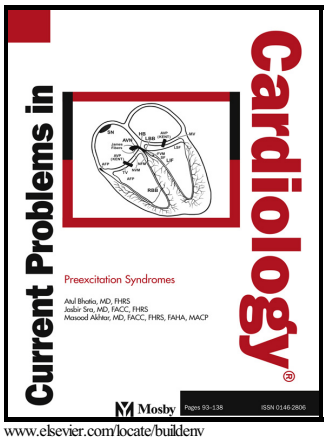
Author's Accepted Manuscript



www.elsevier.com/locate/buildenv

Current Evidence Based Understanding of the Epidemiology, Prevention, and Treatment of Atrial Fibrillation

Paul A. Rogers, Michael L. Bernard, Christopher Madias, Sudarone Thihalolipavan, Daniel P. Morin

PII: S0146-2806(17)30092-0
DOI: http://dx.doi.org/10.1016/j.cpcardiol.2017.06.001
Reference: YMCD353

To appear in: *Current Problems in Cardiology*

Cite this article as: Paul A. Rogers, Michael L. Bernard, Christopher Madias, Sudarone Thihalolipavan and Daniel P. Morin, Current Evidence Based Understanding of the Epidemiology, Prevention, and Treatment of Atrial Fibrillation, *Current Problems in Cardiology,* http://dx.doi.org/10.1016/j.cpcardiol.2017.06.001

Current Evidence Based Understanding of the Epidemiology, Prevention, and Treatment of Atrial Fibrillation

Paul A. Rogers MD PhD[1], Michael L. Bernard MD PhD[1], Christopher Madias MD[2], Sudarone Thihalolipavan MD[3], Daniel P. Morin MD MPH[1,4]

[1] Department of Cardiology, Ochsner Medical Center, New Orleans, LA

[2] Tufts Medical Center, Boston MA

[3]Arkansas Heart Hospital, Little Rock, AR

[4] Ochsner Clinical School, University of Queensland School of Medicine, New Orleans, LA

Correspondence to:
Daniel P. Morin MD MPH
Ochsner Medical Center
1514 Jefferson Highway,
New Orleans, LA 70121. Phone 504-842-4145. Fax 504-842-5823.
E-mail: dmorin@ochsner.org

Financial Disclosures:

Dr. Morin is on the speaker's bureau for Boehringer-Ingelheim, has received honoraria from Biotronik and Medtronic, and has research grants from Boston Scientific and Medtronic.

Dr. Bernard serves on the speaker's bureau for Janssen.

Drs. Madias, Rogers, and Thihalolipavan have no disclosures.

Abstract

Atrial fibrillation (AF) is the most common atrial arrhythmia in adults worldwide. As medical advancements continue to contribute to an ever-increasing aging population, the burden of atrial fibrillation on the modern healthcare system continues to increase. Therapies are also evolving, for treatment of the arrhythmia itself, and stroke risk mitigation. Internists and cardiologists alike are, in most instances, the frontline contact for AF patients, and would benefit from remaining facile in their understanding of care options. In order to continue to deliver high-quality care to this expanding patient group, an updated, concise review for the clinician is prudent. This article provides a comprehensive summary of the current epidemiology and pathophysiology of AF, as well as contemporary procedural therapeutic options.

Key Words: Atrial fibrillation, epidemiology, risk factors, catheter ablation

Epidemiology

AF was discovered in the early 20th century and was initially believed to be a dysrhythmia of clinical insignificance.[1,2] However, towards the end of the 20th and into the 21st century, AF has notably impacted morbidity and mortality, and has become a cog in the wheel of increasing health care utilization and cost.[3,4] AF is the most common clinically significant arrhythmia, with a recent worldwide estimated prevalence of up to 33.5 million patients and affecting 2.5%-3.5% of populations across many countries, with developed countries' incidence of AF twice that found in developing countries.[5] This estimate from the recent Global Burden of Disease study did not include silent AF, which consequently can be associated with cryptogenic strokes, heart failure, and early mortality.[6] 5.2 million people are estimated to suffer from AF in the United States, a number that is expected to increase to 12.1 million over the next one to two decades.[7]

AF significantly financially impacts public health. In the United Kingdom, AF is estimated to account for 1% of the national budget, and AF costs $16-26 billion annually in medical expenditures in the United States.[8,9,10] AF is associated with an estimated incremental medical cost of $8705 per patient per year, including inpatient, outpatient, and pharmacy costs.[9] The majority of increased cost of AF is from hospitalization, stroke and heart failure care, and loss of economic productivity.[8,11,12,13] Evaluation of the disability-adjusted life-years (DALYs) metric, a means of assessing the impact of disability of chronic disorders combining information on premature death (*i.e.,* years of life lost) and disability caused by the chronic disorder (*i.e.*, years lived with disability),[11] indicated that from 1990 to 2010, the worldwide burden of DALY loss attributable to AF increased from 54 per 100,000 person-years to 65 per 100,000 person-years for men, and increased from 39 to 46 per 100,000 person-years for women.[6] These increases reflect a growing global epidemic of AF that is both an economic and disability burden.

With the increasing prevalence of AF and number of patients seeking care for AF, interest in understanding the arrhythmia and risk factors has increased. Several intrinsic traits have been linked to elevated risk of AF, particularly age, race, and gender.

For every decade of life attained, the risk of developing AF doubles.[14] The annual incidence of AF per 1000 persons in the Framingham population for those under 65 is 1.9 in women and 3.1 in men, compared to 31.4 in women and 38 in men among those over 85 years of age.[15] The lifetime risk of AF in the over-40 Framingham population was estimated at 25%.[16] The incidence of AF in a European population was found to be 1.1 per 1000 person-years in patients 55-59 years of age, increasing to 20.7 per 1000 person-years in those over 80 years old.[17]

Caucasians have a higher risk of incident AF than do African Americans, Hispanics, and Asians.[18] There is a risk factor-AF paradox evident in the lower incidence of AF in African Americans despite a higher prevalence of AF risk factors.[19,20] The Cardiovascular Health Study (CHS) first suggested this paradox, finding a 79% lower risk of AF in the African American study population.[21] The CHS study was not the only population study to make this observation. The Analysis of the Atherosclerosis Risk in Communities (ARIC) study also observed that African Americans had a 41% lower adjusted risk of developing AF compared to Caucasians.[19] A meta-analysis of 10 studies examining over 1 million patients suggested that African Americans appeared to be protected from AF, demonstrating a 49% lower risk.[22] To assess whether this was an environmental or genetic factor, Marcus *et al*. used genetic analysis to determine the degree of European ancestry in African Americans in the CHS and ARIC studies, and correlated this information with risk of developing incident AF.[23] The study concluded that for every 10% increase in European ancestry there was a 10% increased risk of incident AF, indicating that there likely is an undiscovered genetic predisposition to AF in those of European descent.

Gender also impacts the incidence and effects of AF. Women tend to be more symptomatic from AF, with longer paroxysmal episodes and faster ventricular response rates during paroxysms.[24] However, compared to men, women had a 46% lower age-matched risk of AF in the ARIC study and a lower incidence of newly diagnosed AF in a Medicare database review (25 compared to 35 per 1000 person-years).[19,25] It is, however, well established that women have a higher risk of cardioembolic stroke from AF.[26,27] In the Copenhagen City Heart Study, a population-based prospective cohort study, women had an independent 2.5-fold increased risk of cardiovascular mortality related to AF.[27]

Comorbidities and AF Risk Reduction

The development of AF in any one patient involves many complex and incompletely understood mechanisms. There are several important comorbid

conditions that promote the development and maintenance of AF. Understanding these factors better is important and may translate into better treatment and prevention of AF. The most well-described modifiable factors that increase risk of AF are congestive heart failure (CHF), hypertension, diabetes mellitus, obesity, alcohol consumption, and obstructive sleep apnea.[28,29] Risk factor modification may impact the development and severity of AF, as illustrated in Figure 1.

Congestive Heart Failure

AF and CHF often share many comorbidities, and AF is associated with a 3-fold increase in the risk of incident heart failure.[30,31] In the international Real-life global survey evaluating patients with Atrial Fibrillation (RealiseAF), the prevalence of CHF was associated with increasing persistence of AF (33% of those with paroxysmal AF had CHF, compared with 44% in persistent AF and 56% in permanent AF).[32] Also, the prevalence of AF is directly associated with New York Heart Association (NYHA) functional class: <10% in NYHA functional class I have AF, compared with up to 55% in NYHA functional class IV regardless of systolic function.[33]

Patients with AF and CHF have a worse prognosis than with either component alone. In the Framingham population, development of CHF in subjects with AF was associated with increased mortality in both men (HR 2.7; 95% CI 1.9-3.7) and women (HR 3.1; 95% CI 2.2-4.2).[34] In the same population, subsequent occurrence of AF in those with CHF was associated with increased mortality in both men (HR 1.6; 95% CI 1.2-2.1) and women (HR 2.7; 95% CI 2.0-3.6).[34] A meta-analysis evaluating CHF patients' prognosis found an increase in mortality related to AF in 30,248 subjects from randomized trials (OR 1.4; 95% CI 1.32-1.48; $p<0.0001$) and in 23,721 subjects from observational studies (OR 1.14; 95% CI 1.03-1.26; $p<0.05$).[35]

The physiologic interactions between AF and CHF that contribute to their co-habitation are complex. Experimental models indicate that AF is initiated and sustained when there is heterogeneity of repolarization throughout the atria, slowed atrial conduction, and a decreased atrial refractory period.[36,37] Atrial tissue stretches in response to increased atrial pressure and volume, increasing triggered activity and changes in refractoriness, predisposing to AF.[38] Atrial hypertrophy and chamber enlargement then leads to increased atrial automaticity and heterogeneity of depolarization.[39] Neuro-hormonal milieu changes via renin-angiotensin-aldosterone system (RAAS) activation in CHF promote extracellular matrix fibrosis, leading to heterogeneity of atrial repolarization and predisposing to the development of AF.[36,37,40] Pulmonary vein cardiomyocyte activity may be angiotensin II sensitive, which may lead to AF initiation.[41] Conversely, AF can lead to RAAS activation and may induce a tachycardia-mediated cardiomyopathy, again highlighting the complex interactions between AF and CHF.[42,43,44]

Hypertension

Hypertension is an independent risk factor for incident AF. The Framingham cohort displayed an independent increased risk of AF by factors of 1.5 in men and 1.4 in women related to hypertension.[14] Pre-hypertension range blood pressure has also been associated with increased risk of AF: data from the Women's Health Study noted that the risk of incident AF during 12.4 years of follow-up was significantly increased in those with baseline systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥90 mmHg.[45] A study in middle-aged men showed similar findings.[46] Baseline systolic blood pressure ≥128 mmHg or diastolic blood pressure ≥80 mmHg were associated with 1.5-fold and 1.79-fold higher risk, respectively, of incident AF. Hypertension increases sympathetic output which may lead to increased left atrial pressure and volume, as well as RAAS activation, thereby leading to atrial fibrosis, structural and electrical atrial remodeling, and promotion of AF.[47]

It is therefore fitting to postulate that aggressive treatment of chronic hypertension could help to reduce the risk of AF. Post-hoc analysis of the standard versus aggressive blood pressure lowering arms of the randomized Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial indicate that targeting a systolic blood pressure of <120 mmHg compared with the "standard" target of <140 mmHg showed a statistically nonsignificant trend toward a lower incidence of AF.[48]

Conceivably, "upstream" therapy with RAAS modulators, angiotensin converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARB) may improve risk of AF, a notion mentioned in the 2014 major societal AF guidelines.[49] Post-hoc analysis of two large hypertension studies, the Losartan Intervention For End Point Reduction in Hypertension (LIFE)[50] and Valsartan Antihypertensive Long-Term Use (VALUE)[51] trials, suggested that ACEi/ARB therapy may be of benefit in reducing incident AF. The LIFE trial included hypertensive patients with left ventricular hypertrophy but without AF and showed therapy with losartan had similar efficacy in lowering blood pressure as atenolol, but was associated with a 33% reduced risk of new-onset AF (p<0.001).[50] In the VALUE trial, valsartan was associated with a lower incidence of AF compared with amlodipine (unadjusted HR 0.843, p=0.046).[51] Conversely, a meta-analysis of 11 studies with 56,308 patients evaluating the efficacy of ACEi or ARB therapy in preventing AF demonstrated no benefit in the hypertension subgroup.[52] However, this meta-analysis did not include the VALUE trial, only had 3 studies in the hypertension subgroup with only 2 evaluating new-onset AF, and there was significant interstudy heterogeneity.[52] A Danish retrospective study of individuals with only hypertension showed that the use of ACEi or ARB as monotherapy was associated with a much lower risk of new-onset AF compared beta-blocker use (ACEi HR 0.12, 95% CI 0.10-0.15; and ARB HR 0.10, 95% CI 0.07-0.14) or diuretics (ACEi HR 0.51, 95% CI 0.44-0.59; and ARB HR 0.43, 95% CI 0.32-0.58), but not compared with calcium channel blocker use.[53] A recent meta-analysis of 4 randomized clinical trials (RCTs) with 1050 patients showed

telmisartan was more effective than other antihypertensive medications in reducing the burden of AF (HR 0.54, CI 0.34-0.86).[54] Overall, these data suggest that there may be a role for RAAS modulation in preventing AF and reducing its recurrence, but certainly more studies are needed.

Diabetes Mellitus

20% of patients with AF have diabetes mellitus (DM).[55] Hyperglycemia likely contributes to inflammation, oxidative stress, and formation of advanced glycosylation end-products (which can lead to hypertrophy and interstitial fibrosis). These factors can lead to electroanatomical remodeling of the left atrium and thereby promote AF.[56]

DM is an independent contributor to new onset AF, as shown in the Framingham population in both men (OR 1.4) and women (OR 1.6).[14] The VALUE trial also showed those with DM during follow-up to have a 50% increased risk of new-onset AF.[57] Furthermore, a meta-analysis including 1,686,097 patients indicated a 40% higher risk of AF in diabetics.[58]

There are no convincing published data in support of “upstream” therapy to prevent AF in patients with DM. However, a few reports suggest that the use of thiazolidinediones (TZDs) may contribute to AF risk reduction. TZDs are drugs that activate peroxisome proliferator-activated receptor-γ, reducing peripheral insulin resistance. The use of these agents is limited by their reported adverse effects including weight gain, CHF, and possibly bladder cancer.[59] A Taiwan population-based cohort study evaluated 12,065 type 2 diabetic patients, and observed that the use of TZDs was associated with a 31% reduced adjusted risk of new onset AF.[60] Gu *et al*. found in their 150 consecutive-patient cohort with type 2 DM undergoing pulmonary vein isolation (PVI) as part of a rhythm control strategy for AF that use of pioglitazone was associated with a higher rate of maintenance of sinus rhythm without antiarrhythmic therapy over nearly two years of follow-up (86 vs. 71%, p=0.034).[61] The mechanism of this effect is

unknown. However, as suggested by animal models, TZDs may attenuate electrical and structural atrial remodeling via their antioxidant and anti-inflammatory properties.[62]

Obesity

Obesity, like AF, is a growing worldwide epidemic.[63] Obesity is associated with increased left atrial dimensions,[64] which may be mediated via lipoapoptosis[65] and autonomic impairment.[66] A 4% increase in the hazard of incident AF for each unit increase in BMI was noted in the Framingham population.[67] Similar findings were noted in the Women's Health Study,[68] the ARIC study,[69] and various other community cohort studies.[70,71] The LEGACY study evaluated the effect and magnitude of weight loss on the burden of AF.[72] They found a 6-fold increase in arrhythmia-free survival among those who achieved a stable weight loss of ≥10%.

Alcohol Consumption

Alcohol consumption and AF are well linked.[73,74] Alcohol intake can depress cardiac function, cause cardiac conduction abnormalities, and worsen interatrial electromechanical conduction delay.[75,76] In addition, alcohol consumption has been noted to increase both vagal activity and possible triggers for paroxysmal AF, indicating a potential vagally mediated mechanism of AF initiation.[77] In the Framingham population, those who consumed >3 drinks per day had a 34% increased risk of AF.[78] A study of Swedish men and women found a 39% higher independent risk of AF in those who drank >14 drinks per week.[79] A recent observation in Germany linked both acute alcohol intake (at Munich's Octoberfest) and chronic alcohol use (in the general community) with autonomic changes that may predispose to arrhythmia.[80] Limiting alcohol consumption could be important for preventing AF and reducing AF episodes.

Sleep Apnea

In otherwise healthy adults, obstructive sleep apnea (OSA) is found in 4% of women and 9% of men.[81] Hypopnea and apnea during sleep, causing cycles of hypoxia and then recovery, is associated with increased sympathetic output and parasympathetic withdrawal, elevated blood pressure, and activation of inflammatory mediators, which may be associated with atrial arrhythmia initiation.[82,83] In one study, 151 consecutive patients presenting for electrical cardioversion for AF were found to have more than twice the prevalence of OSA of 312 consecutive general cardiology patients without a history of AF.[84]

It has been noted that treatment of OSA facilitates AF therapy. There is a higher AF recurrence rate in OSA patients after electrical cardioversion,[85] a lower rate of response to anti-arrhythmic therapy,[86] and an increased recurrence AF risk in patients undergoing PVI.[87] Treatment continuous positive airway pressure (CPAP) has been shown to reduce AF recurrence after electrical cardioversion[85] and improves the success rate of pulmonary vein isolation in OSA patients.[88–90]

Risk Factor Modification

Targeting the numerous risk factors for AF could potentially reduce AF burden. This hypothesis was evaluated in a RCT of 150 overweight or obese patients who underwent aggressive risk factor management, either with or without concomitant intensive weight loss support.[91] The treatment group showed significantly more weight loss (14.3 kg vs. 3.6 kg, $p<0.001$) and a decrease in AF frequency and symptomatic severity. The Aggressive Risk Factor Reduction Study for Atrial Fibrillation (ARREST-AF)[92] was an observational study of patients with a BMI of at least 27 kg/m^2 and at least one other cardiovascular risk factor (hypertension, impaired glucose tolerance or DM, hyperlipidemia, OSA, smoking, or excessive alcohol intake). The intent was to evaluate the effect of weight loss and other risk factor modification on long-term outcomes after PVI. ARREST-AF evaluated 61 patients who participated in a risk factor management program and 88 patients who continued with routine standard care. Following catheter

ablation, all patients were evaluated every 3 to 6 months using a 7-day Holter monitor and a clinic visit. As seen in Figure 2, those in the risk factor management program had remarkably superior arrhythmia free survival following ablation (32.9% vs. 9.7%, *P*<0.001) and also after multiple ablations (87% vs. 17.8%, *P*<0.001). Risk factor modification was also associated with cardiac anatomical improvements such as reduction in left atrial volume, ventricular septal thickness, and left ventricular end diastolic diameter. Larger RCTs are needed to establish the potential benefit of aggressive risk factor modification programs for patients undergoing AF ablation.

AF Pathophysiology

AF is characterized by the absence of distinct P waves on the electrocardiogram, disorderly atrial electrical activity, and most often irregular R-R intervals.[49] The chaotic electrical activity of AF results in an absence of atrial contraction and induces further structural and electrical changes in the atria, which potentiate AF.[37,93] While there is no consensus as of yet regarding the overall electrophysiological, genetic and anatomical basis for the genesis of AF, it seems unlikely that a single mechanism is to blame. Rather, AF is the end product of multiple pathogenic pathways.[93,94]

A major breakthrough in our understanding and treatment AF was the identification of focal AF “triggers,” which usually are in the form of premature atrial depolarizations. The most common sources of these focal triggers are atrial myocytes making up muscle “sleeves” extending from the left atrium into the pulmonary veins (PV). Following transient ectopic tachycardias from PVs, the atrial electrical refractoriness is decreased, promoting AF initiation.[95] Repeated firing and progressive atrial remodeling then enable AF to sustain itself via reentry within atrial tissue with heterogeneous conduction.[96,97,98,99]

There are disparate views on how AF persists and maintains itself following the initiation of AF. The “multiple wavelet hypothesis” proposes that multiple independent reentrant wavelets exist, perpetuating the arrhythmia.[100,101] Other competing theories include focal activity within the ganglionic plexi (collections of autonomic tissue within the atrium) or untethered macro-reentrant circuits in the form of smaller spiral reentrant drivers, often termed “rotors.”[102,103] Likely one of these theories may predominate in a single patient, but all may contribute in some form and fashion in the maintenance in the storm that is AF.

Early in the disease process, when AF is transient (or “paroxysmal”), triggered activity is likely the predominant mechanism. It is often observed that if AF is allowed to persist, it becomes more difficult to treat (*i.e*., that “AF begets AF”).[37] In the later stages of AF, due to ongoing electroanatomical atrial remodeling, the more complex mechanisms contribute to AF persistence. This thought process governs the treatment process of patients with AF. In patients who have symptomatic paroxysmal AF, the focus of therapy is suppression of triggers, while the treatment of persistent AF includes substrate-based strategies.[49,103]

As previously discussed, established risk factors can predispose patients to AF. The promotion of AF is likely linked to structural and electrical remodeling of the atria. Atrial histological remodeling can result from increased left atrial pressure and size, which leads to connective tissue disorganization and interstitial fibrosis, increasing the patient’s susceptibility to AF.[104,105] These histologic alterations can slow atrial conduction velocity while increasing local heterogeneous conduction and conduction block.[40,106,107,108,109] As discussed previously, RAAS activation can contribute as well to adverse remodeling through its proinflammatory and profibrotic characteristics.[111,112,113]

As the atrial changes that promote AF continue, increased automaticity occurs as a result of altered calcium handling that occurs via calcium leak at the level of the sarcoplasmic reticulum, which may also affect conduction velocity and tissue refractoriness.[114,115] Atrial myocytes’ compensatory response to the increased

inward calcium current that results from frequent myocyte depolarization is to downregulate L-type calcium channels. However, these changes also cause shortening of action potential duration, further reducing atrial refractoriness and further promoting AF, embodying the notion that "AF begets AF."[116]

AF also is linked to inflammation.[117,118,119,120,121,122] Inflammatory markers, such as C-reactive protein (CRP) levels, are more elevated in patients with persistent AF than in those with paroxysmal AF.[123] Higher CRP levels predict AF relapse after cardioversion and are associated with increased embolic risk.[124]

Increased autonomic nervous system activity and age-associated structural fibrosis are also involved in AF initiation and maintenance.[125,126] As analyzed on Holter monitor recordings, initiation of AF often occurs following an increase in adrenergic (sympathetic) input, followed by an abrupt parasympathetic predominance immediately prior to the initiation of AF.[127]

The development of AF therefore results from myriad processes, including comorbidities that promote early atrial enlargement, atrial fibrosis causing conduction heterogeneity, inflammation, electrical remodeling, and autonomic remodeling.

Rate Control vs. Rhythm Control

The decision between the "rate control" or "rhythm control" strategies is a shared process between patients and their physicians. Atrioventricular nodal blockade (often with beta blockers, calcium channel blockers, and/or digitalis) is the basis for rate control, limiting the ventricular rate response to AF's atrial electrical chaos. All patients with incident AF should be first treated with a ventricular rate control strategy, if needed, while the decision making process commences regarding the subacute treatment strategy goal, in order to help prevent a tachycardia-mediated cardiomyopathy. Sustained rapid ventricular response can

induce significant CHF symptoms, even in the absence of overt left ventricular (LV) systolic dysfunction.[44,49,128]

The recommended target heart rate for the rate control strategy has developed over time. The randomized prospective trial RACE II found in 614 patients with permanent AF over at least a 2 year time period that a lenient rate control strategy (resting HR <110 bpm) is at least as effective as strict rate control (<80 bpm).[129] Those with lenient rate control had far fewer total clinical visits compared to those in the strict rate control group (75 vs. 684, p<0.001). However, the primary composite endpoint of death from cardiovascular causes, hospitalization for heart failure, stroke, systolic embolism, bleeding, and life threatening arrhythmic events was similar in the two groups.

After acute rate control is achieved, the decision is made whether to both restore and maintain sinus rhythm, termed “rhythm control,” or to continue with long-term rate control in the presence of continued atrial fibrillation. Rhythm control may utilize medical antiarrhythmic therapy, electrical cardioversion, and/or invasive catheter- or surgery-based procedures.[49,130,131,132] Patient-specific factors including stage of AF (*i.e*., paroxysmal, persistent, or permanent), symptoms, age, comorbidities, and, importantly, patient preference should be considered. Although there are no trial data to support which initial treatment strategy is superior, expert consensus seems to support that a trial of restoration of sinus rhythm should be offered at the first presentation of AF.[49,133] This approach offers early control of AF to patients with a potentially reversible cause of AF, or those with an isolated episode of AF. If AF does recur, patients will be in a better-informed position to decide whether to continue simple rate control, or to pursue a rhythm control strategy if there was symptomatic improvement while in sinus rhythm. Particularly suitable patients for the rhythm control strategy include young people, those with “lone” atrial fibrillation, and those with substantial symptoms even with effective control of the ventricular rate.[133]

Currently, the benefit of a rhythm control strategy with antiarrhythmic therapy, whether alone or in conjunction with electrical cardioversion and/or ablation, is recommended solely for symptom improvement and increase in quality of life.[49] No mortality benefit of pharmacological rhythm control has been established in randomized clinical trials, thus allowing limiting exposure to potential side effects of anti-arrhythmic drugs to those who are symptomatic. The Atrial Fibrillation Follow-up Investigation of Rhythm Management trial (AFFIRM) was the largest randomized trial comparing the rate- and rhythm-control strategies, and demonstrated similar all-cause mortality at five years (24 vs. 21%, p=0.08).[134] Some have argued that very symptomatic patients were likely underrepresented in AFFIRM, as those patients may not have been deemed appropriate for a rate control strategy. Others argue that the adverse drug effects and suboptimal efficacy of available antiarrhythmic therapy may have limited the benefit of rhythm control. In support of this argument, a post-hoc analysis of AFFIRM data demonstrated that rhythm restoration resulted in a gross mortality benefit, which was counteracted by an increase in mortality associated with antiarrhythmic use.[135] Even among patients with HF, no differences between treatment strategies were found in overall survival, cardiovascular death, worsened heart failure, or stroke.[136] In a separate study of patients randomized to a rate- or rhythm-control strategy for new-onset AF after cardiac surgery, there was no difference in death or other serious adverse events with a similar rate of freedom from AF on follow-up.[137] To date there have been no randomized trials of an invasive (*i.e.*, ablative) rhythm control strategy to assess its effect on mortality.

Medical Antiarrhythmic Therapy

Patients who are symptomatic from AF may have improved symptoms following the use of antiarrhythmic drugs (AADs) for maintenance of normal sinus rhythm. For those with AF-related cardiomyopathy, AADs may be used to reestablish normal rhythm and restore left ventricular function. AADs may also be helpful in facilitating electrical cardioversion after initially unsuccessful attempts. Generally,

AADs are not used for patients with asymptomatic AF or in those with permanent AF who have elected to forego a rhythm control strategy. AADs' use is often limited by contraindications to their use and by the emergence of adverse drug effects.[138,139,140]

As depicted in Figure 3, several important factors determine the available AAD choices. These factors include the presence or absence of structural heart disease and/or heart failure, renal function, and left ventricular hypertrophy.[138] Use of flecainide and propafenone, which belong to the Class 1C AAD grouping in the Vaughan-Williams drug classification, is limited to patients with structurally normal hearts (*i.e.*, normal left ventricular ejection fraction and LV wall thickness <1.5cm), and are contraindicated in patients with prior myocardial infarction.[138,141,142,143,144,145,146] The Class III agents, sotalol and dofetilide, are contraindicated in those with creatinine clearance below 20 mL/min or QTc interval greater than 440 milliseconds.[143,147–149] Initiation of dofetilide (or any dose increase) requires three days of inpatient monitoring of the QTc interval. Similar inpatient monitoring for sotalol is recommended as well, though not as strongly.[148,149] Dronedarone, another Class III agent, is contraindicated in patients with advanced heart failure or a recent heart failure exacerbation, or in those who have had amiodarone-related lung toxicity.[150–154] Amiodarone and dofetilide are the only antiarrhythmics available for use in the setting of LV systolic dysfunction.[138,149,155–157]

Due to its high efficacy, ability to be used in patients with renal insufficiency and cardiomyopathy, and available intravenous formulation, amiodarone remains in frequent use, despite its typically not being a first line drug.[155,158,159] The use of amiodarone is limited by its well-known potential toxicities including unfavorable effects in the lung, liver, thyroid, skin, and eyes, which requires monitoring (and potential drug discontinuation) during prolonged use.

Long-term AAD efficacy for maintaining sinus rhythm ranges from 30-50%, with amiodarone being the most effective.[138]

Stroke Prophylaxis and Bleeding Risk

Risk Stratification

The most feared complications of AF are stroke and systemic embolism, which carry significant morbidity and mortality.[160,161] AF increases the risk of stroke 5-fold.[161] Valvular AF (*i.e.*, AF related to mitral stenosis) may increase the risk of stroke 20-fold compared to a similar patient without valvular AF.

A patient's bleeding risk must be kept in mind when assessing stroke risk prior to administering anticoagulation. The most widely accepted tools for stroke risk stratification and bleeding risk stratification are the CHA_2DS_2-VASc and HASBLED scores, respectively (see Table 1).[162,163] In addition to the original $CHADS_2$ score, the CHA_2DS_2-VASc score includes as risk factors age ≥65 years, female sex, and vascular disease. The most recent AF guidelines advise oral anticoagulation in patients at high risk (*i.e.*, CHA_2DS_2-VASc ≥2). While moderate risk patients (CHA_2DS_2-VASc=1) can consider no therapy, aspirin, or anticoagulation, expert opinion favors anticoagulation. The use of anticoagulation for moderate risk patients is the current recommendation from the European Society of Cardiology.[164] For low risk patients (CHA_2DS_2-VASc=0), no antithrombotic therapy is recommended.[49] A HASBLED score of 3 or greater predicts high bleeding risk, but no guidelines exist concerning withholding anticoagulation therapy based on bleeding risk. A higher bleeding risk score alone should not result in the decision to withhold oral anticoagulation. Rather, these scores help to identify patients with increased bleeding risk and can guide the clinician to aggressively treat factors that might lower the bleeding risk (*e.g.*, blood pressure control).

In addition to these epidemiological prediction scores, other temporal and anatomical factors are important when considering stroke risk in AF. The

ASSERT trial reported a roughly 2-fold increase in stroke rate for patients with atrial high rate episodes lasting over 6 minutes as detected by and implanted cardiac device (pacemaker or defibrillator).[165] Also, higher complexity of the left atrial appendage's anatomy is associated with higher thrombotic stroke risk in AF.[166]

Warfarin and antiplatelet agents were the focus of early trials examining stroke prevention in AF. Aspirin alone provides no significant stroke reduction, with the SPAF-1 trial alone suggesting any significant benefit.[167,168] The antiplatelet drug clopidogrel was evaluated in conjunction with aspirin in the ACTIVE-A Trial, and showed no benefit in stroke risk reduction compared with aspirin alone, at a cost of increased bleeding events.[169] The ACTIVE-W trial compared clopidogrel and aspirin to warfarin and found a 40% risk reduction for stroke and systemic embolism with warfarin use compared to dual-antiplatelet therapy.[170] Although effective in reducing stroke rates, there are important limitations to the use of warfarin, such as the requirement for frequent INR monitoring, variable time in the therapeutic range (most often, INR 2-3), the required dietary constraints, and numerous drug-drug interactions.[171]

Non-Warfarin Oral Anticoagulants

Since 2010, four non-warfarin oral anticoagulants (also termed novel oral anticoagulants [NOACs] or, more recently, direct oral anticoagulants [DOACs]) have been approved for stroke and systemic embolism risk reduction in patients with non-valvular AF.[172–175] The major trials leading to FDA approval of each agent are summarized in Table 2.

The direct thrombin inhibitor, dabigatran (Pradaxa), was the first DOAC approved by the FDA. The 150 mg dose studied in the RE-LY trial demonstrated stroke risk reduction superiority compared to warfarin (HR 0.66, 95% CI 0.53-0.82), and was non-inferior for major bleeding (HR 0.93, 0.81-1.07).[172] Soon thereafter, a factor Xa inhibitor, rivaroxaban (Xarelto), showed non-inferiority for reduction of stroke

and systemic embolism (0.88, 0.75-1.03) as well as bleeding events (HR 1.04, 0.90-1.20) as compared to warfarin therapy.[173] Apixaban (Eliquis), another factor Xa inhibitor, is the only DOAC showing superiority over warfarin for both stroke risk reduction (HR 0.80, 0.67-0.95) and major bleeding (HR 0.69, 0.60-0.80).[174] Most recently, edoxaban (Savaysa) was compared to warfarin in The ENGAGE AF-TIMI 48 trial, and was non-inferior for reduction of strokes and systemic embolism (HR 0.88, 0.75-1.03) and superior regarding bleeding events (HR 0.80, 0.71-0.91).[175] All four DOACs significantly reduced intracranial hemorrhage compared with warfarin.

There are many factors to consider when choosing a DOAC. They have variable dependence on renal clearance, with some requiring specific dose adjustments. Only apixaban has been approved for those with end-stage renal disease, although this recommendation is based on pharmacokinetic and not trial data. On the other hand, edoxaban should not be used in patients with high kidney performance (GFR >90 ml/min), due to excessively brisk drug clearance. The most recent published AHA/ACC focused update on management of patient's with valvular heart disease (VHD) recommends warfarin therapy in the setting of AF and rheumatic mitral stenosis.[176] However, either DOACs or warfarin may be used with other native VHD (*e.g*. mitral regurgitation or aortic and tricuspid valve disease).[176] No specific recommendation is made for choice of anticoagulant in the setting of AF and a bioprosthetic heart valve, although the ARISTOTLE and ENGAGE AF-TIMI 48 trials included patients with prior valve repair or valvuloplasty, bioprosthetic valves, and native VHD, except for those who had moderate-severe mitral stenosis.[174,175] The only available study evaluating DOAC use in patients with mechanical heart valves, RE-ALIGN, showed *harm* in the dabigatran group.[177] To date, no trials have directly compared DOACs.

Dabigatran is currently the only DOAC with a commercially available reversal agent. Idarucizumab (Praxbind) is a monoclonal antibody fragment that binds free and thrombin-bound dabigatran neutralizing its anticoagulant activity.[178]

Other reversal agents under current investigation include andexanet, which reverses the anticoagulant effects of apixaban and rivaroxaban, and PER977/ciraparantag, a small molecule that reverses all DOACs and heparin agents.[179–181]

The major DOAC trials included patients with a range of average $CHADS_2$ scores, ranging from 2.1±1.1 in the RE-LY and ARISTOTLE trials to 3.5±0.9 in ROCKET-AF. Therefore, caution must be maintained when drawing conclusions about using these drugs in patients with much higher or much lower risk. Overall, the DOACs show favorable efficacy and safety profiles when compared with warfarin. However, warfarin does remain an effective option for many patients, and it remains the only oral anticoagulant approved for use in the setting of prosthetic heart valves.

Left Atrial Appendage Occlusion/Exclusion

Due to its dead-end anatomy and trabeculated inner surface, the left atrial appendage (LAA) is the most common site of intracardiac thrombus formation.[182,183] While OAC reduces thrombus formation risk, it does not completely eliminate stroke risk, and for some patients OAC is undesirable or frankly contraindicated. Because of these limitations, physical exclusion of the LAA in addition to, or as a replacement for, OAC has gained increased considerable interest.

Surgical LAA excision is frequently performed along with other cardiac surgery, whether the “main” procedure is solely targeted at AF treatment or is concomitant with other therapy (*e.g.*, valve repair/replacement).[184] Standalone LAA excision also has been studied, and has been shown to be safe and effective.[185] Newer technologies, such as the AtriClip external closure device, make surgical LAA closure technically easier and more effective.[186] To avoid the inherent disadvantage of invasiveness of a surgical procedure, percutaneous therapies for

LAA exclusion or occlusion have gained favor.[187] The most promising technologies are the intracardiac Watchman LAA occluder (Boston Scientific, Marlborough, MA) and the LARIAT system (SentreHEART Inc., Redwood City, CA), which closes the LAA orifice with a suture delivered via a subxiphoid epicardial approach. These devices are depicted in Figure 4.

The PROTECT-AF trial evaluated the efficacy of stroke risk reduction of the Watchman device compared with OAC in warfarin-eligible AF patients, and at first found LAA occlusion to be noninferior to OAC for stroke reduction (RR 0.71, 95% CI 0.44-1.3).[188,189] There were initial concerns about procedure-related adverse events. However, with experience these events became less frequent, likely related to a significant learning curve.[190] During continued follow-up, the Watchman device was shown to be better than warfarin for stroke risk reduction (HR 0.61, 95% CI 0.38-0.97) and similar regarding safety.[191] The PREVAIL trial and EWOLUTION registry subsequently confirmed Watchman's high implant success rate and acceptably low risk.[192,193] Currently, the Watchman device is FDA-approved for stroke prophylaxis in patients who are warfarin-eligible but for whom long-term OAC is unattractive.

The Watchman device has been shown to be superior to historical controls in patients ineligible for warfarin.[194,195] However, no randomized study has been performed evaluating Watchman and an inactive control.

The LARIAT suture/snare system is FDA-approved for soft tissue closure. It has been used off-label to close the LAA using an epicardial approach. LARIAT's potential advantage over Watchman is that it does not leave a device within the heart, potentially lessening the need for even short-term OAC. However, its weakness may be the higher rate of significant procedural complications and the incidence of incomplete LAA closure.[196] A 309-patient meta-analysis found a procedural success rate of 90%, with a 2.6% rate of severe complications.[197] Similar to the Watchman experience, the rates of successful implantation and

adverse events have shown a substantial learning curve trend.[198] A recent registry of 682 patients found complete LAA closure in 98%, with a severe adverse event rate of only 1.6%.[199] However, at follow-up, incomplete LAA closure was detected in 7% of examined patients.[199]

Currently, only warfarin has been used as the active control in comparison to LAA exclusion. Whether LAA closure maintains similar non-inferiority to DOACs, which appear to be safer than warfarin, remains to be seen.

Atrial Fibrillation Ablation

Catheter ablation of AF has evolved considerably to become safer and more successful over the past 10 years, and is now one of the most common cardiac procedures in the United States.[200]

The electrophysiological principles essential to AF include an inducing trigger paired with an underlying substrate which is required to sustain the arrhythmia.[200,201] As previously noted, the PVs are the most frequent areas where atrial ectopy triggering AF arise.[202,203] Myocardial “sleeves” extending from the PVs are the primary origin of these triggers in >80% of patients with paroxysmal AF.[204,205,206] Because of this common site of initiation, complete electrical isolation of the pulmonary veins (PVI) is usually the primary endpoint in catheter ablation of AF.[49,204,205,207]

During a PVI procedure, lesions are created encircling the antrum the pulmonary veins, which results in non-conducting scar, thereby electrically isolating the PV muscle sleeves and their triggers from the rest of the myocardium.[208] This is commonly performed either with delivery of radiofrequency energy via an ablation catheter delivering connecting circumferential lesions around the veins, or via cryo-injury with a cryoablation balloon-tipped catheter. The recent increase in ablation-based therapy as part of the rhythm control strategy has been driven

by clinical trials noting the superiority of catheter-based PVI over antiarrhythmic medical therapy in longterm maintenance of sinus rhythm.[209,210,211,212] Especially in patients with persistent AF, PVI often is supplemented with other ablation, including isolation of other veins (*e.g.*, the SVC), cavotricuspid isthmus ablation, and/or elimination of other non-PV triggers.

Selecting the appropriate patient for catheter based AF therapy is critical for maximizing success and minimizing procedural risk. Specific patient factors to consider include the severity and frequency of symptoms, tolerability of medical therapy, age, and underlying comorbidities.[200] The physician and patient both should understand the goals of care and procedural risks, and should have realistic expectations of procedural outcomes. While success rates of catheter ablation for AF have varied in clinical trials, the procedure can be very effective in individual patients.

Initial trials evaluated paroxysmal AF patients with minimal structural heart disease who had failed therapy with at least one antiarrhythmic drug. 12-month success rates ranged from 66% to 86%.[209,210,211,212] Clearly, AF ablation is more successful in patients with paroxysmal AF, which likely is related to the presence of less underlying abnormal substrate than in persistent AF patients.[213,214] However, many patients with paroxysmal AF will require repeat ablation procedures before there is durable success.[215,216]

In paroxysmal AF patients who have failed or are intolerant to anti-arrhythmic therapy, PVI currently has a Class I recommendation from the Heart Rhythm Society and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines for the Use of Catheter Ablation to Maintain Sinus Rhythm.[217] Table 3 summarizes the most recent guidelines for AF ablation. Despite the generally high levels of recommendation supporting ablation, it cannot be emphasized enough that the decision to proceed with PVI should be made on an individualized basis. The lower success rates of ablation in those

with more advanced AF and significant structural heart disease, and the frequent need for repeat procedures, resulted in Class IIa and IIb recommendations for ablation in patients with persistent AF and long standing (>12 months) persistent AF, respectively.[217] For example, recent success rates of maintaining sinus rhythm without antiarrhythmic therapy after PVI for paroxysmal AF are over 80% at one year. However, in patients with persistent AF, 40-50% of patients require a repeat procedure, after which the rate of long-term success can reach 70%.[218,219] Table 4 summarizes several RCTs examining efficacy of maintenance of sinus rhythm after PVI.

Currently, in general AF ablation should only be offered to appropriate patients with symptomatic AF, and only for the indication of enhancing quality of life.[200] Though AF is associated with an increased risk of stroke, heart failure, and death, it is currently unclear whether PVI reduces the long-term risk of these consequences;[34,220] Currently, multicenter RCTs are being conducted to assess whether PVI-based intervention early in the AF course can reduce mortality and stroke risk when compared to treatment with rate- and rhythm-control medication alone.[221,222]

In contrast to the conventional dogma that atrial fibrillation is disorganized electrical chaos, more recent evidence implicates arrhythmic maintenance due to sites of organized reentry, termed *rotors*.[201,223] There has been recent interest in identifying rotors in real time, allowing them to be ablation targets, in addition to conventional PVI, in order to potentially increase the therapeutic efficacy of an ablation strategy. This ablation strategy attempts to anatomically localize rotors using 3-d imaging guidance and a multipole “basket” catheter in the atria, and is termed Focal Impulse and Rotor Modulation (FIRM) ablation.[224] Early trials indicated that FIRM ablation plus PVI improved the procedural success rate of compared with standalone PVI.[224,225] Subsequently, however, the OASIS trial, a randomized trial in patients with persistent AF, indicated that FIRM ablation combined with PVI was associated with a *higher* rate of AF recurrence at follow-

up (mean of 12 ± 7 months) compared with more traditional approach, which in this study included PVI with left atrial posterior wall and non-pulmonary vein trigger ablation.[226] However the publishing editor retracted the publication, due to concerns about the randomization process and early enrollment of patients. Nevertheless, ongoing randomized trials assessing the short- and long-term efficacy of FIRM ablation in combination with PVI are eagerly anticipated.

Surgical and Hybrid Approaches to AF Treatment

For AF patients undergoing open chest cardiac surgery for other indications (*e.g.*, valve repair/replacement or coronary bypass surgery), surgical AF treatment should be considered. Surgical AF therapy employs strategic creation of scar lines in order to "debulk" the atrial substrate and prevent AF wavelet propagation.[223] The initial technique, termed the Cox Maze procedure, was developed in the 1980s and involved directly cutting the atria and sewing them back together, in order to form electrically inert scar lines.[227] Currently, more often surgical radiofrequency energy and/or cryoablation techniques are employed to create scar.[227] Due to the invasive nature of the procedure and and its accompanying morbidity, today stand-alone open surgical PVI is infrequently recommended.[217]

A more recent team-based ablation strategy, combining both a minimally invasive surgical approach with a subsequent percutaneous endocardial ablation, has evolved, often termed the "hybrid" or "convergent" procedure.[228] This strategy is thought to offer the "best of both worlds," combining the high efficacy of transmural linear ablation lesions via surgical visualization with the percutaneous catheter-based procedure (performed immediately following surgery or later in a "staged" fashion) of an electrophysiologist, who can confirm PV isolation and/or deliver supplementary endocardial lesions if needed. Reports of individual centers' experience indicate very high success rates in freedom from AF during long-term follow-up in both paroxysmal and persistent AF.[229,230]

Conclusion

Atrial fibrillation continues to expand its status as a global epidemic, with increasing prevalence and clinical importance. To date there remains no definite cure, and our ability to treat symptomatic patients remains suboptimal. Due to the growing recognition of its untoward impact on morbidity and mortality, there is more incentive for physicians and scientists to more closely investigate the underlying mechanisms of AF. Over time, an improved understanding of the epidemiology and underlying pathophysiology of AF will result in further advances in the prevention and therapy of AF.

References

1. Lewis T. REPORT CXIX. AURICULAR FIBRILLATION: A COMMON CLINICAL CONDITION. *Br Med J*. 1909;2(2552):1528. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2321318&tool=pmcentrez&rendertype=abstract. Accessed December 23, 2015.
2. Rothberger C, Winterberg H. Vorhoffummern und Arhythmia Perpetua. *Wien Klin Wochenschr*. 1909;22:839-844.
3. Marijon E, Le Heuzey J-Y, Connolly S, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation*. 2013;128(20):2192-2201. doi:10.1161/CIRCULATIONAHA.112.000491.
4. Thrall G, Lane D, Carroll D, Lip GYH. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119(5):448.e1-19. doi:10.1016/j.amjmed.2005.10.057.
5. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129(8):837-847. doi:10.1161/CIRCULATIONAHA.113.005119.
6. Dilaveris PE, Kennedy HL. Silent atrial fibrillation: epidemiology, diagnosis, and clinical impact. *Clin Cardiol*. March 2017. doi:10.1002/clc.22667.
7. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112(8):1142-1147. doi:10.1016/j.amjcard.2013.05.063.
8. Stewart S, Murphy NF, Murphy N, Walker A, McGuire A, McMurray JJ V. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart*. 2004;90(3):286-292.

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1768125&tool=pmcentrez&rendertype=abstract. Accessed December 23, 2015.

9. Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes*. 2011;4(3):313-320. doi:10.1161/CIRCOUTCOMES.110.958165.
10. Lee WC, Lamas GA, Balu S, Spalding J, Wang Q, Pashos CL. Direct treatment cost of atrial fibrillation in the elderly American population: a Medicare perspective. *J Med Econ*. 2008;11(2):281-298. doi:10.3111/13696990802063425.
11. Brüggenjürgen B, Rossnagel K, Roll S, et al. The impact of atrial fibrillation on the cost of stroke: the berlin acute stroke study. *Value Health*. 10(2):137-143. doi:10.1111/j.1524-4733.2006.00160.x.
12. Blomstrom Lundqvist C, Lip GYH, Kirchhof P. What are the costs of atrial fibrillation? *Europace*. 2011;13 Suppl 2:ii9-12. doi:10.1093/europace/eur087.
13. Sheikh A, Patel NJ, Nalluri N, et al. Trends in Hospitalization for Atrial Fibrillation: Epidemiology, Cost, and Implications for the Future. *Prog Cardiovasc Dis*. 58(2):105-116. doi:10.1016/j.pcad.2015.07.002.
14. 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. http://www.ncbi.nlm.nih.gov/pubmed/8114238. Accessed December 23, 2015.
15. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am*. 2008;92(1):17-40, ix. doi:10.1016/j.mcna.2007.09.002.
16. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110(9):1042-1046. doi:10.1161/01.CIR.0000140263.20897.42.
17. Heeringa J, van der Kuip DAM, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27(8):949-953. doi:10.1093/eurheartj/ehi825.
18. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. *Circulation*. 2013;128(23):2470-2477. doi:10.1161/CIRCULATIONAHA.113.002449.
19. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;158(1):111-117. doi:10.1016/j.ahj.2009.05.010.
20. Amponsah MKD, Benjamin EJ, Magnani JW. Atrial Fibrillation and Race - A Contemporary Review. *Curr Cardiovasc Risk Rep*. 2013;7(5). doi:10.1007/s12170-013-0327-8.
21. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96(7):2455-2461. http://www.ncbi.nlm.nih.gov/pubmed/9337224. Accessed November 17, 2015.

22. Hernandez MB, Asher CR, Hernandez A V, Novaro GM. African american race and prevalence of atrial fibrillation:a meta-analysis. *Cardiol Res Pract*. 2012;2012:275624. doi:10.1155/2012/275624.
23. Marcus GM, Alonso A, Peralta CA, et al. European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation*. 2010;122(20):2009-2015. doi:10.1161/CIRCULATIONAHA.110.958306.
24. Humphries KH, Kerr CR, Connolly SJ, et al. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. *Circulation*. 2001;103(19):2365-2370. http://www.ncbi.nlm.nih.gov/pubmed/11352885. Accessed December 23, 2015.
25. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes*. 2012;5(1):85-93. doi:10.1161/CIRCOUTCOMES.111.962688.
26. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA*. 2003;290(8):1049-1056. doi:10.1001/jama.290.8.1049.
27. Friberg J, Scharling H, Gadsbøll N, Truelsen T, Jensen GB. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol*. 2004;94(7):889-894. doi:10.1016/j.amjcard.2004.06.023.
28. Menezes AR, Lavie CJ, De Schutter A, et al. Lifestyle modification in the prevention and treatment of atrial fibrillation. *Prog Cardiovasc Dis*. 58(2):117-125. doi:10.1016/j.pcad.2015.07.001.
29. Morin DP, Bernard ML, Madias C, Rogers PA, Thihalolipavan S, Estes NAM. The State of the Art: Atrial Fibrillation Epidemiology, Prevention, and Treatment. *Mayo Clin Proc*. 2016;91(12):1778-1810. doi:10.1016/j.mayocp.2016.08.022.
30. Thihalolipavan S, Morin DP. Atrial fibrillation and heart failure: update 2015. *Prog Cardiovasc Dis*. 58(2):126-135. doi:10.1016/j.pcad.2015.07.004.
31. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113(5):359-364.
32. Chiang C-E, Naditch-Brûlé L, Murin J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythm Electrophysiol*. 2012;5(4):632-639. doi:10.1161/CIRCEP.112.970749.
33. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003;91(6A):2D-8D. http://www.ncbi.nlm.nih.gov/pubmed/12670636. Accessed March 5, 2016.
34. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the

Framingham Heart Study. *Circulation*. 2003;107(23):2920-2925. doi:10.1161/01.CIR.0000072767.89944.6E.

35. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail*. 2009;11(7):676-683. doi:10.1093/eurjhf/hfp085.
36. Nattel S. Ionic determinants of atrial fibrillation and Ca2+ channel abnormalities : cause, consequence, or innocent bystander? *Circ Res*. 1999;85(5):473-476. http://www.ncbi.nlm.nih.gov/pubmed/10473677. Accessed March 5, 2016.
37. 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. http://www.ncbi.nlm.nih.gov/pubmed/7671380. Accessed March 5, 2016.
38. Van den Berg MP, Tuinenburg AE, Crijns HJ, Van Gelder IC, Gosselink AT, Lie KI. Heart failure and atrial fibrillation: current concepts and controversies. *Heart*. 1997;77(4):309-313. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=484722&tool=pmcentrez&rendertype=abstract. Accessed March 5, 2016.
39. Tomaselli GF, Marbán E. Electrophysiological remodeling in hypertrophy and heart failure. *Cardiovasc Res*. 1999;42(2):270-283. http://www.ncbi.nlm.nih.gov/pubmed/10533566. Accessed March 5, 2016.
40. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation*. 1999;100(1):87-95. http://www.ncbi.nlm.nih.gov/pubmed/10393686. Accessed March 5, 2016.
41. Chen Y-J, Chen Y-C, Tai C-T, Yeh H-I, Lin C-I, Chen S-A. Angiotensin II and angiotensin II receptor blocker modulate the arrhythmogenic activity of pulmonary veins. *Br J Pharmacol*. 2006;147(1):12-22. doi:10.1038/sj.bjp.0706445.
42. Dixen U, Ravn L, Soeby-Rasmussen C, et al. Raised plasma aldosterone and natriuretic peptides in atrial fibrillation. *Cardiology*. 2007;108(1):35-39. doi:10.1159/000095671.
43. Fenelon G, Wijns W, Andries E, Brugada P. Tachycardiomyopathy: mechanisms and clinical implications. *Pacing Clin Electrophysiol*. 1996;19(1):95-106. http://www.ncbi.nlm.nih.gov/pubmed/8848384. Accessed March 5, 2016.
44. Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *J Am Coll Cardiol*. 1997;29(4):709-715. http://www.ncbi.nlm.nih.gov/pubmed/9091514. Accessed March 5, 2016.
45. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation*. 2009;119(16):2146-2152. doi:10.1161/CIRCULATIONAHA.108.830042.
46. Grundvold I, Skretteberg PT, Liestøl K, et al. Upper normal blood

pressures predict incident atrial fibrillation in healthy middle-aged men: a 35-year follow-up study. *Hypertension*. 2012;59(2):198-204. doi:10.1161/HYPERTENSIONAHA.111.179713.

47. Lau Y-F, Yiu K-H, Siu C-W, Tse H-F. Hypertension and atrial fibrillation: epidemiology, pathophysiology and therapeutic implications. *J Hum Hypertens*. 2012;26(10):563-569. doi:10.1038/jhh.2011.105.
48. Chen LY, Bigger JT, Hickey KT, et al. Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation and P-Wave Indices in the ACCORD Blood Pressure Trial. *Am J Hypertens*. October 2015. doi:10.1093/ajh/hpv172.
49. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2014;64(21):e1-e76. doi:10.1016/j.jacc.2014.03.022.
50. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol*. 2005;45(5):712-719. doi:10.1016/j.jacc.2004.10.068.
51. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens*. 2008;26(3):403-411. doi:10.1097/HJH.0b013e3282f35c67.
52. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol*. 2005;45(11):1832-1839. doi:10.1016/j.jacc.2004.11.070.
53. Marott SCW, Nielsen SF, Benn M, Nordestgaard BG. Antihypertensive treatment and risk of atrial fibrillation: a nationwide study. *Eur Heart J*. 2014;35(18):1205-1214. doi:10.1093/eurheartj/eht507.
54. Pan G, Zhou X, Zhao J. Effect of telmisartan on atrial fibrillation recurrences in patients with hypertension: a systematic review and meta-analysis. *Cardiovasc Ther*. 2014;32(4):184-188. doi:10.1111/1755-5922.12073.
55. Pallisgaard JL, Lindhardt TB, Olesen JB, Hansen ML, Carlson N, Gislason GH. Management and prognosis of atrial fibrillation in the diabetic patient. *Expert Rev Cardiovasc Ther*. 2015;13(6):643-651. doi:10.1586/14779072.2015.1043892.
56. De Sensi F, De Potter T, Cresti A, Severi S, Breithardt G. Atrial fibrillation in patients with diabetes: molecular mechanisms and therapeutic perspectives. *Cardiovasc Diagn Ther*. 2015;5(5):364-373. doi:10.3978/j.issn.2223-3652.2015.06.03.
57. Aksnes TA, Schmieder RE, Kjeldsen SE, Ghani S, Hua TA, Julius S. Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial). *Am J Cardiol*. 2008;101(5):634-638. doi:10.1016/j.amjcard.2007.10.025.
58. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and

case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *Am J Cardiol*. 2011;108(1):56-62. doi:10.1016/j.amjcard.2011.03.004.
59. Cariou B, Charbonnel B, Staels B. Thiazolidinediones and PPARγ agonists: time for a reassessment. *Trends Endocrinol Metab*. 2012;23(5):205-215. doi:10.1016/j.tem.2012.03.001.
60. Chao T-F, Leu H-B, Huang C-C, et al. Thiazolidinediones can prevent new onset atrial fibrillation in patients with non-insulin dependent diabetes. *Int J Cardiol*. 2012;156(2):199-202. doi:10.1016/j.ijcard.2011.08.081.
61. Gu J, Liu X, Wang X, et al. Beneficial effect of pioglitazone on the outcome of catheter ablation in patients with paroxysmal atrial fibrillation and type 2 diabetes mellitus. *Europace*. 2011;13(9):1256-1261. doi:10.1093/europace/eur131.
62. Wilson LD, Tsai C-T. Heart failure-related atrial fibrillation: a new model for a new prevention strategy? *Heart Rhythm*. 2008;5(3):460-461. doi:10.1016/j.hrthm.2008.01.002.
63. Yatsuya H, Li Y, Hilawe EH, et al. Global trend in overweight and obesity and its association with cardiovascular disease incidence. *Circ J*. 2014;78(12):2807-2818. http://www.ncbi.nlm.nih.gov/pubmed/25391910. Accessed December 23, 2015.
64. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size. The Framingham Heart Study. *Hypertension*. 1995;25(6):1155-1160. http://www.ncbi.nlm.nih.gov/pubmed/7768556. Accessed December 23, 2015.
65. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A*. 2000;97(4):1784-1789. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=26513&tool=pmcentrez&rendertype=abstract. Accessed December 5, 2015.
66. Pelat M, Verwaerde P, Merial C, et al. Impaired atrial M(2)-cholinoceptor function in obesity-related hypertension. *Hypertension*. 1999;34(5):1066-1072. http://www.ncbi.nlm.nih.gov/pubmed/10567183. Accessed December 23, 2015.
67. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292(20):2471-2477. doi:10.1001/jama.292.20.2471.
68. Tedrow UB, Conen D, Ridker PM, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). *J Am Coll Cardiol*. 2010;55(21):2319-2327. doi:10.1016/j.jacc.2010.02.029.
69. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123(14):1501-1508. doi:10.1161/CIRCULATIONAHA.110.009035.
70. Knuiman M, Briffa T, Divitini M, et al. A cohort study examination of established and emerging risk factors for atrial fibrillation: the Busselton Health Study. *Eur J Epidemiol*. 2014;29(3):181-190. doi:10.1007/s10654-

013-9875-y.
71. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: The Danish Diet, Cancer, and Health Study. *Am J Med*. 2005;118(5):489-495. doi:10.1016/j.amjmed.2005.01.031.
72. Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol*. 2015;65(20):2159-2169. doi:10.1016/j.jacc.2015.03.002.
73. Menz V, Grimm W, Hoffmann J, Maisch B. Alcohol and rhythm disturbance: the holiday heart syndrome. *Herz*. 1996;21(4):227-231. http://www.ncbi.nlm.nih.gov/pubmed/8805002. Accessed December 23, 2015.
74. Lowenstein SR, Gabow PA, Cramer J, Oliva PB, Ratner K. The role of alcohol in new-onset atrial fibrillation. *Arch Intern Med*. 1983;143(10):1882-1885. http://www.ncbi.nlm.nih.gov/pubmed/6625772. Accessed December 23, 2015.
75. Ettinger PO, Wu CF, De La Cruz C, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the “Holiday Heart”: alcohol-associated cardiac rhythm disorders. *Am Heart J*. 1978;95(5):555-562. http://www.ncbi.nlm.nih.gov/pubmed/636996. Accessed December 23, 2015.
76. Sengul C, Cevik C, Ozveren O, et al. Acute alcohol consumption is associated with increased interatrial electromechanical delay in healthy men. *Cardiol J*. 2011;18(6):682-686. http://www.ncbi.nlm.nih.gov/pubmed/22113757. Accessed December 23, 2015.
77. Mandyam MC, Vedantham V, Scheinman MM, et al. Alcohol and vagal tone as triggers for paroxysmal atrial fibrillation. *Am J Cardiol*. 2012;110(3):364-368. doi:10.1016/j.amjcard.2012.03.033.
78. Djoussé L, Levy D, Benjamin EJ, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. *Am J Cardiol*. 2004;93(6):710-713. doi:10.1016/j.amjcard.2003.12.004.
79. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol*. 2014;64(3):281-289. doi:10.1016/j.jacc.2014.03.048.
80. Brunner S, Herbel R, Drobesch C, et al. Alcohol consumption, sinus tachycardia, and cardiac arrhythmias at the Munich Octoberfest: results from the Munich Beer Related Electrocardiogram Workup Study (MunichBREW). *Eur Heart J*. April 2017. doi:10.1093/eurheartj/ehx156.
81. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328(17):1230-1235. doi:10.1056/NEJM199304293281704.
82. Bradley TD. Sleep Apnea and Heart Failure: Part II: Central Sleep Apnea. *Circulation*. 2003;107(13):1822-1826. doi:10.1161/01.CIR.0000061758.05044.64.

83. Bradley TD, Floras JS. Sleep apnea and heart failure: Part I: obstructive sleep apnea. *Circulation*. 2003;107(12):1671-1678. doi:10.1161/01.CIR.0000061757.12581.15.
84. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004;110(4):364-367. doi:10.1161/01.CIR.0000136587.68725.8E.
85. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation*. 2003;107(20):2589-2594. doi:10.1161/01.CIR.0000068337.25994.21.
86. Monahan K, Brewster J, Wang L, et al. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. *Am J Cardiol*. 2012;110(3):369-372. doi:10.1016/j.amjcard.2012.03.037.
87. Sauer WH, McKernan ML, Lin D, Gerstenfeld EP, Callans DJ, Marchlinski FE. Clinical predictors and outcomes associated with acute return of pulmonary vein conduction during pulmonary vein isolation for treatment of atrial fibrillation. *Heart Rhythm*. 2006;3(9):1024-1028. doi:10.1016/j.hrthm.2006.05.007.
88. Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm*. 2013;10(3):331-337. doi:10.1016/j.hrthm.2012.11.015.
89. Fein AS, Shvilkin A, Shah D, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol*. 2013;62(4):300-305. doi:10.1016/j.jacc.2013.03.052.
90. Patel D, Mohanty P, Di Biase L, et al. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. *Circ Arrhythm Electrophysiol*. 2010;3(5):445-451. doi:10.1161/CIRCEP.109.858381.
91. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. 2013;310(19):2050-2060. doi:10.1001/jama.2013.280521.
92. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64(21):2222-2231. doi:10.1016/j.jacc.2014.09.028.
93. Everett TH, Olgin JE. Atrial fibrosis and the mechanisms of atrial fibrillation. *Hear Rhythm*. 2007;4(3 SUPPL.). doi:10.1016/j.hrthm.2006.12.040.
94. Wakili R, Voigt N, Kaab S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. *J Clin Invest*. 2011;121(8):2955-2968. doi:10.1172/JCI46315; 10.1172/JCI46315.
95. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: Electrophysiological and electroanatomic mapping in humans. *Circulation*. 2003;108(12):1461-1468.

doi:10.1161/01.CIR.0000090688.49283.67.
96. Frustaci A, Chimente C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological Substrate of Atrial Biopsies in Patients With Lone Atrial Fibrillation. *Circulation*. 1997;96(4):1180-1184. doi:10.1161/01.CIR.96.4.1180.
97. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res*. 2002;54(2):230-246. doi:10.1016/S0008-6363(02)00258-4.
98. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a Risk Factor for Atrial Fibrillation. *Circulation*. 2003;108(24):3006-3010. doi:10.1161/01.CIR.0000103131.70301.4F.
99. Burstein B, Nattel S. Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation. *J Am Coll Cardiol*. 2008;51(8):802-809. doi:10.1016/j.jacc.2007.09.064.
100. Moe GK, Rheinboldt WC, Abildskov J. A computer model of atrial fibrillation. *Am Heart J*. 1964;67(2):200-220. doi:10.1016/0002-8703(64)90371-0.
101. Valderrábano M. Atrial fibrillation: the mother rotor and its rebellious offspring take turns sustaining the family. *Heart Rhythm*. 2009;6(7):1018-1019. doi:10.1016/j.hrthm.2009.04.019.
102. Narayan SM, Patel J, Mulpuru S, Krummen DE. Focal impulse and rotor modulation ablation of sustaining rotors abruptly terminates persistent atrial fibrillation to sinus rhythm with elimination on follow-up: A video case study. *Hear Rhythm*. 2012;9(9):1436-1439. doi:10.1016/j.hrthm.2012.03.055.
103. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation with or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol*. 2012;60(7):628-636. doi:10.1016/j.jacc.2012.05.022.
104. Verheule S, Wilson E, Everett T, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. *Circulation*. 2003;107(20):2615-2622. doi:10.1161/01.CIR.0000066915.15187.51.
105. Healey JS, Connolly SJ. Atrial fibrillation: Hypertension as a causative agent, risk factor for complications, and potential therapeutic target. *Am J Cardiol*. 2003;91(10 SUPPL. 1). doi:10.1016/S0002-9149(03)00227-3.
106. Li D, Melnyk P, Feng J, et al. Effects of experimental heart failure on atrial cellular and ionic electrophysiology. *Circulation*. 2000;101(22):2631-2638. doi:10.1161/01.CIR.101.22.2631.
107. Boyden PA, Tilley LP, Pham TD, Liu SK, Fenoglio JJ, Wit AL. Effects of left atrial enlargement on atrial transmembrane potentials and structure in dogs with mitral valve fibrosis. *Am J Cardiol*. 1982;49(8):1896-1908. doi:10.1016/0002-9149(82)90208-9.
108. Boyden P a, Tilley LP, Albala a, Liu SK, Fenoglio JJ, Wit a L. Mechanisms for atrial arrhythmias associated with cardiomyopathy: a study of feline hearts with primary myocardial disease. *Circulation*. 1984;69(5):1036-1047.

doi:10.1161/01.CIR.69.5.1036.
109. Ohtani K, Yutani C, Nagata S, Koretsune Y, Hori M, Kamada T. High prevalence of atrial fibrosis in patients with dilated cardiomyopathy. *J Am Coll Cardiol*. 1995;25(5):1162-1169. doi:10.1016/0735-1097(94)00529-Y.
110. Reil JC, Hohl M, Selejan S, et al. Aldosterone promotes atrial fibrillation. *Eur Heart J*. 2012;33(16):2098-2108. doi:10.1093/eurheartj/ehr266.
111. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation*. 2001;104(21):2608-2614. http://www.ncbi.nlm.nih.gov/pubmed/11714658. Accessed March 5, 2016.
112. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: Insight from the studies of left ventricular dysfunction (SOLVD) trials. *Circulation*. 2003;107(23):2926-2931. doi:10.1161/01.CIR.0000072793.81076.D4.
113. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation*. 1999;100:376-380. doi:10.1161/01.CIR.100.4.376.
114. Ohkusa T, Ueyama T, Yamada J, et al. Alterations in cardiac sarcoplasmic reticulum Ca2+ regulatory proteins in the atrial tissue of patients with chronic atrial fibrillation. *J Am Coll Cardiol*. 1999;34(1):255-263.
115. Nattel S, Dobrev D. The multidimensional role of calcium in atrial fibrillation pathophysiology: Mechanistic insights and therapeutic opportunities. *Eur Heart J*. 2012;33(15). doi:10.1093/eurheartj/ehs079.
116. Singh B. Atrial fibrillation: from ion channels to bedside treatment options. *J Electrocardiol*. 2009;42(6):660-670. doi:10.1016/j.jelectrocard.2009.04.002.
117. Boos CJ, Anderson RA, Lip GYH. Is atrial fibrillation an inflammatory disorder? *Eur Heart J*. 2006;27(2):136-149. doi:10.1093/eurheartj/ehi645.
118. Boos CJ, Lip GYH. Inflammation and atrial fibrillation: cause or effect? *Heart*. 2008;94(2):133-134. doi:10.1136/hrt.2007.119651.
119. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*. 2001;104(24):2886-2891. doi:10.1161/hc4901.101760.
120. Dernellis J, Panaretou M. C-reactive protein and paroxysmal atrial fibrillation: evidence of the implication of an inflammatory process in paroxysmal atrial fibrillation. *Acta Cardiol*. 2001;56(6):375-380. doi:10.2143/AC.56.6.2005701.
121. Asselbergs FW, Van Den Berg MP, Diercks GFH, Van Gilst WH, Van Veldhuisen DJ. C-reactive protein and microalbuminuria are associated with atrial fibrillation. *Int J Cardiol*. 2005;98(1):73-77. doi:10.1016/j.ijcard.2003.12.028.
122. Sata N, Hamada N, Horinouchi T, et al. C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation?

Jpn Heart J. 2004;45(3):441-445.
123. Anderson JL, Allen Maycock CA, Lapp?? DL, et al. Frequency of elevation of C-reactive protein in atrial fibrillation. *Am J Cardiol*. 2004;94(10):1255-1259. doi:10.1016/j.amjcard.2004.07.108.
124. Conway DSG, Buggins P, Hughes E, Lip GYH. Predictive value of indexes of inflammation and hypercoagulability on success of cardioversion of persistent atrial fibrillation. *Am J Cardiol*. 2004;94(4):508-510. doi:10.1016/j.amjcard.2004.04.070.
125. Coumel P, Attuel P, Lavallée J, Flammang D, Leclercq JF, Slama R. [The atrial arrhythmia syndrome of vagal origin]. *Arch Mal Coeur Vaiss*. 1978;71(6):645-656.
126. Kistler PM, Sanders P, Fynn SP, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol*. 2004;44(1):109-116. doi:10.1016/j.jacc.2004.03.044.
127. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation*. 2002;105(23):2753-2759. doi:10.1161/01.CIR.0000018443.44005.D8.
128. Phillips E, Levine SA. Auricular fibrillation without other evidence of heart disease. *Am J Med*. 1949;7(4):478-489. doi:10.1016/0002-9343(49)90397-6.
129. Van Gelder IC, Groenveld HF, Crijns HJGM, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362(15):1363-1373. doi:10.1056/NEJMoa1001337.
130. Wilton SB, Fundytus A, Ghali W a, et al. Meta-analysis of the effectiveness and safety of catheter ablation of atrial fibrillation in patients with versus without left ventricular systolic dysfunction. *Am J Cardiol*. 2010;106(9):1284-1291. doi:10.1016/j.amjcard.2010.06.053.
131. Lee AM, Melby SJ, Damiano RJ. The surgical treatment of atrial fibrillation. *Surg Clin North Am*. 2009;89(4):1001-20, x-xi. doi:10.1016/j.suc.2009.06.001.
132. Calkins H, Brugada J, Packer DL, et al. 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 . *Europace*. 2007;9(6):335-379. doi:10.1093/europace/eum120.
133. Waldo AL. Rate Control versus Rhythm Control in Atrial Fibrillation: Lessons Learned from Clinical Trials of Atrial Fibrillation. *Prog Cardiovasc Dis*. 2015;58(2):168-176. doi:10.1016/j.pcad.2015.08.006.
134. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347(23):1834-1840. doi:10.1056/NEJMoa021375.
135. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 2004;109(12):1509-1513. doi:10.1161/01.CIR.0000121736.16643.11.
136. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for

atrial fibrillation and heart failure. *N Engl J Med*. 2008;358(25):2667-2677. doi:10.1056/NEJMoa0708789.
137. Gillinov AM, Bagiella E, Moskowitz AJ, et al. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. *N Engl J Med*. April 2016. doi:10.1056/NEJMoa1602002.
138. Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane database Syst Rev*. 2015;3:CD005049. doi:10.1002/14651858.CD005049.pub4.
139. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace*. 2011;13(3):329-345. doi:10.1093/europace/euq450.
140. Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. *Circulation*. 2012;125(2):381-389. doi:10.1161/CIRCULATIONAHA.111.019927.
141. Van Gelder IC, Crijns HJGM, Van Gilst WH, Van Wijk LM, Hamer HPM, Lie KI. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. *Am J Cardiol*. 1989;64(19):1317-1321. doi:10.1016/0002-9149(89)90574-2.
142. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342(13):913-920. doi:10.1097/00132586-200012000-00040.
143. Bellandi F, Simonetti I, Leoncini M, et al. Long-term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. *Am J Cardiol*. 2001;88(6):640-645. doi:10.1016/S0002-9149(01)01806-9.
144. Dogan A, Ergene O, Nazli C, et al. Efficacy of propafenone for maintaining sinus rhythm in patients with recent onset or persistent atrial fibrillation after conversion: A randomized, placebo-controlled study. *Acta Cardiol*. 2004;59(3):255-261. doi:10.2143/AC.59.3.2005179.
145. Pritchett ELC, Page RL, Carlson M, Undesser K, Fava G. Efficacy and safety of sustained-release propafenone (propafenone SR) for patients with atrial fibrillation. *Am J Cardiol*. 2003;92(8):941-946. doi:10.1016/S0002-9149(03)00974-3.
146. Echt DS, Liebson PR, Mitchell LB, et al. *Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo. The Cardiac Arrhythmia Suppression Trial.* Vol 324.; 1991. doi:10.1056/NEJM199103213241201.
147. Benditt DG, Williams JH, Jin J, et al. Maintenance of sinus rhythm with oral d,l-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. *Am J Cardiol*. 1999;84(3):270-277. doi:10.1016/S0002-9149(99)00275-1.
148. Singh S, Zoble RG, Yellen L, et al. Efficacy and Safety of Oral Dofetilide in Converting to and Maintaining Sinus Rhythm in Patients With Chronic Atrial Fibrillation or Atrial Flutter : The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study. *Circulation*. 2000;102(19):2385-

2390. doi:10.1161/01.CIR.102.19.2385.
149. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of Dofetilide in the Treatment of Atrial Fibrillation-Flutter in Patients With Reduced Left Ventricular Function: A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Substudy. *Circulation*. 2001;104(3):292-296. doi:10.1161/01.CIR.104.3.292.
150. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in High-Risk Permanent Atrial Fibrillation. *N Engl J Med*. 2011;365(24):2268-2276. doi:10.1056/NEJMoa1109867.
151. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358(25):2678-2687. doi:358/25/2678 [pii]\r10.1056/NEJMoa0800456.
152. Hohnloser SH, Crijns HJGM, van Eickels M, et al. Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation — NEJM. *N Engl J Med*. 2009;360:668-678.
153. Singh BN, Connolly SJ, Crijns HJGM, et al. Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter. *N Engl J Med*. 2007;357(10):987-999. doi:10.1056/NEJMoa054686.
154. Touboul P. Dronedarone for prevention of atrial fibrillation: A dose-ranging study. *Eur Heart J*. 2003;24(16):1481-1487. doi:10.1016/S0195-668X(03)00321-X.
155. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus Sotalol for Atrial Fibrillation. *N Engl J Med*. 2005;352(18):1861-1872. doi:10.1056/NEJMoa041705.
156. Channer KS, Birchall A, Steeds RP, et al. A randomized placebo-controlled trial of pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC cardioversion for persistent atrial fibrillation. *Eur Heart J*. 2004;25(2):144-150. doi:10.1016/j.ehj.2003.10.020.
157. Galperín J, Elizari M V, Chiale PA, et al. Efficacy of amiodarone for the termination of chronic atrial fibrillation and maintenance of normal sinus rhythm: a prospective, multicenter, randomized, controlled, double blind trial. *J Cardiovasc Pharmacol Ther*. 2001;6(4):341-350.
158. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf RM, Kong DF. Comparative Efficacy of Dronedarone and Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2009;54(12):1089-1095. doi:10.1016/j.jacc.2009.04.085.
159. Greene HL. Maintenance of sinus rhythm in patients with atrial fibrillation: An AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol*. 2003;42(1):20-29. doi:10.1016/S0735-1097(03)00559-X.
160. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988. doi:10.1161/01.STR.22.8.983.
161. Lin HJ, Wolf P a, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27(10):1760-1764. doi:10.1161/01.STR.27.10.1760.
162. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical

risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137(2):263-272. doi:10.1378/chest.09-1584.

163. Pisters R, Lane DA, Nieuwlaat R. A Novel User-Friendly Score (HAS BLED) To Assest 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation. *CHEST J*. 2010;138:1093-1100. doi:10.1378/chest.10-0134.
164. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. *Rev Española Cardiol (English Ed*. 2017;70(1):50. doi:10.1016/j.rec.2016.11.033.
165. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366(2):120-129. doi:10.1056/NEJMoa1105575.
166. Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol*. 2012;60(6):531-538. doi:10.1016/j.jacc.2012.04.032.
167. Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane database Syst Rev*. 2005;(4):CD001925. doi:10.1002/14651858.CD001925.pub2.
168. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867. doi:10.7326/0003-4819-146-12-200706190-00007.
169. Investigators A, Connolly SJ, Pogue J, et al. ACTIVE A: Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360(20):2066-2078.
170. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet (London, England)*. 2006;367(9526):1903-1912. doi:10.1016/S0140-6736(06)68845-4.
171. Agarwal S, Hachamovitch R, Menon V. Current Trial-Associated Outcomes With Warfarin in Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation: A Meta-analysis. *Arch Intern Med*. 2012;172(8):623-631. doi:10.1001/archinternmed.2012.121.
172. Connolly S, Ezekowitz M. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561.
173. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638.
174. Granger C. Apixaban versus warfarin in atrial fibrillation. *New Engl J Med (N Engl J Med)*. 2011;365(11):981-992. doi:10.1056/NEJMc1112500#SA2.

175. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907.
176. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol*. 2017. http://www.onlinejacc.org/content/early/2017/03/10/j.jacc.2017.03.011?_ga=2.115360902.1407512275.1494690807-1665501421.1494690807. Accessed May 13, 2017.
177. Eikelboom JW, Connolly SJ, Brueckmann M, et al. RE-ALIGN: Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206-1214. doi:10.1056/NEJMoa1300615.
178. Pollack C V., Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med*. 2015;373(6):511-520. doi:10.1056/NEJMoa1502000.
179. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med*. 2016;375(12):1131-1141. doi:10.1056/NEJMoa1607887.
180. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban. *N Engl J Med*. 2014;371(22):2141-2142. doi:10.1056/NEJMc1411800.
181. Laulicht B, Laulicht B, Laulicht B, et al. Abstract 11395: Small Molecule Antidote for Anticoagulants. *Circulation*. 2016;126(Suppl 21). http://circ.ahajournals.org/content/126/Suppl_21/A11395.short. Accessed May 13, 2017.
182. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996;61(2):755-759. doi:10.1016/0003-4975(95)00887-X.
183. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart*. 1999;82(5):547-554.
184. La Meir M, Gelsomino S, Lucà F, et al. Minimal invasive surgery for atrial fibrillation: an updated review. *Europace*. 2013;15(2):170-182. doi:10.1093/europace/eus216.
185. Ohtsuka T, Ninomiya M, Nonaka T, Hisagi M, Ota T, Mizutani T. Thoracoscopic stand-alone left atrial appendectomy for thromboembolism prevention in nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2013;62(2):103-107. doi:10.1016/j.jacc.2013.01.017.
186. Ailawadi G, Gerdisch MW, Harvey RL, et al. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg*. 2011;142(5):1002-9, 1009.e1. doi:10.1016/j.jtcvs.2011.07.052.
187. Lin AC, Knight BP. Left atrial appendage closure. *Prog Cardiovasc Dis*. 58(2):195-201. doi:10.1016/j.pcad.2015.07.009.
188. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*

(London, England). 2009;374(9689):534-542. doi:10.1016/S0140-6736(09)61343-X.

189. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation*. 2013;127(6):720-729. doi:10.1161/CIRCULATIONAHA.112.114389.
190. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation*. 2011;123(4):417-424. doi:10.1161/CIRCULATIONAHA.110.976449.
191. Holmes DR, Lakkireddy DR, Whitlock RP, Waksman R, Mack MJ. Left atrial appendage occlusion: opportunities and challenges. *J Am Coll Cardiol*. 2014;63(4):291-298. doi:10.1016/j.jacc.2013.08.1631.
192. Holmes DR, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64(1):1-12. doi:10.1016/j.jacc.2014.04.029.
193. Boersma LVA, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J*. January 2016. doi:10.1093/eurheartj/ehv730.
194. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol*. 2013;61(25):2551-2556. doi:10.1016/j.jacc.2013.03.035.
195. Reddy VY, Akehurst RL, Armstrong SO, et al. Cost effectiveness of left atrial appendage closure with the Watchman device for atrial fibrillation patients with absolute contraindications to warfarin. *Europace*. February 2016. doi:10.1093/europace/euv412.
196. Price MJ, Gibson DN, Yakubov SJ, et al. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. *J Am Coll Cardiol*. 2014;64(6):565-572. doi:10.1016/j.jacc.2014.03.057.
197. Chatterjee S, Herrmann HC, Wilensky RL, et al. Safety and Procedural Success of Left Atrial Appendage Exclusion With the Lariat Device: A Systematic Review of Published Reports and Analytic Review of the FDA MAUDE Database. *JAMA Intern Med*. 2015;175(7):1104-1109. doi:10.1001/jamainternmed.2015.1513.
198. Pillarisetti J, Reddy YM, Gunda S, et al. Endocardial (Watchman) vs epicardial (Lariat) left atrial appendage exclusion devices: Understanding the differences in the location and type of leaks and their clinical implications. *Heart Rhythm*. 2015;12(7):1501-1507. doi:10.1016/j.hrthm.2015.03.020.

199. Lakkireddy D, Afzal MR, Lee RJ, et al. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: Results from a US multicenter evaluation. *Heart Rhythm*. February 2016. doi:10.1016/j.hrthm.2016.01.022.
200. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a re. *Hear Rhythm*. 2012;9(4):632-696 e21. doi:10.1016/j.hrthm.2011.12.016.
201. Pandit S V, Jalife J. Rotors and the dynamics of cardiac fibrillation. *Circ Res*. 2013;112(5):849-862. doi:10.1161/CIRCRESAHA.111.300158.
202. Jais P, Haissaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation*. 1997;95(3):572-576.
203. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339(10):659-666. doi:10.1056/NEJM199809033391003.
204. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. *N Engl J Med*. 1998;339(10):659-666. doi:10.1056/NEJM199809033391003.
205. Jaïs P, Haïssaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation*. 1997;95(3):572-576. doi:10.1161/01.CIR.95.3.572.
206. Valles E, Fan R, Roux JF, et al. Localization of Atrial Fibrillation Triggers in Patients Undergoing Pulmonary Vein Isolation. Importance of the Carina Region. *J Am Coll Cardiol*. 2008;52(17):1413-1420. doi:10.1016/j.jacc.2008.07.025.
207. Prabhu S, McLellan AJ, Walters TE, Sharma M, Voskoboinik A, Kistler PM. Atrial structure and function and its implications for current and emerging treatments for atrial fibrillation. *Prog Cardiovasc Dis*. 2015;58(2):152-167. doi:10.1016/j.pcad.2015.08.004.
208. Macedo PG, Kapa S, Mears JA, Fratianni A, Asirvatham SJ. Correlative anatomy for the electrophysiologist: ablation for atrial fibrillation. Part II: regional anatomy of the atria and relevance to damage of adjacent structures during AF ablation. *J Cardiovasc Electrophysiol*. 2010;21(7):829-836. doi:10.1111/j.1540-8167.2010.01730.x.
209. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA*. 2005;293(21):2634-2640. doi:10.1001/jama.293.21.2634.
210. Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol*. 2006;48(11):2340-2347. doi:10.1016/j.jacc.2006.08.037.
211. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus

antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation*. 2008;118(24):2498-2505. doi:10.1161/CIRCULATIONAHA.108.772582.
212. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*. 2010;303(4):333-340. doi:10.1001/jama.2009.2029.
213. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol*. 2009;2(6):626-633. doi:10.1161/CIRCEP.109.856633.
214. Parkash R, Tang AS, Sapp JL, Wells G. Approach to the catheter ablation technique of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomized controlled trials. *J Cardiovasc Electrophysiol*. 2011;22(7):729-738. doi:10.1111/j.1540-8167.2011.02010.x.
215. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol*. 2011;57(2):160-166. doi:10.1016/j.jacc.2010.05.061.
216. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Hear Assoc*. 2013;2(2):e004549. doi:10.1161/JAHA.112.004549.
217. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1-76. doi:10.1016/j.jacc.2014.03.022.
218. Tung R, Buch E, Shivkumar K. Catheter ablation of atrial fibrillation. *Circulation*. 2012;126(2):223-229. doi:10.1161/CIRCULATIONAHA.111.048421.
219. Nault I, Miyazaki S, Forclaz A, et al. Drugs vs. ablation for the treatment of atrial fibrillation: the evidence supporting catheter ablation. *Eur Hear J*. 2010;31(9):1046-1054. doi:10.1093/eurheartj/ehq079.
220. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 2004;109(12):1509-1513. doi:10.1161/01.CIR.0000121736.16643.11.
221. https://clinicaltrials.gov/ct2/show/NCT00911508.
222. https://clinicaltrials.gov/ct2/show/NCT01288352.
223. Nishida K, Datino T, Macle L, Nattel S. Atrial fibrillation ablation: translating basic mechanistic insights to the patient. *J Am Coll Cardiol*. 2014;64(8):823-831. doi:10.1016/j.jacc.2014.06.1172.
224. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol*. 2012;60(7):628-636. doi:10.1016/j.jacc.2012.05.022.

225. Miller JM, Kowal RC, Swarup V, et al. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: multicenter FIRM registry. *J Cardiovasc Electrophysiol*. 2014;25(9):921-929. doi:10.1111/jce.12474.
226. Mohanty S, Gianni C, Mohanty P, et al. Impact of Rotor Ablation in Nonparoxysmal Atrial Fibrillation Patients: Results From the Randomized OASIS Trial. *J Am Coll Cardiol*. 2016;68(3):274-282. doi:10.1016/j.jacc.2016.04.015.
227. Lawrance CP, Henn MC, Damiano Jr. RJ. Surgical ablation for atrial fibrillation: techniques, indications, and results. *Curr Opin Cardiol*. 2015;30(1):58-64. doi:10.1097/HCO.0000000000000125.
228. Kumar P, Kiser AC, Gehi AK. Hybrid Treatment of Atrial Fibrillation. *Prog Cardiovasc Dis*. 2015;58(2):213-220. doi:10.1016/j.pcad.2015.08.001.
229. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. *J Am Coll Cardiol*. 2012;60(1):54-61. doi:10.1016/j.jacc.2011.12.055.
230. Bulava A, Mokracek A, Hanis J, Kurfirst V, Eisenberger M, Pesl L. Sequential hybrid procedure for persistent atrial fibrillation. *J Am Hear Assoc*. 2015;4(3):e001754. doi:10.1161/JAHA.114.001754.

Figure 1. Risk factor modification in atrial fibrillation and its intended effects. Reproduced with permission from Morin *et al.* Mayo Clin Proc. 2016;91:1778-1810.

AF=atrial fibrillation. ACEi=angiotensin converting enzyme inhibitor.
ARB=angiotensin receptor blocker. DM=diabetes mellitus.
CHF=congestive heart failure. CPAP=continuous positive airway pressure.
EtOH=ethyl alcohol consumption. HTN=hypertension. LA=left atrium.
OSA=obstructive sleep apnea. OMT=optimal medical therapy.
SBP=systolic blood pressure. TZD=thiazolidinedione.
RAAS=renin-angiotensin-aldosterone system.

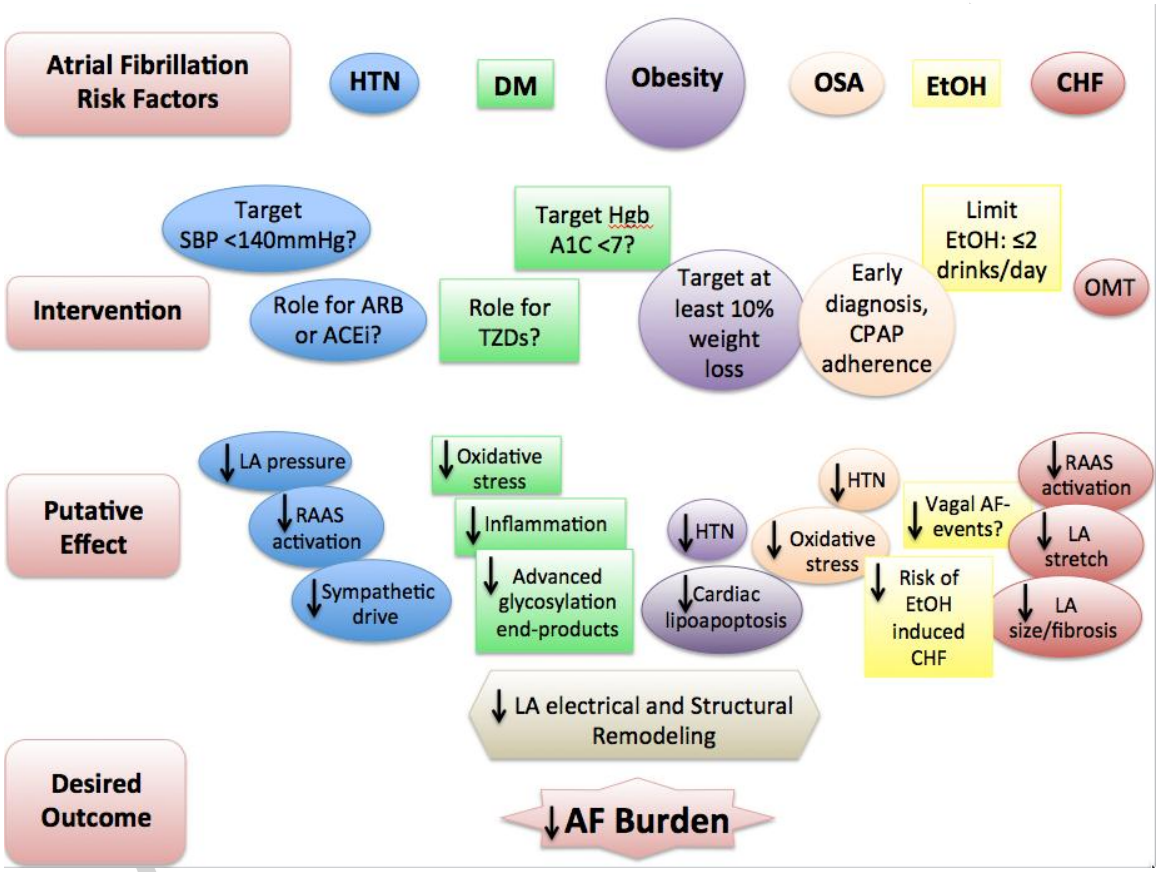


Figure 2. Atrial fibrillation-free survival in the ARREST-AF trial. Reproduced with permission from Pathak *et al*. J Am Coll Cardiol 2014;64:2222-2231.

AF=atrial fibrillation. RFM=risk factor management.

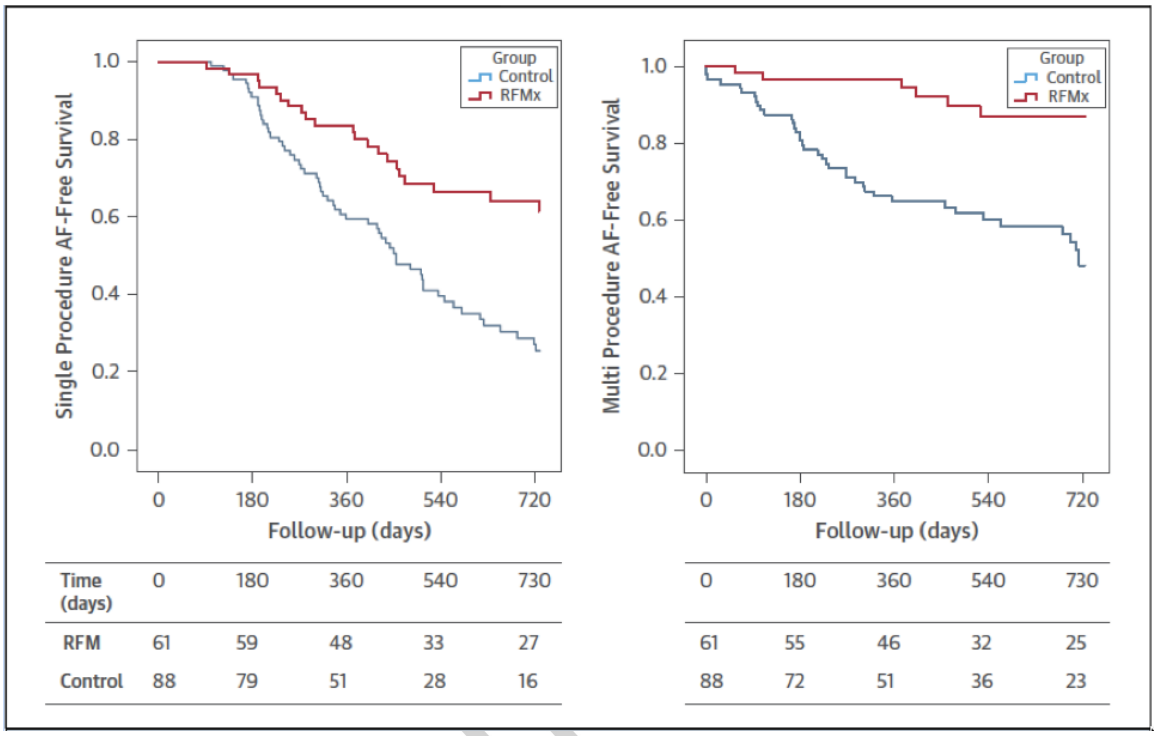


Figure 3. Proposed rhythm control drug therapy of atrial fibrillation. Absent structural heart disease, any antiarrhythmic drug with the exception of amiodarone is first line. In patients with CAD dronedarone, dofetilide and sotalol are first-line agents. For patients with CHF amiodarone and dofetilide are first-line therapy. Only dronedarone and amiodarone are recommended for patients with left ventricular hypertrophy with wall thickness >1.5cm. Catheter ablation prior to antiarrhythmic drug therapy is a IIa and IIb indication for patients with paroxysmal and persistent atrial fibrillation, respectively. Reproduced with permission from Morin *et al.* Mayo Clin Proc. 2016;91:1778-1810.

CAD=coronary artery disease. CHF=congestive heart failure.

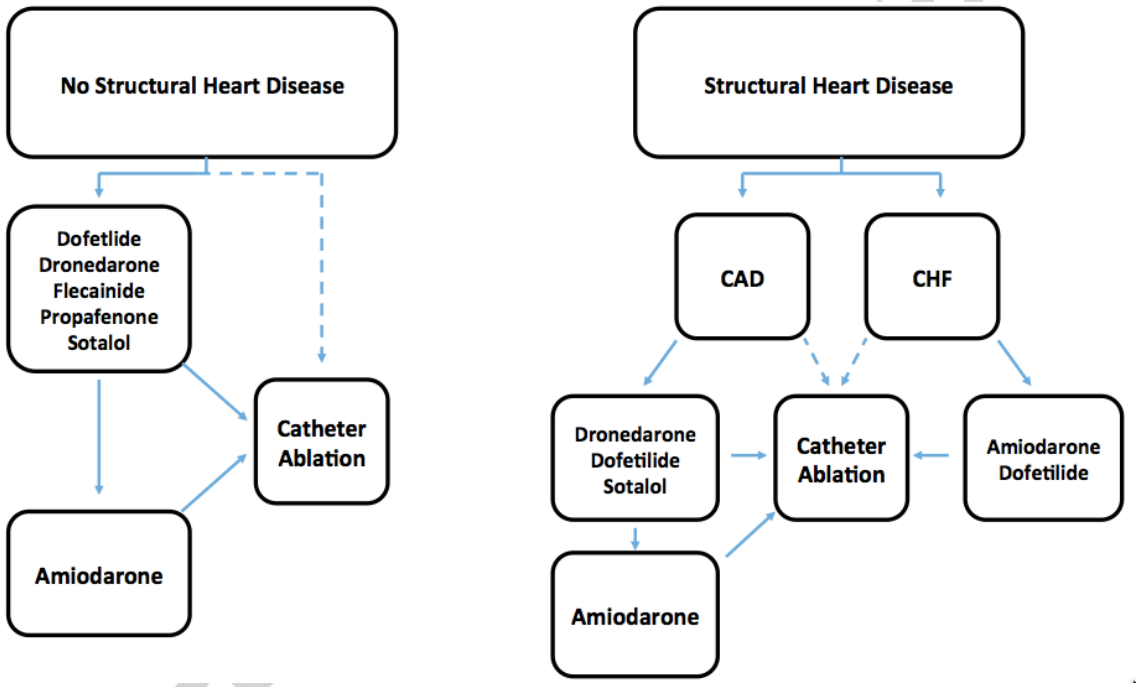
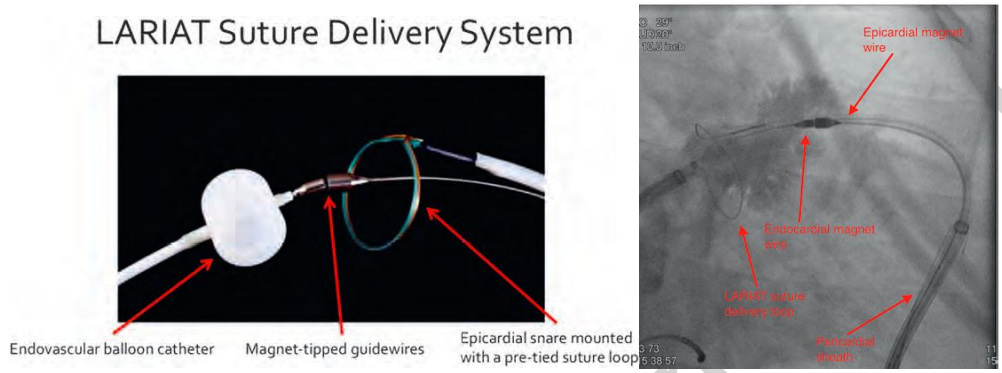


Figure 4. *Panel A* LARIAT system, note the intracardiac (catheter/balloon/magnet) portion interacting with the epicardially-delivered magnetic guidewire and preloaded catheter-delivered suture, a fluoroscopic image just prior to LARIAT suture deployment is provided. *Panel B* Watchman device, consisting of a metallic frame with fixation barbs and a polyester fabric covering the atrial face of the device, fluoroscopic image of a Watchman being deployed is provided. Reproduced with permission from Lin *et al*. Prog Cardiovasc Dis 2015;58(2):195-201 and Fountain *et al*. Am Heart J 2006;151:956- 61.

A.



B.

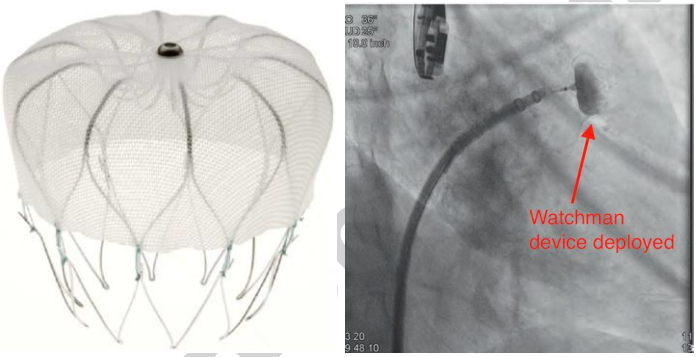


Table 1. CHA_2DS_2-VASc and HAS-BLED components, scoring methods, and risk calculators. Reproduced with permission from Morin *et al.* Mayo Clin Proc. 2016;91:1778-1810.

CHF=congestive heart failure. DM=diabetes mellitus. HTN=hypertension. INR=international normalized ratio. TIA=transient ischemic attack.

CHA_2DS_2-VASc	Points	Score	Stroke Risk
CHF	1	0	0%
HTN	1	1	1.3%
Age ≥75	2	2	2.2%
DM	1	3	3.2%
Stroke/TIA	2	4	4.0%
Vascular disease	1	5	6.7%
Age 65-75	1	6	9.8%
Sex (Female gender)	1	7	9.6%
		8	6.7%
		9	15.2%

HAS-BLED (1 point each)	Score	Bleeding Risk
Hypertension	0	0.9%
Abnormal Liver/Renal function	1	3.4%
Stroke	2	4.1%
Bleeding risk	3	5.8%
Labile INRs	4	8.9%
Elderly, ≥65y	5	9.1%
Drugs/alcohol	6-7	Too Rare

Table 2. A comparison of DOAC approval trials. Average $CHADS_2$ score, and hazard ratios with confidence intervals for stroke and systemic embolism, major bleeding, and intracranial hemorrhage are included. Dose adjustment indications are also listed. Reproduced with permission from Morin *et al.* Mayo Clin Proc. 2016;91:1778-1810.

*indicates that the drug met non-inferiority criteria for the endpoint, compared to warfarin. **indicates that the drug met superiority criteria for the endpoint, compared to warfarin.

bid=twice daily. $CHADS_2$=congestive heart failure; hypertension; age >75 years; diabetes mellitus; stroke, transient ischemic attack, or systemic embolism. GFR=glomerular filtration rate. qd=daily.

	Dabigatran 150 mg bid RE-LY n=18,113	**Rivaroxaban 20 mg qd ROCKET AF n=14,264**	**Apixaban 5 mg bid ARISTOTLE n=18,201**	**Edoxaban 60 mg qd ENGAGE AF/TIMI-48 n=21,105**
$CHADS_2$	2.1	3.5	2.1	2.8
Stroke and systemic embolism	0.66 (0.53-0.82) **	0.88 (0.75-1.03) *	0.80 (0.67-0.95) **	0.88 (0.75-1.03) *
Major bleeding	0.93 (0.81-1.07) *	1.04 (0.90-1.20) *	0.69 (0.6-0.8) **	0.80 (0.71-0.91) **
Intracranial hemorrhage	0.40 (0.27-0.60) **	0.67 (0.47-0.93) **	0.42 (0.30-0.38) **	0.47 (0.34-0.67) **
Dose adjustment	75 mg bid if GFR 15-30 ml/min	15 mg qd if GFR 15-50 ml/min	2.5 mg bid for ≥2 of: Cr >1.5, Age >80y, weight <60 kg	30 mg qd if GFR 15-50 ml/min

Table 3. AHA/ACC/HRS Practice guideline for the management of patients with atrial fibrillation: Recommendations for catheter ablation to maintain sinus rhythm. Reproduced with permission from *January, C.T., et al., 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol, 2014. 64(21):e1-76.*

Class I (Benefit >>> Risk; Procedure/treatment SHOULD be performed)

1. AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired. *(Level of Evidence: A)*
2. Before consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. *(Level of Evidence: C)*

Class IIa (Benefit >> Risk; IT IS REASONABLE to perform procedure/treatment)

1. AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication. *(Level of Evidence: A)*
2. In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy. *(Level of Evidence: B)*

Class IIb (Benefit ≥ Risk; Procedure/treatment MAY BE CONSIDERED)

1. AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired. *(Level of Evidence: B)*
2. AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired. *(Level of Evidence: C)*

Class III (No benefit, or potential HARM; Procedure/treatment IS CONTRAINDICATED)

1. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure. *(Level of Evidence: C)*
2. AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation. *(Level of Evidence: C)*

Table 4. Catheter ablation versus antiarrhythmic drug therapy for management of atrial fibrillation trials. "Second line therapy" indicates atrial fibrillation recurrence despite previous management with at least one antiarrhythmic drug. Reproduced with permission from Morin *et al.* Mayo Clin Proc. 2016;91:1778-1810.

CA, catheter ablation; AAD, anti-arrhythmic drugs; AF, atrial fibrillation; yr, year; mo, month; A4 Catheter Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation; APAF, Ablate and Pace in Atrial Fibrillation; CACAF, Catheter Ablation for the Cure of Atrial Fibrillation; RAAFT, Radiofrequency Ablation for Atrial Fibrillation Trial; STOP-AF, Sustained Treatment of Paroxysmal Atrial Fibrillation; SARA, Study of Ablation versus antiaRrhythmic drugs in persistent Atrial fibrillation.

	Study Design	***Size (n)***	***Paroxysmal (%)***	***Freedom from AF recurrence (%)***		
				Follow-up	***AAD***	***CA***
Krittayaphong, 2003	CA as second line therapy* compared to amiodarone	30	70%	1 yr	40%	79% P 0.018
Wazni, 2005 RAAFT	CA as first line therapy	70	96%	1 yr	37%	87% <0.001
Stabile, 2005 CACAF	CA as second line therapy	137	67%	1 yr	8.7%	55.9% <0.001
Pappone, 2006 APAF	CA as second line therapy in paroxysmal AF	198	100%	1 yr	35%	93% <0.001
Oral, 2006	CA as second line therapy in chronic AF	146	0%	1 yr	58%	74% 0.05
Jais, 2008 A4	CA as second line therapy in paroxysmal AF	112	100%	1 yr	23%	89% <0.0001
Forleo, 2009	CA as second line	70	41%	1 yr	42.9%	80% 0.001

	therapy in paroxysmal AF patients with type 2 diabetes					
Wilber, 2010 Thermocool	CA as second line therapy in paroxysmal AF	167	100%	9 mo 16% (after a 3-mo blanking period)	<0.001	66%
Packer, 2013 STOP-AF	Cryoballoon ablation as second line therapy in paroxysmal AF	245	78%	1 yr 7.3%	<0.001	69.9%
Cosedis Neilsen, 2012 MANTRA-PAF	CA as first line therapy in paroxysmal AF	294	100%	2 yr 71%	0.004	85%
Morillo, 2014 RAAFT2	CA as first line therapy in paroxysmal AF	127	98%	2 yr 41%	0.03	53%
Mont, 2014 SARA	CA as second line therapy in persistent AF	146	0%	1 yr 43.7%	0.002	70.4%