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Jari Halonen

Prevention of Atrial Fibrillation After Cardiac Surgery

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EASTERN FINLAND

JARI HALONEN

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia to occur after cardiac surgery. It is associated with postoperative complications, including increased risk of stroke, prolonged hospital stay and increased costs. The purpose of this study was to find a reliable, effective, safe and well tolerated tools for the prevention of postoperative AF after cardiac surgery. The study consisted of three prospective, randomized clinical trials.

In study I we randomized 240 patients to receive either oral or intravenous metoprolol for 48 hours after cardiac surgery. The incidence of postoperative AF was significantly lower in the intravenous metoprolol group (16.8%) than in oral group (28.1%), (p=0.036). Intravenous metoprolol administration was feasible and easy and turned out to be well-tolerated in postoperative patients.

In study II a total of 241 patients were scheduled to receive either intravenous hydrocortisone or placebo postoperatively for 84 hours. The incidence of postoperative AF was 30.0 % in the hydrocortisone group compared with 47.9% in the placebo group and the relative risk reduction was 37%. Intravenous hydrocortisone therapy turned out to be well tolerated. In addition, no serious complications were associated with intravenous corticosteroid therapy.

In study III intravenous metoprolol therapy showed to be as effective as intravenous amiodarone in the prevention of AF after cardiac surgery. Three hundred and sixteen patients were randomized to receive either metoprolol or amiodarone intravenously starting on the first postoperative morning after cardiac surgery. The incidence of postoperative AF was 23.9% in the metoprolol group and 24.8% in the amiodarone group with no statistical difference between the groups. However, because of the wide range of the confidence intervals, we can not conclude that intravenous metoprolol and amiodarone are equally effective in the prevention of AF after cardiac surgery.

In summary, we suggest that intravenous metoprolol therapy should be a part of routine medication to prevent AF in all patients undergoing cardiac surgery, unless contraindicated. Moderate-dosage corticosteroid (hydrocortisone) should be considered for the prevention of AF in high risk patients undergoing cardiac surgery. Amiodarone should be used for the prevention of postoperative AF only if beta-blocker therapy is contraindicated.

National Library of Medical Classification: QV 150, WG 169, WG 330, WO 184

Medical Subject Headings: Amiodarone; Anti-Arrhythmia Agents; Aortic Valve Surgery; Arrhythmias; Atrial Fibrillation; Cardiac Surgical Procedures; Coronary Artery Bypass Surgery; Hydrocortisone; Metoprolol; Postoperative; Prevention

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TIIVISTELMÄ

Eteisvärinä on yleisin sydänleikkauksen jälkeinen rytmihäiriö. Potilailla, joille tehdään sekä ohitus- että läppäleikkaus samanaikaisesti, eteisvärinän esiintyvyys on suurempi kuin niillä potilailla, joille tehdään pelkkä sydämen ohitusleikkaus. Eteisvärinän ilmaantuvuus on suurin 2-4 leikkauksen jälkeisinä päivinä. Se on suurin ohitusleikkauksen jälkeisen aivohalvauksen aiheuttaja sydän-keuhkokonetta käytettäessä. Eteisvärinä vaatii ylimääräistä lääkehoitoa, pidentää sairaalassaoloaikaa ja lisää myös sydänleikkauksen kokonaiskustannuksia. Joillakin potilailla eteisvärinä huonontaa sydämen pumppausta ja hidastaa näin toipumista leikkauksesta.
Väitöskirjatyön tavoitteena oli selvittää ja kehittää sydänleikkauksen jälkeisen eteisvärinän estohoitoa. Tutkimus koostuu kolmesta etenevästä ja satunnaistetusta potilastutkimuksesta. Ensimmäisessä tutkimuksessa 240 potilasta satunnaistettiin saamaan joko suun kautta tai suonensisäisesti annosteltavaa beetasalpaaja metoprololia 48 tunnin ajan sydänleikkauksen jälkeen. Eteisvärinän esiintyvyys oli 16.8 % suonensisäisesti lääkettä saaneiden ryhmässä ja 28.1 % suun kautta lääkettä saaneiden ryhmässä. Ero potilasryhmien välillä oli tilastollisesti merkittävä. Suonensisäisesti annosteltu metoprololi osoittautui turvalliseksi ja hyvin siedetyksi estolääkitykseksi sydänleikkauksen jälkeisen eteisvärinän estossa.
Toisessa tutkimuksessa 241 potilasta satunnaistettiin saamaan joko suonensisäisesti annosteltavaa hydrokortisonia tai lumelääkettä 84 tunnin ajan leikkauksen jälkeen. Eteisvärinän esiintyvyys oli 30.0 % hydrokortisoni ryhmässä verrattuna 47.9 %:iin lumelääkeryhmässä. Suhteellinen riskin väheneminen oli 37 %. Hydrokortisonihoito osoittautui turvalliseksi eikä mitään vakavia haittavaikutuksia esiintynyt.
Kolmannessa potilastutkimuksessa verrattiin keskenään suonensisäisesti annosteltavaa metoprololia ja amiodaronia. Sydänleikkauksen jälkeisen eteisvärinän esiintyminen oli metoprololi ryhmässä 23.9 % ja amiodaroni ryhmässä 24.8 %. Ryhmien välillä ei ollut tilastollisesti merkittävää eroa. Tilastollisen luottamusvälin laajuuden vuoksi ei voida kuitenkaan suoraan tehdä johtopäätöstä, että hoidot olisivat olleet yhtä tehokkaita.
Kyseisten tutkimusten perusteella voidaan todeta, että suonensisäisesti annosteltava metoprololi tulisi sisältyä eteisvärinän estolääkkeenä jokaisen sydänleikkauspotilaan rutiinilääkitykseen, ellei lääkitykselle ole vasta-aiheita. Suonensisäisesti annosteltavaa hydrokortisonia on aiheellista harkita sydänleikkauksen jälkeisen eteisvärinän estossa korkean riskin potilaille. Amiodaronin käyttö sydänleikkauksen jälkeisen eteisvärinän estossa tulisi rajoittaa ainoastaan niihin potilaisiin, joille beetasalpaaja lääkitys on vasta-aiheinen.

Yleinen suomalainen asiasanasto: rytmihäiriö, eteisvärinä, sydänleikkaus, estohoito

I dedicate this thesis to my
beloved wife Aini and to
our dearest daughters
Anni-Elina and Aada-Loviisa

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Jari Halonen

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II Halonen J, Halonen P, Järvinen O, Taskinen P, Auvinen T, Tarkka M, Juvonen T, Hartikainen J, Hakala T Corticosteroids for the prevention of atrial fibrillation after cardiac surgery. A randomized controlled trial. *JAMA 297:1562–1567 2007.*

III Halonen J, Loponen P, Järvinen O, Karjalainen J, Parviainen I, Halonen P, Magga J, Turpeinen A, Hippeläinen M, Hartikainen J and Hakala T. Metoprolol versus Amiodarone in the prevention of atrial fibrillation after cardiac surgery. A randomized trial. *Ann Intern Med 153:703-709 2010.*

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Contents

Abbreviations

ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
ANP	Atrial natriuretic peptide
AVR	Aortic valve replacement
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiac Society
CK-MBm	Creatinine kinase-MB mass
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
ECG	Electrocardiography
HF	High frequency
HRV	Heart rate variability
INR	International normalized ratio
IV	Intravenous
ICU	Intensive care unit
LVEF	Left ventricle ejection fraction
LVH	Left ventricular hypertrophy
LF	Low frequency
MI	Myocardial infarction
N-ANP	N-terminal atrial natriuretic peptide
OR	Odds ratio
PO	Per oral
SD	Standard deviation
SR	Sinus rhythm
TIA	Transient ischemic attack

1 Introduction

Postoperative cardiac arrhythmias are frequent complications after cardiac and noncardiac surgery. Postoperative atrial fibrillation (AF) is the most common postoperative arrhythmia (Hollenberg and Dellinger 2000). AF complicates up to 8% of noncardiac surgery, and approximately 12% of noncardiac thoracic surgical procedures (Polanczyk et al. 1998, Vaporciyan et al. 2004).

AF is the most common arrhythmia to occur after cardiac surgery. The reported incidence varies between 5.5% and 57% and is higher after combined coronary artery bypass grafting (CABG) and valve surgery than after CABG alone (Buffolo et al. 1996, Patti et al. 2006, Cresswell and Damiano 1993, Almassi et al. 1997). AF is especially common after mitral valve surgery, occurring in as many as 64% of patients (Asher et al. 1998). Postoperative AF is the major cause of stroke after non-pump CABG (Lahtinen et al. 2004). In addition, it is associated with a need for additional treatment, prolonged hospital stay and increased costs (Creswell et al. 1993, Almassi et al. 1997, Hakala et al. 2002a).

It has been shown that prophylactic medical therapy decreases the incidence of postoperative AF after cardiac surgery. Beta blockers are recommended to be used for the prevention of postoperative AF in all patients undergoing cardiac surgery (Dunning et al. 2006). However, the bioavailability of orally administered beta-blockers is markedly reduced during the early phase after CABG (Valtola et al. 2007).

Administration of corticosteroids has been found to reduce the incidence of recurrent AF episodes in non-operative patients (Dernellis and Panaretou 2004). The effects of corticosteroid treatment on postoperative AF have been addressed in a few studies, with divergent results (Halvorsen et al. 2003, Prasongsukam et al. 2005).

Amiodarone has also been shown to be highly effective in the prevention of postoperative AF after cardiac surgery. Both oral and intravenous amiodarone are effective in AF prophylaxis (Daoud et al. 1997, Giri et al. 2001, Hohnloser et al. 1991, Guarnieri et al. 1999). However, prophylactic treatment to prevent AF with intravenous amiodarone is not cost effective if given to all patients (Mahoney et al. 2002). So far, no studies have compared the efficacy and safety of intravenous beta-blockers and amiodarone in the prevention of AF after cardiac surgery.

In this work we have sought to find an effective, safe and well tolerated prevention therapy for postoperative AF after cardiac surgery.

2 Review of the literature

2.1 GENERAL FACTS ABOUT ATRIAL FIBRILLATION

AF is classified as supraventricular arrhythmia, characterised by fast, unorganised electrical activity and mechanical contraction of the atria. The atrial frequency is very high (450-600 min) so the basic ECG line is uneven and the normal P wave cannot be distinguished. Due to the functional fluctuation of atrioventricular conduction together with high atrial rate, the electrical activation and contraction frequency of the ventricles are irregular (Raatikainen and Huikuri 2008).

Clinically, it is reasonable to distinguish five types of AF based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF.

(1) Every patient who presents with AF for the first time is considered to be a patient with first diagnosed AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
(2) Paroxysmal AF is self terminating, usually within 48 h. Although AF paroxysms may continue for up to seven days, the 48 h time point is clinically important– after this the likelihood of spontaneous conversion is low and anticoaculation must be considered.
(3) Persistent AF is present when an AF episode either lasts longer than seven days or requires termination by cardioversion, either with drugs or by direct current cardioversion.
(4) Long-standing persistent AF has lasted for ≥ 1 year when it is decided to adopt a rhythm control strategy.
(5) Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician).

Lone AF is defined as AF occurring in otherwise healthy patients aged under 60 years (Fuster et al. 2001, Kopecky et al. 1987). It occurs in fairly young patients and accounts for about 30-45% of paroxysmal and 20-25% of permanent AF (Fuster et al. 2001).

AF is the most common type of long-term arrhythmia. Its occurrence has increased rapidly during the last few years, and it has been estimated that the number of persons suffering from it will increase 2-4-fold by the year 2050 (Miyasaka et al. 2006) and that one person out of four aged over 40 years (26% of men and 23% of women) will develop AF at some point in his/her life (Lloyd-Jones et al. 2004). Men are almost two times more likely than women to develop AF (Fuster et al. 2006). The occurrence of AF varies considerably according to age and the patient's other diseases. Its occurrence increases with age. Approximately 0.4% of persons aged under 60 years and more than 10% of those aged over 75 years suffer from it. Age is in fact the most important single factor that exposes people to AF.

Among the cardiovascular risk factors associated with AF, hypertension is the most common. Diastolic dysfunction of the ventricles does not allow their normal atrial filling. The resultant back-pressure causes hypertrophy of cardiac myocytesproliferation of fibrous tissue and decreases in intercellular coupling (Aidietis et al. 2007). AF is also common in patients with coronary artery disease. However, ischemia of the atrium rarely causes AF. Patients with coronary artery disease often exhibit left ventricular dysfunction and hypertension with secondary abnormalities in the atrium (McCarthy and Kruse 2007). Structural heart disease (aortic and mitral valve disease, hypertrophic cardiomyopathy) is also strongly associated with AF (Dries et al. 1998, Olsson et al. 2006).

Of non-cardiac factors, hyperthyreosis and chronic obstructive pulmonary disease (COPD) are the most important that increase the risk of AF (Fuster et al. 2001). The role

of physical exercise is somewhat questionable. Intense cardiovascular exercise has been shown to increase the risk of AF (Karjalainen et al. 1998). On the other hand, it reduces blood pressure and can help in weight control. The acute factors triggering temporary AF are alcohol abuse, acute myocardial infarction, pericarditis, myocarditis and pulmonary embolism (Fuster et al. 2001).

Although these risk factors and the ageing of the population are essentially connected with the occurrence of AF, they only account for some of its increased occurrence. New risk factors of AF have emerged during the last few years, such as overweight, sleep apnea and metabolic syndrome. As the body mass index (BMI) increases, the occurrence of AF increases progressively. Sleep apnea increases the risk of developing AF as well (Schoonderwoerd et al. 2008).

The hemodynamic changes caused by AF are affected by irregular ventricular response, specifically too fast ventricular response and the absence of atrial contraction (Daoud et al. 1996, Clark et al. 1997). These factors reduce the heart's minute volume during AF by 20-30% as compared with sinus rhythm. If the contractility of the left ventricle is normal, this does not play a major clinical role, but in the case of compromised LV systolic or diastolic function it can lead to hemodynamic collapse (Alboni et al. 1995, Lau et al. 1990). In addition, a rapid ventricular response can lead to congestive heart failure (tachycardiomyopathy) (Shinbane et al. 1997).

AF is an important risk factor that exposes people to cardiac embolisation. The occurrence of ischemic stroke is 2-7 times higher among patients suffering from AF than in persons of the same age who are in sinus rhythm. In addition, in AF patients with rheumatic heart valve disease, the risk of an ischemic stroke increases 17-fold (Fuster et al. 2001).

Although AF per se is seldom life threatening, extensive epidemiological investigations have shown that the mortality of patients with AF is approximately two times higher than that of persons in sinus rhythm (Flegel et al. 1987, Krahn et al. 1995, Benjamin et al. 1998).

2.2 ATRIAL FIBRILLATION AFTER CARDIAC SURGERY

2.2.1 Incidence

AF is the most common arrhythmia to occur after cardiac surgery. The reported incidence of AF varies widely (between 5.5% and 57%) after cardiac surgery (Buffolo et al. 1996, Patti et al. 2006). The incidence depends on the type of surgery, the patient's profile, the definition of AF used and the type of postoperative monitoring of the patients. The incidence of AF after cardiac surgery in studies involving more than 1000 patients is presented in Table 1. Patients undergoing CABG and combined valve surgery have a higher incidence of postoperative AF than patients undergoing CABG alone (Almassi et al. 1997). It is of interest that there is a large variation in the reported AF incidence in different parts of the world: South America–17.4%, Asia–15.7%, the United Kingdom–31.6%, the USA–33.7%, Europe–34.0%, Canada–36.6%, and Central and Eastern Europe–41.6% (Matthew et al. 2004).

2.2.2 Pathophysiology

Despite the new insights that have been gained into the mechanisms of AF, no specific etiologic factor has been identified as the sole cause or perpetuator of the arrhythmia. The current evidence suggests that the pathophysiology of AF in general, as well as after cardiac surgery, is multifactorial (Kourliouros et al. 2009). It is widely accepted that the initiation and the perpetuation of AF requires a triggering factor (initiating event) and an electrophysiological substrate (perpetuation) in the atria. The substrate is an anatomical/physiological milieu in the atria which allows the wavefront to initiate AF, and the triggers are factors firing these abnormal wavefronts (Allessie et al. 2001, Jurkko 2009).

It is believed that in most cases the pathophysiological mechanism of AF is re-entry. The re-entry mechanism is facilitated when adjacent atrial regions have widely separated refractory periods. In the atrial tissue, this non-uniform dispersion of refractoriness can set up local areas of functional blocks, and the depolarizing wavefront faces both refractory and excitable myocardium. It follows that the re-entry phenomenon is possible and can lead to AF (Cox et al. 1991, Cox 1993, Konings et al. 1994). Cosio and coworkers postulated that prolonged atrial conduction may also favour re-entry, and serve as a substrate to AF (Cosio et al. 1983). The electrophysiological substrate is mandatory for the development of AF. This can explain why some patients get and some do not get AF after the same surgical procedure (Cox 1993). Findings of histopathologic abnormalities such as myolysis and lipofuscin deposition in atrial tissue biopsies before cardiopulmonary bypass in patients with postoperative AF supports this hypothesis (Ad et al. 2001).

In addition to an electrophysiological substrate, a trigger is necessary for the initiation of AF. As early as 1981 Cheung reported arrhythmogenic activity of pulmonary veins in animal models of AF (Cheung 1981). Later it has been shown in non-operative patients that pulmonary venous ectopic foci are common triggers for AF, and in some patients the arrhythmia can be cured the catheter ablation of these foci (Jais et al. 1997, Haissaguerre et al. 1998). This led to a reappraisal of the earlier anatomic work that showed that muscle sleeves extend from the left atrium to the pulmonary veins (Nathan et al. 1966). Since then, focal triggers have also been found in other areas in the atria including the superior caval vein (Tsai et al. 2000), ligament of Marshall (Hwang et al. 2000), coronary sinus ostium, crista terminalis, and the left atrium posterior and anterior free wall (Lin et al. 2003). Most commonly, the trigger exists in the pulmonary veins (more than 90%). Based on the polarity of the ectopic beats in ambulatory ECG recording, the triggering premature atrial complexes (PACs) have been reported to originate from the left atrium in 74% and from the right atrium in 15% of cases, and in 11% the origin of the premature beats could not be determined (Vincenti et al. 2006).

2.2.2.1 Atrial ischemia

It has been suggested that in cardiac surgical patients atrial ischemia plays a significant role in the development of the underlying substrate and as a triggering factor of AF. During cardiopulmonary bypass the atrial tissue is warmer than the ventricular tissue, and atrial electrical activity is often observed as a sign of inadequate atrial protection (Smith et al. 1983, Tchervenkov et al. 1983, Chen et al. 1988). Tchervenkov and coworkers showed that there is a correlation between postoperative atrial arrhythmias and persistent electrical activity (Tchervenkov et al. 1983). On the other hand, in canine heart, augmented atrial hypothermia during cardioplegia arrest had no effect on the atrial effective refractory period or on the inducibility of AF (Sato et al. 1992). Kolvekar and coworkers showed that there is a strong association between arterial insufficiency to the atrioventricular or the sinoatrial node and the incidence of AF after cardiac surgery, which suggests that atrial ischemia contributes to the the development of postoperative AF after cardiac surgery (Kolvekar et al. 1997). However, atrial ischemia cannot be the only triggering factor for AF after cardiac surgery.

2.2.2.2 Inflammation

The possible association of inflammation with postoperative atrial fibrillation after cardiac surgery is composite. Cardiac surgery itself and extracorporeal circulation are known to be associated with systemic inflammatory response (Hall et al. 1997, Wan et al. 1997), which may play a role in the development of postoperative AF. Complement, C-reactive protein complex levels, and the number of white blood cells–markers of inflammatory reaction–are higher in patients who develop AF than in those who do not (Bruins et al.1997, Lamm et al. 2006). Moreover, the efficacy of anti-inflammatory drugs such as statins and steroids in the prevention of AF supports the association between AF and inflammation (Savelieva et al. 2000).

2.2.2.3 Autonomic tone

The impact of variations in the autonomic tone on the heterogeneity of the refractoriness of atrial and action potential duration shortening has been described in animal models, suggesting a role of sympathetic and vagal stimulation in the initiation and maintenance of AF (Liu and Nattel 1997). There are some human studies on dynamic changes in autonomic tone before the onset of AF. They have demonstrated a moderate increase in adrenergic tone with loss of vagal tone (Fioranelli et al.1999, Dimmer et al. 1998), increased vagal activity (Zimmerman and Kalusche 2001, Herveg et al. 1998) or a combination of primary increase in sympathetic activity followed by vagal predominance (Bettoni et al. 2002). Kalman and coworkers showed that the mean postoperative norepinephrine level (reflecting sympathetic nervous activity) was significantly higher in patients with AF than in those without AF (Kalman et al. 1995). In another study, Hogue and coworkers asessed the autonomic balance before the onset of AF after cardiac surgery. Either low or high heart rate variability (HRV) was found before the AF episode. They concluded that in some patients high sympathetic control preceeds the onset of AF, while in others either high vagal tone or dysfunctional autonomic heart rate control contributes the AF onset (Hogue et al.1998).

In conclusion, the pathophysiology of AF after cardiac surgery is most likely multifactorial. There has to be an underlying substrate which predisposes the patient to AF, and a triggering factor which initiates the AF. This triggering factor can be surgical trauma, inflammatory reaction due to surgical trauma and cardio-pulmonary bypass (CPB), atrial ischemia or a change in the balance of cardiac autonomic regulation.

2.2.3 Risk factors

Old age also predicts AF in the general population (Feinberg et al. 1995) and it is the most often reported independent risk factor for AF after cardiac surgery. The incidence of AF after cardiac surgery increases by at least 50% per ten years of increased age (Leitch et al. 1990, Matthew et al. 1996, Almassi et al. 1997, Mahoney et al. 2002). Aging causes cardiac dilatation, myocardial atrophy, decrease of conduction tissue, and atrial fibrosis (Lie and Hammond 1998, Kizman et al. 1990). These age-related changes may be responsible for the increased risk for AF after cardiac surgery.

A preoperative history of AF is a factor which is consistently associated with the incidence of AF after cardiac surgery. Patients with previous episodes of AF appear to have an underlying substrate necessary for the development of AF, and they are thus susceptible to postoperative AF (Matthew et al. 1996, Hashimoto et al. 1991, Svedjeholm and Håkansson 2000).

Hypertension is reported to be an independent predictor of postoperative AF in many studies. This may be related to increased fibrosis and increased dispersion of atrial refractoriness (Almassi et al. 1997, Svedjeholm and Håkanson 2000, Matthew et al. 2004, Zacharias et al. 2005). On the other hand, in many well-conducted studies involving large numbers of patients, hypertension has not been found to be an independent

predictor of AF after cardiac surgery (Matthew et al. 1996, Mahoney et al. 2002, Hakala et al. 2002a, Echahidi et al. 2007).

The blood supply to the right atrium, the sinoatrial node and the atrioventricular node is conveyed mainly via the right coronary artery. It has been shown that obstructive disease of the coronary arteries supplying the sinoatrial node and atrioventricular node are more common in patients developing AF after CABG than in those who remain in sinus rhythm (Mendes et al. 1995, Kolvekar et al. 1996, Pehkonen et al. 1998). Indeed, stenosis of the sinoatrial artery or the right coronary artery has been found to be an independent predictor of AF after CABG (Al-Shanafey et al. 2001, De Jong and Morton 2000).

Some studies have found the preoperative use of digoxin to be an independent risk factor for AF after cardiac surgery (Creswell and Damiano 2001, Almassi et al. 1997, Hakala et al. 2002a). Most probably, the indication for digoxin use rather than digoxin itself explains this finding. It is apparent that digoxin has been used for heart failure and. less compellingly, for the prophylaxis of AF. The use of digoxin is often associated with sicker hearts.

Men appear more likely to develop AF after cardiac surgery than women. Sex differences in ion-channel expression and hormonal effects on autonomic tone may explain this difference between genders (Fuller et al. 1989, Aranki et al. 1996, Zaman et al. 2000, Mahoney et al. 2002). However, there are also conflicting reports in which male gender has not been an independent predictor of AF (Majahalme et al. 2002, Hakala et al. 2002a, Mathew et al. 2004, Zacharias et al. 2005, Echahidi et al. 2007).

Abrupt discontinuation of long-term beta blocker medication results in beta blocker withdrawal effects. It is characterized by increased plasma catecholamine concentration. The withdrawal effect has been proposed as a possible cause of AF after cardiac operation when beta blocker medication has been stopped at the time of surgery (White et al. 1984, Kalman et al. 1995). It has been demonstrated that the absorption of oral beta blocker therapy immediately after cardiac surgery is very poor, which may further strengthen the withdrawal effect (Valtola et al. 2007). COPD is a predictor of AF after cardiac surgery. COPD patients have frequent premature atrial contractions, which can act as triggers for the initiation of AF (Leitch et al. 1990, Creswell and Damiano 1993, Almassi et al. 1997, Ad et al. 1999, Matthew et al. 2004, Zacharias et al. 2005).

Obesity and metabolic syndrome are reported to be independent risk factors for postoperative AF after cardiac surgery. Echahidi and colleagues analyzed retrospectively a total of 5058 patients who had undergone an isolated CABG procedure. They demonstrated that obesity was a powerful and independent risk factor for the occurrence of postoperative AF in patients older than 50 years. In the younger population, obesity was not a risk factor, whereas metabolic syndrome remained an independent risk factor for postoperative AF after cardiac surgery (Echahidi et al. 2007).

Several other factors have been found independently to predict the risk of AF after CABG: impairment of left atrial function (Leung et al. 2004, Benedetto et al. 2007), left atrial enlargement (Ducceshi et al. 1999), previous myocardial infarction (Mahoney et al. 2002), resting pulse rate less than 80 beats per minute (Almassi et al. 1997), precardiopulmonary heart rate over 100 beats per minute (Matthew et al. 1996), peripheral vascular disease (Creswell and Damiano 1993), three vessel coronary artery disease (Ducceschi et al. 1999), low body mass index (Jideus et al. 2000), and large body surface area (Hakala et al. 2002a). In a study involving 4657 patients, congestive heart failure was not a predictor of postoperative AF, but it was an independent risk factor for recurrent AF after cardiac surgery (Mathew et al. 2004) The incidence and independent predictors of AF after cardiac surgery according to studies involving more than 1000 patients are presented in Table 1 and Table 2.

Concerning the intraoperative predictors of AF, the most interesting question is off-pump versus on-pump surgery. Most of the studies comparing the incidence of AF after

on-pump and off-pump CABG are retrospective and involve only small numbers of patients. Several studies have reported a lower incidence of AF after off-pump CABG than after on-pump CABG (Allen et al. 1997, Abrey et al. 1999, Ascione et al. 2000). However, several reports have found no difference between the incidence of AF after off-pump and on-pump CABG (Siebert et al. 2000, Mueller et al. 2001, Hakala et al. 2004). In a meta-analysis comparing the clinical outcome in 30 randomized trials and 3634 patients, off-pump CABG reduced the risk of AF compared to on-pump CABG significantly (RR 0.69; 95% CI 0.57-0.83) (Moller et al. 2008).

The type of cardioplegia seems not to play a role in the incidence of AF after cardiac surgery (Butler et al. 1993, Pehkonen et al. 1995). Nor does the aortic cross-clamp time seem to influence the incidence of AF after cardiac surgery, although there are some reports with conflicting results (Mahoney et al. 2002, Aranki et al. 1996).

Table 1. The incidence of AF after cardiac surgery in studies with at least 1000 patients.

Study	**Number of patients**	**Incidence of AF* (%)**
Leitch et al. 1990	5807	17
Creswell et al. 1993	2833	32
Mathew et al. 1996	2048	26
Almassi et al. 1997	3126	28
Mahoney et al. 2002	8709	18
Hakala et al. 2002	3676	31
Matthew et al. 2004	4657	32
Zacharias et al. 2005	8051	23
Echahide et al. 2007	5085	34

*AF=Atrial fibrillation

Table 2. A summary of the independent predictors of postoperative AF after cardiac surgery. References are the same as in Table 1.

Level of risk	***Risk factor for postoperative AF***
High risk	Previous episodes of AF
	Mitral valve surgery
	Combined valve and CABG surgery
	Increased age
Low risk	Male gender
	Renal failure
	COPD
	PVD
	Digoxin prior to surgery
	CHF
	Preoperative beta-blocker use
	Smoking
	Heart rate <80 or >100
	Previous myocardial infarction
	Low ejection fraction
	Large body surface area
	Beta-blocker withdrawal
	Hypertension
	Obesity
	Metabolic syndrome

AF=Atrial fibrillation

CHF=congestive heart failure

COPD=chronic obstructive pulmonary disease

PVD =peripheral vascular disease

2.2.4 Impact of atrial fibrillation on outcome after cardiac surgery

Although AF related to surgery is usually a temporary problem, it is associated with increased morbidity, increased risk of stroke and a need for additional treatment. It also prolongs hospital stay and increases costs.

The most serious complication of AF is stroke. Chung and colleagues found in their retrospective analysis of 8,389 patients undergoing cardiac surgery that postoperative AF independently increases the risk of embolic stroke 1.8-fold (Chung et al. 1995). Villareal and colleagues reported in their study of 6500 patients undergoing cardiac surgery that patients who had AF had a much higher incidence of stroke than patients who were in sinus rhythm (5.2% vs. 1.7%, respectively, p=0.001) and also an increased risk of short and long-term mortality (Villareal et al. 2004). Stamou and colleagues performed a retrospective analysis of 19,500 patients undergoing CABG. A total of 333 patients had suffered a stroke. Multivariant analysis showed that AF was an independent predictor of stroke, increasing the odds of stroke to 1.7 (Stamou et al. 2001). Two other studies indicated that the risk for perioperative stroke is 3-fold higher in patients with postoperative AF than in patients who remained in sinus rhythm (Creswell et al. 1993, Mathew et al. 1996). In a retrospective analysis of 2630 Finnish patients, 2% of those undergoing on-pump CABG suffered a stroke. The researchers concluded that AF occurring after CABG is a major determinant of postoperative stroke (Lahtinen et al. 2004).

Almassi and colleagues found that hospital mortality (8.6% vs. 3%) and 6-month mortality (9% vs. 4%) were significantly higher in patients with postoperative AF than in patients with no postoperative AF after cardiac surgery (Almassi et al. 1997). In another study, postoperative AF was associated with subsequent greater resource use as well as with cognitive changes, renal dysfunction and infection (Mathew et al. 1996). In a retrospective analysis of 3676 Finnish patients, postoperative AF was associated with increased risk of stroke, confusion, gastrointestinal complications, readmission to intensive care unit, and a longer intensive care unit stay (Hakala et al. 2002a).

The fact that postoperative AF lengthens hospital stay has been shown in many studies (Creswell and Damiano 1993, Lazar et al. 1995, Mathew et al. 1996, Aranki et al. 1996, Chung et al. 1996, Borzak et al. 1998, De Jong and Morton 2000, Hakala et al. 2002a). Furthermore, the impact of postoperative AF on the use of hospital resources is substantial and was estimated to lengthen the hospital stay by 4.9 days, with an extra cost of USD10,000-11,500 in hospitalization costs in the United States (Aranki et al. 1996). In another study, a new onset AF after cardiac surgery increased the total cost of treatment by more than USD6,000 (Hravnak et al. 2002). A third study showed that AF lengthened the hospital stay after cardiac surgery by 3.2 days, and this was independent of other variables (Tamis et al. 2000). In a study by Kim and colleagues, the impact of AF after cardiac surgery on the length of hospital stay was found to be only 1-1.5 days (Kim et al. 2001).

2.3 PREDICTING ATRIAL FIBRILLATION AFTER CARDIAC SURGERY

2.3.1 Standard 12-lead ECG

The findings concerning standard ECG as a tool for preventing the risk of AF after cardiac surgery are conflicting. Buxton and Josephson reported that patients developing AF after CABG had a significantly longer P-wave duration in standard ECG than patients who remained in sinus rhythm (Buxton and Josephson 1981). Chang and colleagues reported that the presence of prolonged P-wave duration (>100ms in lead II) was an independent predictor of AF with a 1.9-fold risk compared to a P-wave duration of less than 100 ms (Chang et al. 1999). The P-wave duration in both signal–averaged ECG and and surface ECG has been reported to be prolonged in patients who develop AF after CABG (Dimmer et al. 1998). In that study, a significant correlation was found

between the P-wave duration in standard ECG and signal-averaged ECG. In the study of Aytemir and colleagues, P-wave duration in lead II and signs of left atrial enlargement were determined from standard ECG. They found that left atrial enlargement (relative risk 2.7-fold) but not the P-wave duration was an independent predictor of AF after CABG (Aytemir et al. 1999). Passman and colleagues found that P-wave duration in lead V1 was an independent predictor of AF after CABG (Passman et al. 2001). The age-adjusted odds ratio (OR) for the development of AF was 2.30 when the P-wave duration in lead V1 was > 110 ms. Tsikouris and colleagues measured the P-wave dispersion and maximum P-wave duration in the 12 lead ECG preoperatively and on postoperative days 1- 4 in patients undergoing open-heart surgery. They found that the P-wave dispersion was greatest on days 2 and 3, and atrial conduction time was greatest on day 3 after open–heart surgery, timings that coincide with the time of greatest risk of AF (Tsikouris et al. 2001).

Stafford and colleagues analysed lead II P-wave duration, total P-wave duration, and P-terminal force in standard ECG. The total P wave duration was the time from the earliest onset of P-wave activity in any of leads I, II or III to the last P-wave activity in any of these leads. No significant differences were observed in any of these variables between patients who developed AF after CABG and those who did not (Stafford et al. 1997). Similarly, another study found no difference in the P-wave duration on standard ECG between patients with and those without AF after CABG (Caravelli et al. 2002).
In conclusion, the sensitivity and specificity of signal–averaged ECG and standard ECG in predicting the risk of AF after cardiac surgery are not sufficient. Thus, they do not play a role in clinical practice and decision making.

2.3.2 Signal average P- wave ECG

Several studies have assessed the feasibility of signal–averaged ECG in evaluating patients at high risk for postoperative AF after cardiac surgery. In particular, abnormal atrial conduction, defined by a prolonged filtered P-wave duration in signal–averaged P-wave analysis, has been shown to be an independent predictor for postoperative AF. In these studies, the abnormal P-wave duration varied from 122 to 155 ms. The sensitivity of the signal–averaged P-wave duration in identifying patients who developed AF postoperatively has been 68–86%, with a specificity of 39–88%. The positive and negative predictive values varied from 34 to 76% and from 83 to 85%, respectively (Steinberg et al. 1993, Klein et al. 1995, Zaman et al. 1997, Stafford et al. 1997, Aytemir et al. 1999, Caravelli et al. 2002, Bodeus et al. 2006, Hayashida et al. 2005).

The predictive value of the signal–averaged P-wave duration is further improved when it is combined with ejection fraction. In patients with P-wave duration >140 ms and ejection fraction <40% the risk of postoperative AF was nearly nine times higher than in patients with a normal P-wave duration and normal ejection fraction (Hutchinson et al. 1996). Similarly, the combination of P-wave duration (>155 ms) and low serum magnesium concentration (<0.7mmol) on the first postoperative day increased the positive predictive value from 37% to 62% (Zaman et al. 1997). When the P-wave duration (>122.3ms) and the precence of a right coronary artery lesion were combined, the positive and negative predictive values were 81% and 76% respectively (Aytemir et al. 1999).

2.3.3 Heart rate variability

Two studies have evaluated heart rate variability (HRV) immediately prior to the onset of AF after CABG. Dimmer and colleagues found that the low frequency/high frequency (LF/HF) ratio was initially significantly lower in the AF group compared with the SR group, but the LF/HF ratio increased before the initiation of AF in AF patients. This study showed that changes in autonomic tone rather than autonomic tone itself are important indicators of AF onset (Dimmer et al. 2003). Hogue and colleagues observed

either lower or higher measures of HRV before AF after CABG, which is consistent with divergent autonomic conditions before AF onset. They argue that in some patients, increased sympathetic tone is present before AF, whereas Hogue and colleagues reported that either high vagal tone or dysfunctional autonomic heart rate control was present before AF onset (Hogue et al.1998).

Two studies evaluated the use of 24-h preoperative Holter monitoring and the risk of postoperative AF after CABG. Frost et al. analyzed the HRV in 102 CABG patients. They calculated that the percentage of successive RR interval differences was >6% (vagal index) and found it to be significantly lower in patients developing AF, whereas the overall HRV was the same in the AF and SR groups. They concluded that an isolated reduction in the basic vagal modulation causes an autonomic imbalance in patients prone to develop AF after CABG (Frost et al. 1995). Jideus et al. found no difference in preoperative time and frequency domain variables between patients who developed AF and those who remained in SR (Jideus et al. 2001). However, they found that a diminished circadian variation in HRV before surgery indicated a propensity for AF. These studies were based on the 24-h monitoring of HRV. Long-term measures of HRV represent responses of cardiac autonomic regulation to challenges of daily life, and the interpretation of these findings is limited by the fact that these challenges are not controlled, the recordings are not stationary and the recording conditions cannot be standardized. These standardization problems could be solved by using an assessment of short-term HRV.

Hakala et al. showed that a short-term preoperative analysis of HRV under standardized physiological conditions could not reliably identify patients at high risk of AF after CABG. Heart rate, the standard deviation of normal to normal RR interval (SDNN) or the square root of the mean squared differences of adjacent RR intervals (RMSSD) did not differ significantly between the AF and SR groups when tested either with spontaneous or controlled breathing. None of the spectral analysis measures (total power, very low frequency power, low frequency power, or high frequency power) differed significantly either. In both groups, heart rate increased and SDNN decreased after tilting to the upright position, but there was no statistical difference between the groups. In power spectral analysis, total power and all of its components decreased after tilting both in the AF and SR groups but there was no statistical difference between the groups. Neither there was any statistical difference between the groups in the LF/HF ratio (Hakala et al. 2002b).

Tarkiainen and colleagues investigated whether there are constant preoperative alterations in the nonlinear R-R interval dynamics that associate with the risk of postoperative AF in patients with preserved left ventricular function. They found that preoperatively altered nonlinear R-R interval dynamics was an independent predictor of postoperative atrial fibrillation and might become a useful tool for the risk assessment of atrial fibrillation (Tarkiainen et al. 2008).

2.3.4 Left atrial enlargement

Some studies have found that left atrial enlargement predicts AF after open heart surgery. Ducceschi et al. reported that left atrial enlargement in transthoracic echocardiography was the strongest predictor of postoperative AF in CABG patients. Left atrial enlargement was defined as an anteroposterior M-mode diameter >41mm measured in the parasternal long-axis view. They found left atrial enlargement in 21% of patients who remained in SR and in 70% of patients who developed AF (Ducceschi et al. 1999). This was confirmed by Giri et al. in patients undergoing CABG, valve surgery or both (Giri et al. 2001). Asher et al. found left atrial enlargement to be an independent predictor of AF early after cardiac valvular surgery. The limit for left atrial enlargement was 40 mm in their study (Asher et al. 1998). In a prospective study by Hakala et al. left atrial enlargement was an independent predictor for postoperative AF in patients

undergoing elective CABG surgery. Each ingreasing cm^2 of left atrial area increased the risk of AF 1.29-fold (p=0.01, 95 CI 1.05-1.57) (Hakala et al. 2002c). This was confirmed in another study of CABG patients (Dogan et al. 2007). There are also some contrary findings. In two studies, left atrial enlargement was not found to be an independent predictor of AF after cardiac surgery (Stafford et al. 1997, Jideus et al. 2000). Another study by Zaman et al. did not reveal any difference in left atrium size between patients who developed AF and those who remained in SR, but their study involved only 64 patients, who were a subgroup of a larger study population (Zaman et al. 2000).

2.3.5 Natriuretic peptides

Atrial natriuretic peptides (ANP) are produced primarily in the cardiac atria, and the dominant stimulus for their release is increased atrial wall tension, reflecting increased intravascular volume. ANP is synthesised from prohormones. Endocrinological active peptide ANP and its N-terminal prohormone fragments (N-ANP) are found in plasma. Brain natriuretic peptide (BNP) is synthesised from prohormones mainly in ventricles (Levin et al. 1998). AF has been shown to be an independent determinant of high N-ANP levels, but high BNP levels are not uniquely associated with AF (Rossi et al. 2000). Longstanding AF causes depletion of N-ANP in patients with congestive heart failure. This finding suggests that longstanding AF leads to an impaired ability of the atria to produce these hormones because of the inherent degenerative processes (van der Berg et al. 2002). ANP or N-ANP levels are not predictors of conversion to SR in non-operative patients (Hornestam et al. 1998, Abrad et al. 2001). However, an elevated ANP level is an independent predictor of AF paroxysm in chronic heart failure. ANP levels higher than 60pg/ml had a hazard ratio of 8.6 for AF in 75 patients who had congestive heart failure but no previous AF (Yamada et al. 2000).

In a prospective study by Akazava et al. 150 patients without a previous history of AF undergoing elective off-pump CABG, plasma BNP levels were measured preoperatively. Twenty-six patients (17.3%) developed postoperative AF. Univariate analysis revealed that the preoperative plasma BNP level was an independent predictor of postoperative AF (Akazawa et al. 2008). In another study, 187 patients without a previous history of AF undergoing CABG were studied. Postoperative AF was documented in 80 patients (42.8%) and preoperative plasma BNP levels were higher in patients developing postoperative AF (615 vs. 444 pg/ml, P=0.005). They concluded that an elevated BNP level is a strong and independent predictor of postoperative AF (Watzni et al. 2004). However, a study of 398 consecutive patients found that the preoperative BNP level does not predict the risk of AF after CABG (Tavakol et al. 2009).

Hakala et al. studied 88 elective CABG patients, measuring N-ANP and BNP preoperatively. Thirty-one patients (35.2%) developed AF postoperatively. In the univariate analysis, atrial peptides were associated with the development of postoperative AF, but in the multivariate analysis only age and left atrial enlargement were independent predictors for postoperative AF. However, atrial peptides were associated with age, but did not independently predict postoperative AF. They concluded that the wide variation in the peptide levels renders the implementation of this measure in clinical practise superfluous (Hakala et al. 2002c).

2.3.6 Induction of atrial fibrillation

Some studies have used intraoperative screening tests to determine the risk of postoperative AF after cardiac surgery. Lowe et al. studied the value of intraoperative induction with alternating current of AF in 50 patients undergoing CABG. The intraoperative induction of AF had a sensitivity of 94%, but the specificity was only 41% for the occurrence of postoperative atrial arrhythmias. The negative and positive predictive values of the tests were 93% and 47%, respectively (Lowe et al. 1991).

In another study, a new intraoperative high-rate atrial pacing test was developed to determine the risk for postoperative AF (Hakala et al. 2002d). After cannulation but before the initiation of cardio pulmonary bypass (CPB), two pacing wires were placed on the lateral surface of the right atrium, which was paced with a rate of 200 beats per minute for 10 seconds. If this did not induce AF, high rate pacing was repeated with a rate of 250 and 300 beats per minute. This test was performed in 80 patients undergoing CABG. High rate atrial pacing induced AF in 27 patients (33.7%). Of the 28 patients who experienced AF during the postoperative period, 17 were inducible in the atrial pacing test (sensitivity 0.61). Of the 52 patients who did not develop AF postoperatively, 42 were not inducible in the atrial pacing test (specificity 0.81). The positive and negative predictive accuracy of the test were 63% and 79%, respectively. The investigators concluded that high rate atrial pacing during CABG is a safe, simple and fast method with a reasonable accuracy to predict postoperative AF (Hakala et al. 2002d).

2.4 PREVENTION OF ATRIAL FIBRILLATION AFTER CARDIAC SURGERY

2.4.1 Beta-blockers

The effectiveness of beta-blockers in the prevention of AF after cardiac surgery has been demonstrated in numerous studies. The results of four meta-analyses have shown that prophylactic beta-blocker therapy reduces the incidence of AF after cardiac surgery (Table 3). According to the meta-analysis, the type of beta-blocker or the dose have no influence on the effectiveness of the prevention.

Yaziciolglu and co-workers reported that combining digoxin with atenolol is more effective than atenolol alone (Yaziciolglu et al. 2002). The study by Balcetyte-Harris et al. compared the efficacy and safety of intravenous beta-blocker (esmolol) and oral beta-blocker (Balcelyte-Harris et al. 2002). The study was terminated when interim analysis revealed a significantly greater incidence of adverse effects in the group receiving intravenous esmolol, and the lack of any reduction in AF incidence. The efficacy and safety of intravenous propranolol was studied earlier by Abel et al. (Abel et al. 1983). They reported that propranolol was more effective in AF prophylaxis than placebo. However, a trend toward more frequent adverse effects in the propranolol treatment group was reported (Abel et al. 1983).

Valtola and colleagues evaluated the bioavailability of perioperative metoprolol tablets in CABG patients in their pharmacokinetics study. Their study showed that the bioavailability of metoprolol is markedly reduced when administered in tablet form during the early phase after CABG (Valtola et al. 2007).

In conclusion, the effectiveness of beta-blockers in the prevention of AF after cardiac surgery is confirmed. Indeed, according to the recent guideline, beta-blocking prophylaxis should be given to every patients undergoing cardiac surgery when there is no contraindications for its use.

Table 3. Beta-blockers in the prevention of postoperative AF. A summary of meta-analyses of randomized controlled trials.

Study	Number of studies	Number of patients	AF% in treatment group	AF% in control group	OR; 95% CI
Andrews et al. 1991	18	1549	9	34	0.28; 0.21-0.36
Kowey et al. 1992	7	1418	10	20	
Crystal et al. 2002	52	3840	19	33	0.39; 0.28-0.52
Burgess et al. 2006	31	4452	17	31	0.36; 0.28-0.47

AF=atrial fibrillation
CI= confidence interval
OR= odds ratio

2.4.2 Sotalol

Sotalol is a Class III antiarrhythmic agent with beta-receptor and potassium channel blocking properties. These properties theoretically prevent postoperative AF by prolonging refractoriness and blocking neurohormonal activation. The effectiveness of sotalol has been demonstrated in several placebo-controlled trials (Pfisterer et al. 1997, Weber et al. 1998, Gomes et al. 1999). The effectiveness of sotalol has also been compared with that of other beta-blockers in three randomized trials. In the trial by Parikka and coworkers, sotalol 75 mg/d was compared with metoprolol 120 mg/d in 191 patients who underwent coronary artery bypass surgery. AF occurred in 32% of the metoprolol group and 16% of the sotalol group. No proarrhythmic effects of sotalol were found during the study (Parikka et al. 1998). Similarly, Janssen and co-workers and also Suttorp and co-workers found that sotalol was more effective than metoprolol (Janssen et al. 1986) or propanolol (Suttorp et al. 1990) in the prevention of AF. Two other studies evaluated the use of sotalol as monotherapy in patients undergoing cardiac surgery (Jaguet et al. 1994, Auer et al. 2004). In these studies sotalol reduced the incidence of postoperative AF by 41-93%. A serious limitation in some of the studies was that preoperative beta-blocker therapy was not continued in the control groups, predisposing them to higher rates of AF after cardiac surgery. Forlani et al. randomized 207 concecutive CABG patients to receive either magnesium, sotalol, both magnesium and sotalol or no antiarrhythmic agents. They found that both sotalol and magnesium were effective in reducing the risk of postoperative AF, and that combination therapy of these drugs was the most effective (Forlani et al. 2003).

A meta-analysis of eight trials and 1294 patients assessed the effect of sotalol in the prevention of AF after cardiac surgery. Individual study sample size varied from 36 to 300 patients. The meta-analysis demonstrated that sotalol reduced the incidence of postoperative AF (OR, 0.35; 95% CI, 0.26-0.49) with no significant heterogeneity between trials (Crystall et al. 2002). Another meta-analysis of 14 trials compared 2583 patients receiving sotalol with 2622 patients receiving either placebo of conventional beta-blockers. Overall, AF was reduced from 33.7% to 16.9% (OR 0.37, 95% CI 0.29-0.48). On the other hand, significantly more patients were withdrawn from treatment in the sotalol groups than in the placebo groups because of side effects, predominantly hypotension and bradycardia (Burgess et al. 2006).

Sotalol is potentially a proarrhythmic agent. In non-surgical patients the proarrhythmic risk has been reported to be 4.3–5.9% (Soyka et al. 1990). Because of the potential proarrhythmic effects of sotalol, ordinary beta-blockers are considered to be a safer alternative than sotalol in the prevention of AF after surgery.

2.4.3 Amiodarone

Amiodarone is a Class III antiarrhythmic agent that inhibits multiple ion channels (potassium and calcium) and adrenegic receptors (α and β). Amiodarone has been shown to be useful in the prevention of postoperative AF. Studies in which amiodarone was given orally starting one or several days preoperatively report that the incidence of AF fell from 53% to 25% and from 38% to 22.5%, or the length of AF shortened when compared with placebo (Daoud et al. 1997, Giri et al. 2001, White et al. 2002)

The effect of intravenous amiodarone therapy has also been evaluated. In these studies the amount of amiodarone given has varied between studies. Amiodarone has reduced the incidence of AF by 25-76% compared with placebo (Hohnloser et al. 1991, Guarnieri et al. 1999, Lee et al. 2000, Giri et al.l 2001,Yazigi et al. 2002).

A few studies have not found amiodarone to be effective in the prevention of AF after cardiac surgery. However, the number of patients has been small in these studies and they are underpowered to draw any conclusion (Redle et al. 1999, Dörge et al. 2000, Treggiari-venzi et al. 2000).

A meta-analysis of 9 randomized trials showed that amiodarone therapy decreased the incidence of AF from 37% to 22.5% (Crystal et al. 2002). However, amiodarone was not found to be a cost-effective alternative for all patients undergoing coronary artery bypass surgery. In contrast, elderly patients, patients with COPD and patients undergoing both bypass and valvular surgery possibly benefit from amiodarone (Mahoney et al. 2002). Other meta-analyses have also examined the feasibility of amiodarone in the prevention of AF after cardiac surgery (Burgess et al. 2006, Aasbo et al. 2005, Gillespie et al. 2005, Patel et al. 2006). Aasbo and colleagues combined the data of 10 trials and reported a significant reduction in the incidence of AF or flutter (RR 0.64; 95% CI 0.21 to 0.76) with amiodarone therapy versus placebo (Aasbo et al. 2005). The length of hospital stay was also significantly reduced with amiodarone. Gillespie et al. reported in their meta-analysis of 15 trials a 50% reduction in postoperative AF with amiodarone treated patients versus placebo treated patients (Gillespie et al. 2005). The type of surgery, use of beta-blockers, and route of the amiodarone administration did not have signifcant effects on the overall results of the analysis.

The safety of amiodarone was evaluated in a meta-analysis of 18 randomized controlled trials and 3408 patients (Patel et al. 2006). The authors reported that the use of amiodarone was associated with increased risk of bradycardia and hypotension, although the risk of heart block, nausea, and myocardial infarction was not significantly increased. The rates of bradycardia and hypotension were higher in studies using intravenous amiodarone than in those using oral amiodarone. Table 4 presents the results of meta-analyses of amiodarone in the prevention of AF after cardiac surgery.

Amiodarone cannot be recommended to be given routinely to all patients undergoing heart surgery. On the other hand, according to the guidelines amiodarone therapy can be considered for patients who are at an especially high risk (old patients, previous episodes of AF, valve surgery) for developing AF postoperatively (Dunning et al. 2006).

Table 4. Amiodarone in the prevention of atrial fibrillation after cardiac surgery. Meta–analyses of randomized controlled trials.

Study	Number of studies	Number of patients	AF in treatment group %	AF in placebo group %	OU ; 95% CI
Crystal et al 2002	9	1384	22.5	37.0	0.48 (0.37-0.61)
Aasbo et al 2005	10	1744	22.2	34.7	0.64 (0.55-0.75)
Gillespie et al 2005	15	1512	19.9	32.9	0.50 (0.42-60.0)
Burgess et al 2006	18	3295	19.8	33.2	0.48 (0.40-0.57)

2.4.4 Magnesium

Low serum magnesium level is common after cardiac surgery (Fanning et al. 1991, England et al. 1993). Low magnesium concentration is also an independent determinant of AF after CABG (Treggiari-Venzi et al. 2000, Zaman et al. 1997). Moreover, this association has been noted even when serum magnesium concentrations do not correlate with intracellular or myocardial magnesium concentrations (Reinhart 1991).

Administration of intravenous magnesium has been shown to decrease the incidence of AF after cardiac surgery (Fanning et al. 1991, Colguhoun et al. 1993, Wistbacka et al. 1995, Toraman et al. 2001, Wilkes et al. 2002 Jensen et al. 1997). In a randomized study in which patients received either magnesium 178 mEq or placebo for 4 days following surgery, the incidence of AF was lower in the magnesium group than in the placebo group (Fanning et al. 1991). Wistbacka and co-workers evaluated the role of magnesium dosage in the prevention of AF. In the high dose magnesium group (4.2 g before surgery, 11.9 g infusion by the morning of the first postoperative day and 5.5 g on the following day) the incidence of AF was lower than in the low dose group (4.2 g, 2.9 g, 1.4 g). Magnesium concentration was also normal in patients receiving the low dose magnesium (Wistbacka et al. 1995). In a trial in which 200 CABG patients were randomized to receive either 6 mmol/days of magnesium or placebo on the day before surgery and the first four days after surgery, the incidence of AF was only 2% in the magnesium group, but 21% in the placebo group (Toraman et al. 2001). In contrast, Jensen and co-workers found that magnesium decreased the duration of AF and flutter, but did not decrease the incidence of AF (Jensen et al. 1997). In a retrospective study patients undergoing off-pump CABG who received magnesium were less likely to experience postoperative AF than control patients (12% vs. 29%, respectively) (Maslow et al. 2001).

Negative studies about the preventive effect of magnesium on postoperative AF have also been published. In a study by Parikka, 70 mmol of magnesium was given during the first 48 h after surgery. Magnesium did not reduce the incidence of AF, and surprisingly a high serum magnesium level was found to increase the incidence of AF (Parikka et al. 1993). Another study in which 14.4 g of magnesium was given during the first 24 h postoperatively found no effect of magnesium on the incidence of supraventricular tachycardias (Karmy-Jones et al. 1995).

In a meta-analysis of 20 studies and 2490 patients, magnesium decreased the incidence of postoperative atrial fibrillation from 28% to 18% (Miller et al. 2005). The effectiveness

of magnesium has been shown also in other meta-analyses (Shiga et al. 2004, Alghamdi et al. 2005).

In conclusion, it seems that magnesium reduces the risk of AF after cardiac surgery. The optimum dose remains to be determined. There is no evidence that magnesium would be of benefit for patients who already are on beta-blocker medication.

2.4.5 Corticosteroids

Cardiac surgery with extracorporeal circulation is known to be associated with systemic inflammatory response (Hall et al. 1997, Wan et al. 1997), which may be in part responsible for postoperative AF. Complement, C-reactive protein complex level, and number of white blood cells (markers of inflammatory reaction) are increased in patients who develop AF (Bruins et al. 1997, Lamm et al. 2006). Corticosteroids have anti–inflammatory activity and reduce exaggerated inflammatory reaction (Brunton et al. 2006). Prospective randomized trials in non-operative patients have reported that corticosteroid therapy reduces the risk of recurrent and permanent AF in patients converted from their first episode of AF (Dernellis and Panaterou 2004).

The effects of corticosteroid treatment on postoperative AF have been addressed also in two randomized controlled trials with postoperative AF as the primary end point. The study by Prasongsukarn et al. studied 86 patients scheduled for CABG surgery who were administered 1000 mg of methylprednisolone or placebo before surgery and 4mg of dexamethasone or placebo every 6 hours for 24 hours after surgery. The postoperative incidence of AF was significantly lower in the corticosteroid group than in the placebo group (21% vs. 51%, respectively) (Prasongsukarn et al. 2005). Halvorsen et al. administered 4mg of dexamethasone or placebo after induction of anesthesia and on the first postoperative morning in 300 patients undergoing CABG surgery. They failed to demonstrate the reducing effect of corticosteroid on the incidence of postoperative AF (Halvorsen et al. 2003).

Two other studies deserve to be mentioned. Rubens et al. enrolled 68 patients undergoing CABG and randomized them to 1000 mg intravenous infusion of methylprednisolone or placebo before the surgery. Methylprednisolone was found to have a statistically significant inhibitory effect on the incidence of postoperative AF (12% in the treatment group vs. 34% in the placebo group) (Rubens et al. 2005). Yared et al. studied 235 patients scheduled for CABG or valve surgery. The patients were given a single dose of 0.6 mg/kg of dexamethasone or placebo after induction of anaesthesia. Compared with the placebo group, the dexamethasone group had a lower incidence of postoperative AF (19% vs. 32%, respectively) (Yared et al. 2000). However, in these trials, postoperative AF was not a primary end point and they had no prospective definition of AF. Thus, these studies were not primarily designed to address the effect of corticosteroids on postoperative AF, but on the activation of inflammatory and coagulation pathways and recovery from cardiac surgery.

A meta-analysis analyzed the effect of perioperative corticosteroid use on the incidence of AF after cardiac surgery. Nine studies with 990 patients were included in the meta-analysis, and it was found that corticosteroids significantly lowered patients` odds of developing postoperative AF by 45% (OR 0.55; 95% CI 0.39-0.78) (Baker et al. 2007). Another meta-analysis of 50 randomized controlled trials and 3323 patients reported that corticosteroid prophylaxis reduced the risk of AF (RR 0.74;95% CI 0.63-0.86, $p<0.01$) (Ho and Tan 2009). A third meta-analysis consisting of 44 trials and 3205 patients confirmed that steroids reduced new onset AF (RR 0.71; 95% CI 0.59-0.987).

2.4.6 Statins

A few studies have reported the use of statins in relation to the development of postoperative AF. The main limitation of these statins studies are that many of them are non–randomized and based on different kind of registry analyses. Numerous mechanisms

have been proposed to explain a possible protective effect of statins in the prevention of postoperative AF after cardiac surgery including antioxidant effects, direct antiarrhythmic effects mediated through cell membrane stabilization, protection of ischemic myocardium, and anti–inflammatory effects (Marin et al. 2006, Patti et al. 2006, Kostapanos et al. 2007, Chello et al. 2006, Pretorius et al. 2007). Although the precise mechanisms by which statins may prevent AF have not yet been identified, it is likely that the effects are multifactorial.

The ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrythmia after cardiac surgery) was the first randomized and placebo controlled trial on statin, it showed a significant decrease in AF incidence in atorvastatin treated patients. Postoperative AF occurred in 35 (35%) of 101 patients in the atorvastatin group vs. 56 (57%) of 99 patients in the placebo group. Also the postoperative hospital stay was significantly lower in the atorvastatin group compared with placebo group (6.3±1.2 vs 6.9 ±1.4 days) (Patti et al .2006).

In an observational study of 362 patients (267 on and 95 not on statin medication) the postoperative AF was less frequent and its duration was shorter in the statin group compared to the non–statin group (8.2% vs. 16.8%, respectively). One important limitation of this study was that the recognisation of AF episodes was not based on continuously ECG recording (Ozaydin et al. 2007). In another study of 234 patients undergoing CABG, 28.2% experienced postoperative AF. Multivariante analysis found that the risk of postoperative AF was decreased with statin use (OR 0.52; 95% CI 0.28-0.96, $p<0.01$). However, there were some remarkable limitations of this study; it was retrospective, included patients with previous history of AF and various statin regiments were used and also the study population was too small to conclude the exact effect of statins in the prevention of AF after cardiac surgery (Marinet al. 2006). A retrospective analysis on statins and postoperative AF among patients receiving amiodarone and beta blocker therapy prophylactically showed that adjunctive statin pre–treatment decreased postoperative AF by 40% (Lertsburaba et al. 2008). Mariscalco and colleagues studied 405 patients undergoing isolated CABG procedures. Postoperative AF occurred in 29.5% of the patients with preoperative statin therapy compared with 40.9% of those patients without statin use ($p=0.017$). Overall, preoperative statin use was associated with a 42% reduction in the risk of postoperative AF (Mariscalco et al. 2007).

Nonetheless, there are also negative studies showing minimal or no benefit of statins in the prevention of postoperative AF. Vrani et al. studied a total of 2096 patients undergoing cardiac surgery, including isolated valve surgery and patients with low ejection fraction. AF occurred in 31.4% in both the statin and non–statin groups. However, this study was retrospective, patients having received different doses of several statins, and also the data concerning duration of statin use prior to cardiac surgery were incomplete (Vrani et al. 2008).

2.4.7 Other medical therapy

Digoxin has not been found effective in the prevention of postoperative AF (Andrews et al. 1991, Kowey et al. 1992, Tyras et al. 1979). Verapamil also seems to be ineffective (Andrews et al. 1991). Intravenous diltiazem has been compared with intravenous nitrate in the prevention of AF in four different studies (Hannes et al. 1993, Seitelberger et al. 1994, El–Sadek and Krause 1994, Malhotra et al. 1997). In these studies diltiazem turned out to be more effective than nitrates. On the other hand, no placebo–controlled trials with diltiazem have been carried out. According to a meta-analysis by Wijeysundera et al., diltiazem has no significant effect on supraventricular tachycardias (SVT) after cardiac surgery (OR 0.73) 95% CI 0.48–1.12. A subgroup analysis in a meta–analysis of calcium channel blockers found that non–dihydropyrinines significantly suppressed post–surgery supraventricular arrhythmias (OR 0.62. 95% CI 0.41–0.93), but with a high heterogeneity (Wijeysundera et al. 2003). In one randomized controlled trial

triiodothyronine was found to decrease postoperative AF in patients who had a low left ventricular ejection fraction (Klemperer et al.1996).

Anglade et al. demonstrated that the preoperative use of thiazolidinediodine, which has some anti-inflammatory properties in diabetic patients undergoing cardiac surgery, was associated with a 20% reduction in postoperative AF, but it did not reach statistical significance due to the study being underpowered (Anglade et al. 2007).

A large prospective observational study of 4657 patients undergoing cardiac surgery demonstrated that postoperative use of angiotensin-converting enzyme inhibitor (ACEI) reduced the incidence of postoperative AF after cardiac surgery (OR, 0.62; 95% CI, 0.48-0.79) (Matthew et al. 2004). Negative studies about the preventive effect of ACEIs and angiotensin receptor blockers (ARB) on postoperative AF have also been published. Coleman and colleagues performed a single center, retrospective study of 1469 matched patients undergoing cardiac surgery. They found that postoperative ACE inhibitor use was not associated with a reduction of postoperative AF after cardiac surgery (OR 0.95; 95% CI 0.57-1.56) (Coleman et al. 2007). Similarly, data extracted from two randomized controlled trials (AFIST II and AFIST III) showed that preoperative use of ACE inhibitors or ARB was not associated with a significant reduction in postoperative AF (OR 0.71; 95% CI 0.42-1.20) (White et al. 2007).

In a prospective trial with 160 patients, the efficacy of preoperative and postoperative treatment of n-3 polyunsaturated fatty acid (PUFA) were assessed. The incidence of postoperative AF was lower in the PUFA group than in the control group (15% vs. 33%, respectively, $p = 0.013$) (Calo et al. 2005). The effect of a new antiarrhythmic agent, dronedarone, has not been assessed in the prevention of AF after cardiac surgery. The efficacy of omega-3 fatty acids for the prevention of recurrent AF has been studied in non-operative patients, but not in the prevention of AF after cardiac surgery (Kowey et al. 2010).

2.4.8 Atrial pacing

The effectiviness of atrial pacing in the prevention of AF occurring after cardiac surgery has been investigated in many studies. Gerstenfeld et al. demonstrated that biatrial and right atrial pacing were well tolerated and safe (Gerstenfeld et al.1999). In another study they found that biatrial pacing combined with beta blockers decreased the incidence of postoperative AF. Patients older than 70 years especially seemed to benefit from the combination treatment (Gerstenfeld et al. 2001). In a randomized trial of 154 patients, dynamic right, left and biatrial pacing decreased the incidence of AF compared with the control group (Greenberg et al. 2000). Correspondingly, in another study dynamic right atrial overpacing decreased postoperative AF after cardiac surgery (Blommaert et al. 2000). In a study comparing the location of atrial pacing, biatrial pacing was more effective than right or left atrial pacing (Fan et al. 2000). The effectiviness of biatrial pacing in the prevention of postoperative AF has also been reported by Levy et al. (Levy et al. 2000). In their prospective study with 118 patients, biatrial pacing but not right or left atrial pacing decreased the incidence of postoperative AF (Daoud et al. 2000).

In a randomized trial of 100 patients, AAI pacing (pacing cut-off 10 beats above the normal pulse rate) was compared with no pacing. No difference was found between the groups. Instead, more atrial premature contractions were found in the pacing group (Chung et al. 2000). In another study by Kurz et al., biatrial pacing was compared with pharmacological treatment in the prevention of atrial fibrillation. The trial was terminated early because of proarrhytmias in the pacing group (Kurz et al.1999). In a study by Hakala et al., dynamic right atrial overpacing or prevention of bradycardia did not decrease the incidence of postoperative AF (Hakala et al. 2005).

Two meta-analyses have investigated the effect of pacing on AF incidence after cardiac surgery. In a meta-analysis by Chrystall et al., 10 studies and 1473 patients, three different methods of atrial pacing (right, left and biatrial) were compared. Only biatrial

pacing was shown to decrease the incidence of postoperative atrial AF (Crystal et al. 2002). Similiarly, another meta-analysis by Burgesset et al. showed that only biatrial pacing had a significant effect in reducing the incidence of AF from an average of 35.3% in the control group to 17.17% in the paced group (OR 0.44, 95% CI 0.31–0.64) (Burgess et al. 2006).

2.4.9 Posterior pericardiotomy

The concept of opening the posterior pericardium to prevent atrial fibrillation is based on the assumption that this would decrease the accumulation of pericardial fluid postoperatively. The posterior pericardium is usually opened with a 4 cm longitudinal incision. Mulay and colleagues were the first to report the effectiviness of this procedure in the prevention of postoperative AF (Mulay et al. 1995). They found that the occurrence of a significant accumulation of pericardial fluid on echocardiogram decreased from 40% in the control group to 8% in the intervention group. At the same time, the incidence of supraventricular tachyarrhythmias decreased from 36% to 8%. Two other randomized trials have also found that posterior pericardiotomy decreases the incidence of postoperative AF (Farsak et al. 2002, Kuralay et al. 1999).

In contrast, in a prospective, controlled trial of 100 patients, posterior pericardiotomy had no effect on postoperative atrial fibrillation (Asimakopoulos et al. 1997). Thus, the role of posterior pericardiotomy in the prevention of AF remains unclear.

2.4.10 Other possible useful strategies

Oxidative stress has been suggested to have a role in the pathogenesis of AF, and some trials have tested antioxidative agents for the prevention of postoperative AF after cardiac surgery. Ozaydin et al. studied in their prospective, randomized, double blind and placebo controlled study with 115 patients the effect of N-Acetylcysteine on postoperative AF. The incidence of AF was significantly lower in the treatment group than in the placebo group (Ozaydin et al. 2008).

In another study Carnes et al. tested the hypothesis that perioperative oxidative stress has a significant role in the etiology of AF. Of the patients treated with ascorbate, 16.3% developed AF or flutter, compared with 34.9% in the control group, the difference beeing statistically significant (Carnes et al. 2001).

The American College of Chest Physicians guidelines also recommend mild hypothermia, the use of posterior pericardiotomy and heparin-coated CPB circuits as possible intraoperative preventive strategies for the reduction of AF following cardiac surgery (Creswell et al. 2005). However, robust evidence for these strategies is more limited.

2.4.11 Comparison of different prevention modalities

A number of studies of the prevention of AF after heart surgery have been published. However, not many of them have compared different prophylaxis methods.

In a prospective, randomised, double-blind and placebo-controlled study, 253 patients were randomized to receive orally administered amiodarone and metoprolol, only metoprolol and only sotalolol or only placebo. In patients receiving the combination medication (amiodarone + metoprolol) and patients receiving sotalolol, the occurrence of atrial fibrillation decreased from 53.8% in the placebo group to 30.2% and 31.7%, whereas in the metoprolol group its occurrence was 40.3%. Treatment effects did not differ significantly between the active drug groups (Auer et al. 2004).

Cardona and colleagues, in turn, compared right atrial pacing, intravenously administered amiodarone and orally administered beta-blocker medication with regard to preventing atrial fibrillation after heart surgery and the duration of hospital stay. However, the sample size was too small for any conclusions to be drawn from their results (Cardona et al. 2003).

Wurdeman et al. compared in their meta-analysis the effectiviness of amiodarone and sotalol in the prevention of AF after cardiac surgery. Ten randomized and controlled trials with 1303 patients were included in the meta-analysis. Both amiodarone and sotalol were more effective than placebo treatment in the prevention postroperative AF. There were no differences between amiodarone and sotalol (sotalol -21.5%; 95% CI -28.3 to -14.6, and amiodarone -14.1; CI -20.1 to -8.1) (Wurdeman et al. 2002).

,Iin their meta-analysis Zimmer and colleagues studied 13 trials and 1783 patients. In this meta-analysis the efficacy of amiodarone, sotalol, pacing and amiodarone were compared. They did not find any difference between these treatment modalities as regards the efficacy of AF prophylaxis (Zimmer et al. 2003).

In another meta-analysis by Crystal et al., 52 randomized trials of beta-blockers, sotalol, amiodarone or pacing were studied in the prevention of AF after cardiac surgery. Each of the three drug treatments were effective in the prevention of AF, with the following odds ratios: sotalol, 0.35 (95% CI 0.26–0.49), beta-blockers, 0.39 (95% CI 0.28–0.52) and amiodarone, 0.48 (95% CI 0.37–0.61). Pacing was also effective: for biatrial pacing the OR was 0.46 (95% CI 0.30–0.71). They concluded that beta-blockers, amiodarone and sotalol all reduced the risk of postoperative AF after cardiac surgery, with no marked difference between them (Crystal et al. 2002).

In their meta-analysis Burggess et al. analyzed 94 trials using beta-blockers, sotalol, amiodarone, magnesium, overdrive pacing, digoxin, and calcium channel blockers in the prevention of AF after cardiac surgery. Amiodarone, sotalol, beta-blockers, magnesium and atrial pacing were effective in the prevention of AF after cardiac surgery. However, they concluded that the effect of beta-blockers is less than previously thought (Burgess et al. 2006).

2.4.12 Impact of prevention on outcome after cardiac surgery

Beta-blockers, sotalol, amiodarone, bi-atrial pacing and magnesium are effective in the prevention of AF after cardiac surgery. In a meta-analysis of 52 prospective randomized trials, the preventive strategy of AF reduced the length of hospital stay by somewhat less than half a day: conventional beta-blockers or sotalol did not significantly reduce the length of hospital stay. Amiodarone reduced the length of hospital stay significantly by 0.91 days. The incidence of stroke was not reduced by AF prophylaxis in this meta-analysis (Crystal et al. 2002). Another meta-analysis comparing AF prophylaxis (amiodarone, sotalol, pacing and procainamide) with placebo involved 13 trials and 1783 patients. The results revealed a decrease in the length of hospital stay by 1.0 ± 0.2 days with the various modalities of antiarrhythmic prophylaxis. However, there was no significant reduction in the cost of the treatment. In addition, the maintenance of sinus rhythm did not decrease the incidence of stroke (Zimmer et al. 2003).

A recently published meta-analysis of 49 prospective randomized trials assessed the efficacy of conventional beta-blockers, amiodarone, sotalol, magnesium and atrial pacing in the prevention of AF after cardiac surgery. Only amiodarone and atrial pacing significantly reduced the length of hospital stay (-0.60 days, 95% CI -0.92 to -0.29, and -1.3 days, 95% CI -2.55 to -0.08, respectively). Collectively, all treatments analysed together also reduced the incidence of stroke (OR 0.63, 95% CI 0.41-0.98). Amiodarone was the only intervention that alone reduced the risk of stroke (OR 0.54, 95% CI 0.30-0.95) (Burgess et al. 2006).

2.5 TREATMENT OF ATRIAL FIBRILLATION AFTER CARDIAC SURGERY

Spontaneous conversion of AF to sinus rhythm (SR) after cardiac surgery is common. Altogether 15% of patients converted to SR within two hours (VanderLugt et al. 1999) and 80% within 24 hours (Cochrane et al. 1994) when either placebo or digoxin was given.

Two management strategies are available to treat AF after CABG: rate control and rhythm control. In addition, anticoagulant therapy is used to reduce the risk of embolic complications (Ommen et al. 1997). There are no specific guidelines about when anticoagulant therapy should be started in patients who develop AF after CABG. Two reviews recommend anticoagulant therapy with heparin and warfarin if AF persist for more than either 24 hours (Ommen et al. 1997) or 48 hours (Maisel et al. 2001). The American College of Cardiology, the American Heart Association and the European Society of Cardiology have published joint guidelines for the management of patients with AF (Camm et al. 2010). The guidelines recommend managing patients with postoperative AF in a similar fashion to AF in non-surgical patients. They recommend the use of anticoagulant treatment with heparin or warfarin with a target INR 2.0–3.0 in high risk patients if AF persist more than 48 hours. In addition, in higher risk patients, even if sinus rhythm returns, warfarin should be continued for 4 weeks as there is a delay in the return of atrial contractility after a period of AF (Daoud et al. 2004).

Initial managements includes the correction of predisposing factors (such as pain management, haemodynamic optimization, weaning of i.v. inotropes, correcting electrolytes and metabolic abnormalities, and addressing anaemia or hypoxia) where possible (Camm et al. 2010). Beta blockers are considered to be the first-line therapy for rate control when ventricular response is rapid (Andrews et al. 1991). Digoxin slows down the ventricular response at rest, but seldom adequately when sympathetic tone is high. When beta blockers alone inadequately control the heart rate, calcium channel blockers may be administered to achieve adequate rate control (Maisel et al. 2001). Infusion of amiodarone can also be used for rate control of AF (Cochrane et al. 1994).

Early electrical cardioversion may be necessary in hemodynamically compromised patients. Unfortunately, AF tends to relapse after cardioversion (Ommen et al. 1997, Camm et al. 2010). Reports on the use of various antiarrhythmic drugs to restore SR in patients with AF after CABG show diverse results. This is partly due to the spontaneous restoration of SR. Some of the drugs (dofetilide, procainamidi, intravenous quinidine) are not available in many countries, including Finland. When antiarrhythmic therapy is indicated, drug-induced proarrhythmia should be avoided. Patients with a history of myocardial infarction, reduced ejection fraction, or high age are at a particularly high risk for proarrhythmias (Friedman and Stevenson 1998).

The efficacy of flecainide, a class IC antiarrhythmic agent for converting AF to SR after cardiac surgery, has been shown (Cavaghan et al. 1988, Wafa et al. 1989). Since flecainide increases mortality after myocardial infarction, this drug should not be the first choice for long-term oral therapy in patients with postoperative AF (Ommen et al. 1997). Another drug with class III antiarrhythmic properties, sotalol, led to conversion to SR in 85% of patients in 12 hours (Campbell et al. 1985). Ibutilide, a class III antiarrhythmic agent, given intravenously converted 44% of AF patients to SR after cardiac surgery, compared with 15% of patients who were given placebo, but ibutilide infusion was associated with an up to 3% risk of torsades de pointes proarrhythmia (Vander Lugt et al. 1999). Less than 10% of patients with postoperative AF after CABG who are discharged in sinus rhythm will have recurrent AF in six weeks after discharge, and prophylactic treatment with calcium-channel blockers, quinine, or amiodarone after discharge does not reduce the rate of recurrence (Yilmaz et al. 1996).

Intravenous amiodarone therapy converts AF to SR within 12 to 24 hours in 40% to 90% of patients, and amiodarone therapy provides effective rate control (McAlister et al. 1990, Cochrane et al. 1994).

In the prospective, randomized and placebo-controlled trial by Kowey et al., vernakalant was effective in treating patients with postoperative AF after cardiac surgery. Vernakalant converted AF to sinus rhythm in 47 of 100 patients, compared with 7 of 50 patients in the placebo group (Kowey et al. Circulation 2009).

Overall, although many antiarrhythmic options are available to convert AF to SR after

CABG, the combination of reasonable efficacy and low risk of proarrhythmia favours amiodarone as the drug of choice for patients requiring antiarrhythmic drug treatment (Ommen et al. 1997).

3 AIMS OF THE PRESENT STUDY

The overall aim of this study was to evaluate different pharmacological methods in the prevention of AF after cardiac surgery.

The specific aims were:

1. To test whether intravenous metoprolol after cardiac surgery is more effective than oral metoprolol in the prevention of AF.

2. To test whether intravenous corticosteroid administration is effective in the prevention of AF after cardiac surgery.

3. To compare the efficacy of intravenous metoprolol and intravenous amiodarone in the prevention of AF after cardiac surgery.

4 PATIENTS AND METHODS

4.1 PATIENTS

4.1.1 Study I

This study took place at Kuopio University Hospital. From September 2004 to August 2005, 240 consecutive patients who were scheduled to undergo their first on-pump CABG, aortic valve replacement or combined aortic valve replacement and CABG were enrolled in the study. The exclusion criteria were previous episodes of AF or flutter, sick sinus syndrome, II- or III-degree atrioventricular block and uncontrolled heart failure. Patients were also excluded if they had had AF before the first postoperative morning and if they had to stay in the intensive care unit beyond the first postoperative day. Patients were also excluded if the systolic pressure was < 100mmHg, if the pulse rate was < 60 beats per minute (bpm) at the time of randomization, or if temporary pacing was not functioning properly, when tested before randomization. The reasons for exclusion and numbers of enrolled patients who were excluded before randomization were as follows: experiencing AF before first postoperative morning (three patients), staying in the intensive care unit longer than one day (18 patients), pulse rate <60 bpm (12 patients), systolic pressure less than 100 mmHg (17 patients), inaccurate function of temporary pacemaker (11 patients), new II- or III-degree atrioventricular block (15 patients), operation was unexpectedly performed off-pump (seven patients), mitral valve repair (two patients), and replacement of ascending aorta (two patients). Also, two patients died before the first postoperative morning. The study protocol was approved by the local ethics committee, and all patients gave informed consent.

4.1.2 Study II

The study took place at Kuopio University Hospital, Oulu University Hospital and Tampere University Hospital. From August 2005 to December 2006, 241 consecutive patients scheduled to undergo their first on-pump CABG, aortic valve replacement or combined aortic valve replacement and CABG were enrolled in the study. The exclusion criteria were previous episodes of AF or flutter, uncontrolled diabetes mellitus, systemic bacterial or mycotic infection, active tuberculosis, Cushing's syndrome, psychotic mental disorder, Herpes Simplex keratitis or renal insufficiency (serum creatinine exceeding 200 μg/ml). Patients were also excluded if they had a history of previous peptic ulcer or thrombophlebitis. Altogether 650 eligible CABG, AVR of combined CABG+AVR were screened for the study. The most common reason for exclusion was that the operation was performed off-pump. The study flow diagram is presented in Figure 1. The study protocol was approved by the Kuopio University ethical committee, and all patients gave informed consent.

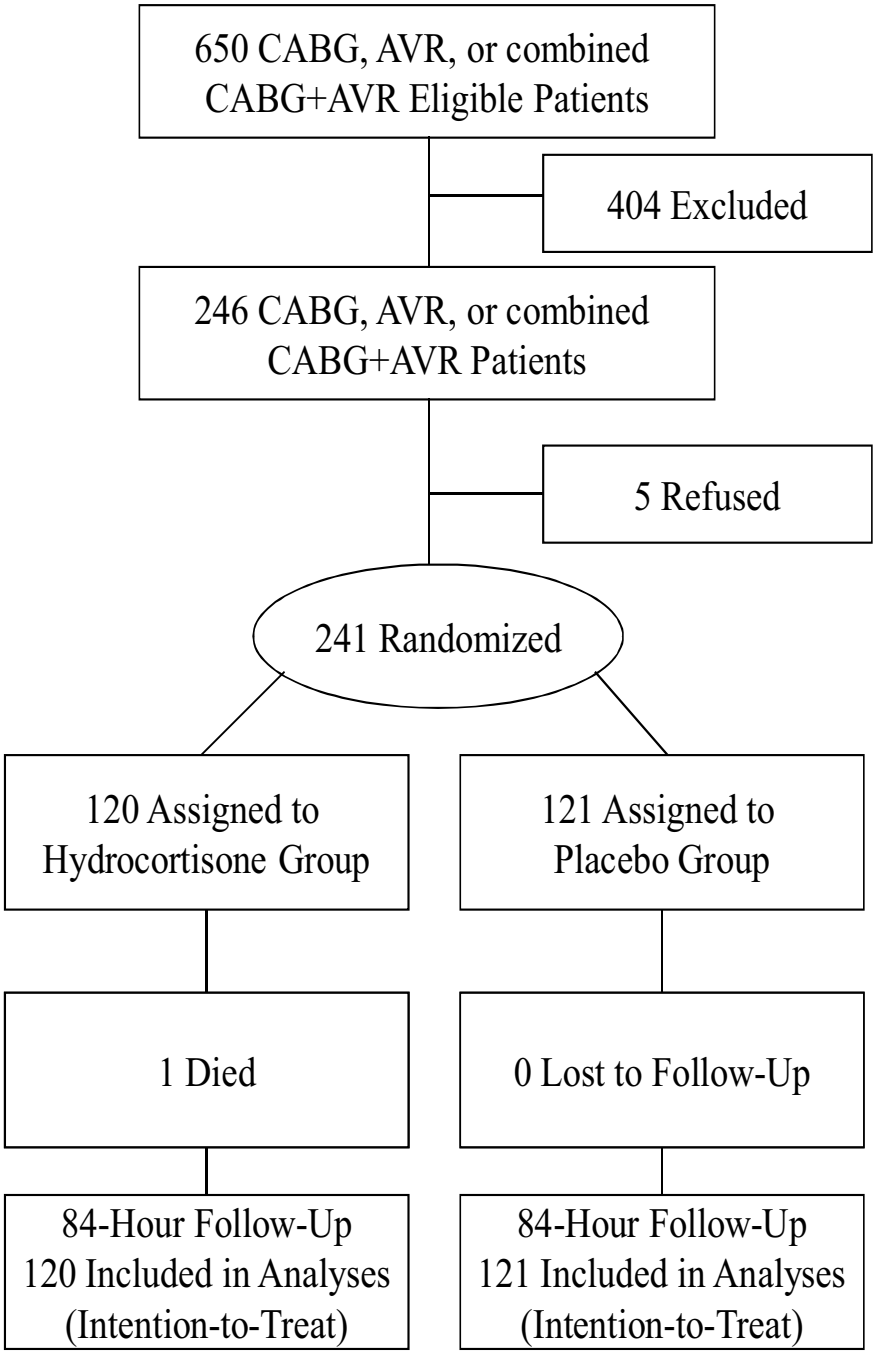

Figure 1. Flow diagram of the study

4.1.3 Study III

The study took place in three cardiac centres in Finland: Kuopio University Hospital, Tampere Heart Centre and Vaasa Central Hospital. The study enrolment occurred from August 2006 to January 2009. We enrolled 316 consecutive patients to undergo their first on-pump CABG surgery, aortic valve replacement, or combined CABG and aortic valve surgery. Patients with previous episodes of AF or flutter, sick sinus syndrome, 2nd or 3rd degree AV block, severe asthma or chronic obstructive pulmonary disease, thyroid dysfunction and allergy to iodine were excluded. Patients were also excluded if they stayed longer than 24 hour in the intensive care unit, if AF occurred before the randomization, if they refused to participate, if temporary pacing was not functioning properly, and if patients had ongoing medication with tioridatsine, erythromycin, pentamidine, terfenadine, sisapridine or corticosteroids. The most common reason for exclusion was the inaccurate function of temporary pacing before the randomization. The study flow diagram is presented in Figure 2. The study protocol was approved by the Kuopio University ethical committee, and all patients gave informed consent.

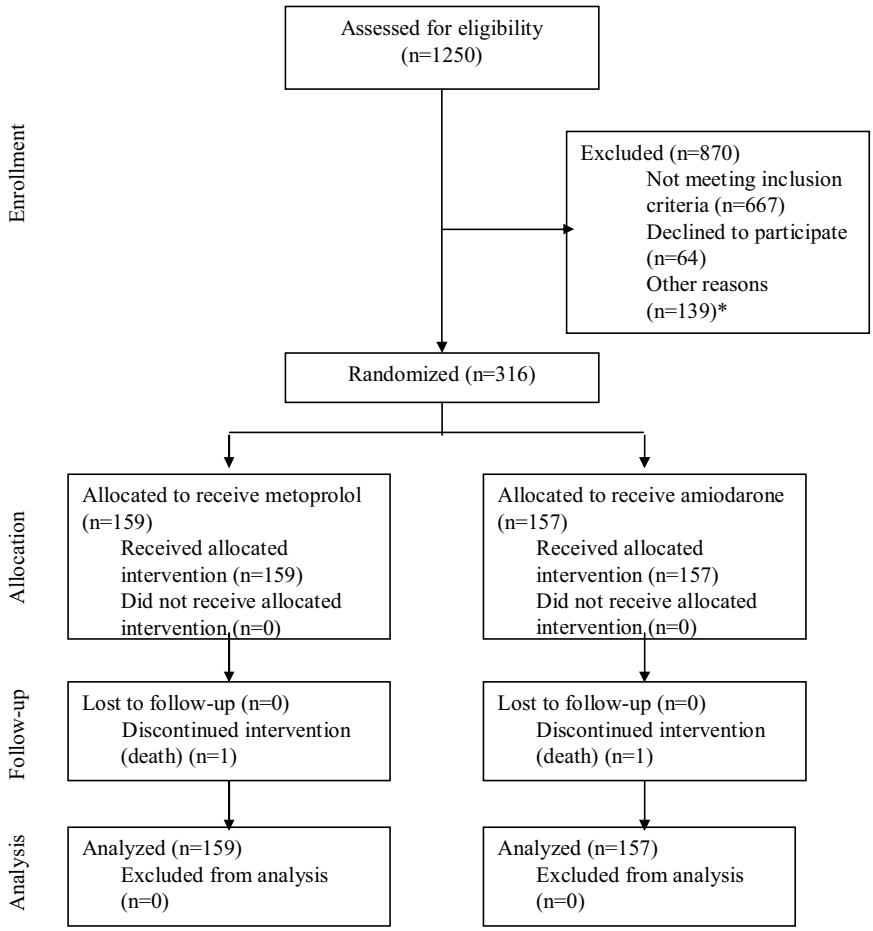

Figure 2. Flow diagram of study

4.2 DESCRIPTION OF PROCEDURES

4.2.1 Operative techniques

All patients underwent on-pump cardiac surgery with standard cardiopulmonary bypass. Intermittent blood or cold crystalloid cardioplegia solution were administered via the antegrade or retrograde route. The cardioplegia solution consisted of magnesium 16mmol/l, and no extra magnesium substitution was given. Cardiopulmonary bypass with moderate systemic hypothermia (venous blood temperature 32°C) and moderate haemodilution (hematocrite >0.22) was used with flow rates of 2.2-2.4 l/m^2 and mean perfusion pressure of 50-85 mm Hg. Epicardial temporary pacing wires were applied for every patient.

4.2.2 Postoperative follow up

After the operation, patients were followed in the intensive care unit and were weaned off the ventilator when they fulfilled the following criteria: haemodynamic stability, peripheral temperature more than 32°C, co-operativity, and no major bleeding. Chest drains were removed on the first postoperative day and the patients were moved to the surgical ward.

All the patients were connected to three-channel ward monitors for continuous ECG monitoring for the whole study period. The ward monitor stored the ECG recordings for subsequent analysis. A 12-lead ECG recording was done if necessary to confirm the rhythm. The endpoint of the study was the occurrence of the first AF episodes or the completion of the study protocol. After the first episode of AF, the study protocol was discontinued.

4.3 STUDY SETTINGS

4.3.1 Study I

The study period started on the first postoperative morning, when randomization was performed. Treatment allocations were sealed in numbered envelopes in a blinded randomized manner. Each enrolled subject was assigned either to the intravenous group or oral group according to the allocation designated in the next envelope opened in sequence. Patients in the intravenous group were given metoprolol according to the heart rate as follows: when heart rate was 60-70 bpm, the metoprolol dose was 1 mg/h; when heart rate was 70-80 bpm, the dose was 2 mg/h; and when the heart rate was > 80 bpm, the dose was 3 mg/h. If heart rate dropped < 60 bpm or systolic blood pressure dropped < 100 mmHg during treatment, intravenous metoprolol was discontinued for one hour and then continued according to heart rate, as described above. Patients in the oral metoprolol group were given metoprolol according to heart rate as follows: when heart rate was 60-70 bpm, the metoprolol dose was 25 mg three times a day; when heart rate was 70-80 bpm, the dose was 50 mg two times a day; and when heart rate was over 80 bpm, the dose was 50 mg three times a day. The study period was 48 hours for both groups.

The endpoint of the study was the occurrence of the first AF episode or the completion of the 48 hours protocol. After the first episode of AF, the study protocol was discontinued.

The sample size was determined on the assumption that the incidence of AF could be reduced from 30% in the oral metoprolol treatment group to 15% in the intravenous metoprolol treatment group. At a level of α=0.05 with a power greater than 0.80, the sample size was calculated to be 121 patients in each group.

4.3.2 Study II

The study period started immediately after the operation was performed. Randomization was performed on the operation day by a biostatistician. The groups were block-randomized with block sizes of six, separately in each hospital. Randomization lists were sent to the hospital pharmacy, where the study drugs were prepared. The investigator sent the name

and date of birth by telefax to the pharmacy each time a new patient had given informed consent. The pharmacy personnel selected the next number on the randomization list, labelled the drug container with the patient's name, and sent the container to the department where the patient was treated. The study group remained blinded to the patient and the doctors. The randomization codes were opened after the end of the study. It was not necessary to break the code for any of the patients, so blinding was assured.

The study drugs were prepared in the hospital pharmacy. Solutions were prepared using aseptic techniques under a laminar flow hood. Reconstituted solutions of hydrocortisone sodium succinate (Solu-Cortef) in 0.9% sodium chloride solution (Natriumklorid Braun 9 mg/ml) were prepared by transferring 100 mg/2ml hydrocortisone sodium succinate into polyethylene infusion containers containing 100 ml of 0.9% sodium chloride solution. Placebo solutions were prepared by transferring 2 ml 0.9% sodium chloride solution (Natriumchlorid Braun 9 mg/ml) into polyethylene infusion containers containing 100 ml of 0.9% sodium chloride solution. Both the active drug and the placebo preparations were identical as regards color and other characteristics.

Each patient was administered either hydrocortisone or placebo as follows: the first dose in the evening of the operative day, and then one dose every eight hours during the next three days. In addition, all patients were given oral metoprolol according to heart rate as follows: when the heart rate was 60-70 beats per minute (bpm), the metoprolol dose was 25 mg two times a day; when heart rate was 70-80 bpm, the dose was 50 mg two times a day; and when it was over 80 bpm the dose was 50 mg three times a day. The study period was 84 hours in both groups.

The endpoint of the study was the occurrence of the first AF episode or completion of the 84 hours study period. All patients in the hydrocortisone and placebo groups had complete courses until the designated endpoints, so intention-to-treat was the same as actual treatment. After the first AF episode, the study protocol was discontinued. Investigators phoned the patients 2-4 weeks after the operation. If the patient reported that he or she had had contact with a physician due to suspected infection, patient charts were ordered to verify and check the event. In addition, the patient charts were checked 6 months after the operation to assess the incidence of major postoperative complications (mediastinitis or other complications requiring hospitalisation).

The sample size determination was based on the assumption that the incidence of AF can be diminished from 30% to 15% with intravenous hydrocortisone treatment. At a level of α=0.05 with a power greater than 0.80, the sample size was 120 patients in each group.

We also performed a meta-analysis of randomized controlled trials of corticosteroid therapy in the prevention of postoperative atrial fibrillation after cardiac surgery. We selected the trials from the PubMed database. The selection criteria were: a randomized, placebo-controlled trial; the primary outcome was AF, and the incidence of AF was reported either in percentages or in numbers together with the total number of patients in the treatment and placebo groups. We found four studies that fulfilled these criteria (Prasongsukarn et al. 2005, Rubens et al. 2005, Halvorsen et al. 2003 and Yared et al. 2000). In a more thorough examination we discerned that two studies did not have defined AF as a primary outcome (Rubens et al. 2005, Yared et al. 2003) and these studies were excluded from the meta-analysis. Finally, two studies (Prasongsukarn et al. 2005, Halvorsen et al. 2003) remained in the meta-analysis together with the present study.

4.3.3 Study III

The study perioid started on the first postoperative morning, when the randomization was performed. Treatment allocations were sealed in numbered envelopes in a blinded randomized manner. Each enrolled subject was assigned to the intravenous metoprolol or intravenous amiodarone groups according to the allocation designated in the next envelope opened in sequence.

Patients in the intravenous metoprolol group were given metoprolol according to the heart rate as follows: when the heart rate was 60-70 bpm, the metoprolol dose was 1mg/h; at heart rate 70-80 bpm, the dose was 2mg/h; and at heart rate >80 bpm, the dose was 3mg/h. If the heart rate dropped < 60 bpm or systolic blood pressure dropped < 100 mmHg during the treatment, intravenous metoprolol administration was discontinued for one hour and then continued according to the heart rate as described above. Patients in the intravenous amiodarone group received amiodarone 15mg/kg, not exceeding a total dose of 1000 mg amiodarone in 24 hours. Also in the amiodarone group, if the heart rate dropped < 60 bpm or systolic blood pressure dropped < 100 mmHg during the treatment, intravenous amiodarone was discontinued for one hour.

The endpoint of the study was the occurrence of the first AF episode or completion of the 48 hours study period. All patients in the metoprolol and amiodarone group had complete courses until the designated endpoints, thus intention-to- treat was the same as actual treatment. After the first episode of AF, the study protocol was discontinued.

The study was planned as an equivalence, open-labelled study. We calculated the sample size using the formula presented by Pocock (Pocock 1983). On the basis of previous studies, we assumed an incidence of AF of 15% in both groups and defined equivalence as a difference in the treatment effect less than 5 percentage points in both directions. As an alpha level of 0.10 with a power greater than 80%, the sample size was calculated to be 158 patients in each group.

4.3.4 Definitions

The rhythm was defined as AF when there were no consistent P waves before each QRS complex and ventricular rate was irregular. AF episodes lasting longer than 5 minutes were recognized.

Perioperative myocardial infarction was defined as the development of new Q waves. A stroke was defined as a new neurological symptom verified by correlative changes in computer tomography. A psychotic mental disorder was defined as a new psychotic symptom diagnosed by the psychiatrist. Mediastinitis was defined as deep sternal infection requiring resternotomy and operative revision. Superficial infections were defined as wound infections in the sternotomy or leg wounds which were treated without surgical intervention. Hypotension was defined as systolic blood pressure less than 100 mmHg, and bradycardia as heart rate less than 60 beats per minute. Resternotomy was defined as reoperation because of bleeding. Thrombophlebitis was defined as local pain, tenderness, redness and bulging of the vein.

4.4 STATISTICS

We analyzed the difference in continuous variables using the unpaired t-test. We tested dependencies between the treatment grups and categorical variables using the chi-square test for independence or, in the case of low expected frequencies, the Fisher exact test. Kaplan-Meier curves were plotted for the development of AF after cardiac surgery. In adition, we used a multivariate Cox proportional hazards model to determine the hazard ratio (HR) of AF in the metoprolol group compared with the amiodarone group (study III) and in the hydrocortisone group compared with the placebo group (study II). Possible confounders (age, sex, left ventricular ejection fraction, type of operation, unstable angina pectoris, chronic obstructive pulmonary disease and right coronary artery bypass) were adjusted in the model. We verified the assumptions of the Cox proportional hazards regression analysis with log-minus-log plots. We performed a meta-analysis of randomized controlled trials of corticosteroid therapy on the prevention of postoperative AF after cardiac surgery. We selected the trials from the PubMed database. The selection criteria included a randomized,

placebo controlled trial and the primary outcome was AF; the incidence of AF was reported either in percentages or in numbers together with the total number of patients in the treatment and placebo groups. We found four studies that fulfilled these criteria. In a through examination, we discerned that two studies did not define AF as a primary outcome; these studies were excluded from the meta-analysis. Thus, two studies remained in the meta-analysis together with our study. We used fixed-effects tests. The three studies were homogeneous (Heterogeneity test: $Q2=4.12$; $p=0.3$). The limit for statistical significance was a p-value less than 0.05. All statistical procedures were performed with SPSS for Windows, release 14.0 (SPSS, Chicago, IL, USA).

5 RESULTS

5.1 STUDY I

A majority (174, 72.5%) of the patients were men. The mean age of the patients was 65.5 ± 9.6 years, with no differences between the groups. Neither was there any difference between the groups as regards demographic data, comorbidities, or cardiac diseases. The preoperative data of the patient groups are presented in Table 5.

Table 5. Demographics of the patient groups

Characteristics	*PO group N=121*	*IV group N=119*	*Univariate p*
Age (years)	65.7±9.8	65.3±9.4	0.743
Gender: male/female (n)	88/33	86/33	0.937
LVEF (%)	63.1±16.4	62.4±13.2	0.753
Hypertension (%)	55.0	58.0	0.642
History of COPD (%)	2.5	0.9	0.662
Diabetes mellitus (%)	24.2	21.9	0.685
CCS class (%)			0.214
I	1.7	3.4	
II	26.1	26.7	
III	52.9	41.4	
IV	19.3	28.4	
Preoperative use of β-blockers (%)	91.5	84.5	0.097
History of stroke or TIA (%)	7.6	4.4	0.300
History of claudication (%)	3.4	4.4	0.685
Unstable angina pectoris (%)	24.8	26.9	0.711
Three-vessel disease (%)	82.5	83.3	0.862

Data are expressed as means (standard deviation) or percentages of patients or number of patients. Abbreviations: CCS=Canadian Cardiac Society, COPD=chronic obstructive pulmonary disease, LVEF=left ventricle ejection fraction, PO=per oral metoprolol, IV=intravenous metoprolol, TIA=transient ischemic attack

Most of the operations in both groups were isolated CABG. There were no differences between the groups in the number of distal anastomoses. Neither was there any difference between the groups with respect to pump time, cross-clamp time or first postoperative creatinine kinase-MB mass. The operative data of the patient groups are presented in Table 6.

Table 6. Perioperative data of the patients

Characteristics	**PO group N=121**	**IV group N=119**	**Univariate p**
Type of operation (%)			0.753
Isolated CABG	81.9	79.6	
Isolated AVR	7.8	10.6	
Combined CABG and AVR	10.3	9.7	
Right coronary artery bypass (%)	77.1	79.0	0.726
Pump time (min)	92.4±42.3	93.2±36.8	0.875
Cross-clamp time (min)	83.4±49.3	79.5±31.6	0.500
Number of peripheral anastomoses (n)	3.7±1.1	3.9±1.1	0.336
First post-operative CK-MBm (g/l)	23.8±11.1	25.2±13.3	0.408

Data are expressed as means (standard deviation) or percentages of patients. Abbreviations: AVR=aortic valve replacement, CABG=coronary artery bypass grafting, CK-MBm=creatinine kinase-MB mass, PO=per oral metoprolol, IV=intravenous metoprolol

The incidence of postoperative AF was significantly lower in the intravenous group than in the oral group (16.8% vs 28.1%). The absolute difference in the incidence of AF was 11.3% and the number needed to treat (NNT) to prevent one AF was 8.8. In addition, the time of AF from the start of the metoprolol medication to the first AF episode was slightly longer in the intravenous group than in the oral group (30.1 h ± 10.1 h vs. 26.5 h ± 11.8 h, p=0.08). The serum potassium concentration at the time of AF did not differ between the groups.

Intravenous metoprolol administration was discontinued for one hour in 18/119 patients (15.1%). The reasons for this were a drop in systolic blood pressure below 100 mmHg in 14/119 (11.8%) patients, and a drop in heart rate below 60 bpm in 4/119 (3.4%) patients.

There was no mortality in the study groups during the study period, but one patient in the intravenous group died on the fourth postoperative day due to myocardial infarction. The incidence of postoperative stroke, conduction disturbances, postoperative mediastinitis, perioperative myocardial infarction or resternotomy due to bleeding did not differ between the groups. The postoperative data of the patients groups are presented in Table 7.

Table 7. Postoperative data of the patients

Characteristics	PO group N=121	IV group N=119	Univariate p
Atrial fibrillation (%)	28.1	16.8	0.036
Onset of AF (hours after operation)	26.5 ± 11.8	30.1 ± 10.1	0.083
Resternotomy due to bleeding (%)	2.5	0.8	0.622
Serum-potassium prior to AF (mmol/l)	4.3 ± 0.37	4.27 ± 0.36	0.782
Stroke (%)	-	-	-
Conduction disturbances (%)	5.0	7.6	0.437
Perioperative MI	-	2.5	0.120
Postoperative mediastinitis (%)	-	-	-

Data are expressed as means. Abbreviations: AF=atrial fibrillation, PO= per oral metoprolol, IV= intravenous metoprolol MI=myocardial infraction

5.2 STUDY II

The age of the patients (66.1 ± 9.5, 64.4 ± 8.5) did not differ significantly between the groups. Most of the patients were men. There were no significant differences between the groups concerning left ventricle ejection fraction, presence of comorbidities or preoperative beta-blocker use. The preoperative data of the patient groups are presented in Table 8.

Table 8. Demographics of the patient groups

Characteristics	**Placebon=121**	**Hydrocortisone n=120**	**Univariate p**
Age (years)	66.1 (9.5)	64.4 (8.4)	0.16
Male gender	89 (73.6)	96 (80.0)	0.24
LVEF (%)	61.4 (11.3)	60.3 (13.1)	0.59
Hypertension	82 (67.8)	70 (58.3)	0.13
Smoking	19 (15.7)	19 (15.8)	0.98
History of COPD	3 (2.5)	4 (3.3)	0.72
BMI (kg/m^2)	27.7 (4.0)	27.9 (4.0)	0.72
Diabetes mellitus	35 (28.9)	26 (21.7)	0.19
CCS class			0.53
I	1 (0.8)	2 (1.7)	
II	46 (38.3)	39 (32.5)	
III	52 (43.3)	62 (51.7)	
IV	21 (17.5)	17 (14.2)	
Preoperative use of □-blockers	103 (86.6)	99 (82.5)	0.39
History of stroke or TIA	7 (5.8)	9 (7.5)	0.59
History of claudication	6 (5.0)	4 (3.3)	0.75
Unstable angina pectoris	27 (22.3)	20 (16.7)	0.27
Three-vessel disease	90 (75.0)	85 (71.4)	0.53

Data are expressed as means (standard deviation) or absolute numbers (%). Abbreviations: CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; BMI = body mass index; LVEF = left ventricle ejection fraction; TIA = transient ischemic attack.

Most of the operations in both groups were isolated CABG. There was no statistically significant difference between the groups in the number of distal anastomoses. Neither were there any differences between the groups with respect to pump time, cross clamp time, right

coronary artery bypass, type of operation, or first postoperative creatinine kinase-muscle brain mass. The perioperative data of the patient groups are presented in Table 9.

Table 9. Perioperative data of the patient groups

Characteristics	**Placebo n=121**	**Hydrocortisone n=120**	**Univariate p**
Type of operation			0.49
Isolated CABG	96 (79.3)	100 (83.3)	
Isolated AVR	17 (14.0)	11 (9.2)	
Combined CABG and AVR	8 (6.6)	9 (7.5)	
Right coronary artery bypass	87 (71.9)	77 (64.2)	0.20
Pump time (min)	93.0 (37.2)	97.9 (41.4)	0.33
Cross-clamp time (min)	77.6 (31.1)	80.0 (31.7)	0.55
N of peripheral anastomoses (n)	3.4 (1.7)	3.5 (1.6)	0.60
First post-operative CK-MBm (mg/l)	24.8 (12.2)	29.2 (45.1)	0.33

Data are expressed as means (standard deviation) or absolute numbers (%).Abbreviations: AVR = aortic valve replacement; CABC = coronary artery bypass grafting; CK-MBm = creatinine kinase-MB mass.

The incidence of postoperative AF during the 84-hour study period was significantly lower in the hydrocortisone group than in the placebo group (30.0% vs. 47.9%, p=0.01) (Figure 3). The relative and absolute risk reductions were 37.4% and 17.9%, respectively and the number needed to treat (NNT) to prevent AF was 5.6. The unadjusted hazards ratio (HR) from the Cox proportional hazards model was 0.54 (95% CI 0.36–0.82). A multivariate Cox proportional hazards model with the most important predictors of postoperative AF ascertained the differences between the study groups (HR=0.54, 95% CI 0.35–0.83). The incidence of in-hospital AF was also significantly lower in the hydrocortisone group than in the placebo group (35.6% vs 51.7%, p=0.01). The concentrations of C-reactive protein on the 1st, 2nd and 3rd postoperative days were significantly lower in the hydrocortisone group than in the placebo group (Table 9).

In the meta-analysis, corticosteroid therapy was associated with lower incidence of postoperative AF (RR 0.67, 95% CI 0.537–0.845) (Figure 4).

The first AF episode (onset of AF) tended to occur earlier (although nonsignificantly) in the hydrocortisone group than in the placebo group. The true meaning of this must be interpreted with caution, because AF onset shows a skewed distribution and very large standard deviations.

One patient in the hydrocortisone group died during the study period (cardiac failure) and one patient in the placebo group died on the ninth postoperative day (multiorgan failure). There were no statistically significant differences between the groups with respect to postoperative infection, mediastinitis, stroke, myocardial infarction, conduction disturbances or resternotomy caused by bleeding. There was no psychotic disorder in either study group. The postoperative data of the patient groups are presented in Table 10.

Table 10. Postoperative data of the patient groups

Characteristics	**Placebo n=121**	**Hydrocortisone n=120**	**Univariate p**
AF (during 84-hour protocol)	58 (47.9)	36 (30.0)	0.01
Onset of AF (hours after operation)	21.3 (25.4)	16.0 (24.6)	0.10
In-hospital AF	62 (51.7)	42 (35.6)	0.01
In-hospital mortality	1 (0.83)	1 (0.83)	1.0
Mortality during study period	- (-)	1 (0.83)	1.0
Resternotomy because of bleeding	3 (2.5)	5 (4.2)	0.50
Serum potassium before AF (mmol/L)	4.2 (0.35)	4.1 (0.43)	0.11
Stroke	1 (0.8)	1 (0.8)	1.00
Conduction disturbances	3 (2.5)	6 (5.0)	0.33
Perioperative MI	2 (1.7)	6 (5.0)	0.17
Postoperative mediastinitis (6 months)	-	-	-
Superficial wound infections	17 (14.0)*	17 (14.1)*	1.0
Postoperative CRP levels			
1^{st} p.op. day	67.2 (30.9)	58.0 (26.9)	0.02
2^{nd} p.op. day	161 (48.0)	118 (38.7)	<0.001
3^{rd} p.op.day	168 (52.2)	97.6 (43.8)	<0.001

Data are expressed as means (standard deviation) or absolute numbers (%).

Abbreviations: AF = atrial fibrillation; CRP = C-reactive protein; MI = myocardial infarction

*(n = 71 in the placebo group and n =78 in the hydrocortisone group).

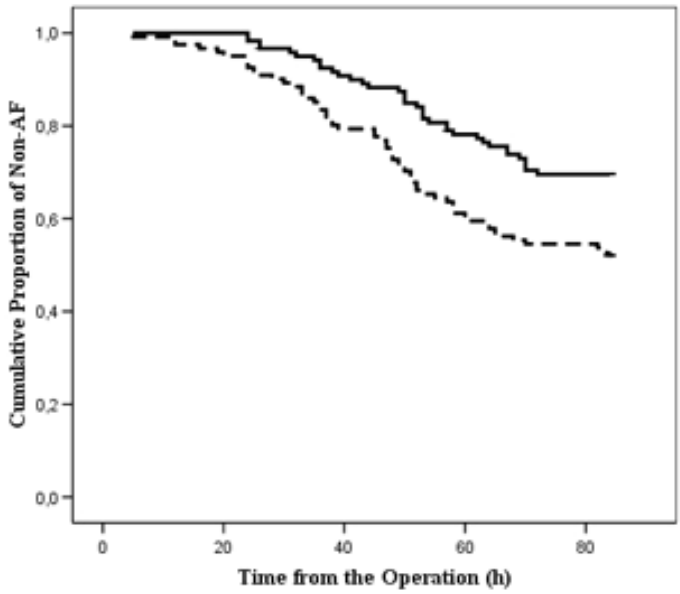

Figure 3. The effect of corticosteroid treatment on the incidence of postoperative atrial fibrillation after cardiac surgery (Kaplan-Meier analysis).

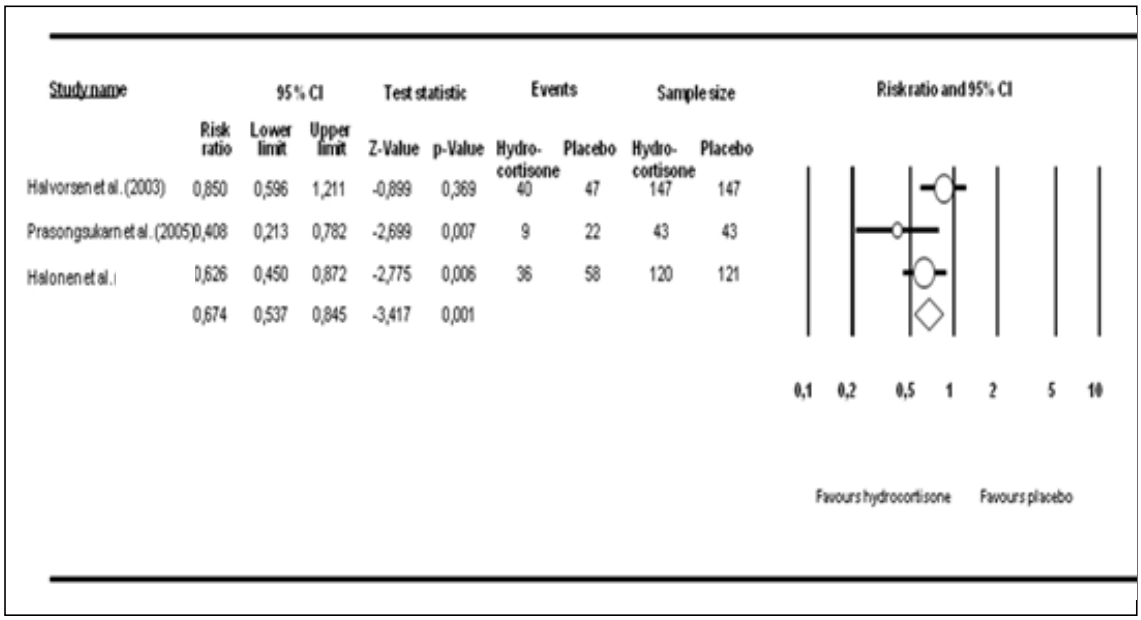

Figure 4. Meta-analysis of randomized controlled trials of corticosteroids therapy on the prevention of atrial fibrillation after cardiac surgery.

5.3 STUDY III

The preoperative characteristics of the patients are shown in Table 11. The mean age of the patients did not differ significantly between the groups. Male gender was more common in the amiodarone group than in the metoprolol group. There were no significant differences between the groups concerning left ventricle ejection fraction, presence of diabetes, COPD, unstable angina pectoris, hypertension, 3-vessel disease, Canadian Cardiovascular Society class, history of stroke or transient ischemic attack history, use of statin medication and history of claudication.

Most of the operations in both groups were isolated CABG (Table 11). There were no statistically significant differences between the groups in the number of distal anastomoses. Neither were there any differences between the groups with respect to pump time, cross clamp time, right coronary artery bypass, type of operation, or first postoperativecreatinine kinase-muscle brain mass.

A total of 75 patients (23.7%) had AF during the 48-hour study period. Atrial fibrillation occurred in 38 of 159 (23.9%) patients in the metoprolol group and 39 of 157 (24.8%) patients in the amiodarone group (p = 0.85) (Table 12, Figure 5). However, the difference between treatments (-0.9 percentage point (90% CI -8.9 to 7 percentage points) did not satisfy the prespecified definition of equivalence that the treatment effect would be between -5 and 5 percentage points. The HR of the metoprolol group compared with the amiodarone group was 0.99 (95% CI 0.63–1.56). This remained unchanged after adjustment for potential confounders (age, sex, left ventricular ejection fraction, type of operation, unstable angina pectoris, chronic obstructive pulmonary disease, and right coronary artery bypass) (adjusted HR 1.09, 95% CI 0.67–1.76).

Atrial fibrillation occurred significantly earlier in patients in the metoprolol group than in those in the amodarone group (mean time to onset of AF 21.1 hours (SD 11.3) vs. 27 hours (SD 10.2: p = 0.020). In addition, after the study period but before hospital disharge, an additional 28 (17.7%) patients in the metoprolol group and 26 (16.9%) patients in the amiodarone group developed AF (p =0.85). The mean time to hospital disharge or transfer to the referring hospital (after cardiac surgery) was 5.6 days (SD 3.5) in the metoprolol group and 5.4 days (SD 2.7) in the amiodarone group (difference 0.23 day (95% CI -0.43 to 0.89 days)).

One patient in the amiodarone group died of cardiac arrest (ventricular fibrillation) 9 hours after the start of the infusion. The patient had had amiodarone infusion without temporary pauses untill ventricular fibrillation occurred. One patient in the metoprolol group developed cardiac tamponade and died on the fifth postoperative day. One patient in the metoprolol group developed AF 30 hours after the start of the infusion and had a stroke 38 hours later. One patient in the metoprolol group was readmitted to the intensive care unit for respiratory failure during the study period.

Amiodarone caused thrombophlebitis of the infusion vein in 11 patients, whereas no thrombophlebitis was observed in the metoprolol group. (7.0% vs. 0%; p = 0.001). The study medication was temporarily discontinued because of hypotension more frequently in the metoprolol group than in the amiodarone group (14.5% vs. 3.8%; p =0.001). In addition, bradycardia occurred more often in the amiodarone group than in the metoprolol group (10.8% vs. 5.0%; p =0.056). Episodes of hypotension and bradycardia did not result in clinically important adverse events but were transient and asymptomatic. The infusion of study medication could be restarted after the interruption in all patients. Resternotomy was needed in 8 patients in the metoprolol group and 5 patients in the amiodarone group (5.0% vs.3.2%; p =0.41). Adverse events are presented in Table 13.

Table 11. Pre- and Perioperative Characteristics

Characteristic	**Metoprolol (*n* = 159)**	**Amiodarone (*n* = 157)**
Preoperative		
Mean age (SD), *y*	63.8 (9.0)	64.5 (9.3)
Male sex, *n (%)*	117 (73.6)	140 (89.2)
Mean LVEF (SD)	0.58 (0.11)	0.59 (0.10)
History of diabetes mellitus, *n (%)*	48 (30.2)	33 (21.0)
History of COPD, *n (%)*	5 (3.1)	2 (1.3)
Unstable angina pectoris, *n (%)*	43 (27.0)	41 (26.1)
Hypertension, *n (%)*	106 (66.7)	101 (64.3)
Three-vessel disease, *n (%)*	123 (77.4)	130 (82.8)
CCS class, *n (%)*		
I	2 (1.3)	2 (1.3)
II	44 (28.0)	53 (33.8)
III	63 (40.1)	67 (42.7)
IV	47 (29.9)	35 (22.3)
Current smoker, *n (%)*	23 (14.5)	28 (17.8)
History of stroke or TIA, *n (%)*	11 (6.9)	7 (4.5)
Use of statins, *n (%)*	125 (85.0)	122 (83.0)
Use of ACE inhibitors, *n (%)*	62 (42.2)	69 (46.9)
History of claudication, *n (%)*	10 (6.3)	11 (7.0)
Perioperative		
Mean number of distal anastomoses (SD)	4.1 (1.3)	4.0 (1.2)
Mean pump time (SD), *min*	94.5 (31.8)	92.8 (33.3)
Mean cross-clamp time (SD), *min*	80.3 (27.3)	79.7 (29.2)
Right coronary artery bypass, *n (%)*	133 (84.7)	128 (82.1)
Type of operation, *n (%)*		
Isolated CABG	144 (90.6)	146 (93.0)
Isolated AVR	7 (4.5)	3 (1.9)
Combined CABG and AVR	8 (5.0)	8 (5.1)

ACE = angiotensin-converting enzyme; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; LVEF = left ventricle ejection fraction; TIA = transient ischemic attack

Table 12. Postoperative Characteristics

Characteristic	Metoprolol	Amiodarone	Univariate *P* Value	Treatment Difference (95% CI)
AF during 48-h protocol, *n (%)*	38 (23.9) (*n* = 159)	39 (24.8) (*n* = 157)	0.85*	-0.94 (-10 to 8.5)
Mean time to onset of AF after randomization (SD), *h*†	21.1 (11.3) (*n* = 37)	27.0 (10.2) (*n* = 38)	0.02‡	-5.9 (-11 to -0.98)
Mean ventricular rate during AF (SD), *beats/min*†	119.6 (26.5) (*n* = 34)	113.8 (20.0) (*n* = 37)	0.29‡	5.9 (-5.2 to 17)
Mean serum potassium level before AF (SD), *mmol/L*†	4.4 (0.45) (*n* = 35)	4.2 (0.44) (*n* = 38)	0.22‡	0.13 (-0.079 to 0.33)
AF after 48 h but before discharge, *n (%)*	28 (17.7) (*n* = 158)	26 (16.9) (*n* = 154)	0.85*	0.84 (-7.6 to 9.3)
Mean first postoperative CK-MBm concentration (SD), *µg/L*	21.9 (12.4) (*n* = 157)	21.8 (10.6) (*n* = 155)	0.95‡	-0.078 (-2.5 to 2.6)
Mean first postoperative CK-MBm concentration (SD), *µg/L*	21.9 (12.4) (*n* = 157)	21.8 (10.6) (*n* = 155)	0.95‡	-0.078 (-2.5 to 2.6)

AF = Atrial fibrillation; CK-MBm = creatinine kinase-MB mass
* Calculated with the chi-square test
† Only patients who had AF were included in the analysis
‡ Calculated with the *t* test

Table 13. Adverse Events*

Adverse Event	**Metoprolol (*n* = 159)**	**Amiodarone (*n* = 157)**	**Group Difference (95% CI), *percentage points***
Death	1 (0.63)	1 (0.64)	-0.008 (-1.8 to 1.7)
Patients with any adverse events	42 (26)	41 (26)	0.30 (-9.4 to 10)
Patients with serious adverse events	2	1	0.62 (-1.5 to 2.8)
Adverse events			
Postoperative stroke	1 (0.63)	–	0.63 (-0.61 to 1.9)
Perioperative MI	1 (0.63)	2 (1.3)	-0.64 (-2.8 to 1.5)
Thrombophlebitis of arm vein	–	11 (7.0)	-7.0 (-11 to -3.0)
Bradycardia	8 (5.0)	17 (10.8)	-5.8 (-12 to 0.16)
Hypotension	23 (14.5)	6 (3.8)	11 (4.3 to 17)
Resternotomy because of bleeding	8 (5.0)	5 (3.2)	1.8 (-2.5 to 6.2)
New conduction disturbances (RBBB, LAHB, LPHB, LBBB)	3 (1.9)	2 (1.3)	0.61 (-2.1 to 3.4)
New atrioventricular block (I–III degree)	1 (0.63)	–	0.63 (-0.61 to 1.9)

MI = myocardial infarction; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LPHB = left posterior hemiblock; RBBB = right bundle branch block.

* Values are reported as numbers (percentages).

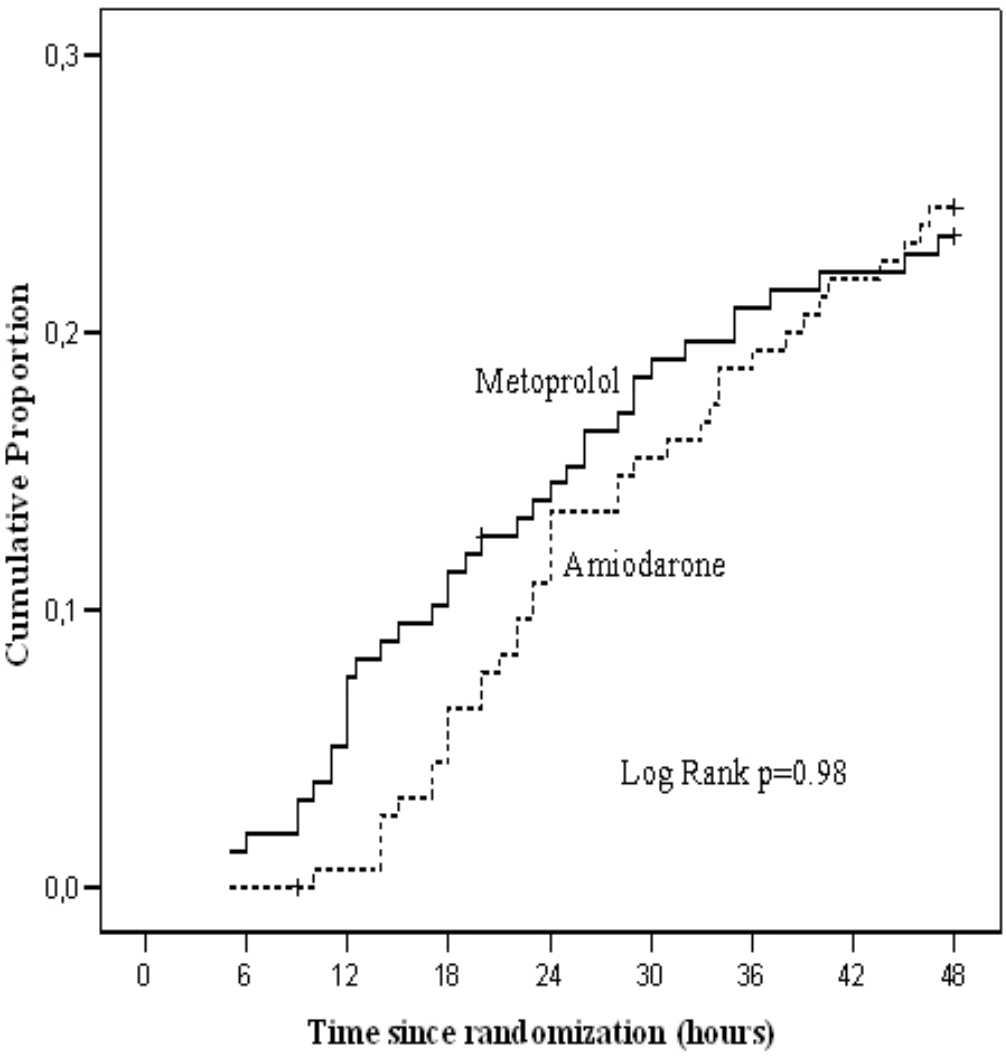

Figure 5. Kaplan-Meier curves of the proportion of patients with postoperative atrial fibrillation after cardiac surgery in the metoprolol and amiodarone groups

Patients at risk, n					
Metoprolol	158	150	135	124	120
Amiodarone	156	154	138	126	117

The exact time of atrial fibrillation was unknown for one patient in each group

6 DISCUSSION

6.1 PATIENTS

Three studies enrolled patients scheduled to undergo on-pump CABG, AVR or combined CABG + AVR. The number of patients who were excluded from the study was quite high. The reasons for exclusions were mainly related to safety aspects. To our knowledge, our studies are the first using iv metoprolol for the prevention of AF after cardiac surgery on a large scale. Thus, we wanted to be very careful not to cause any potential side effects to the patients. On the other hand, in spite of high exclusion numbers, the number of patients in each study was high enough to provide a good representation of the general patient population undergoing CABG, AVR or combined CABG + AVR.

Patients undergoing mitral valve surgery were not included in our studies. Such patients often require temporary pacing and often develop heart block postoperatively. Therefore we considered that iv. amiodarone and iv. metorolol would be contraindicated for a large number of mitral valve surgery patients. In study II we did not include mitral valve patients in order to keep the patient population as uniform with studies I and III as possible. Further studies are warranted to determine whether iv. metoprolol or iv hydrocortisone are also feasible in the prevention of AF after mitral valve surgery.

6.2 EVALUATION OF THE METHODS

The surgical and anaesthesiological methods used in our studies are generally accepted and widely used. Different form of cardioplegia were used, but the type of cardioplegia does not seem to influence the incidence of postoperative AF (Butler 1993, The warm heart investigators 1994, Pehkonen et al. 1995).

All our studies were randomized controlled trials. Study I was a single-center trial, and studies II and III were multicenter trials. In addition, in study II the set up was double blinded. The sample size calculation was performed when designing the studies in order to get an adequately powered sample size to allow clear conclusions. In addition, in study II we performed a meta-analysis of existing randomized controlled trials. The selection criteria included a randomized, placebo controlled trial with the primary outcome of AF.

6.3 INTRAVENOUS METOPROLOL IN THE PREVENTION OF AF AFTER CARDIAC SURGERY

The main finding of study I was that the intravenous metoprolol was significantly more effective than oral metoprolol in the prevention of AF after cardiac surgery. There were no differences between the study groups as regards any known preoperative or perioperative risk factors for postoperative AF. Thus, our study groups are well comparable. Metoprolol is absorbed over a large part of the intestine (Regardh and Johnsson 1980). Despite complete gastrointestinal absorption, only about 50% of single oral therapeutic doses reach the systemic circulation, because of presystemic elimination (Johsson et al. 1975, Jordo et al. 1980). The bioequivalent metoprolol dosage in the intravenous and oral groups in our study was the same, because of this presystemic elimination. One possible explanation for our finding is that orally administered metoprolol is not absorbed from the gastrointestinal tract during the very first postoperative days after cardiac surgery. Diminished visceral blood flow and gastrointestinal motility as well as the use of opioids can reduce the absorption of metoprolol after surgery. Indeed, Valtola and colleagues demonstrated in their

pharmacokinetics study that the bioavailability of metoprolol is markedly reduced when administered in tablet form during the early phase after CABG (Valtola et al. 2007). One previous study compared the efficacy and safety of intravenous and oral beta-blockers: intravenous esmolol was compared with oral β-blocker in a pilot study. The study was terminated when interim analysis revealed a significantly greater incidence of adverse effects in the group receiving esmolol, and the lack of any reduction in AF incidence (Balcelyte-Harris et al. 2002). In contrast, we found no serious adverse effects associated with intravenous metoprolol therapy. Intravenous metoprolol had to be interrupted in 15.1% of the patients because of a decrease in blood pressure or heart rate, but the medication could be restarted in all patients as soon as heart rate or blood pressure had recovered.

The efficacy and safety of intravenous propranolol (Abel et al. 1983) and intravenous timolol (White et al. 1984) have been studied earlier in the prevention of AF after cardiac surgery. These studies concluded that both β-blockers were effective in AF prophylaxis when compared with placebo. However, a trend towards more frequent adverse effects in the propranolol treatment group was reported (Abel et al. 1983).

The main limitation of our study is that many enrolled patients had to be excluded before randomization. Because adverse effects associated with intravenous β-blocker therapy have been reported after cardiac surgery (Balcetyte-Harris 2002, White 1984), we excluded all patients at risk of developing complications associated with intravenous metoprolol therapy. For example, we excluded 11 patients because the functioning of a temporary pace maker was not reliable at the time of randomization. However, the results of our study suggest that this is not necessary, since none of the patients developed bradycardia requiring temporary pacing.

We conclude that intravenous metoprolol therapy is more effective than oral metoprolol therapy in the prevention of AF after cardiac surgery. In addition, we found that intravenous metoprolol turned out to be feasible and well tolerated in postoperative cardiac patients.

6.4 INTRAVENOUS HYDROCORTISONE IN THE PREVENTION OF AF AFTER CARDIAC SURGERY

We report the results of the first randomized, controlled, multi-center trial investigating the effects of corticosteroid treatment on the incidence of postoperative AF after cardiac surgery. We found that intravenous hydrocortisone reduced the relative risk of postoperative AF by 37% compared with placebo in patients undergoing CABG, AVR or combined CABG+AVR. In addition, a meta-analysis in which randomized controlled trials including ours were included clearly demonstrated the beneficial effect of corticosteroid treatment over placebo. Furthermore, hydrocortisone therapy turned out to be feasible and well tolerated, and we found no serious complications associated with corticosteroid therapy.

The effects of corticosteroid treatment of postoperative AF have been addressed earlier in two randomized controlled trials with postoperative AF as the primary endpoint. The results of these trials, however, are somewhat conflicting. In the study by Prasongsukarn et al., 86 patients scheduled for CABG were given 1000 mg of methylprednisolone or placebo before surgery and 4 mg of dexamethasone or placebo every six hours for 24 hours after surgery (Prasongsukarn et al. 2005). In line with our findings, they found that the postoperative incidence of AF was significantly lower in the steroid group than in the placebo group (21% vs. 51%, respectively, p=0.005). Halvorsen et al. administered 4 mg of dexamethasone or placebo after induction of anaesthesia and on the first postoperative morning in 300 patients undergoing CABG (Halvorsen et al. 2003). The incidence of postoperative AF did not differ between the dexamethasone (27%) and placebo group (32%).

There are several possible explanations for these different results. In the study by Halvorsen et al. only two doses of dexaethasone were used, whereas in our study, as well as in the study by Prasongsukarn et al., corticosteroid treatment was continued for 72 and 24 hours, respectively. Another possible explanation is the corticosteroid dose. It is somewhat

difficult to make exact comparisons between the trials, because different corticosteroid preparations were used. However, the anti-inflammatory effect was highest in the study by Prasongsukarn et al., lowest in the study of Halvorsen et al. and in the middle range in our study. Another issue that may explain some differences between these studies is the relatively low incidence of postoperative AF in the placebo group of Halvorsen's study (32%) compared with the study by Prasongsukarn et al. (51%) and our study (48%).

In addition to these trials, there are two studies that deserve to be mentioned here. In one study, 68 patients undergoing CABG were randomized to 1000 mg intravenous infusion of methylprednisolone or placebo before surgery (Rubens et al. 2005). Methylprednisolone was found to have a statistically significant inhibitory effect on the incidence of postoperative AF (12% vs. 34%, respectively, p=0.02). In another study, 235 patients scheduled for CABG or valve surgery were given a single dose of 0.6 mg/kg of dexamethasone or placebo after induction of anaesthesia. Compared with the placebo group, the dexamethasone group had a lower incidence of postoperative AF (19% vs. 32%, respectively, p=0.027) (Yared et al. 2000). Although the results of these studies are interesting, it is difficult to compare them with those of our study. In these trials, postoperative AF was not a primary endpoint, and probably because of AF is not defined in the study protocols. These studies were not primarily designed to address the effect of corticosteroids on postoperative AF but on the activation of inflammatory and coagulation pathways and recovery from cardiac surgery.

Previous studies have found several predicators of AF after cardiac surgery (Crystal et al. 2002). To adjust for these confounding factors, we performed a multivariate analysis in which independent predictors such as age, sex, left ventricular ejection fraction, type of operation, unstable angina pectoris, COPD, and right coronary artery bypass were taken into account. After adjustment for these, corticosteroid treatment remained a significant independent predictor of freedom from postoperative AF.

As regards the mechanism responsible for the beneficial effects of corticosteroids on postoperative AF, several studies have shown that the concentration of complement-C-reactive protein complex (Bruins et al.1997), the number of white blood cells (Lamm et al. 2006) and the concentration of inflammatory cytokines (Aranki et al. 1996)—all markers of increased inflammatory reaction concentration—are higher in patients with postoperative AF than in patients who remain in sinus rhythm. Corticosteroids have anti-inflammatory activity and reduce an exaggerated inflammatory reaction (Ishida et al. 2006). Thus, the anti-inflammatory effect is most likely responsible for the reduced incidence of AF associated with corticosteroid treatment although the causality between anti-inflammatory effects and AF cannot be addressed with this kind of set-up. This is also supported by the finding in our study that the concentration of C-reactive protein was significantly lower postoperatively in the hydrocortisone than in the placebo group. This is also in line with the finding of Dernellis and colleagues that corticosteroid therapy reduces both C-reactive protein values and the risk of recurrent and permanent AF in non-operative patients (Dernellis et al. 2004).

Corticosteroids reduce nausea and vomiting and improve the patient's appetite after CABG (Prasongsukarn et al. 2005). Thus, corticosteroid therapy may improve the absorption of per oral medication, such as beta blockers, and thereby reduce the incidence of AF.

Increased risk of wound infections and gastrointestinal bleeding (stress ulcer) can be a concern with corticosteroid therapy (Ishida et al. 2006). In our study, no adverse effects were related to hydrocortisone therapy. In the study by Prasongsukarn et al. no difference was found between the steroid and placebo group in major complications, but the steroid group had more minor complications. In our study, there were no more complications (minor or major) in the study group than in the placebo group. The different result regarding complications between these two studies may be explained by the different corticosteroid preparations (methylprednisolone and dexamethasone vs. hydrocortisone) and different dosages that were administered. Although in our study intravenous administration of

hydrocortisone was well tolerated, our study was underpowered to assess the safety of corticosteroid therapy.

A limitation of our study is that in order to keep the study population as homogeneous as possible, patients undergoing mitral valve surgery were excluded. Thus, our results should not be applied to this patient population.

One might argue that the incidence of postoperative AF in our study was high (48%). The incidence of postoperative AF depends very much on the definition of an AF episode. In our study, AF was defined as an AF episode lasting > 5 min regardless of whether it was asymptomatic or required therapy. In a recent trial with an almost identical endpoint to that in our study, a 57% incidence of postoperative AF was reported (Miller et al. 2005). In addition, in another study (Prasongsukarn et al. 2005), the incidence of AF in the placebo group was 51%, which is in line with our results.

We conclude that intravenous administration of hydrocortisone is efficacious and well tolerated in the prevention of AF after cardiac surgery. Larger trials will be needed to confirm our findings and determine the short- and long-term safety of corticosteroids to prevent postoperative AF and other arrhythmias.

6.5 COMPARISON OF INTRAVENOUS METOPROLOL VERSUS AMIODARONE IN THE PREVENTION OF AF AFTER CARDIAC SURGERY

We found no difference in the occurrence of postoperative AF in patients treated with intravenous metoprolol or amiodarone after cardiac surgery. Atrial fibrillation occurred in 23.9% and 24.8% of patients in the metoprolol and amiodarone groups, respectively. However, the wide range of the confidence intervals does not satisfy the hypothesized definition of equivalence (between -5 and 5 percentage points) and therefore does not allow us to conclude that the two treatments are equally effective in preventing AF after cardiac surgery. According to current guidelines, beta-blockers should be the first-line preventive treatment of AF in patients having cardiac surgery. Amiodarone should be reserved for patients in whom beta-blocker therapy fails or is contraindicated (Dunning et al. 2006). Despite this, according to a recent survey, 19% of physicians reported using amiodarone as the first-line prophylactic strategy for postoperative AF (Price et al. 2009). This nonadherence to guidelines may be because amiodarone is considered to be the most potent drug in the prevention of AF (Lee et al. 2000) and data directly comparing the efficacy and safety of intravenous beta-blockers and amiodarone in preventing postoperative AF are lacking. Several studies (Study I, Crystal et al. 2002, Burgess et al. 2006, Andrews et al. 1991, Kowey et al. 1991) have demonstrated the effectiveness of beta-blockers in preventing AF after cardiac surgery. A meta-analysis of 27 prospective randomized trials and 3840 patients reported a 61% decrease in the incidence of postoperative AF with beta-blocker therapy (Crystal et al. 2002). In the largest randomized trial, oral amiodarone decreased the incidence of postoperative AF after CABG by 39% compared with placebo (Mitchell et al. 2005). In a meta-analysis of 18 randomized trials, amiodarone decreased the incidence of postoperative AF by 62% (Burgess et al. 2006).

Indeed, only a few studies have compared beta-blockers and amiodarone in a head-to-head setting. In a recent report by Sleilaty and colleagues (Sleilaty et al. 2009), oral bisoprolol and amiodarone were equally effective for the prophylaxis of AF after CABG. Auer and coworkers (Auer et al. 2004) compared oral amiodarone plus metoprolol with oral sotalol, oral metoprolol, and placebo in patients having cardiac surgery. The combination of amiodarone and metoprolol reduced the incidence of AF significantly (44%) compared with placebo, whereas no significant differences were found between the active groups. In these trials, the study drugs were administered orally, whereas the drugs were given intravenously in our study. The bioavailability of oral drugs is markedly reduced when administered in oral form during the early phase after CABG (Valtola et al. 2007). Only one earlier trial compared intravenous beta-blockers with intravenous amiodarone. Solomon and colleagues

(Solomon et al. 2001) randomly assigned patients to either intravenous amiodarone for 48 hours followed by oral amiodarone until discharge, or intravenous propranolol for 48 hours followed by oral propranolol until discharge, in 102 patients undergoing cardiac surgery. Amiodarone was superior to propranolol in preventing postoperative AF, but beta-blocker treatment was continued throughout the study in the patients assigned to amiodarone who took beta-blockers before surgery. Thus, in many cases, the true comparison was amiodarone plus beta-blocker versus beta-blocker alone, rather than amiodarone versus beta-blocker.

With regard to serious adverse events in our study, one patient in each group died during the 48-hour follow-up. In addition, one patient in the metoprolol group had a stroke. In all of these cases, the study medication was unlikely to be related to these adverse events. Both treatments seemed to be well tolerated. No patients required crossover to the other treatment. The only symptomatic adverse effect was venous thrombophlebitis in 11 patients in the amiodarone group. The study drug infusion was temporarily interrupted because of hypotension more often in the metoprolol group than in the amiodarone group and because of bradycardia more often (although nonsignificantly) in the amiodarone group than in the metoprolol group. These findings are in line with those of an earlier study reporting that amiodarone infusion was associated with bradycardia and interruption of the infusion in 18% of patients (Jafari-Fresharaki et al. 1998).

An obvious limitation in our study is that although the incidence of AF was similar (38 and 39 patients in the metoprolol and amiodarone groups, respectively) and did not differ between the study groups, we lacked sufficient power to demonstrate equality. Even after adjustment for potential confounders, the wide range in the confidence intervals (95% CI, 0.67–1.76) does not allow us to conclude that the two treatments were equally effective in preventing postoperative AF. Thus, we cannot exclude the possibility that true differences in efficacy exist between amiodarone and beta-blockers in the prevention of AF. For example, it is possible that the withdrawal of established beta-blocker therapy for patients allocated to amiodarone may have precipitated AF. Although we doubt this was the case, because amiodarone has beta-blocking properties (Singh 2008), we cannot exclude the possibility that this may have biased our results against amiodarone. The blocking effect of amiodarone is supported by our finding that bradycardia (<60 beats/min) developed more frequently in patients treated with amiodarone than in those treated with metoprolol. Our patients were not considered to be at particularly elevated risk for AF and were hemodynamically stable, were off pressors, and were free of mechanical ventilation within 24 hours of cardiac surgery. Thus, our results cannot be safely applied to sicker patients or those at higher risk for AF, such as patients with a history of AF or undergoing mitral valve repair.

The study period of 48 hours starting from the first postoperative morning may be thought to be too short. The incidence of AF is highest on the second and third postoperative days (Arankiet al. 1996, Hakal et al. 2002). A great majority of this time period was well covered in our study. As many as 17% of the patients developed AF after the study period but before hospital discharge. However, the occurrence of AF after the study period did not differ between the groups.

It could also be argued that the amiodarone dose in our study was not sufficient. Amiodarone has been shown to be efficient in various doses and in oral and intravenous administration (Crystal et al. 2002, Burgess et al. 2006, Aasbo et al. 2005, Gillespie et al. 2005, Mitchell et al. 2005, Buckley et al. 2007). In the largest randomized trial, the amiodarone dose was 10 mg/kg, whereas it was 50% more in our study, 15 mg/kg per day (Mitchell et al. 2005). Thus, an insufficient dose is unlikely to explain the results of our study.

Although we did not find any difference in the incidence of AF, larger multicenter trials or meta-analyses are needed to confirm the equality of metoprolol and amiodarone in preventing postoperative AF. In addition, comparisons of metoprolol and amiodarone are needed in patient cohorts with higher risk for AF, such as patients undergoing mitral

operation, patients with a history of AF, and patients who are not hemodynamically stable after operation. Until more data are available, we recommend adherence to current guidelines, namely the use of beta-blockers as first-line prophylaxis of postoperative AF.

We conclude that while the observed incidence of AF during 48 hours of treatment with intravenous metoprolol or amiodarone after cardiac surgery was similar, we cannot conclude that the treatments are equally effective.

7 SUMMARY AND CONCLUSIONS

AF is the most common arrhythmia to occur after cardiac surgery. It is associated with postoperative complications, including increased risk of stroke, prolonged hospital stay and increased costs. The purpose of our study was to find a reliable, effective, safe and well tolerated tool for the prevention of postoperative AF after cardiac surgery.

In study I we randomized 240 patients to receive either oral or intravenous metoprolol for 48 hours after cardiac surgery. The incidence of postoperative AF was significantly lower in the intravenonous metoprolol group (16.8%) than in the oral group (28.1%, p=0.036).

In study II a total of 241 patients were scheduled to receive either intravenous hydrocortisone or placebo postoperatively for 84 hours. The incidence of postoperative AF was 30.0% in the hydrocortisone group compared with 47.9% in the placebo group, and the relative risk reduction was 37%.

In study III intravenous metoprolol therapy was shown to be as effective as intravenous amiodarone in the prevention of AF after cardiac surgery. Altogether 316 patients were randomized to receive either metoprolol or amiodarone intravenously starting on the first postoperative morning after cardiac surgery. The incidence of postoperative atrial fibrillation was 23.9% in the metoprolol group and 24.8% in the amiodarone group, with no statistical difference between the groups.

On the basis of the these studies, the following conclusions can be drawn:

1. Intravenously administered metoprolol therapy is more effective than oral metoprolol therapy after cardiac surgery. Intravenous metoprolol administration was feasible and easy, and turned out to be well tolerated in postoperative patients.

2. Intravenous hydrocortisone administration is highly effective in the prevention of AF after cardiac surgery. Intravenous hydrocortisone therapy turned out to be feasible and well tolerated. In addition, we found no serious complication associated with intravenous corticosteroid therapy.

3. The occurrence of AF was similar in the metoprolol and amiodarone groups. However, because of the wide range of the confidence intervals, we cannot conclude that intravenous metoprolol and amiodarone are equally effective in the prevention of AF after cardiac surgery.

We suggest that intravenous metoprolol therapy should be part of the routine medication to prevent AF in all patients undergoing cardiac surgery, unless contraindicated. Moderate-dosage corticosteroid (hydrocortisone) should be considered for the prevention of AF in high risk patients undergoing cardiac surgery. Amiodarone should be used for the prevention of postoperative AF only if beta-blocker therapy is contraindicated.

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Jari Halonen

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Atrial fibrillation (AF) is the most common arrhythmia to occur after cardiac surgery. It is associated with postoperative complications including increased risk of stroke, prolonged hospital stay and increased costs. The study consisted of three randomized, prospective trials. In the first study intravenous metoprolol showed to be more effective than oral metoprolol in the prevention of AF after cardiac surgery. In the second study intravenous hydrocortisone reduced the risk of postoperative AF by 37 % compared with placebo. In study three intravenous metoprolol therapy showed to be as effective as intravenous amiodarone in the prevention of postoperative AF after cardiac surgery.

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