ATRIAL FIBRILLATION AFTER CARDIAC SURGERY
An analysis of risk factors, mechanisms, and survival effects

Giovanni Mariscalco

Department of Surgical and Perioperative Science,
Umeå University,
Umeå, Sweden
2008
“Dubitando ad veritatem pervenimus”

(René Descartes)
Atrial Fibrillation After Cardiac Surgery. An analysis of risk factors, mechanisms, and survival effects.
ABSTRACT

Background: Despite the recent improvements in surgical techniques and postoperative patient care, atrial fibrillation (AF) remains the most frequent complication after cardiac surgery. Although postoperative AF is often regarded as a benign clinical condition, this arrhythmia has significant adverse effects on patient recovery and postoperative survival. Its exact pathophysiology has not yet been elucidated. The present thesis aims to analyze AF risk factors and their interaction, pre-existing histological explanatory alterations of the atrium, the AF impact on postoperative survival and the compliance of a prophylactic drug regimen.

Methods: During a 10-year period, consecutive cardiac surgery cases with complete data on AF occurrence and postoperative survival were extracted. All patients were operated on for coronary or valvular surgery, with cardiopulmonary bypass (CPB). Hospital and long-term survival data were obtained from Swedish population registry. Study I) Isolated coronary artery bypass grafting (CABG, n=7056), aortic valve replacement (n=690) and their combination (n=688) were considered. Independent AF risk factors and AF effects on early and 1-year mortality were investigated. Study II) Patients affected by postoperative AF among isolated CABG patients (n=7621), valvular surgeries (n=995) and their combination (n=879) were studied. Long-term survival was obtained and prognostic factors identified. Study III) Seventy patients were randomized to on-pump (n=35) or off-pump (n=35) CABG. Samples from the right atrial appendage were collected and histology was evaluated by means of light and electronic microscopy with reference to pre-existent alterations related to postoperative AF. Study IV) Cardiac surgery patients with complete data on smoking status (n=3245) were reviewed. Effects of smoking on AF development and interaction among variables were explored. Study V) CABG patients without clinical contraindications to receive oral sotalol (80 mg twice daily) and magnesium were prospectively enrolled (n = 49) and compared with a matched contemporary control CABG group (n = 844). The clinical compliance to the AF prophylactic drug regimen was tested.

Results: The overall AF incidence was around 26%, subdivided into 23%, 40% and 45% for isolated CABG, valve procedures and their combined surgeries, respectively. Age was the strongest predictor of postoperative AF. Coronary disease superimposed risk factors with reference to myocardial conditions at CPB weaning. Considering the preoperative smoking condition, smokers demonstrated a reduced AF incidence compared to non-smokers (20% versus 27%, p=0.001). An interaction between smoking status and inotropic support was observed: without this interaction smoking conferred a 46% risk reduction of AF (p=0.011). At the histological level, myocyte vacuolization and nuclear derangement represented anatomical independent AF predictors (p=0.002 and p=0.016, respectively). CPB exposure was not associated to postoperative AF nor histological changes. Although, postoperative AF increases the length of hospitalization in all patient groups, it did not affect the hospital survival. However, AF independently impaired the late survival, a phenomenon seen in the CABG group only. With reference to the tested sotalol-magnesium drug regimen, only 55% of CABG patients were compliant to the treatment, with marginal effects on AF occurrence.

Conclusions: In addition to age, details at the CPB weaning period, pre-existing histopathological changes, the hyperadrenergic state and catecholamines are key mechanisms in the pathophysiology of postoperative AF. In particular, the CPB period hides valuable information for timely AF prophylactic stratifications. Further, compliance effects due to patient selection should also be considered in a prophylactic therapy model. Postoperative AF increases late mortality after isolated CABG surgery, but not after valvular procedures. Although the mechanisms are unclear, our results draw the attention to possible AF recurrence after hospital discharge, indicating a strict postoperative surveillance.

Key words: atrial fibrillation; adult; cardiac surgery; coronary artery bypass grafting; valvular surgery; cardiopulmonary bypass; mortality; histology; catecholamines; embolism.
Bakgrund: Trots förfinad teknik och patientomhändertagande fortsätter förmaksflimmer (FF) vara den vanligast komplikationer efter hjärtkirurgi. Även om FF ofta betecknas som en ofarlig händelse är denna hjärtarytmi förknippad med negativa effekter på rehabilitering och överlevnad. De exakta orsakmekanismerna är ännu okända. Denna avhandling syftar till att analysera FF i termer av: riskfaktorer och dessa faktorers inbördes relationer, förklarande cellförändringar i hjärtats förmaksvägg, effekter på patientöverlevnad, och likväl, tillämpbarhet av en skyddande behandling mot FF.

Metoder: Samtliga patienter som genomgått hjärtoperationer under en 10-årsperiod vid Umeå-kliniken studerades, och för vilka man hade komplett information kring FF och överlevnad. Urvalet av patienter var kranskärls och klaffkirurgi med stöd av hjärtlungmaskin. Överlevnadsdata hämtades från folkbokföringsregistret. 

Studie I) Materialet utgjorde isolerad kranskärlskirurgi (CABG, n=7056), aortaklaffkirurgi (n=690) och kombinationer av dessa operationer (n=688). Oberoende riskfaktorer och 1-årsöverlevnad i relation till FF analyserades. 

Studie II) Långtidsöverlevnad och dess prognostiska faktorer studerades hos patienter opererade för isolerad kranskärlskirurgi (CABG, n=7621), klaffkirurgi (n=995) och kombinationer av dessa operationer (n=879). 

Studie III) En grupp av 70 CABG-patienter lottades till att antingen opereras med (n=35) eller utan (n=35) hjälp av hjärtlungmaskin. Cellprov från höger förmakssa togs och utvärderades med mikroskop och elektronmikroskop med avsikt att söka förändringar som samvarierade med förekomsten av FF. 

Studie IV) En patientgrupp för vilken information om rökvanor var tillgänglig analyserades (n=3245). Rökningens effekter på förekomst av FF och faktorers samverkan studerades. 

Studie V) En grupp av 49 CABG-patienter som bedömdes lämpliga för FF-skyddande behandling med Sotalol/Magnesium inkluderades i en studie, och jämfördes med en samtida kontrolgrupp (n=844). Tillämpbarheten av behandlingen utvärderades.

Resultat: Den genomsnittliga förekomsten av FF av ungefär 26 %, uppdelt i 23 % för isolerad CABG, 40 % för klaffkirurgi och 45 % för kombinationsingrepp. Äldre var den starkaste riskfaktorn som förklarar FF. 

Kranskärlssjukdom adde riskfaktorer som återspeglade hjärtmuskelns kondition vid tidpunkten då hjärtlungmaskinen avvecklades. Patienter som var rökare fram till operationen hade en lägre förekomst av efterföljande FF jämför med icke-rökande patienter (20 % mot 27 %, p<.001). En samvariation mellan rökning och behov av läkemedel (vakulorer) och kårnstrukturer (p=.002 respektive p=.016). Dessa förändringar hade ej samband med huruvida hjärtlungmaskin användes eller ej, och maskinen i sig påverkade ej heller förekomsten av FF. 

Konklusioner: Utöver hög ålder utgör hjärtmuskelkonditionen vid avvecklandet av hjärtlungmaskin, förekomst av cellförändringar i förmaket, och adrenalinrelaterade tillstånd nyckelmekanismer som bidrar till FF i efterföljloppet till kirurgi. I synnerhet exponeras viktig information vid tidpunkten då hjärtlungmaskinen avvecklas, och som kan vara värdefull med mål att hitta de patienter som senare utvecklar FF och som kan ges en skyddande behandling. Denna patientgrupp måste även värderas i mån de klarar den skyddande medicinering som står till bud. FF försämrrar långtidsöverlevnaden hos patienter som genomgått CABG-operation, men ej efter klaffingrepp. Även om mekanismerna bakom överlevnadseffekten är osäkra föranleder det till eftertanke i mån FF-episoder återkommer efter utskrivning från sjukhuset och att dessa patienter därmed bör följas noga i efterföljloppet.
ORIGINAL PAPERS

The thesis is based on the following papers that are referred to by their roman numerals I-V:

I. **Mariscalco G**, Engström KG.
   Atrial fibrillation after cardiac surgery: Risk factors and their temporal relationship in prophylactic drug strategy decision.

II. **Mariscalco G**, Engström KG.
    Postoperative atrial fibrillation is associated with late mortality after coronary surgery, but not after valvular surgery.
    *Submitted.*

    Relationship between atrial histopathology and atrial fibrillation after coronary bypass surgery.
    *Journal of Thoracic and Cardiovascular Surgery. 2006; 131: 1364-72.*

IV. **Mariscalco G**, Engström KG.
    Are current smokers paradoxically protected against atrial fibrillation after cardiac surgery?
    *Nicotine & Tobacco Research. In press.*

V. **Mariscalco G**, Cederlund B, Engström KG.
    The clinical noncompliance of oral sotalol/magnesium for prophylactic treatment of atrial fibrillation after coronary artery bypass grafting.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>ACC</td>
<td>aortic-cross clamp</td>
</tr>
<tr>
<td>AVR</td>
<td>aortic valve replacement</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CPB</td>
<td>cardiopulmonary bypass</td>
</tr>
<tr>
<td>CVA</td>
<td>cerebrovascular accident</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IABP</td>
<td>intra-aortic balloon pump</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>OPCAB</td>
<td>off-pump coronary-artery bypass</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

Abstract .................................................................................................................................................. 5
Summary in Swedish ................................................................................................................................. 6
Original papers ....................................................................................................................................... 7
Abbreviations .......................................................................................................................................... 8
Table of contents ..................................................................................................................................... 9
Introduction ............................................................................................................................................ 11
  - Historical notes ............................................................................................................................... 11
  - Epidemiology ................................................................................................................................. 11
  - Etiopathogenesis ............................................................................................................................ 11
  - Clinical features .............................................................................................................................. 12
  - Clinical outcome ............................................................................................................................. 13
  - Economic implications ..................................................................................................................... 13
  - Treatment of AF after cardiac surgery .......................................................................................... 13
  - Prophylaxis .................................................................................................................................... 14
Aims ...................................................................................................................................................... 15
Material and Methods ............................................................................................................................ 17
  - General design ............................................................................................................................... 17
  - Ethics .............................................................................................................................................. 17
  - Patient populations ....................................................................................................................... 17
  - Data collection ............................................................................................................................... 18
  - Patient management ...................................................................................................................... 18
  - Definition and detection of postoperative AF ............................................................................... 19
  - Statistics ....................................................................................................................................... 19
Results .................................................................................................................................................. 21
  - General results ............................................................................................................................... 21
  - Study results .................................................................................................................................. 21
General Discussion ............................................................................................................................... 27
  - Risk factors associated with AF development .............................................................................. 27
  - Histological observations in relation to AF .................................................................................. 28
  - Drug prophylaxis ........................................................................................................................... 28
  - Resource utilization ....................................................................................................................... 28
  - Postoperative survival .................................................................................................................... 29
  - Limitations .................................................................................................................................... 29
  - Clinical implications of the thesis ................................................................................................. 30
Conclusions .......................................................................................................................................... 31
Acknowledgements .............................................................................................................................. 33
Financial support and conflicts of interest ............................................................................................ 34
References .............................................................................................................................................. 35
Included reports ..................................................................................................................................... 41
  Study I ............................................................................................................................................... 41
  Study II .............................................................................................................................................. 53
  Study III ............................................................................................................................................ 61
  Study IV ............................................................................................................................................. 73
  Study V .............................................................................................................................................. 83
INTRODUCTION

Postoperative atrial fibrillation (AF) still represents a relevant complication of cardiac surgery, despite of the progressive improvements in surgical techniques, anesthesiologic procedures and pharmacologic therapies. AF is the most frequent complication after cardiac surgery and its incidence is constantly increasing; this is in part related to the progressive aging of the patient population and the frequent presence of patient comorbidities. Thereby, AF is the subject of an intense research activity in order to improve knowledge about the etiopathology, prevention and prognosis of AF after cardiac surgery.

Historical notes
Postoperative AF was first described in 1950 as a complication after a thyroidectomy. With the development of cardiac surgery in the early 50’s, it was soon realized the magnitude and severity of this arrhythmia, especially considering the absence of effective therapeutic tools, such as an electrocardiogram (ECG) monitoring or the lack of effective arrhythmic drugs. In 1987, Taylor reported the first complete analysis of the AF incidence (19%) after coronary artery bypass grafting (CABG) surgery.

Epidemiology
The incidence of AF after cardiac surgery ranges from 10% to 60%, and the variability was suggested to reflect different type of procedures, patient demographics, and different methods of electrocardiographic monitoring. The incidence of postoperative AF after CABG and valvular surgery is 20-40% and over 40%, respectively, whereas only 10% of patients undergoing cardiac transplantation is affected by this arrhythmia. Postoperative AF is demonstrated in about 10% of patients when the diagnosis leans on extemporary 12 leads ECG; the percentage raises to 40% when a continuous ECG telemetric monitoring is performed, whereas the incidence varies from 16% to 30% when the diagnostic criteria is based on symptomatic recording only. Postoperative AF typically occurs between postoperative days 1 to 5, with a maximal incidence of the first episode (60-70%) in the 2nd postoperative day (Figure 1). Only 22% of patients present several relapses.

Etiopathogenesis
The pathophysiology of AF after cardiac surgery is not precisely known, but the mechanisms are thought to be multifactorial (Figure 2). A re-entry mechanism is regarded as the main contributor for the onset of postoperative AF, resulting from an inhomogeneous distribution of atrial refractoriness. Alterations of automaticity, an intrinsic characteristic of specialized conduction tissue cells, is also considered as an etiopathogenic factor behind AF.

The phenomenon of altered automaticity requires an atrial structural substrate, which may reflect an association to multiple preoperative predisposing factors. Operative and postoperative factors may also contribute to the development of this structural substrate. Among preoperative risk factors advanced age and hypertension are advocated as main AF promoting factors. In particular, ageing is the variable most associated with the AF development, not only after cardiac surgery but in the general population as well. Atrial fibrosis and dilation, both increasing at higher age, both determine alterations and loss of electrical coupling among atrial myocardial fibers. Consequently, AF is promoted when the atrial electrical conduction diminishes. Among postoperative factors, surgical atrial injury and inflammation seem to play a relevant role. It is well known that cardiopulmonary bypass (CPB) is accompanied by a systemic inflammatory response syndrome. Inflammation may alter the atrial conductivity, and facilitate re-entry phenomena and thereby favoring postoperative AF. Postoperative leukocytosis encountered after CPB has recently been reported as an independent AF predictor. In addition to the theory about electrophysiological substrate, a triggering event is required for the onset of AF, such as a premature supraventricular contraction. Ectopic foci arising from the pulmonary veins or other sites have been shown to promote persistent AF in the general population, with catheter ablation as the suggested therapy.
However, the real implication of ectopic foci to explain postoperative AF has not been yet clarified. Nevertheless, in support of this theory a relationship between AF and ventricular venting through the right superior pulmonary vein has been observed. Other triggering events have also been documented in association with electrolyte and autonomic nervous system imbalance. The activation of sympathetic nervous system probably contributes to the onset and maintenance of AF after cardiac surgery. Preoperative alterations of the autonomic nervous system have been registered independently from the typology of the procedure. In the general population an increased sympathetic tone has been documented immediately prior to the onset of AF, as assessed by heart rate variability. A reduction in variability has been demonstrated in patients undergoing CPB, suggesting the existence of postoperative fluctuation in the cardiac autonomic tone. An hyper-rresponsiveness of the autonomic nervous system would reduce the atrial refractory period, thus promoting the onset of the arrhythmia. Moreover, ionic alterations due to hemodilution occurring with CPB, also including the consequent massive use of diuretics, can also be related to postoperative AF.

Hypocalemia causes cellular hyperpolarization, quickens depolarization and increases automaticity and cellular excitability. Magnesium is a main cofactor of the Na/K ATP-ase and regulates specific potassium channels. In the absence of the cation (e.g., magnesium) the channel remains open with a consequent intracellular potassium depletion and cellular depolarization.

Clinical features
The symptoms of AF are essentially related to the hemodynamic effects due to the loss of an effective atrial contraction. The loss of atrial contribution to the ventricular filling gets particularly important in case of depressed left ventricular systolic function. Dyspnoea and asthenia are symptoms associated with high-rate response AF, as well as precordial discomfort; the latter can be sometimes a consequence of myocardial ischemia. However, AF after cardiac surgery occurs often asymptomatic, making diagnosis very difficult, especially when the patient has already been discharged. It is thought that about 60% of the episodes of AF in this kind of patients are asymptomatic and therefore non-diagnosed.

Figure 2. Schematic pathogenetic mechanism of postoperative AF development. Adopted and modified from Echahidi et al.
Clinical outcome

In the past decades, postoperative AF was described as a relatively benign complication of cardiac surgery because, for the most part, it was self-limiting and without severe consequences. However, it has been recently demonstrated that this arrhythmia contributes to a prolonged hospital stay, increased morbidity and mortality, and is associated with a remarkable increase in sanitary costs.

Although a precise cause-effect relationship is often difficult to establish, because of the difficult temporal and causative link between AF and organ complications, in several circumstances a linear relationship between the arrhythmia and postoperative complications have been clearly reported. AF after cardiac surgery can give rise to an increased risk of pulmonary edema, of systemic hypotension due to a reduced ventricular filling, and of embolic events. In general, the risk of stroke is threefold higher in patients affected by AF than in the normal population. Postoperative AF facilitates the formation of thrombi in the atria. Moreover, cardiac surgery and CPB affects the coagulation system in complex ways, including deficiency in coagulative factors, alteration of platelet activity, and altered fibrinogen response. These factors result in a hypercoagulative state, which favors the formation of thrombotic aggregates, mainly in situations of retarded atrial blood flow.

It is postulated that postoperative AF is associated with an increased early and late mortality. Almassi et al. demonstrated a decreased survival rate in cardiac-surgery patients affected by postoperative AF. At 6 months after surgery, the mortality was significantly higher in AF patients compared to patients without the arrhythmia (9.4% vs 4.2%, respectively). Similarly, Villareal et al. recently reported an association between postoperative AF and increased risk for early and late adverse outcomes in CABG patients. In the large case series by Villareal, drawn from 6477 patients undergoing first-time isolated CABG, those affected by AF had a 50% increased risk of death (odds ratio (OR), 1.5; 95% confidence intervals (CI), 1.3-1.8). The adverse long-term mortality persisted after case-control matching (OR, 3.4; 95% CI, 1.6-7.5). The cumulative survival at one and four years postoperatively were 87% vs 94% and 74% vs 87%, for the AF and no-AF populations, respectively. Mahoney et al. reported similar data from more than 8500 isolated CABG patients. A significantly increased risk of death was observed in patients who developed postoperative AF compared to those who did not (OR, 1.2; 95% CI, 1.1-1.3). The explanation for the above-mentioned increased mortality rates is not clear. In the short term the compromised hemodynamic status and the left ventricular dysfunction represent the more likely causes.

More difficult it becomes to distinguish between the underlying reasons to explain the late mortality, although these mechanisms are likely include stroke and other massive embolic events, drug-related side-effects of anti-arrhythmic agents or hemorrhagic events due to anticoagulant therapy.

Economical implications

Many studies have identified a strong impact of AF on sanitary costs. Aranki et al. studied a series of 570 patients who underwent isolated myocardial revascularization and reported a prolonged hospital stay (additional 4.9 days), and calculated an increased cost burden of $10,000-$11,500 per patient. Taylor and Mauldin reported additional costs in the range of $5000 to $6000. In consideration of the high number of patient undergoing cardiac surgery per year, economic implications related to this arrhythmia are considerable.

Treatment of AF after cardiac surgery

In light of the importance of postoperative AF to patient outcome, there has been a great deal of interest in preventing and treat this complication. The optimal management of this arrhythmia has not been determined. The current strategies in the management of postoperative AF include prophylactic use of pharmacologic agents in the perioperative period to prevent the AF occurrence and use of rate-controlling medications to control ventricular response, and if spontaneous conversion does not occur, use of pharmacologic or electrical cardioversion, with or without concomitant anticoagulant therapy.

In overview, current medical treatments of AF after cardiac surgery are largely similar to the standard AF therapy used in the general population. The ACC/AHA/ESC 2006 guidelines for the management of patients with AF identified a class-I indication for atroventricular nodal blocking agents to achieve rate control in postoperative AF. The class-IIa recommendations for the AF management included direct current cardioversion or pharmacologic cardioversion with ibutilide to restore sinus rhythm. Additionally, anti-arrhythmic medications are recommended to maintain sinus rhythm in patients with recurrent or resistant postoperative AF. The use of anti-thrombotic medications is also reasonable in the management of postoperative AF, to achieve therapeutic anticoagulation and potentially reduce the risk of stroke.
Prophylaxis
Several anti-arrhythmic agents have been used in the prophylaxis of postoperative AF with varying degree of success.65-69 A caveat with the use of any such preventive therapy is that most patients undergoing cardiac surgery do not develop postoperative AF. Thus many patients (about 70%) are exposed to side effects of the selected therapy when they are at no or low risk for AF. However, beta-blockers, amiodarone and sotalol alone or combined with magnesium seem to be the most frequent regimen and effective agents.65-69

Amiodarone. The prophylactic use of amiodarone has shown to be effective in decreasing the incidence of postoperative AF.65-69,82 Amiodarone is a Vaughn-Williams class-III anti-arrhythmic agent and it has been associated with a reduction from 33% AF in control patients to 21% in the amiodarone group (OR, 0.54; 95%CI, 0.44-0.67).65 Although many studies have not demonstrated a decrease in morbidity or mortality when applying amiodarone prophylaxis, two recent major meta-analyses of randomized controlled trials have found that the risk of stroke for patients treated with this drug was less than in control subjects (RR, 0.39; 95%CI, 0.21-0.76).82,83 However, there is lack of consensus regarding the homogenous dose period of treatment and administration route.65-69,82

Beta-blockers. Because sympathetic activation might facilitate postoperative AF in susceptible patients, and given the increased sympathetic tone in patients undergoing cardiac surgery, beta-blockers have so far been the most studied drug in terms of AF prophylaxis.53-66 In a meta-analysis of 28 trials evaluating these drugs for the prevention of postoperative AF, including 4074 patients, beta-blockers reduced the percentage of patients with AF from 31% in the control group to 18% in the treatment group (OR, 0.35; 95%CI, 0.26-0.49).65 Beta-blockers are currently recommended for all patients undergoing heart operations, these should be started preoperatively, and should be continued after operation unless otherwise contraindicated.55-69

Sotalol is a beta-blocker agent with class-III anti-arrhythmic effects.70,71 Numerous studies have evaluated sotalol alone or in combination with magnesium in AF prophylaxis.72-81 In a meta-analysis of Crystal et al., evaluating 8 trials with 1294 patients, sotalol reduced the percentage of patients with AF from 40% in the control group to 21% in the sotalol group (OR, 0.36; 95%CI, 0.23-0.56).65 In a recent study, the combined administration of sotalol and magnesium has been demonstrated to markedly decrease the occurrence of postoperative AF to 1.9% after CABG operations.80 However, in another report, this combined regime failed to reduce the incidence of postoperative AF.81 Nonetheless, sotalol strategy clinically implies important side effects, reported to occur in up to 22% of treated patients.72-81

Magnesium. Several studies have been conducted to examine the efficacy of magnesium supplementation for the prevention of AF after cardiac surgery. Most of these studies have reported favorable results, but other have failed to confirm these findings.84-86 Postoperative use of magnesium in combination with amiodarone or sotalol has been demonstrated to exert the most favorable preventive AF effects.80,87 In a recent meta-analysis of Miller and colleagues, analyzing 20 randomized trials with a total of 2490 patients, magnesium administration decreased the proportion of patients developing postoperative AF from 28% in the control group to 18% in the treatment arm (OR, 0.54; 95%CI, 0.38-0.75).88

Other agents have been successfully adopted in the AF-preventive strategy. Preoperative statins and n-3 polyunsaturated fatty acids have recently been related to a significant decrease in AF occurrence, especially after CABG operations.89 Anti-inflammatory agents (steroids) have been also tested with varying degree of success.82,93 Digoxin, calcium channel blockers, angiotensin-converting enzyme inhibitors have also been investigated as potential prophylactic AF agents, although with uncertain results.84-97 There is also no uniform consensus on atrial pacing as a preventive AF strategy.98,99
AIMS

The aims of the thesis were:

I. to identify specific risk factors of postoperative AF and their confounding patterns in the pre- and perioperative periods among patients exposed to CPB.

II. to assess the impact of postoperative AF on late survival in patients undergoing cardiac surgical procedures of different types.

III. to correlate any histological atrial alterations with the occurrence of postoperative AF with reference to surgical stress and CPB effects.

IV. to evaluate the possible influence of smoking on postoperative AF, in view of the known relationship between adrenergic status, smoking habits, and AF trigger mechanisms.

V. to verify the clinical compliance of a prophylactic drug regimen constituted by sotalol and magnesium in patients subjected to CABG.
Atrial Fibrillation After Cardiac Surgery. An analysis of risk factors, mechanisms, and survival effects.
MATERIAL AND METHODS

General design

Study I, II and IV were observational studies obtained from prospectively collected data during a 10-year period, comprising a total of 11,357 heart surgery patients at University Hospital of Northern Sweden. Study III was a prospective-randomized study conducted at Varese University Hospital (Italy), and constituted by 70 CABG patients operated on during a two-year period. Finally, Study V was a prospective pilot study, enrolling a total of 49 patients undergoing isolated CABG over a two-month period at University Hospital of Northern Sweden. The patient populations are schematically illustrated in Figure 3.

Ethics

Studies conducted in Sweden were carried out according to the national ethical laws, and when required, the ethical committee at Umeå University Hospital gave their approval. In Study V, informed consent was obtained from each patient. In Study III, conducted in Italy, ethical committee approval was received from the Varese University Hospital, and all patients provided their consent to participate. All studies were accomplished according to the Helsinki declaration (www.wma.net).

Patient populations

**Study I, II and IV:** A retrospective cohort design was used in which all patients undergoing cardiac surgery between January 1994 and June 2004 were identified (n=10,497) using the computerized database from the University Hospital of Northern Sweden. In this cohort 8,434 patients undergoing CABG or aortic valve surgeries were extracted for Study I. The study population was constituted by isolated CABG (n=7,056) and aortic valve replacement (AVR, n=690), or the combined of CABG with AVR (n=680). For Study II 9,495 patients undergoing CABG or valve procedures, not limited to aortic valves, were evaluated with reference to postoperative survival. For Study II the patient population comprised a somewhat longer period of enrollment (January 1994-December 2004) than in the other two studies. The population comprised isolated CABG (n=7,621), valvular surgery (n=995), and combined coronary and valvular operations (n=879). For Study IV, a subgroup of 3,245 patients with completed data regarding smoking status was obtained. In general, elective, urgent, or emergency procedures were all included as well as reoperations. Patients were excluded if they revealed no sinus rhythm on admission or cardiac rhythm data, and presence of pace-maker device. Patients operated on without CPB or those who died in the operating room were also excluded.

---

**Figure 3.** Data origin of the enclosed manuscripts.
Study III: 70 patients scheduled for primary and isolated elective CABG were prospectively randomized for coronary revascularization with either on pump (CABG, n=35) or off-pump techniques (OPCAB, n=35). Inclusion required a preoperative sinus rhythm. Exclusion criteria encountered history of supraventricular arrhythmias, presence of a pacemaker device, infection within 6 weeks preceding the operation, inflammatory disorders, or immunosuppressive therapy.

Study V: 49 patients undergoing primary isolated on-pump CABG were enrolled (March - April 2003). Patients were eligible if they were in sinus rhythm before surgery. Exclusion criteria were preoperative use of sotalol, digoxin or diltiazem; history of supraventricular arrhythmias; presence of pacemaker device; sick sinus syndrome or atrioventricular node disease; QT interval longer than 450 ms; reduced left ventricular function (ejection fraction < 35%); severe chronic obstructive pulmonary disease, and serum creatinine levels higher than 150 µmol/L. A larger control group (n=844) of contemporary CABG operations was extracted during a 2-year period from the same aforementioned database. These patients shared the same inclusion and exclusion criteria with the study group, with reference to cardiac rhythm, left ventricular function, creatinine level, and pulmonary disease. The matching process was tuned to have identical distribution of stable and unstable angina classification.

Data collection

Study I, II, and IV: The clinical database at the Cardiothoracic Department/Heart Center was used to identify and extract data on the analyzed patients. All clinical and operative data were prospectively recorded. The database remained fairly consistent over the study period, capturing the totality of the cardiac operations. Data describing clinical and surgical details of the procedure and postoperative course were followed by daily entry of information from the operating room, the intensive care unit, and the ward. Inputs were from surgeons, anesthetists, perfusionists, and nurses. A synthesis of these multiple-input parameters was performed in the data processing. The observational period was limited to the length of stay at the Cardiothoracic Unit. Postoperative survival data were collected from the Swedish National Registry, using the 10-digit national Swedish identification number.

Study III: Specimens of the right atrial appendage were collected after opening of the pericardium. In the CABG group only additional samples were taken after weaning from CPB. Subsequently, atrial samples were fixed in buffered formalin (formaldehyde, 4% wt/vol, and acetate buffer, 0.05 mol/L) for 12 hours at room temperature, followed by dehydration, embedding in paraffin, and cutting into 4-µm serial sections. Sections were stained with hematoxylin and eosin and Masson trichrome. Morphometric evaluation was conducted by a trained pathologist blinded to patient characteristics and AF occurrence. Pathology referring to atrial myocytes and connective tissue components were evaluated by using semiquantitative scales similar to that previously described by Ad et al. A small portion of each specimen was also separated for electron microscopic observations. For this purpose, tissue samples were fixed for 2 hours at 4°C in a mixture of 2% paraformaldehyde and 2% glutaraldehyde in 0.05 mol/L (pH 7.3) cacodylate buffer, and postfixed in 1% osmium tetroxide for 1 hour at room temperature.

Study V: Patient data were collected fulfilling a specific and detailed protocol. Other variables together with the control group data were obtained from the aforementioned database (University Hospital of Northern Sweden).

Patient management

Study I, II and IV: Preoperative medications, including diuretics, antihypertensives, statins, and calcium-channel blockers were routinely omitted on the day of the operation and restarted after surgery, unless clinically contraindicated. On the contrary, β-blockers were generally administered in the operative morning. The anesthetic management followed routine methods. All procedures were generally performed using full-sternotomy. CPB included moderate hemodilution at systemic moderate hypothermia (30-34°C). Myocardial protection was accomplished by means of intermittent cold cardioplegia. At the end of the operation, patients were taken and monitored to a dedicated intensive care unit (ICU) followed by an intermediate ward level. Heart rate, ECG, central venous and arterial pressures, and acid-base/blood gases were continuously monitored during the ICU stay. The fluid-management routine in the ICU comprised 12-hour infusion supplemented with potassium and magnesium to maintain electrolyte balance within normal range.

Study III: Preoperative medications were routinely omitted on the day of the operation and restarted after the operation, unless clinically contraindicated. The patients followed identical surgical and anesthetic protocols. CPB was of standardized fashion with ascending aortic and 2-
stage venous cannulation of the right atrium at systemic moderate hypothermia (32°C). Myocardial protection was accomplished by means of antegrade intermittent cold blood cardioplegia. OPCAB procedures were performed at near normothermia (35°C). After the operation, the patients were transferred to the cardiovascular ICU.

**Study V:** The 49 enrolled patients were scheduled to receive oral sotalol (80 mg) and magnesium hydroxide (250 mg/10.3 mmol Mg⁺) twice daily starting from the first postoperative day until discharge. In addition, magnesium sulphate (20 mmol) was intravenously administered on the operative day until discharge from ICU. Hemodynamic parameters were recorded in the morning of the first postoperative day to evaluate the compliance for treatment. Negative compliance considered a systolic/mean arterial blood pressure less than 100 mmHg and 60 mmHg, respectively, heart rate less than 55 beats per minute, or need of inotropic support. The therapy compliance was re-evaluated on a daily basis during the period of hospitalization. Patients sharing with the aforementioned daily criteria were defined as “non-compliant”. All procedures were realized by full-sternotomy approach. Cardiopulmonary bypass was of standardized fashion. Subsequent clinical management followed routine methods.

**Definition and detection of postoperative AF**

**Study I, II and IV:** All patients were monitored by continuous ECG during a minimum period of 48 hours postoperatively. Subsequently, the monitoring was by repeated daily observations by nurses and physicians, at least every 8 hour. In case of any hint of atrial arrhythmia an additional ECG was recorded. The AF definition included arrhythmia successfully treated as well as those persistent at discharge. The arrhythmia, as defined by physician assessment, was on the basis of a telemetry strip or from a 12-lead electrocardiogram recording. In practical terms, the procedure required a minimum of about 15 minutes of AF duration to be considered and documented. The database did not separate AF from atrial flutter, and given the design of the study and the large number of observations, the AF definition was limited to recorded information and for the period of hospitalization.

**Study III:** All patients were monitored daily until discharge with continuous electrocardiographic telemetry, as well as standard 12-lead ECG. Additional recordings were collected at clinical suspicion of AF. Only AF episodes lasting longer than 15 minutes were considered.

**Study V:** Cardiac rhythm assessment followed the daily practice of an integrated clinic encompassing ICU, intermediate ward, and ward level, sharing the same routines and data collection system. Occurrence of postoperative AF was monitored by telemetry during a minimum period of 48 hours after surgery. Beyond this time window, daily and triplicate ECG recordings were performed until 96 hours postoperatively, which was in addition to repeated observations by nurses and physicians until discharge.

**Statistics**

In general, all data were tabulated with Microsoft Excel (Microsoft Corp, Redmond, WA, USA). Continuous variables were compared between groups with unpaired Student’s t test for normally distributed values; otherwise, the Mann-Whitney U test was employed. In case of dichotomous variables, group differences were examined by $\chi^2$ or Fisher exact tests as appropriate. Stepwise logistic regression model was developed to identify patient and procedural variables associated with AF development. Models were built using variables that demonstrated a p-value <.15 at univariate analysis. The strength of the association of variables with the development of AF was estimated by calculating the odds ratio (OR) and 95% confidence intervals (CIs). All the results are expressed as mean ± SD for continuous variables and frequencies for the categorical ones. A 2-sided p-value <.05 was considered statistically significant. Statistical analysis was computed with SPSS, release 13.0 for Windows (SPSS Inc, Chicago, IL, USA) or with Statistica, release 6.1 (StatSoft Tulsa, OK, USA).

**Study I:** Typically, the statistical model compared three groups: CABG, AVR, and combination of these two procedures. Inter-group analyses of categorical data were analyzed by 3-column contingency tables with a log-linear model and maximum likelihood $\chi^2$ output. Post-hoc analysis was conducted by restraining the model for each variable and group. Comparison of parametric data was by one-way analysis of variance with Duncan post hoc analysis. Within-group univariate analysis with reference to AF was done using log-linear approach for categorical data and by Student’s t or Mann-Whitney U-test for numeric data, respectively. Logistic regressions versus AF were carried out as described above, and similarly, to determine multivariately associated predictors against 1-year mortality.
**Study II:** Kaplan-Meier estimates and log-rank test were performed for the mortality rate comparison versus AF. Hazard ratios (HRs) were generated by a Cox regression analysis. A stepwise multivariate approach was used and confirmed by backward and forward methods. To measure survival differences, the final Cox proportional hazards model was adopted to construct adjusted survival curves for AF and non-AF patients.

**Study III:** Histological data were dichotomized and univariate binomial logistic regression and McNemar test were used as appropriate.

**Study IV:** The interaction pattern between smoking status and the use of inotropes was statistically investigated. The interaction was explored by extracting a subset of patients in whom inotropes were not used. The multivariable output was therefore analyzed to suggest two separate AF-predictive models, with and without inotropic use. These models were applied and validated on the study cohort in terms of observed versus predicted output, and the appropriateness of the models was evaluated by the Hosmer-Lemeshow goodness-of-fit test. The predictive influence of age on AF development was tested with respect to inotropic use and smoking status. Subsequent scores were obtained, which were sensitized against the predictive weight of the individual variables of the multivariable output. The scores were assessed with ROC analysis using the same validation set and the results were tested in the two score models.

**Study V:** Parametric data were analyzed by unpaired Student’s t-test with appropriate corrections and by one-way ANOVA. Categorical data were overviewed by $\chi^2$ analysis, and if significant re-evaluated by log-linear analysis with maximum likelihood Chi-square, by Chi-square-Yates correction or by Fisher’s exact test. The study design was powered in view of data acquired by Forlani and colleagues.
RESULTS

General results
In general, the overall incidence of AF in the studied populations ranged from 25.6% to 31.4%. In detail, postoperative AF occurred in 20% to 31% of the patients after isolated CABG and in over 40% of patients after valvular surgery (Table 1). About one third of the patients were females (from 19% to 33%). Generally, patients affected by postoperative AF were older, requiring a longer CPB support and experiencing a longer ICU and hospital stay than those without AF.

Study results

Study I
Clinical results
The three surgery groups showed important differences at univariate level. Patients with combined CABG and aortic valve operations were older and revealed a worst profile for comorbidities. Univariate analysis revealed numerous risk factors associated with AF, although the most consistent risk factors were advances age and the severity of clinical scores. The incidence of the arrhythmia increased on average 7.9% per decade in the CABG group. Multivariable analysis identified different independent risk factors associated with postoperative AF (Table 2). Advanced age was consistently associated with AF in all groups. In patients with coronary disease, variables related to the CPB weaning period independently predict postoperative AF.

Outcome results
No AF-specific difference in hospital mortality was observed for the entire patient cohort or for the separated groups of surgeries. CABG patients affected by postoperative AF demonstrated a reduced 1-year survival compared with patients without AF (4.6% versus 2.0%, p<0.001). Predictors to explain 1-year mortality were multivariably extracted in the CABG group only, and postoperative AF was found significant (OR 1.7, 95%CI 1.16-2.50).

Study II
Outcome results
Median follow-up time was of 7.9 years (maximum 13.4 years). For all analysed groups, Kaplan-Meier analysis revealed a reduced survival for patients affected by AF compared with those without this arrhythmia (Table 3). However, at multivariate analysis, AF independently affected long-term survival in the CABG group only (HR 1.22; 95%CI 1.08-1.37, Table 4). For isolated valve surgery or combined procedures AF did not have this independent effect on the long-term survival (HR 1.21; 95%CI 0.92-1.58 and HR 1.15; 95%CI 0.90-1.46, respectively). The analyses did not reveal overall survival differences against time (e.g., the year when the procedure was conducted), and further, possible interactions (AF*age, AF*years of operation) were also tested and found non-significant.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
<th>Study V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>8434</td>
<td>9495</td>
<td>70</td>
<td>3245</td>
<td>49</td>
</tr>
<tr>
<td>AF incidence (%)</td>
<td>25.6</td>
<td>26.7</td>
<td>31.4</td>
<td>26.2</td>
<td>19.6</td>
</tr>
<tr>
<td>Age (y)</td>
<td>66.2 ± 9.4</td>
<td>66.2 ± 9.5</td>
<td>65.1 ± 8.6</td>
<td>65.7 ± 9.1</td>
<td>66.9 ± 8.8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>26.6</td>
<td>26.8</td>
<td>18.6</td>
<td>28.0</td>
<td>32.6</td>
</tr>
<tr>
<td>EUROscore (score)</td>
<td>4.3 ± 2.9</td>
<td>4.3 ± 2.9</td>
<td>3.3 ± 2.4</td>
<td>4.8 ± 3.8</td>
<td>3.5 ± 2.3</td>
</tr>
<tr>
<td>CPB-time (min)</td>
<td>87.2 ± 38.5</td>
<td>89.1 ± 40.1</td>
<td>85.2 ± 3.6*</td>
<td>97.1 ± 40.8</td>
<td>72.8 ± 22.4</td>
</tr>
<tr>
<td>Inotropic support (%)</td>
<td>27.1</td>
<td>28.9</td>
<td>31.4</td>
<td>29.7</td>
<td>12.2</td>
</tr>
<tr>
<td>ICU time (h)</td>
<td>33.7 ± 65.9</td>
<td>35.9 ± 71.2</td>
<td>29.7 ± 33.4</td>
<td>34.9 ± 66.6</td>
<td>24.4 ± 21.7</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>10.3 ± 4.4</td>
<td>10.4 ± 4.6</td>
<td>11.8 ± 5.3</td>
<td>11.7 ± 4.7</td>
<td>7.1 ± 1.8</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>1.1</td>
<td>0.7</td>
<td>0</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>1-year mortality (%)</td>
<td>3.2</td>
<td>2.9</td>
<td>-</td>
<td>2.8</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* Only for on-pump patients (n=35). Values are percentage or mean (SD).

AF, atrial fibrillation; CPB, cardiopulmonary bypass; ICU, intensive care unit; LOS, length of hospitalization.

Table 1. Clinical characteristics of the subjects of the Studies.
Atrial Fibrillation After Cardiac Surgery. An analysis of risk factors, mechanisms, and survival effects.

### Table 2. Multivariate analysis: predictors of postoperative AF (Study I).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Unit</th>
<th>Wald $\chi^2$</th>
<th>p value</th>
<th>OR</th>
<th>95% CI Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of surgery&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[1,2,3]</td>
<td>63.08</td>
<td>&lt;0.001</td>
<td>1.40</td>
<td>1.29</td>
<td>1.52</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;70 y</td>
<td>207.97</td>
<td>&lt;0.001</td>
<td>2.16</td>
<td>1.95</td>
<td>2.40</td>
</tr>
<tr>
<td>Temporary pacing</td>
<td>yes</td>
<td>9.42</td>
<td>0.002</td>
<td>1.29</td>
<td>1.09</td>
<td>1.52</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>yes</td>
<td>9.36</td>
<td>0.002</td>
<td>1.21</td>
<td>1.07</td>
<td>1.37</td>
</tr>
<tr>
<td>NYHA</td>
<td>[1-5]</td>
<td>8.29</td>
<td>0.004</td>
<td>1.09</td>
<td>1.03</td>
<td>1.16</td>
</tr>
<tr>
<td>Complicated weaning from CPB</td>
<td>yes</td>
<td>6.93</td>
<td>0.008</td>
<td>1.33</td>
<td>1.08</td>
<td>1.65</td>
</tr>
<tr>
<td><strong>CABG patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&gt;70 y</td>
<td>169.98</td>
<td>&lt;0.001</td>
<td>2.22</td>
<td>1.97</td>
<td>2.50</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>yes</td>
<td>20.56</td>
<td>&lt;0.001</td>
<td>1.37</td>
<td>1.20</td>
<td>1.57</td>
</tr>
<tr>
<td>NYHA</td>
<td>[1-5]</td>
<td>7.03</td>
<td>0.008</td>
<td>1.09</td>
<td>1.02</td>
<td>1.18</td>
</tr>
<tr>
<td>Temporary pacing</td>
<td>yes</td>
<td>5.36</td>
<td>0.021</td>
<td>1.28</td>
<td>1.04</td>
<td>1.57</td>
</tr>
<tr>
<td>Defibrillation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>yes</td>
<td>4.61</td>
<td>0.032</td>
<td>1.16</td>
<td>1.01</td>
<td>1.33</td>
</tr>
<tr>
<td><strong>AVR patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&gt;70 y</td>
<td>20.01</td>
<td>&lt;0.001</td>
<td>2.05</td>
<td>1.50</td>
<td>2.82</td>
</tr>
<tr>
<td><strong>COMB patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&gt;70 y</td>
<td>17.48</td>
<td>&lt;0.001</td>
<td>2.37</td>
<td>1.58</td>
<td>3.56</td>
</tr>
<tr>
<td>Complicated weaning from CPB</td>
<td>yes</td>
<td>11.13</td>
<td>0.001</td>
<td>2.26</td>
<td>1.40</td>
<td>3.65</td>
</tr>
<tr>
<td>CVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Type of surgery refers to CABG versus, AVR and COMB

<sup>b</sup> Defibrillation after aortic cross-clamp removal

### Study III

**Clinical results**

Left atrial enlargement (antero-posterior diameter) and inotropic requirement were the only variables related to postoperative AF. A moderate relationship was demonstrated between left atrial diameter and age ($r^2=0.14$, $p=0.002$, $r=0.370$). Patients with AF showed a trend, although non-significant, towards higher age and with longer hospital stay compared with those who did not express this complication ($p=0.217$ and $p=0.101$, respectively).

**Histological results**

Patients affected by postoperative AF demonstrated an increased presence of vacuolization and interstitial fibrosis in right-atrial biopsies. Both these characteristics were detected at an equal rate of 91% in the AF group compared with 21% and 50% in the non-AF counterparts, respectively (Table 5). Myocyte nuclear derangement was also observed in AF patients (Figure 4). At multivariable analysis, myocyte vacuolization and nuclear derangement remained the only independent AF predictors (OR 17.1, 95%CI 2.1-107.8 and OR 7.8, 95%CI 1.1-41.6, respectively).

### Table 3. Percentage survival rates in the different patient subgroups, with our without postoperative AF (Study II).

<table>
<thead>
<tr>
<th>Patients</th>
<th>1 year</th>
<th>2 years</th>
<th>5 years</th>
<th>8 years</th>
<th>10 years</th>
<th>13 years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CABG group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no AF</td>
<td>98</td>
<td>97</td>
<td>92</td>
<td>84</td>
<td>78</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF</td>
<td>96</td>
<td>94</td>
<td>87</td>
<td>74</td>
<td>67</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td><strong>Valve group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no AF</td>
<td>97</td>
<td>95</td>
<td>88</td>
<td>76</td>
<td>71</td>
<td>60</td>
<td>0.001</td>
</tr>
<tr>
<td>AF</td>
<td>96</td>
<td>95</td>
<td>84</td>
<td>65</td>
<td>54</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>CABG+Valve group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no AF</td>
<td>94</td>
<td>90</td>
<td>79</td>
<td>63</td>
<td>51</td>
<td>38</td>
<td>0.018</td>
</tr>
<tr>
<td>AF</td>
<td>90</td>
<td>86</td>
<td>72</td>
<td>54</td>
<td>44</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CABG, coronary artery bypass grafting.
No histological difference were observed in relation with the revascularization technique (e.g., on-pump CABG vs OPCAB). No effects on atrial histology was inflicted by the CPB usage (e.g., on-pump CABG group). Consequently, intraoperative parameters, such as ACC duration, cardioplegia dosage, and further, right coronary grafting did not caused histological derangement.

**Study IV**

**Clinical results**

Current smokers represented 15% (n = 485) of the extracted study cohort, and demonstrated a reduced incidence of postoperative AF compared with non-smoking individuals (20% versus 27%, p < 0.001) An interaction between inotropic requirement and smoking was demonstrated at multivariable level (Table 6). On the basis of this interaction, when the analysis was restrained to patients without inotropic requirement, smoking status was revealed as an independent protector of AF following cardiac surgery (OR 0.54, 95%CI 0.34-0.87).

From the two models (e.g., with or without inotropic support considered), the predicted probability of postoperative AF was obtained. The curves describe the strong influence of age on AF occurrence, and further, show that valvular

<table>
<thead>
<tr>
<th>Variables</th>
<th>Wald X²</th>
<th>p value</th>
<th>HR</th>
<th>95% CI Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CABG group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;60y</td>
<td>231.10</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 60-69y</td>
<td>71.32</td>
<td>&lt;0.001</td>
<td>2.16</td>
<td>1.81</td>
<td>2.58</td>
</tr>
<tr>
<td>Age 70-79y</td>
<td>182.37</td>
<td>&lt;0.001</td>
<td>3.41</td>
<td>2.86</td>
<td>4.08</td>
</tr>
<tr>
<td>Age &gt;79y</td>
<td>136.31</td>
<td>&lt;0.001</td>
<td>5.73</td>
<td>4.28</td>
<td>7.69</td>
</tr>
<tr>
<td>LVF preserved</td>
<td>103.88</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reduced</td>
<td>48.51</td>
<td>&lt;0.002</td>
<td>1.52</td>
<td>1.35</td>
<td>1.71</td>
</tr>
<tr>
<td>depressed</td>
<td>85.56</td>
<td>&lt;0.003</td>
<td>2.43</td>
<td>2.01</td>
<td>2.93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>93.53</td>
<td>&lt;0.004</td>
<td>1.78</td>
<td>1.59</td>
<td>2.00</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>29.26</td>
<td>&lt;0.005</td>
<td>1.52</td>
<td>1.30</td>
<td>1.77</td>
</tr>
<tr>
<td>Inotropic drugs</td>
<td>19.24</td>
<td>&lt;0.006</td>
<td>1.33</td>
<td>1.17</td>
<td>1.51</td>
</tr>
<tr>
<td>CVA postop</td>
<td>16.62</td>
<td>&lt;0.007</td>
<td>1.66</td>
<td>1.30</td>
<td>2.12</td>
</tr>
<tr>
<td>Transfusion</td>
<td>14.27</td>
<td>&lt;0.008</td>
<td>1.25</td>
<td>1.11</td>
<td>1.40</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>13.12</td>
<td>&lt;0.009</td>
<td>1.37</td>
<td>1.16</td>
<td>1.62</td>
</tr>
<tr>
<td>CPB Weaning</td>
<td>11.24</td>
<td>0.0015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative AF</td>
<td>10.47</td>
<td>0.001</td>
<td>1.22</td>
<td>1.08</td>
<td>1.37</td>
</tr>
<tr>
<td>CPB Temp &gt;32°C</td>
<td>8.36</td>
<td>0.0015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB Temp 30-32°C</td>
<td>1.97</td>
<td>0.16</td>
<td>1.09</td>
<td>0.97</td>
<td>1.23</td>
</tr>
<tr>
<td>CPB Temp &lt;30°C</td>
<td>7.38</td>
<td>0.0015</td>
<td>1.59</td>
<td>1.14</td>
<td>2.22</td>
</tr>
<tr>
<td>Vessel disease (n)</td>
<td>4.52</td>
<td>0.033</td>
<td>1.13</td>
<td>1.01</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Table 4. Multivariate predictors of mortality for patients undergoing CABG (Study II).

<table>
<thead>
<tr>
<th>Histological variables</th>
<th>Mode of Dichotomization</th>
<th>Mean score ± SD</th>
<th>Mean score ± SD</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocyte vacuolization</td>
<td>[0/1]</td>
<td>0.21 ± 0.41</td>
<td>0.91 ± 0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>[0/1+2]</td>
<td>0.60 ± 0.71</td>
<td>0.77 ± 0.69</td>
<td>0.224</td>
</tr>
<tr>
<td>Atrophy</td>
<td>[0/1+2]</td>
<td>0.31 ± 0.51</td>
<td>0.36 ± 0.58</td>
<td>0.822</td>
</tr>
<tr>
<td>Lipofuscin</td>
<td>[0/1+2+3]</td>
<td>0.10 ± 0.31</td>
<td>0.18 ± 0.39</td>
<td>0.373</td>
</tr>
<tr>
<td>Nuclear derangement</td>
<td>[0/1+2]</td>
<td>0.15 ± 0.36</td>
<td>1.18 ± 0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>[0+1/2+3]</td>
<td>0.63 ± 0.73</td>
<td>1.91 ± 0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibroelastosis</td>
<td>[0/1+2]</td>
<td>0.60 ± 0.71</td>
<td>0.68 ± 0.84</td>
<td>0.848</td>
</tr>
<tr>
<td>Mononuclear exudate</td>
<td>[0/1+2]</td>
<td>0.06 ± 0.24</td>
<td>0.14 ± 0.35</td>
<td>0.317</td>
</tr>
<tr>
<td>Edema</td>
<td>[0/1+2+3]</td>
<td>0.17 ± 0.38</td>
<td>0.27 ± 0.46</td>
<td>0.307</td>
</tr>
<tr>
<td>Arteriolar Hypertrophy</td>
<td>[0/1]</td>
<td>0.19 ± 0.39</td>
<td>0.27 ± 0.46</td>
<td>0.422</td>
</tr>
</tbody>
</table>

*Analysis obtained by univariate logistic regression

Table 5. Histological key parameters in relation to AF at univariate level of analysis (Study III).
procedures were more likely to develop AF than after isolated CABG. Moreover, patients receiving inotropic support revealed a higher probability of AF (Figure 5A). In patients without inotropic requirement, smoking reduced the probability of postoperative AF development (Figure 5B).

![Figure 4](image) **Figure 4.** Panel A: Myofibrillar loss (vacuolization) on cross-section of right atrial tissue. Vacuolization is indicated by arrow (Hematoxylin and eosin stain, and 400X). Panel B: Severe interstitial fibrosis is indicated by letter “F” (Hematoxylin and eosin stain, magnification 200X). Panel C: Damaged myocyte appearance characterized by cytoplasmic eosinophilia and nuclear pyknotic derangement. Half-moon or sickle nuclei are indicated by arrows. (Hematoxylin and eosin stain, magnification 400X). (Study III).

**Study V**

**Clinical results**

Patients compliant to the sotalol/magnesium treatment accounted for 55% of the study population (n=27). Exclusion criteria on the first postoperative day detected a group of 29% (n=14) non-compliant patients, with an additional 16% (n=8) of patients excluded within the third postoperative day. Compliant subjects were less affected by postoperative AF compared with non-compliant patients (7.4% versus 35.7%, p=0.035) and with a non-significant trend versus control patients, (7.4% versus 24.1%, p=0.076). With an intention-to-treat policy, the overall AF incidence was 18%, which was not significant versus the control group (p=0.363). A skewing phenomenon was observed between compliant and non-compliant patients. Non-compliant subjects demonstrated longer CPB and ACC durations, and with higher pace-maker and inotropic requirements compared with compliant subjects. Non-compliant patients also had a lower body weight compared with their compliant counterparts.
<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Wald $\chi^2$</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>74.31</td>
<td>&lt;0.001</td>
<td>1.06</td>
<td>1.05 1.08</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>12.29</td>
<td>&lt;0.001</td>
<td>1.53</td>
<td>1.21 1.94</td>
</tr>
<tr>
<td>Operation type</td>
<td>9.89</td>
<td>0.002</td>
<td>1.55</td>
<td>1.18 2.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.27</td>
<td>0.012</td>
<td>1.33</td>
<td>1.06 1.67</td>
</tr>
<tr>
<td><strong>All patients with considered interaction between inotropic support and smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.05</td>
<td>&lt;0.001</td>
<td>1.06</td>
<td>1.04 1.07</td>
</tr>
<tr>
<td>Operation type</td>
<td>10.56</td>
<td>0.001</td>
<td>1.58</td>
<td>1.20 2.07</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>7.02</td>
<td>0.008</td>
<td>1.41</td>
<td>1.09 1.82</td>
</tr>
<tr>
<td>Smoking*</td>
<td>5.89</td>
<td>0.015</td>
<td>0.56</td>
<td>0.35 0.89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.81</td>
<td>0.016</td>
<td>1.32</td>
<td>1.05 1.66</td>
</tr>
<tr>
<td>Inotropic x smoking</td>
<td>4.12</td>
<td>0.042</td>
<td>2.05</td>
<td>1.03 4.11</td>
</tr>
<tr>
<td><strong>Patients without inotropic support requirement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36.18</td>
<td>&lt;0.001</td>
<td>1.05</td>
<td>1.04 1.07</td>
</tr>
<tr>
<td>Operation type</td>
<td>7.08</td>
<td>0.008</td>
<td>1.71</td>
<td>1.15 2.53</td>
</tr>
<tr>
<td>Smoking*</td>
<td>6.41</td>
<td>0.011</td>
<td>0.54</td>
<td>0.34 0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.86</td>
<td>0.028</td>
<td>1.38</td>
<td>1.04 1.83</td>
</tr>
</tbody>
</table>

*current smokers

**Table 6.** Multivariable analysis: predictors of postoperative AF (Study IV).
Atrial Fibrillation After Cardiac Surgery. An analysis of risk factors, mechanisms, and survival effects.
GENERAL DISCUSSION

Since the early 1960s, cardiac surgery has evolved with relevant improvements in surgical techniques, medications and patient care. Nevertheless, despite these significant advances in surgical care, AF remains the most frequent complication after cardiac surgery, occurring at incidence rates between 10% and 70%.\(^6,8,15,22,27,66\) Postoperative AF has a significant impact on patient recovery, increasing morbidity, with an increased use of resources, and is suggested to contribute to early and late mortality.\(^6,22,27,34,66\) As a consequence, considerable efforts have been made to identify pharmacologic agents or other strategies for reducing the incidence of this arrhythmia.\(^66,68,101\) Although no consensus has emerged regarding the etiology of postoperative AF, nor the most appropriate strategy for preventing it, many authors have advocate the perioperative use of prophylactic medications such as beta-blocker agents, amiodarone, or sotalol. Many trials, with the aim of studying pharmacologic prophylactic agents have considered only a limited number of patients, most frequently low-risk CABG patients, or have underestimated the AF incidence because of an inadequate mode of AF monitoring.\(^9,66,103\) Furthermore, a problem with the use of any such therapy is that most patients undergoing cardiac surgery do not develop postoperative AF. Thus, many patients are exposed to adverse effects of the selected therapy when they are at no or low risk for AF.\(^102\) The efficacy and the potential hazards of such therapy must be considered. Efficacy should be evaluated not only from the perspective of whether the therapy reduces the frequency of postoperative AF, but also whether patient outcomes are improved.\(^102\) However, despite the fact that many studies have been focused of postoperative AF, the exact pathophysiology of this complication has not yet been elucidated. Evidences suggest that numerous pre- and perioperative factors may substantially influence atrial conduction, and together with pre-existing atrial alterations, may synergistically contribute to explain postoperative AF.\(^106,107\)

**Risk factors associated with AF development**

Among the different identified risk factors for postoperative AF, age is the only consistently reported variable.\(^66,53,103\) Study I focused on possible effects exerted by the underlying coronary disease and their interaction with CPB. An ambition was to identify the predictive value of intraoperative variables, to better forecast AF and to find an optimal timing for AF-prophylactic stratification. Our study confirmed that age was the most important risk factor among all surgery groups. Indeed, age-induced changes of the atrial tissues may promote re-entry arrhythmias, a phenomenon that has been observed in recent studies.\(^100,104,105\) and as addressed in conjunction with study III. More importantly in study I, we demonstrated that the presence of coronary artery disease, in contrast to valvular procedures, resulted in a different profile of AF-specific risk factors. These factors were found during the period of CPB weaning. Our interpretation suggests that coronary disease superimposes risk factors with reference to myocardial conditions during the weaning period. The underlying coronary disease may therefore impair adequate perfusion and protection of the atrial tissues, also including the electrical aspects of the tissue. Atrial ischemia has been demonstrated to create a substrate for maintaining AF by slowing the conduction and favoring re-entry phenomena.\(^37\)

The importance of the factors observed during CPB weaning to explain AF development was also supported in our other studies (III-IV-V) by the recurrent AF-sensitive role of inotropic requirement. The particular importance of inotropic support in relation to AF has been previously addressed.\(^84,105\) However, to what extent inotropic support contributes to AF by the effects of the drug, or inotropic requirement mirrors a co-morbidity that explains AF is not known. The relationship between inotropes and AF suggests that sympathetic activation may play a significant role in the pathogenesis of AF after surgery. The autonomic nervous system has previously been implicated in both the initiation and perpetuation of AF.\(^41\) In the setting of increased sympathetic activity or excessive catecholamines, enhanced automaticity or triggered activity may constitute the mechanisms that initiate the fibrillation process.\(^106,107\) Our Study IV corroborates these observations. Smoking patients demonstrated a lower rate of postoperative AF compared with non-smoking individuals. Our interpretation suggests that smokers are preoperatively adopted to a higher than normal adrenergic state onto which the adrenergic stress from the surgical procedure and the effects of inotropic drugs are overlaid (Figure 6). Effects from nicotine abstinence must also be considered. Study IV, demonstrated a relevant interaction between inotropic support and smoking status. When this interference was avoided, by removing patients with inotropic requirement from the study cohort, smoking status developed as an independent and strong...
protective variable against postoperative AF. These observations underlie the importance of autonomic imbalance for AF development.

**Histological observations in relation to AF**

It is plausible to assume that pre-existing alterations in the atrial substrate contribute to the occurrence of AF. Histological alterations in the tissue may impair the electrophysiological functionality which becomes aggravated by surgical factor and perturbations. This issue was further developed in Study III. It was demonstrated that pre-existing atrial changes in histopathology were associated with postoperative AF: more specifically interstitial fibrosis, myocyte vacuolization and nuclear derangements. Our observations support that of previous studies. Atrial fibrosis has been shown to increase with age, to inflict a loss of side-to-side electrical coupling between groups of atrial muscle fibers, and to provide an arrhythmogenical substrate. Likewise, vacuolization has been demonstrated to represent an important structural alteration for the maintenance of AF. Similarly, vacuolization reflects the aging process, or develops in response to hypoxic or toxic stimuli. A “cause and effect” relationship between vacuolization and nuclear derangement has also been suggested by Ak et al., also considering the influence from atrial myocyte apoptosis as an important marker of AF susceptibility.

**Drug prophylaxis**

Numerous studies have sought to identify predictors of postoperative AF. Their number is testament to the failure of preventing this arrhythmia by prophylactic measures in unselected patients. Our Study V was conceived on the basis of the excellent results obtained by Forlani et al., which reported a consistent and marked reduction in postoperative AF with the combined prophylactic administration of sotalol and magnesium. Our study concluded that compliance phenomena must be taken into account for a prophylactic AF regimen. We observed that only about half of enrolled patients (55%) were compliant with respect to the adopted drug treatment. The non-compliant patients produced skewing phenomena to the protocol and data evaluation. Certainly, the AF occurrence in the compliant group was significantly lower compared with the non-compliant patients (7% versus 36%, respectively). However, with an intention-to-treat policy the overall AF incidence was 18%, with no difference against a contemporary control group. These observations emphasize the importance of a pre-operative risk stratification, which ideally would allow for an accurate identification of high-risk patients in whom a preventive anti-arrhythmic therapy can be justified.

**Resource utilization**

The economical impact of postoperative AF on hospital resources is substantial, with an estimated annual expenditures within the US exceeding $1 billion. Different groups reported that the length of hospitalization increased by a distressing three-to-four days in the presence of AF. Estimated charges for these additional hospital stays are in the range of between $10,055 and $11,500 per affected
Postoperative survival
It is generally believed that the risks associated with postoperative AF decrease substantially within the first month after surgery. The report by Almassi et al.\textsuperscript{22} was first to demonstrate a decreased survival in cardiac surgery patients with postoperative AF. At 6 months after surgery, the mortality was significantly higher in AF patients compared to patients without the arrhythmia (9.4\% vs 4.2\%, respectively). In Study I we came to a similar conclusion, based on 1-year survival data and using logistic regression. The influence of AF on the survival outcome was confirmed in Study II. However, in Study II the negative survival effect of AF was observed in the long-term perspective rather than in the first postoperative year. The differences between the two studies are that in Study II the statistical approach used Cox regression, and further, the parameter selection was partly restrained compared with that of Study I. More importantly, in both Study I and Study II it was demonstrated that postoperative AF was associated with decreased long-term survival in CABG patients only, but not after isolated or combined valve surgeries. These observations are in consonance with data reported by Mahoney et al.,\textsuperscript{2} and the discrepancy between types of surgery may provide essential information about AF-mechanistic details. Plausible mechanisms to support a direct effect in response to postoperative AF are that the arrhythmia induces impaired hemodynamics from a reduced ventricular filling as well as circulatory stasis in the left atrium, rendering the patients susceptible to stroke and embolic events.\textsuperscript{25,119,120} Also, a reduced cardiac output and impaired cerebral circulation predisposed patients to experience cerebrovascular thrombosis and stroke in a non-cardioembolic fashion.\textsuperscript{121}

The finding that postoperative AF did not affect survival in patients subjected to valvular surgeries is interesting. In the first postoperative years the survival rates between AF and non-AF patients undergoing isolated valve procedures were indeed identical. However, in the long-term perspective of these patients, AF appeared associated with an impaired survival at univariate mode of analysis, but this was not confirmed when the confounding effects were considered by the multivariate Cox approach. An intriguing assumption might suggest that patients operated on for valvular surgeries are subject to a better follow-up by means of echocardiographic examinations and regular clinical visits compared to coronary patients. Moreover, a subset of patients with mechanical valves are protected from embolic events by their anticoagulation therapy. The opposing interpretation implies that AF simply is a marker of comorbidities, being differently reflected in CABG patients compared with the ones receiving a valve. Hence possibly, the underlying coronary disease provokes a more complex pattern of AF mechanisms than in valve patients.

Limitations
Studies I, II, and IV had their origin in a database at a single centre, which reveals a limitation in view of their retrospective design and generalization. Although these studies were observational investigation based on prospectively collected data, a selection bias must be considered, as well as numerous of other limitations that can be assigned a clinically derived database. Another encountered limitation is the absence of continuous ECG monitoring, with a period from 48 hours postoperatively until hospital discharge during which time the AF diagnosis was less accurately defined. Although it is possible that short episodes of asymptomatic AF might have been overlooked, this is less likely for sustained episodes of AF, given the fact that patients were assessed several times each day. However, our AF prevalence is within the range reported in the majority of other studies,\textsuperscript{7,22,14,17,24} a fact in support of our data. Furthermore, our database did not include information on pre- and postoperative medication, such as beta-blocking agents. Beta-blockers were routinely administered on the day of surgery and continued in the postoperative period unless contraindicated for clinical reasons. This routine possibly reduced the limiting influence from withdrawal phenomena of these drugs.

In terms of survival, the lack of data regarding cause of death is an important limitation. Autopsy details were not available and all-cause mortality was considered only. In a similar way, the database only provided information about smoking status at admission. It is important to
recognize that cigarette smoking is a complex mixture of chemicals that includes not only nicotine, but also other potentially cardiotoxic substance. Temporal details about when smoking was interrupted and information about the number of consumed cigarettes were unfortunately absent.

Study III is limited for the small number of enrolled patients, and certainly, a larger cohort would result in a more detailed data analysis. Secondly, samples were only derived from the right atrial appendage and not the left atrial tissue. It is generally accepted that the pulmonary veins and the left atrial tissue are the most critical regions in initiating and maintaining AF. However, the ethical aspects in terms of surgical sampling and inflicted risks directed the focus onto the right atrium only, a consideration shared with previous studies in this field of science.

Study V reports the result of a pilot study, in advance of a larger randomized trial. In view of the negative findings of the pilot study the randomized trail was interrupted. Nevertheless, from the pilot study statistical findings regarding treatment compliance were extracted and the observations were compared with a matched contemporary control-group of patients. Study V is seriously limited and was not aimed to exactly evaluate the effect of the AF-prophylactic therapy. The study must be viewed against this ambition only, to describe the statistical effects from the rejection of non-compliant patients.

Clinical implications of the thesis
Postoperative AF was strongly associated with patient age. Moreover, pre-existing histopathological deterioration of the atrial tissue was associated with AF, in an age-dependent fashion. The postoperative occurrence of AF showed interference from adrenergic mechanism, and plausibly, AF reflects a hyperadrenergic state with surgical stress and administered drugs as key mechanisms. Further, in coronary patients but not after valvular procedures, intraoperative events at CPB weaning emerged as independent risk factors. These factors should be considered in an AF-preventive strategy, implying that the optimal timing for a prophylactic stratification should be formulated in the immediate postoperative period rather than preoperatively. In a prophylactic model, effects from treatment compliance should be considered in the selection of patients. Skewing from non-compliance may erroneously affect outcome parameters and statistical interpretations from the treatment. Postoperative AF is associated with mortality after isolated CABG surgery, but not after valvular procedures. Although the mechanisms are unclear in how AF interferes with survival, possibly, AF recurrence after hospital discharge should be considered, a phenomenon that indicates a strict postoperative surveillance of these patients.
CONCLUSIONS

The conclusion of the thesis were:

I. coronary disease, different from valvular procedures, superimposed additional AF risk factors with reference to the myocardial condition at CPB weaning.

II. postoperative AF impaired the late survival in patients undergoing isolated coronary surgery, but not after isolated or combined valvular procedures.

III. pre-existing histological alterations of the right-atrial tissue were associated with postoperative AF.

IV. smoking interfered with AF development, suggesting a possible influence from a hyperadrenergic state to the mechanisms of the arrhythmia.

V. the prophylactic drug regimen constituted by sotalol and magnesium in patients subjected to CABG revealed a reduce clinical compliance which must be statistically considered.
ACKNOWLEDGEMENTS

I would like to express my sincere and deep gratitude to all those who have contributed to this thesis.

My tutor and friend for many years, Professor Gunnar Engström for opening and guiding me into the scientific world. Thanks for your enthusiastic support and patience throughout this project. Thanks for the constructive discussions, statistical controversies, guidelines, and encouragements.

My Chief and second father, Professor Andrea Sala, for unending encouragement, teaching, support, and for giving me the opportunity to work and finish this thesis.

My best friend, Davide Vanoli for the outstanding and unending help in all aspects of this thesis. Thanks for the many happy times and friendship. Thanks for supporting me during my travels between Italy and Sweden.

Patrik Boivie, for his assistance during this PhD project.

Everyone in the operating theatre at the Cardiothoracic Clinic at Umeå University Hospital, for so loyally supporting my research and made me feel welcome in Sweden

Katharina Saveman, for her skillful help with the patients of Study V.

Jan Hentschel, for his expertise regarding the database at the Heart Center/Cardiothoracic Division.

My parents, Laila and Giacomo, my grandfather, Priamo, for truly supporting me every days.

My much loved and loving wife, Nicoletta. Thank you for filling my life with love and joy and meaning. I am grateful for having the privilege to share my life with you.
FINANCIAL SUPPORT AND CONFLICTS OF INTEREST

The publications within this thesis had financial support by grants from the Faculty of Medicine at Umeå University and the Heart Foundation of North Sweden. The research had no support from the industry or from any non-scientific organizations, and with no conflicts of interest.
REFERENCES


Atrial Fibrillation After Cardiac Surgery. An analysis of risk factors, mechanisms, and survival effects.


64. Fuster V, Ryden LE, Cannon DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE,
Atrial Fibrillation After Cardiac Surgery. An analysis of risk factors, mechanisms, and survival effects.


Asbo JD, Lawrence AT, Krishnan K, Kim MH, Trohman RG. Amiodarone


Atrial Fibrillation After Cardiac Surgery. An analysis of risk factors, mechanisms, and survival effects.


