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Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting

Risk factors and clinical outcome

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Abstract

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Postoperative atrial fibrillation (POAF) is a common complication after coronary artery bypass grafting (CABG), and more knowledge is needed regarding prediction of POAF, the extent of early atrial fibrillation (AF) recurrence after discharge, and the associations between POAF and short and long-term overall and cause-specific mortality and morbidity.

After CABG, 31-32% of all patients developed POAF. Several independent risk factors were identified, including increasing age, preoperative S-creatinine ≥150 µmol/l, male gender, NYHA class III/IV, current smoking, prior myocardial infarction (MI), and absence of hyperlipidaemia. The discriminatory ability of the final prediction model was moderate. POAF patients had a higher incidence of early postoperative complications, including stroke and heart failure (HF) and longer hospital stays. In-hospital mortality did not differ between groups.

In long-term follow-up, POAF was independently associated with increased risk of late cardiac mortality after CABG. Examining both underlying and contributing causes of death, POAF was associated with death related to arrhythmia, cerebrovascular disease and HF. The associations remained for more than 8 years.

Observation of heart rhythm during the 30 days following discharge after CABG revealed that 30% of all patients experienced episodes of post-discharge AF. Of all patients with AF, 35% did not experience any symptoms. Patients with POAF had a higher incidence of post-discharge AF, but high incidences were recorded both for patients with POAF (58%) and with sinus rhythm (19%) in-hospital.

POAF was associated with increased long-term risk of overall, cardiac and cerebrovascular mortality, ischemic stroke and HF, and displayed higher incidence rates of these morbidities after CABG. Furthermore, POAF was recognised as a recurrent condition where AF in relation to surgery was a precursor to both first and subsequent events of AF during follow-up. Occurrence of AF, HF, MI and ischemic stroke during follow-up further increased overall mortality.

In conclusion, POAF is common after CABG and remains hard to accurately predict. POAF patients experience more postoperative complications, a higher incidence of post-discharge AF and a recurrent pattern of AF long-term. POAF is also associated with an increased risk of cardiovascular-related mortality, and ischemic stroke and HF in long-term follow-up.

Keywords: atrial fibrillation, coronary artery bypass grafting, coronary artery disease, epidemiology, morbidity, mortality, outcome

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To my family

List of Papers

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

I Thorén E, Hellgren L, Jidéus L, Ståhle E. (2012) Prediction of postoperative atrial fibrillation in a large coronary artery bypass grafting cohort. *Interact Cardiovasc Thorac Surg.* 14(5):588-93.

II Thorén E, Hellgren L, Granath F, Hörte LG, Ståhle E. (2014) Postoperative atrial fibrillation predicts cause-specific late mortality after coronary surgery. *Scand Cardiovasc J.* 48(2):71-8.

III Thorén E, Hellgren L, Ståhle E. (2016) High incidence of atrial fibrillation after coronary surgery. *Interact Cardiovasc Thorac Surg.* 22(2):176-80.

IV Thorén E, Wernroth L, Jidéus, L, Ståhle E. Patients with postoperative atrial fibrillation have an increased long-term risk of ischemic stroke, heart failure, and cerebrovascular and cardiac mortality after CABG. *Manuscript.*

Contents

Abbreviations

ACC	Aortic cross-clamp
ACE-I	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
AUC	Area under the curve
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCS class	Canadian Cardiovascular Society grading of angina pectoris
CDR	Cause of Death Registry
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke/transient ischemic attack/thromboembolism, Vascular disease, Age 65-74 years, Sex category (female)
CI	Confidence interval
CK-MB	Creatine kinase-myocardial band
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CVD	Cardiovascular disease
ECG	Electrocardiogram
EuroSCORE	European System for Cardiac Operative Risk Evaluation
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Liable INR, Elderly (age >65 years), Drugs/alcohol
HF	Heart failure
HR	Hazard ratio
IABP	Intra-aortic balloon pump
ICD	International Classification of Diseases
ICU	Intensive care unit

IMA	Internal mammary artery/internal thoracic artery
INR	International normalised ratio
IQR	Interquartile range
LAD	Left anterior descending artery
LOS	Length of stay
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NOAC	Non-vitamin K antagonist oral anticoagulant/direct oral anticoagulant
NRP	National Patient Registry
NYHA class	New York Heart Association functional classification
OR	Odds ratio
PCI	Percutaneous coronary intervention
POAF	Postoperative atrial fibrillation
py	Person-years
ROC	Receiver operating characteristics
S	Serum
SD	Standard deviation
SR	Sinus rhythm
STEMI	ST-elevation myocardial infarction
TIA	Transient ischemic attack

Introduction

The most common non-communicable disease and the leading cause of death in the world is cardiovascular disease (CVD).[1,2] Even though deaths caused by CVD have declined, coupled with higher numbers of cardiovascular operations and procedures, and new medications, the burden of disease remains high.[3] The majority of this impact is caused by coronary artery disease (CAD), which in turn is caused by atherosclerosis in the coronary arteries.[1] The two revascularisation options for advanced CAD is percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG),[4] and patients undergoing the latter represent the chosen patient population for this thesis.

Atrial fibrillation (AF) is the most common chronic tachycardia.[5] The prevalence of AF in adults is about 1-3% and increases with age,[6,7] and it is an important risk factor for stroke.[8] Preoperative AF has, among a number of other variables, been identified as a risk factor for operative morbidity and mortality after isolated CABG.[9] The association between AF and a negative outcome remains when the arrhythmia is first registered after surgery,[10] known as postoperative atrial fibrillation (POAF). This condition affects about a third of all patients after CABG[10–14] and is the focus of this thesis.

This thesis draws attention to the risk factors that can increase the incidence of POAF after CABG, and the occurrence of AF after discharge and its relation to POAF. Emphasis is also placed upon clinical outcomes related to POAF after CABG with regards to early postoperative complications, early and late mortality, cause of death, and long-term morbidity.

Background

Coronary artery bypass grafting

CABG is a surgical revascularisation method used to improve survival and symptoms in patients with CAD.[4] The diseased coronary artery is bypassed and thus taken out of circulation, allowing the blood to flow through a substitute vessel.

The method first came into use in 1964, more than 50 years ago.[15] Before CABG, surgical treatment for angina pectoris started with sympathectomy, which removed symptoms but did nothing to improve prognosis. Experimental surgical techniques aimed at increasing myocardial perfusion were then explored. These included ligation of the right internal mammary artery (IMA), pericardial abrasion, and suturing of different tissues, such as lung, pectoral muscle and the greater omentum to the myocardium. Finally, sutured anastomoses to the coronary vessels were explored, with successful results.

The standard surgical approach today includes cardiopulmonary bypass (CPB) and cardiac arrest, where the left IMA is used to bypass the left anterior descending (LAD) artery and saphenous vein grafts are used to bypass the remaining coronary arteries.[16] Use of IMA to the LAD has proved superior to only using saphenous vein grafts in terms of improved long-term survival and reduced risk of myocardial infarction (MI), recurrent angina, and need for repeat revascularisation[17] and its use is recommended.[18] The use of bilateral IMAs has shown additional benefits regarding these outcomes,[18,19] but since it is also associated with an increase in complications such as mediastinitis, the recommendation is to consider it only in younger patients (<70 years).[18] CABG can also be performed without CPB and with a beating heart, so-called off-pump CABG, but no early or long-term clinical benefits of this technique have been demonstrated compared to the standard technique.[20,21]

CABG is generally recommended to improve survival in patients with left main stenosis, multivessel CAD (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD), if the patient is a good candidate for surgery.[4] In the case of less advanced disease, PCI is also a recommended revascularisation method to improve symptoms.[4] For patients with acute STEMI (ST-elevation myocardial infarction), PCI can also improve survival compared to fibrinolytic therapy.[22]

PCI was first introduced in 1977, and involved dilatation of the blocked coronary artery using a balloon catheter introduced through an artery.[23]

Around 10 years later, in 1986, the introduction of intracoronary stents improved results. This involves leaving a bare metal or drug-eluding stent in the coronary vessel at the site of occlusion. Further improvements in results are linked to the use of dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor), which is now a standard treatment after PCI.[24,25]

The SYNTAX trial compared CABG and PCI for three-vessel disease and/or left main CAD.[26] CABG was found to benefit this patient group, with lower rates of major adverse cardiac or cerebrovascular events at 1 year. However, the increased rates of stroke in the CABG group (2.2% vs. 0.6% with PCI; p=0.003) was a cause for concern, even though it was no longer significant at 5 year follow-up (3.7% with CABG vs. 2.4% with PCI; p=0·09).[27] The incidence of AF before or after revascularisation was not registered in the SYNTAX trial, but the observed incidence of AF after CABG is around 30%[10–14] and after acute MI treated with PCI 8%,[28] which is a factor worth considering.

Atrial fibrillation

AF is a common arrhythmia with a prevalence of around 1-3%.[6,7] As the prevalence increases with age, and due to an ageing population, AF patients consume a lot of health-care resources and makes AF an important public health issue.[29]

AF is defined as a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction.[30] On an electrocardiogram (ECG), AF is characterised by irregular R-R intervals, an absence of P-waves, and irregular atrial activity. Sub-classification of AF with different duration ranges from paroxysmal (≤7 days) to permanent AF. Another sub-division is valvular or non-valvular AF, which marks the presence or absence of rheumatic mitral stenosis, a mechanical or biological heart valve prosthesis, or mitral valve repair.

Paroxysmal, or intermittent, AF is often triggered by ectopic beats from the pulmonary veins.[31,32] Structural changes, such as left atrial enlargement and increased left ventricular wall thickness, have also been associated with a risk of AF in the Framingham Heart Study.[33]

The long-term effects of primary AF are well researched. AF is associated with a 50% higher relative risk of death[34] and a 30% lower absolute survival at 10 year follow-up.[35] A doubled risk of cardiovascular mortality is seen among AF patients,[34] where heart failure (HF) and sudden cardiac death together account for about a third of all deaths, and stroke for about 10%.[36,37]. AF is also prone to recur[38,39] and is associated with an increased mid to long-term risk of HF,[34] MI[40] and ischemic stroke.[34]

There are some proposed underlying mechanisms that explain the observed negative effects of AF. Loss of atrial systole and a rapid ventricular rate reduce

effective ventricular filling and lead to stasis in the left atrium, while increased platelet activation triggers the coagulations cascade.[41] These factors contribute to a hypercoagulable state, which leaves AF patients at greater risk of MI[42] and ischemic stroke,[41] both associated with a doubled risk among AF patients,[34,39] and potentially non-cerebral thromboembolism. As a consequence, many AF patients receive oral anticoagulants that in turn are associated with an increased risk of haemorrhage.[43,44] The increased risk of HF associated with AF is attributed in part to shared risk factors, such as advanced age, hypertension, diabetes, and CAD.[45] AF can cause tachycardia-mediated HF, while structural changes in dilated or hypertrophic cardiomyopathy, including fibrosis in the left atrium, can encourage AF development.[46,47] AF is also associated with inflammation that can result in cardiac remodelling and ventricular dysfunction associated with HF.[48]. In a recent meta-analysis, AF was associated with a five-fold risk of HF.[34]

Treatment

A main treatment for AF patients is oral anticoagulants for stroke prevention. Warfarin and other vitamin K antagonists were the only recommended treatment for a number of years, and these reduce the risk of stroke by 65% and overall mortality by 25% compared with aspirin or no therapy.[43] Recently, NOACs (non-vitamin K antagonist oral anticoagulants) have been included in the recommendations.[49] Initiation of treatment using oral anticoagulants is based on clinical risk models for stroke, where the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke/transient ischemic attack (TIA)/thromboembolism, Vascular disease, Age 65-74 years, Sex category (female)) is recommended.[50] The risk of bleeding is also considered, which includes assessment with the risk score HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Liable international normalised ratio (INR), Elderly (age >65 years), Drugs/alcohol).[51] Non-pharmacological treatment that may be considered for stroke prevention is left atrial appendage occlusion or exclusion, but convincing evidence for this is scarce.[49]

Other ways to manage AF is to control rate or rhythm. Rate control improves symptoms, and is used in combination with appropriate anticoagulation.[49] Beta-blockers, digoxin and calcium channel blockers (diltiazem and verapamil), or combinations thereof, are all effective. Rhythm control is indicated for patients who remain symptomatic despite rate control therapy. It can be achieved by so-called pharmacological[49,52] or electrical cardioversion,[53] and maintained with antiarrhythmic drugs such as amiodarone, dronedarone, flecainide, propafenone or sotalol.[49] There are no clear benefits with rhythm control compared to rate control combined with anticoagulation. Non-pharmacological treatment includes catheter ablation and Cox maze surgery.

Postoperative atrial fibrillation

POAF is the most common complication after CABG, and affects about a third of all patients after surgery.[10–14] POAF is a type of secondary AF, with an underlying event related to its occurrence, which also includes AF in relation to non-cardiac surgery, infection, MI and thyrotoxicosis.[39] The underlying pathophysiology of POAF is not entirely known. Age-related structural changes in the atria are thought to play a role,[54,55] as well as inflammation[56,57] and sympathetic activation.[58,59] Generally, the underlying mechanisms are considered to be multifactorial.

Definitions vary, but the general description is an episode of AF during the early postoperative period. Some studies include AF of any duration,[10,60] others include only episodes lasting more than one minute,[8,32] or episodes requiring treatment.[11,12] Despite slight variances in definition, the incidences are similar and range from 25 to 33% after isolated on-pump CABG procedures.[10–14] The majority of the POAF episodes make their first appearance during the first four postoperative days,[10,61] which the average hospital stay after CABG exceeds.[62,63]

Risk factors and prediction

The identification of risk factors has produced inconsistent results, with the exceptions of increasing age.[10–13,60,64] Other risk factors include history of AF,[10,12] chronic obstructive pulmonary disease (COPD),[10,13] hypertension,[11,13] HF,[11,62] prior MI,[64] male gender,[62,64,65] smoking,[66] elevated serum (S) creatinine,[67] low resting pulse,[13] and postoperative low cardiac output.[12]

Although individual risk factors have been identified, the quality of the overall models has seldom been assessed, or has been of only moderate value after isolated CABG.[11,12] A model with a high predictive value, including easily assessable preoperative variables, would be most useful in the clinical setting.

It could be beneficial to identify patients with a high risk of developing POAF after CABG. High-risk patients could potentially be targeted for prophylactic treatments, to avoid costs and possible side effects related to treatment for low-risk patients. It could facilitate scheduling of operations and predict resource utilisation, since POAF has been associated with prolonged hospitalisation.[10,11,13,14,60,62–64]

Treatment

A vast array of prophylactic treatments to prevent development of POAF have been tried and assessed.[68,69] In a recently updated (2013) Cochrane review, the current evidence was summarised.[70] Both pharmacological and non-pharma-

cological interventions were evaluated. Interventions that significantly reduced the rate of POAF after cardiac surgery were, in order of efficacy, beta-blockers, sotalol, magnesium, amiodarone, atrial pacing, and posterior pericardiotomy. Prophylactic interventions were also shown to decrease the length of hospital stay and reduce in-hospital treatment costs. However, no intervention significantly reduced early mortality or morbidity, which was examined in the form of overall and cardiovascular mortality and postoperative stroke. Since there is no evidence of causality, i.e. that reducing the rate of POAF leads to improved outcome, the clinical use of prophylaxis remains uncertain. American guidelines recommend both pre- and postoperative beta-blockers,[16] and European guidelines recommend perioperative oral beta-blockers for POAF prevention.[49]

Anticoagulation for POAF after cardiac surgery has not been extensively studied, but warfarin treatment at discharge has in one study been associated with reduced long-term mortality after CABG.[63] The increased risk of bleeding after cardiac surgery should also be considered in this patient group. The current recommendations are to consider long-term anticoagulation in POAF patients at risk of stroke.[49]

Different treatment strategies are used when POAF occurs, aimed at restoring sinus rhythm (SR) or involving rate control, which has in short-term follow-up shown similar complication rates.[71] These strategies include pharmacological treatment (beta-blockers, certain calcium channel blockers, or amiodarone), and/or electric cardioversion.[30]

Early outcome

POAF has been associated with a negative in-hospital outcome after cardiac surgery, with some discrepancies between studies. The numerous complications associated with POAF include infection, MI, HF,[10,11] pulmonary oedema,[10] re-operation because of bleeding, stroke, permanent pacemaker, and acute renal failure.[11] Presence of POAF also leads to an extended length of stay (LOS)[72,73] and LOS in the intensive care unit (ICU),[11] resulting in increased costs.[62] Results regarding early mortality have shown higher rates among POAF patients, ranging from 2.4 to 7.4%.[10,11,13,14,60]

Long-term outcome

The only consistent association between POAF and long-term outcome is increased overall mortality.[60,63,74–79] A recent meta-analysis showed higher mortality for POAF patients, with a pooled hazard ratio (HR) of 1.28 and aggregated 10-year survival of 65.5% in POAF patients and 75.3% in non-POAF patients.[80] However, the reasons behind the increase have not been thoroughly explored. Cause of death has been researched in two previous CABG cohorts.[61,81] One study, including 1419 patients, found higher incidences of death

due to cardiac causes and cerebral ischemia among POAF patients, but not for non-cardiovascular deaths.[61] With a low number of events (134 deaths from cardiac causes and 16 from cerebral ischemia), analyses were not corrected for confounders and independent associations with POAF were not assessed. The other study, including 1832 patients, found an independent association between POAF and cardiovascular mortality and the subgroup embolic death, which included all types of stroke and pulmonary embolism.[81] Only the direct, or primary, cause of death has been examined previously. Analyses of both underlying and contributing causes of death would better explain the morbidities leading to the death of the patient.

There is also sparse information regarding long-term morbidity after CABG. Associations between POAF and recurrent AF have been identified in long-term follow-up after cardiac surgery,[82,83] and after CABG specifically.[14,84,85]. No systematic rhythm surveillance has been made, however. Results vary, especially in terms of the first four to six weeks after discharge.[86–88] Patient material has been mixed, and different methods for detecting AF have been used. These include clinical examination, data from medical records, isolated ECG recordings, 24 hour Holter monitoring, and recordings based on the presence of arrhythmia symptoms.

An area of clinical concern after CABG is ischemic stroke. Treatment with anticoagulants can potentially prevent outcome, but at the price of haemorrhage,[43] which is highly relevant in an open-heart surgery cohort. Only two prior studies have examined the association between POAF and long-term stroke after cardiac surgery. In the only isolated CABG cohort that has been explored, there was an independent association between POAF and stroke (HR 1.3).[89] The definition of stroke was imprecise, however, and did not define ischemic stroke as the outcome. The other study was large, but also heterogeneous.[90] The cohort included patients undergoing any kind of surgery, with a subgroup of open heart surgery patients. An association between POAF and ischemic stroke was found in the heart surgery cohort (HR 1.3). There were no details regarding types of included heart surgery or proportion of patients who had undergone CABG. No other long-term results regarding POAF and morbidity after CABG are available. It is reasonable to hypothesise that similar morbidities associated with primary AF can also be related to POAF.

Aims

The overall aims of this thesis were to increase knowledge about the prediction of POAF, the extent of early AF recurrence after discharge, and the associations between POAF and short and long-term overall and cause-specific mortality and morbidity after CABG.

Specifically, the aim of each paper was:

I To identify predictors of POAF through preoperative and surgical variables in a large CABG cohort, and to evaluate the predictive quality of the model in an effort to find patients at high risk of developing POAF and who could potentially benefit from prophylactic treatment. The associations between POAF and early complications were also analysed.

II To investigate the association between POAF and long-term cause-specific death after CABG, with analyses of both primary and contributing causes of death with a plausible connection to POAF, in an attempt to capture the chain of events leading to increased overall mortality. Analyses were also performed to see if any possible effects of POAF would endure over time.

III To examine the incidence of both symptomatic and asymptomatic episodes of AF for 30 days following hospital discharge after CABG with intermittent ECG registrations, with the hypothesis that POAF predicts early AF recurrence.

IV To explore the association between POAF and the long-term risk of morbidities with underlying mechanisms that can be related to AF, and evaluate whether overall mortality was influenced by the occurrence of these morbidities during follow-up after CABG.

Methods

Study design and populations

Paper I, II and IV were retrospective observational cohort studies. Paper III was a prospective observational cohort study.

All patients underwent primary isolated CABG at the Department of Cardiothoracic Surgery, Uppsala University Hospital, Uppsala, Sweden. Paper I and II included 7428 consecutive patients that underwent surgery between January 1996 and December 2009. In Paper I, patients with AF, other atrial arrhythmia, or permanent pacemaker at admission for surgery (i.e. not SR) were then excluded, which left 7115 in the study cohort. In Paper II, further exclusion criteria included non-Swedish citizenship and operative mortality, and the final study cohort included 6821 patients. Paper IV included patients that underwent surgery between January 1996 and December 2012, and survived the index hospital admission chain, defined as an uninterrupted chain of hospitalisation starting with admission for the index surgery, often including transfer to another hospital facility, and ending with discharge from the hospital. Exclusion criteria included preoperative heart rhythm other than SR, non-Swedish citizenship, perioperative mortality, and mortality during the index hospital admission chain. The final study cohort included 7398 patients. Paper III included patients who underwent non-emergent CABG, with left ventricular ejection fraction (LVEF) >50% and with preoperative SR. Between March 2012 and September 2013, 174 patients met these criteria. Furthermore, patients needed to be able to handle the ECG device and have adequate phone reception, give informed consent, and comply with the study protocol. The final cohort included 67 patients.

All CABG operations in Paper III and the majority (96-97%) in Paper I, II and IV were performed on-pump through a routine technique for CPB and with moderate hypothermia (32° to 34°C). All patients were monitored by continuous five-lead telemetry for a minimum of three days postoperatively, longer in cases of arrhythmia (Paper I, II and IV), or until discharge (Paper III). Twelve-lead ECGs were registered on admission, on postoperative day four, and additionally in cases of arrhythmia.

Data collection

For all Papers, pre- and perioperative data were prospectively collected and obtained through the Department's local database. The quality of the database is regularly validated an maintains a high quality. For Paper III, a separate database included prospectively collected supplementary data regarding pre- and postoperative variables, medications, and heart rhythm. The databases contained very few missing data, which were then retrieved from patient charts, replaced by mean or median values, or presented for a subgroup of the population.

Risk factors

POAF was defined as an episode of AF after CABG lasting for >30 s, recorded postoperatively on continuous telemetry or a 12-lead ECG. No specific prophylactic treatment for POAF was used. Baseline medications, including beta-blockers, were reinstated the day after surgery, if permitted by the patient's clinical status. Beta-blockers were common, and a review of 100 random medical records from patients in Paper I (half with and half without POAF) showed that 98% were prescribed beta-blockers at admission. The corresponding number in Paper III, with complete data on medications, was 86%. Episodes of POAF were typically treated medically with sotalol or amiodarone, and/or electrical cardioversion. In accordance with local protocols, treatment with oral anticoagulants was typically initiated only in patients with multiple POAF episodes or if SR was not reinstated before discharge. In Paper II, a review of 100 random medical records concluded that the proportion of patients discharged without verified SR should be ≤5%. All patients in Paper III were discharged in SR.

Hyperlipidaemia was defined as preoperative treatment with statins or levels of total cholesterol and low-density lipoprotein exceeding criteria for treatment according to guidelines. The New York Heart Association (NYHA) functional classification describes the extent of HF based on the severity of symptoms.[91] Left ventricular function was classified as 'good' (LVEF >50%), 'reduced' (30-50%), or 'poor' (<30%) based on preoperative echocardiography or left ventricular angiography. The Canadian Cardiovascular Society (CCS) grading of angina pectoris classifies the severity of angina symptoms.[92] The European System for Cardiac Operative Risk Evaluation (EuroSCORE) calculates the risk of operative mortality in cardiac surgery.[93] In Paper III, the stroke risk in the presence of AF was assessed by the CHA_2DS_2-VASc score.[50]

In Paper IV, data regarding medical history was obtained for a five-year period prior to the index surgery from the National Patient Registry (NRP). ICD-codes for medical history are presented in Table 1.

Table 1. Classification of medical history (Paper IV).

Medical history	ICD-9 (1996)	ICD-10 (1997-2013)
Atrial fibrillation	427D	I48
Heart failure	428	I50
Ischemic stroke	433, 434, 435, 436	I63, I64
Thrombosis	415B, 444, 451, 452, 453, 557A	G45, H34, I26, I65, I66, I74, I81, I82, N280, O882
Haemorrhagic stroke	430, 431, 432	I60, I61, I62
Non-cerebral bleeding	423A, 456A, 530H, 531A, 531C, 531E, 531G, 532A, 532C, 532E, 532G, 533A, 533C, 533E, 533G, 534A, 534C, 534E, 534G, 569D, 578A, 578B, 578X, 599H, 719B, 784H, 784W, 786D	D62, D683, H356, H431, H450, I230, I312, I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K661, K920, K921, K922, M250, N02, N92, N938, N939, N950, R04, R31, R58
Diabetes	250	E10, E11, E12, E13, E14
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15

Swedish national registries

The Swedish National Board of Health and Welfare is a government agency under the Ministry of Health and Social Affairs, and manages a number of registries in order to analyse developments in healthcare and social services.[94] Data from two registries were accessed for this thesis, namely the Cause of Death Registry (CDR) and the National Patient Registry (NRP). Diagnoses in the CDR and NPR are classified according to the International Classification of Diseases, Ninth or Tenth Revision (ICD-9 or 10).

The time and cause of death for all Swedish citizens have been registered in the CDR since 1961. The registry contains multiple causes of death, in descending order of influence. One primary (underlying) cause of death is registered, defined as the disease or injury that initiated the train of morbid events leading directly to death.[95] Diseases considered to have had a substantial impact on the process leading to the death of the patient are also registered, and are referred to as the contributing causes of death.

The NPR contains data concerning all hospital admissions in Sweden since 1987 and the validity in terms of diagnoses of CVD is approximately 95%,[96] and of AF 97%.[97]

Data linkage

For Paper II and IV, patients were tracked via computerised linkage between the Department's database and National registries by the Swedish National

Board of Health and Welfare. This linkage was based on a unique 10-digit personal identity number assigned to all Swedish residents at birth or immigration. To protect anonymity, all personal identifiers were replaced with sequential numbers in the files returned from the Swedish National Board of Health and Welfare.

Intermittent ECG recordings

In Paper III, patients received a handheld ECG device (Zenicor-EKG®; Zenicor Medical Systems AB, Stockholm, Sweden), which registers a bipolar extremity lead I for 30 seconds when putting two thumbs on the device. The device recordings were previously compared to regular 12-lead ECGs in relation to AF detection, with a sensitivity of 96% and a specificity of 92%.[98] Patients were asked to send rhythm registrations three times a day: in the morning (9 a.m.), afternoon (3 p.m.), and evening (9 p.m.), and additional times where arrhythmia symptoms were present. After every registration the ECG was transmitted to a secure central database through a built-in mobile phone. The registration period lasted for 30 days, starting the morning after discharge. Ninety registrations per patient were expected, and 77 registrations (85%) were required to remain in the study. The registrations were evaluated by two independent cardiologists, blinded to the patient's POAF status, and diagnosed as SR, AF, other, or of non-analysable quality. AF was defined as an irregular ventricular rhythm with no visible P-waves. If an arrhythmia was detected after discharge, the patient and the cardiologist responsible for their follow-up care were informed, to enable treatment to be given in line with relevant guidelines.[30]

Ethics

All studies comply with the Declaration of Helsinki and were approved by the local Ethics Review Board of Uppsala, Sweden. For Paper III, written informed consent was obtained from all participants.

Outcomes

Postoperative complications

Re-operation included reopening of the sternum for any reason, including bleeding, while re-operation because of bleeding was cause-specific. Haemodynamics were classified as unstable when inotropic drugs were required to sustain circulation. Decreased renal function was a need for dialysis or a 50% increase in S-creatinine, compared to the preoperative value. Perioperative myocardial injury was a plasma CK-MB (Creatine kinase-myocardial band)

value >50 µg/l on postoperative day 1. Infection was any type requiring treatment with antibiotics, with or without a positive blood culture. Respiratory complication was prolonged mechanical ventilation >24h or re-intubation. Stroke was severe neurological symptoms lasting ≥6h, verified by computer tomography. Postoperative heart failure was a continuous need for inotropic drugs to sustain circulation, a need for an intra-aortic balloon pump (IABP), or death due to heart or multiple organ failure during hospital stay. LOS was the number of days spent in the ICU and hospital ward during the initial hospitalisation. Pneumothorax was a need for treatment with exsufflation or chest tube to re-inflate the lung.

Mortality and cause of death

In-hospital mortality (Paper I) was death from any cause during the initial hospitalisation. In Paper II and IV, patients were identified as being dead or alive on December 31, 2012 and 2013, respectively. Causes of death were retained from the CDR. In study II, late overall mortality was defined as death from any cause >30 days after surgery. In Paper IV, overall mortality was death from any cause after discharge from the index hospitalisation chain.

In Paper II, cardiac mortality was defined as a cardiac diagnosis as primary cause of death. To better comprehend the impact of diseases with a plausible connection to POAF on the chain of events leading to death, additional analyses included deaths related to arrhythmia, cerebrovascular disease, and HF, and were based on both primary and contributing causes of death. In Paper IV, cardiac and cerebrovascular mortality (including ischemic and haemorrhagic stroke) was based on the primary cause of death. ICD-codes for causes of death are presented in Table 2.

Table 2. Classification of cause of death (Paper II and IV).

Cause of death	ICD-9 (1996)	ICD-10 (1997-2013)
Cardiac	394, 395, 396, 397, 398, 401, 402, 404, 411, 412, 413, 414, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429	I05, I06, I07, I08, I09, I10, I11, I13, I20, I21, I22, I23, I24, I25, I30, I31, I32, I33, I34, I35, I36, I37, I38, I39, I40, I41, I42, I43, I44, I45, I46, I47, I48, I49, I50, I51, I52
Arrhythmia	426, 427	I44, I45, I46, I47, I48, I49
Cerebrovascular	430, 431, 432, 433, 434, 435, 436, 437, 438	I60, I61, I62, I63, I64, I65, I66, I67, I68, I69
Heart failure	428	I50

Long-term morbidity

In Paper IV, morbidity events were defined as hospital admission or death, with any of the predefined morbidity events as primary diagnosis in the NRP or underlying cause of death in the CDR. These included AF, HF, MI, ischemic stroke, thrombosis (including arterial and venous thrombosis and thromboembolism), haemorrhagic stroke, and non-cerebral bleeding. ICD codes for each outcome are presented in Table 3.

Table 3. Classification of morbidity events (Paper IV).

Morbidity event	ICD-9 (1996)	ICD-10 (1997-2013)
Atrial fibrillation	427D	I48
Heart failure	428	I50
Myocardial infarction	410	I21, I22
Ischemic stroke	433, 434, 435, 436	I63, I64
Thrombosis	415B, 444, 451, 452, 453, 557A	G45, H34, I26, I65, I66, I74, I81, I82, N280, O882
Haemorrhagic stroke	430, 431, 432	I60, I61, I62
Non-cerebral bleeding	423A, 456A, 530H, 531A, 531C, 531E, 531G, 532A, 532C, 532E, 532G, 533A, 533C, 533E, 533G, 534A, 534C, 534E, 534G, 569D, 578A, 578B, 578X, 599H, 719B, 784H, 784W, 786D	D62, D683, H356, H431, H450, I230, I312, I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K661, K920, K921, K922, M250, N02, N92, N938, N939, N950, R04, R31, R58

Statistics

Statistical analyses and data processing were carried out using SAS statistical software (versions 9.2, 9.3 and 9.4, SAS Institute Inc. Cary, NC, USA). Continuous variables were compared using the independent sample t-test or Wilcoxon-Mann-Whitney test, and categorical variables were compared with the chi-square or Fisher's exact test, as appropriate. Variables included in logistic regression or Cox proportional hazard analyses were evaluated for linearity and categorised in cases of nonlinearity, and used in the format that was most suitable. A p-value of 0.05 or less was considered statistically significant.

Paper I

Logistic regression was used to compare the incidence of POAF with respect to preoperative and surgical variables. Variables with a p-value of 0.1 or less in univariate analyses, and/or of clinical interest, were included in multivariate analyses. Results are presented as odds ratio (OR) and 95% confidence interval (CI).

To assess potential confounding due to associations between LOS and other risk factors, logistic regression analyses conditioning on LOS (≤6, 7, 8, >8 days) were performed, resulting in essentially unchanged estimates. Multiplicativity between risk factors was assessed by testing two-factor interactions between variables in the final model. This revealed an interaction ($p<0.05$ after Bonferroni correction of multiple testing) between smoking and NYHA class IIIB/IV, suggesting that the effect of smoking is confined to patients with a lower NYHA class than IIIB. Since the presence of one or several other postoperative complications could influence the risk of POAF, the robustness of the models were tested by risk factor analyses. All patients with other complications (HF, IABP, re-operation, infection, haemodynamic instability, and need for inotropic drugs) were excluded.

The calculated risk of developing POAF from the multivariate logistic regression model was compared to the observed outcome using receiver operating characteristics (ROC) curve analysis, presented with the area under the curve (AUC) and 95% CI.

Paper II

The effect of POAF on long-term survival was determined by Kaplan-Meier survival curves,[99] with log-rank tests comparing differences between groups with and without POAF. Univariate, age-adjusted, and multivariate Cox proportional hazard analyses[100] were used to examine predictors of late overall and cause-specific mortality. Variables considered for the analyses were: age, gender, hypertension, diabetes, prior MI, number of diseased coronary vessels, left main stenosis, left ventricular function, NYHA class, CCS class, and EuroSCORE (available since 2001). Variables with a p-value of 0.05 or less in univariate analyses were included in multivariate analyses. Models were developed for each category of mortality, and results were presented as HR and 95% CI. Adjusted survival curves were standardised to the distributions of adjustment covariates in the POAF cohort, and estimated based on cumulative hazard functions analysed in multivariate Cox regression models, stratified by POAF status.

Introduction of an interactions term tested for possible interactions between POAF and the independent risk factors for each outcome, and revealed no significant interactions. Furthermore, since the basic model assumes that the HR is constant over time, the persistence of the effect of POAF was investigated by allowing effects to change between time intervals: less than 3 years, 3 to 8 years, and more than 8 years after surgery. The robustness of the models was tested by risk factor analyses of late mortality, from which patients with one or more postoperative complications (sternum insufficiency, re-operation because of bleeding, perioperative myocardial injury, postoperative dialysis, IABP, prolonged need for inotropic drugs, respiratory complications, infection, and stroke) were excluded.

Paper III

Chi-square tests was used to compare the incidence of AF on intermittent ECG registrations with respect to POAF. To describe the magnitude of the difference, the OR with 95% CI was also calculated.

The study was dimensioned to detect a difference in incidence of AF ≥35% between patients with and without POAF. With an uneven distribution between the groups (ratio 2.5 no POAF; to 1 POAF), a sample size of 67 patients (48 no POAF; 19 POAF) was calculated to obtain a power of 80%, with a criterion for significance (alpha) of 0.05 (two-tailed).

Paper IV

The effect of POAF on overall mortality was determined by Kaplan-Meier survival curves,[99] with log-rank tests comparing differences between groups with and without POAF. Incidence rates for morbidity events were calculated as the sum of events divided by the respective group's total follow-up (POAF group 21 425 person-years (py); non-POAF group 50 561 py), presented as number of events per 100 py with 95% CI. Differences in incidences rates between groups were tested for by Wilcoxon two-sample rank-sum tests, based on the sum of individual incidence rates. Cumulative incidence function (CIF) was used to estimate the cumulative incidence with 95% CI, treating death from other causes as a competing risk.[101]

Cox proportional hazard analyses[100] were used to compare time to overall and cause-specific mortality and first morbidity event among patients with or without POAF in relation to surgery. To adjust for potential confounders, the following variables were considered in the analyses: age, gender, medical history (AF, HF, ischemic stroke, thrombosis, haemorrhagic stroke, non-cerebral bleeding, diabetes and hypertension), number of diseased coronary vessels, left main stenosis, left ventricular function, time of surgery, use of IMA, and aortic cross-clamp (ACC) time. Variables were used in a continuous, dichotomous or categorical format, depending on which provided the best discriminatory power. For multivariable analyses, variables were selected by a backward stepwise elimination, removing variables with a p value ≥0.1 from the primary model until the probability values of all remaining variables were <0.05. The proportional hazard assumption was tested using Schoenfeld residuals, and was supported by the non-significant relationship between residuals and time. The results of the Cox analyses were presented as HR with 95% CI.

For morbidity events associated with POAF in multivariable Cox analyses, the following additional analyses were performed:

The persistence of the effect of POAF on these morbidities and overall mortality over time was investigated by allowing effects to change between time intervals, i.e. ≤1 year, 1 to 10 years, and >10 years after surgery.

Separate adjusted analyses focusing on the effect on recurrent events were performed. The effects of POAF on the risk of one or more, two or more, or three or more events were defined as separate, time-related events, with starting time at discharge after surgery and censoring at the time of death or end of follow-up. Furthermore, a data set was constructed, redefining starting date to time of the preceding event. The number of previous morbidity events, categorised as one, two, or three or more was then considered. Possible interactions between POAF and other risk factors, including the sequence of events (first or subsequent), were tested by the introduction of an interactions term.

Morbidity events occurring during follow-up were introduced into multivariable Cox models regarding overall mortality as time-dependent covariates.

Results

Prediction of POAF (Paper I)

The incidence of POAF was 32% (2270 of 7115). Patients who developed POAF were older, had more often suffered from a prior MI, and had a more advanced NYHA class than patients without POAF (Table 4). Both groups had the same degree of coronary vessel disease, hypertension, diabetes, LVEF, and CCS class. Perioperative variables (off-pump surgery, CPB and ACC time, blood cardioplegia, use of IMA, and number of distal anastomoses) were similar in both groups (Table 5).

The strongest predictor of POAF in multivariate analyses was advancing age, with ORs ranging from 2.0 (95% CI, 1.4-3.0) for patients between 51-60 years to 7.3 (4.7 to 11.4) for patients over 80 years, compared to reference age ≤50 years. Other identified predictors were S-creatinine ≥150 μmol/l (OR 1.6, 1.2 to 2.1), male gender (OR 1.2, 1.1 to 1.4), NYHA class III/IV (OR 1.2, 1.0 to 1.4; ref. class I/II), current smoking (OR 1.1, 1.0 to 1.3), prior MI (OR 1.1, 1.0 to 1.2), and absence of hyperlipidaemia (OR 0.9, 0.8 to 1.0). The estimates were essentially unchanged after correction for other risk modifiers, as well as in analyses stratified for LOS, and excluding patients with other postoperative complications. Explorative analyses for all variables identified no significant interactions. With an AUC of 0.62 (95% CI, 0.61 to 0.64), the discriminatory ability of the final prediction model was moderate (Figure 1).

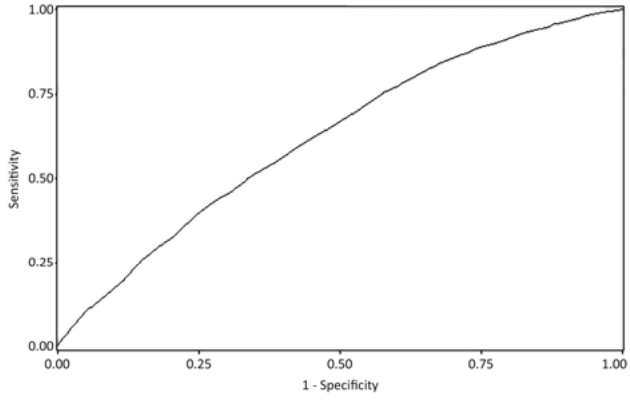


Figure 1. ROC curve for POAF after CABG, based on preoperative and surgical data. AUC 0.62 (95% CI 0.61 to 0.64).

Table 4. Preoperative data by POAF

Variable	POAF (n=2270) n (%)	No POAF (n=4845) n (%)	Univariable OR	95% CI
Age (years)				
≤ 50	34 (1.5)	281 (6.0)	Ref.	-
51-60	271 (12)	1087 (22)	2.0	1.4-3.0
61-70	819 (36)	1803 (37)	3.7	2.6-5.3
71-80	1040 (46)	1558 (32)	5.4	3.7-7.8
>80	106 (4.5)	116 (2.0)	7.4	4.7-11.5
Male gender	1783 (79)	3713 (77)	1.1	1.0-1.3
Current smoker	195 (8.6)	638 (13)	1.1	1.0-1.2
Prior MI	1270 (56)	2525 (52)	1.2	1.1-1.3
Hypertension	1179 (52)	2444 (50)	1.1	1.0-1.2
Diabetes	473 (21)	1045 (22)	1.1	0.8-1.1
Hyperlipidaemia	1141 (50)	2681 (55)	0.8	0.7-0.9
S-creatinine ≥ 150 µmol/l	98 (4.3)	129 (2.7)	1.6	1.3-2.1
NYHA class				
I/II	183 (8.0)	501 (10)	Ref.	-
IIIA	877 (39)	1929 (40)	1.3	1.1-1.6[a]
IIIB	986 (43)	1991 (41)	1.4	-
IV	223 (10)	423 (9.0)	1.4	-
LVEF				
Good (>50%)	1548 (68)	3351 (69)	Ref.	-
Reduced (30-50%)	612 (27)	1282 (27)	1.0	0.9-1.2
Poor (<30%)	110 (5.0)	212 (4.0)	1.1	0.9-1.4
Unstable angina	795 (35)	1541 (32)	1.2	1.0-1.3
CCS class				
0	42 (2.0)	110 (2.0)	0.8	0.6-1.2
1	126 (6.0)	299 (6.0)	1.0	0.8-1.2
2	542 (24)	1238 (26)	Ref.	-
3	1225 (54)	2543 (53)	1.0	0.9-1.2
4	328 (14)	623 (13)	1.1	0.9-1.3
Number of diseased coronary vessels				
1	97 (4.0)	232 (5.0)	Ref.	-
2	455 (20)	1005 (21)	1.1	0.8-1.4
3	1718 (76)	3608 (74)	1.1	0.9-1.5
Left main stenosis	771 (34)	1571 (32)	1.1	1.0-1.2
Priority of surgery				
Elective	1850 (81)	4020 (83)	Ref.	-
Urgent	317 (14)	638 (13)	1.1	0.9-1.2
Emergency	103 (5.0)	187 (4.0)	1.2	0.9-1.5
Haemodynamically unstable	71 (3.1)	109 (2.2)	1.4	1.0-1.9

[a] NYHA class III/IV

Table 5. Surgical data

Variable	POAF (n=2270) n (%)	No POAF (n=4845) n (%)	Univariable OR	95% CI
Off-pump surgery	71 (3.1)	180 (3.7)	0.8	0.6-1.1
Cardiopulmonary bypass time, min (median, IQR)				
< 60	361 (16)	887 (18)	Ref.	-
60-89	1070 (47)	2303 (48)	1.1	1.0-1.3
90-119	619 (27)	1229 (25)	1.2	1.1-1.4
≥ 120	220 (10)	426 (9.0)	1.3	1.0-1.6
Aortic cross-clamp time, min (median, IQR)				
< 30	349 (15)	835 (17)	Ref.	-
30-59	1582 (70)	3375 (70)	1.1	1.0-1.3
60-89	299 (13)	565 (12)	1.3	1.0-1.5
≥ 90	40 (2.0)	70 (1.4)	1.4	0.9-2.1
Blood cardioplegia	463 (20)	963 (20)	1.0	0.9-1.2
Use of IMA	2096 (92)	4461 (92)	1.0	0.9-1.2
Distal anastomoses (n)				
1	60 (2.0)	163 (3.4)	Ref.	-
2	307 (13)	714 (15)	1.2	0.9-1.6
3	969 (43)	2146 (44)	1.2	0.9-1.7
≥ 4	934 (41)	1821 (38)	1.4	1.0-1.9

Postoperative complications and in-hospital mortality (Paper I)

Patients with POAF had a higher frequency of postoperative complications than non-POAF patients. These included re-operation, haemodynamic instability, decreased renal function, infection, respiratory complications, stroke, HF, ICU stay, and LOS (Table 6). There was no difference in the rate of perioperative myocardial injury or in-hospital mortality between the two groups, and the total in-hospital mortality rate was 1.9%.

Table 6. Complications after CABG by POAF.

Postoperative variable	POAF (n=2270)	No POAF (n=4845)	P-value
Re-operation	7.1%	5.0%	<0.001
Haemodynamically unstable	15%	8.7%	<0.001
IABP	1.3%	1.0%	0.280
Decrease renal function	11%	5.9%	<0.001
Perioperative myocardial injury	9.5%	10%	0.523
Infection	7.3%	5.0%	<0.001
Respiratory complication	4.4%	2.3%	<0.001
Stroke	4.1%	2.3%	<0.001
Heart failure	8.9%	5.2%	<0.001
Permanent PM	0.8%	0.7%	0.674
ICU stay, days (median, IQR)	3 (2-5)	2 (2-3)	<0.001
Length of stay, days (median, IQR)	7 (7-9)	7 (6-8)	<0.001
In-hospital mortality	2.1%	1.8%	0.358

Late mortality and cause of death (Paper II)

The incidence of POAF was 32% (2152 of 6821). Patients characteristics, surgical and postoperative variables are presented in Table 7. POAF patients were older, had more often prior MIs, a more advanced NYHA class, and a higher EuroSCORE. The same degree of CAD was observed in both groups. Postoperatively, re-operation because of bleeding, respiratory complications, infection and stroke was more common for POAF patients.

Patients were followed for a median of 9.8 years (range 0.1-17 years). During follow-up, 2302 of 6821 patients (34%) died. POAF was associated with increased late overall mortality. The absolute difference for 5-year survival was 4.2%, for 10-year survival 9.5%, and for 15-year survival 14%.

Cardiac mortality was registered as the primary cause of death among 929 of 2302 patients (40%). This was the most common cause of death, followed by cancer, endocrine disease, respiratory disease, gastrointestinal disease, and infectious disease. When examining both primary and contributing causes of death, 18% were related to arrhythmia, 17% to cerebrovascular disease, and 31% to HF. One of these three diseases contributed to 50% (1144 of 2302) of all deaths, and 31% (710 of 2302) were related to either arrhythmia or cerebrovascular disease.

Table 7. Pre-, peri-, and postoperative variables by POAF.

Variable	POAF (n=2152)	No POAF (n=4669)	P-value
Preoperative			
Age, years (mean ± SD)	69.0 ± 7.7	65.2 ± 9.1	<0.001
Male gender	79%	77%	0.08
Hypertension	52%	50%	0.2
Diabetes	21%	22%	0.4
Prior MI	56%	52%	0.006
Diseased coronary vessels			0.5
1	4%	5%	
2	21%	21%	
3	75%	74%	
Left main stenosis	34%	32%	0.2
LVEF			0.2
Good (>50%)	69%	70%	
Reduced (30-50%)	26%	26%	
Poor (<30%)	5%	4%	
NYHA class			0.008
I/IIIA	47%	51%	
IIIB/IV	53%	49%	
CCS class			0.1
0-2	32%	35%	
3-4	68%	65%	
EuroSCORE (median, IQR)	3 (2-5)	2 (1-4)	<0.001
Perioperative			
Aortic cross-clamp time, min (median, IQR)	43 (35-53)	42 (34-52)	0.3
Cardiopulmonary bypass time, min (median, IQR)	82 (66-97)	80 (65-96)	0.5
Use of IMA	93%	92%	0.6
Number of distal anastomoses (median, IQR)	3 (3-4)	3 (3-4)	0.2
Perioperative myocardial injury	8.8%	9.3%	0.5
Postoperative			
Re-operation, bleeding	3.5%	2.3%	0.005
IABP	0.9%	0.6%	0.2
Respiratory complication	4.1%	2.2%	<0.001
Infection	7.3%	5.0%	<0.001
Stroke	3.7%	2.1%	<0.001
Permanent pacemaker	0.8%	0.7%	0.6

POAF was related to increased cardiac mortality in unadjusted (HR 1.7, 95% CI 1.6 to 1.9; Figure 2A) and adjusted analyses (HR 1.4, 1.3 to 1.5; Figure 2B).

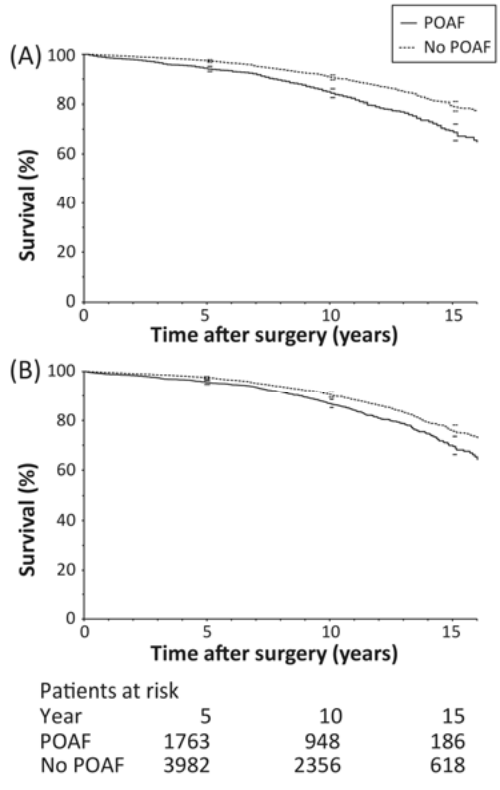


Figure 2. Kaplan-Meier survival curve based on cardiac mortality, (A) unadjusted and (B) adjusted for age, diabetes, number of prior MIs, and LVEF, by occurrence of POAF. The figure shows 95% CI at 5, 10 , and 15 years. Log-rank p<0.0001.

POAF was also associated with death related to arrhythmia (HR 2.1, 1.9 to 2.3), cerebrovascular disease (HR 1.9, 1.7 to 2.1), and HF (HR 1.8, 1.7 to 2.0). After adjustment for baseline characteristics, medical history and preoperative status, POAF was still related to increased mortality in these three categories: death related to arrhythmia (HR 1.8, 1.6 to 2.0), cerebrovascular disease (HR 1.4, 1.2 to 1.6), and HF (HR 1.4, 1.3 to 1.6) (Figure 3). The majority of the effect was reduced due to adjustment for age, and additional variables adjusted the effect marginally.

The effect of POAF on cause-specific death remained more than 8 years after CABG for cardiac mortality (HR 1.3, 1.1 to 1.5), and death related to arrhythmia (HR 1.8, 1.6 to 2.1), cerebrovascular disease (HR 1.4, 1.1 to 1.7), and HF (HR 1.5, 1.3 to 1.7). The results of a modified cohort of patients without other major complications (n=5555) were similar to the overall cohort.

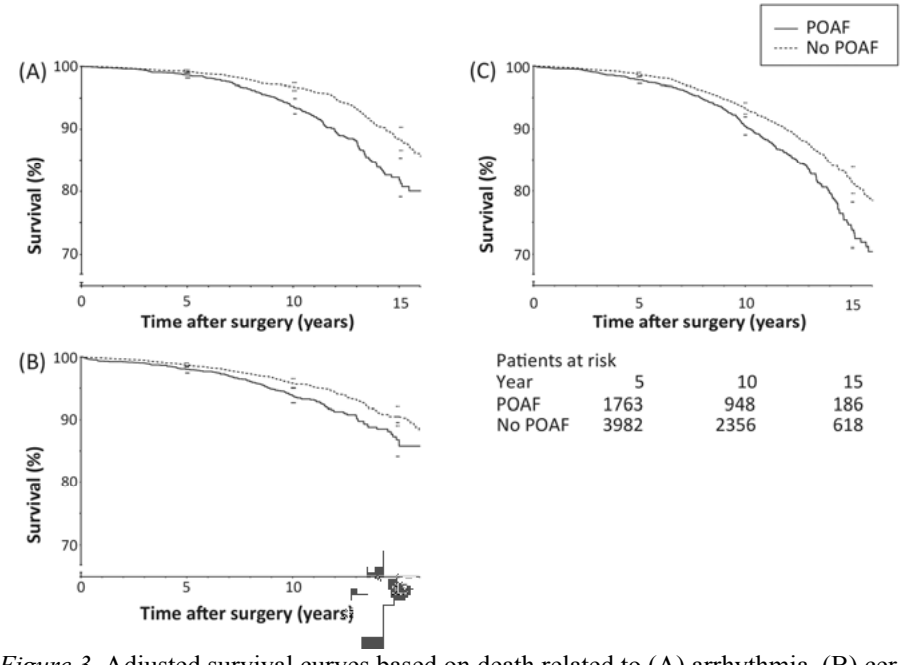


Figure 3. Adjusted survival curves based on death related to (A) arrhythmia, (B) cerebrovascular disease, and (C) heart failure, by occurrence of POAF.
The figures show 95% CI at 5, 10, and 15 years. Log-rank p<0.0001.

Analyses adjusted for (A) age, hypertension, diabetes, diseased coronary vessels, and LVEF; (B) age diabetes, and LVEF; and (C) age, diabetes, number of prior MIs, left main stenosis, and LVEF.

Post-discharge atrial fibrillation (Paper III)

The 67 included patients made on average 90 intermittent ECG recordings over 30 days following discharge after CABG. Median follow-up time after CABG was 35 days (interquartile range (IQR) 34 to 37). Baseline characteristics, perioperative data and postoperative complications for the 19 POAF patients and the 48 non-POAF patients did not differ between the two groups (Table 8). LOS was one day longer in the POAF group (median 6 days; IQR 5 to 8) than the non-POAF group (5 days; 4 to 6) (p=0.02).

Out of 6006 ECG recordings, 144 (2.4%) were diagnosed as AF, and 35 (24%) of these were related to arrhythmia symptoms such as palpitations, fatigue, chest pain, shortness of breath, or anxiety. Thirty-five percent of all patients with AF after discharge were entirely asymptomatic.

Table 8. Patient characteristics and perioperative variables by POAF.

Variable	POAF (n=19)	No POAF (n=48)	P-value
Age, years, (mean, range)	65 (56-82)	64 (34-79)	0.277
Male gender, n (%)	17 (89)	43 (90)	1.000
Hypertension, n (%)	14 (74)	26 (54)	0.142
Diabetes, n (%)	4 (21)	12 (25)	1.000
Previous stroke/TIA/thromboembolism, n (%)	1 (5.3)	4 (8.3)	1.000
Vascular disease, n (%)	1 (5.3)	2 (4.2)	1.000
Diseased coronary vessels, median (IQR)	3 (2-3)	3 (2-3)	0.552
Left main stenosis, n (%)	8 (42)	24 (50)	0.598
CHA_2DS_2-VASc score, (median, IQR)	2 (1-3)	2 (1-2)	0.548
Aortic cross-clamp time, min (median, IQR)	49 (31–71)	47 (42–59)	0.759
Cardiopulmonary bypass time, min (median, IQR)	93 (55–110)	91 (75–102)	0.818
Use of IMA, n (%)	19 (100)	46 (96)	1.000

Twenty out of 67 patients (30%) were diagnosed with post-discharge AF (Table 9). The incidence of post-discharge AF was higher among POAF patients than non-POAF patients (58% vs. 19%), with an OR of 6.0 (1.9 to 19.1). Patients with POAF registered episodes of post-discharge AF earlier during follow-up than non-POAF patients. All AF patients were detected within 14 days after discharge, but episodes were registered up until day 30. More patients with POAF experienced symptoms in relation to post-discharge AF, but the difference was not significant.

Table 9. Patients with post-discharge AF by POAF.

Variable	POAF (n=19)		No POAF (n=48)		P-value
Patients with AF, n (%, 95% CI)	11	(58,36-77)	9	(19,10-32)	0.002
Registrations with AF, mean (range)	11	(1-88)	2	(1-5)	0.261
Duration of AF 30 s, n (%)	124	(98)	13	(65)	0.232
Day of first AF episode, mean (range)	3	(1-9)	10	(7-14)	<0.001
Symptomatic patients, n (%)	9	(82)	4	(44)	0.160

Regarding medications, beta-blockers were commonly used, without any differences between the POAF and non-POAF group. (Table 10). The beta-blockers used were metoprolol, bisoprolol and atenolol. All patients with POAF and all patients with post-discharge AF were treated with beta-blockers at discharge and follow-up. No differences between groups were observed regarding treatment with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), or statins. One POAF patient were under treatment with amiodarone 30 days after discharge and no other anti-arrhythmic agents were used.

Table 10. Medications by POAF.

Medication	Admission n (%)		Discharge n (%)		Follow-up (>30 days) n (%)	
Beta-blockers						
POAF	17	(89)	19	(100)	19	(100)
No POAF	41	(85)	44	(92)	42	(90)
ACE-I/ARB						
POAF	12	(63)	14	(74)	14	(74)
No POAF	34	(71)	30	(63)	32	(67)
Statins						
POAF	18	(95)	18	(95)	19	(100)
No POAF	43	(90)	45	(94)	45	(94)

The median CHA_2DS_2-VASc score at admission among patients who developed post-discharge AF was 3.0 (IQR 1.5-3.0), and 80% (16 of 20) had a score of ≥1 and 75% (15 of 20) a score of ≥2. For patients without post-discharge AF, the median CHA_2DS_2-VASc score was 2.0 (IQR 1.0-2.0), with 79% (37 of 47) with a score of ≥1 and 55% (26 of 47) with a score of ≥2.

Long-term mortality and morbidity (Paper IV)

Patients were followed for a median of 9.8 years (IQR 6.1 to 13.7), with a total of 71 986 py at risk. A total of 253 patients (3.4%) had a history of AF, and 31% of all patients (2298 of 7398) developed POAF after CABG surgery (Table 11). Patients in the POAF group were older than in the non-POAF group, and more commonly had a history of AF, thrombosis, non-cerebral bleeding and hypertension than patients without POAF.

Thirty-five percent of all patients (2589 of 7398) died during follow-up, with a median time to death of 9.1 years (IQR 5.4 to 12.6). Out of all deaths, 1062 (41.0%) were cardiac deaths and 234 deaths (9.0%) were cerebrovascular deaths. The most common non-cardiovascular cause of death was cancer (550 deaths, 21.2%). POAF patients had an increased overall mortality, with an absolute difference of 13.1% at 15 years (Figure 4). POAF was associated with increased overall mortality (HR 1.49, 1.42 to 1.56; adjusted HR 1.19 (1.11 to 1.27) (Table 12). The association between of POAF and overall mortality remained after more than 10 years (HR 1.23, 1.09 to 1.36) (Figure 5). Specifically, POAF was independently associated with both a higher cardiac mortality (HR 1.32, 1.20 to 1.45) and cerebrovascular mortality (HR 1.50, 1.24 to 1.76) (Table 12).

Table 11. Baseline characteristics and surgical variables by POAF

Variable	All (n=7398) n (%)	POAF (n=2298) n (%)	Non-POAF (n=5100) n (%)	P value
Age, years (mean ± SD)	66 ± 9	69 ± 8	65 ± 9	<0.001
Male gender	5747 (77.7)	1808 (78.7)	3939 (77.2)	0.2
Medical history within 5 years of surgery				
Atrial fibrillation	253 (3.4)	115 (5.0)	138 (2.7)	<0.001
Heart failure	526 (7.1)	176 (7.7)	350 (6.9)	0.2
Ischemic stroke	237 (3.2)	85 (3.7)	152 (3.0)	0.1
Thrombosis	162 (2.2)	62 (2.7)	100 (2.0)	0.04
Haemorrhagic stroke	22 (0.3)	4 (0.2)	18 (0.4)	0.2
Non-cerebral bleeding	157 (2.1)	61 (2.7)	96 (1.9)	0.03
Diabetes	1106 (14.9)	345 (15.0)	761 (14.9)	0.9
Hypertension	1393 (18.8)	472 (20.5)	921 (18.1)	0.01
Diseased coronary vessels ≥ 3	5515 (74.5)	1720 (74.8)	3795 (74.3)	0.7
Left main stenosis	2483 (33.6)	791 (34.4)	1692 (33.2)	0.3
Left ventricular function				0.1
Normal (>50%)	5171 (69.9)	1580 (68.8)	3591 (70.4)	
Reduced (30-50%)	1916 (25.9)	607 (26.4)	1309 (25.7)	
Poor (<30%)	309 (4.2)	110 (4.8)	199 (3.9)	
Year of surgery				<0.001
1996-1999	3003 (40.6)	896 (39.0)	2107 (41.3)	
2000-2004	2310 (31.2)	802 (34.9)	1508 (29.6)	
2005-2012	2085 (28.2)	600 (26.1)	1485 (29.1)	
Use of IMA	6808 (92.0)	2120 (92.3)	4688 (91.9)	0.6
Aortic cross-clamp time, min (median, IQR)	43 (34–53)	43 (35–53)	43 (34–53)	0.3

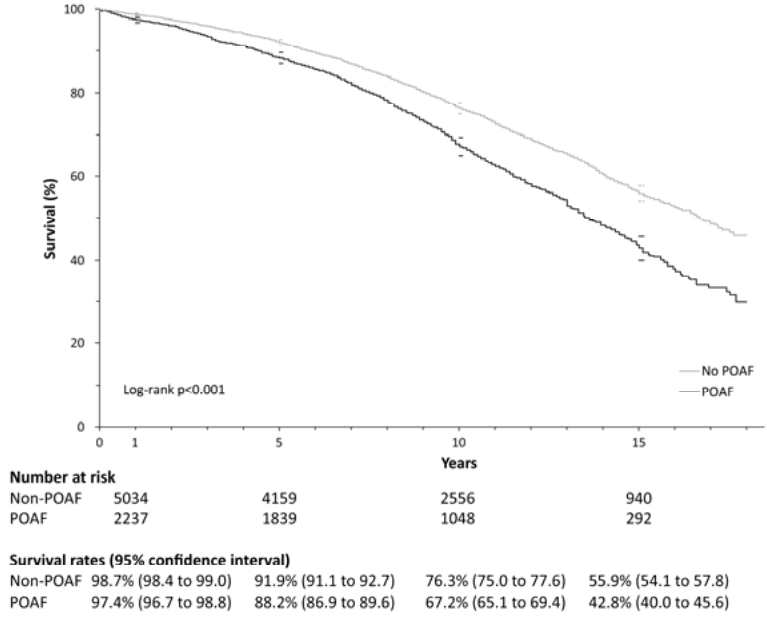


Figure 4. Kaplan-Meier survival curve for overall mortality by POAF, with 95% CI at 1, 5, 10 and 15 years.

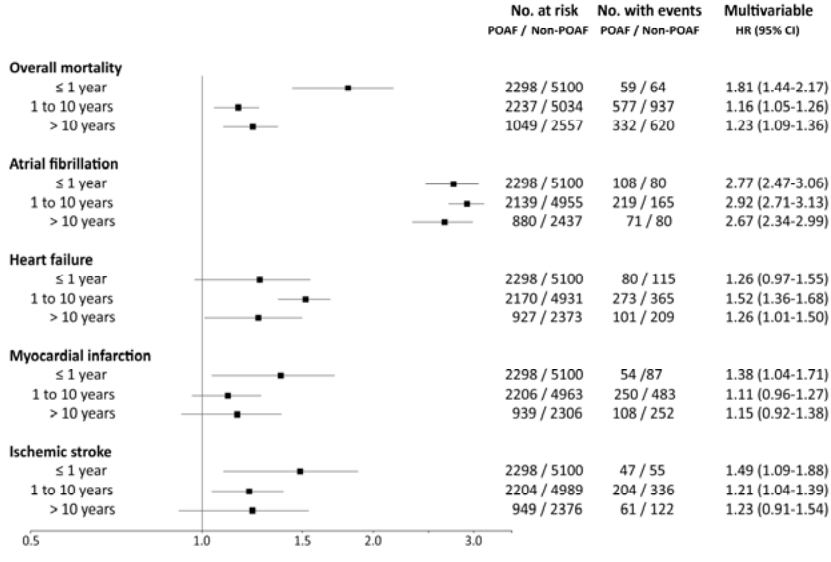


Figure 5. Analysis of the associations between POAF and risk of mortality and morbidity during different follow-up periods.

Table 12. Incidences and Cox proportional hazards models for mortality and first morbidity event by POAF.

	POAF (n=2298)	Non-POAF (n=5100)		Univariable Cox model		Multivariable Cox model	
Event	**Patients with events (%)**		**P value**	**HR(95% CI)**	**P value**	**HR(95% CI)**	**P value**
Overall mortality	968 (42.1)	1621 (31.8)	<0.001	1.49 (1.42-1.56)	<0.001	1.19 (1.11-1.27)[a]	<0.001
Cardiac mortality	422 (18.4)	640 (12.5)	<0.001	1.65 (1.46-1.87)	<0.001	1.32 (1.20-1.45)[a]	<0.001
Cerebrovascular mortality	105 (4.6)	129 (2.5)	<0.001	2.01 (1.56-2.61)	<0.001	1.50 (1.24-1.76)[a]	0.002
Atrial fibrillation	398 (17.3)	325 (6.4)	<0.001	3.14 (3.00-3.29)	<0.001	2.82 (2.67-2.97)[b]	<0.001
Heart failure	454 (19.8)	689 (13.5)	<0.001	1.64 (1.52-1.76)	<0.001	1.38 (1.26-1.50)[c]	<0.001
Myocardial infarction	412 (17.9)	822 (16.1)	0.053	1.22 (1.10-1.34)	0.001	1.14 (1.01-1.26)[d]	0.040
Ischemic stroke	312 (13.6)	513 (10.1)	<0.001	1.47 (1.33-1.61)	<0.001	1.24 (1.10-1.39)[e]	0.003
Thrombosis	208 (9.1)	387 (7.6)	0.032	1.30 (1.13-1.47)	0.003	1.12 (0.95-1.29)[f]	0.19
Haemorrhagic stroke	65 (2.8)	106 (2.1)	0.047	1.48 (1.17-1.79)	0.01	1.26 (0.95-1.58)[g]	0.14
Non-cerebral bleeding	176 (7.7)	324 (6.4)	0.038	1.29 (1.11-1.48)	0.006	1.14 (0.95-1.33)[h]	0.17

Variables included in the final multivariable model:

[a] Age, gender, history of AF, diabetes, hypertension and ischemic stroke, left ventricular function, and use of IMA.

[b] Age, history of AF and hypertension, and left ventricular function.

[c] Age, history of AF, HF, diabetes, hypertension and ischemic stroke, and left ventricular function.

[d] Age, history of AF, HF and hypertension, and left ventricular function.

[e] Age, history of AF, diabetes, ischemic stroke and thrombosis, and left ventricular function.

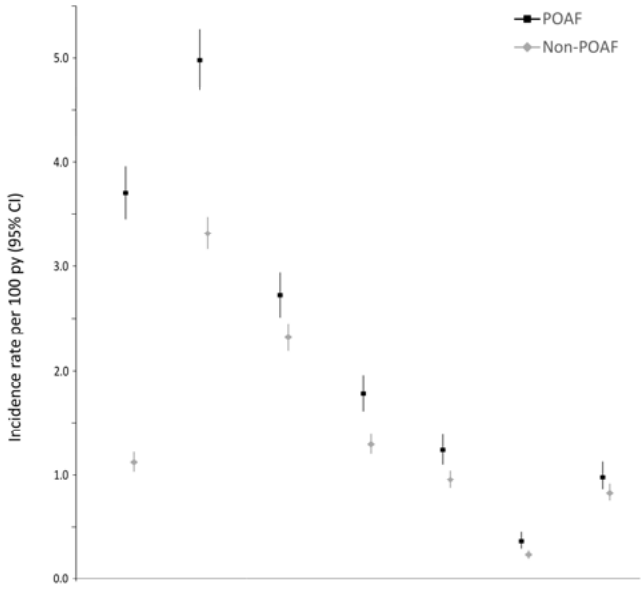
[f] Age, history of AF, diabetes, ischemic stroke and thrombosis.

[g] Age, history of diabetes and non-cerebral bleeding.

[h] Age, history of HF, diabetes and non-cerebral bleeding.

Concerning morbidity, more than half of all patients (54.3%) did not experience any predefined event, while 28.3% had one type, 11.9% had two types, 4.3% had three types, and 1.2% had four types of events during follow-up.

POAF patients had significantly higher incidence rates of AF ($p<0.001$ from Wilcoxon rank sum tests), HF ($p=0.03$), and ischemic stroke ($p<0.001$) during follow-up, while there were no significant differences in incidence rates for the other examined morbidities (p-values 0.09 to 0.4) (Figure 6). At 10 years, the cumulative incidences in the POAF group and non-POAF group of AF was 16.5% and 5.6%, of HF 18.6% and 11.4%, and of ischemic stroke 13.4% and 9.4%. POAF was independently associated with a first event of AF (HR 2.82, 2.67 to 2.97), HF (HR 1.38, 1.26 to 1.50), MI (HR 1.14, 1.01 to 1.26), and ischemic stroke (HR 1.24, 1.10 to 1.39) during follow-up (Table 12).



Number of events							
POAF	792	1066	582	381	265	77	211
Non-POAF	566	1675	1171	653	481	114	416

Figure 6. Incidence rates of morbidity events by POAF with 95% CI.

The association between POAF and AF during follow-up successively increased for higher numbers of AF episodes (≥1 events: HR 2.99, 2.84 to 3.14, ≥2 events: HR 3.61, 3.36 to 3.86, ≥3 events: HR 4.59, 4.24 to 4.95). The association between POAF and HF remained of equal magnitude regardless of the number of episodes (≥1, ≥2 or ≥3 events), whereas there was no association between POAF and higher numbers of MIs or ischemic strokes. The effect of POAF on first and subsequent events differed regarding AF (test for interaction $p<0.001$), HF ($p<0.001$) and ischemic stroke ($p=0.01$). For AF, the association between POAF and subsequent events remained significant (HR 1.26, 1.07-1.47), but for HF and ischemic stroke, an association was found with the first event only.

The association between POAF and AF and HF remained for more than 10 years, and in the case of ischemic stroke remained up to 10 years after surgery (Figure 5). In terms of MI, the association with POAF did not extend past the first post-operative year.

There was an independent association between morbidity events during follow-up and overall mortality for AF (HR 1.73, 1.62 to 1.85), HF (HR 3.67, 3.58 to 3.77), MI (HR 2.45, 2.34 to 2.55) and ischemic stroke (HR 2.26, 2.15 to 2.37).

Discussion

Prediction of POAF

Several risk factors for POAF after CABG were identified in Paper I. The strongest predictor, advancing age, is the only risk factor that has been consistently associated with POAF after cardiac surgery.[10–12,60,64] The oldest patients in our cohort (>80 years) had more than seven times the odds of developing POAF compared to the youngest patients (≤50 years). Crude and adjusted estimates were essentially the same, as were analyses stratified for LOS, and a sub-cohort without other postoperative complications. This implies that advanced age and age-related structural changes in the atria, such as fibrosis, muscle atrophy and dilatation[54,55] have a direct impact on the risk of developing POAF after surgery. Other predictors were not as strong, and results have been inconsistent in past studies regarding elevated preoperative S-creatinine,[67] prior MI, male gender and HF.[64] The inverted impact of hyperlipidaemia could be a results of statin use,[102] but this is speculative since data on medications were not available. Previous prediction models of POAF after isolated CABG show similarly moderate prediction values, with AUC at 0.65[11] and 0.69[12], compared to 0.62 in this Paper.

Postoperative complications and in-hospital mortality

The higher incidence of postoperative complications confirms previous findings regarding infection, HF,[10,11] re-operation, stroke, renal and respiratory complications, and longer ICU and total LOS after cardiac surgery.[11] The need for a permanent pacemaker[11] and perioperative MI[10,11] where not supported by our findings. Neither was the association between POAF and a higher in-hospital mortality. Compared to previous results, with rates from 2.4 to 7.4%[10,11,13,14,60] after cardiac surgery, the present mortality rate was relatively low at 2.1%.

Post-discharge atrial fibrillation

The recurrence rate of AF after discharge following CABG (58%) was considerably higher than previously described.[86,87] Furthermore, almost a fifth of

the patients without POAF during the initial hospitalisation registered post-discharge AF on intermittent ECG recordings. This contradicts previous results showing a low incidence in this patient group,[86] or none at all.[84,88] The method for AF detection might explain the difference, as results are compared to isolated ECG recordings, 24 hour Holter monitoring, or recordings with arrhythmia symptoms. The majority (94%) of the AF episodes on intermittent ECG recordings were 30 seconds long, and should accurately represent AF. The method for recording using the handheld ECG devices has been used previously, and has been found to be more efficient than 24 hour Holter monitoring.[103,104]

Treatment with beta-blockers was common preoperatively and is known to reduce the incidence of POAF,[105] but did not influence the outcome in this patient cohort. Use of beta-blockers, ACE-Is, ARBs and statins did not differ between groups at discharge and follow-up, and should not have influenced the occurrence of AF during follow-up, in support of previous findings.[86]

AF is a known risk factor for stroke.[8] The risk further increases in the presence of further risk factors in the combined CHA_2DS_2-VASc-score. The recommendation is to consider oral anticoagulants for patients with a score of ≥ 1[106], which includes 80% of the patients with AF during follow-up. A score of ≥ 2 has been identified as an independent risk factor of POAF after cardiac surgery,[107] and included 75% of the patients with AF in this cohort. Only two of these fifteen high-risk patients received treatment with warfarin after 30 days, and no patients were prescribed NOACs, and there seems be room for improvement when it comes to adherence to guidelines in this postoperative cohort.

Long-term mortality and cause of death

The association between POAF and increased long-term mortality in Paper II and IV was independent of established risk factors, including medical history and preoperative status. This confirms conclusions from multiple studies, including a recent meta-analysis,[80] and is the only previous long-term outcome with a clear association with POAF.

Cause of death in relation to POAF has not been extensively researched in a post-CABG setting. One previous study demonstrated a higher incidence of death from cardiac causes and cerebral ischemia in POAF patients, but did not correct for confounders.[61] Another identified POAF as an independent risk factor of cardiovascular mortality, and the subgroup embolic deaths.[81] However, embolic deaths included pulmonary embolism in addition to stroke, and the low number of deaths from other subcategories (MI and HF) did not permit reliable analyses. The large cohorts in Paper II and IV allowed for analyses of subcategories of cardiovascular mortality. The cohorts are in part the same,

but with three additional years of inclusion in Paper IV (2010-2012) and a 1 year longer follow-up range.

Cardiac mortality as underlying cause of death was found to be independently associated with POAF in Paper II and IV. The novel approach in Paper II using analyses that included multiple causes of death was an attempt to improve knowledge of the causal complexity of death,[108] and identified a higher risk of death related to arrhythmia, cerebrovascular disease, and HF associated with POAF. The associations all persisted more than 8 years after surgery. POAF has been previously associated with later development of AF after CABG,[14] confirmed by results on long-term morbidity from Paper IV, and it may be late-recurring AF episodes that influence survival. The association between POAF and death related to cerebrovascular disease could also be a consequence of recurring arrhythmias, where 20% of patients with cerebrovascular-related deaths also suffered from arrhythmia as a contributing cause of death. In Paper IV, there was also an independent association between POAF and cerebrovascular mortality as underlying cause of death.

In Paper II, 17% of all deaths were related to cerebrovascular disease, and as many as 31% were related to HF. The association between POAF and HF-related death has not been previously examined after CABG, related to smaller cohorts with few events.[81] The persistent associations found for these causes of death in Paper II motivated closer examination of AF, stroke and HF during follow-up, which was done in Paper IV.

The effect of POAF in Paper II remained when examining a sub-cohort with POAF as the only complication after CABG. This verifies that the impact on long-term survival is driven by POAF, and not solely its association with other postoperative complications.

Long-term morbidity

In Paper IV, POAF was independently associated with a AF for more than 10 years after surgery. POAF patients also had a higher incidence rate of AF during follow-up. It has been previously described that POAF patients more often experience one AF episode during follow-up, but the extent and frequency of these episodes have not been analysed.[14,84,85] The current study showed an association with subsequent events of AF after the first event, as well as an association that became clearer as the number of AF events increased, which makes it the first study to show that POAF is associated with a higher overall AF burden. This demonstrates that POAF does not solely represent an episode of AF in relation to surgery, but is rather a part of a condition with multiple recurrent AF events that continues post-discharge after CABG.

Overall, POAF represents a recurrent condition that tends to result in increased morbidity through a series of proposed mechanisms. These include activation of the coagulation cascade,[41] which contribute to a hypercoagulable

state and leaves AF patients at greater risk of MI[42] and ischemic stroke,[41] and potentially non-cerebral thromboembolism. Data also indicate that AF can create and sustain an inflammatory environment,[109] which can trigger HF by inducing cardiomyocyte loss, hypertrophy and fibrosis, resulting in cardiac remodelling and ventricular dysfunction.[110,111]

Paper IV is the first study clearly demonstrating an independent association between POAF and long-term ischemic stroke in an isolated CABG population, including a higher incidence rate. Previously, the association between POAF and long-term stroke had been examined in only two cardiac surgery cohorts. In a CABG cohort, an association with stroke was found (HR 1.3), but did not specify ischemic stroke.[89] The other study, showing an association between POAF and ischemic stroke (HR 1.3), included all cardiac surgery, and the inclusion of valvular replacement, typically associated with a higher use of anticoagulants, would be expected to influence stroke risk.[90] Moreover, patients were censored if post-discharge AF occurred, which could lead to a skewed exclusion since POAF patients are more likely to have recurrent AF after cardiac surgery.[14,82–85] The current study further revealed that ischemic stroke during follow-up was associated with increased mortality.

Paper IV showed an extensive influence of POAF on long-term HF. HF was independently associated with POAF, which persisted for more than 10 years, as well as an associations between POAF and higher number of HF episodes. There was also a higher incidence rate of HF among POAF patients. There are no available studies on long-term HF after CABG, but primary AF has been associated with HF in a large meta-analysis.[34] Development of HF in patients with primary AF has also been associated with a three-fold increase in mortality,[112] which was similar to the findings in this CABG cohort.

Paper IV identified an independent association between POAF and MI, but it seemed to be limited to the first year after surgery. Furthermore, the incidence rate of MI was not higher in the POAF group. Any clinically relevant influence of POAF on long-term MI should therefore be limited. There are no publications regarding POAF and the risk of long-term MI, but in primary AF patients an independent association between AF and long-term MI has been observed, as well as a higher incidence of MI.[40] Neither are there any previous studies relating to thrombosis or haemorrhagic events in cardiac surgery cohorts. Results from Paper IV did not show any associations between POAF and thrombosis or haemorrhagic events. Analyses were limited due to lack of power, especially regarding haemorrhagic stroke (in total 171 events), but POAF data and outcome data are of high quality[96] and any major impact of POAF on thrombosis or haemorrhagic events can be ruled out.

Limitations

The definition (>30 s) and detection method of POAF after CABG could lead to missed episodes and misclassification of POAF and non-POAF patients. However, in Paper III patients were monitored until discharge, and the incidence of POAF was similar to the other studies and detected no episodes of arrhythmia shorter than 30 s. Patients with a history of arrhythmia, but presenting for surgery with SR, were included in Paper I, II and IV, and this could have affected the results since preoperative AF has been identified as an independent risk factor of late mortality after CABG.[76] Since only 3.4% of all patients had a history of AF in Paper IV based on a consistent source (the NPR), this was not expected to affect results. The incidences of POAF at 31 to 32% (Paper I, II, and IV) were also consistent with previously reported results from similar cohorts.[10–14,61,63,74–79,81]

Cause of death from the Swedish CDR is not always based on autopsy results, but the quality of the registry is regularly assessed.[113] Registration of cause of death involves an interpretation that can be partly subjective. This leads to a risk of random information bias, since the occurrence of POAF was unknown when cause of death was established. Paper I, II and IV do not confirm causality. Despite adjusting for a number of risk factors, undetected pathology present preoperatively may have influenced the results.

In Paper III, patients were monitored by continuous telemetry while in hospital, which should have captured all POAF episodes, but misdiagnosis could have occurred. Intermittent ECG recordings were only scheduled during the day, but additional symptom-triggered recordings could be made at night. Missed AF episodes could have affected the results, especially if unevenly distributed between groups.

In Paper IV, defining outcome events solely on the basis of in-hospital care and death could potentially lead to an underestimation of the incidence of predefined morbidity events, primarily regarding AF, but this should not be biased by POAF status.

Finally, data concerning medications at discharge and during follow-up was not included in Paper I, II and IV, and the possible influence of anticoagulants in particular on both thrombosis and haemorrhage was not accounted for. In Paper III, however, no patients with POAF were prescribed anticoagulants at discharge.

Future perspectives

Our present results show an association between POAF and early complications, recurrent AF, and long-term mortality and morbidity after CABG. There are still many unidentified factors in the period between hospital discharge and death. An interesting question is: which type of procedures are performed

during follow-up, including renewed revascularisation via PCI or CABG. By comparing patients with and without POAF in relation to these outcomes, the extent of CAD and the results of CABG could be added to the equation and thus further isolate the associations with POAF.

The observed association between POAF and recurrent AF after discharge needs to be further examined. Only the first 30 days were observed using rhythm monitoring, and knowledge can be added to this field by extending the follow-up period in a larger cohort. Furthermore, knowledge of treatment for AF and other arrhythmias, including procedures for AF such as electrical cardioversion and ablation, could shed light on resources required for the patient group with recurrent AF, which was also seen from a long-term perspective.

Examination of pharmacological treatment after discharge is another way of identifying associated morbidity and late recurrent AF after CABG. Treatment with anticoagulants would be of particular interest, since ischemic stroke and cerebrovascular mortality was associated with POAF in the long term. As Paper III displays, the use of oral anticoagulants might not be in accordance with guidelines.[49] However, the guidelines regarding the use of oral anticoagulants after cardiac surgery is based on a single CABG cohort that showed beneficial results regarding warfarin and long-term overall mortality.[63] Further studies regarding POAF and the effects of anticoagulation, both for patients after CABG and other types of cardiac surgery including valve surgery, are needed to determine the usefulness of these drugs in this setting. The place for NOACs in a postoperative population also remains unexplored.

Conclusions

Several risk factors for POAF after CABG were identified, including advancing age. The moderate predictive value of the final model confirms the difficulty of identifying a high-risk group prior to surgery. The number of patients with a greatly elevated POAF risk is relatively small, and the absolute number of reduced cases of POAF would be even smaller. This makes it hard to focus prophylactic efforts on a well-defined group of patients, and increases the risk of unnecessary side effects for patients at low or moderate risk of developing POAF after CABG.

An episode of POAF is associated with increased late mortality after CABG, specifically death related to arrhythmia, cerebrovascular disease, and HF, all of which have a plausible relationship to POAF. The effect of POAF was independent of other risk factors such as age, diabetes, and left ventricular function. The effect remained more than 8 years after surgery, so follow-up should not be confined to the early postoperative period but adopt a long-term approach. Findings suggest that POAF should not be solely considered as a sign of more advanced disease at the time of surgery, but also as a predictor of a lasting negative effect on cause-specific survival after CABG.

Postoperative atrial fibrillation predicts recurrence of AF within 30 days of discharge following CABG. Both symptomatic and asymptomatic AF episodes were frequent, and a more thorough follow-up with intermittent ECG recordings can help identify patients at risk. Early initiation of treatment might help reduce further complications associated with POAF from a long-term perspective.

It has been shown by way of extensive evidence that POAF patients have an increased long-term risk of ischemic stroke and increased cerebrovascular mortality, as well as HF and cardiac mortality, after CABG. POAF was confirmed to be a recurrent condition, and should not be considered an isolated event in relation to surgery.

Sammanfattning på svenska

Kardiovaskulära sjukdomar, eller hjärt-kärlsjukdomar, är en av de vanligaste sjukdomsgrupperna och den ledande dödsorsaken i världen. Andelen som dör i kardiovaskulära sjukdomar minskar, tack vare ökade antal kardiovaskulära operationer och andra ingrepp kombinerat med nya läkemedel, men är ändå fortsatt hög. Främst är det kranskärlssjukdom, orsakad av aterosklerotiska plack, som står för den höga sjukdomsbördan. Det finns två typer av revaskularisering vid avancerad kranskärlssjukdom, PCI (perkutan koronar intervention) och CABG (bypass-kirurgi). Denna avhandling undersöker patienter som genomgått CABG.

Förmaksflimmer är den vanligaste kroniska takykardin. Prevalensen i den vuxna befolkningen är 1-3% och ökar med stigande ålder. Förmaksflimmer är en viktigt riskfaktor för stroke och är även förknippat med andra kardiovaskulära sjukdomstillstånd och dödsorsaker. När förmaksflimmer uppträder efter kirurgi kallas det postoperativt förmaksflimmer och kan påverka prognosen negativt. Ungefär en tredjedel av alla patienter som genomgår CABG får postoperativt förmaksflimmer, och det är ämnet för denna avhandling.

Det är främst tidiga komplikationer som har studerats i denna patientgrupp tidigare. Även dödlighet på lång sikt, oavsett dödsorsak, har förknippats med postoperativt förmaksflimmer. Orsakerna bakom den ökade dödligheten är däremot oklara och det finns lite information om dödsorsaker och sjuklighet på lång sikt.

Syftet med avhandlingen var att studera riskfaktorer för att utveckla postoperativt förmaksflimmer och möjligheten att förutsäga vilka patienter som kommer att drabbas efter CABG. Vidare undersöktes förekomsten av förmaksflimmer efter utskrivning från sjukhuset i denna patientgrupp, samt utfallet i form av överlevnad, dödsorsaker och sjukdomarbörda på kort och lång sikt efter kirurgi.

Alla studier inkluderade patienter som genomgått isolerad CABG på kliniken för Thoraxkirurgi och -anestesi, Akademiska sjukhuset, Uppsala. Tre av studierna var retrospektiva i sin design och inkluderade ca 7000 patienter vardera. En studie var en mindre prospektiv observationsstudie. All data samlades prospektivt i klinikens databas. I två av studierna samkördes information från databasen med Dödsorsaksregistret och Patientregistret som förvaltas av Socialstyrelsen.

I den första studien identifierades flera oberoende riskfaktorer för att utveckla postoperativt förmaksflimmer efter CABG, vilka inkluderade stigande ålder, nedsatt njurfunktion, manligt kön, NYHA klass III/IV, rökning, tidigare hjärtinfarkt och avsaknad av hyperlipidemi. Den sammantagna modellen hade ett måttfullt prediktivt värde och bekräftade svårigheten att identifiera en högriskgrupp. Patienter med postoperativt förmaksflimmer hade en högre andel komplikationer efter operationen, inklusive stroke, infektion, andningsproblem, njursvikt, cirkulationssvårigheter, hjärtsvikt, reoperation, en längre vårdtid på intensivvårdsavdelning och en längre sammanlagd vårdtid.

Den andra studien visade en oberoende association mellan postoperativt förmaksflimmer och hjärtdöd på lång sikt, samt död relaterad till arytmi, cerebrovaskulär sjukdom och hjärtsvikt vid undersökningar av multipla dödsorsaker. Kopplingarna fanns kvar mer än 8 år efter CABG.

I den tredje studien observerades hjärtrytmen i 30 dagar efter att patienten skrivits ut från sjukhuset efter CABG. Förmaksflimmer var vanligt under uppföljningstiden och fler patienter med postoperativt förmaksflimmer hade också förmaksflimmer efter hemgång. Så många som 35% av alla patienter hade inga symptom alls av sitt förmaksflimmer.

I den fjärde studien undersöktes kopplingen mellan postoperativt förmaksflimmer och sjuklighet som tidigare kopplats till förmaksflimmer i den ickekirurgisk populationen. Här sågs en association mellan postoperativt förmaksflimmer och ischemisk stroke och hjärtsvikt, och död orsakad av hjärtsjukdom och cerebrovaskulär sjukdom. Sjukdomar under uppföljningstiden ökade risken för död ytterligare. Förmaksflimmer kunde också bekräftas som ett återkommande tillstånd, där postoperativt förmaksflimmer bara ses som en början på fortsatta arytmier på lång sikt efter CABG.

Sammanfattningsvis visar avhandlingen att postoperativt förmaksflimmer är en vanlig komplikation efter CABG, där det är svårt att identifiera en högriskgrupp som skulle kunna få profylaktisk behandling. Vidare fynd pekar på att postoperativt förmaksflimmer återkommer, både på kort och lång sikt, och inte ska ses som en isolerad företeelse i samband med operationen. På lång sikt är postoperativt förmaksflimmer också kopplat till död relaterad till arytmi, cerebrovaskulär sjukdom och hjärtsvikt, samt bakomliggande sjukdomstillstånd i form av förmaksflimmer, ischemisk stroke och hjärtsvikt. Dessa kopplingar kvarstod på lång sikt, vilket visar på vikten av fortsatta studier kring dessa sjukdomar och hur dessa patienter bäst kan följas upp och behandlas på sikt.

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Errata

Published articles

Paper II, page 74, Table 2.

Median and 25th percentile values were misplaced for aortic cross-clamp time and CPB time.

The table should look as follows:

Table 2. Peri- and postoperative variables.

Variables	POAF n=2152 (32%) %	No POAF n=4669 (68%) %	*p*-value
Perioperative			
Aortic cross-clamp time, min [a]	43 (35-53)	42 (34-52)	0.3
CPB time, min [a]	82 (66-97)	80 (65-96)	0.5
Use of IMA	93	92	0.6
Number of distal anastomoses [a]	3 (3-4)	3 (3-4)	0.2
Perioperative myocardial injury [b]	8.8	9.3	0.5
Postoperative			
Re-operation, bleeding	3.5	2.3	0.005
IABP	0.9	0.6	0.2
Respiratory complication [c]	4.1	2.2	<0.0001
Infection [d]	7.3	5.0	<0.0001
Stroke [e]	3.7	2.1	<0.0001
Permanent pacemaker	0.8	0.7	0.6

CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; IMA = internal mammary artery; POAF = postoperative atrial fibrillation.

[a] Median (25th to 75th pctl).

[b] Plasma creatine kinase-band value >50 µg postoperative day 1.

[c] Prolonged mechanical ventilation >24 h, or re-intubation.

[d] Treatment with antibiotics, and/or positive blood culture.

[e] Severe neurological symptoms lasting ≥6 h, verified by computer tomography.

Paper III, page 180, References.

Reference number 19 is mislabelled as number 20, and vice versa.
The end of the reference list should read as follows:

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