

Atrial Fibrillation -

On Its Trigger Mechanisms,

Risks and Consequences

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You cannot be wise without some basis of knowledge; but you may easily acquire knowledge
and remain bare of wisdom.

Alfred North Whitehead

To my dear parents,
(for inspiring me to be who I am)

List of Contents

Abstract	5
List of papers	7
Abbreviations	8
Definition	9
Classification	9
Epidemiology	11
Mechanisms of AF initiation and maintenance	12
Atrial remodelling	13
AF management	15
<i>Pharmacological treatment</i>	16
<i>Rhythm control</i>	16
<i>Rate control</i>	17
<i>Non-pharmacological treatment</i>	17
<i>Stroke prevention</i>	19
<i>Upstream therapy</i>	19
Consequences	20
Risk evaluations score	22
Hypotheses	23
Patients and Methods	25
<i>Patients</i>	25
<i>Methods</i>	28
<i>Definitions</i>	33
<i>Statistical Methods</i>	34
Ethics	35
Results	36
Discussion	56
<i>Triggers of AF re-initiation early after restoration of sinus rhythm</i>	56
<i>Role of bradyarrhythmias immediately after successful DC</i>	57
<i>RV pacing and clinical heart failure after AVJA for drug resistant AF</i>	58
<i>Prognosis of AF in patients with ischemic heart disease</i>	59
<i>Role of the CHADS₂ score in patients with ACS, with or without AF</i>	61
Conclusions	63
Clinical implications	64
Literature	65
Acknowledgments	75

ABSTRACT

Background:

Atrial fibrillation (AF) frequently impairs quality of life, but in long-term it is associated with an increased morbidity and mortality. Persistent AF may cause changes in the sinus node function, and if converted to sinus rhythm (SR), there is a substantial risk of recurrence of AF. Atrioventricular junctional ablation (AVJA) is a therapeutic option for patients with drug refractory persistent/permanent AF, but permanent right ventricular pacing after ablation, according to some reports, has been associated with the development of heart failure (HF).

Methods:

172 patients with persistent AF underwent elective DC cardioversion and analysis of 5 minutes ECG recordings was made in those converted to sinus rhythm (SR). Another 213 patients were followed for 6±3 years after AVJA. Forty-nine of the patients (23%) were known to have HF before AVJA, and aggravated or new HF was in long-term followed. Of 2335 consecutive patients admitted with acute coronary syndromes (ACS), 442 had known AF (n=204), new AF at admission (n=54) or developed new AF during hospitalization (n=184). The short- and long-term mortality and morbidity were followed in patients with and without AF, and were related to their CHADS₂ scores at admission.

Results:

After successful cardioversion of persistent AF, 30% of the patients had a recurrence of AF within 1 week. Premature atrial contractions (PAC) were equally frequent in patients with and without AF recurrence. A low sinus rate and/or sinus pauses >2 s were observed in 31 patients in the first few minutes but did not predict recurrence of AF. One quarter of the patients with known HF before AVJA showed an aggravation of HF, while 13% developed new symptoms of HF during long-term right ventricular pacing after AVJA. High age and low EF were independent predictors of new HF, while high age and coronary artery disease were independent predictors of all-cause mortality. In patients with ACS and AF, short-term mortality (<30 days) was 13.8%, and differed significantly between the AF subgroups. All-cause 10-year mortality did not differ between subgroups, as opposed to the rate of hospitalization for stroke. The all-cause mortality at 10-years showed a strong association with the CHADS₂ scores both in patients with and without AF, although strongest in patients without AF (hazard ratio [HR] and 95% confidence interval per unit increase in the six-graded

CHADS₂ score 1.53 [1.42-1.64], p<0.0001 vs 1.28 [1.16-1.43], p<0.0001 after adjustment for potential confounders).

Conclusions:

PACs and transient sinus bradycardia were the most common potential trigger mechanisms after cardioversion of persistent AF, but they did not predict recurrences of AF. AVJA followed by right ventricular pacing was associated with aggravated HF in a quarter of patients with previously known HF, while development of new symptoms of HF occurred much less often. In patients with ACS the type of AF influenced the 30-day mortality and the long-term risk of hospitalization for stroke. The CHADS₂ score helped to identify patients with a higher risk for subsequent stroke and death, both in patients with and without AF.

Key words: Acute coronary syndromes, atrial fibrillation, AV junctional ablation, CHADS₂ score, electrical cardioversion, mortality, stroke, trigger mechanisms.

Original PAPERS

- I. Poçi D, Abrahamsson B-M, Bergfeldt L, Edvardsson N. Burden and timing of premature atrial contractions after electrical cardioversion of persistent atrial fibrillation do not predict its recurrence. *Clin Cardiol.* 2008;31:492-7.
- II. Poçi D, Abrahamsson B-M, Edvardsson N, Bergfeldt L. Transient impairment of sinus node function immediately after electrical cardioversion of persistent atrial fibrillation. *Submitted.*
- III. Poçi D, Backman L, Karlsson T, Edvardsson. New or aggravated heart failure during long-term right ventricular pacing after AV junctional catheter ablation. *Pacing Clin Electrophysiol.* 2009;32:209-16.
- IV. Poçi D, Hartford M, Karlsson T, Caidahl K, Edvardsson N. Short-term and long-term prognosis in relation to type of atrial fibrillation in patients with acute coronary syndromes. *In manuscript.*
- V. Poçi D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS₂ score in acute coronary syndromes – risk of subsequent death or stroke in patients with and without atrial fibrillation. *Submitted.*

ABBREVIATIONS

ACS – acute coronary syndromes

AF – atrial fibrillation

AMI – acute myocardial infarction

AVJA – atrioventricular junctional ablation

CHADS₂ score - an acronym for Congestive heart failure, Hypertension, Age >75 years,
Diabetes and prior Stroke

CHF – congestive heart failure

ERAF – early relapse of atrial fibrillation

IRAF – immediate relapse of atrial fibrillation

PAC – premature atrial contraction

SN – sinus node

SR – sinus rhythm

DEFINITION

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder and has a broad variety of presentations in clinical practice. In London in 1909, Sir Thomas Lewis established AF as a clinical entity and gave it the name “auricular fibrillation” (1, 2). Lewis considered AF as a chronic and terminal disease because of heart failure and clots found within the auricles.

Later, AF was described to “*occur in a small proportion of mainly elderly patients, usually in association with structural heart disease, but many cases are idiopathic (lone atrial fibrillation). This rhythm disturbance is entirely benign although it may be fiercely symptomatic. It is an acceptable alternative to normal sinus rhythm*”(3). In the current guidelines of the European Society of Cardiology, the American College of Cardiology and the American Heart Association, AF is defined as “a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function (4), and the ventricular response to AF depends on electrophysiological properties of the atrioventricular node and other conducting tissues, the level of vagal and sympathetic tone, the presence or absence of accessory conduction pathways, and the action of drugs” (5).



Fig. 1. Atrial fibrillation

CLASSIFICATION

AF is a progressive disease and has a variety of clinical presentations. The classification terminology has varied with the changes in the definition of AF. The most widely used classification tries to include the convertibility and progression of AF (6) and is recommended by experts (4).

When a patient experiences *the first detected episode of AF*, it is often difficult to make an estimation of its duration, which can be hours, days, months or years. In some cases, the termination of the first detected episode of AF, spontaneously or with the help of the cardioversion, is not followed by more episodes but does often recur. In the case of self-termination, AF is called *paroxysmal* and is characterized by a varied duration of the episode and frequency of occurrence. AF is called *persistent* when AF perpetuates, and cardioversion, electrical or pharmacological, is needed to interrupt the sustention of arrhythmia. *Permanent* AF is ongoing AF when one or more attempts of cardioversion fail and further attempts are planned or if attempts are not made because they are regarded not to be meaningful.

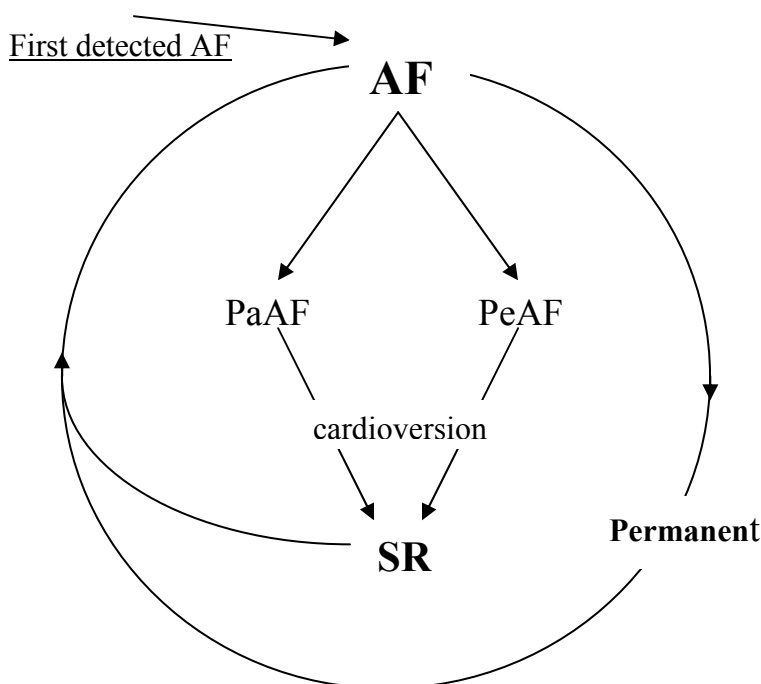


Fig. 2. Schematic classification of atrial fibrillation (PaAF – paroxysmal, PeAF – persistent)

However, new upcoming techniques of cardioversion, electrical (7), pharmacological (8), their combination, catheter techniques (9-11) and AF surgery (12) may result in a restoration and maintenance of sinus rhythm (SR) in patients with longstanding AF. Thus the decision to leave a patient in ongoing AF is serious and should be made only after careful evaluation of the individual patient.

Despite subjectivity, this classification has been clinically useful in describing the progression from paroxysmal to persistent and further to permanent AF, and vice versa.

EPIDEMIOLOGY

The prevalence of AF increases steeply with age, affecting 1–1.5% of the population (13). The estimated prevalence is ~ 1 % in the general population (14) and the life-time risk of AF for adults of age 40 and older is reported to be 26% in men and 23 % in women (15).

The prevalence will grow considerably in the next decades owing to several socio-economic factors, where most probably increasing life expectancy and improved health care are central factors. Projected data from the ATRIA study in California, USA (2001), show that the number of Americans with AF will increase 2.5-fold during the next 50 years (14), while in Olmsted County, Minnesota, USA (2006), the number of patients with AF is estimated to increase 3-fold from 2000 to 2050 (16). The increase of the prevalence in the ATRIA-study ranged from 0.1% among adults younger than 55 years to 9.0% in persons aged 80 years or older.

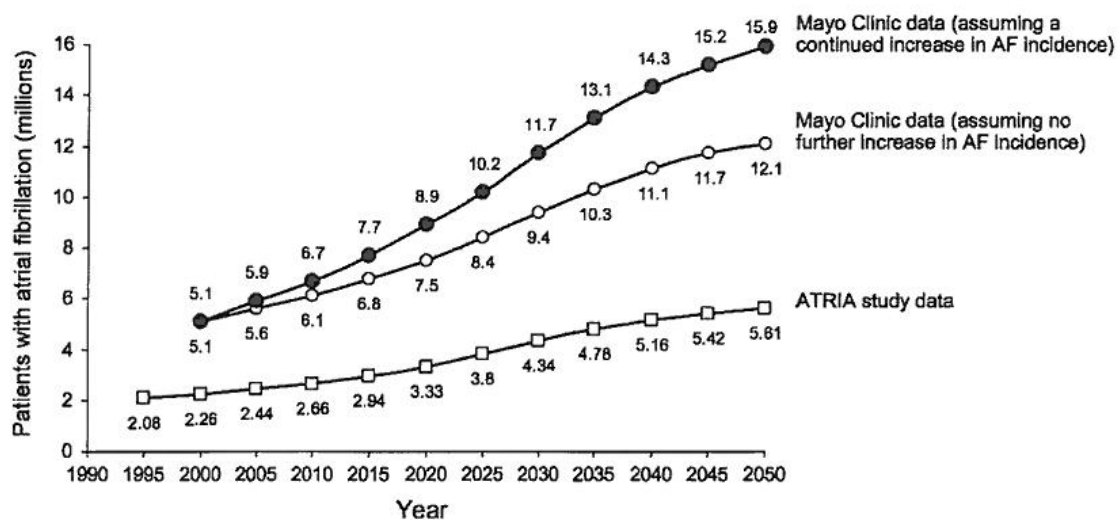


Fig.3. Projected number of adults with atrial fibrillation in the United States by 2050.

(Modified from: Go AS et al.14 and Miyasaka Y et al. 16. ATRIA = AnTicoagulation and Risk Factors In Atrial Fibrillation. By courtesy of Professor John Camm)

AF is furthermore associated with an increased risk of stroke and congestive heart failure CHF (17-19) and a higher number of hospitalizations compared to other arrhythmias. According to surveys done in 2000, the number of hospitalizations because of AF had almost tripled compared to the number two decades ago (20).

In the Framingham Heart study and others AF was associated with an increased risk of premature death, and the relative risk of death after adjustment for age and co-morbidity varied between 1.2 and 2 (21, 22).

MECHANISMS of AF INITIATION and MAINTENANCE

AF initiation requires a *trigger*, which can often be a premature atrial contraction (PAC) or an atrial tachyarrhythmia (10, 23, 24). A trigger alone can not initiate AF, however, a modulator, often the autonomic nervous system, is also necessary (25). Tachyarrhythmia, short- and long episodes of AF, create with time an *electrical substrate*, which helps to re-initiate AF (26-28). The saying “AF begets AF” was first used in the middle of 1990s and described, in a goat model, that the more AF the goats had, the easier AF could be started after restoration to SR.

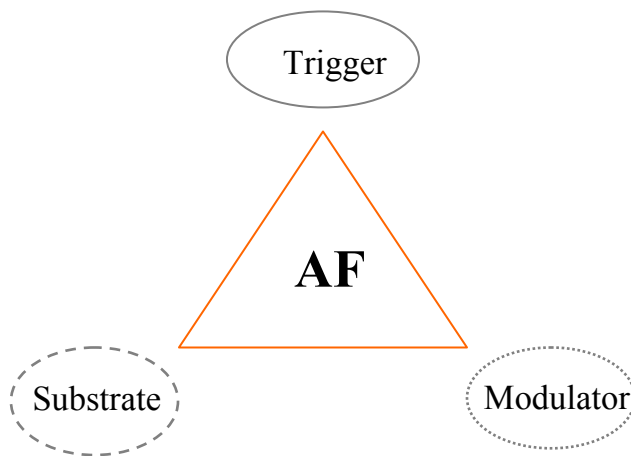


Fig. 4. Necessary factors for development of atrial fibrillation

Theories on the mechanism of AF can roughly be divided into the *single focus* theory (mother fixed or moving rotor) and the *multiple sources* theory (multiple foci and wavelets, unstable reentry circuits).

According to the single focus hypothesis, AF occurs due to a single rapid macro-reentry circuit, during which its wavefronts originate and then break against regions of varying refractoriness by thus creating the irregular activity that characterizes the arrhythmia (29). The very rapid rate, which cannot be followed by the entire atrial tissue, produces fibrillatory conduction.

On the other hand, the multiple wavelet hypothesis states that a heterogeneous dispersion of repolarization in atria, which creates the special area with a functional conduction block, is responsible for wave breaks and the generation of multiple wavelets that sustain AF (30). These wavelets incessantly initiate themselves or each other. The area with heterogeneous dispersion (lines of the conduction block) surrounds the anatomical structures in the atria, which may be different according to acquired anatomical obstacles such as scars, patchy

fibrosis, stretch-induced longitudinal dissociation, or areas of myocardium at different stages of recovery and excitability (31, 32).

Structural changes, such as increased cellular volume and *gap junction* properties, play a key role in the maintenance of the number of simultaneous circuits required for the perpetuation of AF. As a result, a critical mass of atrial tissue, serving as an *arrhythmogenic substrate* necessary for re-initiation and sustention of arrhythmia, is already created. Not surprisingly, an increase in the left atrial diameter of more than 50 mm has been reported to be proved to augment the risk of AF by 40% in population-based studies (33).

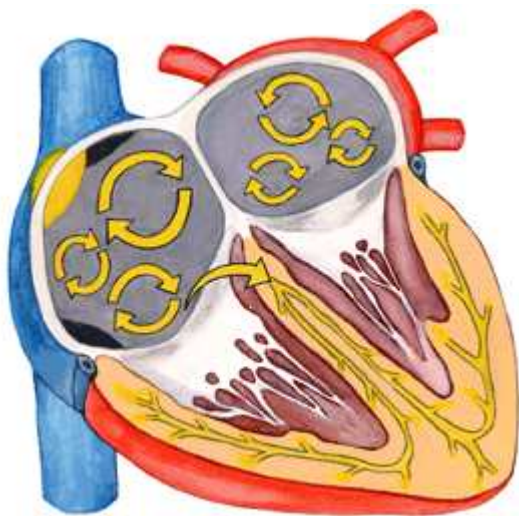


Fig. 5. Multiple wavelets of atrial fibrillation

During the past decade, the development of modern electrophysiology, especially catheter ablation for AF, has further contributed to knowledge about the mechanisms of AF. There is evidence that suggests that AF is preserved by rotors or multiple wavelets with a dominant high frequency resulting in the distribution of excitation frequencies throughout the atria, and from the left atrium towards the right atrium, through spatially distributed conduction block patterns (34-36).

ATRIAL REMODELLING

Atrial electrical properties are altered by sustained AF and the atria become more vulnerable to the initiation and maintenance of the arrhythmia (26, 28, 31). The alteration in the electrophysiological properties and the structure of the atrial myocardium causes a process known as *atrial remodelling*. Atrial tachycardia-induced *electrical* remodelling is associated

with a shortening of the atrial effective refractory period and the atrial action potential (27, 37), as well as areas of slow conduction (31). The shortening of the refractory period and action potential duration occurs within minutes of the onset of AF and is a consequence of altered ion channel function, with calcium overloading in atrial myocytes (38, 39).

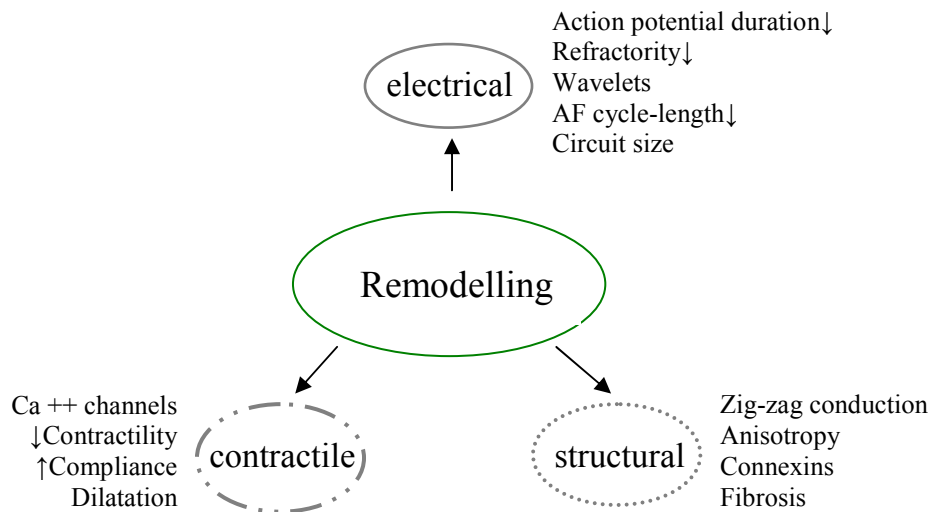


Fig 6. Atrial remodelling during atrial fibrillation

During continuing AF, *structural* changes (increased cellular volume, proteolysis and loss of contractile elements) may develop that result in a specific type of atrial myopathy and later in atrial dilatation (31, 33). As previously mentioned, the alteration will also involve gap-junctions, with a reduction in connexins Cx40 and Cx43 (40). Fibrosis and/or dilated atria are examples of substrates and, together with gap-junctional alteration, such as a *contractile* abnormality, promote the maintenance of AF, once induced (28, 31).

* Electrical and structural remodelling go hand in hand. Both subsequently create the substrate for AF: electrical remodelling starts within hours of an episode of AF and facilitates the initiation of new AF episodes, while structural remodelling acts as a second factor for perpetuation of AF (26, 41). An understanding of electrical and structural remodelling is essential as it explains why paroxysmal AF may become permanent, or why AF is difficult to treat. Furthermore, recovery, or reverse electrophysiological and structural remodelling, following an episode of AF takes time, leaving a varying period of vulnerability. This explains the high relapse rate into AF after an initially successful direct current (DC) cardioversion, whether transthoracic or intracardiac (23, 42, 43).

Re-initiations of AF have been called immediate (*IRAF*) when they occur within the first minute after cardioversion and early (*ERAF*) when they occur within the first five minutes after cardioversion (23). A number of different AF onset mechanisms have been described in the time period immediately preceding an episode of AF, especially episodes captured by different devices (23, 44, 45). According to these studies re-initiation occurs after up to 25% of recorded short AF episodes, creating a picture of electrical instability. Less is known however about the occurrence of such mechanisms and their predictive value when they appear during the first minutes after successful external DC cardioversion of persistent AF, i.e. episodes of longer duration than in the device studies. Once AF has become persistent, the likeliness that relapses will also be persistent, is high.

* Persistent AF is often associated with a depressed sinus node function, which facilitates the perpetuation of AF and reduces the stability of SR (46, 47). Sinus bradycardia, sinus pauses and/or sino-atrial conduction block may occur as features of the sick sinus syndrome (SSS) also occur after spontaneous conversion of AF (48, 49). In patients with AF, sinus bradycardia and pauses after cardioversion can imply pre-existing *sinus node (SN) dysfunction* or AF-induced SN remodelling or reflect normal variations. While SN dysfunction has previously been regarded as limited to the SN and its closest atrial connections, the initiation and maintenance of AF also require the participation of structures outside the SN area. The atria in patients with AF without documented SSS and in patients with SSS without documented AF seem to have important patho-physiological and structural properties in common (47, 50). However, little is known about how common SN dysfunction is in patients with persistent AF and whether it is reversible or predictive of the recurrence of AF after successful cardioversion.

AF MANAGEMENT

The management of AF focuses on symptom relief, prevention of late complications and on prevention of the progression of AF. Symptom reduction can be achieved by restoration and maintenance of SR (*rhythm control*) and/or modification of the ventricular rate during AF (*rate control*). Sudden onset, sustained and symptomatic arrhythmia require termination (cardioversion), and prophylactic therapy must be given to prevent or reduce recurrences, while ventricular rate control may be an option in permanent or accepted AF. The most important late complication of AF is *stroke*, and the risk can be greatly decreased by

antithrombotic treatment, and another complication promoted by ongoing AF is *heart failure* and/or development of cardiomyopathy (51, 52).

The intention of rhythm control strategy is to restore and/or maintain SR by also paying attention to ventricular rate control. The rate control strategy aims to control the ventricular rate and does not involve attempts to restore or maintain SR. In addition to the rate or rhythm control strategies is antithrombotic therapy, which consists prevention of thromboembolic events. The results of the studies carried out at the beginning of the last decade, which enrolled a large number of patients with AF and compared rate and rhythm control strategies, showed that a primary rate control strategy was not inferior to the rhythm control strategy in terms of mortality and morbidity (53-57). These studies also demonstrated that rhythm control strategy was more expensive and complex than the rate control strategy. The trials had different patient selection criteria, endpoints and therapeutic interventions, thus limiting the applicability of the findings to all AF populations. While it is well recognized that both rate and rhythm control strategies are important in AF management, each approach should be chosen according to an accurate evaluation of the individual patient. Treatment should be based on AF history, type and timing of AF, severity of symptoms, concomitant diseases and medication.

Pharmacological treatment

In patients with severely symptomatic AF, rhythm control strategy is obviously a plausible alternative, and more efficient methods to maintain SR are needed to reduce the morbidity related to arrhythmia. On the other hand, tachycardia-induced cardiomyopathy, with or without signs of heart failure can be induced or developed in patients with persistent/permanent AF and rapid ventricular rate during AF and this is the main reason for the necessity of an adequate ventricular rate control at rest and activity

Rhythm control

In patients with ongoing AF one or more *cardioversion* attempts are reasonable. In many patients, the electrical (external, monophasic or biphasic and internal, catheter-related) or pharmacological cardioversion, followed by *antiarrhythmic* (AA) therapy to maintain SR is the main treatment option. Recommended AAs for maintenance of SR include flecainide and propafenon for patients without significant underlying structural heart disease, while sotalol may be used in patients with structural heart disease. Amiodarone is a second-line drug for all subsets of patients with AF. Dofetilide is available in the US but requires special education

and certification. Dronedaronone has recently been approved for rhythm control in the EU and is believed to be at most moderately effective, having its most favourable properties in the safety profile.

A rhythm control strategy is suitable primarily when applied in younger patients, highly symptomatic patients, and patients with sudden-onset AF and AF with associated CHF. The analysis of subgroups in the AFFIRM trial showed better survival in patients in SR and patients on anticoagulant therapy (58). However, available agents for pharmacological rhythm control are neither as effective nor as safe as required, and patients eligible for treatment are instead frequently treated with drugs that are not recommended, i.e. beta-blockers, verapamil and/or digoxin, that may be perceived as safer but have not been proven effective for that purpose (59).

Rate control

In general, rate control strategy and anticoagulation are suitable in older asymptomatic patients. Effective control of the ventricular rate during AF frequently requires more than one AA, most frequently a betablocker, digoxin and/or verapamil and adjustments in the type of drug and dosage may be needed to achieve the desired effect (60). To add to the problem, there is no consensus over a definition of adequate rate control. Lenient rate control, defined as a heart rate at rest of <110 beats/min, was very recently shown not to be inferior to strict rate control, defined as a heart rate at rest of <80 beats/min, in terms of death from cardiovascular causes, hospitalization for heart failure and stroke, systemic embolism, bleeding and life-threatening arrhythmic events (61).

Non-pharmacological treatment

Unfortunately, available AA drugs are moderately effective in reducing recurrences of AF or preventing persistent AF, especially in the long term, and patients may during the course of AF become refractory against AA drugs or develop side effects. The proarrhythmic risk and toxicity of AA drugs is another problem in the management of AF and, in substudies, patients treated with AA drugs to restore and maintain SR had a higher mortality risk (58).

The work done in the past decade has given a better understanding of specific AF mechanisms, such as the role of ectopic beats or tachycardias originating from 'sleeves' of the atrial myocardium inside the pulmonary veins in triggering and sustaining episodes of AF (10, 62), which has led to the development of non-pharmacological treatment alternatives. A variety of techniques for catheter ablation, intra-operative ablation and surgical treatment of AF is now available. Catheter ablation is most effective in patients with paroxysmal and

persistent forms of AF, with success rates, depending on the definition, varying between 75 and 85%, compared to the lower rate of 5–35% in patients on AA drug therapy. The Maze III open-heart surgery procedure is the gold standard of non-pharmacological treatment, with long-term success rates in terms of SR of >90%, even in patients with longstanding ongoing AF, (12, 63). These figures have stimulated the testing of, so called minimally invasive surgical procedures, using an epicardial (thoracoscopic and non-thoracoscopic) approach. The results of these procedures are good but have not yet reached the success rates of the cut and sew surgical Maze III procedure (12, 64-66).

* More than one mechanism might be responsible for AF at a given time in the clinical course, more than one type of therapy might be necessary. In patients in whom both rhythm and rate control strategies have failed another treatment must be selected. Catheter ablation of the atrioventricular junction ablation (AVJA), followed by permanent ventricular pacing, known as the ‘ablate and pace’ strategy, is such a recommended treatment. This is often reserved for older individuals, with drug refractory, symptomatic permanent and/or persistent AF (67). AVJA is used to control the ventricular rate in these patients, and its aim is to destroy the electrical atrio-ventricular connection. Antithrombotic treatment continues, while the benefit consists of rate control and a cessation of previous medication for rhythm and/or rate control.

This palliative treatment, which makes the patient dependent on pacemaker, is used for symptom relief as it reduces the ventricular rate, and it is often associated with an improved quality of life and exercise capacity and a decreased need of hospitalization (68, 69). While many patients have been followed for a long time and have been well, reports have implied that long-term right ventricular (RV) pacing may be harmful and might lead to the development of symptoms of CHF. This would in turn be explained by systolic dysfunction with a reduction of the left ventricular ejection fraction (LVEF) and/or induction of left ventricular dyssynchrony, defined as an abnormality in electromechanical coupling and detectable with echocardiography (70, 71).

Patients in CHF have an increased risk of developing AF (72) and AF *per se* is a predictor of CHF and of increased mortality in patients with CHF (66). The development of new HF or an aggravation of known HF after AVJA may thus have different causes and the possible contribution of RV pacing therefore needs to be explored.

Stroke prevention (Antithrombotic treatment)

AF is associated with an increased risk of stroke, and about 15% of all ischemic strokes are estimated to be caused by an embolism caused by AF (17-19).

The risk of stroke is reduced with anticoagulation treatment, and all placebo-controlled warfarin trials in AF, such as AFASAK, SPINAF, BAATAF, SPAF I, II, III and the SPORTIF trials, have shown great risk reduction with warfarin, and a greater reduction than with aspirin (73-80). Stroke in warfarin groups, with an INR target of 2 to 2.5 at best, occurred after warfarin withdrawal, while a low dose of warfarin with or without aspirin did not show a benefit. However, even in eligible patients, undertreatment with warfarin is common (81). A major problem with warfarin is the risk of bleeding and it is a common perception among physicians and patients that this risk and the logistics involved in warfarin treatment will in many cases make this drug unsuitable or will decrease patient compliance. This has increased expectations for new antithrombotic agents, such as the recently approved dabigatran, which does not require regular INR testing. This and other new agents appear to be promising, but no data concerning long-term efficacy and safety in patients with AF, are yet available (82).

Rate and rhythm strategy trials such as RACE and AFFIRM have stressed that antithrombotic treatment should be continued, even when long term sinus rhythm is obtained, and have shown that factors other than rhythm should be taken into consideration in decisions about continued antithrombotic treatment. In the RACE study, 21 of 35 thromboembolic complications occurred under rhythm control, mostly in patients receiving inadequate anticoagulation therapy (54). In the AFFIRM study, involving patients with one or more stroke risk factors, the stroke incidence was also higher in the rhythm control group when anticoagulation had been stopped (53). Thus, one major lesson from those randomized studies was that anticoagulation should be continued in the presence of risk factors for stroke, even if patients are in SR.

Upstream therapy

Treatment of patients with AF is often started only when patients have had repeated episodes of AF or when they arrive with an ongoing episode of AF. At this point in time, atrial remodelling might have advanced to make AF more difficult to treat. Upstream therapy is a term that has been used to describe that treatment should not only be directed at the triggers and/or the substrate but also at the factors that create the substrate. Pharmacological agents

that act in this way are the angiotensin cardioverting enzyme (ACE) inhibitors, the angiotensin-renin blockers, the statins and the n-3 polyunsaturated fatty acids (PUFAs).

Angiotensin II is an important factor in atrial remodelling. Atrial stretch increases local synthesis of angiotensin II and is followed by promotion of myocyte hypertrophy, proliferation of fibroblast, accumulation of collagen and apoptosis as consequences (83-85). In addition, angiotensin II modifies atrial electrophysiology through indirect effects on ion channels and may impair gap junction properties (85, 86). There is currently strong evidence that angiotensin receptor blockers and angiotensin converting enzyme inhibitors prevent electrical remodelling and reduce interstitial fibrosis in heart failure or rapid atrial pacing models of AF, independently of the reduction in intra-atrial pressure (87, 88). These agents may reduce the risk of AF by approximately 20%–30% depending on the patient population (89, 90). Their efficacy remains to be verified in prospective trials that are under the way.

Furthermore, agents targeting inflammation, atrial myocyte metabolism and fibrosis could theoretically be potential future therapeutic options. The anti-inflammatory and antioxidant effects of statins prevent shortening of the atrial effective refractory period (91). In the ARMYDA-3 trial, atorvastatin reduced the incidence of in-hospital AF following an open heart surgery from 57% in the placebo group to 35% in the treatment group (92).

These and other observations make probable that these agents prevent or delay atrial remodelling during AF. The role of n-3 polyunsaturated fatty acids in preventing or delaying AF episodes is less well known, although some reports imply that they may be of value (93, 94).

CONSEQUENCES (short- and long-term) of AF

Once atrial fibrillation has started, a series of changes are initiated in the heart. The rapid and irregular rates of atria and ventricles initiate inappropriate chronotropic responses which, together with a loss of atrial systolic function, result in decreased cardiac output, increased end-diastolic pressures, decreased blood pressure and tachycardia-mediated atrial and ventricular cardiomyopathy with CHF, thromboembolism and mortality as consequences (17-19).

The association between AF and *risk of stroke* has long been known. Structural remodelling in atria during AF, development of fibrosis (endocardial changes and oedematous or infiltration of the extracellular matrix) in different parts of the atria with dilatation as a consequence and

loss of atria contraction promote stasis in the left atrium, which is seen as a spontaneous echocontrast. Abnormal changes in blood components during AF include haemostatic and platelet activation, as well as inflammation and growth factor changes (95, 96). These changes result in the Virchow triad for thrombogenesis, which includes abnormal changes in vessel walls, blood flow and blood components, resulting in a prothrombotic or hypercoagulable state in AF (97).

The increased burden of AF also contributes to cardiovascular morbidity by causing *CHF* (4) (98) (51). Patients in CHF have an increased risk of developing AF. About 15–30% of them are in AF (72), and AF is an independent predictor of increased mortality in the CHF population.

Hypertension and ischaemic heart disease (IHD) play an important role in the development of AF, and the presence of AF is associated with increased *mortality* partly because of stroke. In patients with structural heart disease and AF, the relative risk for mortality after adjustment for age and comorbidity varies between 1.2 and 2 % (21).

* *IHD* promotes the development of AF, and AF is not uncommon in patients with an acute myocardial infarction (AMI). AF occurs in 5-23% of patients with AMI (99-101) and is an independent predictor of increased in-hospital and long-term mortality (101-103). A sudden development of AF with an increase in ventricular rate, irregularity of ventricular contractions and loss of atrial contribution to left ventricular filling in a patient with acute myocardial infarction may result in a deterioration of cardiac function and an increased risk of complications such as CHF, ventricular arrhythmias, cardiogenic shock and re-infarction, both in the short- and long-term perspectives. The effects of acute AF on coronary circulation and the role of acute coronary syndromes (ACS) in the pathogenesis of AF (104, 105) are well known. New onset AF has been associated with poorer in-hospital adverse outcomes and previous AF with higher long-term mortality than in patients without a history of AF (106, 107). Goldberg et al. reported that patients with AMI and AF had in-hospital mortality rates of 27.6% vs.16.6% in those with SR, and showed the same rates during each of the five years studied (108). Furthermore, the TRACE study, which included 6676 consecutive patients with AMI (109), showed that AF was associated with an increased five-year mortality among in-hospital survivors, regardless of LVEF and symptoms of CHF.

RISK EVALUATION SCORES

The risk of stroke depends on different clinical presentations such as type of AF, the patient's age, concomitant disease and prior stroke or transitory ischemic attacks. Clinical risk stratification is a natural derivation of risk factors identified in large randomized trials.

The *CHADS₂ score* (an acronym for Congestive heart failure, Hypertension, Age >75 years, Diabetes and prior Stroke) is currently used to estimate the risk of ischemic stroke in patients with AF (110). In estimating the score, the first four variables give one point and previous stroke 2 points and, according to this score, patients with any type of AF and a score of higher than one should receive anticoagulation. The CHADS₂ score is a simple system that helps to make an estimation of the stroke risk in AF patients, but it has been found to be “weak” in differentiating patients with “intermediate” risk (111). Restricting the use of the CHADS₂ score to patients with documented AF may underestimate its potential as a prognostic tool since episodes of AF may be asymptomatic and can frequently occur without being recognized.

In 2006, another score was proposed in order to pay attention to patients with intermediate risk. The Birmingham/National Institute for Health and Clinical Excellence (NICE) schema reclassified and included additional risk factors with special attention to the markers of thrombogenesis (112). Recently, a novel, simple stroke risk stratification (Birmingham 2009) schema was proposed to provide some additional variables in the CHADS₂ score, which was retrospectively applied in the AF Euro Heart Survey with the intention to evaluate subjects in the intermediate risk category (111). This score, CHA₂DS₂-VASc (CHADS + vascular disease, sex category), could according to the authors improve the approach used for evaluating stroke risk in patients with AF. From the same survey, de Vos et al. propose the HATCH score (an acronym for Hypertension, Age ≥ 75 years, Transient ischemic attack o stroke, Chronic obstructive pulmonary disease, and heart Failure) as a tool for estimation of AF progression (113).

Individual clinical components used in different schemas or scores are also risk factors commonly seen in patients with other structural heart disease, e.g. *ischemic heart disease*. The CHADS₂ score was recently reported to have an impact on all-cause mortality after stroke, regardless of whether patients had previously known AF(114). The CHADS₂ score was also found to be a powerful predictor of stroke and death in patients who underwent angiography on suspicion of coronary artery disease, and the existence of AF among these patients independently increased the risk of both stroke and death (108). Thus, using the CHADS₂ score in patients with documented AF only may underestimate its role as a prognostic tool.

HYPOTHESES

1. Immediate and early relapses of AF are not common during the first five minutes after successful external electrical cardioversion of persistent AF.
2. Premature atrial contractions in the period after successful external electrical cardioversion of persistent AF commonly precede recurrences of AF during the first week.
3. Sinus bradycardia and pauses seen in the period immediately after successful electrical cardioversion of persistent AF may have a prognostic impact on AF recurrences.
4. Permanent right ventricular pacing is not a common cause of subsequent new heart failure in patients after AV junctional ablation.
5. The short and long term prognosis of patients admitted with an ACS differs according to whether AF was previously known, whether it was first detected at admission or whether it occurred for the first time during hospitalization for ACS.
6. The CHADS₂ score can be used as a risk assessment tool for subsequent events, including thromboembolism and mortality, in patients with ACS, with or without AF.

PAPERS

- I. Poçi D, Abrahamsson B-M, Bergfeldt L, Edvardsson N. Burden and timing of premature atrial contractions after electrical cardioversion of persistent atrial fibrillation do not predict its recurrence.
- II. Poçi D, Abrahamsson B-M, Edvardsson N, Bergfeldt L. Transient impairment of sinus node function immediately after electrical cardioversion of persistent atrial fibrillation.
- III. Poçi D, Backman L, Karlsson T, Edvardsson. New or aggravated heart failure during long-term right ventricular pacing after AV junctional catheter ablation.
- IV. Poçi D, Hartford M, Karlsson T, Caidahl K, Edvardsson N. Short-term and long-term prognosis in relation to type of atrial fibrillation in patients with acute coronary syndromes.
- V. Poçi D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS₂ score in acute coronary syndromes – risk of subsequent death or stroke in patients with and without atrial fibrillation.

PATIENTS and METHODS

Patient evaluation consisted of medical history, risk factors and medication, and other data were retrieved from the hospital medical records.

PATIENTS

I and II

Between January 2000 and July 2001 172 consecutive patients with persistent AF scheduled for elective electrical cardioversion on an outpatient basis were enrolled. Patients were referred for DC conversion mainly due to symptomatic AF, but some patients with newly diagnosed AF detected as part of routine physical examination for other reasons were accepted (Figure 7). There were no protocol-defined exclusion criteria. Patient evaluation consisted of a medical history, including number of previous DC cardioversions and duration of the current AF episode; physical examination; 12-lead electrocardiogram (ECG); and chest x-ray. Laboratory tests included electrolytes, thyroid, and liver tests. Echocardiography was performed according to the clinical routine and was available within 6 month prior to DC cardioversion in 64 (37%) patients. Eighty-one patients (47%) had undergone at least one previous DC attempt.

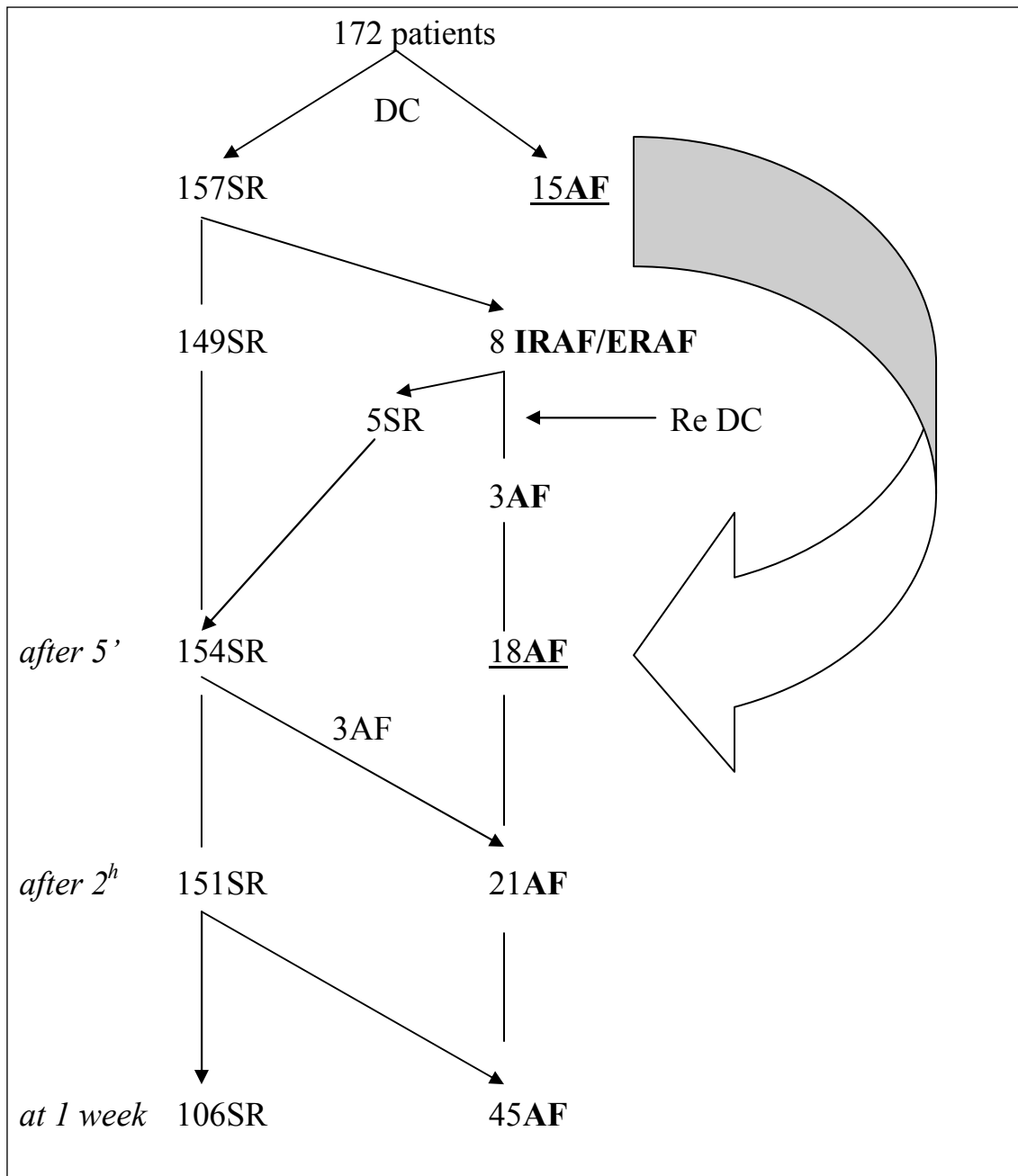


Fig. 7. Patient flow in Paper I

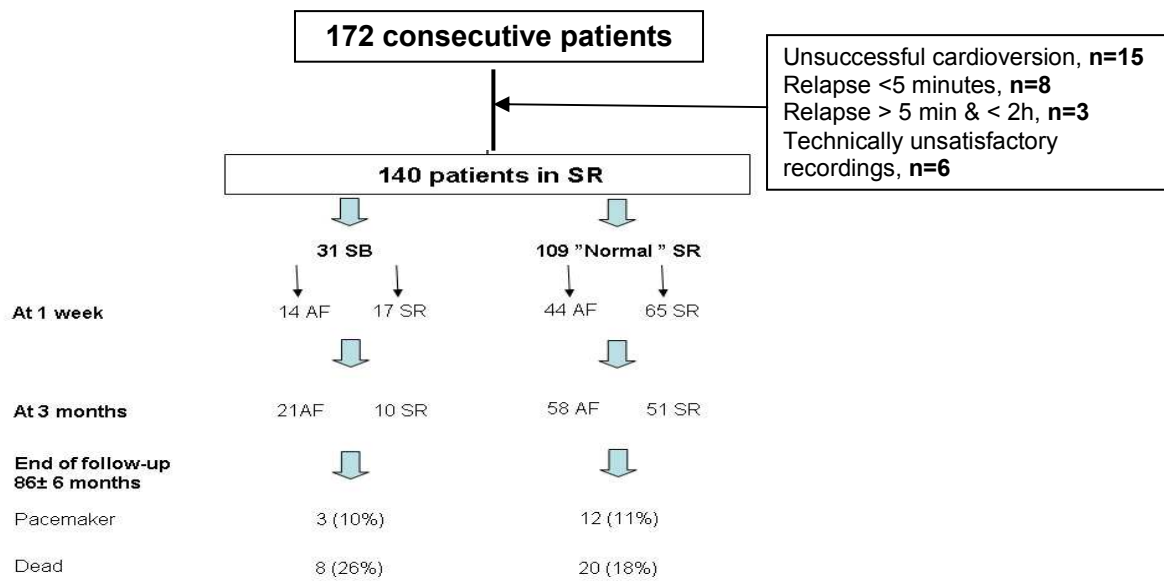


Fig. 8. Patient flow in Paper II

III.

All 213 patients who underwent AVJA for drug refractory paroxysmal (n=103) or persistent/permanent (n = 110) AF at the Sahlgrenska University Hospital during a period of 11 years, from January 1994 to December 2004, were included in this retrospective analysis. Hypertension, coronary artery disease, and dilated cardiomyopathy were the most common underlying conditions. Transthoracic echocardiography was available in 206 patients before AVJA.

IV and V.

2335 patients admitted to the coronary care unit at Sahlgrenska University Hospital with an ACS between 15 September 1995 and 15 March 2001, were enrolled in a study of prognosis and its prediction (PRACSIS = Prognosis and Risk of Acute Coronary Syndromes in Sweden) (Figure 9) (115).

The diagnosis of ACS was based on chest pain or other symptoms suggestive of myocardial ischemia and had to be supported by electrocardiogram (ECG) changes [ST segment elevation ≥ 0.1 mV (0.2 mV in V_1 – V_4) or ST depression ≥ 0.1 mV or T wave inversion in at least two adjacent leads], biochemical markers above the upper reference level [creatine-kinase (CK)-MB 5 μ g/l and/or troponin T 0.05 μ g/l] or previously recognized coronary artery disease. Exclusion criteria were: age ≥ 80 years, residence outside the hospital catchment area, life expectancy < 1 year because of conditions other than coronary heart disease, previous

inclusion in the study and unwillingness to participate. During the recruitment period, approximately 5 % of ACS patients who were admitted to the coronary care unit and lacked any exclusion criteria were missed for logistic reasons. The presumed diagnosis of ACS turned out to be incorrect in 146 of the 2481 patients enrolled in the study, and these patients were excluded from further analysis.

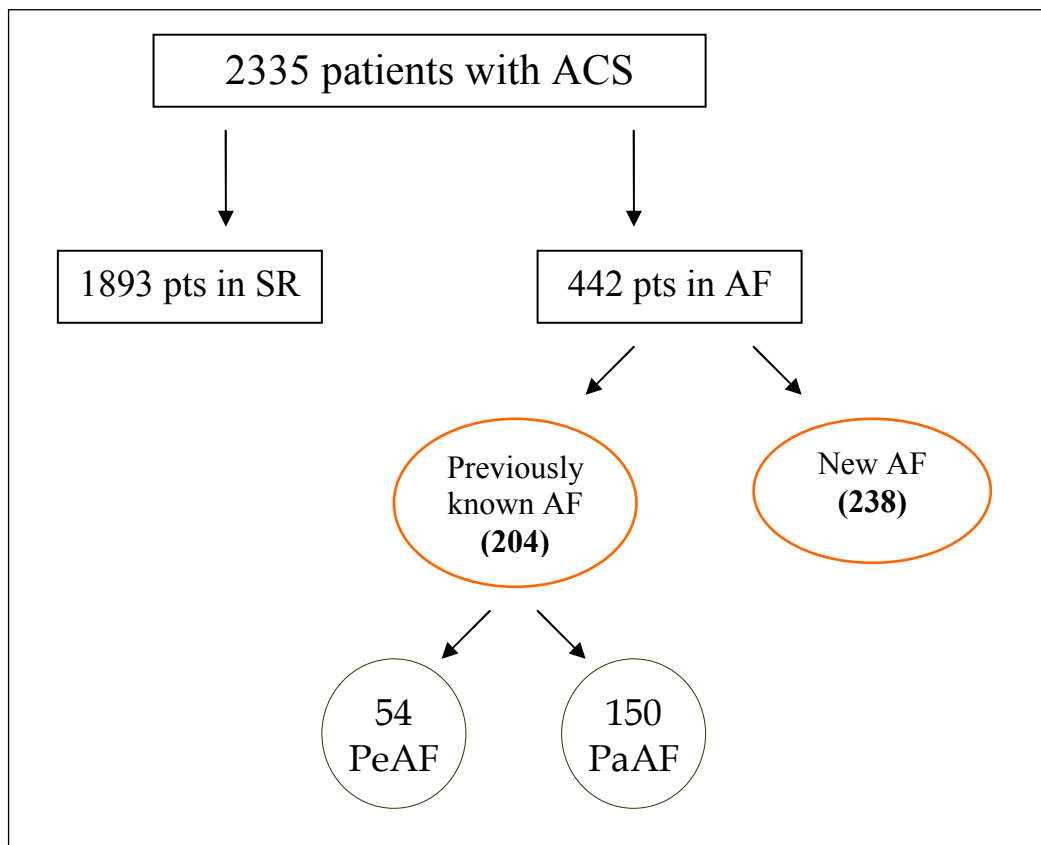


Fig. 9. Patient flow in Paper IV and V (Pa – paroxysmal, Pe – permanent)

METHODS

I and II

The patients were allowed to be on antiarrhythmic agents and all were treated with warfarin for at least 4 weeks before attempting DC cardioversion. The dose was adjusted to maintain an international normalized ratio (INR) target interval of 2.3–3.5. The day before the DC cardioversion all patients had a 12-lead ECG recording for rhythm control and a check of the serum potassium value. International normalized ratio was checked on the day of the procedure. International normalized ratio values varied from 2.0–4.4, and serum potassium

levels varied from 3.7–5.2 mmol/L. The patients were fasting and DC cardioversion was performed under brief general anesthesia with propofol. The defibrillator paddles were generally positioned over the apex of the heart and below the right clavicle. A maximum dose of 5 mg metoprolol intravenously (IV) was given prior to cardioversion in 22 patients with a high ventricular rate. A 200–300 J monophasic shock was delivered in a synchronized mode. If necessary, another shock of 300–360 J was delivered. A maximum of 4 shocks were given. The ECG was monitored with 3–6 leads during the procedure and for 5 min after SR was restored. The heart rhythm was monitored for a minimum of 2 h after DC cardioversion, and a 12-lead ECG was then repeated before discharge at least 2 h after the procedure. Therapy with antiarrhythmic agents was continued. All patients returned to the AF clinic for a rhythm control with a 12-lead ECG 1 week and 3 months after the procedure. Warfarin therapy was continued for at least 3 months after successful cardioversion, and indefinitely in patients in whom cardioversion failed or AF relapsed during the 3 months after DC cardioversion. The long-term INR values were adjusted individually and controlled by the anticoagulation clinic at the hospital.

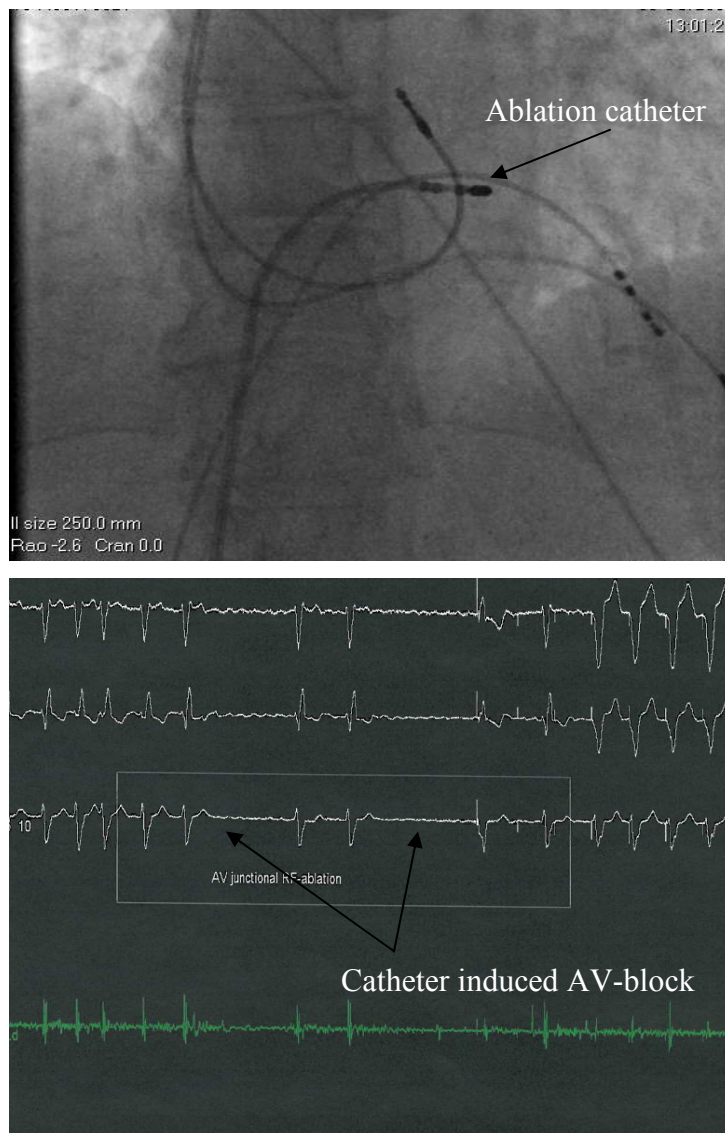
A detailed analysis of the ECG recording obtained after DC conversion was made after the procedure. *In paper I*, the heart rhythm was analyzed in relation to IRAF and ERAF during the first 2 minute because all ERAF occurred during the second minute only. However, the entire 5-minute period was analyzed to identify predictors for AF recurrence during the first week after discharge (n = 45). In addition, for the purpose of the latter analysis, a control group of 45 patients with SR was formed, and they were matched for age and gender with the AF recurrence group. *In paper II*, patients who were not possible to cardiovert, relapsed into AF within 5 minutes and before discharge or had technically unsatisfactory ECGs during and after cardioversion were excluded from analysis. Care was taken to assure good quality recordings for identifying P waves. All assessments were made on a beat by beat basis: PP and RR intervals were measured; P waves were adjudicated as sinus or of other origin. All premature atrial contractions (PAC) were counted.

III.

Ablation, Pacemaker Implant Procedure, and Follow-Up

At the beginning of the period, a permanent pacemaker was implanted on the day of AVJA. After a change in the routines later on in the period, this was done at least 1 month before AVJA. The right ventricular lead was placed in the apex region in all patients, and 128 patients also received an atrial lead in the right atrial appendix. The AVJA was performed

with the patient in the fasting state and under conscious sedation. The permanent pacemaker, if already in place, was programmed to the lowest VVI rate. A bi- or quadripolar electrode catheter was placed in the right ventricular apex region via the right femoral vein for pacing when necessary during the procedure. An ablation catheter was introduced to the His bundle region via the right femoral vein. All patients were treated with radiofrequency ablation, at first using power control and, when it became possible, temperature control. The ablation endpoint was the creation of a complete AV block persisting for at least 30 minutes.



AV junctional ablation and ECG during the ablation

At the end of the procedure, the permanent pacemaker was programmed to VVI(R) mode, or alternatively to DDD(R) mode, at a basic rate of 70–80 beats per minutes, which had to be maintained for at least 3 weeks before programming to a lower rate was allowed. A second

ablation procedure was necessary in 14 patients due to primary failure or recurrent AV conduction. After successful AVJA, antiarrhythmic agents were most frequently discontinued. β -blockers were still prescribed in 70 and digitalis in 35 patients for other reasons than rate control. Warfarin therapy was continued in 161 patients and aspirin was prescribed in 42 patients.

Clinical baseline data for all patients were retrieved from our ablation registry. The hospital records provided a detailed medical history, results of physical examinations, laboratory tests, and 12-lead electrocardiogram (ECG). Transthoracic echocardiography was routinely performed as a preablation procedure.

The first follow-up visit took place at the outpatient pacemaker clinic 1 month after the procedure. This assessment included a 12-lead ECG, an interrogation of the pacemaker including pacing parameters, settings, arrhythmia history, and histograms, when available, and a determination of the pacing thresholds. Pacing rate, mode, and other settings were programmed as needed.

The following visits took place at regular 6- or 12-month intervals and at new symptoms. All-cause death was also recorded. The time of each diagnosis and/or death was recorded to allow for the construction of a Kaplan-Meier curve to show freedom of events.

Outcome Measures

The primary outcome measure was the combination of new and aggravated HF during follow-up. Details on new and aggravated HF were also reported separately. All-cause death was recorded as a secondary outcome measure. In addition, a composite endpoint was formed by combining all three kinds of events, that is, new and aggravated HF and all-cause death.

IV and V.

Clinical data, including information relating to previous clinical history, risk factors and medication, were collected from hospital medical records. At admission, all patients were interviewed by an experienced study nurse, who specifically explored previous episodes of atrial fibrillation. ACS specific information such as delay times between the onset of symptoms and hospital admission, clinical presentation and ECG on arrival, as well as ECG changes during the hospital stay, was registered. Twelve-lead ECGs at a recording speed of 50 mm/s were used. Complications, including arrhythmias, medical treatment and investigations, were recorded in detail during in-hospital care. At discharge, medical treatment, planned investigations, revascularization procedures and the time spent in the hospital were documented.

Patients with AF could have a history of AF, and/or AF on admission, or could have their first AF in the hospital. The CHADS₂ score (an acronym for Congestive heart failure, Hypertension, Age >75 years, Diabetes and prior Stroke), used to estimate the risk of ischemic stroke in patients with AF (110), was calculated from data collected at admission. Patients with scores of 3, 4, 5 and 6 were few, and the scores were therefore divided into four subgroups with scores of 0, 1, 2 and > 2. The CHADS₂ score could not be determined in five patients with AF and three without AF because of missing data. Survival confirmation and dates of death as of January 1, 2007 were obtained from the Swedish National Population Registry and the incidence of stroke (International Statistical Classification of Disease, Ninth Revision (ICD-9) codes 431, 432, 433 or 436 or Tenth Revision (ICD-10) codes I61, I62, I63 or I64), AMI (ICD-9 code 410 or ICD-10 code I21 or I22) or hospital admission for atrial fibrillation (ICD-9 code 427D or ICD-10 code I48) were obtained via linking to the National Swedish Diagnosis Registry for hospitalized patients. Ten patients were lost during follow-up due to emigration.

Definitions:

* Immediate and early re-initiations of AF were defined as re-initiation within the first minute, IRAF, and within the first 5 minutes postcardioversion, ERAF (23).

* Premature atrial contraction density was defined as the number of PACs/minute, and the PAC burden was defined as the total number of PACs during the 5-minutes recording.

* Prematurity index is the ratio between the coupling interval of PAC and the preceding RR interval, where the coupling interval is the one between a PAC and the previous sinus beat.

* Variations in the rhythm and rate before AF relapse were also analyzed, including sudden drop in heart rate (>15 bpm during the preceding 4 beats) and brady-tachy phenomenon (>30 bpm variation compared with a reference of 60–90 bpm 1 min prior to AF relapse) (45).

* Sinus bradyarrhythmia was diagnosed in the presence of a sinus rate <40 bpm calculated from ≥ 2 consecutive P-P intervals and /or a sinus pause >2 s (116).

* CHF was diagnosed if at least two of the following criteria were present: New York Heart Association functional class >2 , an LVEF lower than 45%, and when pharmacological treatment for CHF was prescribed. Aggravated CHF was defined as an increase in the functional class by at least one degree when indicated or on the basis of the symptomatology at examination, anamnestic details, and/or prescription of one or more additional drugs for CHF.

STATISTICAL METHODS

Data are presented as percentages or as means \pm standard deviation (SD). All P-values are two-tailed and considered significant if below 0.05.

I.

Student's t-test has been used for paired comparisons of continuous variables. Multiple logistic regression analysis was used for assessing the predictive value of tentative prognostic factors after successful external electrical cardioversion of persistent AF.

II.

Unpaired t-test was used for comparison of continuous variables. Fisher's exact two-tailed test was used for comparison of categorical data.

III.

We applied a two-step strategy to identify independent predictors of the composite endpoint of new or aggravated CHF during follow-up. We first univariately tested the variables of age, gender, type of AF, bundle branch block, EF, left atrial area, left ventricular end diastolic diameter, and history of coronary artery disease, hypertension, diabetes, and HF. From this analysis all variables with a $P < 0.20$ (age, bundle branch block, EF, left atrial area and history of coronary artery disease, and CHF) were tested for inclusion in a multivariable Cox proportional hazards model, using a forward stepwise selection mode and $P < 0.05$ as a condition for remaining in the model. This two-step strategy was also used for mortality (where age, EF, and a history of coronary artery disease, hypertension, and diabetes were the variables with a univariate $P < 0.20$).

IV.

Fisher's exact test was used for dichotomous variables, when testing for any difference among the four AF subgroups and Kruskal-Wallis test for continuous variables. The log rank test was used in analysis of mortality and morbidity during follow-up, and Kaplan-Meier estimates were used for construction of cumulative mortality and hospitalization rates.

Cox proportional hazard model in a forward stepwise mode was used to identify predictors of all-cause long term mortality in the AF group. The following variables were tested for inclusion in the model: age, sex, previous infarction, angina, heart failure, diabetes, hypertension, stroke, hypercholesterolemia, bypass surgery, percutaneous coronary intervention, valve surgery, smoking habits, index diagnosis and peak creatine-kinase (CK)-

MB. A p-value below 0.05 was needed for inclusion as well as for staying in the model at each step in the selection procedure.

All tests are two-sided and a p-value below 0.05 was considered statistically significant for overall comparisons of the four AF groups. In addition, a p-value below 0.01 was needed for a difference to be considered significantly different in the pair-wise two-group comparisons regarding CHADS₂ score, mortality and morbidity.

V.

The 6-graded CHADS₂ score was used in all p-value calculations of association with outcome, except where explicitly stated. Comparisons were made between patient groups regarding the CHADS₂ score with the Mann-Whitney U test. The log rank test and Cox proportional hazards model were used to test associations between the CHADS₂ score and mortality and hospitalizations for stroke. The latter was also used to calculate hazard ratios and corresponding confidence intervals. Kaplan-Meier estimates were made to assess cumulative mortality and morbidity with all data available up to January 2007. For morbidity, an individual who died during follow-up before an event had occurred was censored at the time of death.

ETHICS

The Ethics Committee of Gothenburg University did not raise any ethical issues regarding paper I and II. The committee considered the retrospective study of paper III to be part of the ongoing quality assurance program of the clinic during that time.

The study described in paper IV and V, was approved by the Ethics Committee of the Gothenburg University and the patients gave their informed consent for participation.

RESULTS

I. Burden and timing of premature atrial contractions after electrical cardioversion of persistent atrial fibrillation do not predict its recurrence

Recurrence of AF during the first five minutes after DC

Initially, SR was obtained in 157 (91%) of the 172 patients (Figure 7). Eight patients had a relapse of AF within five minutes, and three of these were IRAFs. All five ERAFs occurred during the second minute after conversion. Several observations were made in these patients (>1/patient): AF was preceded by one PAC in two patients, by one premature ventricular contraction in three patients, and spontaneously started in three patients. Premature atrial contractions of two morphologies were seen in one patient before relapse, and PACs in bigemini were noted in another patient; both having IRAF. An increasing number of PACs was observed before relapse in three patients. The heart rate during the last ten RR intervals before relapse was 60–90 bpm in three patients and <60 bpm in four patients. A sudden drop in heart rate was noted in two patients and a brady-tachy phenomenon in another patient. Each patient with IRAF or ERAF thus displayed two or three possible onset mechanisms. All patients with IRAF/ERAF received additional DC shocks. Re-cardioversion restored SR in five patients, while it was unsuccessful in three patients. Another three patients relapsed into AF after the first five minutes, but before discharge, and 151 patients had SR at the time of discharge.

AF recurrence during the first week

Sinus rhythm was recorded in 106 (70%) of 151 patients (78 men) at the one-week rhythm control, among them only two of the originally eight patients with IRAF/ERAF. The mean age was 68 ± 11 years and the duration of AF before DC cardioversion was 5.8 ± 4.1 month. The characteristics of the two matched groups of 45 patients each with and without AF relapse within the first week are presented in Table 1. The focus of this part of the analysis was the role of PACs as potential predictors of re-initiation of AF within the first week after cardioversion. Comparisons were made regarding the PAC density, the mean coupling interval of PACs, the prematurity index for the first two minutes after DC cardioversion, and the PAC density during the first five minutes after cardioversion. No differences were found between the groups except that patients with recurrences had an AF episode duration of 5.9 ± 3.4 months compared with 3.8 ± 1.6 months in patients who maintained SR ($p < 0.003$).

Table 1: Age and gender-matched comparison between patients with and without AF recurrence at the 1-week follow-up visit

	AF	SR	p-value
Sex (men/women)	30/15	30/15	
Age (y)	70±9	70±10	
AF duration of index episode (mo)	5.9±3.4	3.8±1.6	0.003
PAC density, 1st min, n	3.0±3.7	3.6±3.5	ns
Range	(1–20)	(1–14)	
PAC density, 2nd min, n	3.5±4.5	3.9±3.8	ns
Range	(1–21)	(1–15)	
Coupling interval, msec	571±244	610±265	ns
Preceding RR, msec	846±390	915±387	ns
Prematurity index	62%	60%	ns

A multiple logistic regression analysis including age, gender, AF duration >3 months and PACs in relation to AF recurrence during the first week did not reveal any independent predictor of AF recurrence.

II. Transient impairment of sinus node function immediately after electrical cardioversion of persistent atrial fibrillation

Fifteen of the 172 consecutive patients could not be cardioverted; eight relapsed within five minutes, three relapsed before discharge (> 5 min) and six had technically unsatisfactory ECG recordings. The study population therefore comprised 140 patients (Figure 8). Sinus bradyarrhythmia (SB) was present during the first minute after conversion in 31 patients (21 men; 22%, 95% CI: 15-29%) and the index cardioversion was their first in 14 of them (45%). Twenty-seven (87%) patients had a sinus bradycardia <40 bpm and 16 (52%) sinus pauses ≥2 s (ten of them >3s; 32%); 12 (39%) had both.

Altogether, 53 patients had undergone at least one previous cardioversion. There was no significant difference in age, duration of the index AF episode, proportion of men vs. women, or therapy with anti-arrhythmic or beta-blocking substances in patients with vs. without SB. Patients with SB had a significantly lower mean heart rate during the first minute after cardioversion (57 ± 13 vs. 63 ± 11 bpm; $p < 0.05$), but the average rates at each of the subsequent four minutes and during the entire five-minute period were not significantly different. The number of PACs during each minute varied among patients but the mean number was similar across the five minutes and there was no significant difference between patients with vs. without SB.

AF recurrence at one week and three months (Table 2)

In total, 58 patients (41%) relapsed into AF within the first week. Fourteen of the relapses (45%) occurred in the group of patients with vs. 44 (40%) among those without SB (ns). In the former group one patient with AF at the one-week follow-up was cardioverted once more and remained in SR at three months, at which time 21 (68%) patients with SB were in AF vs. 58 (53%) patients without (ns). We found no relation between AF recurrence and factors such as age (>75 vs. ≤ 75 years), gender and AF duration (>3 months vs. ≤ 3 months). However, SB was significantly more common in patients with antiarrhythmic therapy. Baseline characteristics were compared in relation to AF recurrence at one week and three months and no statistically significant differences were found.

Table 2. Atrial fibrillation (AF) recurrence at 1 week and 3 months follow-up in relation to specified sub-groups. Proportions are presented with 95% CI within brackets.

	SB		Normal SR	
	31 (22%; 15-29)		109 (78%; 71-85)	
	AF at 1 week	AF at 3 months	AF at 1 week	AF at 3 months
	14	21	44	58
	(45; 27-64)	(68; 48-83)	(40; 31-49)	(53; 44-62)
Age > 75 years	6	9	15	17
	(43; 18-71)	(43; 22-66)	(34; 20-50)	(29; 18-43)
Gender (F)	6	8	16	22
	(43; 18-71)	(38; 18-62)	(36; 22-52)	(38; 26-52)
AF duration > 3 months	11	17	25	37
	(79; 49-95)	(81; 58-95)	(57; 41-72)	(64; 50-76)
AA drug therapy	14	21*	39	40
	(100; 77-100)	(100; 84-100)	(89; 75-96)	(69; 55-80)

AA antiarrhythmic; AF atrial fibrillation; CI confidence interval; F female; SB sinus bradycardia and/or pauses; SR sinus rhythm; *p < 0.01 for comparisons between the sub-groups at 3 months

III. New or aggravated heart failure during long-term right ventricular pacing after AV junctional catheter ablation

Incidence and role of new HF or aggravated HF after AVJA

213 patients underwent AV junctional ablation. Forty-nine (23%) patients, 28 of them men, were known to have been diagnosed with HF before AVJA and were on appropriate medication (Table 3). Thirty-eight patients had permanent AF: 11 patients had complete bundle branch block, five right bundle branch block and six left bundle branch block. At ablation, 32 patients had already had a single-chamber (VVI) pacemaker implanted for other

reasons than the AVJA. The EF was 46 ± 14 , the left ventricular end diastolic diameter 58 ± 8 mm and the left atrial area 29 ± 8 cm.

Table 3. Baseline demographics in patients with documented HF before AVJA and exaggerated or new HF during follow-up

Heart failure	Documented before AVJA	Exaggerated & New heart failure during follow-up
n	49	13
Age, years	73 ± 12	72 ± 16
Men : women, n (%)	28(57) : 21(43)	8 : 5
Permanent AF/ Paroxysmal AF, n (%)	38(78) / 11(22)	5 / 8
Dilated cardiomyopathy, n (%)	20 (41)	5
RBBB : LBBB, n (%)	5(1.1) : 6(1.2)	3 : 1
PM, n (%) (DDD mode:VVI mode)	17(35) : 32(65)	5 : 8
Beta-blockers, n (%)	31 (63)	7
ACE-inhibitors, n (%)	32 (65)	6
Diuretics, n (%)	34 (69)	9
EF (%)	46 ± 14	45 ± 14
LVDD, mm	58 ± 8	56 ± 8
Left atrial surface area, cm ²	29 ± 8	29 ± 9

ACE – angiotensin convertase enzyme, AF – atrial fibrillation, AVJA – atrio-ventricular junctional ablation, EF – ejection fraction, LBBB – left bundle branch block, LVDD – left ventricular diastolic diameter, PM – pacemaker, RBBB – right bundle branch block.

Figure 10 shows the Kaplan-Meier curve for the combination of having **new or aggravated HF** during follow-up. The Cox proportional hazards regression analysis revealed age (per five years) as the only significant risk factor, 1.19 (95% confidence interval [CI]: 1.00–1.41), $p = 0.047$, while LVEF (per 5%) significantly lowered the risk, 0.76 (95% CI: 0.67–0.87), $p <$

0.0001. Thirteen of 49 patients (26%) developed aggravation of known HF during follow-up. This occurred in five patients with permanent AF and eight patients with paroxysmal AF at baseline, and all were detected within three years after AVJA. Ten patients (20%) died 38 ± 31 months after AVJA, six of whom were in permanent AF and four in paroxysmal AF before AVJA. Three of these patients died of HF 15, 35 and 110 months after AVJA (mean 53 ± 33 months). Their baseline EF was 20%, 60% and 30%, respectively. There were no later EF values in the latter two patients, while it remained at 20% in the first. Twenty-two patients developed new HF during follow-up and were detected at a mean time of 44 ± 37 months after AVJA, with 50% occurring at a time less than three years after ablation. Eleven patients each were in paroxysmal and persistent/permanent AF before AVJA. Six patients died during follow-up, one of HF.

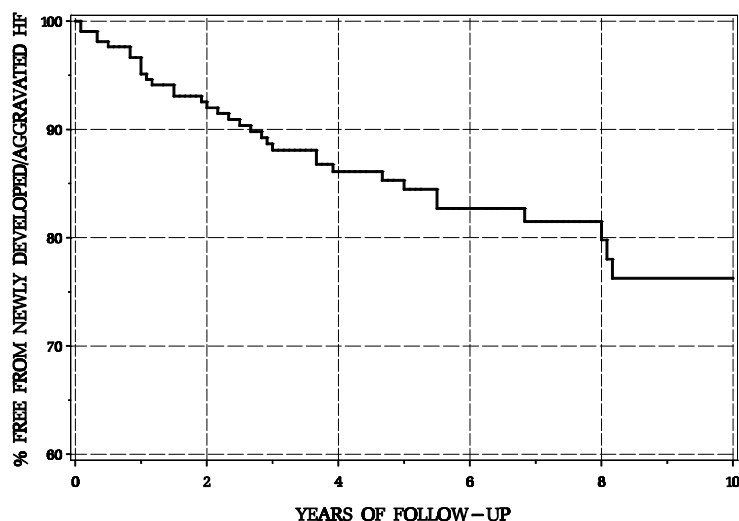


Fig. 10. Freedom from new or aggravated HF

Multiple logistic regression analysis identified age per five years (odds ratio [OR] 95% CI 1.5 (1.0–2.0), $P = 0.02$) and EF per 5% (OR 95% CI 0.7 (0.5–0.8), $P = 0.008$) as independent predictors of an increased and a decreased risk of developing HF during follow-up in patients with no signs of HF before ablation. For the patients with known HF at baseline, none of the variables tested were significantly associated with a worsening of their HF during follow-up.

All-cause mortality

The all-cause mortality was 16%, 35 patients (18M : 17F), occurring at a mean time of 47 ± 30 months after AVJA. Their mean age at AVJA was 78 ± 11 years. Cause of death could be established in 27 patients. Four patients died of deteriorated HF, eight of age, one as a result of brain hemorrhage, nine of myocardial infarction, two of cancer and three patients of

pneumonia. Seventeen patients were in paroxysmal AF at AVJA. Figure 11 shows the estimated freedom from all-cause death in our population. Two predictors of all-cause mortality were identified in the Cox proportional hazards regression analysis: age (per five years), hazard ratio 1.30 (95% CI: 1.08–1.56), $p < 0.005$, and coronary artery disease, hazard ratio 2.58 (95% CI: 1.26–5.31), $p < 0.01$

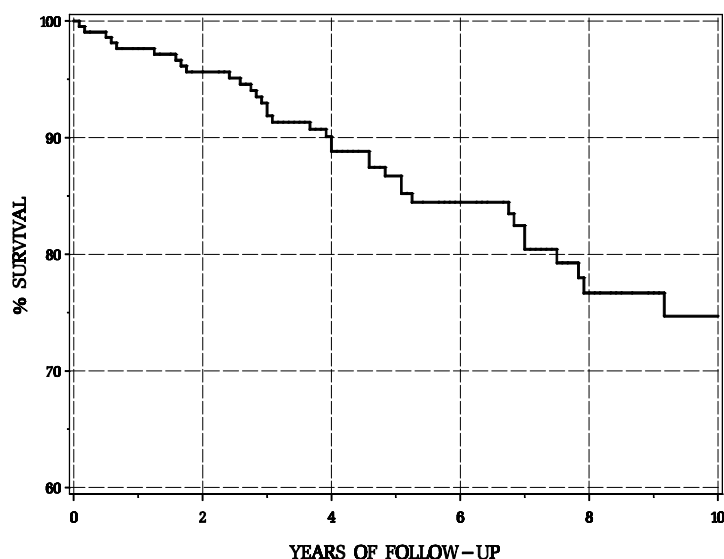


Fig. 11. Freedom from all-cause death

IV. Short-term and long-term prognosis in relation to type of atrial fibrillation in patients with acute coronary syndromes

Prevalence and incidence of different types of AF at the time of ACS

Four hundred forty-two (71 ± 8 years, range 67 to 76 years, 142 women) out of 2335 ACS patients had or developed AF. AF was previously known in 204 patients, persistent/permanent in 54 and paroxysmal in 150. New AF was seen at admission in 54 patients and AF developed during hospitalization in 184 (Figure 9). At admission, 145 patients were in ongoing AF, 54 with known persistent/permanent AF, 37 with known paroxysmal AF and 54 who with their first detected AF. Altogether, 70 patients left the hospital in AF, i.e. all 54 with persistent/permanent AF, eight of 54 with new AF at admission and eight of the 184 patients with new AF that developed in hospital.

At admission, the rates of previous AMI, angina, bypass surgery, percutaneous coronary intervention, hypercholesterolemia and CHF were significantly different among the sub-

groups. CHF was most often observed in patients with persistent/permanent AF (39%), while AMI, angina and hypercholesterolemia were most frequently seen in patients with known paroxysmal AF, 42%, 71% and 35%, respectively. The prevalence of previous stroke differed among the sub-groups ($p=0.04$), with the highest observed proportion in patients with persistent/permanent AF (20%) and the lowest in those with new AF at admission (8%). There was a significant difference in diagnosis among the sub-groups, with the highest observed rate of ST segment elevation myocardial infarction (STEMI) in patients with new AF in hospital (54%), of non-STEMI in patients with AF at admission (56%) and of unstable angina in patients with known paroxysmal AF (31%). A significant difference among the subgroups was also seen in ventricular arrhythmia during hospitalization, where the highest observed proportion was in patients with new AF in hospital (45%).

It is of note that only 14% of patients with any AF were on warfarin at admission, most of them patients with known persistent/permanent AF (41%). Of patients with previously known paroxysmal AF, 18% had warfarin as prophylactic anticoagulation therapy.

CHADS₂ scores at admission

There was a significant difference in CHADS₂ scores among the subgroups, with the highest observed scores in the two sub-groups with previously known AF. In pair-wise sub-group comparisons, patients with new AF in hospital significantly differed from patients with both types of previously known AF, as did patients with new AF at admission from those with previously known persistent/permanent AF (Table 4).

Table 4. CHADS2 score at baseline

CHADS2 score	Patients without AF (%) (n = 1893)	Previously known AF (%)			New AF (%)		p
		PeAF (n=54)	PaAF (n=150)	At admission (n=54)	In hospital (n=184)		
0	40	11	17	27*	26		
1	33	21	28	29*	36		
2	16	38	24	27*	23		
3	6	15	15	14*	9		
4	3	6	9	2*	4		
5	1	9	5	0*	0		
6	<1	0	3	0*	1		
Mean±SD	1.0±1.1	2.1±1.4	1.9±1.5	1.3±1.1 [†]	1.3±1.2 ^{†‡}	<.0001	

AF – atrial fibrillation, Pa – paroxysmal, Pe – persistent/permanent, p – for any difference among AF subgroups, * 5-10 % of cases missing data, [†] significantly different from the subgroup with previously known PeAF, [‡] significantly different from the subgroup with previously known PaAF

Short- and long-term mortality and stroke in AF subgroups

There was a significant difference in mortality among AF subgroups at 30 days ($p=0.02$) (Table 5). The mortality was significantly higher in patients with previously known persistent/permanent AF than in patients with paroxysmal AF. Patients with previously known paroxysmal AF had the lowest observed early mortality (7.3%), and this was similar to that of patients without AF (5.2%).

Table 5. Mortality and stroke

	Patients without AF (n = 1893)	Previously known AF			New AF		p*
		PeAF (n=54)	PaAF (n=150)	At admission (n=54)	In hospital (n=184)		
<u>All-cause mortality (% actuarial)</u>							
Early (<30 day) mortality	5.2	22.2	7.3 [†]	14.8	16.3		.02
Total 10-year mortality	36.3	78.1	69.0	68.0	53.2		.24
<u>Stroke hospitalization(%)</u>	11.6	23.8	40.3	31.3	15.6 [‡]		.007

AF - atrial fibrillation: Pa – paroxysmal, Pe – persistent/permanent, * for any difference among AF subgroups, [†] significantly different from the subgroup with previously known **PeAF**, [‡] significantly different from the subgroup with previously known **PaAF**

The ten-year mortality did not differ significantly among the four AF sub-groups. Patients with persistent/permanent AF had the highest observed mortality at ten years, 78.1%. The Kaplan-Meier curves demonstrating the all-cause ten-year mortality are shown in Figure 12.

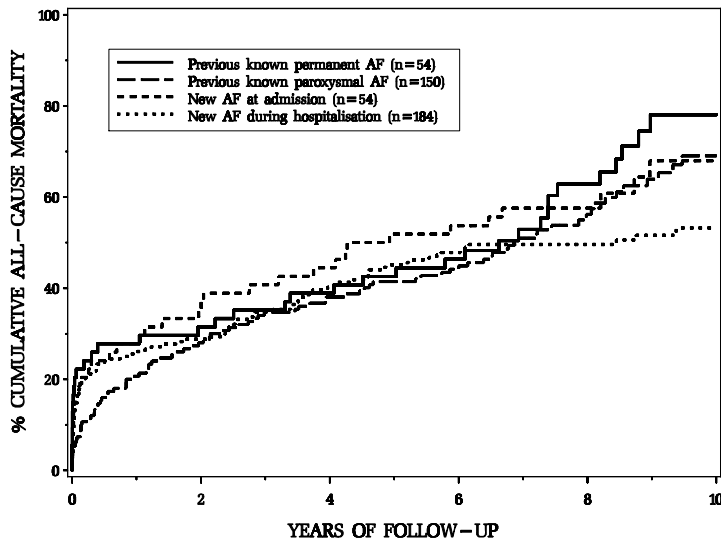


Fig. 12. All-cause mortality in the four sub-groups of atrial fibrillation

During the index hospitalization, ranging from a mean of six to nine days across the sub-groups, new stroke occurred in 4% of patients with new AF developed during hospitalization, in 2% of those with AF at admission and in 1% of patients with previously known paroxysmal AF, while no stroke occurred in patients with previously known persistent/permanent AF. At discharge, 19% of patients with any AF were on warfarin, implying that new AF in the acute phase of an ACS was not regarded as an indication to start anticoagulation. The hospitalization rate for stroke differed significantly among the sub-groups during long-term follow-up ($p=0.007$), being most frequent in patients with known paroxysmal AF, 40.3%, followed by new AF on admission, 31.3%; the lowest observed proportion was in patients with new AF during hospitalization, 15.6% (Table 5). In pair-wise comparisons the latter proportion was significantly lower than that observed in patients with previously known paroxysmal AF.

Predictors of long term mortality

Five variables were identified as predictors of long-term mortality in the total study group of AF patients. These were age ($p<0.0001$, with a hazard ratio (HR) of 1.06 per year and a

corresponding 95% confidence interval (CI) of 1.04-1.09), previous AMI (p=0.04, HR (95%CI): 1.4 (1.0-1.8)), previous CHF (p=0.0002, HR (95%CI): 1.8 (1.3-2.4)), previous diabetes (p=0.0005, HR (95%CI): 1.7 (1.2-2.2)) and current smoking at admission (p=0.001, HR (95%CI): 1.7 (1.2,2.3)). Table 6 shows these variables separately for the four AF sub-groups. The impact was similar across these sub-groups for all predictors except previous AMI, which differed statistically significantly between patients with previously known persistent/permanent AF and those with new AF at admission and new AF in hospital (p for interaction = 0.0007 and 0.03, respectively), and between patients with previously known paroxysmal AF and those with new AF at admission (p for interaction = 0.02).

Table 6. Predictors of long-term total mortality in the four sub-groups of atrial fibrillation

	Previously known PeAF		Previously known PaAF		New AF at admission		New AF in hospital	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (per year)	1.07(1.00, 1.14)	.05	1.05(1.01, 1.09)	.007	1.08(1.02, 1.15)	.01	1.08(1.04, 1.12)	<.0001
Previous AMI	3.3 (1.6, 6.8)	.002	1.6 (1.0, 2.6)	.04	0.5 (0.2, 1.3)	.18	1.0 (0.6, 1.7)	.93
Previous CHF	2.5 (1.2, 5.0)	.01	2.1 (1.3, 3.3)	.003	1.6 (0.5, 4.9)	.39	1.9 (1.0, 3.8)	.05
Diabetes	1.6 (0.8, 3.4)	.22	1.7 (1.1, 2.9)	.03	2.5 (0.9, 6.6)	.06	1.6 (1.0, 2.6)	.04
Smoking	0.9 (0.4, 1.9)	.72	1.7 (1.0, 3.1)	.06	1.6 (0.7, 3.8)	.31	2.1 (1.3, 3.4)	.004

AF - atrial fibrillation; Pa – paroxysmal, Pe – persistent/permanent, AMI – acute myocardial infarction, CHF – congestive heart failure,

HR (95% C.I.) - hazard ratio and corresponding 95% confidence interval

V. Role of the CHADS₂ score in acute coronary syndromes – risk of subsequent death or stroke in patients with and without atrial fibrillation.

CHADS₂ score in patients with and without AF

Almost half of the patients with AF (n=442 patients) had a CHADS₂ score equal to or greater than 2 as compared with one quarter of the patients without AF (n=1893 patients) (Table 7). Patients with AF had a mean score of 1.6±1.4 versus 1.0±1.1 for patients without AF, p<0.0001.

Table 7. CHADS₂ score at baseline in acute coronary syndrome patients with and without atrial fibrillation

	Patients without AF (%) (n=1893)	Patients with AF (%) (n=442)	p
CHADS ₂ score			
0	40	22	
1	33	30	
2	16	26	
3	6	12	
4	3	6	
5	1	3	
6	<1	1	
mean±SD	1.0±1.1	1.6±1.4	<.0001

AF – atrial fibrillation

The burden of previous cardiovascular diseases was somewhat greater in patients with than without AF. Patients with any AF were older and more often had previous heart failure. Previous stroke was almost equally frequent in both groups. With the exception of previous percutaneous coronary interventions (PCI), indicators of ischemic heart disease were more frequent with increasing CHADS₂ score in both groups. The CHADS₂ score correlated inversely with STEMI in both groups whereas non-STEMI was more frequent at higher CHADS₂ scores in patients with AF.

Early and long-term mortality

Survival analysis showed that patients with AF had a higher risk of dying than those without AF (Figure 13).

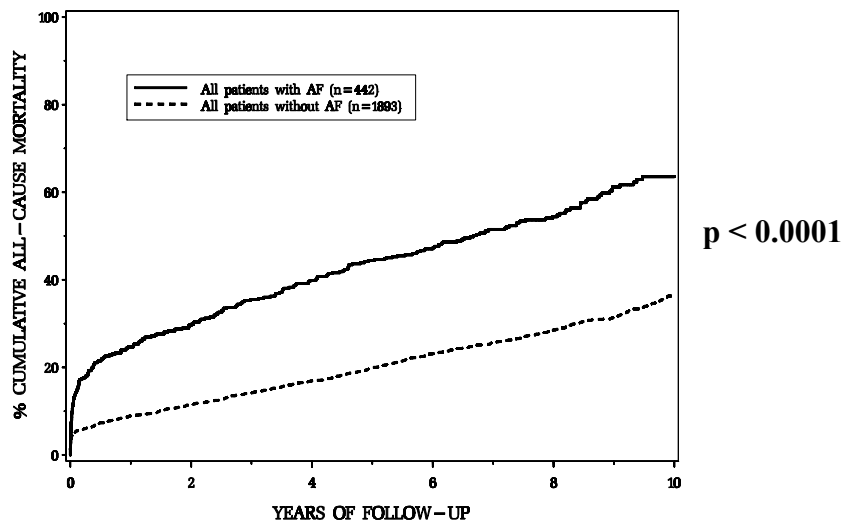


Fig. 13. All-cause mortality in patients with and without AF

Early mortality (less than 30 days) was higher in patients with than without AF but was related to the CHADS₂ score only in patients without AF (Table 8). Thus the risk of dying within 30 days was doubled to tripled at CHADS₂ scores of 0, 1 and 2 and, at CHADS₂ score >2, the risk remained somewhat elevated in patients with AF as compared to patients without AF.

Table 8. Short and long term follow-up in relation to CHADS₂ score in acute coronary syndrome patients with and without atrial fibrillation

	Patients without AF				Patients with AF				p*	
	C	H	A	D S 2	C	H	A	D S 2		
	0	1	2	>2	0	1	2	>2		
	(n=754) (n=628) (n=310) (n=198)				(n=94) (n=133) (n=113) (n=97)				p*	
Early (<30 days) mortality (%)	4.0	3.7	6.1	11.6	<.0001	12.8	6.8	17.7	16.5	.052
10-year mortality (%)	21.2	33.4	53.7	74.0	<.0001	41.1	59.7	66.4	84.8	<.0001
Stroke hospitalization (%)	7.8	11.3	18.6	19.0	<.0001	11.7	30.2	36.4	27.9	.008

AF – atrial fibrillation, * actual CHADS₂ score as an ordered variable used for p-value calculations

All-cause 10-year mortality showed a highly significant association with the CHADS₂ score in both groups. The mortality rates observed at CHADS₂ score 0 were 41.1% and 21.2%, and at CHADS₂ score 1 were 59.7% and 33.4%, in patients with and without AF, respectively. At scores of 2 and higher, the differences remained but were smaller. The absolute mortality level exceeded 50% in both groups, and patients with AF had a 10-year all-cause mortality rate of 84.8%. The Kaplan-Meier curves demonstrate that the all-cause 10-year mortality in patients with AF (Figure 14) and without AF (Figure 15) increased as the CHADS₂ score increased. However, in each of the CHADS₂ score subgroups, including score 0, the mortality risk was consistently higher in patients with AF. Thus the risk of dying within 10 years was almost doubled at CHADS₂ scores 0 and 1, while this difference disappeared at higher scores. The all-cause mortality was lower regarding CHADS scores 0, 1 and 2 in patients without AF, while the curves showing CHADS score >2 were almost similar in both patients without and with AF.

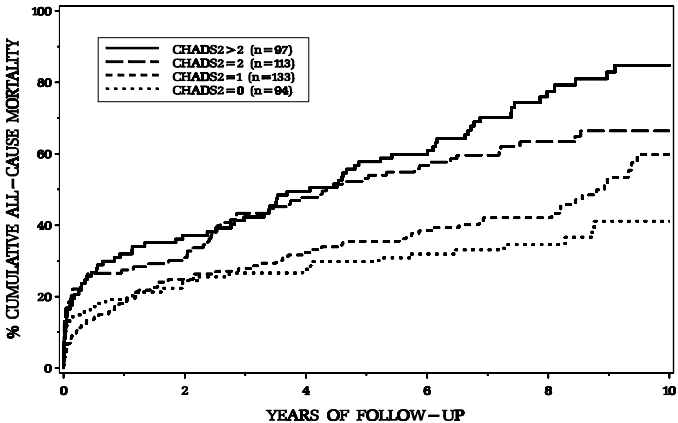


Fig. 14. Cumulative all-cause mortality during follow-up in relation to CHADS₂ score on admission in patients with AF (n=437)

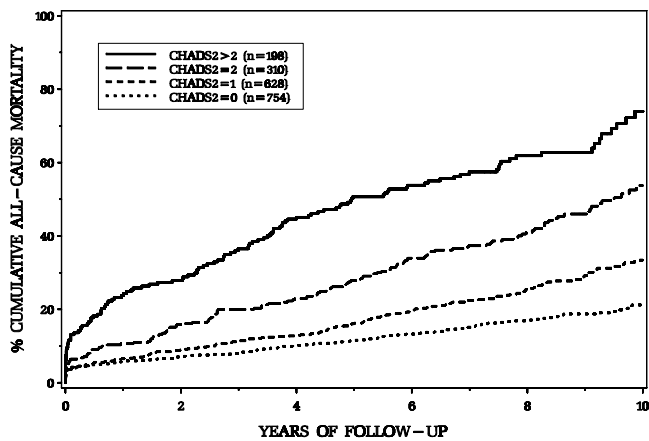


Fig. 15. Cumulative all-cause mortality during follow-up in relation to CHADS₂ score on admission in patients without AF (n=1890).

All-cause mortality correlated significantly with CHADS₂ scores, both unadjusted and when adjusted for potential confounders. The association was stronger in patients without than patients with AF.

Incidence of hospitalization for stroke during long term follow-up

The risk of hospitalization for stroke in the 10 years of follow-up showed an increasing rate with higher CHADS₂ score in both patients with and without AF (Table 8).

In patients with AF and CHADS₂ scores 1 and 2, stroke occurred early and increased through the first seven years (Figure 16). The risk was much lower for CHADS₂ scores >2 and increased slowly until a steep increase occurred at the beginning of year 4. The pattern in patients without AF was different, with patients with a CHADS₂ score >2 demonstrating the highest risk and the others showing a very low risk during the first two years, which thereafter increased but at a slower rate than in patients with AF (Figure 17).

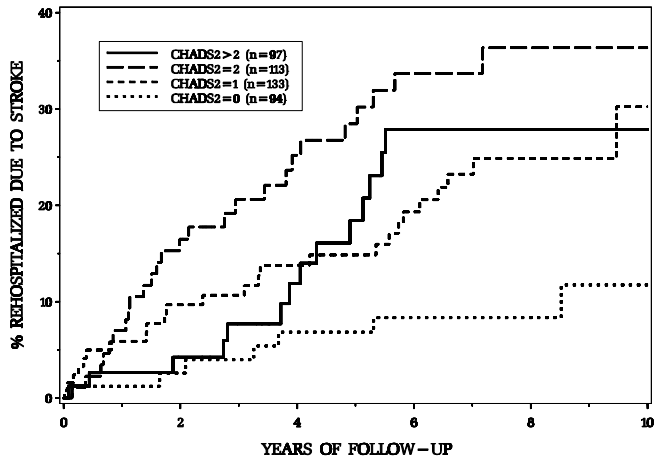


Fig. 16. Cumulative hospitalization for stroke during follow-up in relation to CHADS₂ score on admission in patients with AF (437).

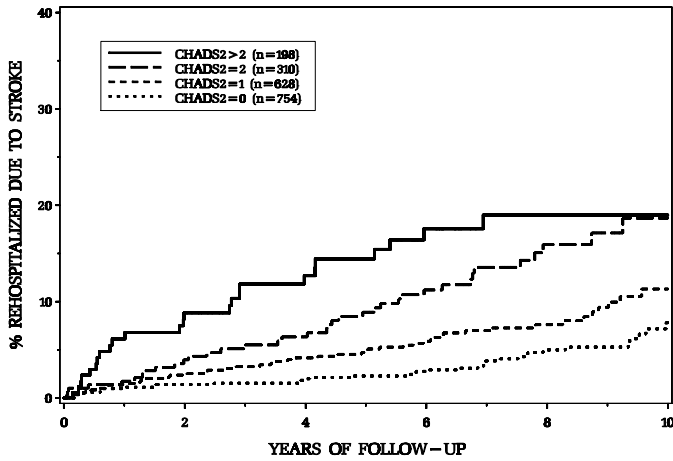


Fig. 17. Cumulative hospitalization for stroke during follow-up in relation to CHADS₂ score on admission in patients without AF (1890)

The CHADS₂ score was significantly associated with the rate of hospitalization for stroke in patients without AF, both unadjusted and after adjustment for potential confounders.

DISCUSSION

Triggers of AF re-initiation early after restoration of sinus rhythm

While premature atrial contractions were common, neither the PAC burden nor PAC prematurity predicted recurrence of AF during the first week. A short duration of the AF episode was the only predictor of the maintenance of SR, and sinus bradycardia during the first minute after successful electrical cardioversion had no prognostic effect on short term AF recurrence, pacemaker implant rate or survival during long term follow-up.

The rate of IRAF/ERAF was 4.6% in our population of persistent AF patients, which is consistent with one report (23) but in contrast to others that have dealt with spontaneous or internal electrical conversion of AF episodes of very short durations (42, 44). Six of our eight patients with IRAF/ERAF relapsed into AF within the first week, which probably implies the presence of a substrate making SR more difficult to maintain. In the case of AF episodes of short duration, Gorenek et al. found a recurrence rate within one minute of 27% and observed that 73% of the recurrences were initiated by PACs, which were found in only 12% of patients who did not experience immediate recurrence of AF (117). These conflicting results may be explained at least in part by the heterogeneity of patient populations. Oral et al. found that recurrences within one minute were more likely when the duration of the AF episode was less than one hour than when it was longer than 24 hours (56% versus 12%; $p < 0.001$) in patients undergoing electrophysiological procedures (118). Similar results were observed in a small study involving 17 patients with an implantable defibrillator, where AF episodes were electrically cardioverted by the patients' activation after a mean of either 6.8 h or of 34.7 hours (119). Our study population had a considerably longer AF episode duration than these studies. In general, the IRAF and ERAF rate seems to be inversely related to the duration of the AF episode.

While the few IRAF/ERAFs conferred a high likeliness of recurrence of AF, PACs and patterns of PACs did not. This is consistent with the results of another study, where neither the frequency of PACs nor the number and length of runs of PACs during the first 24 h following DC cardioversion predicted the recurrence of AF (120). Device studies have identified a number of onset mechanisms in analyses covering several minutes preceding AF initiation (23, 44, 45, 121). We chose to test the trigger mechanism definitions described in one such study (45), that showed that more than one possible onset mechanism per patient are often observed and that PACs are common in the majority of patients. In more than 50% of cases, ERAF episodes were preceded by brady-tachy phenomena, which could be the result of

a change in autonomic tone or transient electrical remodelling of the sinus node by AF (122). Hoffmann et al. showed that the onset of AF in 97 patients with pacemakers was preceded by a heart rate of less than 60 bpm in 33% of 612 episodes of AF (45). These findings highlight the importance of other factors than the trigger *per se* (123).

Role of bradyarrhythmias immediately after successful DC

The results reported in paper II suggest that sinus bradyarrhythmia in the immediate post-cardioversion phase was transient and did not predict a recurrence of AF at one week or three months. In two other series of altogether 57 patients, the SN function was studied invasively in relation to internal cardioversion (n=37) and AF ablation (n=20), respectively, and impaired SN function was found to be reversible and without relevance for AF recurrence during short term follow-up (124, 125).

SN dysfunction might be the result of a remodeling process induced by short periods of atrial pacing and longer periods of AF in animals and humans (46, 124-126). Less is known about AF-induced SN remodeling than about AF-induced atrial remodelling (28, 31, 127-129). Upon restoration of SR, the reversal of AF-induced atrial electrical remodeling seems to be relatively fast (within days) while structural remodeling and its reversal (when possible) is a much slower process (over months). AF is predominantly a condition among elderly people, and the same is true for SN dysfunction. While AF is most often symptomatic, signs of slight or moderate SN dysfunction may be found in completely asymptomatic persons. In an elderly clinical patient population, there is an increased probability of age-related SN impairment, myopathic SN dysfunction and drug-induced impairment of SN function, alone or in combination (46, 50, 126, 130, 131). The prevalence of AF in patients with SSS might be as high as 50% (132, 133), but less is known about the prevalence of significant SN dysfunction among patients with persistent AF, and this was much less in our study population. The results did not support our original hypothesis that post-cardioversion sinus bradycardia might be part of a previously unrecognized SSS. However, there is no single pathognomonic criterion for SN dysfunction. Since maintaining automaticity at a functional rate is the main task of the SN, indicators of disturbed automaticity and/or sino-atrial conduction have been regarded as suitable markers of SN dysfunction. We diagnosed sinus bradycardia according to criteria proven to be relatively specific for SN dysfunction, in the range of 90-95% (47, 126, 134). In the present study, the proportion of patients with SB was 22% (95% CI: 15-29%) and it seems that SB appearing in close temporal relation to AF in most cases has a much more benign course than when it appears without such relation.

RV pacing and clinical heart failure after AVJA for drug resistant AF

Heart failure is one serious late complication of AF and in patients undergoing AVJA, AF is not cured but continues in the atria, while the ventricular rate is dependent on the implanted permanent pacemaker. At the time of the planning of the study reported in paper III, there was also an ongoing discussion about the benefit/risk scenario for candidates for AVJA. Specifically, reports on a small number of patients implied that long-term right ventricular stimulation would harm the heart by its non-physiological activation sequence to give rise to clinical heart failure and deterioration in many patients. In our single-centre experience, age and left ventricular dysfunction were independent predictors of new heart failure, while there were no predictors of aggravation of heart failure during follow-up in the study period. This would fit with what may be expected in this elderly population. In addition, the all-cause mortality of 16% during a mean follow-up period of four years corresponds to an annual all-cause mortality of ~4%, which is consistent with other reports (69). Four patients were confirmed to have died of heart failure, and the cause could not be exactly established in the other eight patients.

New heart failure developed in 22 patients (14%) with only one of these patients dying during the follow-up period. Consistent with this, Oczan and al. showed that survival among patients with lone AF after AVJA was similar to the expected survival in the overall population, and long-term survival was similar for patients with AF, regardless of whether they received pharmacological or non-pharmacological therapy (135). Our findings did not shed light on the cause of the development of new heart failure. High age and left ventricular dysfunction fit well with continuous progress of the AF related to electromechanical remodeling, but this does not exclude the influence of other factors, such as continuous right ventricular pacing since AVJA. This applied to all patients, even if those in paroxysmal AF at the time of AVJA were programmed into DDD mode. During long-term follow-up, 146 patients were in AF versus 115 at baseline, while 58 patients were still in SR as compared to 89 at baseline. Theoretically, it should be beneficial to stay in sinus rhythm, and there was no development of heart failure or aggravated heart failure in this subgroup during follow-up and no patient died of heart failure. This sub-group did not differ in their baseline characteristics from the whole group of patients with paroxysmal AF and, as they were treated at the beginning of the study period, the length of their follow-up was long.

AVJA has often been associated with a reduction of symptoms and an improvement in exercise tolerance and quality of life, while the effects on the EF have been variable.

Improvement has often been seen in the cases of primarily lower EF than normal (136-138), while a slight decrease has not been uncommon in patients with an almost normal EF (139). Patients with echocardiographically demonstrable intra-ventricular dyssynchrony may benefit from resynchronization during biventricular pacing by a reduction of symptoms with or without improvement of the EF, while the proportion of non-responders remains high, around 30% (140). It is of note that resynchronization was not available during most of the period when our patients underwent AVJA, and none of the patients were upgraded to biventricular pacing during the follow-up.

In previous studies, the ventricular function remained stable or improved after AVJA (68, 141, 142), while other reports have concluded that long-term right ventricular pacing can induce ventricular dyssynchrony and/or a deterioration in heart failure symptoms (70, 71, 143-145).

The panorama is changing, and it is more than likely that many of our patients, both with paroxysmal and some with persistent AF, would have been candidates for elective AF ablation if evaluated for treatment today. Others might have received resynchronization therapy, thereby requiring ventricular stimulation. Although the relationship between cause and effect cannot be conclusively demonstrated in our retrospective study, the course of events during the long follow-up period supported our hypothesis that long-term pacing does not frequently induce HF in patients after AVJA.

Prognosis of AF in patients with ischemic heart disease

The study described in paper IV confirmed that AF in patients with ACS is associated with increased short-term mortality and long-term morbidity, and showed that the type of AF is important. The study demonstrated that patients with persistent/permanent AF had a poorer prognosis than patients with other types of AF during the first 30 days after ACS, but this did not remain true in the long-term follow-up. More than half of the patients with any type of AF died during long-term follow-up. Patients with new AF at admission and those with known paroxysmal AF were more likely to have new hospitalizations for AF during the long-term follow-up, and the stroke incidence in patients with known paroxysmal AF was the highest observed among the sub-groups.

Patients with previously known paroxysmal AF had a lower mortality rate than patients with new AF at admission or during hospitalization and a higher risk profile at admission. They also more often had a history of CHF and coronary artery disease that may have led to their

ongoing medication, which may have reduced their risk of dying during the first 30 days after ACS.

Lau et al. showed that new-onset AF conferred poorer in-hospital adverse outcomes and that previous AF meant higher long-term (one year) mortality (106). In the GRACE study, new-onset AF was an independent predictor of in-hospital mortality and other adverse events in patients with ACS (107). In our study, previously known paroxysmal AF had a lower observed, although not statistically significant, early, i.e. <30 days, mortality compared to that of patients in persistent/permanent AF and of those with new AF. As mentioned above, this finding might be explained by the fact that patients with previously known AF may have had a more appropriate therapy than those with new onset AF, which may have resulted in a better short-term prognosis. A few baseline clinical variables were identified as predictors of mortality, i.e. age, previous HF, any previous any AMI, diabetes and smoking, which are consistent with the results of other studies (106, 107, 146, 147). In our study the impact of all predictors was similar across the subgroups with the exception of previous AMI, which differed significantly between patients with previously known persistent/permanent AF and those with new AF at admission and new AF in hospital, and between patients with previously known paroxysmal AF and those with new AF at admission.

AF type and risk of hospitalization for stroke, AMI or recurrence of AF

Patients with ACS and without AF had a substantial risk of having a stroke during the ten-year follow-up, and patients in AF were at a still higher risk with a statistically significant difference among the sub-groups, where the highest observed ten-year stroke risk was seen in patients with known paroxysmal AF. At admission for ACS, a CHADS₂ score ≥ 2 was present in 68% of patients with permanent AF, 57% in those with known paroxysmal AF, 43% in patients with new AF at admission and 37% in those with new AF developed in-hospital. warfarin treatment at admission and at discharge was present in less than half of the patients with persistent/permanent AF. In other sub-groups, prescription of warfarin was even less frequent, although a slightly increased prescription of warfarin was observed at discharge. In-hospital stroke was more often seen in patients with new AF after admission. Our findings with respect to stroke incidence confirm those of previous studies (99, 107, 148), where AF, irrespective of its type, carries an increased risk of stroke during short and long-term follow-up of patients after ACS. They also confirmed that patients who are eligible for warfarin are not always prescribed warfarin. This also holds true when the time period during which the patients in the present study were enrolled is taken into consideration.

The long-term risk of hospitalization for AMI was similar in the subgroups and similar to that of patients without AF. The risk of subsequent hospitalization for AF was different among the subgroups and occurred in more than half of the patients with new AF at admission. Hospitalization for AF was generally observed to be higher in patients with paroxysmal AF, known or new, than in those with permanent AF. We have only been able to obtain information about all relapses leading to a hospitalization, while an unknown number of patients may have had recurrences that did not lead to a hospital admission.

Role of the CHADS₂ score in patients with ACS, with or without AF

Paper V reported that the CHADS₂ score on admission predicted subsequent death and stroke in patients with ACS, with or without known AF. In fact, scores >2 were more predictive of these outcomes in patients without AF than with. The CHADS₂ score, both unadjusted and when adjusted for potential confounders, correlated significantly with all-cause mortality. As expected the score was also significantly associated with the rate of hospitalization for stroke. This association was strong in patients without AF, both unadjusted and after adjustment for potential confounders, while the statistical significance was not sustained after adjustment in patients with AF.

The CHADS₂ score was designed to be a scoring system for the risk of stroke in patients with AF (110) and can thus be used to guide anticoagulation (4). There is currently limited knowledge of the value of the CHADS₂ score in patients without known AF (114, 149). However, in the present study in patients with ACS, the CHADS₂ score proved to be valuable, which may seem reasonable since ischemic heart disease *per se* is often present in patients with AF, and all components of the CHADS₂ score are common known risk factors for ischemic heart disease (150). In fact, 27% of our ACS patients without known AF already had a CHADS₂ score of ≥ 2 at admission. While AF is most often associated with symptoms, it may also be asymptomatic. This means that there may be undiagnosed AF in the group of patients without known AF that would indeed justify the use of the CHADS₂ score. It is impossible for us to know whether or how often this was the case in our patient population, but it may contribute to the considerable risk of death or stroke that was found in patients without known AF.

The one-year mortality in patients with AF in the GUSTO I trial was higher than in patients without AF, which was in contrast to the data related to in-hospital mortality in that study, which showed no difference between the groups (147). This is consistent with the short and long term risks in the present study. An interesting observation in our study was the high

mortality rate among AF patients with a score of 0, which might at least partly be explained by the higher proportion of STEMI in this subgroup.

AF in the TRACE study, which included 6676 consecutive patients with AMI, was associated with an increased five-year mortality among in-hospital survivors, regardless of left ventricular ejection fraction (LVEF) and symptoms of congestive heart failure, except for those with an LVEF <0.25, a subgroup with a poorer prognosis because of heart failure (109). In the same investigation, when outcomes after AMI were considered in relation to hypertension, the multivariate analysis showed that chronic heart failure, hypertension history, increasing age and diabetes were independent risk factors for long-term mortality (151). This is in line with the findings in the present study, where mortality was higher as the CHADS₂ score increased. It is not surprising that patients with higher risk scores had increased mortality rates after ACS. The advantage of the CHADS₂ score in comparison with other risk scores (152, 153) is that it provides an easy mechanism for clinicians in risk evaluation since the score is already in use to assess the risk of thromboembolism in patients with AF.

Little data exist about the incidence of stroke after an ACS. The GUSTO I trial observed an incidence of in-hospital ischemic stroke of 0.5% during hospitalization for AMI in patients with sinus rhythm (147). This study did not provide data on stroke incidence during follow-up, and no risk evaluation was made for subsequent stroke. Our study shows that hospitalization for stroke is significantly more frequent with higher CHADS₂ scores. The incidence was higher in patients with AF and highest in patients with a CHADS₂ score of 2. Interestingly, patients with a CHADS₂ score of 1 had a higher risk of being hospitalized for stroke during the first four years after hospital admission than those with a CHADS₂ score of >2. One probable explanation is that AF patients with CHADS₂ scores of >2 were identified as qualifying for anticoagulation and put on warfarin, which may have reduced the incidence of stroke. It is more difficult to explain why the incidence rather abruptly increased after four years, but one reason could be the cessation of warfarin due to a lower perceived benefit/risk ratio. Equally interesting is that the number of hospitalizations with CHADS₂ scores 1 and 2 started to increase early and substantially, which could be interpreted by pointing out that, in the presence of ACS in AF patients, CHADS₂ scores of 2 and even 1 confer a high enough risk to consider anticoagulation.

CONCLUSIONS

- Premature atrial contractions were common immediately after DC cardioversion in patients with persistent AF, in contrast to IRAFs and ERAFs, which were not.
- The number and characteristics of PACs during the first five minutes after cardioversion did not predict recurrence of AF during the first week after restoration of SR.
- Sinus bradyarrhythmia was relatively common immediately after successful cardioversion. It was transient and without prognostic impact on the short-term AF recurrence rate.
- High age and left ventricular dysfunction were predictive of new heart failure during a mean of four years of follow-up after AVJA.
- The majority of patients who underwent AVJA continued to do well during long-term follow-up: the development of new symptoms of HF occurred in one eighth of patients and HF was aggravated in one fourth of patients with known HF.
- In patients with ACS, the type of AF affected the subsequent risk of early death and hospitalization for stroke and recurrence of AF during long-term follow-up.
- Long-term mortality was not influenced by the type of AF.
- The CHADS₂ score provided important information about risk and prognosis in patients with ACS, both with and without AF.

CLINICAL IMPLICATIONS

- The AF episode duration before DC and analysis of triggers of AF onset, including underlying rhythm after DC cardioversion, are helpful in selecting individualized therapy.
- IRAF and ERAF were less common after successful external electrical cardioversion in patients with persistent AF than reported after short AF episodes in device studies. Although six of eight patients relapsed into AF within a week, the numbers are too small to allow the predictive role of IRAF/ERAF in AF recurrence to be conclusively determined.
- Sinus bradycardia or pauses as common transient phenomena in the post-cardioversion period were not helpful in predicting AF recurrence.
- It is reasonable to believe that other factors, such as structure remodelling, in addition to or in combination with PACs, contribute to the AF recurrence rate after DC cardioversion of patients with persistent AF.
- Patients with permanent right ventricular pacing did not frequently develop new HF after AVJA, while it occurred more often in patients with already known HF. The optimization of HF therapy could be considered in those selected patients with drug-resistant persistent AF, who are candidates for AVJA.
- Identification of any type of AF should prompt the evaluation of underlying risk factors.
- The CHADS₂ score was useful in assessing the risk of subsequent events, including stroke and mortality, in patients both with ACS with and without AF, and routine use of the score will help in optimizing the treatment of important risk factors.

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