ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT

PROTOCOL

Version 2.2

August 10, 1998

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1. INTRODUCTION

A. Importance of Atrial Fibrillation

Atrial fibrillation is an extremely common cardiac arrhythmia whose prevalence increases dramatically with age over 49 years (1-3). The prevalence of atrial fibrillation in the Framingham study is less than 1% for the 50-59 years age decade and approaches 9% in the 80-89 years age decade (3). The prevalence of atrial fibrillation on a 24-hour ambulatory ECG recording of a population study group of Americans over 65 years of age is approximately 5% (4, 5). The age-adjusted prevalence of atrial fibrillation based on biennial examinations in Framingham has nearly doubled in men (but not in women) during the 1980's (PA Wolf, personal communication). The explanation for this apparent increase in prevalence of atrial fibrillation is unknown but may have resulted from improved survival of persons with other cardiac conditions. If these prevalence data can be generalized to the whole country, the impact of atrial fibrillation is very great indeed.

The presence of atrial fibrillation markedly increases the risk of stroke with age over 49 years (1, 3). The independent relative risk for stroke in the presence of atrial fibrillation in the Framingham study is 5.6 after adjustment for age, sex and hypertension (2). The attributable risk of stroke from atrial fibrillation of 1.5% in the 50-59 years age decade increases more than 2- to 3-fold with each successive decade until it reaches 23.5% in the 80-89 years age group (3).

Other consequent morbidity and mortality directly attributable to atrial fibrillation are less well studied. Other than via stroke, it is rare that atrial fibrillation in itself causes mortality and when it does so, it is usually through triggering of fatal ventricular tachyarrhythmias. However, the morbidity due to atrial fibrillation is generally felt to be substantial, although not well documented in the literature. The major problem is reduced functional capacity due to symptoms, including palpitations, fatigue, and dyspnea, or worsening of symptoms of preexisting cardiac conditions, such as angina pectoris and congestive heart failure. Declining functional capacity in patients in whom sinus rhythm cannot be restored and maintained has been demonstrated elegantly in recent studies using serial exercise testing and measurement of peak oxygen consumption (6, 7).

B. Components to Management of Atrial Fibrillation

Management of atrial fibrillation has at least three components: restoration and maintenance of sinus rhythm and thereby heart rate control as well; control of heart rate alone when maintenance of sinus rhythm is imperfect or impossible; and anticoagulation. The optimal utilization of these components has not been established and remains controversial, although considerable progress has been made recently with respect to use of anticoagulation. This study will compare two treatment strategies, each of which utilize two of the three components. Anticoagulation will be used in each treatment strategy in a standardized fashion, taking into account that the strategy of maintenance of sinus rhythm

might allow discontinuation or reduction of anticoagulation or antithrombotic therapy. The two treatment strategies are:

1. Maintenance of Sinus Rhythm:

    • Putative Benefits: better control of symptoms, reduced risk from anticoagulation.

    • Putative Risks: increased risk of adverse effects (including death), higher cost.

2. Control of Heart Rate Alone:

    • Putative Benefits: lower risk of adverse effects (including death), possibly lower cost

    • Putative Risks: poorer relief of symptoms, increased risk from anticoagulation

The competing risks and benefits within each of the two strategies will be evaluated.

C. Antiarrhythmic Drugs to Maintain Sinus Rhythm

Many small randomized clinical trials of antiarrhythmic drug therapy have demonstrated the ability of individual antiarrhythmic drugs to increase the proportion of atrial fibrillation patients who remain in sinus rhythm at the expense of varying degrees of constitutional adverse effects (8-20). Small studies in highly selected groups of patients have also demonstrated hemodynamic benefit from restoration and maintenance of sinus rhythm. However, no trial has demonstrated other tangible benefit, such as reduction of the incidence of stroke or other embolic events. The degree of symptomatic relief obtained with restoration and maintenance of sinus rhythm and its superiority over that of heart rate control alone is also not well established. Furthermore, antiarrhythmic drug trials have avoided study of the elderly who are at greatest risk from atrial fibrillation and from anticoagulation.

Even with continued antiarrhythmic drug therapy, approximately 50% of treated subjects will have a recurrence of atrial fibrillation after 3 to 6 months (8, 21). It is common that alternative antiarrhythmic therapies will be required in a particular patient, either because of inefficacy or intolerance. When an efficacious therapy is changed for intolerance, it is likely that an alternative tolerated therapy will also be efficacious. If atrial fibrillation eventually returns and becomes paroxysmal or if the therapy is changed for inefficacy, it is much less likely that long-term maintenance of sinus rhythm will be possible (22).

Alarmingly, two recent meta-analyses have suggested that quinidine, a common drug used to treat atrial fibrillation, increases mortality three-fold over placebo treatment (21, 23). Although the overall mortality in the populations examined in these

meta-analyses was low (0.6 to 0.8% on placebo and 2 to 3% on quinidine), the magnitude of the effect is hauntingly similar to that found in the Cardiac Arrhythmia Suppression Trial (24-26). It should also be pointed out, however, that the meta-analyses used studies with publication dates from 1966 to 1984 (most are more than 20 years old), were not confined to nonvalvular atrial fibrillation (21, 23), did not limit the analysis to cardiac deaths, and the mean age of the subjects included was only 53 years (21). Nevertheless the use of antiarrhythmic drugs for maintenance of sinus rhythm in patients with atrial fibrillation has been brought into question by these meta-analyses. Furthermore, a recent large trial of bidisomide for atrial fibrillation was terminated for lack of efficacy and a trend towards harm at the highest dose.

Proarrhythmic risk from antiarrhythmic drugs is now well-known. Risk factors for proarrhythmia include bradycardia, hypokalemia, marked variability in R-R intervals (such as seen in atrial fibrillation), poor LV function, severe underlying arrhythmias, long QT intervals (before or after drug administration), left ventricular hypertrophy, and underlying structural heart disease. It will be important in this study to guard against excessive proarrhythmia from these antiarrhythmic drugs.

D. Antiarrhythmic Drug Use in Antithrombotic Trials

Most studies of anticoagulation did not evaluate the use of antiarrhythmic drugs. However, the Stroke Prevention in Atrial Fibrillation Study reported on antiarrhythmic drug use (27). In that study 14% of the patients were reported to be taking an antiarrhythmic drug (some were taking combination therapies). Quinidine was used in 67% of those taking an antiarrhythmic drug. Other drugs used included: procainamide in 30%, flecainide in 18%, encainide in 11% and disopyramide in 8%. None were taking sotalol and only 4% were taking amiodarone. Although there was excess cardiac and arrhythmic mortality in those taking antiarrhythmic drugs, the use of these drugs in the study was not randomized. After adjusting for other clinical variables known to affect cardiac and arrhythmic mortality, all differences disappeared except for increased risk of cardiac and arrhythmic death in those with a history of congestive heart failure. It should be pointed out that this is a subgroup (N = 239) with all the pitfalls inherent to that type of analysis (13), but the results support the conclusions of the previously cited meta-analyses (21, 23), albeit with a much smaller treatment effect.

E. Therapies for Control of Heart Rate Alone

When antiarrhythmic drugs are abandoned because of inefficacy, intolerance or both, patients are treated with a different group of antiarrhythmic drugs or catheter ablation, which are intended merely to control the heart rate. These therapies do nothing to help maintain sinus rhythm. Although the specter of antiarrhythmic drug toxicity from attempts to maintain sinus rhythm and the increasing success and applicability of radiofrequency catheter ablation or modification of the AV node (29-31) have lowered the threshold for undertaking the heart rate control approach earlier, it has not yet been tested as a primary therapy for atrial fibrillation. The emergence of catheter ablation has greatly increased the attractiveness of this approach because when it is successful, it obviates the need for drugs

(although in most patients a permanent pacemaker is needed) and this may have consequences with respect to safety and cost. Furthermore, a hemodynamic benefit of rate control alone has been suggested, (32) and early reports suggest improved quality of life and exercise tolerance (32-34). The major disadvantages of the catheter ablative approach include: early complications of the procedure; the need for a permanent pacemaker; and an as yet incompletely defined risk of late sudden death due to the procedure (32, 33). Finally, the strategy of heart rate control alone mandates use of antithrombotic therapy which may have increased risk in the elderly.

F. Antithrombotic Therapy - Warfarin

There have been five recently published studies of anticoagulation in nonvalvular, recurrent or chronic atrial fibrillation, (35-40) and a pooled analysis of these studies has been published (41). Furthermore, a more recent European study of secondary prevention has also been published (42). The studies show remarkable consistency, at least with respect to warfarin in younger patients. Anticoagulation with warfarin substantially lowers the risk for stroke in these patients; for example, in the Boston VA cooperative study (39) the risk reduction was 79% (95% confidence interval 52% to 90%). Furthermore, there was no statistically significant difference between placebo and warfarin with respect to major bleeding complications (36, 37, 39). There is a small but notable increased risk of intracranial hemorrhage in the patients randomized to warfarin. Furthermore, there is a substantial increase in minor bleeding in the subjects treated with warfarin. For example, in the Boston VA cooperative study (39), the "risk reduction" was -42% (95% confidence interval -98 to -2%), i.e., minor bleeding was <u>increased</u> by 42%.

The Stroke Prevention in Atrial Fibrillation-II Study continued to evaluate anticoagulation with warfarin versus treatment with aspirin. The results suggest that warfarin (INR 2.0 to 4.5) may be more effective in those over 75 years old but has substantial toxicity in this group (43). In this age group the benefit of warfarin in prevention of thrombotic stroke was essentially negated by an increased risk of intracerebral bleeding. A similar high risk of bleeding in those over 75 years was not found in the pooled analysis of the 4 remaining studies (41). The SPAF investigators feel it is unlikely that warfarin (INR 2.0 TO 4.5) will be superior to aspirin in those ?75 years old; however, this remains controversial. A number of studies are underway which address the question of intensity of anticoagulation in patients with chronic atrial fibrillation which cannot be controlled by antiarrhythmic drugs.

G. Antithrombotic Therapy - Aspirin

The results with aspirin were more mixed and remain controversial. One study used 75 mg per day and found no benefit (35). Another used 325 mg per day and found a benefit (38), although subgroup analysis suggested the benefit was confined to those ?75 years of age (40). The effect of aspirin in the pooled analysis was quite modest (41). Furthermore, in the European study aspirin had no effect (42). The risk of bleeding is lower for aspirin.

H. Antithrombotic Therapy - Risk Stratification

The Stroke Prevention in Atrial Fibrillation investigators (44, 45) and the recently published results of a pooled analysis of the five studies (41) have identified a number of clinical risk factors besides age (e.g., hypertension, left ventricular dysfunction, diabetes mellitus, previous stroke) which confer an increased risk of stroke. Furthermore, additional risk factors have been identified from echocardiographic studies (45) and from evaluation of left ventricular function (46). For the purposes of the present study it would seem prudent to follow the guidelines recommended by these investigators with respect to antithrombotic therapy, that is, to identify two strata: one with high risk of stroke (? 65 years or <65 years and ? 1 risk factor) and one with low risk for stroke (<65 years and no risk factors). High risk patients should be treated with warfarin to maintain an INR of 2.0-3.0, while the low risk patients would be excluded from the study.

I. Relevance of Antithrombotic Trials to Present Study

With respect to antiarrhythmic drug use, it is important to point out that the population to be studied in the currently proposed trial will be different from those in the studies of anticoagulation cited above. The study described in this proposal will include patients who present with the problem of atrial fibrillation and for whom it is felt attempts to restore and maintain sinus rhythm are warranted. Most of these patients were excluded from the five anticoagulation studies cited above. Furthermore, it is possible that quinidine will be used less than it was in previous studies.

J. Other Therapies for Atrial Fibrillation

For completeness sake it should be mentioned that there are other therapies under development for management of atrial fibrillation, including surgery (47) and implantable atrial defibrillators (48). These therapies have not yet progressed to the point where they should be considered for inclusion in a clinical trial.

K. Need for a Trial in Management of Atrial Fibrillation

The most urgent need is to determine if there is an absence of clinically important increased risk of major complications (particularly death) and whether there is any measurable objective benefit (e.g.: reduction of symptoms, improved quality of life, hemodynamic improvement), from the strategy of using antiarrhythmic drugs to attempt to control heart rate and maintain sinus rhythm, in comparison to the strategy of heart rate control alone, each used as primary therapy in an appropriately defined population with atrial fibrillation.

2. RATIONALE FOR THE APPROACH

A. Sample Size

For the primary endpoint of total mortality, the sample size needed is large but manageable in the setting of a large, simple trial. The data from the recently completed Stroke Prevention in Atrial Fibrillation-II Study were used for the present sample size calculation (see below) because they are the most contemporary and because they allow for separate calculation for patients ?75 years old and those >75 years old.

B. Burden of Trial on Subjects

The methodology and recruitment techniques of the Digitalis Investigation Group may be directly applied to this study, particularly because simplicity is a key issue to reduce the burden of the trial on the elderly subjects (49) and to decrease the cost of the trial. Some secondary endpoints will be addressed in substudies. In order to minimize the burden of the trial on subjects, substudies and ancillary studies will also be simple.

C. Antithrombotic Therapy

Risk factors for stroke in the presence of atrial fibrillation are: age, prior stroke or TIA, hypertension, congestive heart failure, diabetes mellitus, left atrial size and left ventricular dysfunction. In this study, two groups will be identified: one with high risk of stroke (? 65 years or <65 years and at least one other risk factor) and one with low risk for stroke (<65 years and no other risk factors). High risk patients will be treated with warfarin to maintain an INR target of 2.5 (range: 2.0 to 3.0). Low risk patients will be excluded from the study. The investigators recognize that excluding low risk patients will leave a major segment of the atrial fibrillation population untested. However, inclusion of such patients would unacceptably decrease the power of the study. Nevertheless, it is possible that the results of this study could be extrapolated to the low risk patients.

In the strategy of attempting maintenance of sinus rhythm, antithrombotic therapy could be reduced as part of the strategy when sinus rhythm is demonstrated to be maintained for at least 3 months. This approach would mimic clinical practice.

D. Blinding

An important procedural issue is whether or not there is a need for blinded therapy. The study compares two strategies. An advantage of one of the strategies is possible discontinuation of antithrombotic therapy when sinus rhythm is restored and maintained. In the other strategy catheter ablation will be a major therapy. It is not possible to have effective blinding of subjects and clinical investigators under these circumstances. Some of the disadvantages of an unblinded study are offset by use of death as an endpoint. Some secondary and descriptive endpoints can be evaluated in a blinded fashion. Cause of death and nonfatal endpoints will be adjudicated by a committee blinded to the therapy the patient was receiving. As has been demonstrated by the five studies of anticoagulation cited above (two were double-blind, three were unblinded), such an approach is valid.

E. Secondary Endpoints

Quality of life and cost are considered to be an integral part of the study. Detailed quality of life protocols will be applied to a random subset of patients. Protocols for quality of life and cost have been devised by the Steering Committee. Many secondary endpoints (e.g., drug efficacy in maintenance of sinus rhythm or control of heart rate, improvement in symptoms and functional capacity, total embolic events [transient ischemic

attacks, non-disabling strokes, systemic emboli], and adverse clinical effects of the drugs) will be evaluated.

F. Descriptive Endpoints

The study will also include some descriptive endpoints for which it may not be necessary to perform formal statistical comparisons between treatment groups. However, these endpoints will be useful in the interpretation of the results. The first of these will be tabulation of all bleeding complications. These data are necessary to formulate a complete picture of the risk of antithrombotic therapy. This is particularly important in view of the apparent toxicity of warfarin in the elderly and the fact that anticoagulant use will not be equal in the two treatment strategies. A second descriptive endpoint will be mode of death, as it is anticipated that any effect of antiarrhythmic drugs will be on arrhythmic death or cardiac death (congestive heart failure). The third descriptive endpoint will be stroke and systemic embolus. It is to be anticipated that the occurrence of these events would be reduced by maintenance of sinus rhythm. A number of other descriptive endpoints are possible (e.g., new or worsening congestive heart failure, syncope, discontinuation of therapy, and withdrawals).

G. Substudies

Substudies require collection of additional data beyond that required for the main study but usually will not require independent funding. Much smaller sample sizes are probably needed in such substudies. Initiation of substudies and their protocols will be the prerogative of the Steering Committee and the investigators.

H. Ancillary Studies

There may be some opportunities to plan for important ancillary studies. Ancillary studies are more complex than substudies and may require additional procedures or testing; hence, they will require sources of independent funding. Initiation of ancillary studies and their protocols will be the prerogative of the Steering Committee and the investigators. Ancillary studies of functional capacity and of innovative therapies for maintenance of sinus rhythm and control of heart rate (Step II Therapies, see Figures 2 & 3 on pages 17-18) are particularly encouraged.

3. OBJECTIVES, IMPLEMENTATION AND DESIGN OF STUDY

A. Primary Objective

The study will compare whether optimized antiarrhythmic drug therapy administered to attempt to maintain sinus rhythm has an impact on total mortality when compared to optimized therapy which merely controls the heart rate. The study will be analyzed by intention-to-treat.

Hypothesis: In patients with atrial fibrillation, total mortality with primary therapy intended to maintain sinus rhythm is equal to total mortality with primary therapy intended to control the heart rate.

B. Secondary Objectives

Because stroke is such an important endpoint in trials of patients with atrial fibrillation, composite endpoints will include the following:

1. Total mortality, disabling stroke (embolic or hemorrhagic), and disabling anoxic encephalopathy.

2. Total mortality, disabling stroke or anoxic encephalopathy, major bleeding, and cardiac arrest.

Hypothesis: In patients with atrial fibrillation, composite endpoints defined above are the same with primary therapy intended to maintain sinus rhythm as with primary therapy intended to control the heart rate.

3. Cost

4. Quality of Life

Hypothesis: In patients with atrial fibrillation, cost and quality of life with primary therapy intended to maintain sinus rhythm are the same as with primary therapy intended to control the heart rate.

C. Descriptive Objectives

1. Bleeding Complications

Among the potential adverse effects, bleeding is the one of most importance. Intracranial bleeds and other major hemorrhage are most critical, but minor bleeding is the major reason for poor adherence to therapy in the antithrombotic trials. Both arms of the study will initially include anticoagulation with warfarin. Bleeding endpoints are particularly important because one of the treatment strategies includes the possibility of reduction of antithrombotic therapy when sinus rhythm is maintained successfully. Description of the incidence of bleeding complications may be useful in explaining the overall character of a particular treatment strategy.

Hypothesis: Bleeding complications will be more frequent in patients with atrial fibrillation whose treatment strategy is heart rate control in comparison to those treated to attempt to maintain sinus rhythm.

2. Mode of Death

Any effects of antiarrhythmic drugs on mortality would be anticipated to be in relation to cardiac death (primarily heart failure and arrhythmic death). Statistical comparisons between treatment arms for specific causes of death are not planned. However, description of the modes of death in each arm may be useful in explaining the mechanism by which one therapy was beneficial or why it was not. Death will be classified as noncardiovascular, vascular, or cardiac. Cardiac deaths will be subclassified as arrhythmic or nonarrhythmic. Arrhythmic deaths will be further subclassified according to initiating mechanism as primarily arrhythmic, or due to ischemia or congestive heart failure.

Hypothesis: Arrhythmic death will be more common in patients with atrial fibrillation who are given therapies to attempt to maintain sinus rhythm in comparison to those given therapies merely to control the heart rate.

3. Stroke

Stroke is a major consequence of atrial fibrillation. Statistical comparisons between treatment arms will be conducted, but the overall power for this infrequent event is small. Stroke will be categorized into disabling and non-disabling. Disability will be assessed using the Rankin Scale which assigns 5 levels of disability, in addition to death.

Hypothesis: The incidence of stroke will be lower in patients with atrial fibrillation who are given therapies to attempt to maintain sinus rhythm in comparison to those given therapies merely to control heart rate.

4. Systemic Embolus

Systemic embolus is also a major consequence of atrial fibrillation but has an extremely low frequency. Statistical comparison between treatment arms is not planned. However, it is important to tabulate these events in order to make a complete description of the consequences of the two treatment strategies.

Hypothesis: The incidence of systemic embolus will be lower in patients with atrial fibrillation who are given therapies to maintain sinus rhythm in comparison to those given therapies merely to control heart rate.

5. Miscellaneous

A number of other events will be tabulated as they represent endpoints which may be favorably or unfavorably altered by one of the randomized therapies. These include: syncope, resuscitated cardiac arrest, sustained ventricular tachycardia, new or worsened heart failure, new or recurrent myocardial infarction, new or worsened angina pectoris, hospitalizations, discontinuation of therapy, and study withdrawal.

D. Implementation of the Study

The study will consist of four phases.

Phase I - Planning - 6 months

A Planning Committee, composed of experts in the field, devised the detailed study protocol. The Clinical Trial Center assisted in protocol development. An independent Protocol Review Committee was formed and asked to review the protocol. Twenty-six clinical investigators were selected to enroll patients in the Start-up Phase (Phase II). Once clinical investigators were chosen, the Planning Committee evolved into the Steering Committee, its Executive Committee and various other committees (see below). The latter committees finalized the details of data collection during this phase.

Phase IIA - Start-up - 6 months

Trial methodology was field tested and refined during this period. Data collection is as simplified as possible in the main study. Of course, more detail is needed in the substudies and ancillary studies, but these are also designed to be as simple as possible. Trial methodology was changed slightly after this phase, but there were no significant changes in the main study treatment protocol. The patients entered into the Start-up Phase were thus continued into the main study.

Phase IIB - Main Recruitment and Follow-up - 36 months

After a final protocol and appropriate methodology were developed and found acceptable by the Steering Committee and the Data and Safety Monitoring Board, additional participating Clinical Investigators were selected, for a total of 200, and the main study was begun. A total of 5300 patients will be recruited for the main study over 36 months (an average of 9 patients a year per investigator), and follow-up will continue. Substudies and ancillary studies will be conducted during this phase.

Phase III - Follow-up - 24 months

During this phase, no new patient recruitment will occur. All patients will be followed.

Phase IV - Analysis - 12 months

During this 12 month period, completion of data collection, analysis, and manuscript preparation will take place.

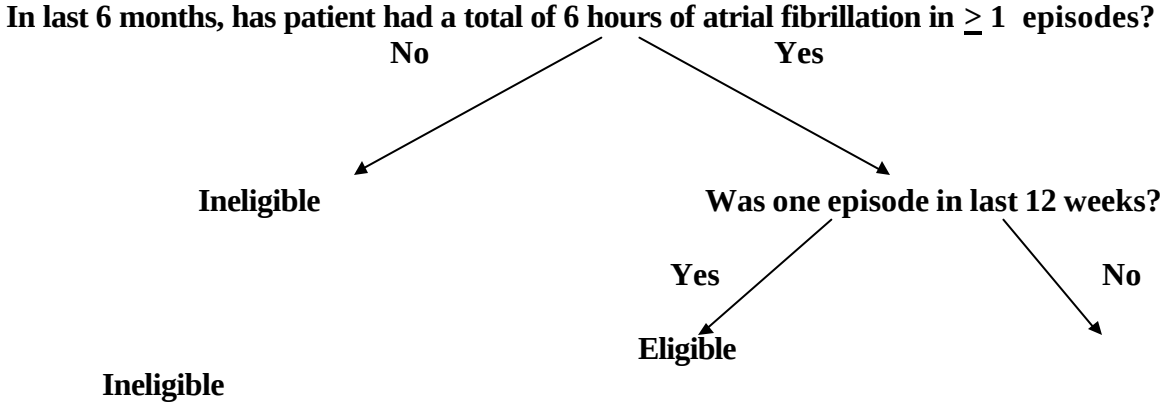
E. Design of the Study

The design of the study is shown in Figures 1 and 2.

Prior history of atrial fibrillation will be obtained in as much detail as possible. Only the episodes occurring in the last 6 months can be used to contribute to the sum of 6 hours of atrial fibrillation required to qualify for randomization. An "episode" of atrial fibrillation is defined as lasting at least 1 hour. Atrial flutter can count as an episode, but it must not be the qualifying arrhythmia. A mixture of atrial fibrillation and atrial flutter can be considered an episode of atrial fibrillation. Atrial flutter is defined by regularity of both cycle length and morphology of atrial complexes in any ECG lead. Type I flutter usually has an atrial rate of 240-340 and cannot be the index arrhythmia for AFFIRM. If irregular cycle length and morphology are clearly seen in any ECG lead, then it is likely that the rhythm in fact is fibrillation, and the lead with apparent flutter should be examined more closely (if possible) for a longer duration. Type II atrial flutter is rare, but an atrial rate of > 340/minute (though regular in rate and morphology) should be considered to be <u>functionally</u> equivalent to atrial fibrillation and can be used as an index rhythm which qualifies a patient for AFFIRM.

Figure 2

Eligibility Schema



Episode = **≥ 1 hour of atrial fibrillation**
Most recent episode must be documented on ECG in the last 12 weeks
To be used in the tally for the required 6 hours of atrial fibrillation, the episode must have occurred within last 6 months

(See Appendix A for eligibility examples.)

This study aims to maintain simplicity of patient management. It attempts to leave as much of the treatment as possible to the choice of the primary physician.

The study will randomize the treatment of atrial fibrillation between heart rate control and anticoagulation or rhythm control with antiarrhythmic drugs (drugs to maintain heart rate control will not be required in all cases) and anticoagulation. The study will include a "mini registry" of patients meeting inclusion and exclusion criteria who refuse to participate.

4. PATIENT SELECTION:

A. Inclusion Criteria

The overriding principles for determination of qualifying atrial fibrillation in AFFIRM are:

- episodes are likely to be recurrent,
- episodes are likely to cause mortality/morbidity,
- the physician would treat the patient long-term, and,
- the patient is eligible for both treatment strategies.
- treatment in both strategies could be initiated immediately after randomization.

It is the intent of the study to include patients with atrial fibrillation in whom a significant risk of mortality or stroke is present. It will exclude low risk patients. Investigators are encouraged to enroll all patients with atrial fibrillation, including patients with a history of congestive heart failure, a low ejection fraction, moderate or severe structural heart disease, and/or ischemic heart disease. **However, patients with structural heart disease must not be given flecainide. All precautions listed in the package insert for flecainide (as well as the AFFIRM restrictions in Section 9.A) must be followed.**

Arbitrary durations of atrial fibrillation are specified in an attempt to avoid enrollment of patients for whom the risk of death or stroke is small. The study investigators acknowledge that measurement of the duration of atrial fibrillation is difficult, if not at times impossible.

Inclusion criteria are the following (all criteria must be met):

1. Atrial fibrillation is documented on electrocardiogram or rhythm strip. Atrial fibrillation must be the qualifying event. Atrial flutter can have been present in the past, but it must not be considered the index arrhythmia.

2. Patient is ≥ 65 years of age, or < 65 years of age plus one clinical risk factor for stroke:

   - hypertension
   - diabetes
   - congestive heart failure
   - prior cerebrovascular accident (CVA) or transient ischemic attack (TIA), or other systemic embolus
   - left atrium ≥ 50 mm by echocardiogram
   - shortening fraction < 25% by echocardiogram (unless paced or LBBB present)
   - left ventricular ejection fraction < 0.40 by radionuclide ventriculogram, contrast angiography, or quantitative echocardiography

3. Duration of atrial fibrillation totals ≥ 6 hours in ≥ 1 episode in the last 6 months. Episodes of atrial fibrillation must be "sustained", defined as lasting ≥ 1 hour. To meet the ≥ 6 hour total duration criterion, 2 or more episodes can be added within the last 6 months. The qualifying episode must have occurred within the preceding 12 weeks and been documented by ECG or rhythm strip.

   For patients enrolled with atrial fibrillation in whom cardioversion is attempted prior to randomization, normal sinus rhythm must persist for at least one hour after cardioversion to qualify as successful conversion and to permit randomization. Antiarrhythmic drugs may be used during this attempt to cardiovert.

4. Duration of continuous atrial fibrillation is < 6 months (that is, the duration of uninterrupted atrial fibrillation is not known to be > 6 months). If atrial fibrillation has been continuously present for > 6 months, the patient must be in sinus rhythm for more than 24 hours prior to enrollment.

5. In the opinion of the clinical investigator, the patient must be eligible for long-term treatment with both strategies (AV blockers and antiarrhythmics).

6. Patient must be eligible for two antiarrhythmic drugs, or both dose levels of amiodarone (See Section 9.A.1), or one antiarrhythmic drug in addition to one amiodarone dose. Two doses of amiodarone are considered to be 2 drug "trials" (1) to allow more patients to be eligible for the study who might not be able to tolerate other antiarrhythmic drugs, (2) to accommodate patients who may have

had prior unsuccessful drug trials, and (3) to allow evaluations of "low" and "high" doses of amiodarone. Patients must also be eligible for at least 2 trials of rate-controlling drugs.

7. Both rate control and rhythm control strategies could be initiated immediately after randomization (or within a maximum of 5 days).

Hospitalization for both early evaluation and treatment will be performed per accepted clinical criteria at the local enrolling site.

Patients who meet the inclusion criteria but who have coronary artery bypass graft surgery or aneurysm resection can enter the study more than 7 days after the surgery (so that any mortality/morbidity of CABG is not attributed to treatment of atrial fibrillation), provided all entry criteria are met (including timing limitations) at the time of randomization.

Patients with atrial fibrillation after myocardial infarction (MI) who meet the inclusion criteria otherwise can enter the study if the atrial fibrillation onset occurs more than 7 days after the onset of the MI.

Revascularization via PTCA, stent, or atherectomy shall not disqualify a patient from randomization, provided all other criteria are met at the time of randomization.

B. Exclusion Criteria

Cardiac exclusions:

1. Valvular heart disease when intervention (surgery or valvuloplasty) is anticipated in the next year.

2. Certain prior valve surgery or valvuloplasty, which includes: mitral, tricuspid, or pulmonic valve replacement (mechanical or tissue), aortic valve replacement with mechanical valve, percutaneous catheter balloon valvuloplasty, commissurotomy, or pulmonic valve repair. Patients with unsuccessful aortic tissue valve replacement or repair of the aortic, mitral, or tricuspid valve with unsatisfactory results are also excluded. Patients with successful aortic tissue valve replacement or successful aortic, mitral, or tricuspid valve repair are not excluded.

Valvular Interventions

Aortic		Eligible?*
Repair (successful)		Yes
Replacement:	Tissue (successful)	Yes
	Mechanical	No
Percutaneous balloon valvuloplasty		No
Commissurotomy		No
Mitral		

Repair (successful)		Yes
Replacement: Tissue		No
	Mechanical	No
Percutaneous balloon valvuloplasty		No
Commissurotomy		No
Tricuspid		
Repair (successful)		Yes
Replacement:	Tissue	No
	Mechanical	No
Percutaneous balloon valvuloplasty		No
Commissurotomy		No
Pulmonic		
ANY intervention		No

**** If "yes", the patient may be enrolled in AFFIRM if all other eligibility criteria are met.***

3. Hypertrophic obstructive cardiomyopathy.

4. Reversible cause of atrial fibrillation, such as severe electrolyte imbalance, thyrotoxicosis, excessive use of beta adrenergic stimulants, acute alcohol intoxication, infection, pericarditis, or within 7 days of thoracic surgery, other major surgical procedure, electrocution, or trauma.

5. Onset of qualifying episode of atrial fibrillation within 7 days of CABG or myocardial infarction.

6. Class IV congestive heart failure (when optimally treated), or on heart transplant waiting list.

7. Other requirement for antiarrhythmic drug treatment.

8. Congenital long QT syndrome. Note: amiodarone can be used if the patient has a history of torsades de pointes VT induced by other antiarrhythmic drugs.

9. Catheter ablation of atrial tissue already performed for atrial flutter or fibrillation, unless recurrence includes at least one episode of atrial fibrillation after the ablation and within the last 12 weeks.

10. Lone atrial fibrillation, patient < 65 years old (i.e., no clinical risk factors for stroke, normal LA size, and normal LV function as defined in 4.A.2).

11. WPW syndrome, unless successfully treated by catheter ablation or surgery. Note: Patients with AV node reentrant tachycardia (AVNRT) or concealed accessory pathways can be included in AFFIRM.

12. Implanted automatic cardioverter-defibrillator.

13. Prior maze or corridor procedure.

14. Prior AV node ablation or modification. Note: Prior ablation for AVNRT does not exclude a patient from AFFIRM, as long as antegrade AV node conduction persists.

15. Prior inability to cardiovert. If a subsequent attempt at cardioversion is successful, the patient may be reconsidered for inclusion.

16. Amiodarone use, totaling more than 6 grams within the last 6 weeks.

Other medical exclusions:

17. Medical condition limiting expected survival to $\leq$ 2 years.

18. Contraindication to warfarin. If a physician is unwilling to use warfarin for any reason, then the patient is not eligible.

19. Renal failure requiring dialysis.

20. Woman of childbearing potential, unless an addendum to the consent form has been approved by the Data and Safety Monitoring Board and signed by the patient.

Non-medical exclusions:

21. Participant in another clinical trial.

22. Prisoner or ward of the state.

23. Unable or unwilling to give informed consent.

24. Geographically inaccessible for follow-up.

25. Psychological problem that might limit compliance.

Note: An implanted permanent cardiac pacemaker does not exclude a patient from this protocol. Furthermore, a patient with a slow ventricular response to atrial fibrillation - who may need little or no AV node blockade if randomized to the rate control arm of AFFIRM - can still be included in the study.

Women of childbearing potential are not specifically excluded from AFFIRM. However, warfarin (and some other cardiac medications) are contraindicated during

pregnancy. If women of childbearing potential are to be included at an individual site, the site must generate a special consent form (or an addendum to the standard consent) which deals with the risks and benefits of the study specifically with regard to both the patient and the potential fetus. Because of the sensitive nature of this issue, the Data and Safety Monitoring Board will review the consent form, as well as the local IRB and the Clinical Trial Center. Such a consent form must include all teratogenic effects of drugs which might potentially be used, particularily warfarin, as well as the psychological and moral risks of participation in the study. For purposes of this study, surgical sterilization by tubal ligation will be considered adequate evidence that the woman is not of childbearing potential. For women of childbearing potential who may wish to enter the study, the consent form needs to specify what types of contraception are acceptable and at what points during the study pregnancy tests will be required.

5. INFORMED CONSENT

No patient may be randomized without signed informed consent on a consent form approved by the Clinical Trial Center and by the local Institutional Review Board. Informed consent must include the statement that some drugs might be used outside FDA - approved indications.

6. BASELINE TESTS

The clinical assessment and laboratory evaluation (including echocardiography) of the patient should be completed prior to randomization. It will include quantification of duration and frequency of atrial fibrillation and a judgment concerning the most likely cause. All tests performed in this study should be compatible with good, standard clinical care. The NHLBI will provide no funding for any of the tests performed; therefore, the tests are not considered required for the protocol. Standard imaging and the metabolic studies should be performed in addition to a comprehensive history and physical examination. These tests should include, but are not limited to:

- electrocardiography
- chest x-ray
- thyroid function tests (particularly TSH)
- electrolytes
- CBC
- echocardiography

These tests should be performed consistently with a diligent search for correctable or primary causes of atrial fibrillation. Sites are required to keep all echo reports and electrocardiograms, whenever available, in the patients' research files. In particular, a copy of an electrocardiogram of the qualifying episode of atrial fibrillation must be retained in the patients' files.

Echocardiography is strongly encouraged, but is not required for randomization. Standard echocardiographic techniques and views will be used. To be considered as

baseline information, the echo should have been performed within one year of the date of the qualifying episode of atrial fibrillation, but preferably within one month. The following data will be collected:

- Rhythm at time of recording
- Left atrial size (measured in centimeters or estimated as normal[$\leq$4.0 cm], mild enlargement [4.1-4.5 cm], moderate enlargement [4.6-5.5 cm], and severe enlargement [>5.5 cm]).
- Presence of left atrial or left ventricular thrombus
- Mitral valve morphology
- Left ventricular wall thickness
- Left ventricular systolic and diastolic dimensions
- The ejection fraction will be reported only if it is planimetered and calculated. Otherwise, the left ventricular function will be qualitatively estimated as normal, mild reduction, moderate reduction, or severe reduction.

There will be no centralized reading of echocardiograms in the main study, although substudies and ancillary studies might consider centralized reading with quality control.

Prior history of angina and congestive heart failure will be noted. The patient's functional status with respect to angina and congestive heart failure will be recorded, with the estimated Canadian Cardiovascular Society anginal class and New York Heart Association congestive heart failure class for the patient's physical capacity within 14 days of randomization.

Quality of life will be assessed in all patients at a randomly selected subset of 25% of the clinical sites. Functional status will be measured by the Six Minute Walk test and the Folstein Mini-Mental State at at a random sample of 10% of the sites.

7. CARDIOVERSION

If atrial fibrillation has been present $\leq$ 48 hours, cardioversion may be attempted without preceding long-term anticoagulation. Some physicians will institute heparin immediately upon evaluating the patient and prior to cardioversion. Many will perform transthoracic echocardiography and/or transesophageal echocardiography prior to cardioversion, and may alter plans for cardioversion based upon the finding of thrombus. These decisions will be left to the clinical judgment of the investigator at the local site. At least 3 weeks of anticoagulation are required before cardioversion if thrombus is noted. If atrial fibrillation has been present for more than 48 hours, patients should be anticoagulated for at least 3 weeks with warfarin prior to cardioversion. Anticoagulation should be continued for at least 4 weeks, and preferably 12 weeks, after cardioversion.

Cardioversion may be attempted prior to randomization at the discretion of the physician. It is the intent of the study that patients with 2 or more episodes of atrial fibrillation will not be cardioverted prior to randomization. However, cardioversion will not

preclude enrollment. Furthermore, patients with only a first episode of atrial fibrillation can be enrolled without prior cardioversion.

If cardioversion is attempted prior to randomization, it must be successful. Successful cardioversion is defined as normal sinus rhythm (including sinus tachycardia, sinus bradycardia, and intermittent junctional rhythm) for at least 1 hour. If atrial fibrillation has been present continuously for > 6 months, sinus rhythm must persist for $\geq$ 24 hours before a patient is considered eligible for AFFIRM.

Cardioversion will be deemed unsuccessful only after maximum energy (360 or 400 Joules) is attempted with antero-posterior paddles. Cardioversion may be attempted, if necessary, after administration of an antiarrhythmic drug to attempt to hold sinus rhythm. Internal cardioversion is acceptable, if needed. Intravenous procainamide, ibutilide, or other antiarrhythmic agents can be used if deemed appropriate by the physician. Drug therapy using any antiarrhythmic drug can be used to achieve normal sinus rhythm, but if randomized to rate control, the antiarrhythmic drug must then be discontinued. Use of amiodarone is discouraged prior to randomization. A patient who has received more than 6 grams of amiodarone within 6 weeks prior to randomization is excluded.

Patients failing cardioversion will not be further considered for randomization unless a subsequent attempt at cardioversion is successful. If symptomatic bradycardia persists after cardioversion, patients can still be considered candidates for this study if a permanent pacemaker is implanted.

After randomization, patients assigned to the rhythm control arm who are not in sinus rhythm should be cardioverted either electrically or pharmacologically. Patients in the rhythm control arm who are not successfully cardioverted or who relapse into atrial fibrillation will proceed to additional antiarrhythmic drug trials and then to innovative therapy.

8. RANDOMIZATION

Randomization will be accomplished by telephone call to the Clinical Trial Center. Eligibility and informed consent will be confirmed at the time of the call. Randomization will be performed by permuted block design with equal allocation and will be stratified only by clinical site. Treatment should start immediately after randomization, or as soon as possible, but no later than 5 days after randomization.

9. INTERVENTIONS

This protocol will be responsive to changes in accepted therapy during the course of the study. The Steering Committee may recommend changes in treatments in both arms of the study during the course of the investigation.

A. Therapeutic Approach to Maintenance of Sinus Rhythm

The order of drugs to be used in this protocol will not be specified. The choice of drugs will be left to the primary treating physician, chosen from the list below. The First Antiarrhythmic Drug Substudy (see Section 15.A) will randomize initial drug choice among amiodarone, sotalol, and Class I drugs. Attempts to maintain sinus rhythm may include multiple cardioversions. Prior drugs which were ineffective or poorly tolerated will not be repeated. It may be necessary to administer an antiarrhythmic drug prior to cardioversion in an attempt to maintain sinus rhythm immediately after the cardioversion, and it may be necessary to change antiarrhythmic drugs or increase doses of antiarrhythmic drugs to attempt to maintain normal sinus rhythm. Relapse into atrial fibrillation in and of itself should not necessarily be considered to be a failure of the strategy to maintain sinus rhythm. For example, a patient who has had multiple episodes of atrial fibrillation in the 6 months preceding randomization and who does not have an episode of atrial fibrillation until month 7 after antiarrhythmic drug treatment would not necessarily be a drug failure. That patient could potentially even continue the same antiarrhythmic drug at the same dose.

Antiarrhythmic drugs may cause both therapeutic and toxic effects at relatively low doses in the elderly. Careful attention should be paid to occult renal and hepatic dysfunction in the elderly. Furthermore, some patients may have impaired drug metabolism even with normal renal and hepatic function. The investigator should be alert to watch for these conditions.

1. Approved drugs, minimum dosage

- Amiodarone - a minimum cumulative loading dose of 10 g of amiodarone will be administered over a period of several weeks prior to the first maintenance dose. The first maintenance dose will be 200 mg per day or 100 mg per day if side effects preclude the higher dose. The second dose will be 300 mg per day or 400 mg per day if necessary for rhythm control and if not precluded by adverse drug effects. Recurrences of atrial fibrillation may require a brief "reloading" phase with higher doses for a few weeks.

- d, l - Sotalol - 120 mg p.o. b.i.d. Dosing should <u>start</u> at 80 mg p.o. b.i.d. with careful attention to excessive effect and to renal dysfunction in the elderly and in females. It may be necessary to limit the dose in some elderly patients to 80 mg p.o. b.i.d. Dose should be modified based on an estimate of the creatinine clearance.

- Propafenone plus A-V nodal blocking drug* - 150 mg p.o. t.i.d.

- Flecainide plus A-V nodal blocking drug* - 50 mg p.o. b.i.d.

- Quinidine plus A-V nodal blocking drug* - 600 mg/day of quinidine base

- Moricizine plus A-V nodal blocking drug* - 400 mg/day
- Disopyramide plus A-V nodal blocking drug* - 300 mg/day of disopyramide base
- Procainamide plus A-V nodal blocking drug* - 1,500 mg/day
- Combinations of above drugs

*unless contraindicated

General Precautions

All patients should be evaluated carefully for potential proarrhythmia from any of the drugs. For patients with baseline, drug-free QTc of >0.46 seconds, quinidine, disopyramide, procainamide, moricizine, and sotalol should not be used. These drugs should be discontinued or the dose reduced if the QTc is > 0.52 seconds. QT intervals should be evaluated as clinically appropriate, and the negative inotropic effects of drugs should be considered, particularly sotalol, propafenone, flecainide, and disopyramide. Care should be taken to evaluate bradycardia and hypokalemia in all patients given antiarrhythmic drugs. Caution regarding proarrhythmia must be exercised in using all antiarrhythmic drugs in the presence of organic heart disease and/or LVH.

AV nodal blocking drugs should be given as appropriate, unless contraindicated, especially with quinidine, disopyramide, flecainide, propafenone, moricizine, and procainamide. Such drugs will likely be less necessary with amiodarone and sotalol. Doses of AV node blocking drugs should be adjusted as appropriate to the patient's heart rate during atrial fibrillation. Only if the ventricular rate during atrial fibrillation is $\leq$ 80 beats per minute without drugs should an AV nodal blocking drug be omitted during therapy with quinidine, disopyramide, flecainide, propafenone, moricizine, and procainamide. Decisions regarding choice of rate-controlling medications (beta blockers, calcium channel blockers, digitalis), and their dosages will be left to the physician at the local site. Antiarrhythmic serum or plasma drug levels should be used as clinically appropriate, but will not be required by the protocol.

If a patient is refractory to AV nodal blockade with rate-controlling medications, AV node ablation can be performed. Use of antiarrhythmic drugs must be continued in order to maintain sinus rhythm.

Precautions with Class I drugs

Investigators should exercise caution in the administration of all Class I drugs to patients with left ventricular dysfunction (manifest by a history of congestive heart failure, a low ejection fraction, or current clinical signs of CHF). Such patients should be considered for hospitalization and monitoring for initiation of treatment. Hospitalization should occur

in accordance with good clinical practice. Some patients with less serious heart disease could have drugs begun as outpatients, but hospitalization is strongly encouraged for all patients with structural heart disease. Alternative treatments should be considered if left ventricular dysfunction is severe. Patients with ischemic heart disease (angina, MI, or laboratory evidence of coronary artery disease) may also have an increased risk of adverse effects from Class I drugs. Patients who have previously experienced ventricular arrhythmias or who have a history of torsades for any reason, including use of ibutilide for cardioversion or prior use of a Class I-A agent, should not receive Class I-A agents or sotalol. In patients considered to be at high risk for proarrhythmic drug effects who are hospitalized, the following items should be considered:

- frequent evaluation for CHF
- monitoring for bradycardia, ectopy, and torsades
- frequent assessment of QT intervals
- lower initial dosing
- less frequent increases in dose
- monitoring serum/plasma levels
- avoiding hypokalemia - use potassium-sparing diuretics or potassium supplementation with non-potassium-sparing diuretics
- frequent measurement of electrolytes to keep potassium greater than 4.0 mEq/L.

Patients treated with procainamide should have blood counts performed every week for 12 weeks (or with a frequency dictated by locally accepted standard practice) and as needed thereafter to evaluate for agranulocytosis. Furthermore, blood tests should be performed every 3-6 months to monitor for the drug-induced lupus syndrome.

The I-C agents (propafenone and flecainide) should not be given to patients with a history of congestive heart failure, structural heart disease, ventricular myocardial disease, left ventricular hypertrophy, coronary artery disease, myocardial ischemia or myocardial infarction. For any patient to be given a I-C agent, both an echocardiogram must show normal ventricular function and wall thickness, and an evaluation for stress-induced ischemia (exercise test, stress thallium or sestamibi, stress echo, pharmacologic stress radionuclide scan, or pharmacologic stress echo) must be normal. Alternatively, a normal coronary angiogram can substitute for the stress evaluation. Thus, the only patients eligible for I-C agents (even if all these tests are normal) are:

- lone atrial fibrillation and no LVH, age $\geq$ 65
- lone atrial fibrillation and no LVH, age < 65 with one of these risk factors:
  - Diabetes (but no coronary artery disease)
  - Hypertension (but no LVH)
  - TIA
  - CVA

Large left atrium (in absence of all other cardiac disease)

Left ventricular hypertrophy should be evaluated by echocardiography. LVH is defined as septal or posterior wall thickness > 14 mm.

An ECG should not be used to determine LVH unless the echo is inadequate to evaluate wall thickness. The ECG criteria for LVH are from the New York Heart Association:

- Sum of R in I plus S in III > 25 mm, or
- Maximum R or S in any limb lead > 20 mm, or
- Maximum R in a VL > 13 mm, or
- Sum of S in V1 plus R in V5 or V6 > 35 mm, or
- Maximum R in V5 or V6 > 30 mm.

Even in the absence of such conditions, flecainide and propafenone must not be given to any patient with LV function outside normal limits by local criteria, ejection fraction < 0.50 (performed by any technique), or definite wall motion abnormality. Patients with hypertension only (no LVH) can be given flecainide or propafenone.

Likewise, even in the absence of a history of congestive heart failure, disopyramide should not be given to patients with an ejection fraction < 0.30.

Precautions with Class III drugs

Patients with any of the following conditions are ineligible for sotalol:

- Asthma
- Renal dysfunction requiring dialysis. Minor renal dysfunction (estimated creatinine clearance $\leq$ 60 ml/min) should prompt adjustment of sotalol dose in accordance with the package insert.
- Current CHF, Functional Class $\geq$ II when best treated
- History of CHF, currently Functional Class I, but LV ejection fraction
- $\leq$ 0.30
- No history of CHF, but LV ejection fraction $\leq$ 0.25
- History of prior excessive QT prolongation with sotalol or other antiarrhythmic drugs.
- Prior inefficacy or serious adverse effects of sotalol.
- History of torsades de pointes VT for any reason, including the use of ibutilide for cardioversion (unless the patient has tolerated sotalol in the past).

Other general principles of drug administration

All drug dosages should be modified as appropriate in the presence of renal or hepatic dysfunction. Serum levels should be used in such circumstances as appropriate. Care should be taken to prevent drug-drug interactions, particularly the interaction of amiodarone with digitalis preparations and warfarin. These drug dosages should be reduced by 1/3 to 1/2 with frequent monitoring of drug levels or prothrombin times.

Care should be taken to avoid drugs which in themselves lengthen the QT interval, particularly in patients receiving quinidine, disopyramide, and sotalol (see Appendix B).

Evaluation for drug efficacy/inefficacy cannot be considered until a patient has had adequate loading and dosing of the drug. Preferably, where appropriate, drug levels should be obtained to document that the recurrence of atrial fibrillation occurred in the presence of adequate serum levels. Amiodarone should be considered a failure at the first maintenance dose only if an adequate 10 g loading phase has been achieved.

Occasionally it will be necessary to administer a different antiarrhythmic drug to a patient who has already received amiodarone. The question of amiodarone wash-out is complex. For patients who have been on amiodarone, a blood level of $\leq$0.3 ?g/ml is adequate "washout". In the absence of blood level information, a wash-out of 3 months is considered adequate if the patient has received >10 g of drug, and 1 month if <10 g of drug has been given. For patients in the study being switched off amiodarone to another drug, a 2 week washout is recommended, then a new drug may be started at a lower initial dose at the investigator's discretion (generally, about 1/2 of the usual daily dose). After the amiodarone blood level has fallen to $\leq$0.3 ?g/ml, full-dose drug may be given. In the absence of blood level information, amiodarone may be considered "washed-out" after 1 month for a total dose of <10 g and after 3 months for doses of >10 g.

If a patient is randomized to either rate-control or rhythm-control and has or develops normal sinus rhythm, it is still strongly suggested that a rate controlling drug (AV-nodal blocker) be used/continued.

2. Drugs for future consideration

The Steering Committee will regularly review the list of approved drugs and dosages. It will evaluate any new drugs which become available during the course of the study which might potentially be used for maintenance of normal sinus rhythm, making additions, deletions, or other changes as necessary.

3. Definitions of rhythm control

Even with recurrence of atrial fibrillation, the patient can be maintained on the same drug and same dose, if the investigator determines that the atrial fibrillation was adequately controlled, based upon the number and frequency of prior arrhythmia recurrences. Patients will be considered controlled if they have no more than 1 episode of atrial fibrillation in a 6 month period, or by investigator judgment if episodes of atrial fibrillation were frequent prior to receiving any antiarrhythmic drugs.

4. Innovative therapy to maintain normal sinus rhythm

After standard modes of treatment are exhausted in Step I, but never before failure of at least two trials of antiarrhythmic drug therapy, patients may be considered for innovative therapy. Each dose of amiodarone is considered to be a single drug trial, so that patients who receive treatment with amiodarone at both dosage levels will be considered to have had two drug trials. If amiodarone is ever to be used, it must be used prior to innovative therapy. It is not mandatory that Step II therapies be applied in any individual patient.

The following innovative therapies are approved for use in this study:

- Ablation of an atrial focus in patients with type I atrial flutter, if it is clinically documented that the atrial flutter leads to atrial fibrillation.

- Pacing alone with or without documented bradycardia. This pacing can include single or multiple site atrial pacing or dual chamber pacing but will not be limited simply to VVI pacing.

- Pacing and antiarrhythmic drugs can be used with either single site or multiple site atrial pacing. Atrial pacing alone or dual chamber pacing can be used as clinically appropriate, but VVI pacing alone will not be allowed in this arm of the study.

- Surgical maze or atrial isolation procedures can be considered at selected institutions as long as this procedure has been performed on at least 5 patients with less than 5% 30-day perioperative mortality. Patients may be referred to appropriate clinical centers for these procedures, if necessary.

- AV node ablation or modification can be used in those uncommon patients in whom intermittent episodes of atrial fibrillation lead to serious symptoms because of inadequate rate control. Use of antiarrhythmic drugs must be continued in order to maintain sinus rhythm.

Catheter-based ablative procedures such as the maze operation are not approved in this study. Implanted atrial cardioverter defibrillators are not approved for use in this study.

B. Therapeutic Approach to Heart Rate Control

This arm of the study will use heart rate as the therapeutic target, rather than dose of heart rate controlling medications. Patients should have assessment of heart rate control both at rest and with some form of functional test, either Holter monitoring or a Six Minute Walk test.

1. Approved Drugs

- Beta Blockers
- Calcium Channel Blockers (verapamil and diltiazem)
- Digoxin (levels are encouraged: target $\geq$ 1.0 ng/ml)
- Combinations of above drugs

2. Drugs for future consideration

The Steering Committee will evaluate any drugs which become available during the course of the study which might potentially be used for heart rate control. The Steering Committee will regularly review the list of approved drugs and make additions, deletions, or other changes as necessary.

3. Definitions of heart rate control

For patients in the rate control arm who are not in normal sinus rhythm, heart rate control should be established initially at the two-month follow-up or subsequent visits, repeating the test at each visit until adequate rate control is achieved. Thereafter, rate control should be assessed if the patient's status changes, after every major drug or dose change, and at every annual anniversary visit (one year, two year, three year, etc.) if the patient is in atrial fibrillation or flutter.

Guidelines for target heart rate control during atrial fibrillation are as follows:

- $\leq$ 80 beats per minute at rest, and at least one of the following functional criteria:
  - $\leq$ 110 beats per minute during a Six Minute Walk test.
  - average $\leq$ 100 beats per minute during atrial fibrillation throughout a 24-hour period (18 hours of recorded analyzable Holter monitoring), with no heart rate recorded which is > 110% predicted maximum exercise heart rate for age.

The Six Minute Walk test is preferred. If both Holter and Six Minute Walk tests are performed, both test criteria must be met. Graded maximum symptom-limited exercise testing will not be used in this protocol.

Doses of drug will be titrated upwards or downwards based upon heart rate and side effects. Clinical judgment will dictate a balance between side effects and resting or exercise heart rate.

4. Innovative therapy for heart rate control

The following treatments are considered acceptable for heart rate control after standard treatment is exhausted, but never before failure of at least two different drug regimens for heart rate control (limited by side effects of medications precluding increase of drug dosage at a time when heart rate control remains inadequate). It is not mandatory that Step II therapies be applied in any given patient.

- AV node ablation and pacemaker
- AV node modification with or without pacemaker, with or without AV node blocking drugs

C. Bradycardia Pacing

Some patients may already have a permanent pacemaker implanted before enrollment in AFFIRM. It may be necessary to reprogram the device or to revise it for optimal pacing. In other patients it may be necessary to implant a permanent pacemaker for control of intermittent bradycardia.

In the **rate control arm**, it is recommended before pacing is used that investigators first try digoxin alone for rate control when bradycardia is a problem. Pindolol could also be considered. When pacing is used, ACC/AHA guidelines should always be followed (50). For patients with continuous atrial fibrillation, pacing should be the single chamber VVIR mode. For patients with intermittent atrial fibrillation or paroxysmal atrial fibrillation, dual chamber pacing should be employed, either the DDD or the DDDR mode with mode switching. In general, settings for pacers in the rate control arm should avoid aggressive pacing which has as its *intent* the maintenance of normal sinus rhythm. The recommended lower rate should therefore usually be 60 BPM.

In the **rhythm control arm**, pacing should be dual chamber, in most circumstances in the DDDR mode (rarely AAIR single chamber pacing might be used). ACC/AHA guidelines should also be employed (50). The minimum rate should be no lower than 70, and 80 is preferred. Mode switching should be used, if available. Rate responsive modes should be activated when clinically appropriate. High rate or dual site atrial pacing may also be considered as innovative therapies.

Pacing and sensing should be tested whenever drugs are changed which affect pacing thresholds and/or sensing.

D. Antithrombotic Therapy Guidelines

Physicians should follow the guidelines for antithrombotic therapy (51). In general, the guidelines are as follows:

- < 65 years old and 1 clinical risk factor for stroke: warfarin
- ≥ 65 years old: warfarin, unless contraindication develops, then aspirin
- INR for warfarin: 2.5 (range 2.0-3.0)
- Caution with warfarin if ≥75 years of age
- In the rhythm control arm, may reduce/modify antithrombotic therapy after ≥ 4 weeks, preferably after ≥ 12 weeks, of continuous sinus rhythm on antiarrhythmic therapy, based on physician judgment. If warfarin is discontinued, most physicians would institute aspirin. In the rate control arm, patients should be anticoagulated with warfarin throughout the study.
- Antithrombotic therapy for cardioversion: follow minimum published recommendations: continue warfarin for ≥ 4 weeks and preferably ≥ 12 weeks after cardioversion if atrial fibrillation continued ≥ 48 hours prior to cardioversion.

The Steering Committee will regularly review antithrombotic therapy guidelines to insure that results and new knowledge from contemporary trials are incorporated.

10. PATIENT FOLLOW-UP

After a patient has been randomized, every effort must be made to maintain therapy with the drugs listed for that strategy. Only when all possibilities have been exhausted because of inefficacy or intolerance should the strategy be changed. All patients will be followed to a common termination date. The study will be analyzed by intention-to-treat.

Patients should be seen and evaluated on a schedule consistent with their clinical condition and good practice. Such a schedule will almost certainly require more frequent visits than suggested by this protocol.

Patients should be followed at the enrolling site whenever possible. Follow-up by non-study physicians and follow-up by phone can be conducted in exceptional situations where personal contact with study staff is impractical. Every effort should be made to obtain all items on the follow-up forms. Regardless of the method of follow-up, the AFFIRM Principal Investigator and Study Coordinator are responsible for adherence to the study protocol and the accuracy and completeness of data collection.

A. Follow-up Schedule

Patients will be seen and evaluated as a part of this protocol at 2 months following randomization, at 4 months, and then every 4 months thereafter. (See Data Collection Schedule below.)

DATA COLLECTION SCHEDULE

Form Name	Base-line	2 mo	4 mo	8 mo	12 mo	16 mo	20 mo	24 mo	28 mo	32 mo	36 mo	40 mo	44 mo	48 mo	52 mo	56 mo	60 mo	As needed
Consent	X																	
Baseline	X																	
Electrocardiogram*	X		X		X													
Echocardiography (TTE and/or TEE)	X																	
Functional Status	B	B			B			B			B			B			B	
Quality of Life	A	A			A			A			A			A			A	
Follow-up		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Innovative Therapy																		X
Drug Discontinuation																		X
Change of Treatment Strategy																		X
CNS Disability																		X
Event Notification**																		X
Death																		X

*At baseline, patients in the rhythm control arm will have a minimum of 3 ECG's (qualifying atrial fibrillation, NSR after cardioversion, and ECG after completion of drug titration). Patients in the rate control arm will have a minimum of 2 ECG's (qualifying atrial fibrillation and ECG after drug titration).

**Events are disabling anoxic encephalopathy, myocardial infarction, non-CNS hemorrhage, torsades de pointes VT, sustained ventricular tachycardia, resuscitated cardiac arrest, stroke or intracranial bleed, systemic embolism, pulmonary embolism, and death.

X = all patients

A = in 25% of sites

B = in 10% of sites (though the Six Minute Walk test may be performed in patients randomized to heart rate control at these and other intervals to assess adequacy of rate control)

B. Tests

At each follow-up visit, the angina and congestive heart failure functional class will be assessed by the Canadian Cardiovascular Society and New York Heart Association classification schemes. The Folstein Mini-Mental State and the Six Minute Walk functional test will be performed at 10% of sites at an initial assessment, at 2 months, 12 months, and yearly thereafter. In other patients, the Six Minute Walk test and/or Holter monitoring will be performed to assess rate control.

Cost will be assessed by counting: 1) the number of days of relevant hospitalizations, 2) the number of major cardiac procedures and device implantations, and 3) number of emergency room and short stay visits.

Assessment of quality of life (including patient concerns and cognitive function) will be performed regularly. Quality of life will be assessed in 25% of patients initially, at 2 months, 12 months, and yearly thereafter. It will utilize the SF-36, the Ladder of Life, the Quality of Life Index, and the Symptom Checklist, as well as some specific questions directed to arrhythmias and functional capacity.

C. Events During Follow-up

The following events will be tracked throughout the study:

- Death (including mode of death)
- CVA (embolic, thrombotic, and hemorrhagic)
- Cardiac arrest with disabling anoxic encephalopathy
- Systemic embolus
- Pulmonary embolus
- Myocardial infarction
- Major and minor bleeding
- Resuscitated cardiac arrest, including ventricular fibrillation, sustained ventricular tachycardia, and torsades de pointes VT

D. Items Left to the Discretion of the Physician

The following items are the major decisions which are left to the discretion of the physician:

- Hospitalization to begin the study
- Heparin administration prior to cardioversion if atrial fibrillation has been present for $\leq$ 48 hours.
- Echo/TEE pre-cardioversion
- Baseline tests
- Drug choice (although selection of first drug is a major randomized substudy in both arms)
- Warfarin for 3-4 weeks after cardioversion if atrial fibrillation has been present for $\leq$ 48 hours
- Serum/plasma drug levels

- Reduction or discontinuation of anticoagulation (substitution of aspirin) in rhythm control arm if sinus rhythm has been present for $\geq$ 12 weeks.

11. ENDPOINTS

A. Primary Endpoint

The primary endpoint of the study is total mortality.

B. Required Secondary Endpoints

Composite endpoints will be classified into two major groups: serious and permanent, and serious/permanent but including serious but reversible conditions.

1. Composite of total mortality, disabling stroke (embolus/thrombosis/ hemorrhage), anoxic encephalopathy, subdural/subarachnoid hemorrhage

2. Composite of total mortality, disabling stroke, anoxic encephalopathy, intracranial bleed (subdural/subarachnoid hemorrhage), major non-CNS hemorrhage, cardiac arrest

3. Cost of therapy

4. Quality of life

C. Other Potential Secondary and Descriptive Endpoints

1. Stroke - When possible, CNS events will be categorized as embolic, thrombotic or hemorrhagic. Disability will be classified by the modified Rankin Scale. An Events Committee will classify all strokes, blinded with respect to treatment assignment. Data required for stroke assessment will include any available reports of CT Scans, MRI, angiography, neuroimaging studies, carotid ultrasound, echocardiogram, hospital discharge summary, and descriptive letter from the Principal Investigator.

2. Systemic embolus

3. Major bleeding, requiring transfusion and/or surgery and/or permanent cessation of warfarin. Minor bleeding will be tracked as a separate endpoint. INR reports will be required.

4. Mode of death - An Events Committee will classify all deaths, blinded with respect to treatment assignment. Data required for death assessment will include all EMT/paramedic/medic notes,

emergency room notes, hospital notes and admission/discharge summaries, operative notes, pathology reports, lab tests, ECG's, and a detailed letter from the Principal Investigator.

5. Resuscitated cardiac arrest, to include ventricular fibrillation, sustained ventricular tachycardia, and torsades de pointes VT.

6. Hospitalization

7. Heart rate control

8. Maintenance of sinus rhythm

12. ANALYSES

Initially, baseline characteristics of patients in the two randomized groups will be compared. Covariates will be examined by graphical methods, descriptive statistics, and tables, and will be compared by chi-square tests, t-tests, and non-parametric tests. Subsequent analyses will adjust for covariates which are found to be significantly different between the groups.

The primary analysis will be an unadjusted comparison of time to death from any cause. Survival curves will be estimated by the Kaplan-Meier method and compared by the log-rank statistic. This analysis will be by "intention to treat", i.e., patients will remain in the assigned treatment arms regardless of crossover or noncompliance. Patients will be censored at last follow-up or at time of withdrawal from the study.

Additional analyses of the primary endpoint will model the effect of covariates using Cox survival analysis. Important covariates will include age, history of congestive heart failure, gender, race, presence of coronary disease, and concomitant drug therapy. While ejection fraction will not be recorded in all patients, sufficient numbers may be available to allow analysis of ejection fraction as a covariate.

Composite secondary endpoints of death or disabling stroke or anoxic encephalopathy, and death or disabling stroke or anoxic encephalopathy or major hemorrhage or cardiac arrest will be examined with time-to-event analyses as described above. Individual events including stroke, systemic embolism, major bleeding, resuscitated cardiac arrest, hospitalization for congestive heart failure or arrhythmia, and maintenance of sinus rhythm will be analyzed by a time-to-event analysis using the first event, by a comparison of counts, and by longitudinal analysis if there are enough events. Death will be used as a censor in the time-to-event analyses of individual events. This method will give an estimate of the event rate alone, although the estimate will be biased if the morbidity event and death are not independent. The composite endpoint and the censored analyses are complementary, and both would be used in most cases. If it happens that the mortality rates are equal in two groups, then the difference in the events rates would give a valid comparison of the events in the two groups even though the estimates of the rates would be biased. A chi-square test will be used to compare acute

pro-arrhythmic effects and 30-day mortality. Logistic regression will be used to incorporate the effect of covariates.

Time-to-event analyses will be used to describe the rate at which patients assigned to rate control convert to taking antiarrhythmic drugs and, correspondingly, the rate at which patients assigned to antiarrhythmic drugs discontinue the drug therapy. For purposes of the power sensitivity analyses, it was assumed that the latter rate would be slightly higher, but the relative rates are unknown for comparable sets of patients. Graphical and longitudinal data analysis methods will be used to analyze patterns of drug use over time. It would also be of interest to conduct an observational analysis of survival after accounting for crossovers in the two groups, although this analysis would have great potential for biases and would not be a primary analysis.

Analysis of quality of life measures will be done using intention-to-treat methods. Since quality-of life has many dimensions, other aspects of the patient data will be incorporated by using both combined outcome measures and multivariate methods. Both parametric and non-parametric, as well as semi-parametric approaches such as described by Hallstrom, et al. (52), will be used to incorporate both morbidity and death in the outcome. The same considerations of censoring due to death which were discussed above are appropriate for the quality of life data. Longitudinal data analysis methods will be used for quality of life outcomes that are collected at specified intervals over the follow-up period.

Since hospitalization and cardiac procedures are expected to be the major costs in this population, number of inpatient days and procedures will serve as surrogate measures of cost. Covariates which may influence cost such as age, race, gender, and type of enrolling institution (university or private clinic) will be considered in the analysis. As for quality of life and the other measures, the impact of any observed cost differences between the two groups must be interpreted in light of any differences in mortality and morbidity and analyses which incorporate multiple outcomes will be done.

13. POWER AND SAMPLE SIZE

The study is planned as a two-arm clinical trial of patients randomized to antiarrhythmic therapy or to heart rate control. The primary endpoint is total mortality. A total of 5300 patients will be entered into the study over the recruitment period. Under reasonable assumptions, this sample size provides the ability to detect a 30% annual mortality difference with 90% power while taking into account several factors that tend to reduce power.

The target sample size of 5300 patients (2650 per group) was based on the method of Lakatos (53) which provides estimates of event rates after adjusting for staggered accrual, losses to follow-up, drop-in rate, noncompliance, and lag in treatment effect. Mortality rates were assumed to be similar across the sites. The following parameter assumptions were used:

1. Significance level - .05 two-sided

2. Power - .90

3. Patient accrual - uniform accrual of 300 patients over the first six months, followed by uniform accrual of 5000 patients over the next three years. A two year minimum follow-up, 3.5 year average follow-up, total study length of 5.5 years.

4. Annual mortality rate - 4.2% in the rate control/anticoagulation group (prior to adjusting for noncompliance, losses, etc.) which is based on the results of the SPAF-II Study (43) and assumes 35% of the enrolled patients are > 75 years of age.

5. Mortality difference - 30% increase, i.e. from 4.2% to 5.5%, between the rate control and antiarrhythmic groups respectively, before adjusting for losses, noncompliance, etc.

6. Loss-to-follow-up - While no loss to follow-up is ever acceptable, an annual rate of 1% in each treatment group might be expected to be the worst case scenario. A loss is defined to be a patient who at some point during the study can no longer be observed for the occurrence of death.

7. Noncompliance - 15% rate of permanent discontinuation of drug in the antiarrhythmic drug therapy group in the first year after randomization, followed by 5% discontinuation in the subsequent years.

8. Drop-in - 5% annual rate of patients assigned to rate control and anticoagulation therapy but having antiarrhythmic drug therapy added. A constant annual rate was assumed.

9. Lag time - Zero lag time since it is assumed that the antiarrhythmic drug therapy would take effect almost immediately after initiation of treatment.

Figures below show the power of the trial under various changes in these assumptions when the sample size is fixed at 5300 patients. It is assumed that loss to follow-up, noncompliance, and drop-in occur randomly and are not specific to excessively sick or excessively healthy patients.

Figure 1 gives the power as a function of the mortality rate in the antiarrhythmic group when the mortality rate in the rate control group is 4.2%. Mortality rates in the antiarrhythmic group are shown ranging from 2% to 6% while the other design assumptions are as described above. Under these assumptions the study will have power greater than 80% for either an increase or a decrease in mortality greater than 30%.

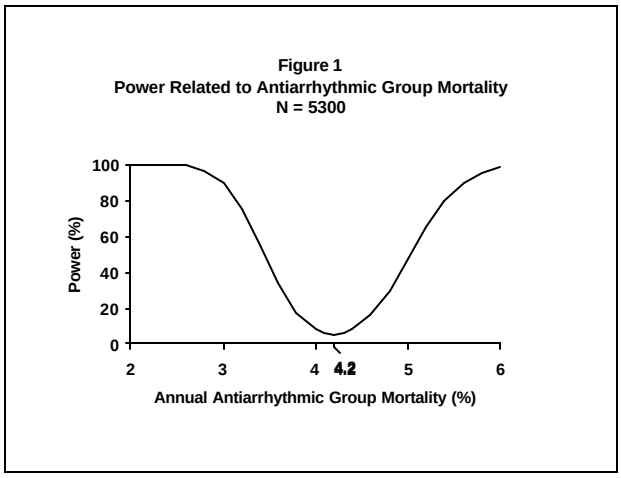


Figure 2 shows the loss in power if the crossover rate from antiarrhythmic drug therapy to rate control in the first year is increased from 15% to 20% or 25%. The power decreases from 89% to 83% if a 30% increase in mortality is assumed, and decreases from 83% to 76% if a 30% decrease in mortality is assumed.

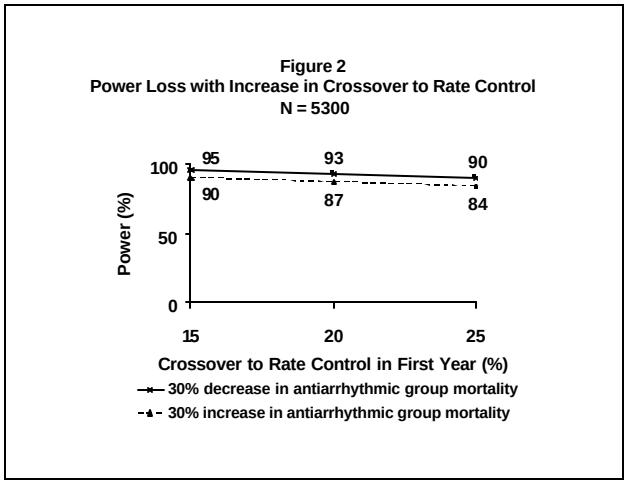
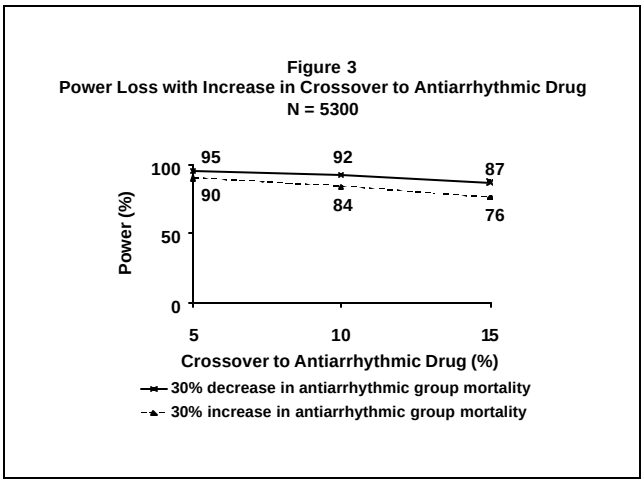


Figure 3 shows the loss in power if the crossover rate from rate control to antiarrhythmic drug therapy is increased from 5% per year throughout the study to 10% or 15%. The power decreases from 89% to 78% if a 30% increase in mortality is assumed, and decreases from 83% to 68% if a 30% decrease in mortality is assumed.



14. SEQUENTIAL MONITORING

A Data and Safety Monitoring Board (DSMB), independent of the clinical investigators, will review the study at least twice yearly and make recommendations to the NHLBI. The mortality rates for the two groups and the log rank statistic will be presented at each meeting of the DSMB. The log rank statistic will be compared to a sequential boundary for a .05 level two-sided test determined by an alpha spending function which corresponds to the O'Brien-Fleming method (54,55).

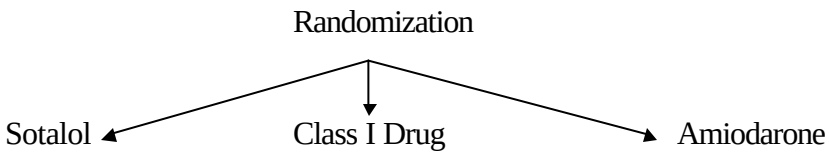
15. SUBSTUDIES/ANCILLARY STUDIES

In general, a substudy is an investigation which requires little or no additional data gathering or testing, whereas an ancillary study requires significant additional data collection or procedures.

A. First Antiarrhythmic Drug Substudy

The following substudy is strongly encouraged, but not mandatory, for all sites:

Randomization of the choice of the first antiarrhythmic drug for patients assigned to the rhythm control arm:



If randomized to a Class I drug, the choice among available (not contraindicated) Class I drugs will be made by the treating physician:

quinidine

- procainamide
- disopyramide
- moricizine
- flecainide
- propafenone

Limitations on Class I drug use are outlined in Section 9, Interventions. If ineligible for one arm of the substudy, the randomization will be made between the other two arms. If ineligible for two of the arms of the substudy, patients cannot be included in this substudy, and choice of the first drug will be made by the physician.

The primary endpoint for this study will be percentage of patients still on drug and in sinus rhythm without any cardioversions at 1 year. Secondary endpoints will include:

:

- time to first recurrence of atrial fibrillation
- atrial fibrillation prevalence at specified time points (4 months, 1 year)
- number of episodes of documented atrial fibrillation per unit of time
- duration between episodes of atrial fibrillation
- number of cardioversions
- time to first cardioversion

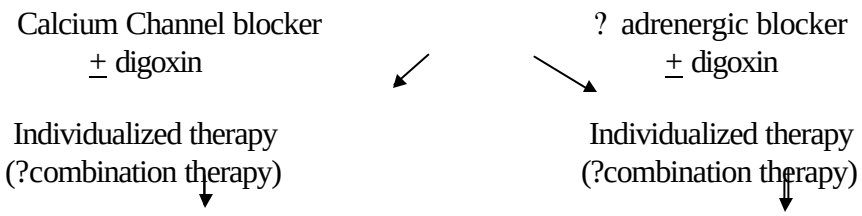
Other important endpoints will be:

- Mortality
- Tolerance
- Safety

B. *First Rate Control Drug Substudy*

The following substudy is also strongly encouraged, but not mandatory, for all sites:

Randomization of the choice of the <u>first</u> rate control drug for patients assigned to the rate control arm:



Innovative Therapy Innovative Therapy

Patients must be eligible for both treatment arms.

The primary endpoint will be adequacy of rate control response with the first therapy.

C. *Other Possible Substudies*

The following substudies could be considered in the future by the Steering Committee:

- Holter monitoring to evaluate rate and rhythm control
- Left ventricular function studies
- More detailed functional capacity assessment
- Echo/TEE - detailed echo evaluation, particularly prior to cardioversion
- Randomization of innovative therapy
- Randomization of AV node modification vs. AV node ablation
- Randomization of single vs. multiple site pacing
- CT scans or other neuroimaging studies for "silent" CVA's
- Evaluation of clotting parameters with respect to subsequent embolic events
- More extensive and detailed quality of life measurements
- Evaluation of the implantable atrial cardioverter defibrillator

16. ORGANIZATION AND COMMITTEES

A. Organization

The AFFIRM study is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and coordinated by the Clinical Trial Center. Day-to-day management of the study will be primarily the responsibility of the Clinical Trial Center, the NHLBI Project Office, and the Executive Committee. The Steering Committee actions are subject to the approval of the NHLBI.

1. National Heart, Lung, and Blood Institute

The NHLBI is responsible for the overall direction of the trial. The NHLBI will monitor the progress of the study and provide organizational and scientific guidance.

While an Investigational New Drug application (IND) is not necessary for the drug treatment proposed in this study, if any innovative therapy requires an IND or Investigational Device Exemption (IDE), it will be held by the NHLBI.

2. Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is composed of an independent group of experts. The primary role of the DSMB is to advise NHLBI on scientific, safety, ethical, and other policy issues relating to the study. The DSMB meets at least twice a year. Specific functions include: review of the study protocol, design or operational changes, and study performance (including progress and findings); formation of recommendations for the continuation or termination of the study based upon evidence of beneficial or adverse effect of the therapy or enrollment of a sufficient number of patients; and assurance of safe and ethical treatment of study participants.

3. Clinical Trial Center

The Clinical Trial Center (CTC) is the Statistics & Epidemiology Research Corporation (SERC) in Seattle, Washington. The CTC has the responsibility of contracting with the selected clinical sites, in close collaboration with the NHLBI. The CTC has primary responsibility for the design of the study, data collection, and statistical analysis of the results of the study. The CTC calculates sample sizes, develops the Manual of Operations and pretests all data forms, and designs and implements the randomization procedure. Moreover, the CTC is responsible for preparing and distributing regular progress reports, minutes, and reports for the Data and Safety Monitoring Board; monitoring endpoint results; ensuring the accuracy and quality of data collection; and presenting study analyses. The CTC also provides training for investigators and study coordinators.

4. Clinical Investigators

The clinical investigators are subcontractors of the CTC. Clinical investigators are responsible for screening and recruitment, patient treatment and follow-up, and collection of all clinical information and test data required by the study protocol. Investigators must be capable of innovative therapy as specified in the protocol or be willing to refer patients to appropriate centers for such therapy. Investigators are paid a fixed amount for each data form submitted to the CTC.

B. Committees

Committees have specific responsibilities for the ongoing process of the trial.

1. Planning Committee

The Planning Committee was chosen by the NHLBI and consisted of experts in the field of atrial fibrillation. It was charged with development of the Protocol for the study.

2. Steering Committee

The Steering Committee consists of the Planning Committee, selected Principal Investigators (PI's) from Clinical Centers, the PI of the Clinical Trial Center, the Project Officer of the NHLBI, and any others appointed by the NHLBI. A neurologist is included. Not all PI's from Clinical Sites, even the initial 26 sites, are included in the Steering Committee. The NHLBI appoints a Study Chair who presides over the Steering Committee and represents the Steering Committee as required by the NHLBI. The chair of each committee listed below is a member of the Steering Committee. The Steering Committee meets in conjunction with annual investigator meetings and at other times as needed.

3. Executive Subcommittee

The Executive Subcommittee consists of the NHLBI Project Officer, the Steering Committee Chair, the CTC PI, and others as designated by the NHLBI. It is a subgroup chosen from the Steering Committee. This subcommittee meets monthly by conference call and reviews the progress of the study, recruitment, data quality and adherence to the protocol. One of its duties is to review other randomized trials for patients who might be considered candidates for two separate trials. In general, inclusion of AFFIRM patients in other studies is discouraged.

4. Recruitment Committee

The Recruitment Committee is charged with the development of recruitment goals, strategies and aids. This committee may be asked for recommendations regarding specific center recruitment.

5. Drug Selection Committee

This committee is composed of clinical investigators and others of appropriate expertise and is charged with development and maintenance of a list of drug doses and protocols for treatment for maintenance of sinus rhythm, rate control, and antithrombotic therapy.

6. Innovative Therapy/Device Therapy Committee

This committee is composed of clinical investigators and others of appropriate expertise who will evaluate emerging innovative therapies for inclusion or exclusion from this trial.

7. Data, Substudy, and Ancillary Study Committee

This committee reviews all proposals for substudies, ancillary studies, and database analyses and makes recommendations to the Steering Committee regarding approval. This committee also reviews any proposed changes to data forms.

8. Authorship and Publication Committee

This committee is charged with reviewing proposed publications and abstracts prior to submission and making recommendations to the Steering Committee regarding approval. This committee will also make recommendations to the authors regarding content. Authorship guidelines (including maximum number of authors per paper and maximum number of papers per author) will be established based upon scientific contribution, patient enrollment, and writing effort, consistent with the National Institutes of Health/ NHLBI guidelines.

9. Events Committees

This committee will review all fatal events to classify for mechanism of death. Arrhythmic events will also be reviewed. A separate committee will review all CNS and embolic events in the study. Furthermore, other endpoints may require detailed review, as determined by the Steering Committee, the DSMB, and the NHLBI.

10. Quality of Life Committee

This committee is composed of investigators and coordinators who have appropriate interest and expertise in collection and analysis of quality of life data. The committee is charged with monitoring the progress of the Quality of Life Substudy and reviewing proposals for analyses involving primarily quality of life data.

17. PUBLICATION POLICY

The Authorship and Publication Committee will review all publications following the guidelines given below and report its recommendations to the Steering Committee.

A. Data Analysis and Release of Results

The scientific integrity of the study requires that the data from all clinical sites be analyzed and reported study-wide. Thus, an individual center or group of centers may not

independently report data. All presentations and publications must protect the integrity of the major objectives of the study; data that would release endpoint results will not be presented prior to the release of the main study results. The timing of presentation of any data and the venue in which the data are presented will be subject to the review and approval of the Steering Committee.

B. Review Process

Each paper, abstract, or presentation of previously unreported data from the AFFIRM trial, must be submitted to the Authorship and Publication Committee for review of scientific merit and of appropriateness for submission or presentation. Slides or posters containing data from AFFIRM should be submitted to the Publications Committee before their initial presentation. All submissions should be at least three weeks before the presentation or the abstract deadline. The committee may recommend changes to the authors and will submit its recommendations to the Steering Committee for approval.

The primary outcome papers present critical endpoint data (such as which treatment arm resulted in the lowest mortality) for the participant group in the trial. The final determination about whether or not a particular analysis represents a primary outcome will be made by the Steering Committee.

C. Authorship: Primary Outcome Paper

Authorship on primary outcome manuscripts will be "The NHLBI AFFIRM Investigators". For such manuscripts, there will be an appendix containing the names of the various organizational units and their Principal Investigators and Coordinators. The Data and Safety Monitoring Board will also be listed.

D. Other Study Papers, Abstracts and Presentations

All studies other than those designated “primary outcome” fall into this category. Papers or abstracts resulting from these studies will have named authorship of individuals involved, ending with the phrase "and the NHLBI AFFIRM Investigators". Suitability of authorship will be subject to approval of the Publications Committee. Papers will either have an appendix with the names of the organizational units and their Principal and Co-Investigators, or a reference to a methods or primary outcome paper with such a list. All papers and abstracts must be approved by the Authorship and Publications Committee before they are submitted.

18. CONFLICT OF INTEREST POLICY

Investigators and participants in this study should not have significant conflict of interest with respect to financial holdings in companies which may benefit from the results of this study. Full disclosure of all ties to pharmaceutical and device manufacturers will be required. The Executive Committee, in conjunction with the NHLBI, will determine if a significant conflict of interest exists and will make recommendations about courses of actions.

19. CLOSEOUT PROCEDURE

At the end of the study all appropriate medical and background information will be communicated to the patient and the patient's personal physician to aid in future care. The results and any recommendations will be presented to the patients and participating physicians. The Investigators and the Clinical Trial Center will supply the NHLBI with a study archive of important study documents, computer tapes for the main computer file and simplified "rectangular" or "flat" files that may be more easily used for analysis. A description of the format and how to use the material will also be supplied.

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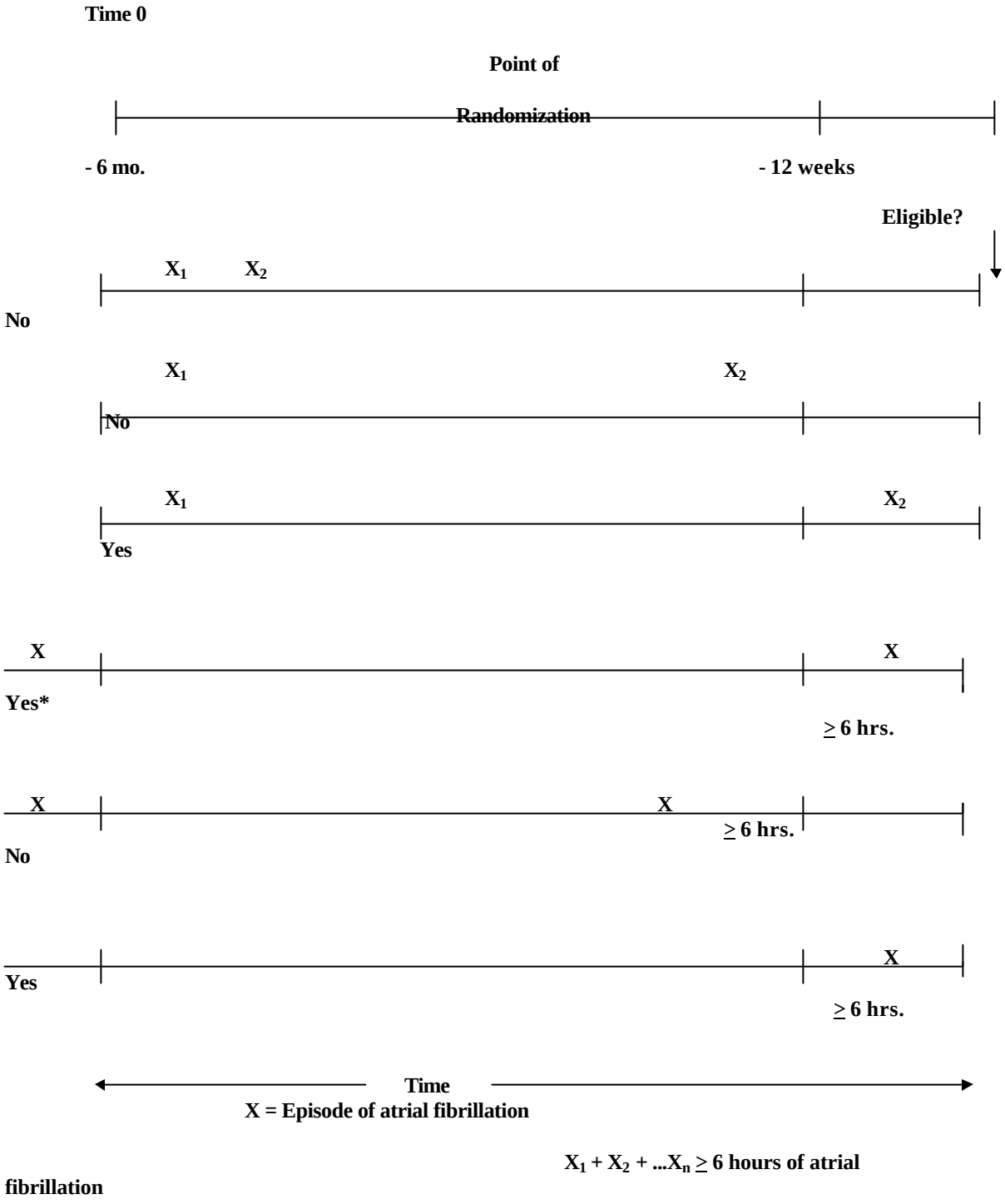
Appendix A

Eligibility Examples



Appendix B

DRUGS TO AVOID
For patients taking QT-prolonging drugs to minimize the risk of Torsades de Pointes Ventricular Tachycardia

I. Calcium blockers
Bepridil (Vascor)
Lidoflazine

II. Psychiatric drugs
Phenothiazines (thioridazine [Mellaril], chlorpromazine [Thorazine], etc.)
Tricyclics (amitriptyline [Elavil], etc.)
Haloperidol (Haldol)
* Doxepin (Sinequan)

III. Antibiotics
Azithromycin (Zithromax)
Chloroquine (Aralen)
Erythromycin (E-Mycin, Ery-Tab, PCE Dispertab, and others) - especially intravenously
Pentamidine (Pentam, NebuPent)
Trimethoprim-sulfa (Septra, Bactrim)

IV. Toxins
Arsenic
Organophosphate insecticides
Liquid protein diets

V. Antihistamines
Terfenadine (Seldane), especially with ketoconazole and/or liver disease or overdose
Astemizole (Hismanal)

VI. Antihyperlipidemics
Probucol (Lorelco)

VII. Miscellaneous (and potentially risky)
Amantadine (Symmetrel)
Diuretics without potassium, and sometimes magnesium, supplementation
Chloral hydrate
Cisapride (Propulsid), especially with ketoconazole
Cocaine
Terodiline (Mictrol, Micturin)

* Unconfirmed or rarely reported cases of torsades