Management of Atrial Fibrillation

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Abstract: Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. It is common in the elderly and those with structural heart disease. Clinical classification can be helpful in treatment decisions and the most widely accepted classification scheme (first episode, recurrent paroxysmal, recurrent persistent, permanent) is found in the ACC/AHA/ESC guidelines.

The pathophysiology of AF remains unclear at this time. It is unlikely that a single pathophysiology is operative in all or even a majority of cases. Therapies to be considered for AF include prevention of thromboembolism, rate control, and restoration and maintenance of sinus rhythm. These therapies and specific treatments for these purposes are discussed under these headings, including a section on the relative merits of the rate control and rhythm control strategies. Risk stratification is a fundamental part of the treatment for thromboembolism. When risk warrants treatment, prevention of thromboembolism is achieved either pharmacologically with aspirin, or with warfarin or new agents like ximelagatran, or by nonpharmacological approaches. Schema to assist in risk stratification and selection of appropriate antithrombotic therapy are provided. Recent trials comparing the strategy of rate control to the strategy of rhythm control failed to demonstrate that the rhythm control approach is superior to the rate control approach in patients and
therapies studied so far. Rate control is an acceptable primary line of therapy in many patients, particularly the elderly with persistent AF who are not highly symptomatic. However, the risk and benefit of each treatment modality should be individualized according to the patient circumstances and comorbidity. Algorithms to help individualize which of the two strategies to use are provided. There are a number of pharmacologic and nonpharmacologic therapies available for rhythm management of AF. Pharmacologic cardioversion is an alternative to electrical cardioversion for recent onset AF but the latter is preferred for persistent AF. Current drug therapy to maintain sinus rhythm is neither highly effective nor completely safe. An algorithm to guide selection of the most appropriate antiarrhythmic drug for an individual patient is provided. Nonpharmacologic therapies for maintenance of sinus rhythm include surgery, radiofrequency ablation, devices, and hybrid (combination) therapies. Much remains to be learned about the role and application of such therapies. Pharmacologic heart rate control can be achieved for most patients with available agents and, when it cannot, there are effective nonpharmacologic therapies. A few specific situations in which AF occurs and for which there are some special considerations are described. (Curr Probl Cardiol 2005;30:175–234.)

**Atrial fibrillation (AF)** is a supraventricular tachyarrhythmia characterized by uncoordinated electrical activation of the atria with consequent deterioration of atrial mechanical function. Electrocardiographically it is characterized by absence of P-waves before each QRS complex. P-waves are replaced by rapid oscillations (400 to 700 per minute), irregularly spaced and of variable size and shape called “f” waves. Sometimes very small “f” waves are difficult to see unless a 12-lead electrocardiogram (ECG) is done. In the absence of heart block, the ventricular deflections (QRS) may be normal or exhibit various degrees of QRS widening due to aberrant conduction when there is physiologic (rapid rates), or, pathologic prolongation of the refractory period of the bundle branches, especially the right bundle. Less commonly, a widened QRS is associated with the Wolf–Parkinson–White
syndrome. The ventricular rate in AF is usually inappropriately rapid, unless the patient is on AV node-blocking agent or has a coexisting AV node disease.\textsuperscript{1} Regular RR intervals during AF are possible in the setting of complete AV block or ventricular paced rhythm.

**Classification of Atrial Fibrillation**

AF has multiple clinical presentations, occurring in many different clinical settings. Classification of AF is helpful in management (see below). There are several classification schemes for AF in the literature.\textsuperscript{2,3} For the purposes of the following discussion, the classification scheme proposed by the ACC/AHA/ESC guidelines\textsuperscript{4} is recommended:

- **Paroxysmal AF:** Episodes that start and stop by themselves, generally lasting less than 24 hours but sometimes lasting up to 7 days.
- **Persistent AF:** Episodes lasting more than 7 days or that require termination, either pharmacologically or electrically.
- **Permanent AF:** Long-standing continuous episodes where repeated attempts to terminate have either failed or were not tried.

Note that this is a time-based classification of individual episodes of AF. When a patient has had two or more paroxysmal or persistent episodes, AF is termed recurrent. These definitions apply to episodes of AF more than 30 seconds and that are unrelated to a reversible cause, such as cardiac surgery, myocardial infarction, pulmonary embolism, myocarditis, or hyperthyroidism. When there are identifiable reversible causes, treatment of the underlying cause simultaneously with the management of the episode of AF will often eliminate the arrhythmia and the need for long-term rhythm management. In this article, we will focus on management of AF in the absence of reversible causes.

**Pathophysiology**

The pathophysiology of AF remains unclear at this time. It is unlikely that a single pathophysiology is operative in all or even a majority of cases. Insight into pathophysiology, particularly if it could be determined at the bedside, would help in the formulation of a rational rather than the current empiric approach to therapy. AF mechanisms (Fig 1) proposed include rapidly firing ectopic foci or single reentry circuits with fibrillatory conduction, and multi-circuit reentry.\textsuperscript{5,6} Until recently, multi-circuit reentry was felt to be the final common pathway.\textsuperscript{5} Remodeling (electrical, contractile, and structural) is an important part of the pathophysiology of AF (Fig 1). Wijffels et al\textsuperscript{7} were the first to show that prolonged AF causes changes in the electrical properties (electrical remodeling) of the atrium promoting maintenance of AF. These investigators implanted an atrial
lead in conscious goats connected to a rapid impulse generator designed to induce AF with burst pacing whenever sinus rhythm resumed. Their findings led to the concept that “AF begets AF.”

**B. J. Gersh:** This is an intriguing and important concept with quite-major clinical implications, in that if proven, this could be the impetus for the prompt, early treatment of paroxysms of atrial fibrillation using different approaches such as transesophageal echocardiographic-guided cardioversion, the development of new antiarrhythmic drugs, and perhaps the implantable atrial defibrillator. It must be emphasized, however, that this remains a concept based upon an animal model, and to what extent this will be clinically relevant remains to be seen.

The key electrical change noted by Wijffels et al\(^7\) was a decrease in the atrial effective refractory period (ERP). A reduced ERP decreases the size of the smallest circuit that can maintain reentry (the wavelength), thereby increasing the number of simultaneous circuits that can be accommodated by the atria and stabilizing multi-circuit reentry. Since these initial
observations, there has been an explosion of research into atrial remodeling during AF and the converse process of “reverse remodeling”. More recent observations concerning the importance of foci arising where the great veins enter the atria, particularly the pulmonary veins, have lessened the predominance of the multi-circuit reentry hypothesis.\(^8\) The interested reader is referred to the review by Waldo\(^9\) for a more detailed discussion of pathophysiology. An emerging part to the pathophysiology of AF is the importance of “modulating factors”\(^8\) in the development and maintenance of AF. Modulating factors can be very important in the rational treatment of this rhythm disturbance in certain settings. Better knowledge concerning pathophysiology has already increased our understanding of phenomena such as antiarrhythmic drug resistance\(^10\) and early relapse after electrical cardioversion\(^8\) of longstanding AF.

M. M. Scheinman: Allessie and colleagues nicely demonstrated that rapid overdrive atrial pacing (goats) resulted in decreased atrial effective refractory periods and showed that continued pacing in time resulted in a reverse use-dependent effect. Normally the atrial refractory period will shorten with pacing but this effect is lost with continued high-rate pacing. In addition, ease of provocation of atrial fibrillation decreases as pacing is continued. This is thought to be in part related to a Ca\(^{++}\) overload state, hence, explaining the possible benefits of verapamil therapy.

Other modulating factors appear to be important in both the initiation and the perpetuation of atrial fibrillation. For example, alternations in autonomic tone associated with either increased sympathetic or parasympathetic focus may trigger or serve to sustain atrial fibrillation. In addition, animal studies have highlighted the importance of atrial fibrosis as a substrate for perpetuation of atrial fibrillation. Agents that decrease fibroses (ie, ACE or ARBs) may play an important preventive role. Moreover, heart failure per se may serve to ignite arrhythmogenic foci (Stambler et al) as well as produce atrial fibrosis, both of which may explain the increased association between the two entities.

Epidemiology

AF is the most common sustained arrhythmia treated by physicians. It is primarily a problem of older subjects.\(^11\)-\(^18\) The relationship between age and AF was most recently demonstrated in a cross-sectional study of 1.89 million subjects in a health maintenance organization in Northern California.\(^11\) In this study the overall prevalence of AF was 1%. The prevalence of AF ranged from 0.1% among adults <50 years of age to 9% among those ≥80 years of age (Fig 2). AF prevalence was higher in men than women (1.1 versus 0.8%), a difference seen in every age group.
among patients over 50 years of age. AF prevalence was also greater in Caucasians than in African Americans (2.2 versus 1.5).

**B. J. Gersh:** These apparent racial differences are of interest and somewhat puzzling. The fact is that there is a paucity of data on the incidence and prevalence of atrial fibrillation in African Americans and other racial groups (Saksena S, Domanski MJ, Benjamin EF, et al. Report of the NASPE/NHLBI Round Table on Future Research Directions in Atrial Fibrillation. Pacing Clin Electrophysiol 2001;24(Part 1):1435-51).

In this study it was estimated that 2.3 million adults in the United States currently have AF and that this will increase to 5.6 million by the year 2050 with more than 50% being in patients over 80 years of age. The overall prevalence of AF is estimated as 3 per 1000 persons years in men and 2 per 1000 persons years in women aged between 55 and 64 years of age in the Framingham Heart Study.\(^{19,20}\) Moreover in the Framingham Heart Study the prevalence doubled for every decade increment in age.

**B. J. Gersh:** A recent study from Rochester, MN, demonstrated a striking increase in the prevalence of atrial fibrillation over a 30-year period after adjusting for age. The reasons are as of yet unclear, and one wonders about
the role of obesity, but the implications are profound. What is not in doubt is that we are certainly in the midst of a rapidly growing epidemic (Tsang TSM, Petty GW, Barnes ME, et al. The prevalence of atrial fibrillation in incidence stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. J Am Coll Cardiol 2003;42:93-100).

AF is more common in patients with structural heart disease\textsuperscript{18,21} such as coronary artery disease, hypertension, valvular heart disease, and congestive heart failure disease.\textsuperscript{22}

AF is associated with increased morbidity and mortality. The three commonest associations with AF are hypertension,\textsuperscript{22} stroke (Fig 3), and congestive heart failure\textsuperscript{24} (Fig 4). The risk of dying from AF after adjustment for age, heart disease, and other risk factors has an odds ratio of 1.5 in men and 1.9 in women in Framingham.\textsuperscript{25} As mentioned above, AF is also associated with an increased risk of developing embolic complications, particularly stroke.\textsuperscript{12} In the Framingham Heart Study, for example, the risk of stroke was more than five times greater in nonrheumatic AF patients than in sinus rhythm patients.\textsuperscript{23} AF is also associated with a number of cardiac and hemodynamic changes that in an unknown, but probably small, proportion of patients can lead to decreased myocardial systolic function and tachycardia-induced cardiomyopathy.\textsuperscript{26} Aside from these major associations, a number of minor associations have been recently reported, including inflammation,\textsuperscript{27} personality traits,\textsuperscript{28} and heavy alcohol consumption.\textsuperscript{29}

\begin{figure}[h]
\centering
\includegraphics{fig3}
\caption{Risk ratios (vertical axis) for stroke and death comparing AF to sinus rhythm in several epidemiologic studies (reproduced with permission).}
\end{figure}
Antithrombotic Therapy

**Stroke Risk Stratification in Atrial Fibrillation**

AF is thought to be responsible for approximately 15 to 25% of ischemic strokes. In addition to clinical stroke with major neurological deficits, AF may also be associated with silent cerebral infarction. The stroke rate varies from 0.5% per year for young patients without structural heart disease to 12% per year for patients with AF who have had a previous stroke. Risk stratification has been an essential element for making decisions about stroke prevention treatment for the last 20 years. The decision to treat a patient with anticoagulation should be based on the clinician’s judgment that the risk of a thromboembolic event without treatment is substantially greater than the risk of clinically significant bleeding caused by the treatment.

B. J. Gersh: To my mind, this is why the treatment of atrial fibrillation is so interesting from a clinical standpoint. One has to individualize therapy, taking into account age, risk factors for stroke and bleeding, and the patient’s lifestyle. Warfarin is not a good drug for people subject to trauma, whether it be due to occupation, leisure activities, frailty, or comorbidity.

Numerous studies have identified multiple risk factors associated with increased likelihood of stroke; these include age, gender, hypertension,
ischemic or rheumatic heart disease, prosthetic heart valve, congestive heart failure, history of stroke or transient ischemic attack (TIA), diabetes mellitus, and thyrotoxicosis. Postmenopausal hormone replacement therapy, smoking, and alcohol consumption are less well-defined risk factors.37,41-56

Data from five randomized stroke prevention trials in patients with nonvalvular AF have been used to refine risk stratification schemes for such patients.44,45,59-60 The Atrial Fibrillation Investigators (AFI) systematically pooled data from these five trials of anticoagulation therapy in patients with AF.32 That analysis demonstrated that several risk factors are associated with stroke risk of more than 5% per year without warfarin therapy. Patients with none of these risk factors had a low risk of less than 1% per year without warfarin (Fig 5).32 For example, age was shown to increase the risk of stroke by a factor of 1.4 per decade. These investigators published a simple table to express the relationship of age with other risk factors selected as having the greatest effect, namely a history of hypertension, a history of diabetes, and a history of previous stroke or TIA (Table 1).32

In another scheme, the Stroke Prevention in Atrial Fibrillation trial (SPAF) investigators assessed the risk for stroke in patients with AF
given only aspirin therapy to prevent stroke in three separate studies. This risk stratification scheme differed slightly, identifying women >75 years, hypertension, history of stroke or TIA, and impaired left ventricular function as clinical high risk factors for stroke (Table 2). Other schemes have been proposed and published and, although they are all similar, the presence of multiple schemes has lead to some confusion. Some, for example, also include echocardiographic characteristics. In general we favor schemes that recognize a continuum of risk rather than a simple dichotomy of “low” and “high” risk; that are simple and useful at the bedside; and that do not require tests such as

### TABLE 1. Annual stroke event rates from the Atrial Fibrillation Investigators Analysis by age group and presence or absence of other risk factors

<table>
<thead>
<tr>
<th>Age category</th>
<th>Risk category</th>
<th>Event rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 yrs</td>
<td>No RFs</td>
<td>1.0 (0.3-3.1)</td>
</tr>
<tr>
<td></td>
<td>1 or more RFs</td>
<td>4.9 (3.0-8.1)</td>
</tr>
<tr>
<td>65-75 yrs</td>
<td>No RFs</td>
<td>4.3 (2.7-7.1)</td>
</tr>
<tr>
<td></td>
<td>1 or more RFs</td>
<td>5.7 (3.9-8.3)</td>
</tr>
<tr>
<td>&gt;75 yrs</td>
<td>No RFs</td>
<td>3.5 (1.6-7.7)</td>
</tr>
<tr>
<td></td>
<td>1 or more RFs</td>
<td>8.1 (4.7-13.9)</td>
</tr>
</tbody>
</table>

RFs, history of hypertension, history of diabetes, previous stroke or TIA.

### TABLE 2. Thromboembolic risk in nonvalvular AF patients given aspirin from the SPAF I to III trials by individual risk factor and combined with other risk factors (RF)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Risk factor</th>
<th>Patient population</th>
<th>Thromboembolic rate per year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>SBP &gt;160 mm Hg</td>
<td>Single RF</td>
<td>7.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1 additional RF</td>
<td>9.6%</td>
</tr>
<tr>
<td></td>
<td>Female &gt;75 yrs</td>
<td>Single RF</td>
<td>7.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1 additional RF</td>
<td>7.9%</td>
</tr>
<tr>
<td></td>
<td>Age &gt;75 yrs, history of HTN</td>
<td>Single RF</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1 additional RF</td>
<td>6.9%</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Age ≤75 yrs, history of HTN</td>
<td>Single RF</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1 additional RF</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>Single RF</td>
<td>2.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1 additional RF</td>
<td>2.9%</td>
</tr>
<tr>
<td>Low risk</td>
<td>All moderate risk</td>
<td>Single RF</td>
<td>2.6% (1.9-3.6)</td>
</tr>
<tr>
<td></td>
<td>All low risk</td>
<td>Single RF</td>
<td>0.9% (0.6-1.6)</td>
</tr>
</tbody>
</table>

HTN = hypertension
(Reproduced with permission40).
TABLE 3. CHADS$_2$ stroke risk stratification scheme for patients with nonvalvular AF

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Recent congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age $\geq$ 75 yrs</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S$_2$ History of stroke or transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>

FIG 6. Relationship between CHADS$_2$ score and annual risk of stroke (reproduced with permission$^{61}$).

an echocardiogram. Such a scheme is the recently proposed CHADS$_2$ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke/TIA) risk assessment outlined in Table 3 and Fig 6. It incorporates features from both SPAF and AFI and was validated in a population of 1733 Medicare beneficiaries with nonvalvular AF who were not receiving warfarin at hospital discharge.$^{61}$

Pharmacologic Antithrombotic Therapy

There are two distinct aspects of antithrombotic therapy to be considered in the management of AF. The first of these is the assessed need for antithrombotic therapy on a long-term basis. The fundamental need for this type of antithrombotic therapy is determined by the assessment of the ongoing risk of stroke as outlined in the previous section. Pharmacologic and nonpharmacologic therapies for this purpose are the topic of the next two sections. The second aspect of antithrombotic therapy is separate from, and in addition to, this background antithrombotic therapy, that is,
the need for antithrombotic therapy around the time of electrical or pharmacological cardioversion. That aspect of antithrombotic therapy will be discussed in a later section that deals specifically with cardioversion.

Five randomized controlled trials of warfarin versus placebo and/or aspirin (Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF),\textsuperscript{43} Canadian Atrial Fibrillation Anticoagulation (CAFA),\textsuperscript{57} Stroke Prevention in Nonrheumatic Atrial fibrillation (SPINAF),\textsuperscript{42} SPAF,\textsuperscript{59} and Copenhagen Atrial Fibrillation Aspirin Anticoagulation (AFASAK)\textsuperscript{58}) for primary prevention of thromboembolism among patients with nonvalvular AF have been reported. The trials enrolled patients with predominantly chronic (now called permanent) AF detected on routine screening or screening ECG (mean age 69 years). AFASK and SPINAF excluded patients with intermittent AF, whereas the proportion of patients with intermittent AF (not the same as Paroxysmal AF defined above) was 16\% in BAATAF, 34\% in SPAF, and 7\% in CAFA. AFASAK compared warfarin, aspirin, and aspirin placebo. SPAF allocated patients as being warfarin eligible (group 1) or warfarin ineligible (group 2). Group 1 patients in SPAF were randomized to open-label warfarin or usual therapy, whereas group 2 patients were randomized to open-label warfarin, aspirin, or aspirin placebo.

The target International Normalized Ratio (INR) range in these trials varied from 1.2 to 2.5 to 2.8 to 4.2. Three trials were stopped early by their Data and Safety Monitoring Boards because interim analysis was strongly positive and CAFA was stopped early because of the positive results in the other trials. As previously outlined, the AFI\textsuperscript{60} provided a meta-analysis of all the trials and reported an overall risk of ischemic stroke without antithrombotic therapy that was 4.5\% per year. This risk was reduced by warfarin to 1.4\% per year (Relative Risk Reduction (RRR) = 68\%). The rate of major hemorrhage with warfarin (intracranial, transfusion of two or more units, hospitalization) in these trials was 1.3\% per year versus 1\% per year in the control group. Hence the overall picture is one of the major benefits from warfarin, with only modest increase in the risk of major hemorrhage and intracerebral bleeding. The European Atrial Fibrillation Trial (EAFT)\textsuperscript{38} was a secondary prevention trial which randomized patients with AF and with history of prior TIA or stroke within the preceding 3 months to warfarin, aspirin, or placebo. The risk of recurrence in the placebo group was 12\% in EAFT. This risk was reduced to 66\% (RRR) by warfarin therapy. The absolute risk reduction in EAFT was even greater than in the primary prevention trials because
of the high baseline risk of stroke in this population. However, major bleeding risk was also higher (2.1% per year), but the risk benefit ratio still strongly favored warfarin use.

Comparison of aspirin to placebo resulted in a less impressive relative risk reduction for stroke of about 16 to 44%. The meta-analysis found an overall RRR of 21% in the rate of stroke with aspirin compared to placebo. Direct comparison of aspirin versus warfarin was undertaken in AFASAK, AFASAK-II, EAFT, SPAF-II, and Primary prevention of Atrial Thromboembolism in patients with nonrheumatic Atrial Fibrillation trial (PATAF). A meta-analysis of these trials showed that there is a highly statistically significant 36% (95% CI 14 to 52) RRR of all stroke (ischemic plus hemorrhagic) with warfarin compared to aspirin. Major bleeding was more frequent with warfarin than aspirin.

The major concern with use of warfarin is the risk of bleeding. It is more common in older patients: probably higher in clinical practice than it is in the rigorous setting of clinical trials, and greater with high or fluctuating INRs. Most major bleeding occurred at INRs ≥5.0 and no treatment effect was seen with INRs <2.0. Accordingly, the most widely recommended INR range is 2.0 to 3.0, with a target of 2.5.

Warfarin can be a very difficult drug to use. For this reason there has been much interest in the evaluation of other or newer antithrombotic therapies. Among these, the oral antithrombin drug, ximelagatran, has been most thoroughly evaluated. Ximelagatran is an orally administered direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin by thrombin. It has consistent and predictable pharmacokinetics and the patient is fully anticoagulated within a few hours of taking the first dose, eliminating the need for monitoring. The role of ximelagatran in preventing thromboembolism in AF was evaluated in SPORTIF II and SPORTIF III (Stroke Prevention with the ORal direct Thrombin Inhibitor ximelagatran compared with warfarin in patients with nonvalvular atrial Fibrillation trial). In SPORTIF II three different doses of ximelagatran were compared to warfarin in a small number of patients. At 3 months follow-up ximelagatran was safe and effective in the short term.

That trial was followed by a larger SPORTIF III trial, a non-inferiority trial, in which 3407 patients with AF were randomized to open-label fixed-dose ximelagatran (36 mg BID) or adjusted-dose warfarin (INR 2.0-3.0). The patients had AF and at least one additional risk factor for stroke. The primary event rate by intention to treat was 2.3% per year with warfarin and 1.6% per year with ximelagatran (absolute risk reduction 0.7% [95% CI −0.1 to 1.4], \( P = 0.10 \) and inferiority is
rejected. Rates of disabling or fatal stroke, mortality, and major bleeding were similar between groups, but combined minor and major hemorrhages were lower with ximelagatran than with warfarin (29.8% versus 25.8% per year; relative risk reduction 14% [4 to 22]; \( P = 0.007 \)). Raised serum alanine aminotransferase was more common with ximelagatran. The results of the similar but double-blinded SPORTIF V trial have been presented at a major meeting with similar but slightly less favorable findings, again rejecting inferiority. These findings are promising and ximelagatran may be a good alternative to warfarin in patients who cannot take warfarin if this drug is approved for this indication. The long-term significance of the increase in liver enzymes remains unknown and will require further monitoring. It will be important for physicians to emphasize that the drug needs to be taken twice a day.

**M. M. Scheinman:** The initial reports involving use of Ximelagatran appear very exciting and will likely result largely in replacement of warfarin therapy. The increase in hepatic enzymes usually resolve spontaneously and the fixed dose without need for checking INR will be widely accepted. It is important to point out that the efficacy and safety of Ximelagatran for patients with artificial cardiac valves is not known. In addition, treatment of severe hemorrhage in patients treated with Ximelagatran is not clear. It is known that the drug is dialyzable. Treatment of patients who have had a breakthrough cerebrovascular accident on this drug is also not clear (ie, higher dose or switch to warfarin).

Approximately 20% of patients with AF in whom anticoagulation is indicated have a relative or absolute contraindication to warfarin. Because of an ambiguity in the previous guidelines for antithrombotic therapy, many physicians believed that restoration and maintenance of sinus rhythm using antiarrhythmic drugs was an alternative to antithrombotic therapy. However, in both the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trials, a large majority of the strokes in both arms of these trials occurred in patients not taking warfarin or with a subtherapeutic INR and this resulted in an excess of thrombotic strokes in the rhythm control arms. Accordingly, antithrombotic therapy in AF should be considered totally independent of the approach to rhythm management. Rhythm control is not an alternative to antithrombotic therapy in high-risk patients. In patients who cannot take warfarin, other approaches such as the combination of aspirin and clopidogrel have been used because of its efficacy in acute coronary syndromes, for example. Although this drug combination for prevention
of stroke is currently being evaluated in a large randomized trial, there is no current evidence that it is effective or safe in this setting.

**Nonpharmacologic Antithrombotic Therapy**

Antithrombotic therapy in high-risk patients who cannot take warfarin remains problematic. Among the approaches proposed for this situation are some nonpharmacologic therapies. Since a high proportion of strokes in patients with AF is thought to be cardio-thromboembolic and to originate from the left atrial appendage (LAA), exclusion of the LAA might be a useful approach.

**B. J. Gersh:** An important caveat is that, in some patients, atrial fibrillation may be a “marker” of other causes of stroke, for example, aortic atherosclerosis, hypertension, cerebrovascular disease, and perhaps inflammation. In such patients, ligation or exclusion of the left atrial appendage may be of little benefit in reducing stroke risk. In what proportion of patients this is the case and how to identify them is a priority for further investigation.

Ligation of the LAA at the time of mitral valve surgery in patients with AF is in fact recommended by the ACC/AHA Guidelines for Valvular Heart Disease to reduce the risk of postoperative thromboembolism. Another experimental approach is percutaneous LAA transcatheter occlusion with an implanted device designed to exclude the LAA from the rest of the left atrium. However, there are no data at the present time to serve as a foundation for appropriate patient selection and no evidence that these therapies are effective compared to other alternatives. Accordingly, they cannot be recommended at this time except in appropriate research protocols.

**M. M. Scheinman:** It is clear that alternative opinions would be expected in terms of treatment modalities. I agree that antiarrhythmic drug therapy is indicated for those with persistent atrial fibrillation (Fig 8), but I would be inclined to continue therapy if found to be safe and effective, since it is well appreciated that atrial fibrillation recurrence is very frequent with discontinuance of arrhythmia drug therapy.

With regard to Fig 10, my own feeling is that when patients fail appropriate trials of antiarrhythmic or rate control drugs, then pulmonary vein isolation with or without left atrial ablation is a reasonable alternative at this point in time. The reported success rates range from 75 to 85% and long-term studies (Pappone) suggest that the ablative technique is associated with improved quality of life. These techniques are currently available at most university medical centers in North America.
TABLE 4. ACCP stroke risk stratification scheme and therapeutic guidelines

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Patient features</th>
<th>Therapeutic guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Age ≤65 yrs</td>
<td>Aspirin (325 mg daily)</td>
</tr>
<tr>
<td></td>
<td>No additional risk factors</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Age 65-75 yrs</td>
<td>Warfarin (target INR 2.5, range 2.0–3.0) or aspirin 325 mg daily</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Age &gt;75 yrs</td>
<td>Warfarin (target INR 2.5, range 2.0-3.0)</td>
</tr>
<tr>
<td></td>
<td>History of hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricular dysfunction*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More than one intermediate risk factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mitral valve disease or prosthetic heart valve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of stroke, transient ischemic attack, or systemic embolus</td>
<td></td>
</tr>
</tbody>
</table>

*Moderate to severe wall motion abnormality or reduced systolic function by any imaging technique, or clinical heart failure.

TABLE 5. ACC/AHA/ESC treatment guidelines for antithrombotic therapy in patients with AF

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Patient features</th>
<th>Antithrombotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>Age &lt;60 yrs</td>
<td>Aspirin 325 mg/day or no therapy</td>
</tr>
<tr>
<td></td>
<td>No heart disease (lone AF)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Age &lt;60 yrs Heart disease but no risk factors for thromboembolism (including heart failure, LV ejection fraction &lt;0.35, and history of hypertension)</td>
<td>Aspirin 325 mg/day</td>
</tr>
<tr>
<td></td>
<td>Age ≥60 yrs, no risk factors for thromboembolism</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Age ≥60 yrs with diabetes mellitus or coronary artery disease</td>
<td>Oral anticoagulation (INR 2.0-3.0); optional addition of aspirin 8–162 mg/day</td>
</tr>
<tr>
<td></td>
<td>Age ≥75 yrs, especially women</td>
<td>Oral anticoagulation (INR ~ 2.0)</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LV ejection fraction ≤0.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thyrotoxicosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>Rheumatic heart disease (mitral stenosis)</td>
<td>Oral anticoagulation (INR target of at least 2.0-3.0, INR 2.5-3.5 or higher may be appropriate)</td>
</tr>
<tr>
<td></td>
<td>Prosthetic heart valves</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior thromboembolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent atrial thrombus on transesophageal echocardiography</td>
<td></td>
</tr>
</tbody>
</table>

LV = Left Ventricular
INR = International Normalized Ratio
Comment on the Guidelines

The ACCP and the ACC/AHA/ESC guidelines\textsuperscript{4,41} for this aspect of antithrombotic therapy are outlined in Tables 4 and 5. Both sets of guidelines follow the same general principles, assigning a risk and recommending no therapy, aspirin, or warfarin on the basis of risk assessment. As stated above, we generally favor schemes that allow for assignment of intermediate risk and, as previously mentioned, use the CHADS\textsubscript{2} system in this regard because it is easy to remember and use at the bedside. A score of 0 is “low risk” and no specific antithrombotic therapy is required. A score \( \geq 3 \) is “high risk” and adjusted dose warfarin (INR 2.0 to 3.0) is recommended. Scores of 1 or 2 are “intermediate risk” and either aspirin or warfarin can be used, depending on patient and physician preference. As the current versions of the guidelines were published before the results of RACE, AFFIRM, and SPORTIF III were available, the key information from those trials needs to be incorporated into current practice. Specifically, pharmacologic rhythm control does not obviate the need for antithrombotic therapy and ximelagatran if approved will probably be an acceptable alternative to warfarin in those patients where there is no contraindication to warfarin.

The risk of stroke in intermittent AF is probably the same as permanent AF and the risk of stroke in atrial flutter should be considered the same as that for AF itself. For patients who have thromboembolic events despite an apparently therapeutic INR (2.0 to 3.0), the first alternative is to increase the target INR to 2.5 to 3.5. When thromboembolic events persist, aspirin or clopidogrel can be added to warfarin. Although there are no clinical trials to support the latter recommendation, we know from other settings\textsuperscript{80} that such combinations increase the risk of bleeding.

Rhythm versus Rate Control

Review of the Evidence

A total of five randomized trials (Pharmacological Intervention in Atrial Fibrillation trial (PIAF),\textsuperscript{81} Paroxysmal Atrial Fibrillation 2 trial (PAF2),\textsuperscript{82} AFFIRM,\textsuperscript{74} RACE,\textsuperscript{75} Strategies of Treatment of Atrial Fibrillation trial (STAF)\textsuperscript{83}; see Table 6 for full names of trials) comparing rate versus rhythm control have been completed and published at the time of writing this monograph. The main findings of these trials have been summarized in a recent review\textsuperscript{83} and will be reviewed only briefly here.

Before reviewing the trials, it is interesting to review the genesis of this research question. Historically the rate control approach came first; however, with the advent of effective antiarrhythmic medication
### TABLE 6. An overview of published randomized trials of rhythm control versus heart rate control in the management of atrial fibrillation

<table>
<thead>
<tr>
<th>Name</th>
<th>Pharmacological intervention in atrial fibrillation</th>
<th>Paroxysmal atrial fibrillation 2</th>
<th>Atrial fibrillation follow-up investigation of rhythm management</th>
<th>Rate control versus electrical cardioversion for persistent atrial fibrillation</th>
<th>Strategies of treatment of atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIAF</td>
<td>Rate control; Amiodarone, propafenone, flecainide, sotalol</td>
<td>\n</td>
<td>Amiodarone; sotalol; propafenone; other class 1; ECV; few nonpharmacologic</td>
<td>Amiodarone; sotalol; propafenone; other class 1; ECV; few nonpharmacologic</td>
<td></td>
</tr>
<tr>
<td>PAF 2</td>
<td>Amiodarone; propafenone, flecainide; sotalol; ECV not allowed</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td></td>
</tr>
<tr>
<td>AFFIRM</td>
<td>AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td></td>
</tr>
<tr>
<td>RACE</td>
<td>Amiodarone; sotalol; propafenone; other class 1; ECV; few nonpharmacologic</td>
<td>Amiodarone; sotalol; propafenone; other class 1; ECV; few nonpharmacologic</td>
<td>Amiodarone; sotalol; propafenone; other class 1; ECV; few nonpharmacologic</td>
<td>Amiodarone; sotalol; propafenone; other class 1; ECV; few nonpharmacologic</td>
<td></td>
</tr>
<tr>
<td>STAF</td>
<td>Amiodarone; propafenone, flecainide; sotalol; ECV not allowed</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td></td>
</tr>
<tr>
<td>Number enrolled</td>
<td>252</td>
<td>141</td>
<td>4060</td>
<td>522</td>
<td>200</td>
</tr>
<tr>
<td>Average follow-up</td>
<td>1.0 years</td>
<td>1.3 years</td>
<td>3.5 years</td>
<td>2.3 years</td>
<td>1.7 years</td>
</tr>
<tr>
<td>Patients</td>
<td>60 years old; 92% male; 50% hypertension and 23% coronary disease; 16% no heart disease; few CHF</td>
<td>68 years old; 42% male; 35% no heart disease; 30% hypertension and 16% coronary disease; few CHF</td>
<td>70 years old; 61% male; 71% hypertension &amp; 38% coronary disease; 13% no heart disease; 9% CHF</td>
<td>68 years old; 63% male; 49% hypertension and 27% coronary disease; 21% no heart disease; half CHF</td>
<td>65 years old; 64% male; 63% hypertension and 44% coronary disease; 11% no heart disease; 46% CHF</td>
</tr>
<tr>
<td>AF</td>
<td>Persistent 7 days to 1 year</td>
<td>Paroxysmal; severely symptomatic</td>
<td>Persistent (≥69%) &amp; Paroxysmal</td>
<td>Persistent; median 32 days; recurrent after ECV</td>
<td>Persistent &gt;4 weeks</td>
</tr>
<tr>
<td>Rhythm therapies</td>
<td>Amiodarone; ECV</td>
<td>Amiodarone; propafenone, flecainide; sotalol; ECV not allowed</td>
<td>Amiodarone; sotalol; propafenone; other class 1; ECV; few nonpharmacologic</td>
<td>Sotalol; flecainide/propafenone, amiodarone; ECV (prescribed sequence)</td>
<td>Amiodarone; propafenone; flecainide; ECV</td>
</tr>
<tr>
<td>Rate therapies</td>
<td>Diltiazem; beta-blockers; digitalis; AV junction RF ablation</td>
<td>AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
<td>Beta-blockers; diltiazem, verapamil; digitalis; AV junction RF ablation</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Continued for duration of study</td>
<td>Discontinuation for SR permitted by guidelines</td>
<td>Discontinuation for SR permitted by guidelines</td>
<td>Discontinuation for SR permitted by guidelines</td>
<td>Discontinuation for SR permitted by guidelines</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Proportion symptomatically improved</td>
<td>Development of permanent AF</td>
<td>Death</td>
<td>Composite of clinical events</td>
<td>Composite of clinical events</td>
</tr>
</tbody>
</table>

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TABLE 6. continued.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AFFIRM</th>
<th>RACE</th>
<th>STAF</th>
<th>PA2</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other endpoints</td>
<td>QoL; functional capacity; bleeding; hospitalization; adverse drug effects</td>
<td>QoL; functional capacity; bleeding; hospitalization; adverse drug effects</td>
<td>QoL; functional capacity; bleeding; hospitalization; adverse drug effects</td>
<td>QoL; functional capacity; bleeding; hospitalization; adverse drug effects</td>
<td>QoL; functional capacity; bleeding; hospitalization; adverse drug effects</td>
</tr>
<tr>
<td>Composite of clinical events</td>
<td>Lower hospitalizations; and a decrease in adverse drug effects, worsening CHF and rate; no difference in primary endpoints; worsening heart failure; bleeding; adverse drug effects; cost</td>
<td>Lower hospitalizations; and a decrease in adverse drug effects, worsening CHF and rate; no difference in primary endpoints; worsening heart failure; bleeding; adverse drug effects; cost</td>
<td>Lower hospitalizations; and a decrease in adverse drug effects, worsening CHF and rate; no difference in primary endpoints; worsening heart failure; bleeding; adverse drug effects; cost</td>
<td>Lower hospitalizations; and a decrease in adverse drug effects, worsening CHF and rate; no difference in primary endpoints; worsening heart failure; bleeding; adverse drug effects; cost</td>
<td>Lower hospitalizations; and a decrease in adverse drug effects, worsening CHF and rate; no difference in primary endpoints; worsening heart failure; bleeding; adverse drug effects; cost</td>
</tr>
</tbody>
</table>

Results summary:
- No difference in primary endpoint (trend favors rate), QoL, and functional capacity; rate.
- Fewer hospitalizations and adverse drug effects.

Rate not inferior on primary endpoint; no difference in QoL; rate.
- Fewer hospitalizations and adverse drug effects.

No difference in primary endpoint and all secondary endpoints; rate.
- Fewer hospitalizations.

AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; New York Heart Association Class II; ECV = Electrical Cardioversion; QoL = Quality of Life perceived by patient (questionnaire).

(Reproduced with permission from Ref 84).

AF = AF fibrillation; AV = AV nodal conduction; CHF = Congestive Heart Failure; QoL = Quality of Life as perceived by the patient (questionnaire).
and electrical cardioversion, the rhythm control approach became more popular among physicians based on a plausible theory that rhythm control improved hemodynamics and reduced the frequency of thromboembolism. However, this approach often requires long-term antiarrhythmic drug therapy, which is not always effective (over 50% develop recurrent AF despite such therapy) and is associated with many side effects, including death. For these reasons there has been dissatisfaction with the antiarrhythmic drug therapy for maintenance of sinus rhythm, and much research effort is now being directed at alternative, nonpharmacological therapies. Moreover the efficacy of anticoagulation in the prevention of thromboembolism has been demonstrated (see above). The inefficacy and adverse effect of antiarrhythmic drugs, coupled with the efficacy of warfarin, led many to question whether or not the rhythm control strategy and selective anticoagulation should be the primary approach compared to the rate control strategy and anticoagulation.

The AFFIRM trial is the largest of these trials with 4060 AF (paroxysmal and persistent) patients randomized to rate control using drugs or atrioventricular (AV) junction ablation and anticoagulation, or rhythm control with the most effective and best tolerated of several approved antiarrhythmic drug therapies. Treatment was frequently changed based on the patients’ clinical status. Patients had to be at least 65 years of age or have other risk factors for stroke or death and with no contraindications to anticoagulation. The predominant cardiac diagnoses were hypertension (71%) and coronary artery disease (38%); 13% had no apparent structural heart disease. All patients were initially anticoagulated, but those in the rhythm control strategy who were thought to have maintained sinus rhythm for at least 3 months could come off warfarin. After a mean follow-up of 3.5 years, there was a trend toward a lower incidence of death with rate control (21.3% versus 23.8%). There was a trend toward a higher risk of ischemic stroke with the rhythm control approach and the majority of strokes in both groups occurred in patients receiving no or suboptimal anticoagulation. The number of patients requiring hospitalization during follow-up was significantly lower in the rate control group than the rhythm control group.

The RACE trial randomized 522 patients (mean age 65) with recurrent persistent AF that had been previously electrically cardioverted to rate control (beta-blockers, calcium channel blocker, or AV junction ablation) or rhythm control (sotalol, flecainide, propafenone). There was a protocol-determined sequence for changing antiarrhythmic drugs and repeat electrical cardioversion in the rhythm control arm. After a mean fol-
low-up of 2.3 years, there was a trend toward a lower incidence of the primary composite endpoint (cardiovascular death, admission for heart failure, thromboembolism event, severe bleeding, pacemaker implantation, or severe side effect from antiarrhythmic drugs) with rate control (17.2% versus 22.6% with rhythm control, hazard ratio 0.73, 90% CI 0.53 to 1.01). There was no difference in cardiovascular mortality between the two groups.

The STAF Trial began as a pilot study and randomized 200 patients with persistent AF to cardioversion and pharmacological prevention of AF recurrence (anticoagulation stopped after 1 month according to guidelines) or to rate control and anticoagulation. After a mean follow-up of 20 months, there was no significant difference between the two groups in the primary composite endpoint (death, stroke, TIA, cardiopulmonary resuscitation, systemic bleeding, or systemic embolization). However the number of hospitalizations and length of stay were greater in the rhythm control group, and only 23% of patients in the rhythm control group remained in sinus rhythm.

The PIAF trial, the first reported trial, randomized 252 patients with persistent AF to rate control with diltiazem or rhythm control with amiodarone. All patients were supposed to receive anticoagulation during the trial. After 1 year of follow-up patients on the rhythm control arm had slightly (10% increase) better exercise tolerance; there was no difference in the symptoms of AF or quality of life between the two groups.

The PAF2 trial randomized 141 patients with paroxysmal AF who were highly symptomatic and scheduled for implantation of a DDD pacemaker followed by radiofrequency ablation of the AV junction. Then patients were assigned to either antiarrhythmic drugs added to pacemaker or no antiarrhythmic drugs. After a mean follow-up of 1.3 years, patients on the rate control arm had less worsening of heart failure and fewer hospitalizations.

In summary, the combined evidence of these trials has failed to confirm any of the presumed benefits of the pharmacologic rhythm control approach. There are some clear advantages of the rate control approach, which is elevated to the status of primary therapy in patients similar to those enrolled in the trials. Finally, the apparent success of the pharmacologic rhythm control approach does not remove the need for anticoagulation in high-risk patients. [Note added in proof: Two additional small trials have been completed and published, which do not materially alter the summary above. (J Cardiovasc Pharmacol Ther 2004;9:65 and Chest 2004;26:476)]
Individualized Approach

As these trials have not shown one approach to be clearly superior to the other, it is necessary to individualize the therapeutic approach for each patient. It is also important to point out that the results of these trials cannot be generalized to all patients with AF. Patients with congestive heart failure and young patients with paroxysmal AF were underrepresented in these trials. Moreover, subgroup analysis in AFFIRM provides point estimates that include the possibility that, in patients <65 years and those with a history of congestive heart failure, rhythm control might be a better approach.

B. J. Gersh: One important lesson is that the majority of strokes occurred in patients among whom anticoagulants have been withdrawn or the INR was subtherapeutic. We now know that many episodes of recurrent atrial fibrillation are asymptomatic, and this makes a strong case for lifelong anticoagulation, even in patients who apparently returned to sinus rhythm, unless one can be confident (a difficult task) that asymptomatic recurrences are not recurring. As stated by the authors below, new guidelines in this respect are forthcoming and needed.

Accordingly, several schema to assist in the decision-making process about rhythm control versus rate control are presented in Figs 7 through 10. These schema require the classification of the current episode of AF, taking into consideration whether or not it is the first episode or recurrent and paroxysmal or persistent AF.4

Fig 7 deals with the first episode of paroxysmal AF. By definition, the episode has ended. The objective here is to try and prevent further episodes without any specific antiarrhythmic therapy. The figure lists a number of treatments that have been demonstrated to help prevent AF (not reviewed here) that should be applied if applicable. This recommended approach is based on observational data from registries that show paroxysmal AF, particularly “lone” paroxysmal AF, may not occur for months or years after the first episode88 (Personal communication, C.R. Kerr, 2004). In this situation one wishes to avoid needless and potentially toxic therapies.

Fig 8 is a schema for the first episode of persistent AF. The difference here is that there is no evidence for delayed recurrence or no recurrence in this situation as there is for paroxysmal AF. Nevertheless, we feel it is “preferred” to restore sinus rhythm in this situation. Restoring sinus rhythm may require electrical cardioversion and temporary use of antiarrhythmic drugs. At the same time all the appropriate preventative
therapies from the list in the figure should be applied. However, once sinus rhythm is restored, antiarrhythmic drug therapy should be discontinued and the patient should be followed for recurrence of AF. When that approach seems unreasonable, including for the reason that recurrence is highly likely, the rate control approach is a perfectly acceptable alternative. It should be pointed out that about one-third of the patients enrolled in AFFIRM were randomized after their first episode using such a rationale.

Fig 9 is a schema for those with recurrent paroxysmal AF. Although some patients with paroxysmal AF were enrolled in AFFIRM and all the PAF2 patients had highly symptomatic recurrent paroxysmal AF, these patients were underrepresented in the rate versus rhythm trials. For this reason, we feel that either approach is warranted at this time. From subgroup analysis and other literature, a number of factors are listed in the figure that would favor the use of the rhythm control approach in such patients.

Fig 10 outlines an approach to the patient with recurrent persistent AF. This type of patient is typical of most of the patients enrolled in the rate versus rhythm control trials. For this reason we recommend starting with
rate control in such patients. When good rate control (see below) is achieved, the patient should be reassessed for symptoms. If the patient’s symptoms are adequately relieved by this approach and there are no intolerable adverse effects, rate control should be continued. When symptoms are not relieved, the choices are to proceed to a trial of rhythm control or to use the “ablate and pace” rate control approach. The “ablate and pace” approach is also an alternative when pharmacologic rate control relieves the symptoms of AF but the drugs cause intolerable adverse effects.

Finally, the patient who is deemed to have permanent AF is treated with rate control, either pharmacologically or with the “ablate and pace” approach.

**Comment on the Guidelines**

The current ACC/AHA/ESC guidelines were written prior to the completion and publication of the rate versus rhythm control trials. The
actual recommendation of the guidelines on this point is not contained in the shorter executive summary versions published in Circulation and Journal of the American College of Cardiology but can be found in the published version cited here. They recommend that the rhythm control approach is the preferred approach for patients with disabling symptoms. In this respect, these guidelines are prescient, in that there is no clear advantage of the rhythm control over the rate control approach. The ACC/AHA/ESC guidelines are not dissimilar, therefore, to the more detailed recommendations made here. Recently the American College of Physicians and the American Academy of Family Physicians (ACP/AAFP) guidelines for the management of newly detected AF in the primary care setting has been published. They recommend rate control and anticoagulation for most patients, with the main indication of rhythm control being persistent symptoms with rate control strategy, and patient preference. We do not, however, agree with this recommendation for the reason outlined above. That is, many of these patients will not have recurrent AF when their underlying cardiac condition is optimally treated and such an approach would deny some patients sinus rhythm. Although only an association, sinus rhythm is related to lower risk of death, and therefore, we believe that the basic decision about rate control versus
rhythm control should be delayed until patients have recurrent AF; most patients should have sinus rhythm restored after their first episode of AF.

**Restoring and Maintaining Sinus Rhythm**

**Cardioversion—Electrical or Pharmacological**

Once the decision has been made to restore sinus rhythm, the physician needs to decide on the method of doing so and to assess the need for anticoagulation. Cardioversion could be achieved by both electrical and pharmacological means. “Electrical” includes the possibility of pace-termination but these techniques are only effective for organized atrial arrhythmias (atrial tachycardia, atrial flutter) and have very low or no efficacy for AF. Accordingly, in this context “electrical” means a shock therapy.

Transthoracic electrical cardioversion is more often successful than pharmacological cardioversion with overall success rate of 75 to 93%, which is related inversely to the duration of AF, chest wall impedance, and the left atrial size. Reported success rate is also partly related to the point in time that “success” is defined and, when that time point is

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**FIG 10.** Treatment algorithm for recurrent persistent AF. AAD = antiarrhythmic drugs, CAD = coronary artery disease, CHF = congestive heart failure.
more than a few minutes, lack of success is partly due to immediate recurrence of AF. The success rate of transthoracic electrical cardioversion is only 50% when AF has been present for 5 years. The details of the technique and patient preparation are beyond the scope of this review. However, some of the practical points to keep in mind are electrode position, waveform used, and initial energy setting.

There are two conventional positions for the electrode placement: anterolateral and anteroposterior. Several studies showed that less energy is required and higher success rate is achieved with the anteroposterior position. However other studies failed to confirm these findings. We generally favor the anteroposterior location with the posterior position infrascapular and slightly to the right of the spine and the anterior position slightly to the left of the sternum centered at the level of the palpated maximal apical impulse. Because chest wall impedance is an important determinant of success, delivery of the shock during chest compression can be helpful. Chest compression is easily done with handheld paddles, but with “no-hands” systems, compression through a folded towel placed over the anterior electrode is effective. After unsuccessful shocks, chest compression should be used before changing electrode position. In some patients, one, but not the other position, may be effective, so if a maximal shock with chest compression is unsuccessful, the electrode position should be relocated and cardioversion repeated.

The energy required for cardioversion of AF is often >200 joules. However, even more energy may be required in obese patients and long-standing AF. Less total energy is delivered when a higher initial shock energy is used and we favor starting with at least 200 joules and with 360 joules for a large patient using a monophasic waveform. The initial energy used depends in part upon the waveform of the current delivered by the defibrillator. Biphasic devices, which reverse current polarity 5 to 10 milliseconds after shock delivery begins, have been shown in two randomized clinical trials to be more effective and deliver less energy than monophasic devices. Therefore, with a biphasic device we favor starting with at least 150 joules and with 250 joules for a large patient. Since biphasic devices have become more widely available, it is less likely one will have to resort to using two defibrillators to increase the strength of transthoracic shock delivery or to use transvenous cardioversion. Transvenous cardioversion is now primarily used as a tool in the electrophysiology lab. These techniques will not be discussed here.

Although electrical cardioversion is very effective, the recurrence rate following cardioversion without concurrent antiarrhythmic drug use is
substantial in the case of episodes of recurrent persistent AF. Most of these recurrences are “immediate” (within a few minutes) recurrences or “early” (few minutes to 2 weeks) recurrences postcardioversion. The frequency of recurrences in the first 2 weeks has led to the notion of pretreatment with antiarrhythmic drugs to increase the likelihood of long-term success at maintaining sinus rhythm after electrical cardioversion. Pretreatment with 1 mg of ibutilide prior to cardioversion, or oral amiodarone for 1 month, has shown to decrease the likelihood of reversion and increase the likelihood of maintenance of sinus rhythm.107,108 Intermittent verapamil when given in combination with continuous propafenone for 3 days before and 3 months after cardioversion reduced the incidence of recurrence to 6%, compared to 10% if given for 3 days prior and 3 days after, or 30% if propafenone was given alone.109 Verapamil given around the time of electrical cardioversion also works with other antiarrhythmic drugs.110 Use of an angiotensin receptor blocker with amiodarone also has been reported to lessen the likelihood of early recurrence compared to amiodarone alone.111 We recommend using either of these drugs (verapamil or angiotensin receptor blocker/angiotensin converting enzyme inhibitor) with an antiarrhythmic drug when electrical cardioversion has failed because of early recurrence of AF. Of course, there is also the need to reexamine the need for repeated attempts at electrical cardioversion in such patients in comparison to some other mode of therapy or switching to the rate control strategy.

Electrical cardioversion is the preferred method for achieving sinus rhythm when AF has been present continuously for more than a week, but for those with recent onset AF (<7 days, preferably <72 hours), pharmacological cardioversion is an acceptable alternative. Pharmacological cardioversion has been recently reviewed.112 The success rate for pharmacologic cardioversion in appropriately selected patients approaches 70%112 but over 50% of these patients spontaneously convert with placebo treatment within 24-48 hours of randomization in some of the trials, probably because of inclusion of a lot of patients with paroxysmal AF. Thus, the major purpose of pharmacological cardioversion is to accelerate the process and the ideal drug will achieve conversion within an hour. Table 7 summarizes the reported efficacy, doses, and risks of antiarrhythmic drugs for which there is a reasonable evidence base for efficacy of pharmacological cardioversion. Intravenous formulations of propafenone and flecainide are available in Europe but not in North America and therefore only oral usage is outlined in Table 7. The conversion rate reaches 90% after 1 hour of intravenous flecainide or propafenone, or 50 to 80% if used orally.113-116 These two drugs have
slightly greater efficacy for AF than for atrial flutter. The concept behind the evaluation of these drugs in this setting has been the “pill-in-the-pocket” approach of self-treatment. However, thus far, the drugs have not been tested in an unmonitored situation and therefore we recommend that for now they be administered only to monitored patients. [Note added in proof: A recent trial of outpatient use of these drugs suggests it may be safe if previously successful and tolerated when given in a monitored setting. (New Engl J Med 2004;351:2384)] Amiodarone does have efficacy and in particular has some, albeit less, efficacy for AF that has been present for longer than 7 days. However, amiodarone does not act rapidly and an effect should not be expected until at least 8 hours after drug initiation and may not occur for days or weeks. Thus, we do not use this drug to achieve rapid cardioversion. Ibutilide also has limited efficacy for AF that has been present for longer than 7 days but we do not recommend it for such patients. Because of the risk of Torsade de pointes ventricular tachycardia, patients receiving ibutilide should have their serum potassium over 3.8 mmol/L before the drug is administered and we routinely give 2.5 g of intravenous magnesium sulfate before each dose of 1 mg ibutilide. One milligram of ibutilide is given over 10 minutes and the second 1 mg dose is given after waiting 20 minutes, stopping the drug when conversion is noted. Ibutilide has slightly better efficacy for atrial flutter than for AF and is only given during continuous ECG monitoring. An intravenous formulation of dofetilide has been tested but is not available and therefore dofetilide is only available in an oral form and, given this way, does not act rapidly. However, it does often work within a few days and like amiodarone has some efficacy for AF that has been present for more than 7 days. Strict labeling restrictions for dofetilide require it be started in hospital with continuous ECG monitoring and dose adjustment based on creatinine clearance, drug-free corrected QT interval.

**TABLE 7.** Drugs for which there is a reasonable evidence base for efficacy for pharmacological cardioversion of AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose*</th>
<th>Efficacy</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class 1C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>450-600 mg po</td>
<td>+++</td>
<td>Hypotension, 1:1 flutter</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>200-400 mg po</td>
<td>+++</td>
<td>Hypotension, 1:1 flutter</td>
</tr>
<tr>
<td><strong>Class 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Combined iv followed by oral</td>
<td>+++</td>
<td>Hypotension Phlebitis</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1-2 mg iv</td>
<td>++</td>
<td>Torsade de pointes</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>125-500 mcg po bid</td>
<td>+++</td>
<td>Torsade de pointes</td>
</tr>
</tbody>
</table>

*bid, twice daily; iv, intravenous; po, by mouth.*

*Consult the Physicians’ Desk Reference (PDR) for dosages and specific formulations.*
(QTc), and QTc after a test dose of the drug (refer to the package insert for detailed instructions about starting therapy with dofetilide). Pharmacologic cardioversion is an active area of research and newer useful agents are to be expected.

M. M. Scheinman: With reference to Table 8, it should be pointed out that both propafenone as well as flecainide can produce a paradoxical increase in ventricular rate owing to development of atrial flutter associated with a slower flutter rate and 1:1 AV nodal conduction. Hence, AV nodal blocking drugs should always accompany use of the 1C agents. Both of these drugs may produce atrial flutter with very wide QRS complexes that may completely mimic ventricular tachycardia. The correct diagnosis may be made by unmasking the underlying flutter rhythm with carotid sinus massage or adenosine. In addition, both drugs can produce an incessant, refractory “sine wave” ventricular tachycardia pattern.

It should be emphasized that both sotalol and dofetilide are cleared by renal excretion. Hence, periodic checks of creatinine clearance and dose adjustments are required as part of patient follow-up. Finally, though rare, Amiodarone retinal toxicity carries the risk of blindness and this risk must be appreciated by the patient.

Anticoagulation for Cardioversion

In addition to the baseline risk for thromboembolic events, there is increased risk around the time of cardioversion, regardless of whether this is done electrically or pharmacologically. The increased risk is due to a combination of factors that have been incompletely defined, but include the same risk factors cited above concerning the need for long-term anticoagulation, plus additional concerns about hypercoaguability and atrial stunning. The need for anticoagulation should be assessed in each individual instance. Although no study has rigorously determined the incidence of systemic thromboembolism (mostly stroke) around the time of cardioversion, it is believed the risk is increased. One study, using prospective cohort design, has shown the reduction of thromboembolism from 5.3 to 0.8% among anticoagulated patients. Current wisdom suggests that when the onset of AF can be accurately determined, the risk of clot formation in the left atrium and therefore the risk of embolism rise as time passes. Although such increasing risk is a continuum, the current suggested cutoff for considering cardioversion without anticoagulation is AF duration <48 h. For AF of longer duration and AF of undetermined duration, anticoagulation should always be administered. We recommend anticoagulation for cardioversion be considered in patients with stroke risk factors even when the duration of AF is shorter than 48 hours. It is
believed that a newly formed thrombus will organize and become adherent to the left atrial wall within 2 weeks of formation. Moreover, pooled data from several studies found that 98% of thromboembolic events occur within 10 days of cardioversion of AF, and atrial contraction sometimes will not normalize for weeks after successful cardioversion.\(^{118}\) Accordingly, the conventional approach is to recommend anticoagulation with a therapeutic INR (2.0 to 3.0) for 3 weeks before and 4 weeks after cardioversion.\(^4,119\) Anticoagulation prior to cardioversion can be shortened if transesophageal echocardiogram (TEE) is done and shows no evidence of thrombus or dense “smoke” in the left atrium and left atrial appendage. The TEE-guided approach has been evaluated in the Assessment of Cardioversion Utilizing Echocardiography (ACUTE) Trial.\(^{120,121}\) However, absence of left atrial thrombus on TEE does not mean that a period of 4 weeks of anticoagulation following cardioversion may be safely omitted.\(^{122,123}\) In this approach, heparin is given immediately and concurrently with warfarin and heparin is continued until the INR is therapeutic. Cardioversion is done immediately when the TEE suggests low risk and the warfarin is continued for at least 4 weeks. Either intravenous unfractionated heparin or subcutaneous low molecular weight heparin may be used.\(^{124}\) Consideration of discontinuation of warfarin after 4 weeks can be made when there is no recurrence of AF and there are no stroke risk factors. When there are stroke risk factors (see section above), warfarin should be continued even when it appears that AF has not recurred.

**B. J. Gersh:** It is important to remember that the same guidelines for anticoagulation apply to patients in whom the initial attempt at cardioversion is pharmacologic or in those who are pretreated with antiarrhythmic drugs in an attempt to enhance the success rate of delayed electrical cardioversion. Restoration of sinus rhythm increased the risk of embolism irrespective of how this was achieved.

**Pharmacological Rhythm Control**

Antiarrhythmic drugs are the main therapy currently available for maintenance of sinus rhythm. Their efficacy and safety has been the subject of two recent comprehensive reviews.\(^{86,125}\) Current antiarrhythmic drugs for this purpose are neither highly efficacious nor completely safe. Antiarrhythmic drugs have their greatest impact on recurrences more than 2 weeks after electrical cardioversion for episodes of recurrent persistent AF. One-year recurrence rate of AF in the absence of
antiarrhythmic therapy was about 75% in the quinidine meta-analysis\textsuperscript{85} but can be higher than that in recurrent persistent AF unless repeated cardioversion is undertaken.\textsuperscript{126} So antiarrhythmic therapy is usually necessary to decrease number of episodes (paroxysmal AF) and prevent recurrence (persistent AF) in patients with recurrent episodes of AF. Having said that, the maintenance of sinus rhythm is not indicated in all AF patients and this topic has been discussed in detail above. Before deciding to attempt sinus rhythm maintenance in an individual, the physician must consider the likelihood of recurrence, degree of disability/symptoms attributable to AF, the likelihood of maintaining sinus rhythm with an antiarrhythmic drug, and the risk of cardiac (primarily proarrhythmia) or noncardiac adverse events.

**Fig 11.** Antiarrhythmic drug selection algorithm for drugs used to maintain sinus rhythm. AF = atrial fibrillation, CAD = coronary artery disease, CHF = congestive heart failure, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy.

Of the presently available antiarrhythmic drugs, oral amiodarone has been demonstrated in comparative clinical studies to be more efficacious than other drugs.\textsuperscript{127,128} The recurrence rate is approximately 30-40\% with amiodarone. However amiodarone also has significant noncardiac side effects and interacts with a number of other drugs,
such as warfarin, beta-blockers, and digoxin, limiting its widespread use as an agent of first choice. The recurrence rate of AF is approximately 50% in patients treated with Class 1 drugs or sotalol.\textsuperscript{86,125,129} Sotalol offers an advantage over Class 1 drugs because, unlike Class 1 agents, it slows ventricular response rate during AF recurrence.\textsuperscript{129} The importance of this is that recurrences of AF may often be asymptomatic with sotalol because the rapid ventricular rate is often the source of symptoms. We routinely add concurrent therapy with a drug to slow atrioventricular conduction (beta-blockers, calcium channel blockers, digoxin) in those prescribed propafenone or flecainide because of the risk of conversion to atrial flutter with a high ventricular rate. Patients without structural heart disease can be treated with propafenone, flecainide, sotalol, or dofetilide.

We prefer to start with propafenone because of familiarity with this drug and a sound evidence base, including recent evidence concerning a new sustained release formulation. Amiodarone is an alternative but careful

\begin{table}
\centering
\caption{Dosages, estimated efficacy, and common adverse effects of some drugs frequently used for maintenance of sinus rhythm (Except for disopyramide, there is a reasonable evidence base for each of these drugs for the purpose of maintaining sinus rhythm)}
\begin{tabular}{llll}
\hline
\textbf{Drug} & \textbf{Dose}\textsuperscript{*} & \textbf{Estimated efficacy} & \textbf{Adverse effects} \\
\hline
Class 1A & & & \\
Disopyramide & 400-750 mg/day & 50\% & CHF \\
& & & Torsade de pointes \\
& & & Dry mouth, blurred vision, urinary retention \\
\hline
Class 1C & & & \\
Propafenone & 450-900 mg/day & 50\% & CHF \\
Flecainide & 100-300 mg/day & 50\% & Ventricular tachycardia \\
& & & Bradycardia \\
& & & Atrial proarrhythmia (1:1 flutter) \\
\hline
Class 3 & & & \\
Sotalol & 80-320 mg/day & 50\% & Bradycardia \\
& & & Torsade de pointes \\
& & & Beta-blocker effects \\
Amiodarone & 100-400 mg/day & 70\% & Bradycardia \\
& & & Torsade de pointes (rare) \\
& & & Neuropathy \\
& & & GI upset \\
& & & Hepatic toxicity \\
& & & Thyroid dysfunction \\
& & & Many others less common \\
& & & Torsade de pointes \\
\hline
Dofetilide & 250-1000 \textmu g/day & 60-70\% & \\
\hline
\end{tabular}
\end{table}

Consult the Physician’s Desk Reference (PDR) for doses and dosage frequency for the various specific formulations.

\textit{CHF}, congestive heart failure; \textit{GI}, gastrointestinal.
consideration should be given to using this drug in this setting because of its many adverse effects. Alternative modes of therapy (see below) should be considered in highly symptomatic patients and switching to the rate control strategy should be considered in less symptomatic patients (see above) before considering amiodarone in those with a relatively normal heart. We believe such patients can be started on antiarrhythmic drugs safely as an outpatient, but this has only been actually reported in the case of amiodarone.\textsuperscript{130}

\begin{flushright}
B. J. Gersh: This is a controversial area. If outpatient management is selected, meticulous follow-up including frequent measurement of the QT interval is mandatory. Proarrhythmia is uncommon, but potentially fatal.\end{flushright}

All such antiarrhythmic agents have the potential to cause proarrhythmia, including potentially fatal arrhythmias. We do not use flecainide or propafenone in patients with structural heart disease, and when given to patients with structural heart disease, antiarrhythmic drugs should be started in the hospital with continuous ECG monitoring.\textsuperscript{86,131,132} Amiodarone and dofetilide have a clear evidence base of safety in the setting of congestive heart failure and poor ventricular function. Amiodarone, like sotalol, can control heart rate even if AF is recurring and absence of symptoms cannot be taken to mean AF has not recurred. We believe sotalol may also be tried as a secondary agent in this setting, provided the left ventricular ejection fraction is $\geq 0.25$ and there is a low risk of Torsade de pointes ventricular tachycardia (male patients with a normal QTc). Sotalol is the preferred initial agent in patients with coronary artery disease because of its beta-blocking properties. The risk of proarrhythmia is less well established in patients with hypertension but, based on animal experiments, we use caution in those with significant left ventricular hypertrophy (wall thickness $\geq 1.3$ cm on echocardiogram) (see Fig 11). Vagally mediated AF (arises from bradycardia, often after meals or during sleep) may be preferentially treated with flecainide or disopyramide but this is the only situation in which we use one of the older antiarrhythmic drugs. Quinidine has a poor reputation\textsuperscript{85} and we almost never use it or procainamide. Recently, two large as yet unpublished trials done in Germany suggest quinidine combined with verapamil may be as safe and effective as sotalol, albeit not completely safe. Research on newer antiarrhythmic drugs for control of AF continues but preliminary reports do not suggest there will be highly effective drugs with excellent safety profiles in the near future.
Nonpharmacologic Rhythm Control

Because of the high recurrence rate of AF despite antiarrhythmic drug therapy for maintenance of sinus rhythm and the adverse effects of these drugs, there has been growing interest in nonpharmacological strategies.\textsuperscript{133-160} It is beyond the scope of the present article to review these modalities of therapy in detail but some discussion can be found in standard arrhythmia textbooks, such as Zipes and Jalife.\textsuperscript{133} Highly symptomatic patients who have failed medical therapy or for whom there is another compelling reason to persist with the rhythm control strategy should be referred to an arrhythmia specialist for consideration of nonpharmacologic therapy. We will review briefly here our current perception of the status of these therapies under the headings of surgery, devices, and catheter ablation.

**Surgery.** Surgery for treatment of atrial fibrillation has been around for some time. It ranges from simple procedures such as removal or plication of the left atrial appendage to reduce the risk of thromboembolic complications, to a variety of procedures aimed at preventing recurrence of AF. In the latter instance, current procedures often are partly surgical incisions and partly radiofrequency or cryoablation lesions. The procedures have become considerably simpler than they were a decade ago, partly based on the experiences of catheter-based ablation. Unfortunately, there are no randomized trials with well-constructed clinical endpoints and carefully thought-out selection criteria. Thus, it is difficult to offer sound advice. At present, we feel this procedure should be limited to patients undergoing heart surgery for another indication, primarily mitral valve surgery, who appear to be highly symptomatic from AF, independent of symptoms from their other heart problems, and who are being operated on in a center that is experienced. Better yet, all such patients should be enrolled in a research protocol, even if that is merely a good registry.

**Devices.** The range of devices is also quite broad.\textsuperscript{164-170} Atrial-based pacing is integral to all devices. Some include multisite pacing in the atria. Some include shock therapies delivered to the atria specifically. Some include a variety of software options for pacing maneuvers intended to either prevent AF, terminate AF, or a combination of these. Stand-alone atrial shock devices have disappeared. It is our impression that atrial-based pacing may help as primary prevention AF in patients with sick sinus syndrome who are receiving a pacemaker for symptomatic bradycardia and who have enough bradycardia that they are paced in the atrium for >90% of the time. In those who are already having AF, we are
not terribly impressed with the ability of these devices to prevent or treat episodes of AF. However, the monitoring capability of such devices can be quite useful. In a few individual patients, on the other hand, these devices seem to help a lot, but thus far we do not know how best to select the patients prior to device implantation. As a general statement about the current state of knowledge, patients who have a bradycardia indication, who have periods of organized tachyarrhythmia (atrial flutter or atrial tachycardia) with their AF, and who can take an antiarrhythmic drug seem best suited for these devices. Thus, devices are currently part of a “hybrid” therapy, defined as the combination of an antiarrhythmic drug and a nonpharmacologic therapy or two nonpharmacologic therapies. Shock therapies are painful and we do not use them routinely. Again, we would encourage the use of this therapy in the setting of a research protocol that will help us to understand how we can use this technology better. We try to enroll all patients being considered for device therapy into a research study.

**Catheter Ablation.** Catheter ablation for the maintenance of sinus rhythm has also progressed considerably in recent years.\(^{148-156}\) The initial procedures tried to reproduce with radiofrequency energy the lesions described in the earlier Maze surgical procedures. Now either radiofrequency or cryoablation techniques are used. Lesions can be made in only the right atrium, only the left atrium, or both. Recent evidence suggests that the important sites are those where the thoracic veins, particularly the pulmonary veins, enter the atria. However, the endpoint for the ablation is not clear and the earlier concept of “pulmonary vein isolation” seems inadequate to explain the results obtained, and, denervation by ablating vagal ganglia located in the fat pad of the atrioventricular groove may be important. Imaging of the anatomy before, during, and after the procedure may be or may not be important. Nevertheless, a salutary beneficial effect is clearly seen in some patients, although it is inappropriate to speak of “curing” AF in the great majority of patients with this tachyarrhythmia. Much remains to be learned about patient selection, endpoints for ablation in the electrophysiology lab, shortening and simplifying the procedure, and minimizing adverse effects.

**B. J. Gersh:** The most feared complication is that of pulmonary vein stenosis, but the frequency has fallen from approximately 9 to 2 to 3%. Hopefully, evolving techniques will reduce this further because the percutaneous treatment of pulmonary vein stenosis is difficult and occasionally requires recourse to surgery.
Unlike catheter ablation for atrioventricular nodal tachycardia, atrioventricular tachycardia, and isthmus-dependent atrial flutter, we do not consider catheter ablation for AF as an alternative to effective and well-tolerated drug therapy at the present time. It can be considered for highly symptomatic patients, primarily with paroxysmal AF, who have failed drug therapy due to inefficacy or intolerance, and, who are willing to undertake a lengthy procedure, not without substantial risk, that may have to be repeated to achieve a high likelihood of success. The techniques and equipment are rapidly evolving, however, and there is some optimism about and enthusiasm for this procedure. Local experience is an important factor. We would encourage all patients having these procedures to be in some sort of a research protocol, even if that is only a well-constructed registry.

M. M. Scheinman: I take issue with the authors’ statement that “it is inappropriate in speaking of “curing” AF in the great majority of patients with this tachyarrhythmia.” The current evidence suggests that cure is possible in over 65% of those patients and hence ablative therapy remains an attractive alternative for symptomatic patients who fail or who are intolerant of drug therapy.

B. J. Gersh: Long-term follow-up data beyond 12 to 18 months are sparse, but should be available in the next 2 to 3 years. Hopefully the initially encouraging results will be maintained but only time will tell. I suspect that the presence of comorbidities, which could effect the underlying atrial substrate, will be an important determinant of long-term outcome.

Comment on the Guidelines

We are in general agreement with the ACC/AHA/ESC guidelines concerning the approach and techniques for electrical cardioversion. The ACC/AHA/ESC guidelines provide a longer list of agents suitable for pharmacologic cardioversion. These guidelines have recommended that for AF less than 7 days’ duration, propafenone, and flecainide (oral), ibutilide (intravenous), or dofetilide (oral), be the first line agents and amiodarone or quinidine be the second line agents. We do not include dofetilide in our recommendations and, in particular, unlike the guidelines, we do not recommend the use of older drugs such as procainamide or quinidine for this purpose. We suggest amiodarone and dofetilide be considered for AF that has a longer duration and in clinical situations where rapid conversion is not an issue. In the latter situation it may ultimately be necessary to perform an electrical cardioversion.
The main developments with respect to anticoagulation for cardioversion since several sets of guidelines have been published are twofold. First, it is now recognized that anticoagulation should not be discontinued after cardioversion and apparent maintenance of sinus rhythm in high-risk patients who are being treated with pharmacologic agents. Revised guidelines to reflect this are expected soon from the American College of Chest Physicians (ACCP) and the ACC/AHA/ESC guidelines are currently being revised to be more explicit on this issue. Second, there is now a randomized trial to show that low molecular weight heparin is not inferior and has some potential advantages over intravenous unfractionated heparin when the TEE-guided approach is being used.

The antiarrhythmic drug selection algorithm presented here (Fig 11) is similar to that in the ACC/AHA/ESC guidelines with some minor differences. We believe it is reasonable to use dofetilide as a first-line agent in patients with minimal or no heart disease. We also believe sotalol is a reasonable second-line agent in selected patients who have had congestive heart failure, even with reduced systolic function when the risk of Torsade de pointes ventricular tachycardia is low. We are influenced in the latter recommendation by the evidence of the benefit of beta-blockers in patients with congestive heart failure. We do not recommend the older agents, such as quinidine, procainamide, or disopyramide, except in unusual situations, for example, disopyramide for vagally mediated AF.

Not much is included in the current guidelines considering nonpharmacologic therapies for AF. Given the paucity of good data, we think this is appropriate and not much has changed since the guidelines were published. Our own view is that such therapies have little applicability to the vast majority of patients with AF at the present time and that most patients getting nonpharmacologic therapies should be in some type of research protocol. We do not feel these therapies are an alternative in patients who are doing well on antiarrhythmic drug therapy, but rather are to be considered in highly symptomatic patients who have failed drug therapy. The rate control strategy should always be considered at the time consideration is given to nonpharmacologic therapy.

Rate Control

Definition of Rate Control

There are several elements to be considered in defining heart rate control. There is a paucity of evidence on this topic and now that rate control has been elevated to the status of a good primary therapy, much more research is needed. The first element of heart rate control is the
resting heart rate and there is some evidence that this should be less than 100 beats per minute.\textsuperscript{171} Since it is well known that control of heart rate at rest does not preclude rapid heart rates during exercise,\textsuperscript{172} it is widely believed that heart rate should also be assessed during activity to define “good” heart rate control. However, the evidence for the need to control heart rate during exercise as a second element of heart rate control is nonexistent. “Good” heart rate control should actually increase exercise tolerance and increased ability to exercise may be more important than the actual heart rate during exercise. Regularization of the ventricular rate is another important element in “good” heart rate control\textsuperscript{173} but has received much less attention. Taking into account the limitations due to little data, a reasonable, albeit arbitrary, definition of rate control is that used by the AFFRIM trial\textsuperscript{74}: a heart rate at rest <80 beat per minute and assessment of the heart rate with activities of daily living by doing a 6-minute walk test and keeping that rate <110 beats per minute. Using Holter monitoring is an alternative and in that case the average heart rate should be \( \leq 100 \) per minute over 24 hours and no maximum hourly rate should exceed 110\% of the maximum predicted rate during exercise based on age and gender. We generally follow this guideline but place less emphasis on the activity-induced rate when the patient is otherwise doing well.

**Pharmacological Rate Control**

In a typical patient with AF and no evidence of AV node disease, the ventricular rate ranges from 90 to 170 beats per minute. Excessively rapid ventricular rates can contribute to symptoms and other problems as outlined in the pathophysiology section. Hence there is need to control the ventricular rate in some patients when it is not intended to restore sinus rhythm. The pharmacological agents that are used to achieve rate control include digoxin, nondihydropyridine calcium channel blocker such as verapamil and diltiazem, and beta-blockers.

Digoxin is less effective than calcium channel blockers or beta-blockers for controlling heart rate during activity and thus thought to be less useful as a single agent in younger patients who are physically active. We rarely use it as a single agent for first-line therapy for rate control, except for elderly, but we usually include it in treating patients with heart failure.\textsuperscript{174,175} In heart failure patients, digoxin is believed to increase contractility and improve hemodynamics and consequently improve symptoms and decrease hospitalization. On the other hand, digoxin is very useful when added to a beta-blocker or a calcium channel blocker.\textsuperscript{172,176} In this situation, its use often allows a lower dose of beta-blocker or calcium
channel blocker to be used and thus preserves systolic function and the capacity for the heart rate to increase with activity. These can be important determinants of whether exercise tolerance increases\textsuperscript{177} or decreases\textsuperscript{178} with heart rate control therapy. Digoxin can be given orally or intravenously. It is necessary to consider both the digitalization dosage and the maintenance dose. Table 9 provides some common dosages for both intravenous and oral digoxin. Intravenous digoxin begins to act within 15 to 30 minutes, with a peak effect attained in 1 to 5 hours. This relatively slow action is undesirable in highly symptomatic patients who have AF and rapid ventricular response. For such patients, we recommend the use of intravenous non-dihydropyridine calcium channel blocker or beta-blocker (see below). Renal function and a number of drug interactions need to be considered when using digoxin (Table 9).

Beta-blockers are an effective therapy for heart rate control in AF.\textsuperscript{177-179} Studies have shown that beta-blockers can be effective both at rest and during activity\textsuperscript{179} but care must be taken not to produce chronotropic incompetence and reduce exercise capacity.\textsuperscript{178} Chronotropic incompetence is more likely in patients who spontaneously alternate between rapid and slow ventricular rates and sometimes it is necessary to consider hybrid therapy by adding a pacemaker to protect from symptomatic bradycardia. Rapid acting esmolol, metoprolol, or propranolol are very effective when used intravenously to slow down the ventricular rate (Table 9). Oral beta-blockers are widely used as primary therapy for rate control in AF and are preferred therapy in patients with depressed left ventricular function and/or ischemic heart disease because of the known salutary benefit of beta-blockers in such patients. We generally favor metoprolol as a beta-blocker because of familiarity and a strong evidence base in other conditions such as heart failure and angina and we prefer a shorter acting agent with twice a day dosing.

The other major group of drugs used for pharmacological heart rate control is the calcium channel blockers verapamil and diltiazem. These two drugs are very effective in controlling the ventricular rate in the acute as well the chronic setting. Although these agents are less likely to cause chronotropic incompetence compared to beta-blockers, they have a negative inotropic effect. Because diltiazem is believed to have less negative inotropic effect than verapamil, it is more widely used. Intravenous diltiazem is very effective\textsuperscript{180}; in one study the overall success rate in slowing the ventricular rate was 98%.\textsuperscript{181} Oral calcium channel blockers are used as first-line therapy when there is contraindication to beta-blockers, such as in patients with bronchospasm. Similar to the situation with beta-blockers, adding digoxin can be a useful adjunctive therapy as well as lowering the dose of calcium...
<table>
<thead>
<tr>
<th>Drug</th>
<th>IV loading dose</th>
<th>IV maintenance dose</th>
<th>Oral maintenance dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>0.5 mg, then 0.25 mg Q6H for total of 1.5 mg</td>
<td>0.0625-0.25 mg daily</td>
<td>0.125-0.375 mg daily</td>
<td>Bradycardia, heart block, digitalis intoxication</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.075-0.15 mg/kg</td>
<td>N/A</td>
<td>80-480 mg daily</td>
<td>Hypotension, bradycardia, heart block, depressed LV function, flushing, constipation, edema, increased digoxin levels</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg</td>
<td>5-15 mg/hour</td>
<td>120-480 mg daily</td>
<td>Hypotension, bradycardia, heart block, depressed LV function, flushing, constipation, edema, constipation, edema, increased digoxin levels</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>2.5-5 mg N/A</td>
<td>N/A</td>
<td>25-100 mg BID</td>
<td>Bradycardia, hypotension, asthma, heart block</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.15 mg/kg</td>
<td>N/A</td>
<td>80-240 mg daily</td>
<td>Same as metoprolol</td>
</tr>
<tr>
<td>Esmolol</td>
<td>0.5 mg/kg</td>
<td>0.05-0.2 mg/kg/hour</td>
<td>N/A</td>
<td>Same as metoprolol</td>
</tr>
<tr>
<td>Nadolol</td>
<td>N/A</td>
<td>N/A</td>
<td>20-160 mg daily</td>
<td>Same as metoprolol</td>
</tr>
<tr>
<td>Atenolol</td>
<td>N/A</td>
<td>N/A</td>
<td>50-150 mg daily</td>
<td>Same as metoprolol</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>N/A</td>
<td>N/A</td>
<td>100-400 mg daily BID</td>
<td>Same as metoprolol</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>N/A</td>
<td>N/A</td>
<td>3.125-50 mg BID</td>
<td>Same as metoprolol</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>N/A</td>
<td>N/A</td>
<td>2.5-20 mg daily</td>
<td>Same as metoprolol</td>
</tr>
</tbody>
</table>

Refer to the Physician’s Desk Reference (PDR) for doses of various formulations.

*BID*, twice a day; *IV*, intravenous; *LV*, left ventricular; *mg*, milligrams; *mg/kg*, milligrams per kilogram; *mg/hour*, milligrams per hour; *Q5min*, every 5 minutes; *Q6H*, every 6 hours.
channel blocker needed to achieve effective heart rate control. Dosages, precautions, and adverse effects of these two calcium channel blockers are listed in Table 9. Of the two agents, we prefer diltiazem for the reason cited above.

When there is no evidence of structural heart disease and no contraindication to beta-blocker usage, we believe that calcium channel blockers and beta-blockers are interchangeable and in the AFFIRM trial effective heart rate control was achieved in a high percentage of patients with these drugs. On the other hand, in those situations where there is a known benefit of beta-blockers, such as ischemic heart disease and congestive heart failure, beta-blockers are the preferred therapy and we prefer an agent that has demonstrated efficacy for a beneficial effect in these conditions that has been established in a large multicenter study. As mentioned above, there is more evidence to suggest that beta-blockers are more effective at reducing heart rate during exercise, but the clinical benefits of this finding are unknown and sometimes such an effect can actually decrease exercise tolerance. On the other hand, more data support the benefit of calcium channel blockers for improving exercise tolerance and patients’ feeling of well being than is the case for beta-blockers. Sometimes it is necessary to use a combination of beta-blocker and calcium channel blocker when a single agent is not effective in controlling the heart rate. One study tested the efficacy of atenolol, diltiazem, and digoxin alone versus the combination of digoxin and diltiazem or digoxin and atenolol. Based on heart rate alone, digoxin and atenolol were apparently the “most effective” regimen and the “least effective” regimen was digoxin and diltiazem alone. However, this study did not assess exercise capacity or patients’ symptoms. One advantage of combining two or three different classes of drug is that lower doses of each can be used with an additive (or even synergistic) effect at the atrioventricular node and less chance of adverse effects elsewhere.

One of the puzzling aspects of heart rate in AF is the observation that some patients alternate between rapid heart rates and bradycardia over even relatively short periods of time. In these patients, the risk of symptomatic bradycardia is greater when using pharmacological heart rate control. For them it may be necessary to control the rapid heart rate episodes with pharmacological agents while simultaneously protecting them from symptomatic bradycardia with a pacemaker. As will be discussed below, one theoretic advantage of this approach is that it contributes to regularization of the ventricular heart rate, an effect that is not readily achieved with pharmacological therapy alone.
Nonpharmacological rate control. Nonpharmacological heart rate control strategy is reserved for patients who have severe symptoms highly likely to be due to rapid ventricular rate, who cannot be effectively controlled with medications, or who develop intolerable adverse drug effects during pharmacological therapy. There are two approaches that can be used—atrioventricular junction ablation with a permanent pacemaker and ventricular pacing with specific software capabilities designed to control ventricular rate during AF.

Radiofrequency ablation of the atrioventricular junction has a much more robust evidence base. Patients should be informed that improvement after radiofrequency ablation of the atrioventricular junction and a permanent pacemaker is not guaranteed. Some patients may develop unexpected functional deterioration.

M. M. Scheinman: On the other hand, our group has reported that, in patients with preceding depressed left ventricular function, there are subsets who experience an improvement in ejection fraction after AV nodal ablation and this in turn is associated with improved survival (Ozcan C, Jahangir A, Friedman PA, et al. Significant effects of atrioventricular node ablation and pacemaker implantation on left ventricular function on long-term survival in patients with atrial fibrillation and left ventricular dysfunction. Am J Cardiol 2003;92:33-7).

Patient selection is a matter of judgment. Patients most likely to benefit are those for whom major symptoms (eg, palpitation) are most likely secondary to rapid heart rate, irregularity of the heart rate, or due to symptomatic bradycardia. Those with nonspecific symptoms, such as fatigability, are less likely to benefit. Ventricular function should not be expected to improve unless it is already depressed and patients doing well with pharmacological therapy do not improve with such nonpharmacological therapy.182

There are two transcatheter radiofrequency ablation procedures to help to achieve ventricular rate control.183-190 One is ablation of the “slow pathway” to the atrioventricular node; the other is complete atrioventricular junction ablation with permanent pacemaker implantation. The first approach can be effective in patients who have dual atrioventricular node physiology and there is about 20% possibility of developing complete heart block. Dual atrioventricular node physiology can be inferred from a bimodal distribution of ventricular heart rates during atrial fibrillation determined from a 24-hour ambulatory ECG recording. The ablate and pace approach has a success rate of 97.4%, with 3.5% recurrence of AV
conduction during follow-up. The two approaches were compared in a randomized clinical trial and, although the atrioventricular node modification technique eliminated the need for pacemaker implantation in most but not all patients, it was ultimately less successful than the total atrioventricular junction ablation and pacemaker implantation approach. “Slow pathway” ablation may not provide adequate rate control in patients with AF who only have a fast pathway with a short refractory period and during sympathetic stimulation, which can enhance the conduction through the fast pathway. For all of these reasons, “slow pathway” ablation has generally fallen out of favor. There have been several randomized clinical trials comparing pharmacological rate control versus ablate and pace approach in symptomatic patients with both paroxysmal and persistent AF. The ablate and pace approach significantly reduced symptoms and the peak ventricular rate both during rest and exercise when compared to pharmacological approach, particularly in those with paroxysmal AF. It is important to emphasize that patients with stroke risk factors need to continue anticoagulation therapy, although antiarrhythmic drugs and heart rate control drugs may be discontinued after atrioventricular junction ablation. Most of these patients will develop permanent AF and except in unusual circumstances we use the VVIR pacing mode. Until recently, it was thought that the ablate and pace approach was associated with a risk of ventricular fibrillation (VF) arrest or sudden cardiac death postprocedure but recent evidence suggests this risk is very small. The reported risk may be as high as 2.1% following this procedure, presumably related to sudden slowing of the heart rate that leads to Torsade de pointes ventricular tachycardia and cardiac arrest. It is believed that this risk can be circumvented by pacing for at least 6 weeks at rate of ≥80 beats per minute.

M. M. Scheinman: A new and interesting alternative therapy for patients undergoing AV junctional ablation has recently been reported in the PAVE trial, which was reported at the last ACC meeting. In this trial patients were randomized to either right ventricular (RV) pacing or dual chamber ventricular pacing. Of interest was the finding that the biventricular paced group had greater preservation of left ventricular (LV) function. These patients had, in general, fairly well-preserved LV function and the study population was relatively small. In most prior ablate and pace studies, the LV ejection fraction increased (with RV pacing), especially in those with poor baseline LV systolic function. Nevertheless, this study is quite interesting and further larger studies are needed.
It has been demonstrated that pacing in the ventricle with intact atrioventricular node conduction in itself can help to control the heart rate in AF. Some pacemakers have specific software that tries to take advantage of these observations and pace in the ventricle just above the average heart rate during AF. However, the applicability of this technique in a broad sense remains to be proven. In some patients an attempt to use these techniques have led to worsening congestive heart failure in a few cases.

Comment on the Guidelines

We do not have any substantive disagreement with the current guidelines with respect to the preferred agents and treatments to be used for heart rate control but we do think that more research is needed on this topic.

Miscellaneous Aspects of AF Management

AF in Patients with Wolf–Parkinson–White Syndrome

Patients with Wolf–Parkinson–White syndrome are at risk of sudden cardiac death if they develop AF and conduct at high rates to the ventricle over the accessory pathway. When such patients have hemodynamic instability at presentation, they should be immediately electrically cardioverted. If the patient is hemodynamically stable, intravenous procainamide is said to be the drug of choice, although there is no reason to believe ibutilide is unsafe in this setting. AV blocking agents have been reported to accelerate heart rate and precipitate VF cardiac arrest when given intravenously. There has been some debate about the mechanism that explains this phenomenon but it is probably related to sudden hypotension that can occur with intravenous use of such agents. After stabilization, the patient should be considered for catheter ablation of the accessory pathway as the favored long-term treatment.

AF in Patients with Hypertrophic Cardiomyopathy

If AF is prolonged or associated with symptoms in this population, the therapeutic options include suppression of the arrhythmia with disopyramide, amiodarone, or sotalol, and a rate-controlling agent of either beta-blocker or calcium channel blocker. Patients with hypertrophic cardiomyopathy and AF have a high tendency to develop thromboembolic events; hence, all such patients should be anticoag-
ulated, even those with paroxysmal AF.\textsuperscript{195} The need for anticoagulation in these and other high-risk patients (eg, hyperthyroidism, atrial septal defect, even when corrected, rheumatic valvular disease, mechanical prosthetic valve) often is under-recognized because of recent emphasis on risk factors for nonvalvular AF.

**AF in Patients with Heart Failure**

AF is common in patients with left ventricular dysfunction regardless of the underlying etiology. The prevalence of AF in patients with heart failure varies from 10 to 30\%, depending on the severity of the heart failure.\textsuperscript{196-201} In this group of patients the onset of AF could further impair the left ventricular myocardium and/or lead to overt cardiac decomposition. However, there is no solid evidence that the presence of AF in patients with heart failure is an independent predictor of worse outcome.\textsuperscript{199} Heart failure patients are more sensitive to the adverse effects, including arrhythmic death, of antiarrhythmic drugs. Hence the main indications for therapy are to control symptoms, including worsening heart failure, which related to loss of atrial contraction and/or the rapid ventricular rate. Given the current data and awaiting the results of the Atrial Fibrillation and Congestive Heart Failure trial (AF-CHF),\textsuperscript{201} the rate control or the rhythm control approach can be used interchangeably to achieve relief of symptoms. For pharmacological rhythm control, amiodarone or dofetilide as first-line agents, and beta-blocker, with or without digoxin, for pharmacological rate control can be used. The ablate and pace approach has been reported to improve ventricular function in selected patients with heart failure that have been resistant to drug therapy.

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**M. M. Scheinman:** Summary: We are greatly indebted to Drs Hersi and Wyse for a very complete, authoritative, and well-reasoned approach to the management of patients with atrial fibrillation. This essay has fulfilled an important role in that it beautifully integrates important new studies that became available after publications of the AHA/ACC/ESC guidelines. The treatment algorithms are simple to follow, are based on solid evidentiary data, and as such, will be a valuable addition to the clinicians caring for these patients. The authors are commended for a superb effort.

**B. J. Gersh:** There are three epidemics of cardiovascular disease in the 21st century: atrial fibrillation, congestive heart failure, and the metabolic syndrome/diabetes. It is likely that these three entities are interrelated to a considerable extent, and everyone in clinical practice will encounter these
patients with increasing frequency. This superb monograph is therefore not only timely, but extremely authoritative.

REFERENCES


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