Atrial Fibrillation: Current Treatment Options and Future Therapies

Richard C. Wu, MD, FACC, FAHA

Associate Professor of Medicine

Division of Cardiology

Internal Medicine Grand Rounds

University of Texas Southwestern Medical Center at Dallas

August 22, 2008

This is to acknowledge that Richard Wu, M.D. has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Wu will be discussing off-label uses in his presentation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the United States adult population. Approximately 2.3 million Americans were affected in the year 2000 and the number is expected to double by 2050 (Figure 1).[1] Lifetime risks for development of AF are 1 in 4 for both men and women above the age of 40.[2] The incidence of AF doubles with each decade of life and the prevalence of the disease increases as the longevity of the population increases (Figure 2).[1, 3]

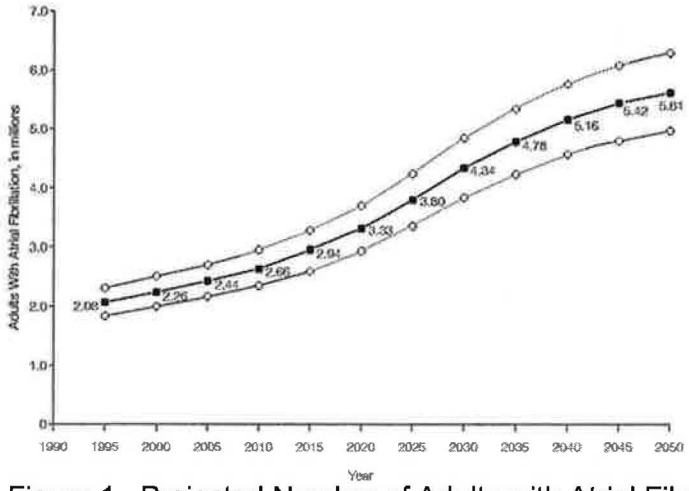

Figure 1. Projected Number of Adults with Atrial Fibrillation in the United States between 1995 and 2050[1]

AF is associated with an increased risk of stroke, heart failure, and all cause mortality, especially in women (OR 1.5 for men and 1.8 for women) across all age ranges.[4] Based on observational data, AF is more common in patients of European descent (approximately 2 fold) compared to those of African descent.[5] Globally, the annual health care cost is approximately $3500 per AF patient [6]. The total cost in the United States in 2001 was over $6.65 billion, including $2.93 billion (44%) for primary hospitalizations and $1.95 billion for additional inpatient costs as a co-morbid condition.[7]

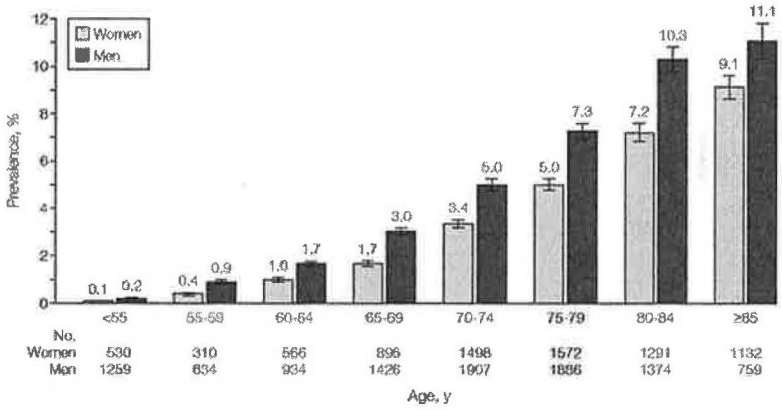

Figure 2. Prevalence of Diagnosed Atrial Fibrillation Stratified by Age and Sex[1]

One of the challenges in the management of AF is the presence of asymptomatic or "silent" AF. The prevalence of sustained or silent AF is believed to be 25-30%, however, recent studies using implantable heart rhythm devices such as pacemakers and

cardioverter-defibrillators have revealed that approximately 50% of patients with a history of AF may have unsuspected episodes of AF, with almost half of these episodes lasting more than 48 hours in duration.[8] Antiarrhythmic drugs and catheter ablation have been shown to convert symptomatic AF into asymptomatic AF.[5] Patients with unrecognized AF may not receive appropriate preventative care and are at greater risk for stroke or heart failure.[9]

Pathophysiology

Atrial fibrillation is characterized by uncoordinated atrial electrical activity with rates greater than 300 beats per minute, deterioration of atrial contractility, and irregular ventricular response or rate. The initiation and continuation of AF depend on a multitude of factors which can affect the atria. Several theories have emerged regarding the mechanisms of AF and are likely a combination of a single source focus (automatic focus, mother wave, fixed rotor, moving rotor) and multiple sources (multiple foci, multiple wavelets, unstable reentry circuits (Figure 3).[9] Moe hypothesized in 1962 that atrial activity in AF proceeds as multiple "wavelets" that move around the atrium, some of which circle back on themselves, propagating reentry.[10] However, for this to occur, fibrillation must be initiated by transient "triggers" which collide with normally propagating electrical waves.[11] Due to anatomical heterogeneities in the atriae (e.g. spatial orientation of myocytes) or alterations in the "substrate" (e.g. patchy fibrosis), circuits are created which are predisposed to sustain AF.

Disorders that either increase atrial size (hypertension, sleep apnea, valvular disease), decrease tissue wavelength (aging, fibrosis), decrease refractory periods (thyrotoxicosis), or both (ischemia, autonomic tone) favor continuation of atrial fibrillation.[12] Atrial electrical properties are altered by sustained AF, such that the atrial tissue becomes more susceptible to the initiation and maintenance of the arrhythmia. With time, this atrial "remodeling" of tissue (myocyte calcium overload, reduction in the expression of calcium current, reduction in expression of connexins, stimulation of angiotension II receptors, activation of mitogen –activated protein kinases, etc) prevents spontaneous termination of AF and creates persistent AF which is difficult to convert without electrophysiological manipulation.[9] This progression of atrial remodeling during AF is supported by animal models and has been described as "AF begets AF."[13]

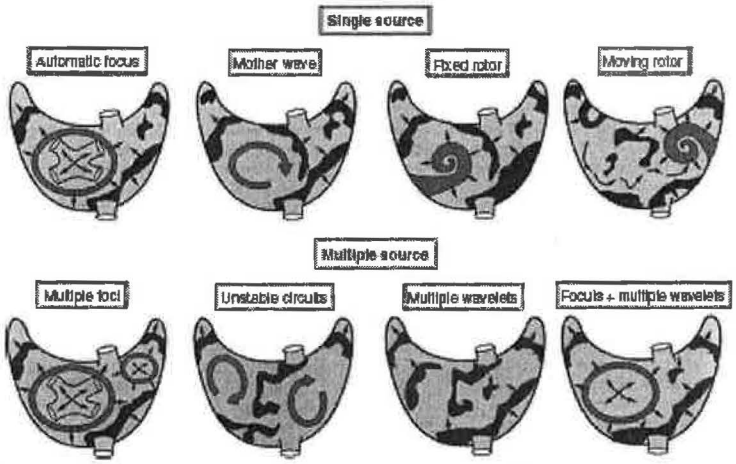

Figure 3. Mechanisms of atrial fibrillation[9]

A paradigm shift in the management of AF has been to target and eliminate the triggers or ectopic foci that initiate AF. It is thought that by preventing the initiation of AF, atrial remodeling will be less likely to occur. Frequently, ectopic foci are located in the pulmonary veins or left atrium. Atrial myocytes have been identified extending into the pulmonary veins and are likely remnants of embryonic development. Ectopic foci are more commonly found in the superior pulmonary veins. Haissaguerre and colleagues were the first to describe spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins and to demonstrate that AF could be abolished by targeting the pulmonary vein triggers by focal radiofrequency ablation.[14]

Clinical Classification

AF is characterized on the electrocardiogram (ECG) by the replacement of organized P waves with oscillations or fibrillatory waves that vary in amplitude, shape, and timing with an irregular ventricular response. Multiple clinical classification schemes have been proposed. After the first detected episode, AF is considered recurrent. AF may be asymptomatic or symptomatic. The ACC/AHA 2006 Guidelines classifies AF based on the duration of episodes: paroxysmal (self terminating within 7 days), persistent (sustained greater than 7 days), and permanent (sustained greater than 1 year or fails to terminate with cardioversion).[5] When AF is persistent, termination with pharmacological therapy or electrical cardioversion does not change the designation. Other terms such as "lone AF" are used to describe individuals younger than age 60 with no clinical or echo evidence of cardiac disease and no history of hypertension. Secondary AF occurs in the setting of cardiopulmonary or metabolic diseases such as acute myocardial infarction, cardiac surgery, pericarditis, hyperthyroidism, pulmonary embolism, pneumonia, acute pulmonary disease, or other acute illness. The term "chronic AF" is now avoided since the term is not specific. For example, a patient may have a 10 year history of paroxysmal AF which is "chronic," however, sustained episodes may never last more than 48 hours in duration.

Stroke Risk and Prevention

The annual incidence of ischemic stroke is 5% among patients with non-valvular AF, between 2 to 7 times that of people without AF.[5] However, the risk increases with age and for those with major risk factors. Multiple clinical trials have demonstrated the benefits of anticoagulation therapy for the prevention of stroke in patients with major risk factors. The data below are a compilation of results from the stroke Prevention in Atrial Fibrillation (SPAF) I-III studies (Table 1). [15]

Table 1. Risk Factors for Stroke and Systemic Embolism with Non-valvular AF[15]

Risk Factors (Control Groups)	Relative Risk
Previous stroke or TIA	2.5
History of hypertension	1.6
Heart failure or impaired left ventricular systolic function	1.4
Advanced age (continuous, per decade)	1.4
Diabetes mellitus	1.7
Coronary artery disease	1.5

- Age <75 yr and no risk factors, stroke risk = 1% annually
- Age <75 yr with hypertension or diabetes, risk 2.5% annually
- Age >75 yr with hypertension, risk 7.5% annually
- Age >75 yr with history of TIA or stroke, risk 13% annually

Multiple large randomized clinical trials have demonstrated the benefits of oral anticoagulation for the prevention of stroke in AF patients.[5] Warfarin has been consistently shown to reduce the risk of ischemic stroke or systemic embolism between 50-70% (Figure 4) compared to no treatment (placebo) and by 30-40% compared to aspirin in high risk patients with AF.[9]

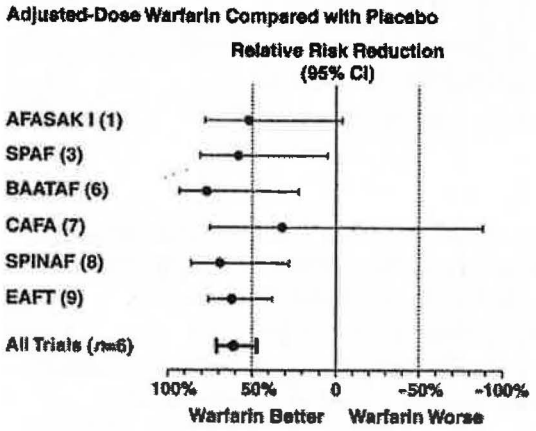

Figure 4. Stroke risk reduction with Warfarin[5]

The CHADS(2) clinical classification scheme was created by assigning 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and by assigning 2 points for history of stroke or transient ischemic attack (Table 2).[16]. The data was based from a National Registry of AF consisting of Medicare beneficiaries aged 65 to 95 years who had non-rheumatic AF and were not prescribed warfarin at hospital discharge.

Table 2. Stroke Risk Index[16]

$CHADS_2$ Criteria	Risk Score
Prior stroke or transient ischemic attack	2 points
Age 75 years or older	1 point
Hypertension	1 point
Diabetes mellitus	1 point
Heart failure or impaired left ventricular systolic function	1 point

The American College of Cardiology and American Heart Association (ACC/AHA) 2006 AF treatment guidelines (Table 3) are more definitive about the use of anticoagualation for patients at highest risk for stroke, specifically, those with prior stroke, TIA or

embolism, mitral stenosis, and prosthestic valves. These patients should be treated with Warfarin. If a patient has no risk factors, daily aspirin is recommended. No distinction is made between patients with paroxysmal versus persistent AF. There is leeway for the patient or physician for prophylactic treatment with 1 moderate risk factor, such that either daily aspirin or dose adjusted warfarin may be selected. The age cut off has been raised to 75. Healthy low risk patients age 65 to 75 may be treated with aspirin. Patients with 2 or more risk factors should be treated with Warfarin.

Table 3. Recommended Antithrombotic Therapy for Nonvalvular AF[17]

Risk Category	Recommended Therapy
No risk factors	Aspirin 81 to 325 mg daily
One moderate-risk factor	Aspirin 81 to 325 mg daily or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor[†]	Warfarin (INR 2.0 to 3.0, target 2.5)[†]

Vitamin K antagonists, such as warfarin, however, have a narrow therapeutic range and have unpredictable pharmacokinetics and pharmacodynamics affected by genetic factors, drug-drug interactions, and consumption of foods containing vitamin K. Subtherapeutic anticoagulation increases the risk of stroke, whereas over-anticoagulation increases the risk of bleeding (Figure 5).[5] Due to these factors, regular coagulation monitoring and dose adjustment of warfarin is required to ensure that anticoagulant effects remain within the therapeutic range International Normalized Ratio (INR) 2.0-3.0.

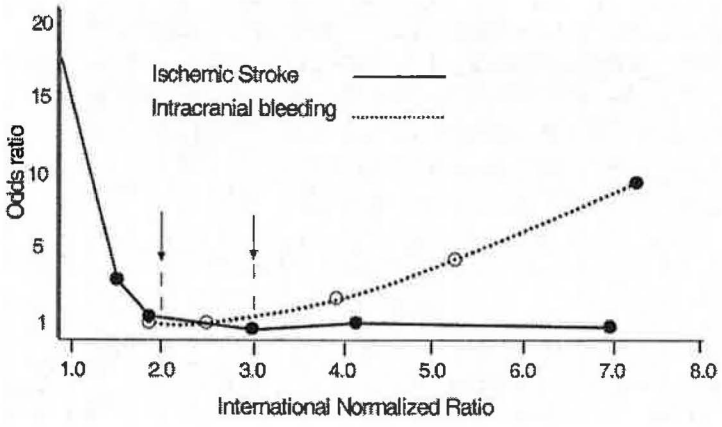

Figure 5. Anticoagulation with Warfarin: Stroke vs Intracerebral Hemorrhage[5]

Several anticoagulant drugs with novel mechanisms are currently undergoing clinical development and may offer advantages to warfarin (Figure 6). The ideal anticoagulant would have rapid and dependable pharmacokinetics, lack drug interactions, and not require monitoring. Ximelagatran (AstraZenica), a direct thrombin inhibitor was shown to be noninferior to dose-adjusted warfarin in stroke prevention and marginally superior in bleeding risk, however, hepatotoxicity and adverse cardiovascular events were observed in two phase III clinical trials and the drug was withdrawn from further development.[18] Dabigatran (Boehringer-Ingelheim), also a direct thrombin inhibitor, has reached phase

III clinical trials but its safety, particularly its effects on the liver, remains to be established.[9] Most promising perhaps are the oral factor Xa inhibitors. Apixaban (Bristol-Meyers Squibb) and rivaroxaban (Bayer AG and Johnson & Johnson) have been studied in the prevention of venous thrombo-embolism following orthopedic surgery, and have been shown to have similar efficacy (DVT, PE, and all-cause mortality) compared to low molecular weight heparin or warfarin in phase II clinical trials with an incidence of major bleeding from 0.0-3.3%.[18] Both drugs are currently in phase II clinical trials for stroke prevention in patients with AF.

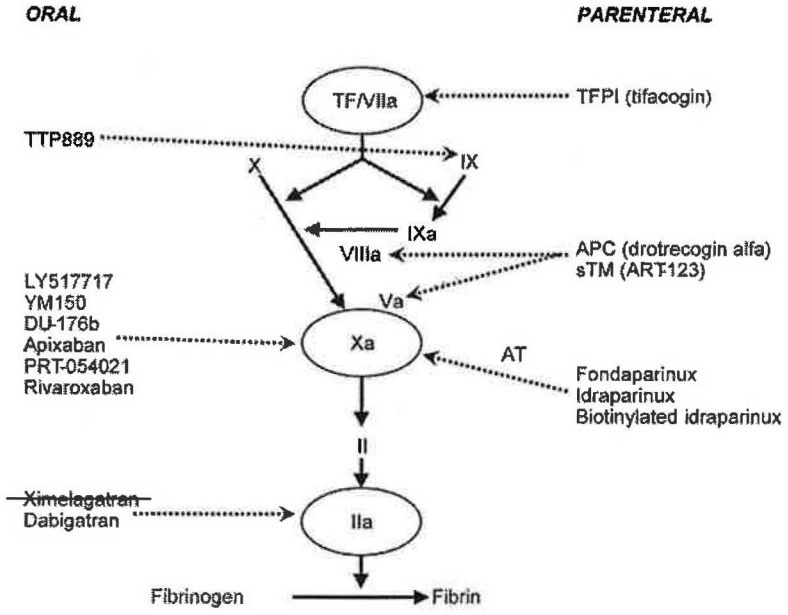

Figure 6. Targets for novel anticoagulants in the coagulation pathway[18]

Role of Rate Control Drugs

Patients with atrial fibrillation are at increased risk for heart failure and stroke.[5] AF can lead to heart failure or a tachycardia mediated cardiomyopathy through several mechanisms including excessive ventricular rate, loss of atrial contraction, and irregular ventricular filling.[19] Most physicians have assumed in the past that maintaining sinus rhythm through drug therapy is preferable to allowing the heart to stay in AF. However, the use of antiarrhythmic drugs to maintain sinus rhythm carries a risk of proarrhythmia such as bradycardia, monomorphic ventricular tachycardia, *torsades de pointe* (polymorphic ventricular tachycardia), and an increased risk for sudden cardiac death.[5]

Two similar studies, AFFIRM[20] and RACE[21] were published in 2002, and demonstrated that rate control with the objective of controlling ventricular rate in elderly patients (age≥65) with stroke risk factors is not inferior to rhythm control with antiarrhythmic drugs. In these studies, AV nodal blocking agents (beta-blocker, calcium channel blocker, digoxin) were used to control ventricular rate with an average goal of ≤80 beats/min at rest and ≤110 beats/minute with exercise. A separate arm included patients treated with class IC or III antiarrhythmic drugs. All patients were initially treated with warfarin. Both demonstrated that the mortality rate between two arms (rate vs rhythm control) were similar (Figure 7). In fact, these studies showed that rhythm control was more costly and patients receiving antiarrhythmic drugs required more hospitalizations and procedures.[9]

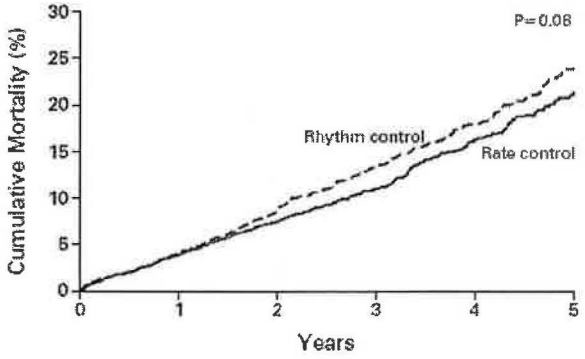

Figure 7. AFFIRM [20] Cumulative Mortality from Any Cause in the Rhythm Control and Rate Control Group.

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial was a recent prospective multicenter study comparing a rhythm control strategy and a rate control strategy for patients with heart failure.[19] All 1376 patients in the study (average age 66) had a left ventricular ejection fraction of 35% or less, symptomatic heart failure (NYHA class II-IV CHF or prior hospitalization for CHF), and a history of atrial fibrillation. Most patients in both arms (~90%) were treated with warfarin. The primary outcome was death from cardiovascular causes. After a mean follow-up of 37 months, there was no significant difference in the rate of death (27% in the rhythm control group vs 25% in the rate control group). Additionally, there was no significant difference in secondary outcomes, including death from any cause, worsening heart failure, or composite of stroke, heart failure, or death (Figure 8).

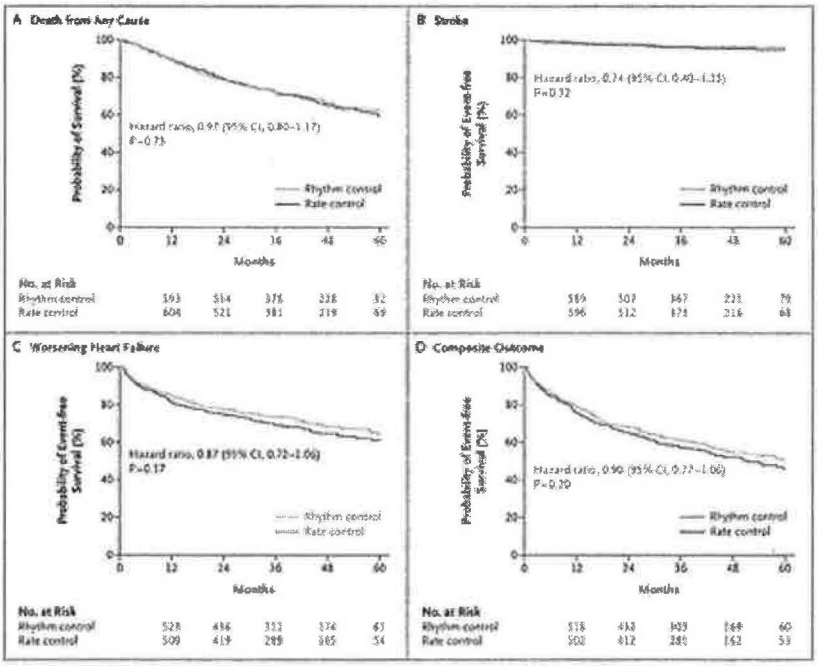

Figure 8. AF-CHF trial. No significant difference in rhythm vs rate control. Panels: A. Death from any cause, B. Stroke, C. Worsening Heart Failure, D. Composite Outcome.

It may appear that rhythm control offers no advantages to a rate control strategy. However, a rhythm control strategy does not guarantee maintenance of sinus rhythm. In fact, rhythm control drugs are effective in less than 2/3 patients with chronic (>1 year) treatment (Figure 9). [22] Among antiarrhythmic drugs, amiodarone and dofetilide have neutral effects and beta-blockers exert a positive survival advantage in patients with heart failure. The majority of patients in the AF-CHF study received amiodarone (>80%), however, many were intolerant of therapy (>10%). Patients taking amiodarone were more likely to have beta-blocker therapy withdrawn (~10%) or may have received a suboptimal dose of beta-blocker for CHF treatment.

For patients that fail an attempt at rhythm control with a drug such as amiodarone, the antiarrhythmic drug should be stopped to avoid the risk of adverse side effects. Additionally, anticoagulation therapy should not be stopped for patients treated with either antiarrhythmic or rate control drugs when AF is suppressed if significant stroke risk factors are present (CHADS score $\geq$ 2), since the use of drugs may convert symptomatic AF to silent AF.[5]

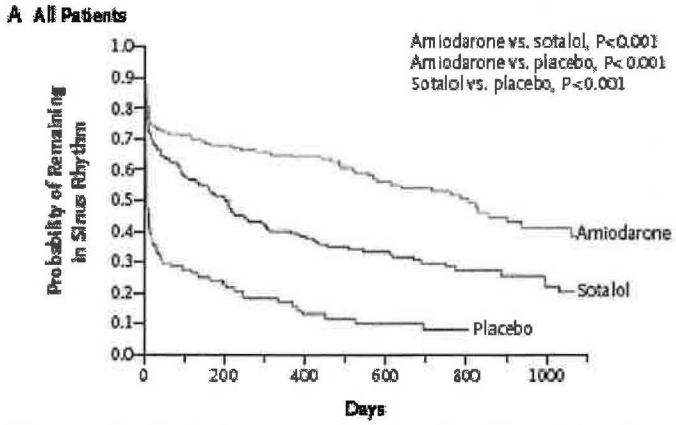

Figure 9. Amiodarone versus sotalol for atrial fibrillation.[22] Time to recurrence of AF among patients in whom sinus rhythm was restored.

Role of Rhythm Control Drugs

Although primary rate control and anticoagulation are good options for elderly asymptomatic patients, a rhythm control strategy is still preferable for a large number of patients. These include younger individuals (<age 65), symptomatic patients, those with recent onset of AF, patients that have failed treatment with a rate control strategy, and some patients with congestive heart failure. In a VA study examining patients with persistent AF (mostly symptomatic, no history of severe heart failure), those that remained in sinus rhythm while taking amiodarone or sotalol reported significantly better quality of life and exercise capacity compared to placebo patients. [22]

Antiarrhythmic drugs are commonly classified by their effects on the cardiac action potential (Vaughn Williams classification) and generally correspond to selective ion channel blockade. Class I agents block the sodium channel (Class Ia: quinidine, procainamide, disopyramide and Class Ic: flecainide and propafenone), class II agents block beta-adrenergic receptors, class III agents generally block potassium channels (amiodarone, dofetilide, sotalol), and class IV drugs block calcium channels. Class Ic agents are first-line treatment for paroxysmal AF in structurally normal hearts but are contraindicated otherwise because of the risk of ventricular proarrhythmia.[5] Class III

agents are used in persistent AF patients with structural heart disease, including heart failure and coronary artery disease, but carry the risk of *torsades de pointes*.[5] Amiodarone, which combines properties of all the Vaughn Williams classes, is the most effective drug for AF, the least pro-arrhythmic drug but carries potential non-cardiac toxicities (pulmonary, ocular, thyroid, skin, and hepatic) and drug interactions that limit its utility.[23] Amiodarone is the most commonly prescribed drug for AF but it is not FDA approved for the treatment of AF and its use is considered "off-label."[5]

One of the most promising new investigational drugs for the treatment of AF is dronedarone (Sanofi-Aventis), a non-iodinated benzofuran derivative of amiodarone that has been shown to have similar electrophysiological effects. Two efficacy and safety studies, ADONIS and EURIDIS were recently published demonstrating that dronedarone was modestly effective in preventing recurrent AF and controlling ventricular rates. [24] At 12 months, 67.1% of patients in the dronedarone group and 77.5% of patients in the placebo group had a recurrence of AF (Figure 10). However, a post hoc analysis of these studies showed a 27% reduction in relative risk of death and hospitalization for cardiovascular causes. No significant pulmonary toxicity or thyroid abnormalities were reported for dronedarone compared to control.

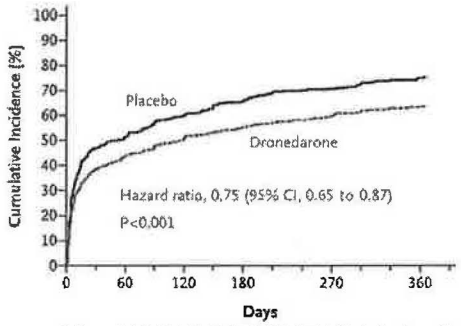

Figure 10. ADONIS/EURIDIS trials, time to AF recurrence with dronedarone.[24]

Results of a large (>4000 patients) phase III, randomized, placebo controlled, double blind trial with dronedarone using a combination primary endpoint of time to first cardiovascular hospitalization or all-cause mortality were reported at the 2008 Heart Rhythm Society Meeting. These patients had paroxysmal or persistent AF and were age ≥ 70 years with 1 or more stroke risk factors (hypertension, prior CVA, diabetes, LA diameter ≥ 50 mm, or LVEF ≤ 40%). The study showed a significant 25% reduction in risk for CV hospitalization for the dronedarone group as well as lower cardiovascular mortality in the drug arm compared to placebo group (Figure 11).

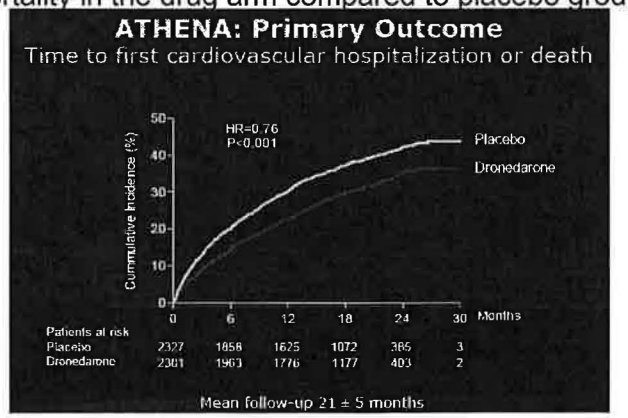

Figure 11. ATHENA Trial, Hohnloser SH, Heart Rhythm Society 2008, SF, CA

These studies demonstrate that newer antiarrhythmic drugs and patient selection may be the key to rhythm control. Besides dronedarone, other analogues of amiodarone are being developed with possibly better risk to benefit ratios. Another line of investigation is to target ion channels more specific to the atria. Agents have been developed which selectively block the ultrarapid delayed rectifier potassium current (I_{Kur}), transient outward current (I_{to}), and acetycholine-dependent potassium current (I_{KACh}).[23]

Vernakalant hydrochloride (Cardiome, Canada) is an investigational drug in advanced phase of development. [25] This compound is a relatively atrium-selective, early-activating potassium and frequency-dependent sodium channel blocker with half-life of 2-3 hours. Patients with recent onset AF (3 hours to 7 days) have the greatest efficacy with vernakalant (51.7%) compared to placebo (4.0%) without risk of ventricular arrhythmia (Figure 12). However, serious adverse events including hypotension, complete AV block, and cardiogenic shock occurred in <1% of study patients. Nevertheless, this may be a future alternative to electrical cardioversion, which also has adverse effects such as skin burns, heart block, ventricular proarrhythmia, and complications from sedation.

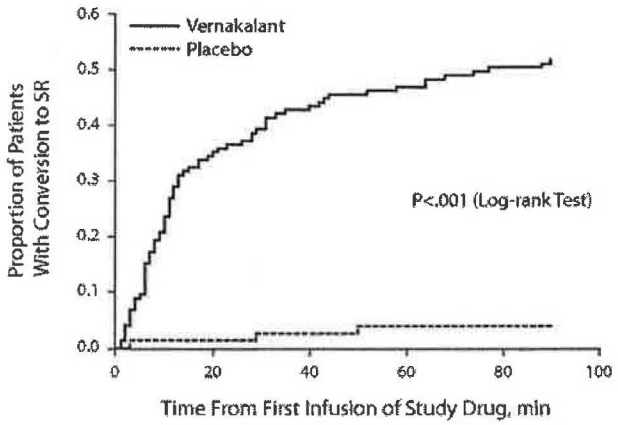

Figure 12. Vernakalant conversion success rate after the start of study drug infusion for short-duration AF. [25]

Role of Pacing

The use of permanent pacemakers for the treatment of symptomatic bradycardia is well established. Sinus node dysfunction and bradycardia are frequently associated with paroxysmal AF. The terms sick sinus syndrome and "tachy-brady syndrome" refer to the sudden oscillations between sinus brady-arrhythmia and atrial tachy-arrhythmia or AF. Single chamber (atrial or ventricular) and dual chamber pacemakers are implanted for sinus node dysfunction depending on the status of intrinsic atrioventricular (AV) conduction and the desire for rate response or AV synchrony. [26] In some patients with bradycardia-dependent AF, atrial pacing may be effective in reducing the frequency of recurrences. However, right ventricular pacing due to 1st degree or intermittent AV block with conventional dual chamber pacemakers have been shown to create ventricular dyssynchrony and increase the incidence of atrial fibrillation. Dual chamber pacing paradoxically leads to an increased risk of heart failure and death.[27]

Newer pacemakers have pacing algorithms which minimize right ventricular pacing in patients with sinus node disease and intact AV conduction. A study published last year demonstrated that dual chamber pacing with devices designed to promote AV

conduction, preserve intrinsic ventricular conduction, and prevent ventricular dyschronization decrease the risk of developing persistent atrial fibrillation (40% reduction in relative risk, 4.8% absolute risk reduction) compared to conventional dual chamber pacemakers. [28]

Heart failure often co-exists with AF. The estimated prevalence of AF in patients with heart failure ranges between 5 to 50%, depending on the stage of CHF.[5] Cardiac resynchronization therapy (CRT) is indicated for patients with dilated cardiomyopathy, NYHA class III to IV heart failure, left ventricular ejection fraction $\leq$ 35%, and QRS duration $\geq$ 120ms. CRT therapy in these selected CHF patients has been shown to reduce all cause mortality (36% RR reduction) and cardiovascular hospitalizations (52% RR reduction). [26] However, the large clinical trials which validated the effectiveness of CRT studied CHF patients in sinus rhythm and excluded patients with persistent or permanent atrial fibrillation. More recent observational studies and a single randomized trial suggest that CHF patients meeting indications for CRT with permanent AF may also benefit.[29]

Role of Catheter Ablation

As discussed earlier, AF requires both a trigger and a substrate (Fig 13). The goals of AF ablation procedures are to either eliminate the triggers that inititate AF, most commonly originating near the ostium of the pulmonary veins, or to alter the arrhythmogenic atrial substrate. The most common catheter ablation strategy involves electrical isolation of the pulmonary veins (PV isolation) by creating circumferential lesions around the left and right PV ostia or antrrum (Fig 14).[30] The cirumferential lesions may also alter the atrial substrate by eliminating muscle tissue near the atrial-PV junctions that can act as reentrant circuits which can perpetuate AF, or reduce the mass of atrial tissue needed to sustain reentry. Other less common trigger sites for AF, including the vein (ligament) of Marshall, the posterior left atrial wall, superior vena cava, and areas of "complex fractionated electrograms" are sometimes targeted. The addition of linear lesions connecting the circumferential lesions or extending the lesions to the mitral annulus further compartmentalizes the left atrium, potentially preventing reentry.[30]

Catheter ablation of AF or pulmonary vein isolation is an alternative to pharmacological therapy. In selected patients with paroxysmal AF, particularly those with minimal structural heart disease (little or no left atrial enlargement) and age < 65 years, small randomized clinical trials using PV isolation or circumferential PV ablation techniques have demonstrated a significant reduction in AF burden compared to antiarrhythmic drugs. Success rates for AF ablation for paroxysmal AF approach 75-85% compared to 5-35% efficacy with antiarrhythmic drug therapy (Table 3).[31, 32] Based on these small trials, the American College of Cardiology /American Heart Association/ European Society of Cardiology (ACC/AHA/ESC) have issued guidelines and recommendations for catheter ablation of AF. [30] There is a consensus that the primary indication for AF ablation is the presence of symptomatic AF refractory to at least one Class I or III antiarrhythmic drug (or patient intolerance to antiarrhythmic drug therapy). In rare situations, it may be appropriate as first line therapy. Catheter ablation may be performed in selected patients with persistent AF[33], and those with symptomatic heart failure or reduced ejection fraction. [34]

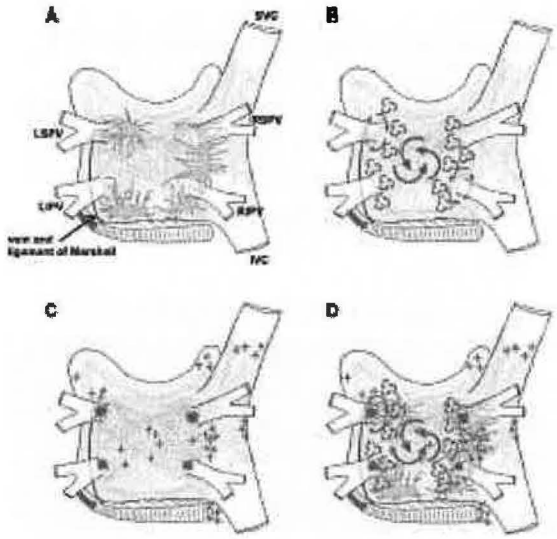

Figure 13.[30] Structures and mechanisms of atrial fibrillation are depicted by the drawings of the left and right atria. The first 4 diagrams show the following: A. The posterior left atrium, the left superior, left inferior, right superior and right inferior pulmonary veins (LSPV, LIPV, RSPV, RIPV) and their relationship to the right atrium, superior vena cava (SVC) and inferior vena cava (IVC). B. Large and small reentrant wavelets that play a role in initiation and sustaining AF. C. Common locations of PV and non PV triggers. D. Composite mechanisms.

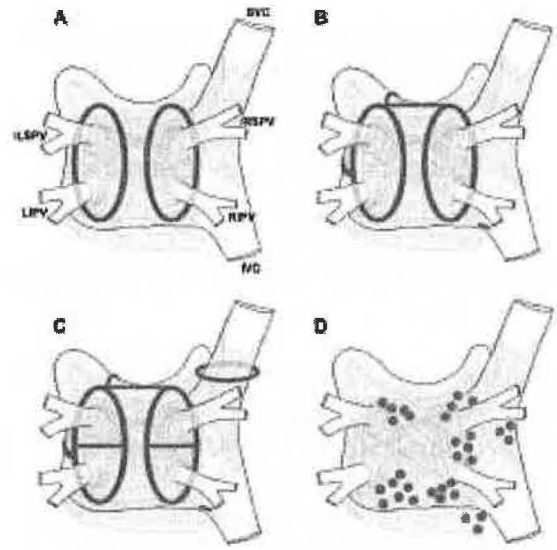

Figure 14.[30] The second 4 diagrams show common lesion sets employed in AF ablation. A. Circumferential ablation lesions created around the left and right PVs. B. Some common sites of linear ablation lesions including the left atrial "roof" and a "mitral isthmus" line connecting the lesion encircling the left PVs to the mitral annulus. C. Similar to B but with the addition of lesions between the superior and inferior PVs and lesions encircling the superior vena cava. D. Some common sites of ablation lesions when complex fractionated electrograms are targeted.

It is important to recognize that the randomized studies of AF ablation have been relatively small, employed soft endpoints such as a reduction in symptomatic AF at 1 year with intermittent monitoring (as opposed to absolutely no AF recurrence with continuous monitoring), and were performed at few experienced centers. Approximately one-quarter to one-third of patients, particularly those with chronic (persistent) AF required antiarrhythmic drug therapy, including amiodarone, to prevent recurrences.[31, 33] A significant proportion of patients (between 20-40%) may have undergone multiple repeat or "redo" procedures. [30]

Table 4. Randomized clinical trials of ablation versus antiarrhythmic drugs for AF.[31]

Study	Number of patients	Type of AF	AF free at 1 year: Ablation	AF free at 1 year: AAD/control	Adjunct use of AAD in the ablation group
Wazni et al, 2005[17]	70	98% paroxysmal	87%	37% (54% after the 2nd AAD)	43% β-blockers
Stabile et al, 2005[18] (CACAF)	137	67% paroxysmal	56%	9%; 57% crossed over to ablation	100% (by design)
Oral et al, 2006[19]	146	Persistent – cardioversion required	74%	4% (without amiodarone); 77% crossed over to ablation	100% amiodarone for 3 months, repeat ablation in 32%
Pappone et al, 2006[20] (APAF)	189	Paroxysmal	87%	29%; 51% crossed over to ablation	12%; repeat RFA in 4.6%
Jais et al, 2006[a] (A4 study)	112	All paroxysmal	75%	7%; 63% crossed over to ablation	Not stated, but frequent repeat ablations (1.8 ablation procedures per patient)

[a] Presented at the 27th Annual Scientific Sessions of Heart Rhythm Society in Boston, Massachusetts. Abbreviations: AAD – antiarrhythmic drugs; AF – atrial fibrillation; APAF – Ablation for Paroxysmal Atrial Fibrillation study; CACAF – Catheter Ablation for the Cure of Atrial Fibrillation study; A4 – Atrial fibrillation Ablation versus Anti-Arrhythmic drugs)

Additionally, AF ablation carries a risk of procedural complications which approach 6% based on a worldwide survey on the outcomes of AF catheter ablation.[35] Serious complications of AF catheter ablation include stroke (1-2%), pericardial effusion or tamponade (1-3%), pulmonary vein stenosis (1-3%), phrenic nerve injury (0.5%), injury to the esophagus or formation of an atrio-esophageal fistula (0.25%), and rare instances of death. Additionally, early recurrence of AF (~40%) and iatrogenic atrial arrhythmias (>10%) are observed in the first one to three months after ablation, likely due to inflammation, and may cause patients to transiently experience worsening of symptoms following an ablation. [30]

A large NIH sponsored randomized trial, Catheter ABlation versus ANtiarrhythmic drug therapy for Atrial fibrillation (CABANA) was designed to test whether left atrial catheter ablation will reduce total mortality compared to current rate control or antiarrhythmic drug therapy. Each pt will have 1) Characteristics similar to AFFIRM patients (>65 years or <65 with >1 risk factor for stroke, 2) Documented AF warranting treatment, and 3) Eligibility for both catheter ablation and >2 anti-arrhythmic or >3 rate control drugs. Patients will be followed every 6 months for >2 yrs and will undergo repeat trans-telephonic monitor, Holter monitor, and CT/MR studies to assess the impact of treatment. The CABANA trial is currently recruiting patients and will help disclose the role of medical and non-pharmacologic therapies for AF, establish the cost and impact of therapy on quality of life and will help determine if AF is a modifiable risk factor for increased mortality (ClinicalTrials.gov, NCT00578617, PI – Douglas Packer, Mayo Clinic).

Currently, no ablation device is approved by the Food and Drug Administration (FDA) specifically for the treatment of AF. The standard approach is to use conventional 4-mm or 8-mm electrode tip radiofrequency ablation catheters (approved for treatment supraventricular tachycardias or ventricular tachycardias) to perform the procedures. Catheter ablation of AF is performed in most centers using electroanatomical mapping systems, which allow for computerized reconstruction of the cardiac anatomy to facilitate catheter manipulation. The two most widely used systems are the CARTO (Biosense Webster Inc, Johnson and Johnson, USA) and the NavX system (Endocardial Solutions, St Jude Medical, USA). A recent advance in electroanatomical mapping is the ability to use pre-acquired CT/MR/echo images to guide catheters without the use of fluoroscopy. These systems have decreased procedure times and reduced radiation exposure to both patients and operators.[30] New technologies, including alternate energy sources for ablation (cryoablation, high intensity focused ultrasound, laser) and robotic catheter navigation systems are undergoing testing. [30] The efficacy, safety, and cost effectiveness of these innovative techniques are promising but are not established.

For patients that are refractory to drug or AF ablation therapy, radiofrequency ablation of the atrioventricular junction (AVJ) to create high grade AV block with simultaneous implantation of a permanent pacemaker is an effective method for controlling ventricular rate. Several studies have reported that AVJ is associated with a reduction of symptoms, an improvement in exercise tolerance, an increase in the quality of life, and augmentation of left ventricular ejection fraction (LVEF) in selected patients. [5] However, continuous right ventricular pacing may lead a decline in LVEF in ~15% of patients receiving this therapy, possibly worsening heart failure and increasing mortality.[36] Implant of a biventricular pacing device (cardiac resynchronization therapy - CRT pacemaker) may prevent deterioration of LVEF in patients undergoing ablation of the AVJ for management of AF with rapid ventricular rates.[37] However, the beneficial effects of CRT appear to be greater in patients with impaired systolic function or with symptomatic heart failure.[29] The results of ongoing, rigorously designed clinical studies are needed to clarify the role of AF ablation, resynchronization therapy, and drugs when atrial fibrillation complicates the course of heart failure.

Conclusions

Atrial fibrillation (AF) is a morbid and costly cardiovascular condition that will affect 3% of the U.S. population and a greater proportion of individuals above the age of 65 in the coming years. AF significantly increases the risk of stroke, heart failure, and cardiovascular mortality. Patients with multiple risk factors for stroke, particularly those with a history of Congestive heart failure, Hypertension, Age >70, Diabetes, or prior Stroke (CHADS score $\geq$ 2) benefit from anticoagulation therapy. Conventional anticoagulation therapy is highly effective but not consistently applied either because of difficulties with management or concerns of bleeding complications. New antithrombotic agents with favorable pharmacological characteristics have reached the final stages of development and may eventually replace warfarin. Rate control of heart rate with AV nodal blocking drugs or pacemakers is well established in the treatment of AF, particularly for asymptomatic individuals or elderly patients. In selected patients, a rhythm control strategy with antiarrhythmic drugs or catheter ablation may offer advantages to rate control. Newer antiarrhythmic drugs and catheter ablation are under clinical investigation and may have benefits which include the potential to reduce hospitalizations or cardiovascular mortality. AF catheter ablation has become a commonly performed procedure throughout the world. Innovative devices and techniques may improve the safety and efficacy of this rapidly evolving procedure.

References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama.* 2001;285(18):2370-2375.
2. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation.* 2004;110(9):1042-1046.
3. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *Jama.* 1994;271(11):840-844.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98(10):946-952.
5. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *Journal of the American College of Cardiology.* 2006;48(4):854-906.
6. Le Heuzey JY, Paziaud O, Piot O, Said MA, Copie X, Lavergne T, Guize L. Cost of care distribution in atrial fibrillation patients: the COCAF study. *American heart journal.* 2004;147(1):121-126.
7. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health.* 2006;9(5):348-356.
8. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *Journal of the American College of Cardiology.* 2004;43(1):47-52.
9. Savelieva I, Camm J. Update on atrial fibrillation: part I. *Clinical cardiology.* 2008;31(2):55-62.
10. Moe GK. A conceptual model of atrial fibrillation. *Journal of electrocardiology.* 1968;1(2):145-146.
11. Jalife J. Experimental and clinical AF mechanisms: bridging the divide. *J Interv Card Electrophysiol.* 2003;9(2):85-92.
12. Narayan SM, Cain ME, Smith JM. Atrial fibrillation. *Lancet.* 1997;350(9082):943-950.
13. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation.* 1995;92(7):1954-1968.
14. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *The New England journal of medicine.* 1998;339(10):659-666.
15. Ziv O, Choudhary G. Atrial fibrillation. *Primary care.* 2005;32(4):1083-1107.
16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama.* 2001;285(22):2864-2870.
17. Estes NA, 3rd, Halperin JL, Calkins H, Ezekowitz MD, Gitman P, Go AS, McNamara RL, Messer JV, Ritchie JL, Romeo SJ, Waldo AL, Wyse DG. ACC/AHA/Physician Consortium 2008 clinical performance measures for adults with nonvalvular atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task

Force on Performance Measures and the Physician Consortium for Performance Improvement (Writing Committee to Develop Clinical Performance Measures for Atrial Fibrillation): developed in collaboration with the Heart Rhythm Society. *Circulation.* 2008;117(8):1101-1120.

18. Turpie AG. New oral anticoagulants in atrial fibrillation. *European heart journal.* 2008;29(2):155-165.
19. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *The New England journal of medicine.* 2008;358(25):2667-2677.
20. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *The New England journal of medicine.* 2002;347(23):1825-1833.
21. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *The New England journal of medicine.* 2002;347(23):1834-1840.
22. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD. Amiodarone versus sotalol for atrial fibrillation. *The New England journal of medicine.* 2005;352(18):1861-1872.
23. Page RL. Medical management of atrial fibrillation: future directions. *Heart Rhythm.* 2007;4(3 Suppl):S91-94.
24. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *The New England journal of medicine.* 2007;357(10):987-999.
25. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Nielsen T, Rasmussen SL, Stiell IG, Coutu B, Ip JH, Pritchett EL, Camm AJ. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation.* 2008;117(12):1518-1525.
26. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Journal of the American College of Cardiology.* 2008;51(21):e1-62.
27. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *Jama.* 2002;288(24):3115-3123.
28. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, Sheldon T, Lamas GA. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *The New England journal of medicine.* 2007;357(10):1000-1008.
29. Koneru JN, Steinberg JS. Cardiac resynchronization therapy in the setting of permanent atrial fibrillation and heart failure. *Current opinion in cardiology.* 2008;23(1):9-15.
30. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ, Jr., Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H,

Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2007;4(6):816-861.

31. Savelieva I, Camm J. Update on atrial fibrillation: part II. *Clinical cardiology.* 2008;31(3):102-108.
32. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *Jama.* 2005;293(21):2634-2640.
33. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F, Jr., Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *The New England journal of medicine.* 2006;354(9):934-941.
34. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquie JL, Scavee C, Bordachar P, Clementy J, Haissaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. *The New England journal of medicine.* 2004;351(23):2373-2383.
35. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Packer D, Skanes A. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation.* 2005;111(9):1100-1105.
36. Chen L, Hodge D, Jahangir A, Ozcan C, Trusty J, Friedman P, Rea R, Bradley D, Brady P, Hammill S, Hayes D, Shen WK. Preserved left ventricular ejection fraction following atrioventricular junction ablation and pacing for atrial fibrillation. *Journal of cardiovascular electrophysiology.* 2008;19(1):19-27.
37. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *Journal of cardiovascular electrophysiology.* 2005;16(11):1160-1165.