Peri-operative atrial fibrillation in cardiac surgery : impact on outcome

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PERI-OPERATIVE ATRIAL FIBRILLATION
in CARDIAC SURGERY
impact on outcome

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PERI-OPERATIVE ATRIAL FIBRILLATION **in CARDIAC SURGERY** *impact on outcome*

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CONTENTS

Chapter 1	Introduction and objectives of this thesis	7
Chapter 2	The impact of preoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting	21
Chapter 3	Body mass index predicts new-onset atrial fibrillation after cardiac surgery	37
Chapter 4	The impact of new-onset postoperative atrial fibrillation on mortality after coronary artery bypass grafting	51
Chapter 5	New-onset postoperative atrial fibrillation predicts late mortality after mitral valve surgery	73
Chapter 6	Does new-onset postoperative atrial fibrillation after coronary artery bypass grafting affect postoperative quality of life?	87
Chapter 7	Discussion and perspectives	99
Chapter 8	Summary	111
	Samenvatting (Dutch summary)	115
	Dankwoord	119
	Curriculum vitae	121
	List of publications	123

CHAPTER 1

Introduction and objectives of this thesis

In 1628 an important work on the circulatory system, called 'Exercitatio anatomica de motu cordis et sanguinis in animalibus', was published by William Harvey (1578-1657) [1,2]. In this book Harvey describes what is believed to be the first direct observation of a fibrillating atrium. Despite numerous studies on AF ever since, much is still unknown about AF, and questions about this rhythm disturbance are still emerging in the 21st century.

DEFINITION

AF is an atrial tachyarrhythmia with predominantly uncoordinated atrial activation with consequent deterioration of atrial mechanical function [3]. It is defined by irregular RR-intervals on the surface ECG, without distinct P-waves, and an atrial cycle length of <200 ms, corresponding to atrial contractions of >300/min [4]. Usually AF starts with short self-terminating episodes, and tends to progress (years) into more sustained forms of AF. When AF episodes self-terminate within a week, it is called paroxysmal AF. When it does not self-terminate within a week, but can be converted to normal sinus rhythm, electrically or pharmacologically, it is called persistent AF. If the persistent AF lasts for > 1 year it is called long-standing persistent AF. AF that is accepted and/or cannot be terminated is referred to as permanent AF [3]. After restoration into SR, persistent AF recurs in $\frac{1}{4}$ to $\frac{1}{2}$ of the patients within a month after cardioversion [5,6]. Symptoms can vary from none at all (EHRA I) to disabling (EHRA IV), where daily activity is discontinued [7]. Symptomatology is not per se related to clinical relevance of AF: highly symptomatic patients may have very low risk for events such as stroke, where other patients present with AF related stroke as a first expression of asymptomatic AF.

MECHANISMS

The onset of AF is induced by triggers and maintained by substrate. Triggers for instance include bradycardia, atrial premature beats, and acute atrial stretching, but also come from ectopic foci, of which most of them, particularly in paroxysmal AF, originate from the pulmonary veins [8,9]. Reentering wavelets may be initiated by these foci. The AF may perpetuate by the persistence of foci themselves, but eventually also without them, when electrical and mechanical remodeling have become a substrate to maintain AF [9]. This is characterized by atrial dilatation and shortening of the atrial effective refractory period. These factors, and other remodeling changes, may facilitate a final common pathway, known as multiple reentrant wavelets [9].

DEMOGRAPHICS

Atrial fibrillation is the most common sustained heart rhythm disturbance. In a large cohort study (1.89 million subjects) in the US, Go et al. estimated a prevalence of 1% in the general population [10]. Lifetime risk to develop AF is about $\frac{1}{4}$ as was shown by Lloyd et al. [11], in a study in which all participants in the Framingham Heart Study who were free of AF at index ages of 40 years and older (3999 men and 4726 women) were included and followed from 1968 to 1999 (176166 person-years). Heeringa et al. showed similar figures in a large European population based study with 6808 participants [12]. AF is more common in men than women [10,11,12] and the prevalence of AF rises with age, with a prevalence of well under 1% in subjects under the age of 60 to a prevalence of 10% or even higher in those aged over 85 [10,12].

RHYTHM OR RATE CONTROL?

Once diagnosed, the rhythm disturbance itself can be treated with one of two strategies. The rhythm control strategy tries to convert to, and maintain normal sinus rhythm, whereas the rate control strategy tries to reduce the ventricular response rate, without necessarily converting to sinus rhythm. Neither therapy has proven better outcome with respect to mortality, major bleeding, and thrombo-embolic events [13,14,15,16].

MORBIDITY

Atrial fibrillation is associated with morbidity and mortality. Amongst the morbidities, stroke is the most important and often most devastating one. The left atrial appendage is the most apparent source of the stroke causing emboli [17]. Approximately 20% of all strokes are caused by AF [18], and strokes caused by AF tend to be more severe [19]. Hence, stroke prevention is a major goal in AF treatment [13,20]. Patients with paroxysmal AF have the same risk for stroke as patients with persistent or permanent AF [21] with event rates of approximately 30/1000 patient-years [21,22], which is about twice as much as in the general population. It has to be mentioned that the event rates are also dependent of other risk factors, like age and hypertension. Oral anticoagulation therapy is highly effective in reducing stroke by thrombo-embolism, but is associated with increased bleeding risk [22]. In almost all patients with AF, the risk of ischemic stroke without anticoagulant therapy is higher than the risk of intracranial bleeding with anticoagulant treatment [21]. Nowadays the CHA₂DS₂-VASc score is used to estimate the adjusted stroke rate for AF patients, and is used as guidance in antithrombotic manage-

ment [23]. The CHA₂DS₂-VASc score contains congestive heart failure, hypertension, age, diabetes, stroke history, vascular disease, and female sex as risk factors for thromboembolism in AF patients.

MORTALITY

Atrial fibrillation is associated with increased and premature death [24,25,26]. Death rates are estimated to be doubled in AF patients, independent of other known predictors of death [7,26]. However, it is important to keep in mind that many predictors of AF are also predictive for death, which can easily bias the results when searching for the independent effect of AF on death. Hence, careful statistical analysis is warranted, and conclusions about AF being a risk factor for death, should be made with caution. The risk of mortality is highest during the first 6 months after the initial diagnosis [4]. Only the use of anticoagulants has shown to be effective in reducing AF-related death [27].

QUALITY OF LIFE

Patients with AF have significantly poorer quality of life (QoL) compared to healthy controls, and the general population [28]. Symptoms, anxiety, and uncertainty of the course of the treatment as well as the (side) effects of the treatment could all play a role in this reduction of QoL. More frequent cerebrovascular accidents will obviously decrease the 'mean' QoL in AF patients, compared to the general population. Both rate and rhythm strategies improve QoL in AF patients, but neither strategy proves to be superior [29,30,31,32]. One theory is that control of ventricular rate is associated with better exercise tolerance and thereby better QoL [33], although this theory has been debated [34]. This observation might explain why patients with paroxysmal AF, often with episodes with higher ventricular rates than patients with continuous forms of AF, experience worse QoL than patients with permanent AF [28].

POAF

New onset postoperative atrial fibrillation (POAF) is one of the most frequent complications after cardiac surgery, with reported incidences between 10 and 60% [35,36,37,38,39,40,41,42,43,44,45,46]. POAF after coronary artery bypass surgery (CABG) is described in up to 40% of the cases, POAF after valve or combined coronary plus valve surgery in up to 60%. It should be noted that the wide range of reported incidences can

be caused by differences in definition of POAF, and differences in detection methods (continuous vs. intermittent, length of follow up, etc). Most of the first episodes of POAF happen within the first 4 to 6 days after surgery, with an incidence peak on the second day [38,46,47,48]. The use of β -blockers or sotalol pre- and postoperatively reduces the incidence of POAF [49,50], and is therefore a class I level A recommendation in the guidelines for the management of atrial fibrillation by the European Society of Cardiology [4].

Riskfactors

As with AF in the general population, age is the most important risk factor for the development of POAF [36,41,51,52,53,54,55,56,57,58,59]. Fibrosis and dilatation of the atria are associated with advanced age, and may explain this association between age and POAF [9,60,61]. These factors may also explain the predictive value of heart valve surgery, and especially mitral valve surgery, for the development of POAF. Furthermore ageing goes along with slowing of conduction, which possibly also contributes to the more frequent occurrence of POAF in the elderly [62]. The role and importance of other possible risk factors, such as hypertension, chronic obstructive pulmonary disease, off-pump CABG versus on-pump, body mass index, and gender, is more controversial.

Morbidity

POAF is associated with morbidities such as cerebrovascular accidents, congestive heart failure, infections, and renal failure [35,37,38,39,40,41,46,47,63], where stroke is, as in AF in the general population, often the most devastating one.

Mortality

POAF is associated with increased early and late mortality after cardiac surgery [35,39,41,42,43,44,64]. Whether POAF is predicting early and late mortality *independently* of other risk factors is much less clear. Results of studies in the past show conflicting results, and the methodology of some of these studies is debatable. Stroke and heart failure might play an important role in the higher incidence of mortality in POAF patients, but this has never been proven.

OBJECTIVES OF THIS THESIS

The aim of this thesis is to investigate the impact of peri-operative atrial fibrillation on survival and quality of life after cardiac surgery. The following topics are discussed in this thesis.

1. The effect of pre-existing atrial fibrillation on the survival of patients after coronary artery bypass grafting.
2. Predictors of new-onset postoperative atrial fibrillation after cardiac surgery.
3. The effect of new-onset postoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting.
4. The effect of new-onset postoperative atrial fibrillation on early and late mortality after mitral valve surgery.
5. The effect of new-onset postoperative atrial fibrillation on health related quality of life after coronary artery bypass grafting.

OVERVIEW OF THIS THESIS

In **Chapter 2** the independent effect of pre-existing AF on early and late survival after CABG has been described. Data of 8,854 patients, who consecutively underwent first-time, non-emergency, isolated CABG were retrospectively analyzed. Of those 2.5% (n=221) were diagnosed with pre-existing AF. Multivariate logistic regression, and Cox proportional hazard analyses and propensity score matching were used. Furthermore survival was compared with survival in age and sex matched cohorts from the general Dutch population.

Possible risk factors for the development of POAF are presented in **Chapter 3**. Data from 9,348 patient without a history of AF, who consecutively underwent cardiac surgery, where retrospectively analyzed. Multivariate logistic regression analyzes were performed for men and women separately, as the distribution of these predictors, and especially BMI, could be different between the sexes.

A study on the independent effect of POAF on survival after isolated CABG surgery is described in **Chapter 4**. The analysis included 5,098 patients with preoperative SR, without a history of AF. Of those, 22% (n=1122) was diagnosed with POAF. Multivariate logistic regression and Cox proportional hazard analyses and propensity score adjusting were used.

In **Chapter 5** the independent effect of POAF on survival after mitral valve surgery was studied. A total of 856 consecutive patients, who underwent mitral valve surgery, with or without concomitant coronary or tricuspid valve surgery, were analyzed. POAF was documented in 42% (n=361) of the patients. Multivariate logistic regression and Cox proportional hazard analyses as well as propensity score adjusting techniques were used.

Chapter 6 describes our study on the effect of POAF on health related quality of life. Data of 1,580 patients, who consecutively underwent elective first-time CABG, and did survive 6 months afterwards, were analyzed. Of those patients pre- and postoperative completed SF-36 surveys were compared to investigate the effect of POAF on mental and physical health. Multivariate linear regression was used to assess the independent effect of POAF.

In **Chapter 7** the results as described in chapters 2-6 are discussed and put into perspective.

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CHAPTER 2

The impact of preoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting

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Eur J Cardiothorac Surg 2010;38:373-9

ABSTRACT

Objectives:

There are still doubts on the effect of preoperative atrial fibrillation (AF) on early and late mortality after coronary artery bypass grafting (CABG). This retrospective study demonstrates the effects of preoperative AF on the short-term and long-term survival after CABG.

Methods:

We retrospectively analysed the data of 10 626 patients who underwent CABG between January 1998 and December 2007. The data of 221 patients with a history of preoperative AF (2.5%) and 8631 patients with preoperative sinus rhythm were eligible for analysis. Survival of these patient groups was compared to survival of age- and sex-matched groups of the Dutch general population.

Results:

Mean follow-up duration was 4.6 ± 2.9 years. Multivariate logistic regression analysis showed preoperative AF to be an independent risk factor for early mortality after CABG, with an odds ratio of 2.06 (95% confidence interval (CI): 1.08-3.95; $P = 0.029$). Multivariate Cox proportional hazard analysis revealed that preoperative AF is an independent risk factor for late mortality after CABG, with a hazard ratio (HR) of 1.67 (95% CI: 1.21-2.31; $P = 0.002$). Using propensity score matching, AF was also an independent risk factor for late mortality after CABG, with an HR of 2.77 (95% CI: 1.6-4.79; $P < 0.001$). In comparison with the general Dutch population, patients with preoperative AF who undergo CABG have a worse long-term survival, while patients with preoperative sinus rhythm experience a better survival.

Conclusions:

Preoperative AF is an independent risk factor for early and late mortality after first-time elective CABG.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder and has an estimated prevalence of 1% in the general population [1]. The prevalence of AF is increasing with age [1,2,3]. As the elderly population increases, the prevalence of AF and its associated morbidity and mortality are expected to rise.

Many studies have shown that AF is a risk marker for mortality [6,7]. At least part of this risk is explained by the association of AF with other cardiovascular diseases and advancing age [4]. Some studies have identified AF as an independent risk factor for mortality [4,5,6]. The effect of pre-existing AF on early and late mortality after coronary artery bypass grafting (CABG) has not been studied extensively [8,9,10,11,12].

This study aims to investigate the independent effect of pre-existing AF on survival of patients undergoing CABG. The long-term survival of these patients was compared with age and sex-matched cohorts from the general Dutch population.

METHODS

Patients

Data of patients who consecutively underwent first-time, elective, isolated CABG at a single centre in the Netherlands (Catharina Hospital, Eindhoven) between January 1998 and December 2007 were prospectively collected into our database, including demographic data, known risk factors for mortality and in-hospital complications. Patients were divided into two groups: sinus rhythm (SR) group ($n = 8630$) and AF group ($n = 221$). Patients with any history of paroxysmal, persistent or permanent AF were included in the AF group. The local medical ethical committee approved the study.

Definitions

Early mortality was defined as any-cause mortality occurring ≤ 30 days postoperatively, and late mortality was defined as any-cause mortality beyond this period. Impaired left ventricular function (LVF) was defined as left ventricular ejection fraction $< 50\%$. Body mass index (BMI) was calculated by dividing body weight (kg) by the square root of the height (m) of the patient. Creatinine clearance was calculated using the Cockcroft and Gault formula [13].

Operative technique

Anti-arrhythmic medication was continued until the day of operation. All patients received short-acting anaesthetic drugs to facilitate early extubation. Normothermic extracorporeal circulation was performed using non-pulsatile flow. Intermittent, cold

crystalloid cardioplegia ('St. Thomas' solution) or intermittent, warm blood cardioplegia was used to induce and maintain cardioplegic arrest, according to the surgeon's preference.

None of the studied CABG patients was surgically treated for AF. In most cases, the left internal thoracic artery was used for the left anterior descending artery, and a saphenous vein or second arterial graft was used for the other coronary arteries, depending on the age of the patient and preference of the surgeon. Nine percent of all operations were performed without the use of extracorporeal circulation (off-pump). All patients who underwent CABG with the use of extracorporeal circulation received low-dose aprotinin (2 million kallikrein inactivating units) during extracorporeal circulation, administered in the prime solution.

Follow-up

Postoperatively, all patients were treated with metoprolol to suppress AF, and one or more electrical cardioversions were performed when indicated. The rhythm of patients was continuously monitored until at least 48 h postoperatively. Treatment regimen of AF after discharge was determined by the referring cardiologist.

Follow-up data with regard to mortality were gathered from databases of health insurance companies, information requests to general practitioners and city authorities.

To calculate survival of a general population cohort, data were obtained from the Dutch Central Bureau for Statistics. We have matched each group in the present study with the general population according to age and sex. As the incidence of mortality within the general population varies per year, matching was also done to compare the survival of each group with the survival of the general population for the same year the studied patients underwent surgery. We considered the survival of the matched general population cohort to represent the expected survival of the patient groups.

Statistical analyses

SPSS version 15.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

Categorical variables were compared using the chi-square test (or Fisher's exact test when appropriate) and are presented as percentages. Continuous variables were compared using the Student's unpaired t-test and are presented as means $\pm$ standard deviations.

Univariate and multivariate logistic regression analyses were performed to evaluate predictors of early mortality. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify the predictors of late mortality. Only variables that were significant ($P < 0.05$) in the univariate analyses were included in the multivariate models. Age, creatinine clearance and year of operation were incorporated into the models as continuous variables. Due to the nonlinear effect of BMI on mortality, BMI was entered as two dichotomous variables ($BMI < 20$ and $BMI > 35$). Long-term survival

curves were estimated according to the Kaplan-Meier method, comparing differences between groups with the log-rank test.

Propensity score matching

Univariate logistic regression analyses were used to identify variables that were associated with preoperative AF. Only significant ($P < 0.05$) variables were entered into a multivariate logistic regression model. This analysis generated a unique propensity score for each patient, representing the patient-specific probability of having AF, whether the patient had AF or not. This propensity score was used to match a unique control patient who had the nearest propensity score to each treatment patient to exclude the effect of confounders that were associated with AF [11,14,15]. To ensure similarity in the matched pairs we used 'caliper matching' [16].

RESULTS

In 98.9% of selected CABG patients, mortality data were collected until 31 March 2008, leaving 8851 patients for further analysis. Preoperative AF was documented in 221 (2.5%) patients. Mean follow-up period was 4.6 ± 2.9 years (range: 0-10 years).

The characteristics of patients of both groups are summarized in Table 1. Patients in the AF group were significantly older and had a lower mean creatinine clearance level, greater incidence of chronic obstructive pulmonary disease (COPD), prior cerebrovascular accidents (CVAs), reduced LVF and a higher mean BMI than patients in the SR group.

Table 1. Demographics and Clinical Characteristics of the Patient Population

	SR n=8630	AF n=221	P-value
Mean age (years)	64.3 $\pm$ 9.6	69.8 $\pm$ 7.8	< 0.0001
Male	77.0	75.6	0.63
Diabetes	21.4	24.0	0.35
Creatinine Clearance (ml/min)	75.1 $\pm$ 24	69.2 $\pm$ 26	< 0.0001
Hypertension	42.1	47.5	0.11
COPD	12.2	17.2	0.026
Prior CVA/TIA	3.8	8.1	0.001
Peripheral Vascular Disease	11.3	15.4	0.062
Reduced LVF	18.5	33.5	< 0.0001
Mean BMI (kg/m ²)	27.2 $\pm$ 3.8	27.8 $\pm$ 4.8	0.015
Obesity (BMI $\geq$ 35 kg/m ²)	3.2	4.7	0.24
Underweight (BMI < 20 kg/m ²)	1.2	0.9	0.68

AF = preoperative atrial fibrillation; SR = preoperative sinus rhythm; COPD = chronic obstructive pulmonary disease; CVA = cerebro vascular accident; TIA = transient ischemic attack; LVF = left ventricular function; BMI = body mass index.

Fig. 1 shows a 10-year Kaplan—Meier curve after CABG, according to the preoperative heart rhythm. The survival of patients in the AF group was significantly worse than that of patients in the SR group (log-rank, $P < 0.0001$).

Early mortality

The results of the univariate and multivariate analyses of possible predictors of early mortality are shown in Table 2. The multivariate analysis identified AF as an independent risk factor of early mortality, wherein the associated odds ratio was more than twofold. Age, reduced creatinine clearance, COPD and reduced LVF were also independent predictors of early mortality after CABG.

Late mortality

The results of the univariate and multivariate Cox regression analyses of possible predictors of late mortality are shown in Table 3. In the multivariate analysis, preoperative

Figure 1. Kaplan-Meier survival curves after CABG, stratified by preoperative rhythm.

Patients At Risk: SR: 8631, 7559, 6549, 5638, 4718, 3793, 2969, 2205, 1458, 719, 96. AF: 221, 187, 149, 127, 96, 69, 55, 32, 24, 15, -.

Log-rank $P < 0.001$

Table 2. Predictors of Early Mortality (≤ 30 Days) After CABG (Univariate and Multivariate Logistic Regression Analyses)

	Univariate Analyses		Multivariate Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
AF	3.22 (1.72-6.05)	< 0.001	2.06 (1.08-3.95)	0.029
Age*	1.10 (1.08-1.12)	< 0.0001	1.06 (1.03-1.09)	< 0.0001
Male	0.79 (0.55-1.13)	0.195		
Diabetes	1.60 (1.12-2.28)	0.009	1.42 (0.99-2.05)	0.059
Creatinine Clearance*	0.96 (0.95-0.97)	< 0.0001	0.98 (0.97-0.99)	< 0.001
Hypertension	0.92 (0.66-1.28)	0.617		
COPD	2.76 (1.92-3.98)	< 0.0001	2.11 (1.43-3.09)	< 0.001
Prior CVA/TIA	1.98 (1.06-3.69)	0.029	1.30 (0.67-2.53)	0.44
PVD	1.50 (0.96-2.33)	0.071		
Reduced LVF	2.79 (1.99-3.89)	< 0.0001	2.29 (1.61-3.25)	< 0.0001
Obesity (BMI ≥ 35)	1.07 (0.43-2.62)	0.888		
Underweight (BMI<20)	2.94 (1.18-7.33)	0.015	1.61 (0.56-4.65)	0.38
Year of Operation*	0.96 (0.91-0.96)	0.174		

Only significant univariate predictors are included in the multivariate model. OR: odds ratio; CI: confidence interval; AF: preoperative atrial fibrillation; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; TIA: transient ischemic attack; PVD: peripheral vascular disease; LVF: left ventricular function; BMI: body mass index. *Entered as a continuous variable.

Table 3. Predictors of Late Mortality (> 30 Days) After CABG (Univariate and Multivariate Cox Proportional Hazard Analyses)

	Univariate Analyses		Multivariate Analysis	
	HR (95% CI)	p-value	HR (95% CI)	P-value
AF	2.76 (2.03-3.75)	< 0.0001	1.67 (1.21-2.31)	0.002
Age*	1.10 (1.09-1.11)	< 0.0001	1.07 (1.05-1.08)	< 0.0001
Male	0.85 (0.72-0.99)	0.041	1.45 (1.22-1.72)	< 0.001
Diabetes	1.77 (1.51-2.06)	< 0.0001	1.49 (1.27-1.76)	< 0.0001
Creatine Clearance*	0.97 (0.96-0.97)	< 0.0001	0.98 (0.98-0.99)	< 0.0001
Hypertension	1.27 (1.10-1.46)	0.001	1.13 (0.97-1.31)	0.11
COPD	1.84 (1.55-2.20)	< 0.0001	1.53 (1.28-1.84)	< 0.0001
Prior CVA/TIA	2.35 (1.82-3.03)	< 0.0001	1.52 (1.16-1.98)	0.002
PVD	2.23 (1.87-2.66)	< 0.0001	1.56 (1.30-1.88)	< 0.0001
Reduced LVF	1.96 (1.72-2.33)	< 0.0001	1.72 (1.47-2.02)	< 0.0001
Obesity (BMI ≥ 35)	1.05 (0.69-1.60)	0.830		
Underweight (BMI<20)	1.69 (1.03-2.77)	0.039	1.32 (0.78-2.23)	0.30
Year of Operation*	0.99 (0.95-1.02)	0.480		

* entered as a continuous variable; HR = hazard ratio; CI = confidence interval; AF = preoperative atrial fibrillation; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; PVD = peripheral vascular disease; LVF = left ventricular function; BMI = body mass index.

Only significant univariate predictors are included in the multivariate model.

AF was an independent predictor of late mortality and was associated with a 1.67-fold increased hazard ratio (HR). Age, male gender, diabetes mellitus (DM), reduced creatinine clearance, COPD, prior CVA/transient ischaemic attack (TIA), peripheral vascular disease (PVD) and reduced LVF were also identified as independent risk factors for late mortality.

Propensity score matching

The univariate logistic regression of possible predictors of preoperative AF showed a significant association with age, creatinine clearance, COPD, prior CVA/TIA and reduced LVF. These factors were incorporated into the multivariate logistic regression model for preoperative AF. Age (OR: 1.07; 95% CI: 1.05-1.09; $P < 0.0001$), reduced LVF (OR: 2.13; 95% CI: 1.6-2.84; $P < 0.0001$) and prior CVA (OR: 1.8; 95% CI: 1.09-2.97; $P = 0.021$) were independent predictors of preoperative AF.

Next, the propensity scores of 221 AF cases and 8558 SR controls were calculated (Table 4). A total of 221 SR controls were matched to the AF cases. Early mortality was 5% in the AF group versus 3.2% in the matched control group ($P = 0.34$). In Fig. 2, the 10-year survival curves of the AF and SR groups after propensity matching is shown. In addition, after propensity matching, we demonstrated that CABG patients with preoperative AF experienced significantly worse survival than patients with preoperative SR (log-rank, $P = 0.001$). The adjusted HR for all-cause death after CABG was 2.68 (95% CI: 1.58-4.53; $P < 0.001$) for patients in the AF group, compared with the matched SR group.

Table 4. Clinical Characteristics after Propensity Score Matching

	SR n=221	AF n=221	P-value
Mean age (years)*	70.2 ± 7.7	69.8 ± 7.8	0.64
Male	74.2	75.6	0.74
Diabetes	19.0	24.0	0.20
Creatinine Clearance (ml/min)*	66.9 ± 25	69.2 ± 26	0.064
Hypertension	40.7	47.5	0.15
COPD*	17.2	17.2	1.00
Prior CVA/TIA*	10.9	8.1	0.33
Peripheral Vascular Disease	14.5	15.4	0.79
Reduced LVF*	30.8	33.5	0.54
Obesity (BMI ≥ 35)	2.3	4.7	0.18
Underweight (BMI < 20)	2.3	0.9	0.26

AF = atrial fibrillation; SR = sinus rhythm; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; LVF = left ventricular function; BMI = body mass index; *=variable significantly associated with pre-operative AF.

Categorical variables are presented as percentage; continuous variables as mean ± standard deviation.

Figure 2 Kaplan-Meier survival curves after CABG, stratified by preoperative rhythm after propensity score matching.

Patients At Risk: Matched SR: 221, 188, 169, 144, 111, 93, 57, 42, 33, 15, -. AF: 221, 187, 149, 127, 96, 69, 55, 32, 24, 15, -.

Log-Rank test $P = 0.001$

Population comparison

Figs. 3 and 4 show the 10-year survival curves for CABG patients in the AF and SR groups compared with the sex- and age-matched cohorts of the Dutch general population. The survival of patients in the SR group was significantly higher than that of the matched general population (log-rank, $P < 0.0001$), and patients in the AF group had a worse survival compared with the matched Dutch general population (Log-rank, $P = 0.007$).

DISCUSSION

In our study, 2.5% of the coronary bypass patients showed AF prior to the operation. According to the literature, this is a realistic incidence, considering the mean age of the patients in this analysis [1,2,8,10,11].

Figures 3&4. Kaplan Meier survival curves of patients with preoperative SR (fig. 3) or AF (fig. 4) after CABG and the sex- and age-matched general population.

Log-Rank test $P < 0.001$ (fig3) and $P = 0.007$ (fig4)

Early mortality

In this study, it is shown by multivariate logistic regression that AF is an independent risk factor for early death after CABG, a finding that has also been reported by Banach et al. [9]. Early mortality in the propensity score-matched control group is also lower than in the AF group, but this difference lacks statistical power, possibly due to the relatively small group size. Quader et al. [11] found a relationship between preoperative AF and early mortality of CABG patients after comparing them with propensity score-matched patients without AF. However, they could not prove AF to be an independent risk factor. As the adjusted risk analysis of early mortality was performed by matching propensity scores, the sample size of their analysis was limited to two groups of 451 patients, which suggests an explanation for the lack of significance.

Ngaage et al. [10] showed no significant relationship between early mortality after CABG and preoperative AF; in a study in which they matched 257 patients with preoperative AF to 269 patients with preoperative SR, the AF group had an operative mortality of 1.6%, which was lower than the 1.9% mortality in the SR group [10]. Recently, Ad et al. [8] found a positive correlation between preoperative AF and early postoperative mortality in a large study (281 567 patients with isolated CABG) using data from the Society of Thoracic Surgeons' National Cardiac Surgery Database. They reported an early mortality of 2.2% in SR patients versus 5.2% in the AF group ($P < 0.001$). These figures are consistent with our data.

The correlation between preoperative AF and higher early mortality in CABG patients can be explained by the higher incidence of both preoperative co-morbidities and the

postoperative complications in the AF group. In our study, patients in the AF group were significantly older and had a lower mean preoperative creatinine clearance level, greater incidence of COPD, prior CVAs, reduced LVF and a higher mean BMI than patients in the SR group. Moreover, Ad et al. [8] showed that patients with preoperative AF undergoing CABG suffer a higher incidence of postoperative stroke, prolonged ventilation time and renal dysfunction than those with preoperative SR. This might explain the higher early mortality in AF patients than in SR patients.

Late mortality

Several studies have been published regarding long-term survival after valve surgery, in which most authors have reported a negative effect of preoperative AF on postoperative survival [17,18,19]. The effect of preoperative AF on late mortality after CABG has not been studied extensively. Our analysis identified AF as an independent risk factor for late mortality, with an HR of 1.67.

Banach et al. [9] also demonstrated worse survival in patients with preoperative AF after CABG, compared with patients without preoperative AF, but they did not correct for confounders. Ngaage et al. [10] identified preoperative AF as an independent risk factor for late cardiac death (HR: 2.5; $P < 0.0001$). The effect of AF on all-cause mortality was not significant in their multivariate analysis (HR: 1.3; $P = 0.054$).

Quader et al. investigated the effect of preoperative AF on long-term survival after CABG by matching propensity scores and observed a significant reduction in survival due to preoperative AF [11]. Rogers et al. [12] demonstrated a survival deficit up to 5 years after CABG in patients with preoperative AF compared with SR, with an adjusted effect size of 1.49 (95% CI: 1.06-2.08). Only patients who had permanent or multiple recurrent episodes during the last 6 months were included, which could have had an effect on the outcome [12]. In a recent report of Kalavrouziotis et al. [20], increased late mortality and recurrent cardiovascular events after cardiac surgery was associated with preoperative AF. Patients with preoperative AF had a higher incidence of re-hospitalisation after cardiac surgery than patients with preoperative SR. Causes of re-hospitalisation in these patients were AF, stroke, congestive heart failure, acute coronary syndrome and coronary re-vascularisation. However, ~20% of their patients had combined CABG and valve surgery [20].

Comparison with the matched general population

Age at the time of operation is an important predictor of early and late postoperative survival. The effect of age on long-term survival is nonlinear, which is one reason that regression analysis can have a residual confounding effect on survival when the effect of AF is examined. To exclude the effect of age (and sex), we designated two large groups of the Dutch population that had the same age and sex distribution as our patient groups.

Using the mortality data of these population groups, we estimated the predicted survival (based on age and sex) of our patient group. Our analysis showed that patients who underwent CABG with preoperative SR had greater long-term survival than persons from the matched general population cohort.

We hypothesise that this survival benefit is attributed to the protective effect of the grafts, in combination with strict follow-up and treatment with aspirin, cholesterol-lowering drugs, anti-diabetic medication, beta-blockers and angiotensin- converting enzyme (ACE) inhibitors. Despite the possible positive effects of undergoing CABG on long-term survival, patients with preoperative AF experienced worse-than-expected long-term survival compared with the matched general population.

Similarly, Eguchi et al. [18] compared survival in mitral valve-repair patients with expected survival and found a negative effect of preoperative AF on late survival after mitral valve repair. Caution should be taken in making conclusions about the comparison of the CABG groups with the general population. In the general population, a certain percentage of people have AF and coronary artery disease. In patients with SR undergoing CABG, the coronary problem is treated. Most patients after CABG are given aspirin and hypocholesterolaemic drugs and are treated for underlying diseases such as hypertension and diabetes. This treatment, as well as the protection provided by re-vascularisation, may contribute to improved survival and may explain why patients with preoperative SR have improved survival compared with a matched general population cohort. Furthermore, before undergoing CABG, patients are screened for other severe underlying disease. If severe underlying disease is present, alternative treatment is considered instead of CABG, thus enriching the CABG group with patients of above-average health (except for the coronary artery disease). However, the results of our study can help in informing patients with SR that their prognosis after CABG is favorable.

Limitations

The observational nature of this study creates the possibility of confounding effects of measured and unmeasured variables on the role of preoperative AF. Due to the inconsistent definitions of AF types that have been used, we did not differentiate between paroxysmal, persistent and permanent AF. Permanent AF has a worse outcome than paroxysmal and persistent AF [10].

Because we could not match the population groups for AF, it was not possible to determine the effect of CABG separately from the effect of AF on mortality. We did not differentiate between patients with AF preoperatively who converted to SR during the follow-up after CABG and those who remained in AF. As discussed, we could not distinguish between cardiac and non-cardiac causes of death.

CONCLUSIONS

Preoperative AF is an independent risk factor for early and late mortality after elective, first-time, isolated CABG. Compared with age- and sex-matched persons from the general population, CABG patients with preoperative SR experience better long-term survival, and CABG patients with preoperative AF have worse survival rates. Further prospective studies are necessary to confirm these results. Whether concomitant surgical treatment of preoperative AF improves survival has to be investigated in well-designed, randomised controlled trials.

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CHAPTER 3

Body mass index predicts new-onset atrial fibrillation after cardiac surgery

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ABSTRACT

Objective:

New-onset postoperative atrial fibrillation (POAF) after cardiac surgery is associated with increased morbidity and mortality. Since obesity is becoming increasingly prevalent, identifying body mass index (BMI) as a risk factor for POAF could be of importance. The aim of our study is to investigate the effect of BMI on POAF, independent of other risk factors.

Methods:

We analyzed data of 6788 men and 2560 women who underwent coronary artery bypass grafting, valve surgery, or a combination of both, and who had no history of atrial fibrillation. Men and women were analyzed separately because risk factors of POAF were expected to be distributed unequally over both sexes.

Results:

The independent effect of gender was analyzed in a combined model. POAF occurred in 2517/9348 (27%) of patients. Multivariate logistic regression analyses showed that BMI (odds ratio (OR) 1.03; 95% confidence interval (CI): 1.01-1.04; $p < 0.001$ in men and OR 1.03; 95% CI: 1.02-1.05; $p < 0.001$ in women), age (OR 1.06; 95% CI: 1.05-1.07; $p < 0.001$ in men and OR 1.05; 95% CI: 1.04-1.06; $p < 0.001$ in women), valve surgery compared to coronary surgery (e.g., mitral valve surgery compared to coronary artery bypass grafting: OR 3.4; 95% CI: 2.4-4.6; $p < 0.001$ in men and OR 2.9; 95% CI: 2.0-4.3; $p < 0.001$ in women) and male gender (OR 1.23; 95% CI: 1.09-1.38; $p = 0.001$) were the only independent risk factors for POAF, whereas chronic obstructive pulmonary disease, hypertension, off-pump coronary artery bypass grafting, extra corporal circulation time, and transfusion of blood products were not.

Conclusion:

Body mass index, age, undergoing valve surgery and male gender, are independent risk factors for POAF.

INTRODUCTION

New-onset postoperative atrial fibrillation (POAF) is a well-known and frequently occurring complication after cardiac surgery [1,2,3] and is associated with postoperative morbidities such as cerebrovascular accidents (CVAs), infections (e.g., septicemia, pneumonia and mediastinitis), renal failure [1,4,5,6], and mortality [4,5,6,7]. Reduction in the incidence of POAF may reduce the risk for morbidity and mortality associated with atrial fibrillation (AF). Identification of patients at increased risk of POAF is therefore important, as preventive measures in these patients can be taken accordingly.

Previous studies have identified several risk factors for POAF, with age being the most consistent independent risk factor [2,3,6,8,9,10,11,12,13,14,15,16]. Obesity is a known risk factor for AF in the general population [17]. Whether obesity is a risk factor for POAF is less obvious, with only few studies identifying obesity as an independent predictor of POAF [3,10,12] and many other studies that do not find obesity to be a risk factor [2,6,8,9,11,13,14,16]. The effect of body mass on POAF may have been underestimated in these studies, as body mass is not equally distributed over age groups and gender, with the mean age of women undergoing surgery generally being higher than the mean age of men [18]. Since obesity is getting more prevalent in the general population [19] and it is a potentially treatable factor, further investigation of body mass in relation to POAF is warranted.

The aim of our study was to investigate the effect of body mass index (BMI) on POAF after coronary, valve, and combined surgery, independent of other risk factors. BMI was investigated in men and women separately, as the distribution of these predictors may be different within men and women.

METHODS

Patients

Data of patients who consecutively underwent coronary artery bypass grafting (CABG), aortic or mitral valve surgery, or a combination of coronary and valve surgery, between January 2003 and June 2009 in the Catharina Hospital, Eindhoven, the Netherlands, were prospectively collected in our database. Only patients with documented preoperative sinus rhythm (SR) and without a history of AF were included. Patients who deceased during or within 24 h after the procedure were excluded. The Institutional Research Review Board approved this study and waived the need for patient consent.

Demographical and clinical characteristics

Demographic data included age and gender. Clinical characteristics included possible risk factors for POAF, including hypertension, chronic obstructive pulmonary disease (COPD), prior CVA, left ventricular function, peri-operative transfusion of blood products, BMI, body surface area (BSA), and in-hospital complications. BMI was calculated by dividing body weight (in kilograms) by the square root of the length (in meters) of the patient. Five BMI groups were defined [20]: underweight (BMI < 20 kg m⁻²), normal weight (BMI: 20.0-24.9 kg m⁻²), overweight (BMI: 25.0-29.9 kg m⁻²), obesity (BMI, 30.0-34.9 kg m⁻²), and morbid obesity (BMI > 34.9 kg m⁻²). BSA was calculated using the Mosteller formula [21].

Endpoint

POAF was defined as any evidence of new-onset AF (by electrocardiography or continuous monitoring) with duration of at least 30 min during the postoperative stay in our hospital. Hospital stay was defined as days after cardiac surgery until discharge to the referring hospital or home.

Operative technique and postoperative policy

Cardiac medication, including β -blocking agents and acetylsalicylic acid, was continued until the day of the operation. Extracorporeal circulation (ECC) was performed using normothermic non-pulsatile flow. Intermittent cold crystalloid cardioplegia (St. Thomas solution) or intermittent warm blood cardioplegia was used to induce and maintain cardioplegic arrest, according to the surgeon's preference. In most cases of coronary surgery, the left internal thoracic artery was used for the left anterior descending artery, and either the great saphenous vein, or a second arterial graft for the other coronary arteries, depending on the age of the patient, and preference of the surgeon. In mitral valve surgery, two-stage right atrial appendage, or bi-caval cannulation, was performed, according to the preference of the surgeon. In all other patients, the right atrial appendage was cannulated for venous drainage. Postoperatively, metoprolol was prescribed as AF prophylaxis in all patients (unless β -blocking agents are contra-indicated) and electrical cardioversions were done when indicated. The heart rhythm was monitored continuously during at least 48 h postoperatively and afterwards at least 3 times a day or continuously in case of dysrhythmia. If AF persisted for more than 48 h, an anticoagulant was started. The referring cardiologist determined AF treatment regimen after discharge.

Statistical analysis

SPSS version 17.0 (SPSS Inc, Chicago, IL, USA) software was used for all statistical analyses and a p-value < 0.05 was used for all tests to indicate statistical significance.

Categorical variables were compared with the Chi-square test and are presented as percentages. Continuous variables were compared with the Student's t-test and are pre-

sented as mean $\pm$ standard deviation (or with the Mann–Whitney U-test and presented as median with interquartile range (IQR) in case of non-normal distribution). The Bonferroni post hoc test was used to test for differences of continuous variables between groups. Univariate and multivariate logistic regression analyses were performed to evaluate predictors of POAF. Variables with a p-value < 0.05 in one or both sexes in univariate analyses were included in the multivariate models. Predicted mean imputation was used for missing data. BMI (or BSA) was included irrespective of p-values in univariate analysis. BMI (or BSA), and age were entered as continuous variables in the regression models. To investigate the independent effect of gender on POAF, a multivariate model with both sexes was used. Odds ratios (OR) with 95% confidence intervals (CI) and p-values are reported. The area under the receiver operating characteristics (ROC) curve of the multivariate models of predicting POAF was calculated to evaluate the discriminatory capacity of these models, with a value of > 0.7 indicating a fair capacity. Hosmer-Lemeshow statistics were used to describe the calibration of the models, with $p > 0.05$ indicating adequate fit. For each patient, the independent effect of BMI, compared to mean BMI, on POAF was calculated, thus adjusted for all other predictors. Scatter plots were produced of this calculated independent effect of BMI on POAF, against BMI. Regression lines were drawn in these scatter plots.

RESULTS

Data of 9348 patients were analyzed. Twenty-seven percent of the patients were women and the mean age of patients was 65 ± 10 years. Median hospital stay was 5 days (IQR: 3-7). In women, 43% of the procedures involved any kind of valve surgery, in men this percentage was 24% ($p < 0.001$). POAF was more frequent in men than in women (29% vs 26%, $p = 0.002$). Table 1 shows the incidence of POAF in both genders according to the type of procedure performed.

Table 2 displays differences between patients with and without POAF, stratified by gender. Age is significantly higher in men and women with POAF compared to patients without POAF. BMI and BSA were significantly higher in women with POAF, compared to women without POAF, although differences were small. Mean BMI and BSA did not differ between men with and without POAF.

Overweight, obese, and morbidly obese men were younger compared to normal-weight men ($p < 0.001$ for all) (Table 3). The mean age of the overweight, obese, and morbidly obese women did not differ from women with normal weight ($p = 0.72$, $p = 1.0$, $p = 0.97$, respectively). The percentage of POAF is 27% in women with normal BMI, rising to 37% in morbidly obese women ($p = 0.011$ for morbidly obese compared to normal-weight

Table 1. Number of procedures and percentage POAF in men and women for each procedure.

Procedure	Men		Women	
	Number	POAF (%)	Number	POAF (%)
OPCAB	618	19.1	199	17.1
CABG with ECC	4562	23.1	1269	22.0
AVR	587	29.5	424	37.5
MVPR	185	42.2	156	36.5
AVR & MVPR	45	42.2	53	50.9
CABG & AVR	482	36.3	269	39.8
CABG & MVPR	271	47.2	157	42.7
CABG & AVR & MVPR	38	60.5	33	54.5

POAF = new onset post operative atrial fibrillation; OPCAB = off pump coronary artery bypass grafting; CABG = coronary artery bypass grafting; ECC = extra corporal circulation; AVR = aortic valve replacement; MVPR = mitral valve repair or replacement

Table 2. Demographics and clinical characteristics in men and women with and without postoperative atrial fibrillation (POAF).

Variable	Men			Women		
	No POAF n=5019	POAF n=1769*	P-value	No POAF n=1812	POAF n=748*	P-value
Age (years)	62.9 ± 10	67.7 ± 9	< 0.001	66.6 ± 11	70.8 ± 8	< 0.001
BSA (m ²)	2.00 ± 0.18	2.00 ± 0.18	0.93	1.79 ± 0.18	1.82 ± 0.18	< 0.001
BMI (kg/m ²)	27.1 ± 3.7	27.0 ± 3.7	0.44	27.3 ± 4.8	27.9 ± 5.1	0.002
Diabetes Mellitus	19.5	18.8	0.52	25.2	26.6	0.466
Hypertension	44.0	46.2	0.10	55.6	58.3	0.208
COPD	10.8	13.4	0.003	11.9	13.8	0.198
PVD	11.8	14.1	0.013	12.0	10.6	0.309
Prior CVA	5.1	6.8	0.009	5.2	4.9	0.801
Prior MI	38.7	38.2	0.71	29.7	25.1	0.019
LVEF<50%	18.9	21.0	0.050	15.0	14.0	0.527
Creatinine (μmol/ml)	97 (86-110)	99 (86-113)	0.007	85 (73-99)	87 (73-102)	0.013
ECC duration (min)**	76 ± 34	85 ± 40	< 0.001	81 ± 38	94 ± 47	< 0.001
Redo operation	5.2	5.6	0.501	4.2	5.6	0.119
Emergency	5.2	4.9	0.64	6.0	6.4	0.660
IABP	1.9	2.6	0.056	2.4	2.8	0.579
RBC transfusion	20.6	28.8	< 0.001	57.2	61.6	0.037
FFP transfusion	11.7	17.5	< 0.001	10.8	16.8	< 0.001
Platelet transfusion	7.3	11.8	< 0.001	7.5	11.5	0.001
Reop for Bleeding	3.2	5.4	< 0.001	2.8	4.1	0.069
Postop MI	3.2	4.1	0.104	3.0	3.2	0.818

POAF = post operative atrial fibrillation; BSA = body surface area; BMI = body mass index; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; CVA = cerebrovascular accident; MI = myocardial infarction; LVEF = left ventricular ejection fraction; ECC = extra corporal circulation; IABP = intra aortic balloon pump; RBC = red blood cell; FFP = fresh frozen plasma; reop = reoperation; postop = postoperative

*26% POAF in men versus 29% in women (p=0.002)

**Analysis without OPCAB patients

Table 3. Percentage new onset postoperative atrial fibrillation (POAF) and mean age for each body mass index (BMI) group in men and women.

Gender	BMI	<20	20-25	25-30	30-35	>35
Men	%POAF (p-value)	26.5 (0.94)	26.9	25.9 (0.46)	25.2 (0.32)	24.9 (0.55)
	Mean Age (p-value)	60.7 (0.001)	65.5	64.1 (<0.001)	62.6 (<0.001)	60.0 (<0.001)
Women	%POAF (p-value)	24.2 (0.51)	27.4	28.8 (0.51)	30.9 (0.18)	37.1 (0.011)
	Mean Age (p-value)	63.3 (0.001)	67.5	68.8 (0.72)	68.0 (1.0)	66.1 (0.97)

BMI = body mass index; POAF = post operative atrial fibrillation.

p-values calculated from comparison with the normal BMI group (20-25).

women). In male patients, patients with POAF were equally distributed over the weight groups.

Results of multivariate logistic regression analyses are shown in Table 4 . BMI, age, and valve surgery compared to on-pump CABG were independent predictors for POAF in both men and women. BSA was an independent predictor if used in the model instead of BMI. In a separate analysis with only on-pump CABG patients, BMI was also an independent predictor for POAF in both men (OR 1.025; 95% CI: 1.004-1.046; $p = 0.017$) and women (OR 1.044; 95% CI: 1.012-1.077; $p = 0.007$). In the model with both sexes, male gender proved to be an independent risk factor for developing POAF (OR 1.23; 95% CI: 1.09-1.38; $p = 0.01$). Fig. 1 shows the increasing risk of POAF with increasing BMI, independent of other risk factors.

OPCAB was not an independent predictor for POAF compared to on-pump CABG. Hypertension, COPD, peripheral vascular disease, ECC time, transfusion of blood products,

Fig. 1. Independent effect of body mass index (BMI) on risk of new onset postoperative atrial fibrillation (POAF), compared to mean BMI. For both men (squares) and women (rounds) a linear regression line is drawn.

Table 4. Results of multivariate logistic regression analysis of risk factors for post operative atrial fibrillation (POAF) after cardiac surgery in men and women.

Variable	Men N=6788 OR (95% CI)	p-value	Women N=2560 OR (95% CI)	p-value
Age (year) *	1.058 (1.051-1.065)	< 0.001	1.049 (1.038-1.061)	< 0.001
BMI (kg/m ²) *	1.025 (1.009-1.041)	0.002	1.034 (1.015-1.053)	< 0.001
BSA (m ²) **,**	2.82 (2.00-3.98)	< 0.001	4.73 (2.77-8.06)	< 0.001
COPD	1.01 (0.85-1.12)	0.92	1.08 (0.83-1.41)	0.55
PVD	1.08 (0.91-1.28)	0.38	0.97 (0.73-1.29)	0.82
Prior CVA	1.13 (0.89-1.43)	0.31	0.87 (0.58-1.32)	0.51
Prior MI	1.05 (0.93-1.19)	0.42	1.01 (0.81-1.26)	0.94
LVEF †				
35-50%	0.95 (0.81-1.11)	0.51	0.73 (0.54-0.99)	0.043
<35 %	1.11 (0.84-1.46)	0.48	1.38 (0.83-2.29)	0.21
Creatinine (μmol/ml) *	0.999 (0.998-1.001)	0.38	1.001 (0.998-1.003)	0.69
Procedure ††				
OPCAB	0.87 (0.70-1.08)	0.21	0.83 (0.55-1.25)	0.37
AVR	1.48 (1.21-1.81)	< 0.001	2.04 (1.58-2.64)	< 0.001
MVPR	3.36 (2.44-4.63)	< 0.001	2.94 (2.01-4.31)	< 0.001
AVR & MVPR	2.29 (1.21-4.31)	0.011	3.96 (2.18-7.19)	< 0.001
CABG & AVR	1.45 (1.18-1.79)	< 0.001	1.82 (1.35-2.44)	< 0.001
CABG & MVPR	2.67 (2.05-3.47)	< 0.001	2.56 (1.77-3.69)	< 0.001
CABG & AVR& MVPR	3.66 (1.86-7.19)	< 0.001	3.61 (1.74-7.50)	0.001
ECC duration *‡	1.001 (0.999-1.003)	0.41	1.002 (0.999-1.005)	0.15
RBC's (units) ††				
1-3	1.04 (0.89-1.23)	0.60	0.92 (0.75-1.13)	0.41
>3	1.17 (0.77-1.34)	0.91	1.05 (0.74-1.49)	0.80
FFP transfusion	1.03 (0.83-1.27)	0.80	1.11 (0.76-1.61)	0.59
Platelet transfusion	1.19 (0.93-1.52)	0.17	1.11 (0.74-1.66)	0.62
Reop for Bleeding	1.24 (0.90-1.71)	0.20	1.13 (0.66-1.93)	0.66

OR = odds ratio; CI = confidence interval; BMI = body mass index; BSA = body surface area; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; CVA = cerebrovascular accident; MI = myocardial infarction; LVEF = left ventricular ejection fraction; OPCAB = off pump coronary artery bypass grafting; AVR is aortic valve replacement; MVPR is mitral valve plasty or replacement; CABG = on pump coronary artery bypass grafting; ECC is extra corporal circulation; RBC = red blood cell; FFP = fresh frozen plasma; Thrombo = thrombocytes; Reop = reoperation.

* entered as continuous variable

** different model with BSA entered instead of BMI

† compared to normal

†† compared to CABG

‡ entered in a model without OPCAB patients

‡‡ compared to no RBC's

creatinine level, and left ventricle ejection fraction < 35% did not show to be independent predictors either.

The Hosmer and Lemeshow test showed a good fit of the model with p-values of 0.393 and 0.680 for men and women. The area under the ROC curve for the model for men and women was 0.69.

DISCUSSION

The main finding of this study is that BMI is an independent predictor of new-onset AF after CABG, valve surgery, or combined procedure. This finding applies to both male and female patients. Previous reports [17,22,23] have found an association between BMI and LA size. Moreover, Wang et al. [17] found BMI to be an independent predictor for new-onset AF in the general population. However, after including data of LA size in their model, the association of BMI with AF disappeared, suggesting associated LA size accounted for the effect of BMI on AF. Our database did not contain data about LA size, and therefore we could not investigate this association in our patient population. The association of BMI and POAF is described by a few other investigators [3,10,12].

Most studies did not investigate BMI when investigating the preoperative predictors of POAF, and those who did rarely entered BMI in a multivariate model, since univariate analysis did not show a significant effect of BMI on POAF. Like in our male cohort, the effect of higher BMI on POAF could have been camouflaged by the younger mean age and thereby reduced chance of POAF of the patients with higher BMI. Zacharias et al. [3] were the first to describe obesity as an independent risk factor for POAF after cardiac surgery in 2005. They studied 8051 patients undergoing cardiac surgery, and found BMI to be a predictor of POAF, with an OR of 1.04, after adjusting for age and other covariates. These data are in agreement with our data. However, they did not analyze men and women separately. In 2007, Echahidi et al. showed that mild obesity and moderate severe obesity were independent risk factors for POAF in a retrospective study in 4583 patients over 50 years of age, undergoing CABG [10]. However, they did not study BMI as continuous factor and men and women were not analyzed separately. They did not study POAF after both valve and combined surgery. Filardo et al. [12] recently presented a retrospective study in which they found a relation between BMI or BSA and POAF in 5038 men and 1989 women after CABG.

Age is the most consistently found risk factor for new-onset OAF after cardiac surgery [2,3,6,8,9,10,11,12,13,14,15,16]. Our data confirm age as an important risk factor. Fibrosis and dilation of the atria are associated with advanced age and may explain the association between age and POAF [24,25]. These factors may also explain the predictive value

of valve surgery, and especially mitral valve surgery, which was also shown by other investigators [2,3,5,6,9,14].

COPD, hypertension, off-pump CABG, compared to on pump, ECC duration, and transfusion of blood products did not independently predict POAF.

Limitations

As in all observational studies, there is a chance for residual confounding of measured and unmeasured variables. Onset of POAF after discharge was not registered, and therefore the incidence of POAF may have been underestimated. However, most of the first episodes of POAF occur within the first 4-6 days after cardiac surgery with an incidence peak on the second day [5]. Duration of AF and whether the patient had AF at discharge from our hospital were not documented in our database and therefore could not be analyzed. Episodes of (asymptomatic) paroxysmal AF after the 2nd day postoperative could have been missed since continuous monitoring was not standard procedure after 3 days. Identification of risk factors for POAF is important in identifying patients with high risk of developing POAF, since POAF is associated with increased postoperative morbidity and mortality. Prophylactic strategies can be adjusted in these patients and adjustable factors such as obesity can be tackled. Prophylactic surgical interventions or postoperative administration of anticoagulants in high-risk patients might reduce poor outcome, but this remains to be investigated in randomized trials.

Conclusions

Among other previously described factors, we found BMI, age, valve surgery compared to CABG, and male gender to be independent predictors of POAF.

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CHAPTER 4

The impact of new onset postoperative atrial fibrillation on mortality after coronary artery bypass grafting

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Invited commentary
Turki B. Albacker

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Letter to the editor: Impact of postoperative atrial fibrillation after CABG
Adil Polat, Bulent Mert, Ebru B. Polat, Cihan Yucel, Vedar Erentug

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Reply
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ABSTRACT

Background:

New onset postoperative atrial fibrillation (POAF) is a frequent rhythm disturbance after coronary artery bypass grafting (CABG). The aim of this study was to investigate the independent effect of POAF on early and late mortality after isolated CABG.

Methods:

Data of patients who consecutively underwent isolated CABG between January 2003 and December 2007 were prospectively collected in our database. Patients with preoperative sinus rhythm and no history of atrial fibrillation ($n = 5098$) were included in the analysis. Logistic regression analysis for early mortality and Cox regression analysis for late mortality were performed. Propensity score matching was performed to eliminate the effect of confounders.

Results:

Median follow up was 2.5 years (range, 0 to 5.2). In 1122 (22.0%) patients, postoperative atrial fibrillation was documented. Though early mortality was more frequent in POAF patients compared to non POAF patients (3.1% versus 1.6%, $P = 0.002$), multivariate logistic regression analysis could not identify POAF as an independent predictor of early mortality ($P = 0.169$). This outcome did not change after adjusting for quintiles of the propensity score of POAF ($P = 0.100$). Multivariate Cox proportional hazard analyses demonstrated POAF to be an independent predictor of overall and late mortality with hazard ratios of 1.35 ($P = 0.012$ and $P = 0.039$, respectively). Analyses after propensity score matching showed that patients with POAF had similar hazard ratios of 1.36 for overall and 1.34 for late death ($P = 0.009$ and $P = 0.042$, respectively).

Conclusions:

Postoperative atrial fibrillation is an independent predictor of overall and late mortality after isolated CABG but not of early mortality.

INTRODUCTION

New-onset postoperative atrial fibrillation (POAF) is observed in about 20% to 40% of patients undergoing coronary artery bypass grafting (CABG) [1,2,3,4,5,6,7,8,9,10,11,12]. Postoperative AF after cardiac operations is associated with postoperative morbidities such as cerebrovascular accidents (CVA), infections (eg, septicemia, pneumonia and mediastinitis), and renal failure [1,2,3,4,5,6,13,14]. Previous studies have suggested that POAF after CABG is related to early [3,4,6,9] and late mortality [4,9,11,12]. Many of the predictors of POAF, of which age seems to be the strongest [1,2,3,6,7,13,14], also relate to early and late mortality after CABG [4,5,15,16].

This study used multivariate analyses and propensity score matching to investigate if POAF is an independent predictor of early and late mortality after isolated CABG.

METHODS

The Institutional Research Review Board approved this study and waived the need for patient consent.

Patients

The study included patients who underwent isolated CABG in a single center in the Netherlands (Catharina Hospital, Eindhoven) between January 2003 and December 2007. Demographic data, known risk factors for mortality, and in-hospital complications were prospectively collected in a computerized database. Only patients with documented preoperative sinus rhythm, without a history of AF were included. Follow-up mortality data were gathered using databases of health insurance companies and by information requests to general practitioners or municipal authorities.

Definitions

Early mortality was defined as death within 30 days postoperatively or death at anytime if the patient did not leave the hospital or a transfer to a tertiary hospital alive. Late mortality was defined as death from any cause that occurred at any time after hospital discharge. POAF was defined as any evidence of new AF by electrocardiography or continuous monitoring, which lasted at least 30 minutes, during the postoperative period in our hospital.

Operative technique and postoperative policy

Our policy was to continue the use of β -blocking agents preoperatively until the day of the operation. All patients received short-acting anesthetic drugs to facilitate early

extubation. Normothermic extracorporeal circulation was performed using nonpulsatile flow. Intermittent cold crystalloid cardioplegia (St. Thomas solution) or intermittent warm blood cardioplegia was used to induce and maintain cardioplegic arrest, according to the surgeon's preference. Eleven percent of all operations were performed without the use of extracorporeal circulation.

Postoperatively, all patients without a contraindication for β -blocking agents received metoprolol as AF prophylaxis, and one or more electrical cardioversions were done when indicated. Rhythm was continuously registered for at least 48 hours postoperatively. Afterwards, registration was performed at least 3 times a day or continuously in case of dysrhythmia. If AF persisted for more than 48 hours, an anticoagulant was started. The referring cardiologist determined AF treatment regimen after discharge, according to the guidelines of the American College of Cardiology/American Heart Association/ European Society of Cardiology [17].

Statistical analysis

All statistical analyses were done with SPSS 15.0 software (SPSS Inc, Chicago, IL). Categorical variables were compared using the χ^2 test or the Fisher's exact test, if appropriate, and are presented as percentages. Continuous variables were compared using the t test and are presented as means $\pm$ standard deviations or median with range or interquartile range (IQR).

Univariate and multivariate logistic regression analyses were performed to evaluate predictors of early mortality. In addition, a separate analysis with a model stratified by quintiles of the propensity score of POAF was performed [18,19]. This propensity score was calculated with a multivariate logistic regression model in which univariate predictors of POAF with a value of $p < 0.10$ were included. The area under the receiver operating characteristics curve of the multivariate model of predicting early mortality was calculated to evaluate the discriminatory capacity of this model.

Univariate and multivariate Cox proportional hazard analyses were performed to investigate predictors of late mortality. A model stratified by quintiles of the propensity score of POAF was used for a separate analysis of late mortality. Variables with a value of $p < 0.10$ in univariate analyses were included in the multivariate models.

Long-term survival curves were produced according to the Kaplan-Meier method, and differences between groups were compared with the log-rank test. Two Cox proportional hazard models were used to construct adjusted Kaplan-Meier survival curves for patients with and without POAF. In the first model, all independent predictors of overall mortality were included, and adjusted survival was calculated for the POAF and non-POAF groups. In the second model, survival was adjusted for quintiles of the propensity score of POAF. For both models hazard ratios (HR) for overall death after CABG were calculated. HRs and odds ratios (OR) with 95% confidence intervals (CI) and p values are reported. A value of $p < 0.05$ was used for all tests to indicate statistical significance.

RESULTS

Between January 2003 and December 2007, 5352 patients underwent isolated CABG. Mortality data of 5320 patients (99.4%) were collected until March 31, 2008. After excluding patients with a history of AF or without sinus rhythm preoperatively, data of 5098 patients were used for the analysis. Postoperative AF was documented in 1122 patients (22.0%). Median length of hospital stay was 5 days (IQR, 3 to 6 days) in non-POAF patients and 6 days (IQR, 4 to 7 days) in POAF patients. Median follow-up was 2.5 years (range, 0 to 5.2 years). Characteristics of POAF and non-POAF patients are summarized in Table 1. Patients with POAF were older, more likely to have a preoperative CVA and hypertension, and to have

Table 1. Demographic and Clinical Characteristics.

	No POAF n=3976	POAF n=1122	P-value
Age years, mean	64.0 ± 9.7	68.5 ± 8.1	< 0.0001
Male (%)	77.5	78.8	0.347
BMI (kg/m ²), mean	27.3 ± 3.8	27.4 ± 3.9	0.393
Obesity (BMI≥35), (%)	3.3	4.0	0.264
Underweight (BMI<20), (%)	1.1	1.2	0.884
Diabetes (%)	23.0	20.7	0.105
Hypertension (%)	47.4	51.5	0.014
COPD (%)	9.7	11.6	0.058
Peripheral Vascular Disease (%)	11.8	13.7	0.090
Prior CVA (%)	4.6	6.2	0.028
Normal LVF (%)	83.0	82.4	0.643
NYHA class, mean	2.1 ± 1	2.2 ± 1	0.049
CCS class, mean	2.6 ± 1	2.6 ± 1	0.825
Preoperative Hb (g/dL), mean	13.9 ± 1.4	13.8 ± 1.4	0.445
Preoperative CRP > 6.0 (%)	35.4	35.3	0.953
Cr CL (mL/min), mean	77.7 ± 26	72.7 ± 25	< 0.0001
Redo (%)	4.6	3.7	0.182
Emergency (%)	3.4	3.4	0.956
IABP (%)	1.7	2.1	0.311
CABG with ECC (%)	88.3	90.8	0.019
Number of Grafts, mean	3.5 ± 1.1	3.6 ± 1.0	< 0.001
Perioperative RBC Transfusion (%)	23.5	27.5	0.007
Reoperation for Bleeding (%)	2.1	3.2	0.028
Perioperative Infarction (%)	2.8	4.0	0.041
Postoperative CVA (%)	0.8	1.5	0.019
Mediastinitis (%)	0.4	1.2	0.002
Pneumonia (%)	1.4	3.7	< 0.0001
Early Death (%)	1.6	3.1	0.002

BMI=body mass index; CCS=Canadian Cardiovascular Society; COPD=chronic obstructive pulmonary disease; CRP=C-reactive protein; Cr CL= creatinine clearances; CVA= cerebrovascular accident; ECC= extracorporeal circulation; Hb=haemoglobin; IABP=intraaortic balloon pump; LVF=left ventricular function; NYHA=New York Heart Association; POAF= postoperative atrial fibrillation; RBC= red blood cell. Categorical variables are presented as percentage; continuous variables as mean ± standard deviation.

lower mean creatinine clearance. Patients with POAF more often underwent CABG with the use of extracorporeal circulation, had a reoperation for bleeding, and received more perioperative blood transfusion. Patients with POAF presented more often with perioperative infarction, mediastinitis, postoperative in-hospital pneumonia, and CVA. A significant difference in New York Heart Association (NYHA) class and number of grafts was also present.

Early mortality

The univariate and multivariate predictors of early mortality are reported in Table 2. The incidence of early mortality was 2.0% in the total patient population, 3.1% in the POAF

Table 2. Uni- and multivariate logistic regression analyses of early mortality.

	Univariate Analyses		Multivariate Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Male	0.60 (0.39-0.92)	0.019	1.25 (0.76-2.07)	0.381
Age (year) *	1.11 (1.08-1.14)	< 0.0001	1.09 (1.05-1.13)	< 0.0001
BMI <20 kg/m ²	2.82 (0.87-9.18)	0.085	2.50 (0.66-9.41)	0.176
BMI >35 kg/m ²	0.88 (0.27-2.79)	0.821	1.01 (0.28-3.63)	0.992
Diabetes	1.64 (1.07-2.51)	0.021	1.66 (1.03-2.66)	0.037
Hypertension	0.95 (0.64-1.41)	0.797		
COPD	3.07 (1.94-4.88)	< 0.0001	2.63 (1.59-4.35)	< 0.001
PVD	1.27 (0.73-2.21)	0.399		
Cr Cl= 60-90 ml/min	2.12 (1.01-4.42)	0.047	0.92 (0.41-2.10)	0.847
Cr Cl <60 ml/min	6.26 (3.09-12.7)	< 0.0001	1.05 (0.43-2.57)	0.922
LVEF= 35-50%	1.72 (1.04-2.85)	0.034	1.85 (1.08-3.16)	0.024
LVEF <35%	3.90 (1.91-7.96)	< 0.0001	2.74 (1.24-6.03)	0.012
Preop CVA	1.92 (0.96-3.85)	0.062	1.20 (0.56-2.59)	0.644
Preoperative Infarction	1.05 (0.70-1.56)	0.829		
Preoperative Hb *	0.71 (0.63-0.80)	< 0.0001	0.95 (0.82-1.10)	0.446
NYHA class *	1.10 (0.90-1.36)	0.349		
CCS class *	0.91 (0.75-1.10)	0.321		
Use of ECC	1.27 (0.64-2.53)	0.499		
Redo Procedure	3.73 (2.09-6.67)	< 0.0001	1.30 (0.62-2.70)	0.488
Emergency	5.84 (3.34-10.2)	< 0.0001	1.60 (0.75-3.40)	0.223
IABP	17.3 (10.1-29.9)	< 0.0001	6.59 (3.22-13.5)	< 0.0001
Number of Grafts *	0.83 (0.69-0.99)	0.042	0.86 (0.70-1.06)	0.169
ECC time (min)*	1.02 (1.01-1.02)	< 0.0001	1.01 (1.00-1.02)	0.009**
Re-op for Bleeding	3.28 (1.49-7.24)	0.002	1.35 (0.56-3.25)	0.567
RBC Transfusion	6.91 (4.51-10.6)	< 0.0001	3.29 (2.00-5.41)	< 0.0001
Perioperative Infarction	5.04 (2.75-9.23)	< 0.0001	2.83 (1.41-5.68)	0.003
POAF	1.94 (1.28-2.94)	0.002	1.38 (0.87-2.18)	0.169

BMI = body mass index; CCS=Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; Cr Cl= creatinine clearance; CVA = cerebrovascular accident; ECC = extra-corporeal circulation; Hb = haemoglobin; LVEF = left ventricular ejection fraction; NYHA=New York Heart Association; OR= odds ratio; PVD = peripheral vascular disease; POAF = postoperative atrial fibrillation; RBC= red blood cell

* Entered as continuous variable

** Analyzed in a model without off pump coronary artery bypass grafting

group, and 1.6% in the non-POAF group ($p = 0.002$). Multivariate analysis did not identify POAF as an independent risk factor for early mortality ($p = 0.169$). Older age, diabetes, chronic obstructive pulmonary disease, and impaired left ventricular function were independent preoperative risk factors for early mortality. Use of intraaortic balloon pump, perioperative myocardial infarction, perioperative use of blood products, and duration of extracorporeal circulation were independent operative and postoperative predictors of early mortality. The calculated area under the receiver operating characteristic curve of this multivariate model for predicting early mortality was 0.862. After adjusting for quintiles of the propensity score, POAF was not identified as a risk factor for early mortality in logistic regression analysis (OR, 1.43; 95% CI, 0.93 to 2.19; $p = 0.100$).

Late mortality

The univariate and multivariate predictors of late mortality are reported in Table 3. In multivariate analysis, POAF was an independent predictor of late mortality and associated with a 1.35-fold increased risk (95% CI, 1.02 to 1.80; $p = 0.039$). Male gender, older age, underweight, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, impaired left ventricular function, previous CVA, lower preoperative hemoglobin level, redo procedures, and perioperative myocardial infarction were also independent predictors of late mortality. After adjusting for quintiles of propensity scores, POAF remained an independent predictor of late death with a HR 1.34 (95% CI, 1.01 to 1.77; $p = 0.042$).

Overall mortality

Patients with POAF were at a cumulative increased risk of overall mortality at 5 years after CABG compared with CABG patients without POAF (15% vs 10%, $p < 0.0001$; Fig 1). Figure 2 shows the overall survival after CABG, stratified by POAF, adjusted for age, gender, weight group, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, preoperative CVA, left ventricular function, preoperative hemoglobin, reoperation, use of intraaortic balloon pump, use of blood transfusions, and perioperative myocardial infarction. Postoperative AF remained an independent risk factor in this multivariate analysis, with a HR of 1.35 (95% CI, 1.07 to 1.71; $p = 0.012$). The HR of POAF for overall mortality, adjusted for quintiles of the propensity score of POAF, was 1.36 (95% CI, 1.08 to 1.72; $p = 0.009$; Fig 3).

Table 3. Uni- and multivariate Cox proportional hazard analyses of late mortality.

	Univariate Analyses		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Male	1.09 (0.79-1.49)	0.611	1.78 (1.27-2.51)	0.001
Age (year) *	1.08 (1.06-1.10)	< 0.0001	1.05 (1.03-1.07)	< 0.0001
BMI <20 kg/m ²	2.67 (1.19-6.02)	0.018	2.66 (1.15-6.14)	0.022
BMI >35 kg/m ²	0.97 (0.46-2.05)	0.931	1.20 (0.55-2.63)	0.645
Diabetes	1.76 (1.34-2.32)	0.0001	1.59 (1.20-2.12)	0.001
Hypertension	1.19 (0.92-1.54)	0.180		
COPD	2.21 (1.58-3.09)	< 0.0001	1.83 (1.31-2.56)	< 0.001
PVD	2.20 (1.59-3.05)	< 0.0001	1.70 (1.22-2.39)	0.002
Cr Cl= 60-90 ml/min	1.85 (1.16-2.96)	0.010	1.12 (0.68-1.85)	0.648
Cr Cl <60 ml/min	4.35 (2.76-6.86)	< 0.0001	1.59 (0.91-2.75)	0.101
LVEF 35-50%	1.77 (1.28-2.46)	0.001	1.62 (1.16-2.29)	0.005
LVEF <35%	3.87 (2.43-6.15)	< 0.0001	2.93 (1.82-4.74)	< 0.0001
Preoperative CVA	2.93 (2.01-4.28)	< 0.0001	1.86 (1.25-2.76)	0.002
Preoperative Infarction	1.38 (1.07-1.79)	0.015	1.14 (0.87-1.50)	0.334
Preoperative Hb *	0.76 (0.70-0.83)	< 0.0001	0.88 (0.80-0.97)	0.007
NYHA class *	1.07 (0.92-1.24)	0.380		
CCS class *	1.04 (0.92-1.18)	0.521		
Use of ECC	1.12 (0.73-1.72)	0.610		
Redo Procedure	2.08 (1.31-3.29)	0.002	1.78 (1.11-2.85)	0.016
Emergency	1.21 (0.60-2.45)	0.599		
IABP	1.56 (0.65-3.79)	0.323		
Number of Grafts *	1.07 (0.95-1.21)	0.270		
ECC time*	1.00 (1.00-1.01)	0.162		
Re-op for Bleeding	1.86 (0.99-3.51)	0.055	1.55 (0.79-3.01)	0.201
RBC Transfusion	2.00 (1.53-2.60)	< 0.0001	1.29 (0.95-1.74)	0.102
Perioperative Infarction	2.42 (1.41-4.15)	0.001	2.22 (1.28-3.86)	0.005
POAF	1.75 (1.33-2.31)	0.0001	1.35 (1.02-1.80)	0.039

BMI = body mass index; CCS=Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; Cr Cl= creatinine clearance; CVA = cerebrovascular accident; ECC = extra-corporeal circulation; HR= hazards ratio; Hb = haemoglobin; LVEF = left ventricular ejection fraction; NYHA=New York Heart Association; PVD = peripheral vascular disease; POAF = postoperative atrial fibrillation; RBC= red blood cell

* Entered as continuous variable

Fig 1. Cumulative survival is shown in 5098 patients after coronary artery bypass grafting (CABG), stratified by those with new-onset postoperative atrial fibrillation (POAF) and without POAF. Patients At Risk: No POAF: 3976, 3205, 2393, 1668, 905, 122. POAF: 1122, 857, 634, 426, 234, 27. Log-Rank test $P < 0.001$

Fig 2. Risk adjusted cumulative survival is shown in 5098 patients after CABG, stratified by those with POAF and without POAF. HR = 1.35; $P = 0.012$

Fig 3. Cumulative survival, adjusted for quintiles of propensity score of POAF is shown in 5098 patients after CABG, stratified by those *with* POAF and *without* POAF.

HR 1.36; $P = 0.009$

COMMENT

This study shows that the incidence of newly developed POAF after CABG in our population is 22%. This incidence is consistent with other studies [1,2,3,4,5,6,7,8,9,10,11,12]. POAF was an independent predictor for late but not for early mortality.

Early mortality

Although the incidence of early mortality was almost twofold in the POAF group, POAF was not identified as an independent risk factor for early mortality in multivariate and propensity score adjusted analyses. The probability of developing POAF is strongly dependent of age [1,2,3,6,7,13,14]. This obviously explains why the mean age of the POAF patients is 4.5 years higher than the age in the non-POAF group. Age is also strongly associated with early mortality [5,15,16]. Correction for age (and other risk factors for early mortality) shows that POAF is not an independent risk factor of early death. Kalavrouziotis and coworkers [5] concluded the same in a large study on POAF in cardiac surgery patients after multivariate analysis and propensity score matching. In the study of Villareal and colleagues [4], POAF was a significant predictor of early death after adjusting for risk factors, but as suggested by Levy and colleagues [20], adjusting for age as a dichotomous variable might have been inadequate because age is such a

powerful predictor of early death and POAF. A large number of studies [3,5,9,12,14] show significantly higher incidences of early death in patients with POAF after CABG or cardiac operations, but none of these studies identified POAF as an independent predictor of early mortality.

Overall and late mortality

A few other studies have evaluated the effect of POAF on long-term survival after CABG [4,9,11,12]. Villareal and colleagues [4] reported an increased risk of overall and late death in patients with POAF (adjusted HR of 1.5 and 1.4, respectively) in a study of 6475 patients after first time isolated CABG. However, age was entered as a dichotomous variable in their multivariate model, which could have resulted in underestimation of the effect of age on mortality, thereby leaving a possible residual confounding effect. In the same study, a case matched analysis resulted in a HR of 3.4 for POAF regarding long-term mortality. However, only 20% of all cases of POAF were used in that particular analysis. The investigated patient group was not representative for the whole POAF group and therefore interpretation of the mentioned HR should be done cautiously.

Mariscalco and colleagues [9] calculated an adjusted HR of 2.13 for POAF on all-cause mortality after isolated CABG in a study in 1832 patients. Although data were prospectively collected, 8% of the patients were lost to follow-up, which may have influenced the study outcome. In their study, only patients with a history of permanent AF were excluded, which implies that potentially, patients with preoperative paroxysmal and persistent AF were included. By including such patients, it might be possible that part of the effect of POAF on survival could be attributed to preoperative AF. Recently, Mariscalco and Engström [11] described 7621 patients who underwent a CABG procedure in whom multivariate analysis found a HR of 1.22 for POAF. In contrast to our study, patients operated on without the use of extracorporeal circulation were not included. They did not include gender in the multivariate model; gender was an independent risk factor in different studies [21,22] as well as in our study. Not including gender in the analysis could have biased the results.

A recent report by Ahlsson and colleagues [12] indicated POAF was an age-independent risk factor for late mortality after CABG (HR, 1.56) in a study with 1419 patients. Only POAF, age, diabetes, and lower left ventricular ejection fraction were significant predictors of late death in multivariate analysis in their study.

Limitations

We were not able to retrieve the causes of death in our study, which is an important limitation. The study of Mariscalco and colleagues [9] showed that embolic events might play an important role in postoperative death in patients with POAF. This is consistent

with our findings of a significantly higher incidence of postoperative in-hospital CVA in patients with POAF.

We did not separately study the effect of therapeutic interventions for POAF on mortality. The effect of those interventions for POAF on survival might be small, because almost every patient receives β -blocking agents postoperatively, and most of the patients with POAF return to sinus rhythm [13,23] and can be weaned from antiarrhythmic drugs.

The in-hospital follow-up period was relatively short, with a median of 5 days (IQR, 3 to 6 days). Onset of POAF after discharge was not registered, and therefore, the incidence of POAF may have been underestimated. However, most of the first episodes of POAF happen within the first 4 to 6 days after cardiac operations, with an incidence peak on the second day [1,13,14,24]. Duration of POAF was not documented in our database, and therefore, its effect on mortality could not be analyzed.

As in all observational studies, there is a risk for residual confounding of measured and unmeasured variables. By adjusting for quintiles of the propensity score of POAF, we attempted to minimize the effect of residual confounders. Multivariate analysis and propensity score adjusted methods both produced very similar results for both early and late survival. Furthermore, the area under the receiver operating characteristic curve of the multivariate logistic regression model for predicting early mortality indicates an excellent discriminatory capacity of this model.

Although postoperative use of β -blocking agents, sotalol and amiodarone decrease the incidence of POAF [25,26], it remains to be investigated whether the use of these agents improves overall survival after CABG. More aggressive surgical and preventive measurements in high-risk patients might possibly favor long-term survival after CABG, but well-performed prospective studies to support this theory are currently not available.

Conclusion

In conclusion, postoperative atrial fibrillation is an independent predictor of overall and late mortality after CABG but was not identified as an independent predictor of early mortality.

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INVENTED COMMENTARY

Atrial fibrillation is a common postoperative complication after cardiac surgery with an incidence of 40% or less. Multiple prophylactic strategies have been tried to prevent or decrease its incidence without significant change. Given this failure of primary prevention, the question that needs to be answered is what therapeutic strategies should we use for postoperative atrial fibrillation and how aggressively should we treat it? The answer to this question will largely depend on how postoperative atrial fibrillation will impact the outcomes of the cardiac surgical patients. Most cardiologists will extrapolate the results of the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) trial [1] to cardiac surgical patients and argue that there is no difference between rate and rhythm control for managing atrial fibrillation patients. This extrapolation is not necessarily valid, because cardiac surgery patients are different from the AFFIRM patients. Only 25% of the AFFIRM study population had coronary artery disease, less than 5% had valvular heart disease and greater than 75% had normal ventricular function. In addition, 75% of the AFFIRM patients were still anti-coagulated during the full length of study follow-up duration, regardless of the treatment strategy used. Such anticoagulation policy can not be loosely used in cardiac surgery patients, given their high risk for bleeding and late tamponade. The study by Bramer and colleagues [2] echoed the findings of other investigators [3,4] and showed that postoperative atrial fibrillation had a significant negative impact on long-term survival of patients undergoing coronary artery bypass grafting. All these reports are nonrandomized and do not provide information on the causes of long-term mortalities of those patients and whether it was directly related to atrial fibrillation (ie, congestive heart failure, stroke, or bleeding from anti-coagulation) or whether it was a representation of other comorbidities of those patients. Although the authors in this study used the Cox regression analysis to control for the effect of these comorbidities, the degree of their severity in different patients cannot be accounted for. However, these reports are still important and their results should not be underestimated. The question remains as to what survival advantage can be gained by trying to aggressively discharge these patients from the hospital in sinus rhythm. The only way to answer this question is by conducting a randomized, controlled trial comparing rate control versus rhythm control in treating postoperative atrial fibrillation in cardiac surgery patients.

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LETTER TO THE EDITOR

To the Editor:

We have read the interesting article by Bramer and colleagues [1] in the latest issue of the journal. Postoperative atrial fibrillation is an important cause of morbidity in the postoperative period of coronary artery bypass grafting (CABG) patients. They have addressed the question well and made a satisfactory analysis. However, there are few points that should be clarified.

In the comparison of both groups (Table 1), it can be seen that the following measurements, among many others, are found to be statistically different: perioperative myocardial infarction, creatinine clearance, on-pump CABG, number of grafts, reoperation for bleeding, and prevalences of postoperative mediastinitis and pneumonia.

We have previously reported that the use of postoperative beta-blockers decreased the new onset atrial fibrillation significantly in patients both with normal and depressed left ventricular function [2]. In case of beta-blockers, the prevalence of atrial fibrillation was approximately 5%. Although the incidence in this cohort is reported to be compatible with other studies, it is still a high percentage. How would the authors comment on this incidence considering the differences between the two groups?

The creatinine clearance is lower in the postoperative atrial fibrillation group (Table 1) and the use of cardiopulmonary bypass is higher in this group. The authors did not give the prevalence of preoperative renal failure. Is there a difference? The analysis of early mortality shows that the duration of cardiopulmonary bypass is associated with early mortality. We have previously reported the advantages of off-pump coronary artery bypass surgery in these patients [3]. Could this be a contributing factor to the increased mortality rates in the long-term? Also, the significant differences in the incidences of pneumonia and mediastinitis have not been addressed in the univariate or multivariate analyses. An institutional report has found no adverse effect on the graft patency in patients with mediastinitis [4]. The authors found no significant affect of graft number on the mortality, although there is a significant difference between the two groups. How would the authors like to comment on this subject?

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REPLY

To the Editor:

We appreciate the comments from Polat and coworkers [1] about our previously published work [2].

The low percentage (5%) of new-onset postoperative atrial fibrillation (POAF) reported by Guler and colleagues [3] in their study does not match the percentage of 20% to 40% in the studies we referred to in our publication [2]. Furthermore, in a large meta-analysis by Crystal and associates [4], the use of β -blocking medication or sotalol reduced new-onset atrial fibrillation after cardiac procedures to 18% and 21%, respectively, in an analysis of 36 randomized controlled trials investigating mostly patients who underwent elective coronary artery bypass grafting (CABG). As mentioned, all patients without a contraindication for β -blocking medication received metoprolol postoperatively. We therefore think that the incidence of POAF in our population is still within the average incidence in the recent reports.

Concerning preoperative renal failure, we found the prevalence, defined as creatinine clearance less than 60 mL/min, to be higher in patients with POAF compared with other patients (32% versus 26%; $p < 0.001$). Neither off-pump operations nor extracorporeal circulation time was predictive of late mortality in our population. We did not perform a subgroup analysis for patients with renal failure.

As Polat and associates [1] correctly mentioned, pneumonia and mediastinitis were not entered in our analyses of predictors for mortality. The scope of our study was to determine the effect of the preoperative, perioperative, and direct postoperative factors, including new-onset atrial fibrillation, on mortality. As was shown earlier by our group, POAF is related to mediastinitis, which is subsequently related to postoperative mortality [5]. We agree that it is interesting to investigate the role of POAF in the mortality of patients with mediastinitis, but again this was not within the scope of our study.

The mean number of grafts was significantly different between the 2 groups and was a significant predictor of early mortality only in the univariate analysis. However in the multivariate analysis, with exclusion of other confounders, the number of grafts per patient was not a significant predictor of early mortality.

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CHAPTER 5

New-onset postoperative atrial fibrillation predicts late mortality after mitral valve surgery

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ABSTRACT

Background:

New-onset postoperative atrial fibrillation (POAF) is a common rhythm disturbance after mitral valve surgery. In this study we investigated the independent effect of POAF on early and late mortality after mitral valve surgery.

Methods:

Data of patients who consecutively underwent mitral valve surgery with or without concomitant coronary or tricuspid valve surgery between January 2003 and June 2010 were prospectively collected. The study included 856 patients with preoperative sinus rhythm, and no history of atrial fibrillation. Logistic regression and Cox proportional hazard analyses were performed to investigate independent predictors of early and late mortality. Propensity score adjustment was performed to reduce the effect of confounders.

Results:

The median follow-up was 3.1 years (range, 0 to 7.4 years). The POAF was documented in 361 patients (42%). Early mortality did not differ in patients with and without POAF ($p = 0.93$). Postoperative atrial fibrillation was not identified as predictor for early mortality. Late survival was worse in patients with POAF (log-rank, $p < 0.001$). Multivariate and propensity score adjusted Cox proportional hazard analyses demonstrated that POAF was an independent predictor for late mortality with hazard ratios of 2.09 and 1.61 ($p = 0.001$ and $p = 0.033$, respectively).

Conclusions:

Postoperative atrial fibrillation is an independent predictor for late all-cause mortality after mitral valve surgery but not for early all-cause mortality.

INTRODUCTION

New-onset postoperative atrial fibrillation (POAF) is common after mitral valve and combined mitral valve and coronary surgery. The incidence of POAF is reported to be up to 50% in isolated mitral valve surgery, and up to more than 60% in combined procedures [1,2,3]. The POAF after coronary artery bypass grafting (CABG) is associated with higher early and late mortality [4,5,6,7]. However, little is known about the effect of POAF on early and late mortality after mitral valve surgery. The incidence of morbidity, such as stroke and congestive heart failure, is higher in patients with POAF than in patients without POAF after mitral valve surgery [8], which might lead to higher mortality in patients with POAF. However, to the best of our knowledge, there are no reports about the relation between POAF after mitral valve surgery and early and late mortality. The aim of this study was to investigate the independent effect of POAF after mitral valve surgery on early and late survival by multivariate analyses and propensity score adjusting methods.

METHODS

Patients

The Institutional Research Review Board approved this study and waived the need for patient consent. This study included patients who consecutively underwent mitral valve repair or replacement with or without concomitant CABG, and with or without concomitant tricuspid valve surgery, in a single center in the Netherlands (Catharina Hospital, Eindhoven) between January 2003 and June 2010. Patients who died within 24 hours after the procedure were excluded, as were patients with active endocarditis. Patients undergoing other cardiac surgical procedures such as aortic valve replacement were also excluded from the study. Only patients with documented preoperative sinus rhythm and without a history of atrial fibrillation (AF) were included. Demographic data, known risk factors for mortality, and in-hospital complications were prospectively collected in a computerized database.

Endpoint

Follow-up mortality data were gathered using databases of health insurance companies and by information requests to general practitioners or municipal authorities. Early mortality was defined as death within 30 days postoperatively. Late mortality was defined as death from any cause beyond 30 days.

Operative Technique and Postoperative Policy

Cardiac medication, including β -blocking agents and acetylsalicylic acid were continued until the day of the operation. Extracorporeal circulation was performed using normo-

thermic nonpulsatile flow. Intermittent cold crystalloid cardioplegia (St Thomas solution), or intermittent warm blood cardioplegia, was used to induce and maintain cardioplegic arrest, according to the surgeon's preference. Two-stage right atrial, or bicaval cannulation, was performed for venous drainage, depending on the need for tricuspid valve surgery, and on the preference of the surgeon. The mitral valve was approached through a left atriotomy or superior-transseptal [9], depending on the need for tricuspid valve surgery and the preference of the surgeon. We did not perform surgery in patients with asymptomatic mitral valve disease. Postoperatively, metoprolol was prescribed as an AF prophylaxis in all patients (unless β -blocking agents were contraindicated). In case of POAF, extra metoprolol was prescribed if not contraindicated. Intravenous amiodarone and electrical cardioversions were used when indicated. The first day postoperative, oral anticoagulation with coumarin derivatives was started and continued for at least 3 months, in case of repair and replacement with biological valve prosthesis, and life-long after replacement with a mechanical valve prosthesis. The heart rhythm was monitored continuously during at least 48 hours postoperatively and afterward at least 3 times a day, or continuously in case of dysrhythmia. After discharge to the referring hospital or homeward, diagnosis and treatment of AF were performed by the referring cardiologist. The POAF was defined as any evidence of new AF (by electrocardiography or continuous monitoring) that lasted at least 30 minutes during the postoperative stay in our hospital.

Statistical Analyses

Categorical variables were compared using the χ^2 test and are presented as percentages. Continuous variables were analyzed using the t test for independent samples or Mann-Whitney U test in case of data without normal distribution, and are presented as mean $\pm$ standard deviation, or median with range or interquartile range.

Univariate and multivariate logistic regression analyses were performed to evaluate predictors of early mortality. The area under the receiver operating characteristics curve was calculated to evaluate the discriminatory capacity of this model. Univariate and multivariate Cox proportional hazard analyses were performed to investigate predictors of late mortality. Variables with a p value less than 0.05 in the univariate analyses were included in the multivariate models.

To minimize the effect of possible confounders in the analyses of early and late mortality, separate analyses with models stratified by quintiles of the propensity score of POAF were performed [10,11]. This propensity score was calculated with a multivariate logistic regression model in which possible predictors of POAF were included, with a higher propensity score indicating a higher risk of POAF. Cases with non-overlapping propensity score were excluded.

Long-term survival curves were produced according to the Kaplan-Meier method and differences between groups were compared with the log-rank test. Two Cox proportional

hazard models were used to construct adjusted late survival curves for patients with and without POAF. In the first model all independent predictors of late mortality were included, and survival, adjusted for those predictors, was calculated for both groups. In the second model, survival was adjusted for quintiles of the propensity score of POAF in both groups. All statistical analysis was done with SPSS 17.0 software (SPSS Inc, Chicago, IL). Odds ratios and hazard ratios with 95% confidence intervals (CI) and p values were reported. A value of p less than 0.05 was used for all tests to indicate statistical significance.

RESULTS

Between January 2003 and June 2010, 1,302 patients underwent mitral valve surgery with or without concomitant coronary or tricuspid valve surgery. Until July 1, 2010, mortality data of 1,296 (99.5%) patients were known. After excluding all patients with a history of AF or without sinus rhythm preoperatively (n = 390; 30%), patients with active endocarditis, and patients who died within 24 hours after the procedure, 856 patients were left for the analysis.

Postoperative AF was documented in 361 patients (42%). Characteristics of POAF and non-POAF patients are summarized in Table 1. Patients with POAF were older ($p < 0.001$), more likely to be undergoing a CABG procedure ($p = 0.026$), more often experienced a cerebrovascular accident (CVA) prior to the procedure ($p = 0.029$), and had a worse preoperative creatinine clearance ($p = 0.001$). Age, concomitant coronary surgery, prior CVA, creatinine clearance, gender, body mass index, diabetes, and extracorporeal circulation duration were used as factors in the calculation of the propensity score of POAF. Ten patients had a non-overlapping propensity score and were excluded from the propensity-adjusted analysis. After stratifying for quintiles of POAF, the analyzed factors were equally distributed in POAF and no-POAF patients within the 5 groups, except for gender in 1 of the groups (46% vs 64%, $p = 0.015$) and creatinine clearance in another group (90 mL/minute vs 98 mL/minute, $p = 0.032$). Postoperative patients with POAF were more likely to experience an in-hospital CVA ($p = 0.003$). The incidence of POAF did not differ in patients after repair and replacement (2.8% vs 2.2%, $p = 0.60$). Of the implanted prostheses, 300 of 318 (94%) were mechanical.

Median length of stay in our hospital was 6 days (interquartile range, 4 to 9 days) in non-POAF patients and 9 days (interquartile range, 6 to 15 days) in POAF patients ($p < 0.001$). Median follow-up was 3.1 years (range, 0 to 7.4 years). The total of follow-up years was 2,614. Cumulative survival was worse in patients with POAF (Fig 1; log-rank, $p < 0.001$), with estimated survival in 82% in non-POAF patients and 67% in POAF patients at 6 years of follow-up.

Table 1. Demographic and Clinical Characteristics

Variable ^a	No POAF n=495	POAF n=361	P-value
<i>Pre-operative characteristics</i>			
Male	58.6	62.6	0.24
Age, y	62.6 ± 11	67.0 ± 9.5	<0.001
BMI, kg/m ²	26.1	26.5	0.15
Obesity (BMI ≥ 35)	3.5	4.6	0.45
Underweight (BMI < 20)	6.5	2.3	0.005
Diabetes	17.4	22.2	0.080
Hypertension	40.2	39.6	0.86
COPD	12.9	13.0	0.97
Peripheral vascular disease	10.1	10.2	0.94
Prior CVA	3.8	7.2	0.029
Prior MI	34.9	38.0	0.37
Reduced LVF (EF < 50)	33.1	28.3	0.13
NYHA class	2.6 ± 1	2.5 ± 1	0.058
Preoperative hemoglobin, g/dL	13.4 ± 1.5	13.5 ± 1.4	0.17
Creatinine clearance, mL/min	73.1 ± 26	66.9 ± 27	0.001
Redo operation	12.1	13.9	0.46
Emergency procedure	7.9	6.4	0.40
IABP	8.1	7.8	0.86
CABG	52.7	60.4	0.026
TVS	11.9	13.9	0.40
Superior-transseptal incision	27.1	30.7	0.24
Ischemic mitral disease	33.5	37.7	0.21
MV replacement	34.9	40.2	0.12
ECC time, min	118 ± 48	124 ± 46	0.070
<i>Peri-operative characteristics</i>			
Peri-op RBC transfusion	58.0	63.4	0.11
Re-op for bleeding	5.7	6.6	0.55
Peri-op MI	6.9	7.5	0.72
<i>Post-operative characteristics</i>			
Post-op CVA	1.2	4.4	0.003
Mediastinitis	1.6	1.4	0.79
Early death	7.1	6.9	0.93
Euroscore	6.0 ± 3.0	6.6 ± 2.8	0.006

^aCategorical variables are presented as percentage; continuous variables as mean ± standard deviation

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; ECC = extracorporeal circulation; EF = ejection fraction; IABP = intra-aortic balloon pump; LVF = left ventricular function; MI = myocardial infarction; MV = mitral valve; NYHA = New York Heart Association; POAF = postoperative atrial fibrillation; RBC = red blood cell; TVS = tricuspid valve surgery

Fig 1. Cumulative survival after mitral valve surgery (n = 856).

Patients At Risk: No POAF: 495, 402, 332, 262, 187, 114, 50, 13. POAF: 361, 271, 223, 165, 116, 65, 27, 6.

Log-Rank test $P < 0.001$

Early Mortality

The results of the univariate and multivariate analyses of predictors of early mortality are shown in Table 2. Incidence of early mortality was 7.1% in the non-POAF group versus 6.9% in the POAF group ($p = 0.93$), which was in the range predicted by additive European system for cardiac operative risk evaluation ($6.0\% \pm 3.0\%$ and $6.6\% \pm 2.8\%$, respectively). Multivariate analysis also did not identify POAF as an independent risk factor for early mortality ($p = 0.35$).

Older age, emergency procedure, use of intraaortic balloon pump, perioperative myocardial infarction, replacement of the mitral valve, and duration of extracorporeal circulation were independent risk factors for early mortality. The calculated area under the receiver operating characteristics curve of the multivariate model for predicting early mortality was 0.88, which indicates a good discriminatory power of this multivariate model. After adjustment for quintiles of the propensity score, POAF was not identified as a risk factor for early mortality in logistic regression analysis (odds ratio, 0.70; 95% confidence interval [CI], 0.40 to 1.23; $p = 0.22$).

Late Mortality

The results of univariate and multivariate analyses of late mortality are shown in Table 3. Multivariate analysis showed that POAF was an independent predictor of late mortality and associated with a more than twofold increased hazard (hazard ratio, 2.09; 95% CI,

Table 2. Univariate and Multivariate Logistic Regression Analyses of predictors of Early Mortality.

Variable	Univariate Analyses		Multivariate Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Male	0.99 (0.58-1.69)	0.96	1.21 (0.62-2.37)	0.58
Age,y ^a	1.08 (1.05-1.12)	<0.001	1.10 (1.05-1.15)	<0.001
Body mass index		0.12		
<20 kg/m ²	0.36 (0.05-2.64)	0.31		
>35 kg/m ²	2.41 (0.90-6.50)	0.81		
Diabetes	2.05 (1.15-3.63)	0.014	1.43 (0.74-2.75)	0.29
Hypertension	1.16 (0.68-1.97)	0.58		
COPD	1.38 (0.68-2.80)	0.38		
PVD	1.18 (0.52-2.69)	0.69		
Pre-op CVA	0.95 (0.28-3.14)	0.93		
Pre-op MI	1.48 (0.87-2.52)	0.14		
LVEF		0.013		0.14
0.35-0.50	2.14 (1.18-3.89)	0.012	1.74 (0.88-3.45)	0.11
<0.35	2.34 (1.11-4.97)	0.026	2.13 (0.86-5.30)	0.11
NYHA class ^a	2.23 (1.37-3.63)	0.001	1.64 (0.89-3.03)	0.11
Pre-op Hemoglobin ^a	0.72 (0.61-0.85)	<0.001	0.91 (0.73-1.12)	0.37
Creatinine Clearance		0.001		0.78
60-90 ml/min	1.50 (0.58-3.84)	0.40	0.80 (0.27-2.40)	0.69
<60 ml/min	3.64 (1.50-8.82)	0.004	1.02 (0.32-3.23)	0.97
Redo procedure	2.99 (1.64-5.46)	<0.001	1.86 (0.86-4.00)	0.11
Emergency	4.74 (2.44-9.23)	<0.001	2.52 (1.08-5.88)	0.032
IABP	7.79 (4.23-14.4)	<0.001	3.37 (1.57-7.24)	0.002
CABG	0.96 (0.57-1.63)	0.88		
TVS	1.41 (0.69-2.87)	0.35		
Ischemic	1.24 (0.72-2.13)	0.43		
MV replacement	3.44 (1.99-5.97)	<0.001	2.53 (1.29-4.93)	0.007
ECC time, min ^a	1.01 (1.01-1.02)	<0.001	1.01 (1.00-1.01)	0.029
RBC transfusion	6.51 (2.77-15.3)	<0.001	2.43 (0.92-6.42)	0.075
Re-op for bleeding	1.45 (0.55-5.40)	0.45		
Peri-op MI	2.52 (1.18-5.40)	0.017	4.14 (1.69-10.1)	0.002
POAF	0.98 (0.57-1.67)	0.93	0.75 (0.40-1.38)	0.35

^a Entered as continuous variable.

CABG = coronary artery bypass grafting; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; ECC = extracorporeal circulation; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MV = mitral valve; NYHA = New York Heart Association; OR = odds ratio; POAF = postoperative atrial fibrillation; PVD = peripheral vascular disease; RBC = red blood cell; TVS = tricuspid valve surgery.

Table 3. Univariate and Multivariate Cox Proportional Hazard Analyses of predictors of Late Mortality

Variable	Univariate Analyses		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Male	1.21 (0.80-1.84)	0.37	1.67 (1.06-2.64)	0.027
Age,y ^a	1.07 (1.04-1.10)	<0.001	1.04 (1.01-1.08)	0.010
Body mass index		0.19		
<20 kg/m ²	0.17 (0.02-1.22)	0.078		
>35 kg/m ²	1.21 (0.44-3.28)	0.72		
Diabetes	3.52 (2.33-5.32)	<0.001	2.33 (1.48-3.67)	<0.001
Hypertension	1.74 (1.17-2.61)	0.007	1.44 (0.94-2.22)	0.096
COPD	1.20 (0.69-2.08)	0.52		
PVD	2.37 (1.38-4.08)	0.002	0.93 (0.51-1.67)	0.80
Pre-op CVA	3.60 (1.96-6.62)	<0.001	2.12 (1.07-4.20)	0.031
Pre-op MI	2.00 (1.34-2.99)	0.001	1.16 (0.73-1.84)	0.53
LVEF		<0.001		0.003
0.35-0.50	2.44 (1.55-3.84)	<0.001	2.04 (1.24-3.34)	0.005
<0.35	3.07 (1.76-5.35)	<0.001	2.42 (1.31-4.46)	0.005
NYHA class ^a	1.10 (0.78-1.56)	0.60		
Pre-op Hemoglobin ^a	0.72 (0.63-0.81)	<0.001	0.83 (0.71-0.96)	0.015
Creatinine Clearance		<0.001		0.11
60-90 ml/min	1.88 (0.82-4.32)	0.014	1.26 (0.52-3.03)	0.61
<60 ml/min	5.53 (2.53-12.1)	<0.001	2.07 (0.82-5.21)	0.12
Redo procedure	1.44 (0.84-2.46)	0.19		
Emergency	1.46 (0.73-2.92)	0.28		
IABP	2.52 (1.35-4.73)	0.004	2.24 (1.12-4.47)	0.022
CABG	2.41 (1.53-3.79)	<0.001	0.85 (0.48-1.49)	0.57
TVS	1.31 (0.74-2.31)	0.36		
Ischemic MR	1.77 (1.18-2.65)	0.006	0.85 (0.52-1.38)	0.50
MV replacement	1.12 (0.74-1.69)	0.60		
ECC time, min ^a	1.01 (1.01-1.01)	<0.001	1.00 (1.00-1.01)	0.22
RBC transfusion	3.76 (2.20-6.44)	<0.001	1.59 (0.86-2.97)	0.14
Re-op for bleeding	1.47 (0.71-3.03)	0.30		
Peri-op MI	2.27 (1.21-4.26)	0.011	2.85 (1.43-5.67)	0.003
POAF	2.56 (1.69-3.89)	<0.001	2.09 (1.34-3.26)	0.001

^aEntered as continuous variable.

CABG = coronary artery bypass grafting; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; ECC = extracorporeal circulation; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MV = mitral valve; NYHA = New York Heart Association; OR = odds ratio; POAF = postoperative atrial fibrillation; PVD = peripheral vascular disease; RBC = red blood cell; TVS = tricuspid valve surgery.

1.34 to 3.26; $p = 0.001$; Fig 2). Male gender, older age, diabetes, previous CVA, impaired left ventricular function, lower preoperative hemoglobin level, use of intraaortic balloon pump, and perioperative myocardial infarction were also independent predictors for late mortality. After adjusting for quintiles of propensity scores, POAF also was an independent predictor of late mortality (hazard ratio, 1.61; 95% CI, 1.04 to 2.49; $p = 0.033$, Fig 3).

Fig 2. Risk-adjusted cumulative late survival after mitral valve surgery ($n = 790$).
HR 2.09; $P = 0.001$

Fig 3. Adjusted cumulative late survival after mitral valve surgery ($n = 780$) using propensity score.
HR 1.61; $P = 0.033$

COMMENT

Our results indicate that newly developed AF after mitral valve surgery predicts late mortality, independent of the well-known mortality risk factors such as age, gender, and left ventricular function. On the other hand, POAF had no impact on early mortality in the present study. The effect of POAF after valve surgery on late mortality is studied by few investigators [1,6,12], with conflicting results. Almassi and colleagues [1] studied POAF-related 6-month survival after cardiac surgery. In a population of 3,855 mostly male patients, only 2% underwent mitral or combined coronary and mitral valve surgery. Valve patients were not analyzed separately and therefore no conclusions can be drawn about late survival after valve surgery. Mahoney and colleagues [13] studied the cost-effectiveness of intravenous amiodarone to prevent POAF in 1,841 patients undergoing valve or combined coronary and valve surgery. They found no effect of POAF on late (5-year) survival. They did not provide figures about this analysis and did not differentiate between aortic and mitral valve surgery. Mariscalco and colleagues [6] showed an increased hazard for late mortality in CABG patients ($n = 7,621$) with new onset postoperative AF, whereas patients after valvular or combined coronary and valvular surgery ($n = 1,874$) with new onset postoperative AF did not have an increased risk. Again, aortic and mitral valve surgeries were not studied separately. Filardo and colleagues [12] were able to show an independent effect of POAF on late mortality after aortic valve surgery. To our knowledge the effect of POAF on late survival after mitral valve or combined mitral valve surgery exclusively was never described before.

Several mechanisms may link POAF after valve surgery to late mortality. Similar to findings of other studies in CABG patients [4,7], we found significant more in-hospital CVAs in POAF patients. These embolic events may play an important role in postoperative late mortality in POAF patients. In addition, patients experiencing POAF may be more susceptible to develop AF in the period after discharge as well. This post-discharge AF could lead to an increased risk for congestive heart failure, cerebrovascular accidents, and associated mortality. When this post-discharge AF remains undetected, the risk of mortality could even be higher in these patients.

We were not able to retrieve the cause of death in our study, which is an important limitation. Onset of POAF after discharge was not registered in our database and therefore incidence of POAF could be underestimated. However, most of the episodes of POAF occur within 4 to 6 days, with a peak incidence on the second day [2]. Duration of POAF and rhythm at discharge was not documented and therefore its effect on mortality could not be analyzed.

As in all observational studies, there is a risk for residual confounding of measured and unmeasured variables. By adjusting for quintiles of the propensity score of AF we attempted to reduce the effect of residual confounders. Multivariate and propensity score

adjusted analyses produced comparable results in the analyses of the effect of POAF on early and late survival. Furthermore, the area under the receiver operator characteristics curve of the multivariate logistic regression model for predicting early mortality indicates a good discriminatory capacity of this model.

It is not possible to determine whether POAF is a risk marker or risk factor for late mortality. Factors not analyzed in this study, like pulmonary hypertension, left atrial diameter, and preoperative and postoperative extent of mitral and tricuspid regurgitation might have played a role as well. However, AF seems to be associated with death in the general population [14], indicating that at least part of the relation of POAF and late mortality after mitral valve surgery could be causal.

We had no postoperative data regarding use of oral anticoagulation. Patients undergoing mitral valve replacement, mostly mechanical, were expected to receive oral anticoagulants postoperatively, whereas most patients undergoing repair only received for 3 months postoperatively. Undetected recurrence of AF in the repair group without anticoagulants could be associated with a higher incidence of CVAs and thereby be an explanation for the lack of late survival benefit in the repair group compared with patients after replacement.

With an increasingly older and progressively more obese population, POAF will be expected to occur more frequently after cardiac surgery, and thus mitral valve surgery [3]. Reducing the incidence of POAF might improve late survival after mitral valve surgery. More intensive medical therapy [15] and prophylactic surgical AF ablation [16] may reduce the incidence of POAF, and thereby possibly the associated late mortality, but this has to be investigated in prospective randomized controlled trials. Prophylactic treatment with oral anticoagulation in patients at high risk for developing POAF, or post-discharge AF, may also be beneficial for late survival. Prospective randomized trials are warranted to validate this hypothesis.

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CHAPTER 6

Does new-onset postoperative atrial fibrillation after coronary artery bypass grafting affect postoperative quality of life?

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ABSTRACT

Objectives:

New-onset postoperative atrial fibrillation (POAF) is a common complication after cardiac surgery. We investigated the effect of POAF on quality of life after coronary artery bypass grafting.

Methods:

All patients who underwent nonemergency coronary artery bypass grafting between March 2009 and January 2011 were requested to complete a Short Form-36 Health Survey before and 6 months after the procedure. Norm-based scores of 8 health status domains and 2 component summary scores were calculated. Only patients undergoing first-time coronary artery bypass grafting, with no history of atrial fibrillation, were included in the analyses.

Results:

Of 1608 patients, 360 (22.4%) had POAF diagnosed. Twenty-eight patients died within half a year after the procedure (1.7% in the no POAF group and 1.8% in the POAF group; $P = 0.90$). After excluding these patients, data from 1580 patients were analyzed. Preoperative questionnaires were returned by 66% of the patients and postoperative questionnaires by 65%. Preoperative scores did not differ between patients with and without POAF in any subcategory (0/10). After the procedure, 4 of 10 scores were worse in the group with POAF compared to patients without POAF. Patients without POAF improved in all subcategories (10/10) after the procedure, whereas those with POAF did so in only 7 of 10. Multilinear regression showed POAF to be an independent negative predictor for improved quality of life 6 months postoperatively in 7 of 10 subcategories, including both mental and physical component summary scores.

Conclusions:

New-onset POAF does affect 6-month postoperative mental and physical health, possibly warranting more aggressive POAF treatment.

INTRODUCTION

It is well known that new-onset postoperative atrial fibrillation (POAF) after coronary artery bypass grafting (CABG) is related to morbidity and mortality [1,2,3,4,5]. Although the negative effects of atrial fibrillation on quality of life (QoL) have been demonstrated in the general population [6] no data are available concerning new-onset atrial fibrillation after cardiac surgery. There have been several reports on QoL after cardiac surgery. Among those, few reported both preoperative and postoperative data, and none reported the effects of POAF on QoL [7]. The aim of this study was therefore to investigate the independent effect of POAF on health-related QoL after CABG by comparing scores from preoperative and postoperative responses to the Short Form-36 Health Survey version 2.0 (Dutch, SF-36v2) in patients with and without POAF.

METHODS

Patients

The institutional research review board approved this study and waived the need for patient consent. This study included patients who consecutively underwent nonemergency nonreoperative CABG in a single center in the Netherlands (Catharina Hospital, Eindhoven) between March 2009 and January 2011. Only patients with documented preoperative sinus rhythm and without a history of atrial fibrillation were included. Demographic data and risk factors for postoperative morbidity and mortality, including POAF, were prospectively collected in a computerized database. POAF was defined as postoperative occurrence of atrial fibrillation for at least 30 minutes. Mortality data were gathered from databases of health insurance companies and by information requests to general practitioners or municipal authorities.

SF-36v2 Questionnaire

In January 2009, we started a quality control program in our department. As a part of this program, all patients undergoing nonemergency cardiac surgery are requested to complete the SF-36v2 before the operation and again at 6 and 12 months after the operation. This survey is a widely used, reliable, and validated standardized questionnaire to measure both physical and mental status of a patient [8,9]. The SF-36v2 assesses 8 health status domains: Physical Functioning (ability to perform all types of physical activities without limitations from health), Role Physical (problems with daily activities or work as a result of physical health), Bodily Pain (pain or limitations imposed by pain), General Health (perception of general health), Vitality, Social Functioning, Role Emotional (problems with work or daily activities as a result of emotional problems), and Mental Health

(feelings of nervousness or depression). From these 8 subscales, the Physical and Mental Component Summary scores can be generated, reflecting the patient's overall physical and mental health status [8]. Missing data were estimated and substituted according to the half-scale rule [8]. Subcategory and component scores were transformed to a scale from 0 to 100, with higher scores indicating a better health status. These transformed scores were then standardized to the general Dutch population (mean = 50, 1 standard deviation = 10) [8,10].

Operative Technique and Postoperative Policy

It was our policy to continue the use of β -blocking agents preoperatively until the day of the operation. All patients received short-acting anesthetic drugs to facilitate early extubation. Normothermic extracorporeal circulation was performed with nonpulsatile flow. Intermittent cold crystalloid cardioplegia (St. Thomas solution) or intermittent warm blood cardioplegia was used to induce and maintain cardioplegic arrest, according to the surgeon's preference. Sixteen percent of all operations were performed without the use of extracorporeal circulation. After the operation, all patients without contraindication for β -blocking agents received metoprolol as prophylaxis against atrial fibrillation. Rhythm was continuously registered for at least 48 postoperative hours. Afterward, until discharge to the referring hospital or home, registration was performed at least 3 times a day, or continuously in case of dysrhythmia. POAF was treated by rate control with metoprolol in hemodynamically stable patients, and electrocardioversion or cardioversion with amiodarone was attempted otherwise. If atrial fibrillation persisted for longer than 48 hours, an anticoagulant was started. The referring cardiologist determined the atrial fibrillation treatment regimen after discharge, according to the guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology [11].

Statistical Analyses

Patient demographics and characteristics were compared with independent t tests for continuous variables, and categoric variables were compared with the χ^2 test. The dependent t test was used to compare differences in preoperative and postoperative SF-36v2 scores within the POAF and non-POAF groups. SF-36v2 scores of patients with and without POAF were compared with the independent t test. A multiple linear regression model was used to investigate the independent effect of POAF on each subscale of the SF-36v2 survey 6 months postoperatively, adjusted for the preoperative scores. In a previous article, we reported several independent risk factors for POAF, such as body mass index, age, and male sex [12]. To account for possible confounders, these were included in the current regression model. All statistical analyses were done with the SPSS statistical software package (version 19.0; IBM Corporation, Armonk, NY).

RESULTS

After excluding emergency and reoperative procedures and patients with a history of atrial fibrillation (n = 60; 3.6%) or pacemaker (n = 9; 0.5%), 1608 patients were eligible for analysis. Of those 1608 patients, 360 (22.4%) had POAF diagnosed. Twenty-eight patients died within half a year after the procedure (1.7 % in the non-POAF group vs 1.8 % in the POAF group; P = .90). Patients with POAF were older than those without (69.3 vs 63.8 years; Table 1).

Compared with patients who did not complete a preoperative SF-36v2 form, patients who did were more frequently men (79.0% vs 74.5%; P = 0.040). Death rate within half a year did not differ between responders and nonresponders (1.9% vs 1.5%; P = 0.55). No differences in frequency of POAF (22.7% vs 21.8%; P = 0.70) and other demographic and other characteristics were observed between responders and nonresponders.

Preoperative scores of patients alive at 6 months after CABG were significantly better in 6 subcategories, compared with patients who did not survive the first half year. After excluding the patients who died within half a year after surgery, data of 1580 patients were used for further analyses.

Preoperative SF-36v2 forms were returned by 1043 patients (66%). From 977 forms (94%), all subcategories could be analyzed. Postoperative SF-36v2 forms were returned

Table 1. Demographic and Clinical Characteristics

Variable ^a	No POAF (n=1248)	POAF (n=360)	p Value
Age, y	63.8 ± 9.9	69.3 ± 8.4	< 0.001
Male	78.2	75.0	0.20
BMI, kgm ⁻²	27.4 ± 4.0	27.6 ± 4.0	0.41
Diabetes	21.2	21.4	0.95
Hypertension	56.2	56.4	0.94
COPD	9.8	11.1	0.46
PVD	15.1	16.9	0.39
Prior CVA	4.2	3.9	0.77
Normal LV function	84.1	80.0	0.064
CABG with ECC	83.0	86.1	0.16
Grafts, No.	3.46 ± 1.0	3.54 ± 1.0	0.18
ECC, min ^b	69.0 ± 23	69.4 ± 22	0.77
AoX, min ^b	48.2 ± 23	47.1 ± 16	0.42

^aCategoric variables are presented as percentage; continuous variables as mean ± standard deviation.

^bAnalysed in patients with on pump surgery (n=1351).

Distribution of risk factors of post operative atrial fibrillation (POAF) and other possible risk factors for post-operative morbidity and mortality in non-POAF and POAF patients. AoX = Aortic cross clamp time; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ECC = extracorporeal circulation; LV = left ventricular; POAF = post-operative atrial fibrillation; PVD = peripheral vascular disease

Table 2. Pre- and Post-operative Norm Based SF-36 Scores in POAF and non-POAF Patients.

	Non-POAF (n=554)			POAF (n=156)		
	Pre	6 month	p-value	Pre	6 month	p-value
Physical Component Summary	41.7	49.0	< 0.001	42.2	47.6	< 0.001
Mental Component Summary	45.1	46.7	< 0.001	45.9	45.8	0.60
Physical Functioning	38.8	47.4	< 0.001	38.4	44.1	< 0.001
Role Physical	41.8	46.3	< 0.001	42.9	44.9	0.004
Bodily Pain	44.0	51.1	< 0.001	44.0	50.7	< 0.001
General Health	44.5	47.6	< 0.001	45.3	46.9	0.010
Vitality	43.7	48.3	< 0.001	44.0	47.5	< 0.001
Social Functioning	43.2	48.6	< 0.001	45.3	47.8	0.009
Role Emotional	45.2	47.5	< 0.001	45.6	45.8	0.80
Mental Health	42.2	44.9	< 0.001	42.3	43.6	0.11

Pre- and 6 months post-coronary artery bypass grafting norm-based scores compared in non-POAF and POAF patients who completed pre- and post-operative SF-36 survey (n=710).

by 1019 patients (65%), and from 978 forms (96%), all subcategories could be analyzed. Both preoperative and 6-month postoperative forms were returned by 710 patients (45%). The response percentages at both preoperative and 6-month postoperative intervals were equal for patients with and without POAF ($P = 0.77$ and $P = 0.59$, respectively). In patients without POAF, scores of all SF-36v2 subscales improved after 6 months, whereas in patients with POAF, Role Emotional, Mental Health, and Mental Component Summary scores did not improve (Table 2). For all components (10/10) of the preoperative SF-36v2 survey, scores did not differ between patients with and without POAF (Figure 1). For 4 of 10 of the components of the 6-month postoperative SF-36v2 survey, scores were worse in

Figure 1. Preoperative Short Form-36 Health Survey version 2 (Dutch) norm based scores for patients without (n = 807) and with (n = 236) postoperative atrial fibrillation, showing no significant difference. BP, Bodily Pain; GH, General Health; MCS, Mental Component Summary; MH, Mental Health; PCS, Physical Component Summary; PF, Physical Functioning; RE, Role Emotional; RP, Role physical; SF, Social Functioning; VT, Vitality.

patients with POAF than in those without POAF (Physical Component Summary, $P = 0.032$; Physical Functioning, $P = 0.003$; Role Physical, $P = 0.033$; and Role Emotional, $P = 0.012$; Figure 2). When only data of patients who completed both preoperative and postoperative surveys ($n = 710$) were analyzed, Physical Component Summary ($P = 0.037$), Physical Functioning ($P = 0.003$), and Role Emotional ($P = 0.021$) scored significantly worse. Multivariate linear regression showed POAF to be an independent negative predictor for improvement in 7 of 10 subcategories 6 months after the operation (Table 3).

Figure 2. Six-month postoperative norm-based Short Form-36 Health Survey version 2 (Dutch) scores for patients without ($n = 795$) and with postoperative atrial fibrillation ($n = 224$), showing significant worse scores on Physical Component Summary, Physical Functioning, Role Physical, and Role Emotional components in patients with postoperative atrial fibrillation compared with those without.

BP, Bodily Pain; GH, General Health; MCS, Mental Component Summary; MH, Mental Health; PCS, Physical Component Summary; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; VT, Vitality.

Table 3. Multiple linear regression analyses for prediction of improvement of SF-36 scores 6 months post-operative by POAF.

	B	se B	β	p-value
Physical Component Summary	-2.3	0.96	-0.097	0.017
Mental Component Summary	-2.2	0.90	-0.099	0.014
Physical Functioning	-3.1	1.06	-0.115	0.004
Role Physical	-3.0	0.84	-0.140	< 0.001
Bodily Pain	-1.1	1.13	-0.039	0.321
General Health	-2.1	0.93	-0.089	0.023
Vitality	-1.7	1.06	-0.062	0.12
Social Functioning	-3.8	1.18	-0.125	0.001
Role Emotional	-2.7	0.92	-0.117	0.003
Mental Health	-1.6	0.87	-0.072	0.070

Results of multiple linear regression analyses for prediction of improvement of norm-based scores of components of the 6 months post-operative SF-36 survey compared to the pre-operative survey by POAF. POAF and known risk factors for POAF (BMI, age, gender) are included in the model. se=standard error.

DISCUSSION

In addition to prolonging survival, improvement of QoL is one of the major goals in cardiac surgery. Our results indicate that new-onset atrial fibrillation after CABG has a negative impact on QoL.

Preoperative overall physical health (Physical Component Summary score) did not differ between patients who developed POAF and those who did not. Physical Component Summary score improved in both groups, but the improvement was more pronounced in patients without POAF: after 6 months, physical health was significantly better in patients without POAF than in those with POAF. Patients with POAF had lower scores on the Physical Functioning and Role Physical subscales, which could account for this difference.

Preoperative overall mental health (Mental Component Summary score) did not differ between POAF and non-POAF patient groups. Only patients without POAF, however, showed improved overall mental health after 6 months. Lack of improvement in the Role Emotional and Mental Health subscales seems to account for the failure to improve overall mental health among patients with POAF 6 months after CABG.

Patients who developed POAF were older, which independently predicts a worse postoperative QoL [13,14]. By adjusting for age, and other predictors of POAF, however, we showed POAF to be an independent negative predictor of postoperative improvement in 7 of 10 subcategories, including both the Mental and Physical Component Summary scores. POAF thus was related to poor QoL independent of body mass index, age, and sex. This study was not designed to determine why patients with POAF had a lower QoL. Palpitations, side effects of medical treatment, and complications of atrial fibrillation such as stroke or anticoagulant-related bleeding all could account for the impaired health of patients with POAF relative to those without POAF. Fear of complications may also play a role.

The extent of POAF most likely determines the extent of impairment in health outcome, although no previous study has investigated this issue. Unfortunately, in our database no data were available on the extent of POAF, and that is one of the limitations of this study. The impossibility of excluding patients with clinically irrelevant POAF (eg, only 1 episode of 30 minutes) warrants further research into the effect of duration of POAF on QoL. Furthermore, onset of POAF after discharge was not registered, and therefore its effect could not be analyzed.

Only 66% of the patients returned the preoperative SF-36v2 questionnaire. Similar studies have reported comparable percentages, although group numbers were smaller [15,16,17,18]. Care should be taken in applying the results to the whole CABG group, because predictors of QoL could be different between responders and nonresponders. The response percentage was equal in POAF and non-POAF groups, however, and any

potential difference in predictors of QoL by nonresponders would therefore be expected to be the same in the POAF and non-POAF groups.

Interestingly, from our analyses we found that preoperative health status predicts survival within 6 months after the procedure. The rationale behind this finding is not within the scope of this study but certainly deserves more profound research. Others have reported similar findings with less specific parameters of QoL, such as preoperative New York Heart Association class.

Rhythm surgery in patients with symptomatic atrial fibrillation improves QoL [19,20,21,22]; whether reduction of the occurrence of POAF or more aggressive treatment of POAF will improve postoperative QoL needs to be investigated in well-designed randomized clinical trials.

Conclusions

New-onset POAF is negatively correlated with mental and physical health 6 months after CABG, independent of age, sex, and body mass index.

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CHAPTER 7

Discussion and perspectives

The impact of atrial fibrillation (AF) on human health has not been recognized until the second half of the 20th century. It then became apparent that patients with AF had an up to 7-fold increased risk of stroke, and a more than 2-fold increased risk of mortality [1,2]. Large scale trials, such as the Framingham study, revealed the magnitude of the effects on health of this rhythm disturbance [1,2,3,4,5]. Although the introduction of anticoagulants for the prevention of embolic events dramatically reduced the incidence of stroke and mortality in AF patients [6], both morbidity and mortality was, and still is, more frequent in treated patients, compared to subjects without AF. Furthermore treated patients are subjected to the increased risk of bleeding by the use of these anticoagulants. The subsequent impact on the use of health care resources also became clear the latest decennia, with estimated annual costs per patient of €3000, leading to a total burden in the European Union of €13.5 billion [7].

Atrial fibrillation after cardiac surgery (POAF) has been described as a frequently occurring rhythm disturbance ever since cardiac surgery is performed. Although the negative effect of AF on the health of the general population was clear, AF after surgery initially was not recognized as a predictor, or a causative, for increased morbidity or mortality.

Mortality:

Nevertheless, mortality after cardiac surgery is increased in patients with new onset postoperative atrial fibrillation, as it is in patients with a history of atrial fibrillation before the procedure. There is a possibility of AF being just a confounder, since AF and mortality 'share' important risk factors, such as age and gender. Therefore careful analyses are warranted to come to conclusions about the *independent* effect of pre- and postoperative AF on mortality after cardiac surgery.

In the studies on the effect of (PO)AF on postoperative mortality that were discussed in chapters 2, 4 and 5, different techniques were used to correct for these possible confounding effects of mutual predictors of (PO)AF and mortality. Multivariate regression models were constructed for the prediction of early mortality, multivariate proportional hazard models for the prediction of late mortality. Besides these multivariate models, propensity score matching and adjusting techniques were used as an alternative method to reduce the effect of bias. The propensity score methods are meant to correct for predictors for the development of (PO)AF, e.g. to produce groups with similar a priori chance of having (PO)AF, based on the presence of risk factors of (PO)AF [8]. In the literature multivariate models and propensity score adjusted (or matched) models tend to produce similar results [9,10]. In our studies on mortality, both methods also produced corresponding results, which strengthens the power behind the conclusions we could draw. As in all retrospective studies, the effect of unmeasured variables could also bias the results. Of course it was not possible to adjust for these variables. However, it is presumable that the most important ones were analyzed. Hence, we concluded that a history of

AF independently predicts early (OR = 2.1) and late (HR = 1.7) mortality after coronary artery bypass surgery (CABG), and POAF is an independent predictor of late mortality after coronary artery (HR = 1.4), and mitral valve (with or without tricuspid valve, with or without coronary artery) surgery (HR = 2.1). Data on the cause of death were not available, and therefore it was not possible to draw conclusions about the cause of the higher mortality rates. Higher incidences of cerebrovascular accidents, as found in our in-hospital follow-up, and as found in long term follow-up in other studies [11], might be part of the explanation.

Risk factors:

In the search for predictors of POAF, age was found to be the most important one, and this is a consistent finding in most of the studies performed on this topic [12,13,14,15,16,17,18,19]. Age was an independent predictor with an OR of 1.06 in men and 1.05 in women for each year older. Furthermore, male gender was an independent predictor of POAF, with an OR of 1.2. The chance of developing POAF was also dependent of the performed procedure, with POAF being more frequent in on pump than in off pump coronary surgery, more frequent in valve surgery than in coronary surgery, and more frequent in mitral than in aortic valve surgery. Again, this is a common finding in other studies [12,13,14,16,19,20]. Off pump coronary surgery, although less frequently complicated by POAF than on pump surgery, was not an independent (negative) predictor for POAF.

The most important finding in our research on predictors of POAF, is the independently predicting role of body mass index (BMI). Few other studies did identify BMI as an (independent) predictor for POAF [13,17,18]. Whenever BMI was studied, this factor was rarely entered into the multivariate analyses, since univariate analysis did not show any difference. In our population, mean BMI was also not different in male patients with, and without POAF, but did differ in the female cohort, with a higher mean BMI in the POAF group. In male patients the higher BMI groups had a lower mean age, and thereby age could have camouflaged the predicting effect of higher BMI on POAF in the male cohort. Therefore BMI was entered in the multivariate models. Multivariate analyses revealed BMI to be independently predictive in both male and female (OR 1.06 and 1.05 respectively, for each point of BMI), which endorses the above mentioned theory.

Higher BMI is associated with larger left atrial size [21,22,23]. In the general population larger left atrial diameter is associated with higher incidence of AF [21]. Unfortunately, we did not have data on left atrial sizes of our patients, and therefore we could not investigate whether the effect of BMI on POAF could also be explained by an associated left atrial size. Hence, future trials are warranted to answer this question.

Quality of life:

Besides mortality, the occurrence of POAF is also associated with poorer quality of life (QoL) as assessed by Short-Form 36 (SF-36) surveys. Though the negative effect of AF in the general population was already known [24], to our best knowledge, there were no data on the effect of POAF on QoL until now. The SF-36 survey measures physical and mental health related QoL in 8 subcategories, from which 2 component (mental and physical) summary scores can be calculated. Baseline quality of life did not differ in patients who did, and who did not develop POAF. Six months after the procedure 4 out of 10 categories of the SF-36 survey were worse in POAF patients compared to non POAF patients. Furthermore non POAF patients improved in all of the 10 categories after 6 months, whilst POAF patients did in only 7/10. As we know, these results can be biased by the presence of other risk factors for POAF, such as BMI, age, and gender, and therefore these factors were entered in a multivariate regression model, to adjust for these factors. In 7/10 categories, including the 2 summarizing ones, the increase 6 months after the procedures was significantly more in the non POAF group. Hence, we concluded POAF predicts improvement of QoL 6 months after the procedure, independent of BMI, age and gender.

Final considerations:

One of the limitations of the studies we performed is the lack of data on duration and time of onset of AF, and onset of AF after discharge. It is conceivable that permanent AF after the procedure is associated with higher risk of morbidity and mortality than a single episode of less than 1 hour, as it will be associated with a more distinct effect on QoL. Therefore it is important to further study the effect of duration of POAF on morbidity, mortality, and QoL. Since POAF is associated with an up to 8-fold risk of developing AF in the future [25], research on the incidence of AF after discharge could be of great interest as well. This associated higher incidence could answer part of the question what causes late survival disadvantage, especially when AF is undetected and thereby untreated. To investigate the onset, and duration of POAF, we recently initiated a prospective study with an implantable loop recorder in patients without a history of AF, undergoing elective coronary artery bypass surgery. In this study we will be able to detect the burden of AF during a 1 year postoperative period.

The character of the studies is retrospective. Retrospective studies have the disadvantage of possible bias. Selection bias is one of the most important biases. By including *all* patients undergoing cardiac surgery in our database, selection bias does not play an important role in our studies. Bias is furthermore reduced by prospective imputation of the data, by specially trained independent research employees. Observational bias by misjudging diagnoses or data is expected to be minor since these misjudged data are expected to be evenly distributed between the compared groups, although it has

the possibility to dilute the magnitude of its effect. Bias by loss to follow up is another pitfall for retrospective studies. This bias did not blur our results, since long term follow up is excellent (over 99% long term mortality data), and in hospital follow up is 100%. An advantage of this database research is the inclusion of *all* patients, resulting in 'real life' outcome, and the possibility of analyzing large quantities of data, allowing powerful analyses.

Future perspectives:

If high risk of POAF or future AF can be predicted, prophylactic pharmacologic regimen can be intensified in this group, and more frequent controls, or even implantation of an event-monitor can be used to catch (possibly asymptomatic) episodes of AF. Whether the risk of stroke in POAF patients can be predicted by scores such as the CHA₂DS₂-VASc-score [26], or need an own scale, has yet to be investigated. Furthermore, research on other/new possibilities to prevent POAF, such as peri-operative administration of colchicine [27] or vitamin C [28,29], is of interest.

The amputation or closure of the left atrial appendage during cardiac surgery to prevent future strokes, might be of benefit for patients with high risk for POAF. Although some [30,31] report the exclusion of the left atrial appendage to be a safe procedure, concerns have risen as well [32]: Incomplete exclusion might increase the risk of clot formation, instead of decreasing it. To prove possible benefit and safety of the exclusion of the left atrial appendage, Crystal et al. [33] designed the LAAOS trial (Left Atrial Appendage Occlusion Study) which is a prospective clinical trial in which 'high risk' patients will be randomized for the occlusion of the left atrial appendage, concomitant to coronary artery bypass surgery. This trial did not proceed after the pilot phase.

Whether reduction of POAF, by a more intense prophylactic regimen, will lead to reduction of morbidity and mortality has yet to be proven. Anticoagulants might be profitable in the high risk group, even without developing POAF during hospital stay; though this has not yet been investigated properly. The use of alternatives for vitamin K antagonists, such as dabigatran (an oral direct thrombin inhibitor), or rivaroxaban (an oral direct factor Xa inhibitor), possibly offers advantages [34,35,36]. Although these new anticoagulants seem evenly effective in preventing (embolic) stroke, and associated with less (bleeding) complications in patients with AF [35,36], this has not been proven for patients with POAF after cardiac surgery, and therefore future research will be necessary to test these anticoagulants in these patients.

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CHAPTER 8

Summary

Samenvatting (summary in Dutch)

Dankwoord

List of publications

SUMMARY

Chapter 1 presents an introduction, and the objectives of this thesis. Atrial fibrillation (AF) is the most common sustained heart rhythm disturbance, with an estimated prevalence of 1% in the general population. AF is more common in men, and the prevalence rises with age. AF is associated with morbidity and mortality. Stroke is the most important and most devastating morbidity, and stroke prevention by anti-coagulants is therefore important in the treatment of AF. Furthermore, patients with AF experience significantly poorer quality of life.

New onset postoperative atrial fibrillation (POAF) is one of the most frequently occurring complications after cardiac surgery, with reported incidences between 10% and 60%. POAF most frequently occurs within the first week after the procedure. As with AF in the general population, age is the most important risk factor for POAF. The role and importance of other possible risk factors is more controversial in POAF. POAF is associated with morbidity such as stroke, and mortality. The independent effect of POAF on mortality is less clear than the effect of AF on mortality in the general population.

The objectives of this thesis are to study a) the effect of pre-operative AF and POAF on early and late survival after CABG, b) the effect of POAF on survival after mitral valve surgery, c) the effect of POAF on quality of life after CABG, and d) predictors of POAF.

There are still doubts on the effect of preoperative AF on early and late survival after CABG. In **Chapter 2** we retrospectively analyse data of 10 626 patients who underwent CABG. Patients with preoperative AF (2.5%) are compared with patients with pre-operative sinus rhythm. We show that pre-operative AF independently predicts early (<30 days) and late survival after CABG. In comparison with the (age and sex matched) general Dutch population, patients with pre-operative AF have worse late survival, while patients with pre-operative SR experience better survival.

As with AF in the general population, age is an important predictor of POAF. Other predictors of POAF are more controversial, and less extensively studied than risk factors for AF in the general population. In **Chapter 3** we describe a study in which data of 9 348 patients who underwent cardiac surgery are retrospectively analysed to find predictors of POAF. By multivariate analyses, we show that age, male gender, valve surgery (compared to CABG), and body mass index independently predict the occurrence of POAF. In our cohort, other possible predictors, such as the use of extra corporeal circulation, chronic obstructive pulmonary disease, and hypertension, did *not* prove to be an independent predictor of POAF.

Previous studies suggest that POAF is related to early and late mortality after CABG. Many of the possible predictors of POAF also relate to mortality. In **Chapter 4** we investigate the *independent* effect of POAF on early and late mortality after CABG. Data of 5 098 patients who underwent CABG are used in multivariate regression analyses. We show that POAF independently predicts overall and late mortality after CABG, not early mortality. Propensity score adjusted analyses reveal the same outcome.

The effect of POAF on survival after mitral valve surgery has not been studied extensively. Morbidity, such as stroke and heart failure, is more frequent in patients with POAF after mitral valve surgery, suggesting a higher associated mortality, in this group with POAF. In **Chapter 5** we show, by multivariate regression analyses and propensity score adjusted analyses in 856 patients, that POAF independently predicts late mortality after mitral valve surgery, not early mortality.

Although the negative effects of atrial fibrillation on quality of life (QoL) have been demonstrated in the general population, no data are available concerning new onset atrial fibrillation after cardiac surgery. In **Chapter 6** we show the results of our study on the effect of POAF on QoL after CABG. Data of 1 580 patients surviving 6 months after CABG are used to analyse QoL. Completed SF-36 health surveys, pre-operative, and 6 months postoperative, are compared between patients with and without POAF. The improvement of postoperative QoL is more pronounced in patients without POAF, and post-operative QoL is worse in patients with POAF compared to no-POAF patients, whilst pre-operative scores do not differ between these groups. By multilinear regression, we show POAF to be a negative predictor for improved QoL 6 month postoperatively, independent of age, sex, and body mass index (all independent predictors for POAF).

In **Chapter 7** the results are discussed and put in perspective.

By using multivariate regression models and propensity score matching or adjusting techniques we were able to show negative effects of AF and POAF on survival after cardiac surgery. Part of this negative effect could be due to the higher incidence of stroke in patients with POAF, as found by us, and other investigators. Furthermore, we could identify independent risk factors for the development of POAF in our population, also by multivariate regression analyses. Besides the effect of POAF on survival, it also had a negative effect on QoL 6 months after CABG. Again, part of this might be explained by the higher incidence of stroke in the POAF group.

This chapter also discusses the limitations of the presented studies, due to the retrospective character of the studies, and the limited information we had on duration of AF, onset of AF, and AF after discharge.

Reduction of POAF might reduce morbidity and mortality, although this has to be proven in future trials. Prophylactic anticoagulation in patients with high risk for POAF by vitamin K antagonists, or with possible alternatives, such as dabigatran and rivaroxaban, could also be of benefit in this group, although this has not yet been investigated properly.

SAMENVATTING

Hoofdstuk 1 bevat een introductie en een uiteenzetting van de doelstellingen van dit proefschrift. Atriumfibrilleren (AF) is een veel voorkomende ritmestoornis, met een geschatte prevalentie van 1% van de bevolking. AF komt vaker voor bij mannen, en de prevalentie neemt toe met de leeftijd. AF is geassocieerd met morbiditeit en mortaliteit. Een beroerte is een van de belangrijkste en meest gevreesde complicaties van AF. Het voorkomen van deze beroertes door middel van het gebruik van anticoagulantia is dan ook een belangrijk onderdeel van de behandeling van AF. Verder is de kwaliteit van leven minder bij patiënten met AF.

Nieuw ontstaan postoperatief atriumfibrilleren (POAF) is één van de meest voorkomende complicaties na hartchirurgie, met gerapporteerde incidenties tussen de 10% en 60%. POAF ontstaat meestal gedurende de eerste week na de ingreep. Zoals bij AF in de bevolking, is ook bij POAF hogere leeftijd de belangrijkste risicofactor. De rol en importantie van andere mogelijke risicofactoren is bij POAF is niet altijd even duidelijk. POAF is geassocieerd met morbiditeit, zoals de beroerte, en mortaliteit. Het onafhankelijke effect van POAF op sterfte is veel minder duidelijk dan die van AF in de algemene bevolking.

De doelstellingen van dit proefschrift zijn het onderzoeken van a) het effect van preoperatief AF en POAF op sterfte na bypass chirurgie, b) het effect van POAF op sterfte na mitralisklepchirurgie, c) het effect van POAF op de kwaliteit van leven na coronair chirurgie, en d) voorspellers van POAF.

Er zijn nog steeds onzekerheden over het effect van preoperatief AF op de korte en lange termijn overleving na een CABG operatie. In **Hoofdstuk 2** analyseren we retrospectief de data van 10.626 patiënten die een CABG ondergingen. Patiënten met AF voor de ingreep (2,5%) worden vergeleken met patiënten met preoperatief sinus ritme. We laten zien dat preoperatief AF een onafhankelijke voorspeller is van vroege (<30 dagen) en late sterfte na CABG. In vergelijking met de (voor leeftijd en geslacht gecorrigeerde) Nederlandse bevolking, hebben patiënten met preoperatief AF een slechtere lange termijn overleving, terwijl de patiënten met preoperatief sinusritme een betere overleving hebben.

Zoals ook met AF in de algemene bevolking, is leeftijd een belangrijke voorspeller voor het optreden van POAF. Andere voorspellers van POAF zijn meer controversieel en minder uitgebreid onderzocht dan risicofactoren van AF in de algemene bevolking. In **Hoofdstuk 3** beschrijven we een studie met data van 9.348 patiënten die een CABG ondergingen. Multivariate regressie analyse laat ons zien dat leeftijd, mannelijk geslacht, klep chirurgie (ten opzichte van coronair chirurgie) en body mass index onafhankelijke voorspellers zijn van het optreden van POAF. In ons cohort blijken andere factoren, zoals

chronisch obstructief longlijden, hypertensie en het gebruik van de hart-longmachine *geen* onafhankelijke voorspellers van POAF.

Eerdere studies suggereren dat POAF is gerelateerd aan vroege en late sterfte na CABG. Veel van de mogelijke voorspellers van POAF zijn eveneens voorspellers van sterfte. In **Hoofdstuk 4** onderzoeken we het *onafhankelijke* effect van POAF op vroege en late sterfte na CABG. Data van 5.098 patiënten die een CABG operatie ondergingen worden gebruikt in multivariate regressie analyses. We laten zien dat POAF een onafhankelijke voorspeller is voor late sterfte, niet voor vroege. Propensity score adjusted analyses laten de zelfde uitkomst zien.

Het effect van POAF op overleving na mitralisklepchirurgie is niet uitgebreid onderzocht. Morbiditeit, zoals hartfalen en beroerte, komt meer voor bij patiënten die POAF ontwikkelen na mitralisklepchirurgie, wat suggereert dat ook de geassocieerde mortaliteit hoger zou kunnen zijn in deze groep. In **Hoofdstuk 5** laten we met behulp van multivariate regressie analyses en propensity score adjusted analyses bij 856 patiënten na mitralisklepchirurgie zien dat POAF een onafhankelijke voorspeller is van late sterfte, niet voor vroege.

Het negatieve effect van atrium fibrilleren op de kwaliteit van leven (QoL) is duidelijk aangetoond in de algemene bevolking; data met betrekking tot kwaliteit van leven bij patiënten met AF na hartchirurgie zijn niet bekend. In **Hoofdstuk 6** laten we de resultaten zien van onze studie naar het effect van POAF op QoL na CABG. Ingevulde SF-36 score-formulieren van vóór en 6 maanden na de ingreep worden vergeleken tussen patiënten met en zonder POAF. De postoperatieve verbetering is meer uitgesproken bij patiënten zonder POAF en de postoperatieve QoL 6 maanden na de ingreep is beter bij patiënten zonder POAF vergeleken met patiënten met POAF, terwijl de QoL niet verschillend was voor de ingreep. Met multilineaire regressie laten we zien dat POAF een negatieve voorspeller is van verbetering van QoL 6 maanden na de ingreep, onafhankelijk van leeftijd, geslacht en body mass index (onafhankelijke voorspellers van POAF).

In **Hoofdstuk 7** worden de resultaten bediscussieerd en in perspectief geplaatst. Met multivariate regressie modellen en het gebruik van propensity score matching en adjusting technieken zijn we in staat geweest om de negatieve effecten van preoperatief AF en POAF op de overleving na hartchirurgie te laten zien. Een deel van dit negatieve effect zou verklaard kunnen worden door een hogere incidentie van beroertes, zoals wij en ook andere onderzoekers al vastlegden. Verder konden we, wederom met behulp van multivariate regressieanalyse onafhankelijke voorspellers voor het optreden van POAF identificeren in ons cohort. Naast het negatieve effect van POAF op overleving, hebben

we eveneens een negatief effect van POAF op de kwaliteit van leven een half jaar na bypass chirurgie kunnen aantonen. Ook hier zou één van de factoren het hogere percentage beroertes kunnen zijn in deze groep.

In dit hoofdstuk worden verder de beperkingen van de gepresenteerde studies, zoals het retrospectieve karakter en de beperkte informatie over duur en start van POAF en het optreden van AF na ontslag, besproken.

Het verminderen van de incidentie van POAF na de ingreep zou de morbiditeit en mortaliteit na hartchirurgie kunnen verbeteren. Dit is echter nog niet aangetoond. Profylactische behandeling van patiënten met een hoog risico op POAF met vitamine K antagonisten, of mogelijk zelf nieuwere anticoagulantia zoals dabigatran of rivaroxaban, zou eveneens een voordeel kunnen opleveren voor patiënten na hartchirurgie. Deze hypothese zal echter wel nog met gedegen onderzoek onderbouwd moeten worden.

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Onze zoon **Pim**. Nog nooit was ik zo trots. Nog nooit was iemand zo belangrijk voor mij. Zonder het te weten liet je mij zien hoe relatief alles kan zijn!

CURRICULUM VITAE

Sander Bramer is geboren op 16 oktober 1972 te Houten. In 1991 behaalde hij zijn VWO diploma aan het Koningin Wilhelmina College te Culemborg. Hij studeerde geneeskunde aan de Universiteit van Amsterdam, alwaar hij zijn doctoraal behaalde in 1997 en zijn arts-diploma in 1999. Na 4 jaar als art-assistent (niet in opleiding) cardio-thoracale chirurgie gewerkt te hebben in het Onze Lieve Vrouwe Gasthuis te Amsterdam, startte hij in 2004 als arts-assistent cardio-thoracale chirurgie (niet in opleiding) in het Catharina Ziekenhuis, alwaar hij in 2005 met de opleiding tot cardio-thoracaal chirurg begon; de eerste 2 jaar bij de algemene chirurgie (Dr. G.A.P. Nieuwenhuizen), de laatste 4 jaar bij de cardio-thoracale chirurgie (Dr. J.P.A.M. Schönberger en Dr. E. Berreklouw). In 2011 werd hij geregistreerd als cardio-thoracaal chirurg. Gedurende 11 maanden was hij als cardio-thoracaal chirurg werkzaam in het Catharina ziekenhuis. Vervolgens werkte hij gedurende 9 maanden in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Sinds april 2013 is hij werkzaam in het Amphia ziekenhuis te Breda.

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