# Dilemmas in the Management of Atrial Fibrillation

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Background and recent developments

- Etiology and epidemiology
- Pathophysiology: What is atrial fibrillation?
- Cardioversion and maintenance of sinus rhythm
- Warfarin and aspirin in chronic atrial fibrillation

Dilemmas

- Does conversion to sinus rhythm improve symptoms better than rate control?
- Does conversion to sinus rhythm reduce strokes better than anticoagulation?
- Risk stratification and overall management

**Summary:** For most patients with structural heart disease, the goals of treating atrial fibrillation are the same: prevention of systemic emboli and stroke, and optimization of hemodynamics. Two strategies to achieve these goals are available: cardioversion and maintenance of sinus rhythm with antiarrhythmic agents, or rate control plus warfarin anticoagulation. Properly handled, the risk of cardioversion to sinus rhythm is low. Unfortunately, antiarrhythmic drugs are neither highly effective nor well-tolerated, and their safety is an open question. On the other hand, drugs for rate control are reasonably effective, well-tolerated, and safe. Anticoagulation with warfarin is effective for both primary and secondary prevention of stroke and systemic emboli. Because of uncertainties about the long term eficacy and safety of antiarrhythmic therapy, it is possible that the routine approach - cardioversion followed by antiarrhythmic drugs - should be reserved only for those patients in whom rate control plus warfarin anticoagulation is unacceptable.

By itself, atrial fibrillation is seldom life-threatening and it may be asymptomatic. Associated problems may range from relatively trivial complaints (occasional palpitations) to significant symptoms (dyspnea, limitation of exercise capacity and progression of heart failure) to catastrophic events (stroke and other systemic emboli). In spite of this spectrum of possible complications, most management decisions reduce to two therapeutic goals which must be considered in every patient with atrial fibrillation (AF). One objective is prevention of systemic emboli or ischemic events. Although cerebral emboli and stroke are properly emphasized, mesenteric, renal, cardiac and limb embolization also have a disastrous impact. The second objective is optimization of hemodynamics by controlling the ventricular response. Specifically, rate control is needed for comfort at rest, maintenance of exercise tolerance, and prevention of angina or heart failure in the setting of other heart disease. If both goals are achieved, mortality and morbidity will be reduced.

Cardioversion plus maintenance of sinus rhythm with drug therapy might be one means to achieve these universally-accepted goals. In this review, maintenance of sinus rhythm is compared to rate control plus anticoagulation for the management of atrial fibrillation in ambulatory patients with structural heart disease. The management of patients with known underlying noncardiac disease such as atrial fibrillation associated with thyrotoxicosis, drug or alcohol use, acute pulmonary emboli, etc., will not be considered. The details of cardioversion and the management of patients with bypass tracts (accessory pathways, Wolf-Parkinson-White syndrome) is excluded.

## 1. Etiology and epidemiology

*Etiology*

Atrial fibrillation is not a single problem, and it can occur in association with virtually any structural heart disease. It is useful to divide the associated conditions into diseases with normal or abnormal cardiac anatomy (Table 1). Included in the latter category are conditions which cause mechanical stress on the atria or ventricles. It is very important to recognize AF in the absence of significant structural heart disease because once the underlying condition is removed, AF is unlikely to recur (with the exception of idiopathic AF). Most of the remarks in this review are devoted to patients with structural heart disease.

*Prevalence*

Although AF usually is not considered a particularly interesting arrhythmia, it is the most common sustained arrhythmia. Its prevalence is about 0.4% of the adult population, much less than hypertension or coronary artery disease, and roughly equivalent to congestive heart failure. AF will occur at some point in 2-6% of individuals over 60 years old. Like hypertension, strokes, coronary artery disease and heart failure, atrial fibrillation is much more prevalent in the elderly population (Figure 1). However, the true incidence and prevalence of atrial fibrillation across age groups is difficult to determine. Although the ECG diagnosis is usually straightforward, most studies record a standard 12 lead ECG at selected intervals (months apart) or during a suspicious symptomatic event. Intermittent AF which is minimally symptomatic may be underestimated. On the other hand, AF associated with a rapid ventricular response may be represented accurately because it may present as palpitations; a slower ventricular response may go unnoticed. Thus, there are gaps in our knowledge of the natural history of AF. For example, we assume that chronic AF is generally preceded by earlier intermittent episodes, but this is unknown.

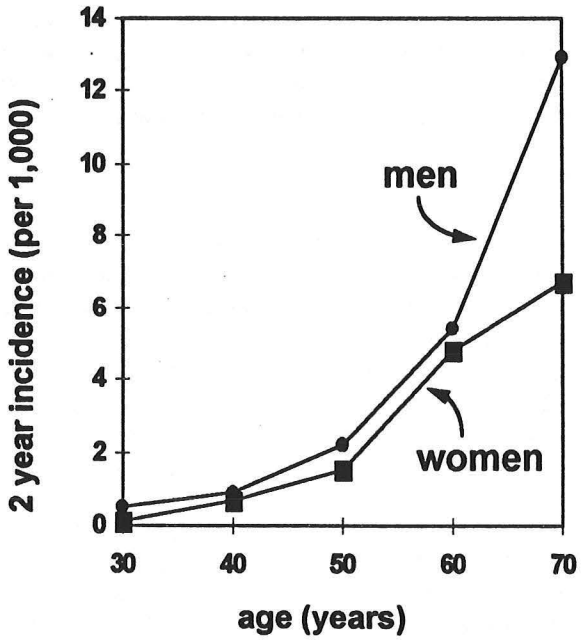


**Figure 1. Age, gender and the prevalence of atrial fibrillation. Data from reference 3.**

A minor problem in AF epidemiology is the absence of agreed definitions for subsets of AF which has been termed chronic, fixed, permanent, established, intermittent, isolated, paroxysmal, transient, brief, periodic, and recurrent. The lack of definitions is illustrated by the "lone fibrillator" which has come to mean a patient with atrial fibrillation and no known associated cardiovascular condition. As we shall see, AF generally is associated with an increased risk of stroke. However, the Mayo study of lone fibrillators (*1*) found no increase, while the Framingham study (*2*) found a fourfold increase in risk. The difference in these two studies likely is the definition of patient populations. In the Mayo Clinic study, patients over 60 and with any history of cardiovascular disease including hypertension were excluded. In the Framingham study, patients over 65 were included, and a history of hypertension (but not hypertensive heart disease) was also allowed. The Framingham patients had more risk factors for stroke than the Mayo Clinic patients, even though both populations were called "lone fibrillators."

**Table 1. Conditions associated with atrial fibrillation. Data from the Framingham Trial.**

**Structural heart disease**

- acute or chronic right or left atrial pressure load
  - valvular heart disease
  - intracardiac tumors or thrombi
  - cardiomyopathies
  - systemic hypertension
  - pulmonary hypertension
- abnormalities of the mitral valve ($Ca^{++}$, MVP)
- coronary artery disease and its complications, including acute MI
- inflammatory or infiltrative diseases
- pericarditis
- congenital heart disease ± surgical repair
- bypass tracts (WPW)

**No obvious cardiac abnormalities**

- alcohol, other drugs
- pheochromocytoma
- thyrotoxicosis
- digitalis intoxication
- stress - surgery, pneumonia, pain, hypoxia, etc.
- idiopathic ("lone fibrillator")

*Atrial fibrillation and mortality*

In the Framingham study, AF conferred a twofold increase in cardiovascular deaths and deaths from all causes (*3*). The mechanism of this excess mortality is not known, but it has been attributed to two factors. First, AF may directly cause fatal events due to emboli, progression of heart failure, or conceivably development of ventricular arrhythmias due to chronic effects of AF on ventricular repolarization (*4*). Second, AF may be the result of underlying cardiovascular disease and it may serve as a marker of a disease which causes excess mortality.

*Atrial fibrillation and morbidity*

AF is undoubtedly a major risk factor for strokes and systemic emboli in many patient subgroups (*5*, *6*); overall, it increases stroke risk fivefold. Although the cause of strokes is usually not determined, these ischemic events are assumed to result from thrombus formation in the nearly mechanically quiescent left atrium, followed by embolization. Available information (*7*, *8*) suggests that 60-70% of strokes in patients with atrial fibrillation are embolic, although the embolic source was not identified. Therefore, adequate anticoagulation should eliminate about 2/3 of strokes.

AF also causes diverse hemodynamic complications. The effects of AF on mechanics of the left ventricle are difficult to predict, but cardiac output may be reduced. With a rapid ventricular response, diastolic filling times may be inadequate and left atrial pressures may rise, resulting in dyspnea. This may be particularly troublesome for patients with left ventricular hypertrophy and reduced left ventricular compliance. A poorly controlled ventricular response is clearly associated with progression of heart failure. In patients with coronary disease, AF may reduce the exercise threshold for angina by increasing myocardial oxygen demand and reducing diastolic coronary flow.

## 2. Pathophysiology: What is atrial fibrillation?

The diagnosis of atrial fibrillation is made based on two ECG findings: absent P waves, and an irregularly irregular ventricular rhythm (in the absence of digitalis intoxication). Atrial activity is seen as fibrillatory waves, also called f waves, which appear to be fine irregularities or oscillations in the baseline of the ECG. Rarely, it may be difficult to distinguish atrial fibrillation from atrial standstill. Less frequently, the atrial fibrillatory waves can be coarse with amplitudes up to 2-4 mm in the standard ECG.

*Possible mechanisms of sustained atrial fibrillation*

The electrophysiological mechanism(s) responsible for clinical atrial fibrillation are unknown. One goal of current research is to understand both the initiation and maintenance of AF at a level similar to, for example, certain ventricular tachycardias. The clinical benefit could be identification of patients at high risk for complications of antiarrhythmic therapy and the development of devices or procedures which maintain sinus rhythm and eliminate the need for the drug therapies described below. All clinical arrhythmias are generally attributed to of one of three basic mechanisms (Table 2), although reentry is thought to be by far the most important cause of both supraventricular and ventricular tachycardias. A basic question is the role of ectopic foci (abnormal impulse generation) *vs.* reentry in the maintenance of atrial fibrillation. In experimental preparations atrial fibrillation can originate in a local injured region of tissue. If this portion of the atrium is excluded, the remainder of the atrium recovers normal function. Thus, an isolated abnormal region of atrium can be responsible for AF (consistent with abnormal impulse generation). On the other hand, anatomically normal atria (either in humans or in experimental animals) can be converted to atrial fibrillation with suitable stimulation protocols. Since many of the recent developments in the electrophysiology of AF center on the role of reentry, the three subdivisions will be reviewed briefly.

**Table 2. Mechanisms of arrhythmias: three classes, subdivisions and clinical examples. EADS, early afterdepolarizations; DADS, delayed afterdepolarizations.**

| | |
|---|---|
| 1. Spontaneous impulse generation | |
| normal | automatic atrial tach |
| abnormal | idioventricular rhythms |
| 2. Afterdepolarizations | |
| early (EADS) | torsade de pointes |
| delayed (DADS) | digitalis intoxication |
| 3. Reentry | |
| Anatomic | many forms of VT, AVRT, etc. |
| Functional | ? atrial fibrillation |
| Anisotropic | ? |

*Anatomical reentry* is the classical phenomenon observed by Mayer and by Mines early this century. There are two essential features of the reentrant circuit: 1) a fixed structure with a central region of inexcitibility (i.e., there is a core of dead tissue or scar, or an anatomical structure such as an atrioventricular valve ring), and 2) differences in refractory period in the limbs of the circuit. If these conditions apply, then a single premature beat is sufficient to induce the tachycardia (Figure 2).

Clinically, there are several characteristics of classical reentry. First, the reentrant circuit is well-defined. The wavefront progresses through the same pathway, returns to the point of origin, and repeats the process continuously. Thus, the observed arrhythmia is reproducible and morphology on the surface ECG is constant. Second, anatomical reentry exhibits an excitable gap (Figure 3) which refers to tissue in the circuit which has fully recovered electrical excitibility. Another way of describing the excitable gap is the concept of arrhythmia wavelength (wavelength = conduction velocity x refractory period). According to this view, the pathlength of the anatomic circuit must be longer than the wavelength of the tachycardia. The availability of an excitable gap (which can be demonstrated in humans in the EP lab) means that properly timed premature beats can reset the phase of the tachycardia, and that the tachycardia can be terminated by a single beat or pacing. A third feature is permanent termination of the tachycardia by destruction (cutting, freezing, burning, infarcting) of one segment of the circuit.

*Functional reentry* (also known as leading circle reentry) was predicted in computer models reported by Moe in 1964 (*9*), and demonstrated in experimental preparations in 1977 by Allessie (*10*). In this type of reentry there is no central area of fibrosis, and there is no well-defined anatomical pathway. Rather, the existance of the arrhythmia depends on dispersion in the refractory periods of a sufficient volume of tissue. The premature impulse propagates into the tissue with short refractory periods and circulates around, without penetrating, tissue with longer refractory periods (Figure 4). According to this formulation, the arrhythmia assumes the smallest possible circuit, and if the electrical properties of the tissue are changed (for example, by drug therapy), the size of the circuit will change.

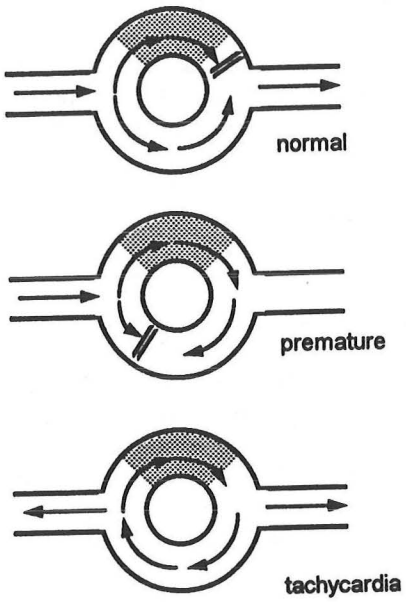


**Figure 2. Anatomical reentry.**

Therefore, in contrast to anatomical reentry, functional reentry 1) has no fully excitable gap, and stimulation from outside the circuit cannot reset the arrhythmia; and 2) does not lend itself to cure by destruction of a small volume of tissue. Recently, the distinction between functional and anatomic reentry has been blurred somewhat by studies in which both mechanisms were studied in comparable preparations. For example (*11*), in an animal model of anatomic reentry, an excitable gap could be measured and premature stimuli always reset the tachycardia, as anticipated. In a similar model of functional reentry, a short excitable gap could be detected, but premature stimuli could reset the tachycardia only in a minority of hearts, and the magnitude of resetting was small.

*Reentry due to tissue anisotropy* was suggested in 1981. This type of electrical nonuniformity in tissue is an important concept and probably relevant to atrial fibrillation because functional reentry (i.e., nonuniformities of repolarization in isotropic tissue) requires a rather large volume of tissue in which it can be established. Spach (*12*) reported that electrical discontinuities in small volumes of tissue may also be responsible for reentry. The distinctive feature of this type of reentry (compared to anatomical and functional) is that the electrical properties of the myocardium are assumed to be anisotropic at a microscopic level. The theoretical foundation for both anatomical and functional reentry assume that cardiac muscle is continuous and that its electrical properties are homogeneous over cellular distances, although dramatic inhomogeneities may exist over larger volumes. The microscopic inhomogeneities in electrical properties arise from differences in cell to cell resistance along the long axis of myocytes compared to resistance to propagation across the short axis. Consequently, every cell experiences nonuniformities of electrical loading. In

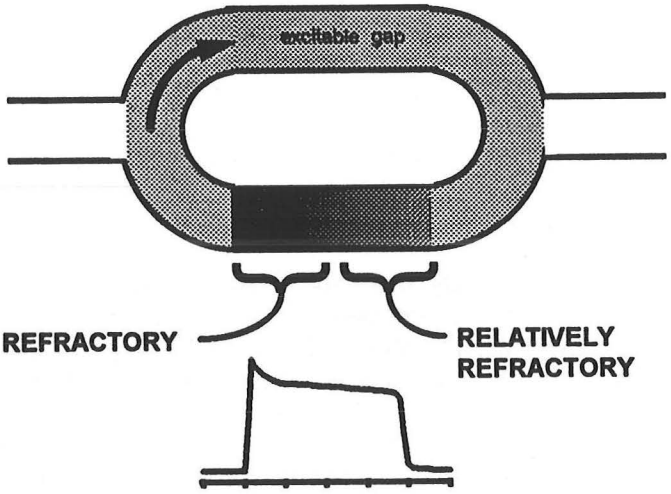


**Figure 3. The excitable gap during reentry.**

isolated tissue studies, human atrial muscle bundles show two- to threefold differences in conduction velocity depending on whether the velocity is measured across the long axis or short axis of a bundle. The difference may be age-dependent, and more prominent in elderly atria. It has also been observed that collagenous tissue causes fragmentation of the electrogram and conduction delays in atria of experimental animals. Thus, one might speculate that both aging and diseases causing collagen deposition might increase the potential for reentry at the microscopic level.

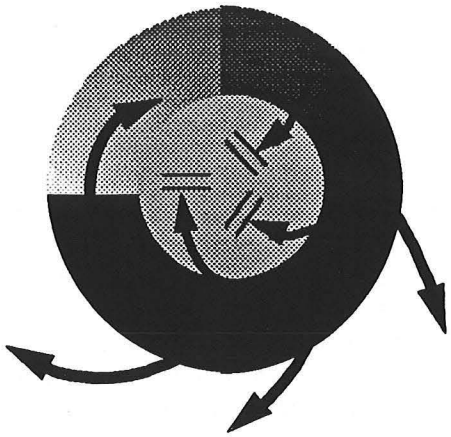

**Figure 4. Functional reentry.**

*Clinical atrial fibrillation*

The relevance of these concepts in atrial fibrillation and in humans is unknown. Functional reentry causing atrial arrhythmias has been shown in animal preparations (*13*). Recently, it has been shown that atrial fibrillation in animals may have a short and variable excitable gap. This critical observation suggests that AF can be entrained by local stimulation and perhaps terminated by programmed stimulation. For example Allessie *et al.* (*14*) studied AF induced by burst pacing in dogs. Rapid pacing at rates slightly slower or faster than the median AF cycle length resulted in regional capture covering an area about 4 cm in diameter. The area of entrainment (electrical capture), however, was limited by conduction block due to fibrillatory waves arriving from other parts of the atria.

Since intracellular electrograms and other tools are for the most part impractical in humans, the best method for evaluating mechanisms of atrial fibrillation is high density epicardial mapping of the arrhythmia. These studies use two dimensional array of electrodes to monitor a wave of depolarization as it propagates across the atrium. These methods have been extended in a limited way to humans (*15*). In 25 patients with accessory pathways (WPW), the patterns of right atrial activation during induced AF were studied during open heart surgery. In contrast to the relatively homogeneous results from dogs, the activation pattern of the RA varied widely among patients. In some patients a single broad wave of depolarization propagated across the right atrium. In others, a small (2 or 3) number of wavelets could be detected propagating across the RA at variable rates. In a third group the pattern of atrial depolarization was highly fragmented and disorganized. Various parameters of atrial conduction were also variable: average conduction velocity, incidence of electrical silence, and apparent reenty varied among all three groups. This important study showed that even in a

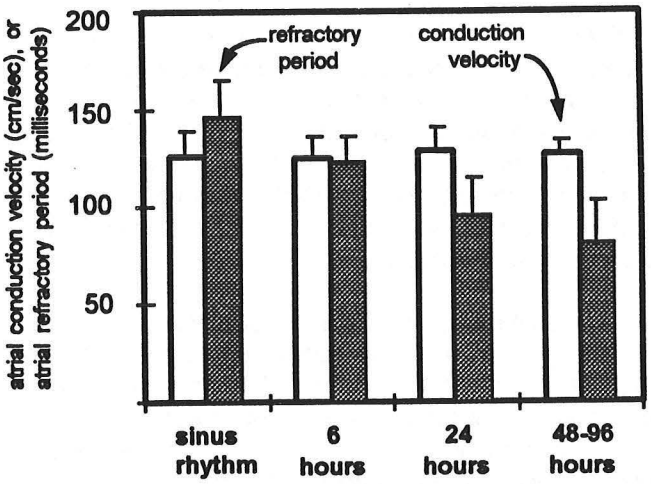


**Figure 5. Effect of induced AF on atrial conduction velocity (open bars) or atrial effective refractory period (shaded bars). Data from reference 16.**

relatively homogeneous human population with transient AF, diverse patterns of activation and various dimensions of intra-atrial reentrant circuits are apparent.

*Electrical remodeling: Does AF beget AF?*

Some patients, particularly individuals less than 50 years old, may have intermittant or paroxysmal AF. It is assumed, but without solid evidence, that AF normally follows a course of rare paroxysms followed by more sustained but intermittant episodes, culminating in chronic AF. Prolonged AF is also more difficult to cardiovert than brief AF. The progressively resistant behavior of AF may be due to alteration of atrial electrical properties, particular the ion channels which control repolarization, which is induced by AF itself and makes its recurrence more likely. Evidence for this concept comes from studies of AF repeatedly induced in experimental animals with chronically-implanted atrial electrodes (*16*). The atrial effective refractory period was quickly and significantly shortened by several hours to days of atrial fibrillation, whereas the atrial conduction velocity was not altered over the period of study (Figure 5). After AF had been maintained for several days, it could be induced more easily and a single induced episode was more prolonged. In these animals with no underlying cardiovascular disease, the process was reversible.

## 3. Cardioversion and maintenance of sinus rhythm: The intuitive choice

As already discussed, atrial fibrillation is strongly associated with stroke, and it causes palpitations, exertion intolerance, and variable effects on left ventricular function. Conversion from AF to sinus rhythm clearly has beneficial effects on hemodynamics and exercise tolerance in some patients (*17,18*). A poorly controlled ventricular response is clearly associated with progression of heart failure or resistance to therapy in some patients, and it may precipitate angina. Since AF is a self-sustaining arrhythmia, it is very attractive to attempt cardioversion in every patient. Presumably, elimination of AF will both reduce the risk of AF later in life and eliminate the associated adverse events. Since cardioversion and drugs to suppress AF are effective (Table 4, but read on), a decision to accept AF, control the ventricular response and reduce embolic events with warfarin seems rather pathetic.

Once the decision is made to attempt cardioversion, anticoagulation is usually essential during the pre and post cardioversion period to reduce the risk of embolic events. Sinus rhythm can be restored using transthoracic DC shocks (*19*), antiarrhythmic drugs, or a combination of the two. Typical success rates combining both methods are 60-95%. However, comparison of studies is difficult since inclusion criteria are often not explicitly stated. Although many clinical features have been proposed to predict successful cardioversion (Table 3), only short duration of AF and low age have been consistently found to predict success (*20, 21, 22*). Any report with a preponderance of young patients with brief duration of AF will report outstanding success rates. The favored drugs for cardioversion are in Vaughn-Williams classes IA and IC (quinidine, procaineamide, propafenone, and flecainide), and amiodarone is also very effective and possibly superior to these agents. Although the "best" agent is not known, all appear to be effective in cardioversion of atrial fibrillation.

Generally, standard procedures for cardioversion are so reliable that significant risks of attempting cardioversion should be less than 1%, once appropriate workup and treatment of associated diseases is complete. Although short term anticoagulation (weeks before and after) reduces the risk of embolic events, other risks are inherent such as exposure to antiarrhythmic agents, cardioversion itself, anesthesia, sedation and electrical complications such as ventricular fibrillation or unexpected bradycardias.

**Table 3. Factors which may influence or predict the success of cardioversion.**

| |
|---|
| patient age |
| duration of atrial fibrillation |
| size of f waves |
| size of left atrium |
| associated mitral valve disease |
| associated left ventricular disease |
| associated other diseases |
| success of prior cardioversion |
| current drug/electrolyte status |

**Table 4. Selected studies of drug therapy for maintenance of sinus rhythm after conversion to sinus rhythm.**

| first author (reference) | drug (#patients) | untreated control group? | randomized? | study duration (months) | efficacy: % of patients in sinus rhythm* |
|---|---|---|---|---|---|
| Hillestad (23) | quinidine (100) | yes | yes | 12 | T: 31%<br>C: 15% |
| Bryne-Quinn (24) | quinidine (92) | yes | yes | 12 | T: 45-54%<br>C: 16% |
| Hartel (25) | quinidine (175) | yes | yes | 3 | T: 59%<br>C: 34% |
| Hartel (26) | disopyramide (52) | yes | yes | 3 | T: 72%<br>C: 30% |
| Lloyd (27) | quinidine vs. disopyramide vs. placebo (82) | yes | yes | 6 | T(quinidine): 42%<br>T(disopyramide): 44%<br>C: 32% |
| Sodermark (28) | quinidine (176) | yes | yes | 12 | T: 51%<br>C: 28% |
| Juul Moller (29) | sotalol vs. quinidine (183) | no | yes | 6 | T(sotalol): 49%<br>T(quinidine): 42% |
| Antman (30) | propafenone (60) | no | no | 6 | T: 40% |
| Porterfield (31) | propafenone (26) | no | no | 12 | T: 60% |
| Karlson (32) | disopyramide (90) | yes | yes | 12 | T: 54%<br>C: 30% |
| Suttorp (33) | assorted (124) | no | no | 12 | T: 50% |
| Reimold (34) | propafenone vs. sotalol (100) | no | yes | 12 | T(propafenone): 30%<br>T(sotalol): 37% |
| Gosselink (35) | amiodarone (89) | no | no | 12 | T: 60% |
| Vitolo (36) | amiodarone vs. quinidine (54) | no | yes | 6 | T(amiodarone): 78%<br>T(quinidine): 46% |
| Hammill (37) | propafenone (47) | no | no | 19 | T: 53% |

* In some studies, results are reported as "free of atrial fibrillation" which was assumed to mean in sinus rhythm in this table. T refers to the treatement group(s), and C indicates control or placebo group.

The critical problem is maintenance of sinus rhythm in these patients with underlying cardiovascular disease. Without therapy, it will recur within 1 year in 50-75% of patients (*20, 22*, and see table 4). Therefore, antiarrhythmic therapy (Vaughn-Williams class I and class III agents) frequently is used to suppress recurrence of AF. Unfortunately, it is clear that all antiarrhythmic drugs have the potential for worsening the arrhythmias a patient experiences or inducing new and possibly fatal arrhytymias, *i.e.*, proarrhythmia (Table 5). Thus, we are faced with the problem of selecting both an effective agent as well as a safe agent.

**Table 5. Types of proarrhythmic responses to antiarrhythmic drugs used for atrial fibrillation.**

| |
|---|
| Polymorphous ventricular tachycardia (quinidine, sotalol) |
| Incessant ventricular tachycardia (class IC agents) |
| Atrial proarrhythmia (conversion to flutter with 1:1 conduction) |
| Sinoatrial node suppression |
| Atrioventricular node suppression |

The efficacy of antiarrhythmic drugs for maintenance of sinus rhythm after cardioversion has been studied in prospective randomized trials since the 1960s. Some of these trials are summarized in Table 4. Quinidine has been studied in several placebo-controlled trials and has been shown to be effective. Due to this early emphasis, quinidine has become the standard against which other, newer, agents are often compared. Examination of Table 4 suggests three other conclusions. First, the untreated relapse rate is about 75% at one year. Second, the available agents have not been systematically compared for efficacy. Third, none of these agents are very good, with the possible exception of amiodarone. Typically, only 50% of patients were in sinus rhythm after 1 year of therapy with a class I agent, and many trials only report results to 6 months or less. Even in very good candidates for maintenance of sinus rhythm, patients with normal LV function and atrial fibrillation of very short duration, the recurrence rate was 50% at one year (*33*). Nevertheless, perhaps this efficacy of 50-60% or so should be accepted if the risks of therapy are negligible.

The safety of long-term (2-4 years) antiarrhythmic therapy with class I or class III agents in chronic AF is uncertain. The most important study to date regarding proarrhythmia is the Cardiac Arrhythmia Suppression Trial (CAST). Although this study is not directly relevant to patients with atrial fibrillation (since it was a study of suppression of ventricular ectopy), it found a surprising and highly significant excess mortality among patients randomized to either of two class IC agents, flecainide or encainide.

In light of this result and the longstanding concerns about sudden death associated with quinidine, Coplen *et al.* performed a meta-analysis of 6 studies involving 808 patients randomized to placebo or quinidine. The efficacy analysis found that quinidine therapy was more effective in maintaining sinus rhythm at 1 year: 50% in treated patients compared with only 25% of control, as described above. These reviewers defined a "full exposure group" as any patient who was randomized and received study medications even if sinus rhythm or long term follow up was not available. In the full-exposure groups 12 patients died (2.9%) compared to 3 in the control group (0.8%). These results indicated and excess mortality rate attributable to quinidine of 2.1%. Although only 3 of the 12 deaths in the quinidine groups were known to be sudden cardiac death, the circumstances surrounding 5 of the deaths were unknown and may have been sudden. Of the 3 deaths in the control groups, 1 was due to MI, 1 was due to CVA, and 1 was unknown.

This study can be criticized in many respects. Little patient information is available from the original trials and most of the patients were enrolled more than 30 years ago. At that time, drug level monitoring was not widely available, and relevant drug interactions (particularly the digoxin-quinidine interaction) were not known. It is possible that the physicians were not attuned to clues to proarrhythmia. The conclusions are based on a relatively small number of deaths and the details surrounding those fatalities are sketchy or absent.

**Table 6. Selected studies suggesting excess mortality of class I antiarrhythmic agents.**

| drug | trial | type of study | patients | observation |
|---|---|---|---|---|
| flecainide or encainide vs. placebo | CAST (*38*) | prospective randomized | minimally symptomatic with PVCs after MI | substantial increase in death associated with drug therapy |
| quinidine vs. placebo | Coplen, et al. (*39*) | meta-analysis | AF | 2% annual excess mortality on quinidine |
| flecainide vs. quinidine | Touboul, et al. (*40*) | prospective randomized | AF | 1 death of 60 patients on flecainide |
| flecainide vs. placebo | Henthorn, et al. (*41*) | prospective randomized | SVTs | 2 significant proarrhythmic events out of 51 patients |
| sotalol vs. quinidine | Juul-Moller, et al. (*29*) | prospective randomized | AF | approximately 1% risk of severe proarrhythmic events in 1 year |
| diverse, mainly type I agents | Flaker, et al. (*42*) | retrospective | SPAF patients | 2.8% excess mortality associated with drug therapy, increased risk confined to patients with heart failure |
| sotalol vs. propafenone | Reimold, et al. (*34*) | prospective randomized | AF resistant to type I agents | 2 sudden deaths out of 50 patients on sotalol; both patients had normal ejection fractions. |

A subsequent analysis of a single trial by Flaker *et al.* (*42*) examined 1330 patients enrolled in the SPAF trial which is described in more detail later. In this study patients were randomly allocated to anticoagulation therapy, and the use of antiarrhythmic agents was not randomized. Of the 189 patients on antiarrhythmic therapy, most (127) were on quinidine. Procainemide was the second most widely used drug, and disopyramide, flecainide, encainide and amiodarone were also used. Cardiac mortality was 2.2% annually for patients not on antiarrhythmic therapy, and 5% for patients on these agents. This excess mortality was confined to patients with heart failure; those patients without heart failure had an excellent prognosis regardless of the coadministration of antiarrhythmic agents.

Antiarrhythmic agents are not as well tolerated as many other drugs used for chronic conditions. Gastrointestinal complaints are common, particularly with quinidine, and the significant prevalence of other complaints are well-documented. Amiodarone in low doses (100-200 mg/day) is often said to be a very well-tolerated drug. However, Gosselink (*35*) reported a 4% incidence of "severe" adverse reactions to low dose amiodarone, and a 13% incidence of minor or moderate adverse effects.

In sum, antiarrhythmic drug therapy for chronic AF is not highly effective, and evidence for long-term tolerance and safety of these drugs for suppression of AF is conspicuously absent. Table 6 summarizes other studies which provide anecdotal evidence of excess mortality with antiarrhythmic drugs. Very little information is available to assist stratification for risk of proarrhythmia, other than the suggestion that patients with heart failure are at high risk. If these agents were known to be safe, then there would be little to loose by a trial of cardioversion followed by chronic suppression of AF ("every patient deserves a chance at sinus").

## 4. Warfarin and aspirin in chronic atrial fibrillation

By 1980 it was apparent that atrial fibrillation was associated with systemic emboli and ischemic stroke. For example, the Framingham trial indicated that the risk of stroke was about 6 fold higher than comparable patients without AF. However, other trials did not support these high risk estimates in certain subpopulations. For example, the Mayo Clinic retrospective study examined patients with no risk factors for stroke (*1*); 97 patients were identified. These patients were 60 years old or younger at the time of diagnosis of AF and had no evident cardiovascular disease, although detailed evaluations were not performed in all patients. About half of these patients (56%) had recurrent AF, and the remainder were evenly split between a single episode of AF and chronic AF. The average age at the time of diagnosis was 44 years and the average followup was 14.8 years. 4 patients had strokes thought to be due to emboli from AF, leading to an estimate of a stroke rate ot 1.3% per 15 years. There was no difference in the stroke rate among these three types of atrial fibrillation (isolated, recurrent, and chronic). In this study, low risk patients less than 60 years old had a low risk of ischemic stroke. Other studies have also identified populations with atrial fibrillation but very low risk of stroke. Flegel *et al.* (*43*) analyzed two cohort studies of men with AF not associated wtih rheumatic heart disease. They found that the absolute rate of stroke was lower than those reported in the Framingham study, and in one study (the British Regional Heart Study) only 1 man with AF had a stroke.

Thus, AF can be associated with systemic emboli, but there are subgroups which appear to be at low risk. Therefore, by the mid 1980s the benefit of aspirin or warfarin as preventive therapy was not clear, and it appeared that certain subgroups may be at very low risk of complications. Five trials (see Tables 7 and 8) were organized to compare warfarin to control for the prevention of systemic emboli, and a sixth trial (EAFT) was designed as a secondary prevention trial in patients with prior CVAs or TIAs plus atrial fibrillation. All 6 trials had been reported by 1993, and a cooperative meta-analysis of the 5 primary prevention trials using the original patient data was published last year (*44*). In these 5 studies, 26% of patients were female and most were white. Coexisting conditions such as diabetes (14%), peripheral vascular disease (11%), congenstive heart failure (20%), angina (23%), and prior MI (13%) were relatively common. Both in the separate trial reports as well as the combined analysis, these trials have confirmed the efficacy of warfarin in chronic atrial fibrillation to prevent stroke and embolic events (Table 8). The value of aspirin remains less certain, although it is likely also beneficial.

*Warfarin vs. control*

Warfarin has been studied in randomized prospective trials in 2461 patients with chronic atrial fibrillation. With one exception, the efficacy of warfarin was consistent across all patient groups; the single exception was patients less than 65 years old with no risk factors for stroke (defined as a history of diabetes, hypertension or prior TIA or stroke). The risk reduction due to warfarin is at least 60%, since the data in these trials were reported on an intention-to-treat basis. In other words, patients who were assigned to warfarin but did not take it were included in the "treated" category. In BAATAF and SPINAF, there were no strokes among patients assigned to warfarin who actually were taking warfarin. The incidence of stroke in subsets stratified by underlying cardiovascular disease (Table 9) was reduced in every group. The risk of various adverse outcomes (stroke, stroke with residual deficit, systemic embolism, death) was significantly reduced by warfarin (Table 10). Thus, except for the youngest patients with no risk factors, the clear message is that oral anticoagulation with warfarin substantially reduces the risk of limited outcome events (stroke) as well as combined outcome events (stroke, systemic embolism, death).

**Table 7. Recent trials of anticoagulation in patients with atrial fibrillation.**

AFASAK - Atrial Fibrillation Aspirin Anticoagulation Study
BAATAF - Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA - Canadian Atrial Fibrilation Anticoagulation study
EAFT - European Atrial Fibrillation Trial
SPAF - Stroke Prevention in Atrial Fibrillation (trials 1 and 2)
SPINAF - VA Stroke Prevention in Nonrheumatic Atrial Fibrillation

**Table 8. Randomized, controlled studies of anticoagulation with warfarin in patients with atrial fibrillation.***

| | AFASAK (45) | SPINAF (46) | BAATAF (47) | SPAF-1 (48) | CAFA (49) | EAFT** (50) |
|---|---|---|---|---|---|---|
| publication date | 1989 | 1992 | 1990 | 1991 | 1991 | 1993 |
| double blind? | no | yes | no | no | yes | no |
| double blind and completed? | no | yes | no | no | no | no |
| follow up, years | 2.0 | 1.7-1.8 | 2.2 | 1.3 | 1.2 | 2.3 |
| % male | 54 | 100 | 70 | 71 | 74 | 59 |
| average age, years | 75 | 67 | 68 | 67 | 67 | 71 |
| hypertension (%) | 31 | 59 | 51 | 55 | 39 | 44 |
| diabetes (%) | 10 | 18 | 15 | 19 | 12 | 13 |
| prior MI (%) | 8 | 19 | 13 | 6 | 13 | 8 |
| CHF (%) | 51 | 30 | 26 | 19 | 22 | 10 |
| a. fib. > 1 year (%) | n.r. | 86 | 68 | 72 | 82 | 55 |
| # patients (placebo) | 336 | 290 | 208 | 211 | 191 | 214 |
| # patients (warfarin) | 335 | 281 | 212 | 210 | 187 | 225 |
| INR target (or estimate from PT target) | 2.8-4.2 | 1.4-2.8 | 1.5-2.7 | 2.0-4.5 | 2.0 - 3.0 | 2.5-4.0 |
| actual INR | nr | nr | nr | nr | 2.4 | 2.9 |
| primary endpoint | stroke, TIA, emboli | cerebral infarction, emboli | ischemic stroke, emboli | ischemic stroke | ischemic stroke, ICB | vascular death, stroke, nonfatal MI |
| secondary endpoint | death | bleeding, death | ICB, unstable angina, TIA | death, MI | death, TIA, lacunar infarct | all cause death, all strokes, all emboli |
| monitored intercurrent events | bleeding | TIA, MI, venous thrombosis | bleeding | | | |
| events (placebo) | 21 | 19 | 13 | 18 | 11 | 67 |
| events (warfarin) | 5 | 4 | 2 | 6 | 6 | 43 |
| risk reduction | 69% | 79% | 85% | 67% | 45% | 36% |

* Events refer to primary endpoint ischemic events which include strokes but inclusion of other systemic emboli varied among studies. Risk reduction was calculated as [events(placebo-warfarin)]/[events(placebo)].

** secondary prevention trial

abbreviations: nr, not reported, ICB, intracranial bleeding.

*Optimal warfarin anticoagulation*

The target INR or prothrombin time ratio in these studies varied somewhat (Table 8). Since the risk of major bleeding complications increases with marked prolongation of prothrombin time, the minimal effective warfarin dose should be used. That level of anticoagulation has not been determined in dose-ranging studies.

**Table 9. Incidence of stroke in subsets of patients with atrial fibrillation. *Prior TIA/CVA, hypertension or diabetes were the most powerful predictors of stroke in a multivariate analysis.**

| | Annual Stroke Rate (%/y) | |
|---|---|---|
| VARIABLE | Control | Warfarin |
| CVA/TIA* | 11.7 | 5.1 |
| diabetes* | 8.6 | 2.8 |
| myocardial infarct | 8.2 | 3.3 |
| heart failure | 6.8 | 1.6 |
| angina | 6.7 | 0.9 |
| PVD | 6.0 | 1.8 |
| hypertension* | 5.6 | 1.9 |

This question can be addressed in two ways. First, the 6 trials in Table 9 reported INR goals (or PT ratios which allowed estimates by the authors of INR) which differed somewhat among trials. For example, the actual INR in EAFT would not have been accepted in patients from the SPINAF and BAATAF (the warfarin dose would have been adjusted down). If there was a strong relation between INR in warfarin-treated patients and prevention of systemic emboli, one might expect a better outcome (lower adverse event rates) in trials targeting higher INRs. This was not the case: there was no clear relation between event rates and target INRs among the 6 studies (Figure 6). There was no obvious lower limit to warfarin efficacy in the sense that trials with lower target INR (or PT ratio) had the same efficacy as higher target INR. However, this analysis is limited by the absence of INR reports in all studies.

Instead of comparing target anticoagulation and event rates among trials, the actual relation between events in every patient and the simultaneous INR could be determined. This has been reported in one trial (*51*), the EAFT. The INR-specific incidence rates were determined in 214 patients who experienced both strokes as well as major bleeding complications. The major bleeding complications were more likely in patients with an INR > 5, whereas the rate of thromboembolic events was lowest at INRs above 2. It appears that a suitable INR target to optimize the anti-embolic effects of warfarin and to minimize bleeding complications lies between 2 and 3.

*Safety of warfarin*

A remarkable feature of these studies, when pooled, is the safety of warfarin (Table 10). The rate of major bleeding was 1%/year in patients on placebo, 1.3%/year in warfarin-treated patients, and 1.0%/year in patients on aspirin. Of the 1225 patients on warfarin, 6 suffered and intracranial bleed. In the 1236 patients on placebo, 2 sustained intracranial bleeds. The risk of major hemorrhage (defined in table 10) was 18 patients in the placebo group and 24 in the warfarin group. Although patients enrolled in these studies were selected for low risk of bleeding, and the degree of anticoagulation weas carefully monitored, these patients were not young and not free of comorbid diseases (Table 8).

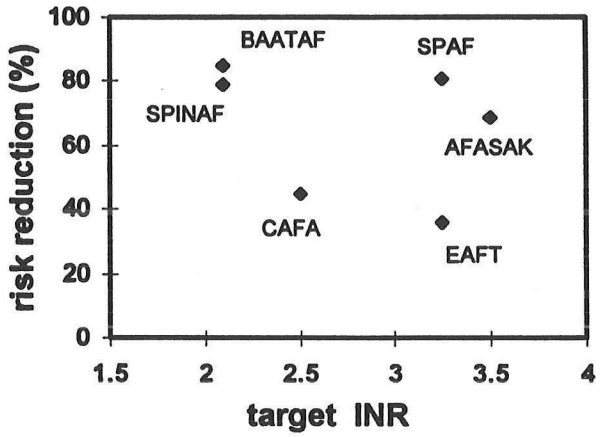


**Figure 6. Target anticoagulation and risk reduction in 6 warfarin trials.**

**Table 10. Outcome events among 5 pooled trials (*44*).**

| Outcome Event | control %/year | warfarin %/year | reduction (%) | *P* |
|---|---|---|---|---|
| stroke | 4.5 | 1.4 | 68 | <0.001 |
| stroke with residual deficit* | 2.0 | 0.6 | 68 | <0.001 |
| systemic embolism | 0.5 | 0.3 | | |
| stroke or systemic embolism | 5.0 | 1.7 | 65 | <0.001 |
| death | 5.4 | 3.6 | 33 | 0.01 |
| stroke, systemic embolism, death | 9.8 | 5.0 | 48 | <0.001 |
| transient ischemic attack | 1.3 | 0.7 | | |
| major hemorrhage** | 1.0 | 1.3 | | |
| intracranial bleeding | 0.1 | 0.3 | | |
| intracerebral bleeding | 0.0 | 0.2 | | |

* left a functional deficit 1-3 months after the event
** intracranial bleeding, bleeding requiring > 2 U of blood, or bleeding requiring hospital admission

**Table 11. Effect of warfarin therapy on ischemic stroke in subgroups. Incidence is shown in bold (conficence interval).**

| Risk Catagories | placebo | warfarin |
|---|---|---|
| < 65 y | | |
| no RF | **1.0** (0.3-3.1) | **1.0** (0.3-3.0) |
| 1 or more RF | **4.9** (3.0-8.1) | **1.7** (0.8-3.9) |
| 65-75 y | | |
| no RF | **4.3** (2.7-7.1) | **1.1** (0.4-2.8) |
| 1 or more RF | **5.7** (3.9-8.3) | **1.7** (0.9-3.4) |
| >75 y | | |
| no RF | **4.3** (1.6-7.7) | **1.7** (0.5-5.2) |
| 1 or more RF | **5.7** (4.7-13.9) | **1.2** (0.3-5.0) |

RF: risk factors, a history of hypertensioln, a history of diabetes and a history of prior stroke or transient ischemic attack.

*Aspirin vs. control: Is ASA a useful hedge?*

Three trials included an aspirin-only arm: AFASAK, SPAF-1 and EAFT (Table 12). Perhaps it could be noted that the rationale for use of aspirin is not clear if the goal is to prevent thrombus formation in a fibrillating atrium. Warfarin is required to achieve this goal in either the atria or ventricles. On the other hand, if AF is assumed to be a marker of vascular disease which might benefit from aspirin (such as coronary artery or cerebrovascular disease), then the inclusion of the aspirin arms of these studies is important.

In any case, when the 2 primary prevention trials were analyzed together (AFASAK and SPAF-1), aspirin decreased the risk of stroke by 36%; this effect was most prominent among patients with hypertension (*44*, *52*).

**Table 12. Randomized, placebo-controlled studies of aspirin in patients with atrial fibrillation.**

| | AFASAK | SPAF-1 | EAFT* |
|---|---|---|---|
| publication date | 1989 | 1991 | 1993 |
| actual follow up (years) | 2.0 | 1.3 | 2.3 |
| % male | 54 | 72 | 56 |
| age | 75 | 66 | 73 |
| # patients (placebo) | 336 | 568 | 378 |
| # patients (ASA) | 336 | 552 | 404 |
| ASA dose (mg/d) | 75 | 325 | 300 |
| events placebo | 21 | 46 | 136 |
| events ASA | 20 | 26 | 130 |
| risk reduction | ** | 42% | - |

* secondary prevention trial

** later (*44*), an 18% decrease was reported in the aspirin group.

**5. Does conversion to sinus rhythm improve symptoms any better than rate control?**

Certainly for some patients with left ventricular dysfunction or modest mitral valve disease, conversion to sinus rhythm with preservation of AV synchrony and atrial transport has real symptomatic benefit. In principle, restoration of sinus rhythm should optimize hemodynamics at rest and with exercise. A well-established but poorly understood model for inducing reversible left ventricular dysfunction in animals is rapid ventricular pacing ("tachycardiomyopathy"). In dogs, chronic pacing reduces ejection fraction which normalizes within 2 weeks after pacing is terminated, although end diastolic volumes may remain elevated for up to 3 months (*53*). Patients with chronic supraventricular tachycardias and poorly controlled ventricular rates may develop left heart failure; reversal of cardiac dysfunction after rate control suggests that rapid ventricular rates alone may cause a cardiomyopathy in humans. Specifically, it has been suggested that rapid ventricular rates which occur as a consequence of poorly controlled atrial fibrillation may initiate or cause progression of left ventricular dysfunction. Thus, rate control may be important for immediate symptoms and as well as long-term prevention of heart failure. There may also be a role for aggressive rate control (including cardioversion, possibly withouth antiarrhythmic therapy) in patients with heart failure who do not respond well to conventional (diuretics, ACE inhibitor) therapy.

However, although it is widely stated that the "atrial kick" accounts for about 25% of cardiac output, many patients with atrial fibrillation can function quite well if the ventricular response is controlled. In other words, the importance of sinus rhythm as opposed to rate control in the typical outpatient with AF is somewhat less evident. Three classes of drugs are available for chronic rate control: digitalis glycosides, calcium channel blockers, and ß adrenergic blockers. The target heart rate should be 65-90 beats per minute at rest and the heart rate response during exercise should be proportionate.

Digoxin has both direct and indirect effects on the heart, whereas the calcium channel blockers (diltiazem or verapamil) or ß blockers have direct effects on the av node. An important effect of digoxin in atrial fibrillation is the reflex increase in vagal tone. When sympathetic tone is dominant, digoxin is less likely to be beneficial, for example during extreme stress and a hyperadrenergic state. ß adrenergic blockers or calcium channel blockers are likely to be more effective. Digoxin, as monotherapy, is also limited by its poor efficacy in rate control during exercise. A reasonable approach is to select agents for rate control based on both efficacy and associated diseases. For example, a patient with diabetes and peripheral vascular disease may be a good candidate for rate control with diltiazem, whereas a patient with a prior MI and coronary artery disease is likely to require a ß adrenergic blocker. If a patient has heart failure and atrial fibrillation, digoxin could be effective monotherapy, although levels must be monitored, particularly in patients with renal disease.

For some patients, pharmacologic therapy is simply inadequate because of side-effects, complications due to bradycardias, or inadequate rate control at rest or during exercise with maximal tolerated doses. Therefore, several invasive approaches have been suggested to modify AV nodal conduction. Since 1982 it has been possible to ablate the AV node (using electrical or chemical injury) and thereby control the ventricular response, although permanent ventricular pacing is required. Importantly, these tools allow us to examine whether rate control alone (in the absence of drug therapy which complicates assessment of ventricular function) may have a beneficial effect on left ventricular function.

Heinz (*54*) reported 10 patients predominantly (9/10) with atrial fibrillation referred for drug refractory rapid ventricluar response. Patients with regional wall motion abnormalities, bundle branch block and valvular heart disease were not included. The ventricular response was usually > 120 bpm. After ablation, echocardiograms were obtained in the absence of drug therapy, and again 49 days after ablation. Results of all 10 patients are shown in Figure 7. Support for this conclusion was reported by Rodriguez, *et al.* (*55*).

Although the most direct solution is to ablate the AV node and implant a rate responsive ventricular pacemaker. Others (*56*) have suggested modification of AVN conduction. In this approach rf energy is applied near the ostium of the coronary sinus at the posterior septal or midseptal right atrium. Persistent third degree av block is a significant risk using this approach, as is the unmasking of bradycardia dependent ventricular arrhythmias. Although other groups have reported similar promising results (*57*), this technology is still evolving and the long-term relevance to most patients is uncertain. Nevertheless, it offers the possiblity of rate control in previously refractory patients and perhaps drug therapy solely for rate control may be eliminated.

Surgical reorganization of the atria to eliminate reentrant pathways may prove helpful in some patients (*58*, *59*). A fascinating procedure, the corridor operation, was introduced by Guiraudon and colleagues (*60*). In this operation, a corridor or conduit of atrial tissue is created which connects the area of the sino-atrial node with the atrioventricular node. The bulk of right and left atrial tissue is excluded from the circuit and is therefore free to fibrillate without influencing the physiological impulses arriving at the AV node from the SA node. Between 1987 and 1993, 36 patients underwent surgery. At a mean followup of 41 months, 69% were free of arrhythmias and were not taking any drugs. If this procedure were to become refined such that a high success rate could be assured, it raises the

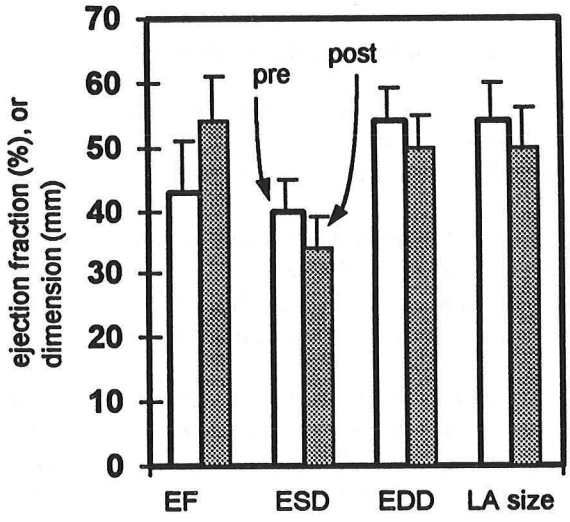


**Figure 7. Effect of rate control with AVN ablation on left ventricular function. Data from reference 56.**

question of whether anticoagulation should still be used since the atria remain in fibrillation even when impulses from the SA node proceed normally through the atrioventricular node to stimulate the ventricles.

## 6. Does conversion to sinus rhythm reduce the rate of systemic emboli compared to anticoagulation?

There are no reports comparing the following strategies: treat atrial fibrillation with rate control and warfarin anticoagulation compared to cardioversion followed by antiarrhythmic therapy. There is at least some suspicion that the balance of risks of antiarrhythmic agents compared to warfarin may favor warfarin, for two reasons.

First, although there is no doubt that systemic emboli can originate in the fibrillating left atrium, the modest efficacy and tolerability of antiarrhythmic drugs plus concerns about their safety reduces enthusiasm for cardioversion followed by drug therapy. If these agents were completely safe, there probably would be little to lose by a trial of cardioversion plus drug therapy. However, the balance between proarrhythmia and stroke risk is simply unknown.

Second, it is possible that a portion of emboli in patients in AF do not originate in the left atrium. If embolic events in AF originate solely in the left atrium, then it is not clear why associated risk factors should be such powerful predictors of embolic complications. However, patients with AF plus hypertension, diabetes, older age groups, etc., are at higher risk for strokes. AF may be one outcome of a disease (such as coronary disease with infarction and left ventricular thrombus formation) which also causes emboli but the risk of emboli will not benefit from cardioversion. Perhaps the reason for the striking success of warfarin therapy in all 6 trials in relatively high risk populations is simply that AF is a very good marker for patients with vascular disease who will benefit from warfarin.

The alternative is simply to accept AF and rely on warfarin to prevent emboli. Both primary and secondary prevention efficacy have been shown, and the risk of major bleeding complications appears low in these selected patients, an excess rate of 0.3% per year. Unfortunately, warfarin is a very unappealing drug to take for a lifetime. The risk of bleeding complications is real although seldom catastrophic, and the continuous monitoring of INR is tiresome.

## 7. Risk stratification and management of chronic atrial fibrillation

*Prevention of systemic emboli by anticoagulation*

Like all therapeutic decisions, management of atrial fibrillation requires value judgements as well as estimates of risk and benefit. Unlike many therapeutic decisions, we have reasonable quantitative estimates of many relevant factors such as the risk of stroke with and without therapy. Let:

$S_u$ = stroke/emboli risk if not treated
$S_t$ = stroke/emboli risk if treated (anticoagulated or converted to sinus rhythm)
$R$ = reduction in the risk due to treatment = $(S_u - S_t)/S_u$
$C$ = risk of major complication if treated (serious bleeding complication or proarrhythmic event)

The number of patients which must be treated to prevent a stroke is $1/(S_u-S_t)$. Thus, if the risk of stroke is 0.06 without treatment and the risk of stroke is 0.02 with treatment, then 1/0.04 or 25 patients must be treated to prevent 1 stroke. Similarly, if the risk of major complications due to treatment is 0.01, then 1/C or 100 patients must be treated to cause 1 major complications. These relationships may be summarized:

$$\text{(strokes prevented)/(major complication)} = RS_u/C$$

This formulation does not identify patients for whom we should recommend chronic warfarin therapy, and it becomes meaningless if the risk of complications due to therapy is near 0, since it indicates benefit for every patient. However, it does highlight four critical judgments:

*R: What is the risk reduction due to treatment?* A reasonable estimate is 60% (R=0.6) based on the pooled data shown in Tables 8. There is one subset for which this does not appear to apply, patients less than 65 years old with no risk factors for CVA. In these patients warfarin does not confer any benefit compared to untreated patients.

*$S_u$: What is the risk of stroke or embolic event if not treated?* This ranges from 1.0% per year in patients less than 65 years old with no risk factors up to 8.1% per year in patients over 75 years old with one or more risk factors (Table 9).

*C: What is the risk of major bleeding complications due to warfarin?* In the pooled results of 5 trials which included only patients at low risk of bleeding, the excess bleeding due to warfarin was 0.3% per year (control, 1.0%; warfarin 1.3%). It should be noted that these patients were randomized because they were thought to be at low risk for bleeding complications and that associated comorbidities were minimal. In community-based studies the risk of major bleeding complications was not significantly higher than in these 5 trials, but minor or modest bleeding complications were more frequent (*61*). All-in-all, an estimate of 0.5% excess major bleeding events per year is probably reasonable in patients who are at a low risk of bleeding and are well monitored.

*What is the value of preventing a stroke compared to the risk of a major bleeding complication?*

For example, if the reduction in stroke risk due to warfarin is 60% (from Table 8), the risk of stroke in a patient is 5% (from Table 9) and the risk of major bleeding complications is 0.5%, then (0.60)(0.05)/(0.005) = 6.0. Thus, 6 strokes will be prevented in exchange for 1 episode of major bleeding due to warfarin. These relations are illustrated in Figure 6 for patients at very low (0.5%), intermediate (2%), and moderately increased risk of embolic events (5%). In this figure the ratio of the number of strokes prevented compared to major bleeding events is shown on the y axis. For patients at high risk of stroke, there will be more benefit of anticoagulation compared to patients at lower risk. For all groups, the risk/benefit ratio diminishes as the risk of bleeding increases.

*Prevention of systemic emboli by cardioversion followed by antiarrhythmic therapy*

The same analysis could be applied to the same patient if cardioversion followed by antiarrhythmic therapy is considered. For the moment, we shall make the incorrect assumption that antiarrhythmic drugs are 100% effective in maintaining sinus rhythm. The stroke risk if untreated ($S_u$) can be estimated, but there are two remaining variables: *R*, the risk reduction due to treatment, and *C*, the risk of major proarrhythmic events due to antiarrhythmic therapy. In the absence of *any* prospctive data, *R* will be assumed to be 0.67, that is, 2/3 of strokes will be prevented by maintenance of sinus rhythm. This assumption is based on the small number of retrosepctive studies which have attempted to identify the source of embolic events in AF (*7, 8*). *C*, the risk of major arrhythmic events due to antiarrhythmic therapy, might be roughly estimated as 2% ($C$ = 0.02). With these assumptions, $RS_u/C$ = (0.67)(0.05)/(0.02) = 1.7. Thus, about 1.7 strokes will be prevented in exchange for 1 major proarrhythmic event. If these assumptions are correct, then warfarin is superior to maintenance of sinus rhythm for the goal of preventing strokes or systemic emboli, if we "value" major bleeding complications the same as a major proarrhythmic event. However, to repeat, we have little solid information regarding two crucial variables: the risk reduction if a patient is converted to sinus rhythm, and stratification for risk of major proarrhythmic complications if antiarrhythmic therapy is used. It also must be emphasized again in the context of this comparison that warfarin is a difficult drug for patients to tolerate because of the close monitoring required as well as the bleeding risks.

*Risk stratification*

In a nutshell, for most patients in AF, almost everything we do is to some degree unsatisfactory. The physician must choose from among the unattractive alternatives described here. Perhaps the best approach is to stratify patients according to the risk of stroke and the need for optimizing hemodynamics without automatically aiming for sinus rhythm as an end in itself.

If hemodynamics are difficult to optimize, then cardioversion plus drug therapy should be strongly considered, keeping in mind that recurrence is almost inevitable over the next 4 - 5 years. If heart failure is significant, then the option of cardioversion without subsequent antiarrhythmic therapy could be considered, although long-term success is even less likely. A cautious interpretation of the SPAF data is to avoid antiarrhythmic drugs in patients with CHF. If hemodynamic symptoms are well controlled with ß adrenergic blockers or other relatively safe and well tolerated medications, then the hemodynamic indication for cardioversion should be reconsidered.

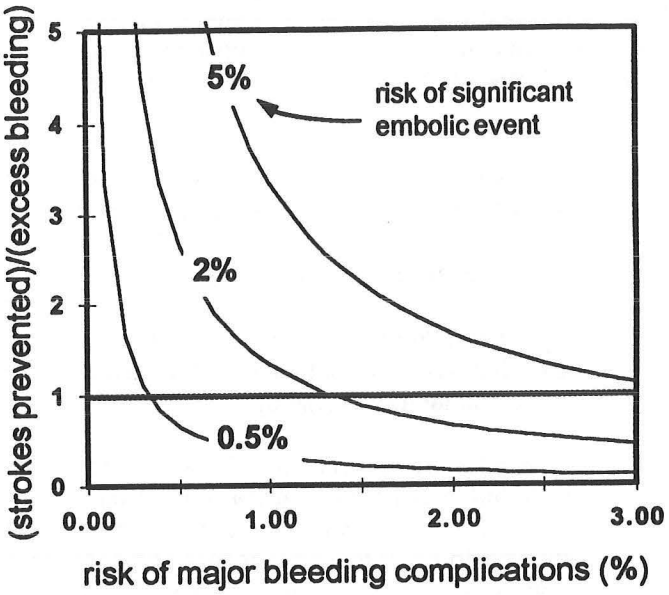


**Figure 8. Stroke reduction compared to major complications due to therapy. Curves are shown for a stroke risk (untreated) of 0.5%, 2% and 5%. See text for details.**

For a patient in AF who is over 65 years old, or less than 65 with one or more risk factors, warfarin anticoagulation is appropriate to an INR of 2-3 in the absence of significant risks of major bleeding. If anticoagulation is unacceptable, then aspirin can be considered a marginal but probably effective second choice. The decision to attempt cardioversion to prevent stroke should be considered in view of 1) the absence of trials about its efficacy in reducing stroke risk in patients who have other risk factors for stroke, 2) uncertain risk of antiarrhythmic therapy, and 3) the small (but well documented) risk and nuisance of warfarin therapy.

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