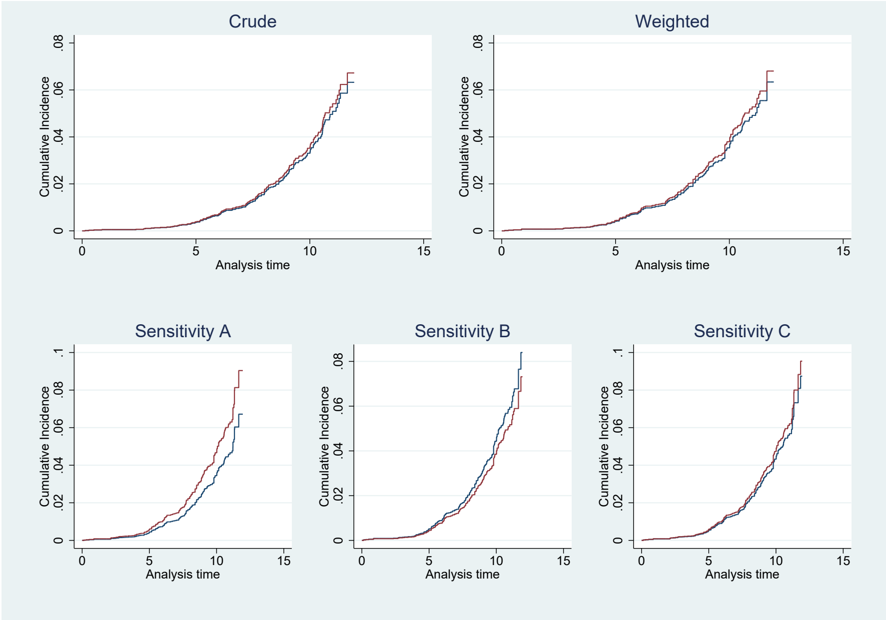
The exposure was POAF, and the outcome was postoperative stroke beyond 30 days after the day of surgery. The method used for adjustment was a weighting scheme balancing the important risk factors for POAF between the two groups.

*Results:*

Of the 7812 patients included in this study, 2048 (26.2%) developed POAF, and 195 (2.5%) patients had a postoperative ischemic stroke. There was no difference between the groups in the risk of ischemic stroke (HR 1.08; 95% confidence interval (CI) 0.74-1.56) or all-cause mortality (HR 1.09; 95% CI 0.98-1.23) when adjusting for confounding risk factors.

Although not statistically significant, patients with POAF had a higher incidence of cardioembolic stroke (Table 5), whereas non-POAF patients had a higher incidence of large-artery occlusion stroke.

**Figure 6. Competing risk of ischemic stroke – crude and adjusted**




*Red=POAF, Blue= non-POAF*

*Top row: 1) Risk of ischemic stroke 2) Adjusted risk of ischemic stroke*

*Bottom row: Sensitivity analyses; A) Assuming unvalidated strokes were ischemic in patients who had POAF, B) Assuming unvalidated strokes were ischemic in patients not experiencing POAF, and C) Assuming unvalidated strokes were ischemic regardless of POAF status[111]*

**Table 5. Incidence rates (per 1000 patient years) of subtypes of postoperative cerebral infarctions with/without POAF**

| Type of ischemic stroke | Incidence rate in non-POAF patients | 95% CI | Incidence rate in POAF patients | 95% CI |
|---|---|---|---|---|
| Large-artery atherosclerosis | 1.1 | 0.8; 1.5 | 0.7 | 0.4; 1.4 |
| Cardioembolism | 0.5 | 0.3; 0.8 | 1 | 0.6; 1.6 |
| Small-vessel occlusion | 0.7 | 0.5; 1 | 0.8 | 0.4; 1.5 |
| Stroke of undetermined etiology | 0.6 | 0.4; 0.9 | 0.7 | 0.3; 1.3 |

*Abbreviations: POAF: postoperative atrial fibrillation; CI: confidence interval.*

*Conclusion*:

Contrary to our hypothesis, we found no difference in the adjusted risk of postoperative ischemic stroke or all-cause mortality in POAF vs. non-POAF patients. However, we did find a trend towards a higher rate of cardioembolic stroke among POAF patients than in non-POAF patients.

# CHAPTER 7. GENERAL METHODOLOGICAL CONSIDERATIONS

All scientific studies will be subject to errors, either systematic or random[112]. Although no study can avoid random errors, they can be reduced by enlarging the sample size and cohort as much as possible. The systematic errors include confounding and bias, and the following section will highlight some of the precautionary measures taken to reduce this in the aforementioned studies.

*Information bias*

Information bias is a distortion in the measure of association caused by either an incorrect classification of information or a lack of accurate measurements of key study variables. Misclassification can be differential or nondifferential. Differential misclassification bias results if information is gathered differently for one group than for another and thereby either raises or lowers the relative risk or odds ratio depending on the direction of the bias. In contract, nondifferential misclassification tends to obscure real differences between groups[112,113].

Studies I and III relied on data regarding POAF from WDHB, and the diagnosis and registration may have been susceptible to misclassification. In a Danish study from 2015[114], the positive predictive value for the POAF diagnosis was found to be 82.5%(95% CI: 78.8-85.7), which is considered relatively valid when applied to epidemiologic studies such as these.

The positive predictive value of a stroke diagnosis in the DNPR has been reported to be between 57.3 and 69.3%[115,116]. Generally, the validity of stroke diagnoses is low when registered in emergency wards. We could confirm this in study III, where all stroke diagnoses were validated.

Studies I and III relied entirely on Danish registries, and even though the merging of datasets from different sources, made some corrections of the diagnoses possible, it is inevitable that some of the data will contain information bias.

In study II, all data concerning patient characteristics were entered into the project database with double entry, to reduce misclassification.

*Selection bias*

Selection bias is introduced when the characteristics of individuals or groups in a study differ from the population of interest[112]. In study II, we included all eligible patients, i.e., those for whom the recording of an up to two-minute-long ECG was possible, thereby excluding patients in a worse state. Most likely, this would have caused a selected healthier group and excluded patients at higher risk of POAF.

Studies I and III included all of the patients within the study time frame. However, there may have been patients with a TIA or other smaller cerebral event that could qualify as a stroke and thereby distort the data. Research based on registries is only as good as the entries put in, meaning that complete and valid information on the diseases and complications entered in the databases is a prerequisite for providing trustworthy results.

In an audit of WDHB from 2013, the proportion of errors in the cardiac surgery registries was 3.3% in the history and EuroSCORE module, 1% in the procedure model and 1.6% in the discharge module [57]. In Studies I and III, there were many missing data concerning dates of discharge, which had to be handled by multiple imputation or replaced by a mean in the analyses.

*Confounding*

In epidemiologic research, confounding is a mixing or blurring of effects. A confounding variable is a risk factor for both the exposure and the outcome but is not a mediator/causal link between exposure and outcome[112]. In study III, we reported crude and adjusted results in different models. Potential confounders were carefully selected based on the relevant literature, and we tried to estimate the causal effect of confounding by using the statistical method of inverse probability weighting. We chose this method to illustrate the timing of the ischemic stroke in relation to cardiac surgery.

*Etiology and prediction*

In Studies I and II, we tested and developed prediction models based on the statistical associations between predictors and the outcome POAF. It is important to keep in mind that the premise in studies of prediction is not to establish a causal effect. Rather, the prediction models use multiple predictors that are not necessarily is in a causal relationship with the outcome[117].

# CHAPTER 8. DISCUSSION

In recent years, patients offered cardiac surgery have become increasingly older with many comorbidities, and the operating procedures are ever more complex. Nevertheless, the most common complication after open chest cardiac surgery is still new-onset POAF. In Study I, we analysed whether the $C_2$HEST score would be of use in predicting POAF in a population undergoing cardiac surgery. The performance of the risk score was moderate, and the predictive capabilities were no better than the $CHADS_2$ and $CHA_2DS_2$-VASc scores; hence, the use of the $C_2$HEST score in predicting POAF in a cardiac surgery population was limited.

Study II demonstrated that using atrial-derived electrograms together with clinical variables in a prediction model increased the model's performance compared with using only clinical or ECG variables.

Study III examined the types of ischemic strokes after CABG and the association with POAF. This study showed that the adjusted risk of ischemic stroke and mortality did not differ between the POAF and non-POAF groups. We found no difference in the distribution of the types of ischemic strokes between the two groups. Although not statistically significant, patients with POAF had a higher proportion of cardioembolic strokes, whereas patients not suffering from POAF had a higher proportion of large vessel atherosclerosis.

*Discussion of Studies I+II*

The $C_2$HEST risk score was designed to function as an easily applicable tool in a busy clinical setting, using only readily available components. The results of Study I are in accordance with most literature that states that age is a risk factor for POAF. In the practice advisory from 2019 by the Society of Cardiothoracic Anesthesiologists/European Association of Cardiothoracic Anesthetists[118], it is suggested that additional POAF prophylaxis should be given for patients aged >75 years.

The interpretation of the AUC value is dependent on the investigated model (e.g., $CHA_2DS_2$VASc score) as well as on the distribution of risk factors in the sample. For instance, in all of the risk models mentioned in this thesis, age is an important risk factor for the development of POAF. A given model can appear to perform much better when utilised in a population with a wide range of age compared with a population with a narrow age range. The highly selected population of cardiac surgery patients might explain why all variables other than age serve as very poor predictors of the outcome POAF. The higher AUC values obtained in other studies examining the $C_2$HEST score were largely obtained in a general population, where risk factors such as hypertension and diabetes may be more strongly associated with AF/POAF.

Limitations to many of the reviewed (including Study I) studies on prediction models should be kept in mind. The majority of the studies are registry based, and the US-based data, will only capture POAF that occurred before discharge and “required treatment” (the STS definition). Moreover, this strict definition has in one study been shown to miss approximately 20% of the isolated CABG patients who experience POAF before discharge[41]. The risk score performance may have been altered by these drawbacks.

Future studies aimed at developing predictive models or scores should preferably be based on prospectively collected data where the above points are taken into consideration. Of note, the registration of POAF can be optimized. Furthermore, separate analyses on isolated CABG and valve procedures will also be needed, as different surgical procedures are known to carry different risks of subsequent POAF.

The increasing mean age of patients undergoing cardiac surgery will inevitably result in an increased incidence of POAF and greater health care costs[9,44]. Thus, the identification of specific factors, e.g., ECG changes or clinical variables, that predispose patients to the development of POAF will enable high-risk patients to be targeted for prophylactic clinical trials and low-risk patients to be spared from potentially harmful electrical and pharmacologic therapy.

*Discussion Study III*

The primary objective of study III was to explore the incidence and the etiology of ischemic strokes in patients undergoing isolated CABG among patients who developed new-onset POAF compared with non-POAF patients.

The observed overall stroke rate of 4.2% in study III is consistent with previous reports. Mérie *et al.*[119] reported an overall incidence of stroke of 7,6% during the 10-year follow-up, but with no distinction by etiology and not excluding patients with known preoperative AF. In a study investigating postoperative complications and outcomes following isolated CABG, Jawitz *et al.*[99] reported an incidence of stroke of 1.9% in the first 90 days postoperatively. In general, patients undergoing CABG have a lower risk of postoperative stroke than patients undergoing valve or concomitant valve surgery, where stroke rates can be significantly higher[100,120].

There is substantial evidence that POAF increases the likelihood of an increased length of intensive care unit and hospital stay[39,99]. This is most likely not solely attributed to the POAF event itself but is related to the general increased morbidity in relation hereto. Altogether, this leads to an increased cost of hospitalization. Although we did not calculate the hospital costs in study II, the increased length of hospital stay for POAF patients was significant. LaPar *et al.*[39]demonstrated that the increased hospital stays associated with POAF translated into additional costs exceeding 9000

US dollars in 2001-2012. POAF is certainly not the most expensive complication after cardiac surgery, but its frequency results in high cumulative costs.

The long-term consequences of POAF have been investigated over the last decades, with conflicting results in terms of thromboembolic risk, including stroke[102,105,121]. In recent systematic reviews and meta-analyses, POAF has been associated with an increased risk of both short-term and long-term stroke and mortality[6,122]. However, the pooled estimates of stroke and survival were based on studies with a variety of heterogeneity in terms of definitions of POAF and outcomes. Hence, we chose to limit our cohort in Study III to patients undergoing isolated CABG and exclude patients with concomitant valvular surgery to minimize confounding, for example, reasons for initiating OAC treatment.

Several points suggest that early adverse events should be handled differently than later events. Adverse events in relation to the surgery most likely have a different pathophysiology than later events. The definition of postoperative stroke varies in the literature. Most studies refer to perioperative incidents even though the strokes occur well after the day of surgery.

As newer studies highlight, there is an increased risk of later AF in patients experiencing POAF after cardiac surgery[4,105]. For that reason, it would be fair to hypothesize that the reported increased risk of stroke and death associated with POAF after cardiac surgery would at least partly stem from the possible larger burden of AF in this group of patients. We were not able to confirm this in Study III. As such, the findings are in line with those of Conen *et al.*[102] and Almassi et al.[63], but in contrast to several larger multiple centre series that did find an association between POAF and an increased risk of stroke and mortality[11,62,105].

There are many known and unknown contributing factors to postoperative complications after cardiac surgery; the patient's comorbidities, the trauma of surgery and how well the patient recovers all interact with in many cases an impaired systolic and diastolic function, high pressure in the left atrium and increased stasis. All components will inevitably worsen if the patient develops POAF. Most likely, more factors come into play as the (assumed) increased risk of stroke increases with POAF. In general, a time-dependent association between POAF after cardiac surgery and a postoperative stroke will most likely diminish, and possible confounders will influence the outcome.

When analyzing data, it is possible to approximate a real risk by applying certain statistical methods. In Study III and in the study of Taha *et al.*[11], the methods included inverse probability weighted Cox models. Thorén *et al.*[105] and Butt *et al.*[121] both investigated the role of POAF in the method of matching controls. As no randomized controlled trial is available, this is the best we can do to explain the possible role of POAF in long-term stroke risk. However, it can make it difficult to compare studies as they are matched/adjusted for different risk factors.

Other studies investigating possible causal mechanisms behind later postoperative stroke have demonstrated that patients suffering from postoperative strokes have no evidence of significant carotid vascular disease[123,124].

*How can the POAF patient be treated after discharge? An unanswered dilemma*

The identification of recurrent POAF in patients discharged in SR largely relies on the patient and their general practitioner. Given that symptoms of AF only occur in one of three AF episodes[125], it can be an unreliable guide to diagnostics. Furthermore, many symptoms of AF, such as shortness of breath, dizziness and fatigue, are not very specific, and all are expected in the recovery period after major cardiac surgery.

Although the conducted studies and literature review show that it is difficult to predict which patients may be at high risk of postoperative atrial fibrillation, it is important to note that many steps can be taken to reduce the complications associated with increased long-term mortality and readmissions. For instance, the use of beta blockers, especially among patients who were already prescribed them, has been shown to significantly reduce the rate of POAF[9].

In current American and European guidelines, there are no clear suggestions on the indication or duration of potential OAC treatment for POAF patients[126,127]. Study III showed a low absolute risk of a postoperative ischemic stroke, and most clinicians are rightfully apprehensive in administering OAC to POAF patients, as they have a substantial risk of bleeding, especially in the first 30 days postoperatively[128].

An ongoing randomized study is investigating the efficacy and safety of OACs for stroke prevention after cardiac surgery and POAF (ClinicalTrials.gov Id: NCT04045665).

## 8.1. STRENGTHS AND LIMITATIONS OF THE STUDIES

The strengths and limitations of the studies included in this thesis have been discussed in detail in the respective studies (I-III), and the following section will therefore highlight only the most significant points.

The development of prediction models should preferably be undertaken in a study population that is collected for the purpose. Early identification of patients at high risk of POAF will spare low-risk patients from the risk of antiarrhythmic toxicity or the added drug cost.

As mentioned, Study II tested whether adding predictors derived from atrial electrograms would improve an existing risk model from our research group. In this context, we wanted to be able to compare our new findings with the earlier analyses; however, there are methodological approaches that would be more appropriate when evaluating which predictors derived from the postoperative ECG would be strongest, such as stepwise variable selection.

One of the strengths of study III was the prospective nature of the collected patient database. In general, differences in capturing incidences of POAF during the postoperative period make comparisons between studies difficult. As previously stated, the peak incidence of POAF occurs 2 to 3 days postoperatively, and many patients will be out of intensive care units at this time and not necessarily on telemetry. Furthermore, correct diagnosis of POAF will be complicated by the often transient and self-limiting nature of POAF and the differing definitions of POAF in terms of its duration and frequency. Experiences with the data collection for Study I-III as well as reading the available literature on the topic reveal that the absence of electronic medical records systems during retrospective analyses and deficiencies in record keeping complicate research into POAF.

Another strength of study III is the fact that it relies on data from an entire population from three cardiac centres and not just a single cardiac centre in a large country, which is the case with most literature on the subject. All patients undergoing cardiac surgery in western Denmark are registered in WDHB, which reduces missing data to a minimum.

Denmark is often highlighted as a unique setting for conducting large epidemiologic studies. The unique CPR number makes it possible to connect data across all registries and provide researchers with complete follow-up data. However, we found multiple errors in WDHB and coding of stroke diagnoses in the DPR. The registration of a stroke diagnosis came with high variability and many errors.

Even though the weight-adjusted Cox regression models included many known risk factors for the outcome, some residual confounding could have persisted and influenced the results.

# CHAPTER 9. PERSPECTIVES

The development of POAF in relation to cardiac surgery seems to be multifactorial. Extensive research has identified numerous risk factors and predictors, but we still lack a convincing predictive tool to guide the decision of prophylactic intervention for patients at high risk of developing POAF after cardiac surgery.

This PhD thesis emphasizes that there is still a need for the improvement of risk prediction models for POAF. This confirms that although patients with AF and POAF share many of the same risk factors, the prediction of POAF in patients undergoing cardiac surgery necessitates stronger predictors than currently available. The review in Chapter 5 and Study I emphasized that preoperative risk stratification models are of limited applicability, as they do not show sufficient reliability (the highest AUC was 0.78).

Future studies should focus on developing existing prediction models as well as undertaking impact studies[129]. Whether the effort should focus on administering prophylactic therapy to a larger group or whether the intervention should target specific patients with a high risk of developing of POAF remains undetermined. Even though study II obtained good and promising results, the study sample and performance were insufficient for implementation in the clinical setting. The development of machine learning and AI may aid future risk model building, as well as the inclusion of other physiological monitoring techniques. In the conduction of Study II, several parameters from the patients' Swan Ganz catheters where collected. While missing data made the inclusion of these parameters in our study impossible, additional studies with a larger sample size could reveal potential new strong predictors.

The Danish health registries provide a unique possibility of conducting large population-based studies on patients undergoing cardiac surgery. Study III presented one of many interesting topics in relation to long-term outcomes, and several follow-up questions became apparent. For instance, it would be interesting to explore the incidence of recurrent AF in patients with POAF discharged in SR. Another future subject could be analyses of the compliance, use, and duration of OACs in patients prescribed antithrombotic medicine in relation to POAF and later thromboembolic events.

# CHAPTER 10. CONCLUSION

There is nothing simple about POAF. Compared with the major impact of undergoing open cardiac surgery, a mostly short-lived postoperative rhythm disturbance seems at first glance not very offsetting for the successful recovery of the patient.

This thesis clarifies that POAF and incident AF in a nonsurgical setting differ in many aspects in terms of prediction as well as the risk of later thromboembolic events. Targeted therapy for POAF patients and optimal long-term treatment of the arrhythmia long-term are major topics in ongoing research and debates in both clinical and research communities.

The main findings in the individual studies included in this thesis are described below.

Study I showed that the performance of the $C_2$HEST score to predict POAF after cardiac surgery in a large Danish population was limited.

In Study II, the results indicated that atrial-derived electrograms recorded in the early postoperative phase may be helpful for predicting POAF in patients undergoing cardiac surgery.

The results of study III do not support current guidelines that encourage the initiation of OAC for selected POAF patients, as there were no differences in the incidence of cardioembolic stroke in POAF vs. non-POAF patients. However, POAF should be considered an important marker for later risk of ischemic stroke until a direct causal pathway has been proven.

In conclusion, this PhD dissertation underlines that there is a continued need for improvement of the prediction of POAF and stroke prevention in relation to cardiac surgery.

# LITERATURE LIST

[1] Dansk Hjerteregister; Årsrapport 2020 [Internet]. RKKP - Regionernes kliniske kvalitetsudviklingsprogram; 2020. p. 281. Available from: https://www.sundhed.dk/sundhedsfaglig/kvalitet/kliniske-kvalitetsdatabaser/hjerte-kar-sygdomme/hjerteregister/.

[2] Adult Cardiac Surgery Database: Executive Summary: 10 Years: STS Period Ending 06/30/2017. Society of Thoracic Surgeons website. [Internet]. 2020. Available from: https://www.sts.org/sites/default/files/documents/ACSD2017Harvest3_ExecutiveSummary.pdf.

[3] Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med. 2001;135:1061–1073.

[4] Ahlsson A, Fengsrud E, Bodin L, et al. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2010;37:1353–1359.

[5] Caldonazo T, Kirov H, Rahouma M, et al. Atrial Fibrillation after Cardiac Surgery – A Systematic Review and Meta-Analysis. J Thorac Cardiovasc Surg [Internet]. 2021; Available from: https://www.sciencedirect.com/science/article/pii/S0022522321005584.

[6] Kerwin M, Saado J, Pan J, et al. New-onset atrial fibrillation and outcomes following isolated coronary artery bypass surgery: A systematic review and meta-analysis. Clin Cardiol. 2020/07/21 ed. 2020;43:928–934.

[7] Dobrev D, Aguilar M, Heijman J, et al. Postoperative atrial fibrillation: mechanisms, manifestations and management. Nat Rev Cardiol. 2019;16:417–436.

[8] Eikelboom R, Sanjanwala R, Le M-L, et al. Postoperative Atrial Fibrillation After Cardiac Surgery: A Systematic Review and Meta-Analysis. Ann Thorac Surg. 2021;111:544–554.

[9] Arsenault KA, Yusuf AM, Crystal E, et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2013;2013:CD003611.

[10] Butt JH, Xian Y, Peterson ED, et al. Long-term Thromboembolic Risk in Patients With Postoperative Atrial Fibrillation After Coronary Artery Bypass

Graft Surgery and Patients With Nonvalvular Atrial Fibrillation. JAMA Cardiol. 2018;3:417.

[11] Taha A, Nielsen SJ, Bergfeldt L, et al. New-Onset Atrial Fibrillation After Coronary Artery Bypass Grafting and Long-Term Outcome: A Population-Based Nationwide Study From the SWEDEHEART Registry. J Am Heart Assoc. 2020;e017966.

[12] Mullan CW, Mori M, Pichert MD, et al. United States national trends in comorbidity and outcomes of adult cardiac surgery patients. J Card Surg. 2020;35:2248–2253.

[13] Alexander KP, Anstrom KJ, Muhlbaier LH, et al. Outcomes of cardiac surgery in patients age ≥80 years: results from the National Cardiovascular Network. J Am Coll Cardiol. 2000;35:731–738.

[14] Hogue CW, Gottesman RF, Stearns J. Mechanisms of cerebral injury from cardiac surgery. Crit Care Clin. 2008;24:83–98, viii–ix.

[15] Lawton Jennifer S., Tamis-Holland Jacqueline E., Bangalore Sripal, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization. J Am Coll Cardiol. 2022;79:e21–e129.

[16] Warren OJ, Smith AJ, Alexiou C, et al. The Inflammatory Response to Cardiopulmonary Bypass: Part 1—Mechanisms of Pathogenesis. J Cardiothorac Vasc Anesth. 2009;23:223–231.

[17] Larmann J, Theilmeier G. Inflammatory response to cardiac surgery: cardiopulmonary bypass versus non-cardiopulmonary bypass surgery. Anaesth Surg Inflamm Response. 2004;18:425–438.

[18] Diegeler A, Börgermann J, Kappert U, et al. Off-Pump versus On-Pump Coronary-Artery Bypass Grafting in Elderly Patients. N Engl J Med. 2013;368:1189–1198.

[19] Pahwa S, Bernabei A, Schaff H, et al. Impact of postoperative complications after cardiac surgery on long-term survival. J Card Surg. 2021;36(6):2045-2052. doi:10.1111/jocs.15471.

[20] Adelborg K, Horváth-Puhó E, Schmidt M, et al. Thirty-Year Mortality After Coronary Artery Bypass Graft Surgery. Circ Cardiovasc Qual Outcomes. 2017;10:e002708.

[21] D'Agostino RS, Jacobs JP, Badhwar V, et al. The Society of Thoracic

Surgeons Adult Cardiac Surgery Database: 2017 Update on Outcomes and Quality. Ann Thorac Surg. 2017;103:18–24.

[22] Ohri SK, Benedetto U, Luthra S, et al. Coronary artery bypass surgery in the UK, trends in activity and outcomes from a 15-year complete national series. Eur J Cardiothorac Surg. 2022;61:449–456.

[23] Greenberg JW, Lancaster TS, Schuessler RB, et al. Postoperative atrial fibrillation following cardiac surgery: a persistent complication. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2017;52:665–672.

[24] Filardo G, Damiano RJJ, Ailawadi G, et al. Epidemiology of new-onset atrial fibrillation following coronary artery bypass graft surgery. Heart Br Card Soc. 2018;104:985–992.

[25] El-Chami MF, Kilgo P, Thourani V, et al. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. J Am Coll Cardiol. 2010;55:1370–1376.

[26] Kosmidou I, Chen S, Kappetein AP, et al. New-Onset Atrial Fibrillation After PCI or CABG for Left Main Disease. J Am Coll Cardiol. 2018;71:739–748.

[27] Lee S-H, Kang DR, Uhm J-S, et al. New-onset atrial fibrillation predicts long-term newly developed atrial fibrillation after coronary artery bypass graft. Am Heart J. 2014;167:593-600.e1.

[28] Fuster V, Rydén LE, Asinger RW, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. Circulation. 2001;104:2118–2150.

[29] Echahidi N, Pibarot P, O'Hara G, et al. Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery. J Am Coll Cardiol. 2008;51:793–801.

[30] Villareal RP, Hariharan R, Liu BC, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol. 2004;43:742–748.

[31] Almassi GH, Pecsi SA, Collins JF, et al. Predictors and impact of postoperative atrial fibrillation on patients' outcomes: A report from the Randomized On Versus Off Bypass trial. J Thorac Cardiovasc Surg. 2012;143:93–102.

[32] Mathew JP, Fontes ML, Tudor IC, et al. A Multicenter Risk Index for Atrial Fibrillation After Cardiac Surgery. JAMA. 2004;291:1720–1729.

[33] Hogue CW, Creswell LL, Gutterman DD, et al. Epidemiology, Mechanisms, and Risks: American College of Chest Physicians Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery. Chest. 2005;128:9S-16S.

[34] Bidar E, Bramer S, Maesen B, et al. Post-operative Atrial Fibrillation - Pathophysiology, Treatment and Prevention. J Atr Fibrillation. 2013;5:781.

[35] Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. Am Heart J. 1964;67:200–220.

[36] Wang J, Liu L, Feng J, et al. Regional and functional factors determining induction and maintenance of atrial fibrillation in dogs. Am J Physiol-Heart Circ Physiol. 1996;271:H148–H158.

[37] Kaireviciute D, Aidietis A, Lip GYH. Pathophysiological insights into atrial fibrillation following cardiac surgery: implications for current pharmaceutical design. Curr Pharm Des. 2009;15:3367–3383.

[38] Chandy J, Nakai T, Lee RJ, et al. Increases in P-wave dispersion predict postoperative atrial fibrillation after coronary artery bypass graft surgery. Anesth Analg. 2004;98:303–310, table of contents.

[39] LaPar DJ, Speir AM, Crosby IK, et al. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg. 2014;98:527–533; discussion 533.

[40] Marazzato J, Masnaghetti S, De Ponti R, et al. Long-Term Survival in Patients with Post-Operative Atrial Fibrillation after Cardiac Surgery: Analysis from a Prospective Cohort Study. J Cardiovasc Dev Dis [Internet]. 2021;8. Available from: https://www.mdpi.com/2308-3425/8/12/169.

[41] Filardo G, Pollock BD, da Graca B, et al. Underestimation of the incidence of new-onset post-coronary artery bypass grafting atrial fibrillation and its impact on 30-day mortality. J Thorac Cardiovasc Surg. 2017;154:1260–1266.

[42] Jayam VKS, Flaker GC, Jones JW. Atrial fibrillation after coronary

bypass: etiology and pharmacologic prevention. Cardiovasc Surg. 2002;10:351–358.

[43] Melby SJ, George JF, Picone DJ, et al. A time-related parametric risk factor analysis for postoperative atrial fibrillation after heart surgery. J Thorac Cardiovasc Surg. 2015;149:886–892.

[44] Rostagno C, La Meir M, Gelsomino S, et al. Atrial fibrillation after cardiac surgery: incidence, risk factors, and economic burden. J Cardiothorac Vasc Anesth. 2010;24:952–958.

[45] Yadava M, Hughey AB, Crawford TC. Postoperative Atrial Fibrillation: Incidence, Mechanisms, and Clinical Correlates. Heart Fail Clin. 2016;12:299–308.

[46] Stamou SC, Hill PC, Dangas G, et al. Stroke after coronary artery bypass: incidence, predictors, and clinical outcome. Stroke. 2001;32:1508–1513.

[47] Likosky DS, Marrin CAS, Caplan LR, et al. Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. Stroke. 2003;34:2830–2834.

[48] Kaireviciute D, Aidietis A, Lip GYH. Atrial fibrillation following cardiac surgery: clinical features and preventative strategies. Eur Heart J. 2009;30:410–425.

[49] Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42:373–498.

[50] Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. Eur Heart J. 2006;27:2846–2857.

[51] Zebis LR, Christensen TD, Thomsen HF, et al. Practical Regimen for Amiodarone Use in Preventing Postoperative Atrial Fibrillation. Ann Thorac Surg. 2007;83:1326–1331.

[52] Zebis LR, Christensen TD, Kristiansen IS, et al. Amiodarone Cost Effectiveness in Preventing Atrial Fibrillation After Coronary Artery Bypass Graft Surgery. Ann Thorac Surg. 2008;85:28–32.

[53] Dunning J, Treasure T, Versteegh M, et al. Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2006;30:852–872.

[54] Mitchell LB, Fibrillation A, Committee G, et al. Society Guidelines Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery. CJCA. 2011;27:91–97.

[55] Ha ACT, Mazer CD, Verma S, et al. Management of postoperative atrial fibrillation after cardiac surgery. Curr Opin Cardiol. 2016;31:183–190.

[56] Gillinov AM, Bagiella E, Moskowitz AJ, et al. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. N Engl J Med. 2016;374:1911–1921.

[57] Rasmussen LA, Bøtker HE, Jensen LO, et al. Quality assurance of the Western Denmark Heart Registry, a population-based healthcare register. Dan Med J. 2017;64.

[58] Schmidt M, Maeng M, Madsen M, et al. The Western Denmark Heart Registry: Its Influence on Cardiovascular Patient Care. J Am Coll Cardiol. 2018;71:1259–1272.

[59] Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29:541–549.

[60] Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;39:30–33.

[61] Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011;39:38–41.

[62] Saxena A, Dinh DT, Smith JA, et al. Usefulness of Postoperative Atrial Fibrillation as an Independent Predictor for Worse Early and Late Outcomes After Isolated Coronary Artery Bypass Grafting (Multicenter Australian Study of 19,497 Patients). Am J Cardiol. 2012;109:219–225.

[63] Almassi GH, Hawkins RB, Bishawi M, et al. New-onset postoperative atrial fibrillation impact on 5-year clinical outcomes and costs. J Thorac Cardiovasc Surg [Internet]. 2019; Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2004306540&from=export.

[64] Steyerberg E. Clinical Prediction Models. 1st ed. Springer-Verlag New York;

[65] Zou KH, O'Malley AJ, Mauri L. Receiver-Operating Characteristic Analysis for Evaluating Diagnostic Tests and Predictive Models. Circulation. 2007;115:654–657.

[66] Shen J, Lall S, Zheng V, et al. The persistent problem of new-onset postoperative atrial fibrillation: A single-institution experience over two decades. J Thorac Cardiovasc Surg. 2011;141:559–570.

[67] Burgos LM, Ramírez AG, Seoane L, et al. New combined risk score to predict atrial fibrillation after cardiac surgery: COM-AF. Ann Card Anaesth. 2021;24:458–463.

[68] Pollock BD, Filardo G, da Graca B, et al. Predicting New-Onset Post-Coronary Artery Bypass Graft Atrial Fibrillation With Existing Risk Scores. Ann Thorac Surg. 2018;105:115–121.

[69] Thorén E, Hellgren L, Jidéus L, et al. Prediction of postoperative atrial fibrillation in a large coronary artery bypass grafting cohort. Interact Cardiovasc Thorac Surg. 2012;14:588–593.

[70] Magee MJ, Herbert MA, Dewey TM, et al. Atrial Fibrillation After Coronary Artery Bypass Grafting Surgery: Development of a Predictive Risk Algorithm. Ann Thorac Surg. 2007;83:1707–1712.

[71] Sun X, Boyce SW, Hill PC, et al. Association of Body Mass Index With New-Onset Atrial Fibrillation After Coronary Artery Bypass Grafting Operations. Ann Thorac Surg. 2011;91:1852–1858.

[72] Mariscalco G, Biancari F, Zanobini M, et al. Bedside Tool for Predicting the Risk of Postoperative Atrial Fibrillation After Cardiac Surgery: The POAF Score. J Am Heart Assoc. 3:e000752.

[73] Amar D, Shi W, Hogue CW, et al. Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. J Am Coll Cardiol. 2004;44:1248–1253.

[74] Zaman AG, Archbold RA, Helft G, et al. Atrial Fibrillation After Coronary Artery Bypass Surgery. Circulation. 2000;101:1403–1408.

[75] Yin L, Ling X, Zhang Y, et al. CHADS2 and CHA2DS2-VASc Scoring Systems for Predicting Atrial Fibrillation following Cardiac Valve Surgery.

PLOS ONE. 2015;10:e0123858.

[76] Selvi M, Gungor H, Zencir C, et al. A new predictor of atrial fibrillation after coronary artery bypass graft surgery: HATCH score. J Investig Med. 2018;66:648.

[77] Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263–272.

[78] Cameron MJ, Tran DTT, Abboud J, et al. Prospective External Validation of Three Preoperative Risk Scores for Prediction of New Onset Atrial Fibrillation After Cardiac Surgery. Anesth Analg. 2018;126:33–38.

[79] Borde D, Gandhe U, Hargave N, et al. Prediction of postoperative atrial fibrillation after coronary artery bypass grafting surgery: is CHA 2 DS 2 -VASc score useful? Ann Card Anaesth. 2014;17:182–187.

[80] Burgos LM, Seoane L, Parodi JB, et al. Postoperative atrial fibrillation is associated with higher scores on predictive indices. J Thorac Cardiovasc Surg. 2019;157:2279–2286.

[81] Li YG, Pastori D, Farcomeni A, et al. A Simple Clinical Risk Score (C 2 HEST) for Predicting Incident Atrial Fibrillation in Asian Subjects: Derivation in 471,446 Chinese Subjects, With Internal Validation and External Application in 451,199 Korean Subjects. Chest. 2019;155:510–518.

[82] Li Y-G, Bisson A, Bodin A, et al. C2 HEST Score and Prediction of Incident Atrial Fibrillation in Poststroke Patients: A French Nationwide Study. J Am Heart Assoc. 2019;8:e012546.

[83] Rasmussen LF, Andreasen JJ, Lundbye-Christensen S, et al. Using the C2HEST Score for Predicting Postoperative Atrial Fibrillation After Cardiac Surgery: A Report From the Western Denmark Heart Registry, the Danish National Patient Registry, and the Danish National Prescription Registry. J Cardiothorac Vasc Anesth [Internet]. [cited 2022 May 28]; Available from: https://doi.org/10.1053/j.jvca.2022.03.037.

[84] Attia ZI, Noseworthy PA, Lopez-Jimenez F, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. The Lancet. 2019;394:861–867.

[85] Nielsen JB, Kühl JT, Pietersen A, et al. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. Heart Rhythm. 2015;12:1887–1895.

[86] Rader F, Costantini O, Jarrett C, et al. Quantitative electrocardiography for predicting postoperative atrial fibrillation after cardiac surgery. J Electrocardiol. 2011;44:761–767.

[87] Gu J, Andreasen JJ, Melgaard J, et al. Preoperative Electrocardiogram Score for Predicting New-Onset Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth. 2017;31:69–76.

[88] Sovilj S, Van Oosterom A, Rajsman G, et al. ECG-based prediction of atrial fibrillation development following coronary artery bypass grafting. Physiol Meas. 2010;31:663–677.

[89] Wong JK, Lobato RL, Pinesett A, et al. P-wave characteristics on routine preoperative electrocardiogram improve prediction of new-onset postoperative atrial fibrillation in cardiac surgery. J Cardiothorac Vasc Anesth. 2014;28:1497–1504.

[90] Feilberg Rasmussen L, Andreasen JJ, Riahi S, et al. Prediction of postoperative atrial fibrillation with postoperative epicardial electrograms. Scand Cardiovasc J. 2022;56:378–386.

[91] Puskas JD, Stringer A, Hwang SN, et al. Neurocognitive and neuroanatomic changes after off-pump versus on-pump coronary artery bypass grafting: Long-term follow-up of a randomized trial. J Thorac Cardiovasc Surg. 2011;141:1116–1127.

[92] Shroyer AL, Hattler B, Wagner TH, et al. Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass. N Engl J Med. 2017;377:623–632.

[93] Selnes OA, Gottesman RF, Grega MA, et al. Cognitive and neurologic outcomes after coronary-artery bypass surgery. N Engl J Med. 2012;366:250–257.

[94] Selnes OA, Goldsborough MA, Borowicz LM, et al. Neurobehavioural sequelae of cardiopulmonary b ypass. The Lancet. 1999;353:1601–1606.

[95] Mao Z, Zhong X, Yin J, et al. Predictors associated with stroke after coronary artery bypass grafting: a systematic review. J Neurol Sci. 2015;357:1–7.

[96] ElBardissi AW, Aranki SF, Sheng S, et al. Trends in isolated coronary artery bypass grafting: An analysis of the Society of Thoracic Surgeons adult cardiac surgery database. J Thorac Cardiovasc Surg. 2012;143:273–281.

[97] McKhann GM, Grega MA, Borowicz LM, et al. Stroke and Encephalopathy After Cardiac Surgery. Stroke. 2006;37:562–571.

[98] Barbut D, Grassineau D, Lis E, et al. Posterior Distribution of Infarcts in Strokes Related to Cardiac Operations. Ann Thorac Surg. 1998;65:1656–1659.

[99] Jawitz OK, Gulack BC, Brennan JM, et al. Association of postoperative complications and outcomes following coronary artery bypass grafting. Am Heart J. 2020;222:220–228.

[100] Hogue CWJ, Barzilai B, Pieper KS, et al. Sex differences in neurological outcomes and mortality after cardiac surgery: a society of thoracic surgery national database report. Circulation. 2001;103:2133–2137.

[101] Dacey LJ, Likosky DS, Leavitt BJ, et al. Perioperative Stroke and Long-Term Survival After Coronary Bypass Graft Surgery. Ann Thorac Surg. 2005;79:532–536.

[102] Conen D, Wang MK, Devereaux PJ, et al. New-Onset Perioperative Atrial Fibrillation After Coronary Artery Bypass Grafting and Long-Term Risk of Adverse Events: An Analysis From the CORONARY Trial. J Am Heart Assoc. 2021;10:e020426.

[103] Mauro MD, Calafiore AM, Di Franco A, et al. Association between cardioplegia and postoperative atrial fibrillation in coronary surgery. Int J Cardiol. 2020;

[104] Benedetto U, Gaudino MF, Dimagli A, et al. Postoperative Atrial Fibrillation and Long-Term Risk of Stroke after Isolated Coronary Artery Bypass Graft Surgery. Circulation. 2020;1320–1329.

[105] Thoren E, Wernroth M-L, Christersson C, et al. Compared with matched controls, patients with postoperative atrial fibrillation (POAF) have increased long-term AF after CABG, and POAF is further associated with increased ischemic stroke, heart failure and mortality even after adjustment for AF. Clin Res Cardiol Off J Ger Card Soc. 2020;

[106] Schulman S, Cybulsky I, Delaney J. Anticoagulation for stroke prevention in new atrial fibrillation after coronary artery bypass graft surgery. Thromb Res. 2015;135:841–845.

[107] Horwich P, Buth KJ, Légaré J-F. New Onset Postoperative Atrial Fibrillation is Associated with a Long-Term Risk for Stroke and Death Following Cardiac Surgery. J Card Surg. 2013;28:8–13.

[108] Mariscalco G, Klersy C, Zanobini M, et al. Atrial Fibrillation After Isolated Coronary Surgery Affects Late Survival. Circulation. 2008;118:1612–1618.

[109] Lahtinen J, Biancari F, Salmela E, et al. Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg. 2004;77:1241–1244.

[110] Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.

[111] Rasmussen LF, Andreasen JJ, Riahi S, et al. Risk of subtypes of strokes following new-onset postoperative atrial fibrillation in cardiac surgery. A population-based cohort study. JAHA. In Press;

[112] Rothman KJ. Epidemiology: an introduction. Oxford university press; 2012.

[113] Grimes DA, Schulz KF. Bias and causal associations in observational research. The Lancet. 2002;359:248–252.

[114] Munkholm SB, Jakobsen C-J, Mortensen PE, et al. Validation of post-operative atrial fibrillation in the Western Denmark Heart Registry. Dan Med J. 2015;62:A5162.

[115] Krarup L-H, Boysen G, Janjua H, et al. Validity of Stroke Diagnoses in a National Register of Patients. Neuroepidemiology. 2007;28:150–154.

[116] Luhdorf P, Overvad K, Schmidt EB, et al. Predictive value of stroke discharge diagnoses in the Danish National Patient Register. Scand J Public Health. 2017;45:630–636.

[117] van Diepen M, Ramspek CL, Jager KJ, et al. Prediction versus aetiology: common pitfalls and how to avoid them. Nephrol Dial Transplant. 2017;32:ii1–ii5.

[118] O'Brien B, Burrage PS, Ngai JY, et al. Society of Cardiovascular Anesthesiologists/European Association of Cardiothoracic Anaesthetists Practice Advisory for the Management of Perioperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth. 2019;33:12–26.

[119] Merie C, Kober L, Olsen PS, et al. Risk of stroke after coronary artery bypass grafting: effect of age and comorbidities. Stroke. 2012;43:38–43.

[120] Salazar JD, Wityk RJ, Grega MA, et al. Stroke after cardiac surgery: short- and long-term outcomes. Ann Thorac Surg. 2001;72:1195–1201.

[121] Butt JH, Xian Y, Peterson ED, et al. Long-term Thromboembolic Risk in Patients With Postoperative Atrial Fibrillation After Coronary Artery Bypass Graft Surgery and Patients With Nonvalvular Atrial Fibrillation. JAMA Cardiol. 2018;3:417.

[122] Woldendorp K, Farag J, Khadra S, et al. Postoperative Atrial Fibrillation After Cardiac Surgery: A Meta-Analysis. Ann Thorac Surg. 2021;112:2084–2093.

[123] David K DK Murdock, L Rosemary LR Rengel, Audrey A Schlund, et al. Stroke and atrial fibrillation following cardiac surgery. WMJ Off Publ State Med Soc Wis. 2003;102:26–30.

[124] Li Y, Walicki D, Mathiesen C, et al. Strokes after cardiac surgery and relationship to carotid stenosis. Arch Neurol. 2009;66:1091–1096.

[125] Healey JS, Connolly SJ, Gold MR, et al. Subclinical Atrial Fibrillation and the Risk of Stroke. N Engl J Med. 2012;366:120–129.

[126] January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019;140:e125–e151.

[127] Frendl G, Sodickson AC, Chung MK, et al. 2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures. Executive summary. J Thorac Cardiovasc Surg. 2014;148:772–791.

[128] Matos JD, McIlvaine S, Grau-Sepulveda M, et al. Anticoagulation and amiodarone for new atrial fibrillation after coronary artery bypass grafting: Prescription patterns and 30-day outcomes in the United States and Canada. J Thorac Cardiovasc Surg. 2020;

[129] Kappen TH, Vergouwe Y, van Klei WA, et al. Adaptation of Clinical Prediction Models for Application in Local Settings. Med Decis Making.

2012;32:E1–E10.

# Appendix A.

**Search terms:**

Search terms: POAF risk models (14/12/21):

PubMED:

((((((((((new onset[Text Word]) OR (newly onset[Text Word])) OR (postoperative*[Text Word])) OR (postsurg*[Text Word])) OR (post-surg*[Text Word])) OR (post-operative*[Text Word])) OR ("Postoperative Complications"[Mesh])) OR ("Postoperative Period"[Mesh])) AND (("Atrial Fibrillation"[Mesh]) OR (atrial fibrillat*[Text Word]))) OR (poaf[Text Word] OR noaf[Text Word])) AND ((((("Cardiac Surgical Procedures"[Mesh]) OR (cardiac surger*[Text Word] OR cardiac surgical[Text Word])) OR (coronary artery bypass[Text Word])) OR (cabg[Text Word])) OR (valve surge*[Text Word]))) AND (((((((("Clinical Decision Rules"[Mesh]) OR (clinical decision rule*[Text Word])) OR (clinical prediction rule*[Text Word])) OR (prediction model*[Text Word])) OR (risk scheme*[Text Word])) OR (risk score*[Text Word])) OR (risk model*[Text Word])) OR (clinical predict*[Text Word])) OR (risk predicti*[Text Word])) Sort by: Publication Date

Embase:

(('clinical decision rule'/de OR (predict* NEAR/2 (clinical OR risk OR model* OR score*)):ti,ab,kw OR (risk NEAR/2 (model* OR score* OR scheme*)):ti,ab,kw OR 'clinical decision rule*':ti,ab,kw) AND ((((('new-onset atrial fibrillation'/de OR 'postoperative complication'/exp OR 'postoperative period'/exp OR (postoperative*:ti,ab,kw OR 'post-operative*':ti,ab,kw) OR (postsurg*:ti,ab,kw OR 'post-surg*':ti,ab,kw) OR (new* NEAR/1 onset):ti,ab,kw) AND ('atrial fibrillation'/exp OR 'atrial fibrillat*':ti,ab,kw)) OR (poaf:ti,ab,kw OR noaf:ti,ab,kw)) AND ('heart surgery'/exp OR ('cardiac surg*':ti,ab,kw OR 'heart surg*':ti,ab,kw) OR 'coronary artery bypass':ti,ab,kw OR 'valve surg*':ti,ab,kw OR cabg:ti,ab,kw)) OR 'postoperative atrial fibrillation'/de)) AND ('article'/it OR 'article in press'/it OR 'review'/it)

Search terms: CABG, POAF and Stroke (16/11/21):

(((((((((((((("Brain Ischemia"[Mesh]) OR transient ischemic attack*[tw]) OR cerebral ischemia*[tw]) OR brain ischemia*[tw]) OR cerebral infarct*[tw]) OR brain infarct*[tw]) OR brain vascular accident*[tw]) OR apoplex*[tw]) OR cerebrovascular accident*[tw]) OR stroke*[tw]) OR "Stroke"[Mesh])) AND ((((Aortocoronary Bypass*[tw]) OR CABG[tw]) OR coronary artery bypass*[tw]) OR "Coronary Artery Bypass"[Mesh]))) AND (((auricular fibril*[tw]) OR atrial fibrill*[tw]) OR "Atrial Fibrillation"[Mesh]))))))))))

and Embase with the terms

(('coronary artery bypass surgery'/exp OR ‘coronary artery bypass graft'/exp OR 'coronary artery bypass* OR ‘cabg’ OR ‘aortocoronary bypass':ti,ab,kw) AND (‘cerebrovascular accident’/exp OR ‘brain infarction’/exp OR brain ischemia/exp OR stroke*’:ti,ab,kw OR apoplex*’:ti,ab,kw OR ‘brain vascular accident*’:ti,ab,kw OR brain infarct*’:ti,ab,kw OR ‘cerebral infarct*’:ti,ab,kw OR ‘brain ischemia*’ti,ab,kw OR ‘cerebral ischemia*’ti,ab,kw OR ‘transient ischemic attack*’:ti,ab,kw) AND (‘postoperative atrial fibrillation’/exp OR ‘atrial fibrillation’/exp OR atrial fibrill*’:ti,ab,kw))

# Appendix B. Papers I-III

Paper

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-794-9

AALBORG UNIVERSITY PRESS