Atrial Fibrillation in 2017: How Times have Changed

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This is to acknowledge that Mark S Link, MD has no financial interests or relationships with commercial concerns related directly or indirectly to this program.

Dr. Link will be discussing off label uses of amiodarone (not FDA approved for treatment of atrial fibrillation) and andexanet (a reversal agent for the direct factor Xa inhibitors)

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The purpose of this presentation is to update the audience regarding the management of patients with atrial fibrillation. This presentation will focus on more recent data regarding the risk factors for atrial fibrillation, the use of the direct acting anticoagulants, and the role of ablation in the management of atrial fibrillation.

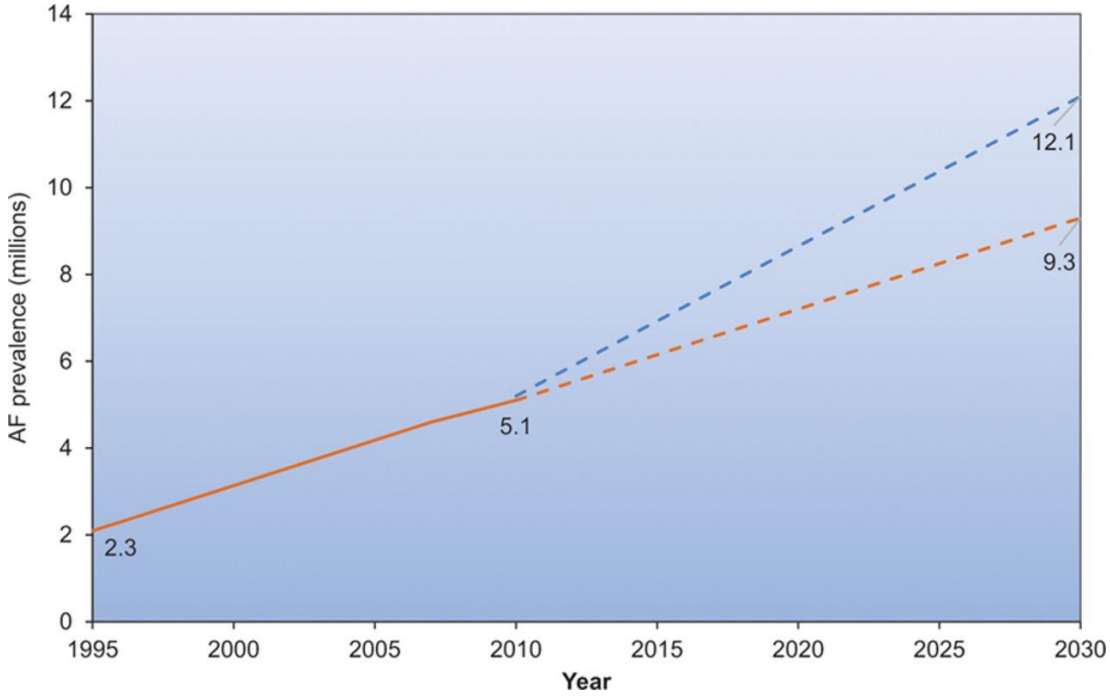
Educational Objectives
At the conclusion of the lecture the listener should be able to:

1. Know the risk factors for atrial fibrillation
2. Appreciate the indications for anticoagulation
3. Know the risks and benefits of the direct anticoagulants
4. Be familiar with the indications for ablation

INTRODUCTION

Currently, in the United States approximately five million individuals have a diagnosis of atrial fibrillation (AF) and the American Heart Association AF writing group estimates that the number of patients with AF will double over the next 25 years (figure 1).[1]

Figure 1. Growth in prevalence of atrial fibrillation with no increase (dashed red line) or logarithmic increases (dashed blue line). From Emelia J. Benjamin et al. Circulation. 2017;135:e146-e603.

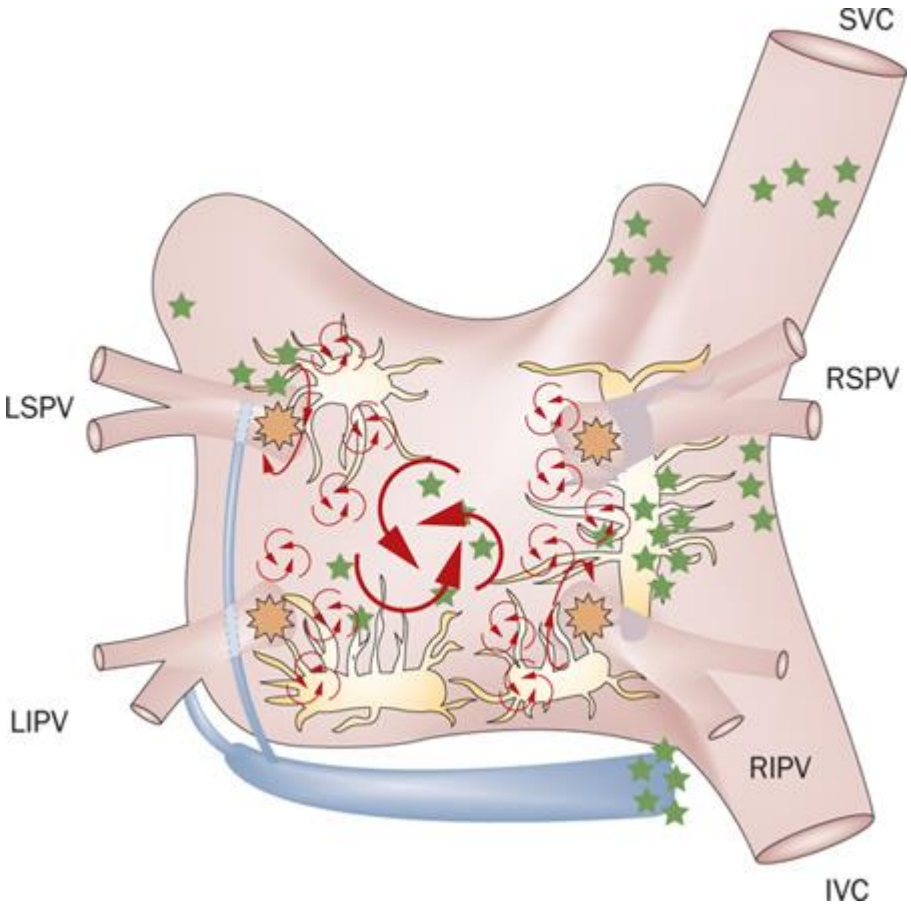


AF is a significant contributor to morbidity and mortality. Patients with AF have a 5-fold risk of stroke,[2] a 3-fold risk of heart failure,[3] and a doubling of mortality.[2] Options for treatment have exploded over the last decade, particularly with regard to anticoagulation and ablation. Ablation of AF has evolved from a concept difficult to imagine in the early 1990s, to a rare and very lengthy procedure in the late 1990s[4] to now a generally safe and reasonably successful procedure.[1, 5, 6]

The understanding of putative mechanisms of AF have changed over time. Traditionally, AF was thought secondary to spiral depolarization waves in the atria.[7, 8] These spiral waves randomly collided, bounced off barriers and subsided, similar to what happens when pebbles are dropped in a bucket of water. However, a landmark study in 1998 demonstrated that AF could be due to pulmonary vein atrial premature beats/tachycardia in atrial musculature lying within the pulmonary veins.[4] Furthermore, ablation of these triggers could eliminate AF.[4] However, it is also clear that the mechanism of AF is more complex than just triggers, and includes autonomic

modulation, fibrosis, remodeling, ischemia, dilatation and stretch among others (Figure 2).[6] A more complete understanding of the mechanism(s) of AF will hopefully translate into improved treatment.

Figure 2. Atrial fibrillation is complicated. The mechanisms include focal triggers, rotors, , LA enlargement and increased pressure, wall stretch, fibrosis, ischemia, atrial myopathy, and autonomic ganglionic plexi. From Dewire et al. Nat Rev Cardiol 2009.



RISK FACTORS FOR ATRIAL FIBRILLATION

There are some modifiable and other nonmodifiable risk factors for AF. The risk factors of age, male gender, and genetic predisposition to AF are unavoidable. But most of the other risk factors for AF can be addressed. These other risk factors include hypertension, diabetes, sleep apnea, obesity, excessive alcohol, smoking, hyperthyroidism, pulmonary disease, exposure to air pollution[9] and possibly excessive exercise.[10, 11] Recent prospective registry data (Arrest-AF) have demonstrated that in a controlled goal-directed clinic that aggressively manages hypertension, obesity, lipids, diabetes, sleep apnea, smoking and alcohol, the risk of recurrence AF after ablation is markedly decreased.[11]

CLINICAL ISSUES

AF has two major clinical implications; symptoms and thromboembolic events, including strokes. Symptoms secondary to AF include palpitations, dyspnea on exertion, fatigue, weakness, and occasionally chest pain and lightheadedness. Some patients may have minimal or no symptoms, while others can be significantly disabled.

Strokes are the most feared complication from AF. The risk of thromboembolism is related to the number of clinical factors in the CHADS VASC score. Individuals get 1 point for a clinical history of CHF, HTN, Age 65-74, vascular disease, diabetes, female gender, and 2 points for age $\geq$ 75 and prior embolic events. The higher the score the more at risk for embolic events.

Table 1. The CHADS-VASC score for predicting stroke risk in atrial fibrillation.

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/y)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

TREATMENT

ANTICOAGULATION

The vitamin K antagonist, warfarin, has been the gold standard for anticoagulation in AF. Its ability to lower the risk of thrombo-embolism has been established by large randomized controlled trials (RCTs) in the 1980s and early 1990s.[12] Yet warfarin therapy is complicated by the need for dietary compliance, sensitivity to multiple medications, frequent blood draws for monitoring, and often unexplained INR fluctuations. Thus, there has been a wide-spread desire to develop warfarin substitutes which are safer and easier to administer.

Dabigatran,[13] a direct thrombin inhibitor, and the direct factor Xa inhibitors, rivaroxaban,[14] apixaban,[15] and edoxaban,[16] are presently available (Table 2). All of these newer/direct anticoagulants were tested against warfarin; none have been directly compared to another in a clinical trial. While the clinical results of the trials are similar there are differences in trial design, patient thrombo-embolic risk, and endpoints that prevent their direct comparison.

Table 2. Comparison of warfarin with the 4 novel anticoagulants available for administration in the prevention of thrombo-embolism in patients with atrial fibrillation (From Link et al, Circulation. 2016).

	Warfarin	Dabigatran, RELY[20]	Rivaroxaban, ROCKET-AF[21]	Apixaban, ARISTOTLE[22]	Edoxaban, ENGAGE[23]
Mechanism	Vitamin K antagonist	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Time to peak levels	Days	3 h	3 h	3 h	2h
Half life, h	NA	12–17	5–13	9–14	10–14
Renal excretion, %	NA	80	36	27	50
Dose	Variable	150 mg twice daily	20 mg once daily	5 mg twice daily	For CrCl 50–95 mL/min, 60 mg once daily (do not use if CrCl >95 mL/min
Dose decrease	Based on INR	75 mg twice daily if CrCl is 15–30 mL/min	15 mg once daily if CrCl is 15–50 mL/min	2.5 mg twice daily if 2 of 3 of the following: Age ≥80 y Weight ≤60 kg SCr >1.5 mg/dL	30 mg once daily if CrCl 15–50 mL/min
Common drug interactions	CYP3A4 inhibitors or inducers (erythromycin ketoconazole) CYP2C9 (amiodarone) CYP1A2 (fluvoxamine, cimetidine, OCPs)	P-GP inhibitors (dronedarone, ketoconazole) P-GP inducer (rifampin)	Combined P-GP and CYP3A4 inhibitors (ketoconazole, ritonavir), Combined P-GP and CYP3A4 inhibitors (carbamazepin, phenytoin, rifampin)	Combined P-GP and CYP3A4 inhibitors (ketoconazole, ritonavir) Combined P-GP and CYP3A4 inducers (carbamazepine, phenytoin, rifampin)	P-GP inhibitors (dronedarone, ketoconazole) P-GP inducers (rifampin)
Food interactions	Vitamin K (eg, kale, spinach, Brussel sprouts, cabbage, asparagus)	None	Take with evening meal	None	None
Reversal agent	Vitamin K FFP PCC	Idarucizumab	Andexanet alfa*	Andexanet alfa*	Andexanet alfa*

AF indicates atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CrCl, creatinine clearance; ENGAGE, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; FFP, fresh-frozen plasma; INR, international normalized ratio; NA, not applicable; OCP, oral contraceptive; PCC, prothrombin complex concentrate; P-GP, phosphorylated glycoprotein; RELY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once-Daily oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; and SCr, serum creatinine.

*Not approved by the US Food and Drug Administration.

RATE CONTROL

For patients with minimal or no symptoms, a rate control strategy may be appropriate. The AFFIRM trial has demonstrated that there is no difference in mortality in individuals randomized to a rate control vs a sinus rhythm strategy. However, before relegating a patient who is in persistent AF to a rate control strategy, a cardioversion is useful to ascertain if they are truly asymptomatic. Rate control agents include beta blockers, non-dihydropurine calcium channel blockers and digoxin. Ablation of the AV node, with implantation of a PPM is occasionally needed as a last resort.

RHYTHM CONTROL

Maintenance of sinus rhythm will require antiarrhythmic drugs (AAD) or ablation. For patients with no structural heart disease flecainide or propafenone are options and generally the first AAD chosen. For individuals with structural heart disease sotalol, dofetilide, and amiodarone are options. Efficacy is variable. For those without heart disease AAD may be quite effective, but are still associated with potential side effects. AAD tend to be less effective in those with structural heart disease.

Because of issues with AAD, ablation may be an attractive alternative for patients. This decision is to be placed in context of the frequency of AF, the symptoms during AF, age and comorbidities of the patient, and other available options for AF management. For asymptomatic or minimally symptomatic individuals, especially if elderly or frail, rate control may be appropriate. The risks and benefits of antiarrhythmic agents must be balanced against the risks and benefits of ablation. Patient selection for ablation is a shared decision by the patient and physician.

The odds of a successful ablation are not only related to the technique of the procedure but also critically to patient characteristics. The ideal patient with the highest likelihood of procedural success is one with paroxysmal AF, no underlying cardiac disease and a non-dilated left atrium (Figure 3). Paroxysmal AF is defined as AF less than 7 days in duration. Success rates with these patients approaches 80%.[17-19] However, it has become clear in the last decade that even patients with persistent (> 7 days), and longstanding persistent (continuous AF > 1 year) may also benefit from AF ablation.[1, 5, 6] In addition, patients with congestive heart failure and/or decreased left ventricular ejection fraction may be candidates for AF ablation (Figure 4).[20-22] Yet, it is clear that the greater the underlying heart disease the odds of a successful ablation are diminished. In particular left atrial enlargement, mitral valve disease and chronic heart failure are associated with poorer outcomes.[1, 5, 6] It was once believed that patients need fail at least one antiarrhythmic agent prior to AF ablation. However, given the known toxicities of antiarrhythmic agents and the success of ablation, ablation is now acceptable as an initial rhythm control strategy, at least for paroxysmal AF.[1, 5]

Figure 3. Treatment options for those with no or minimal structural heart disease (From Link et al, Circulation. 2016).

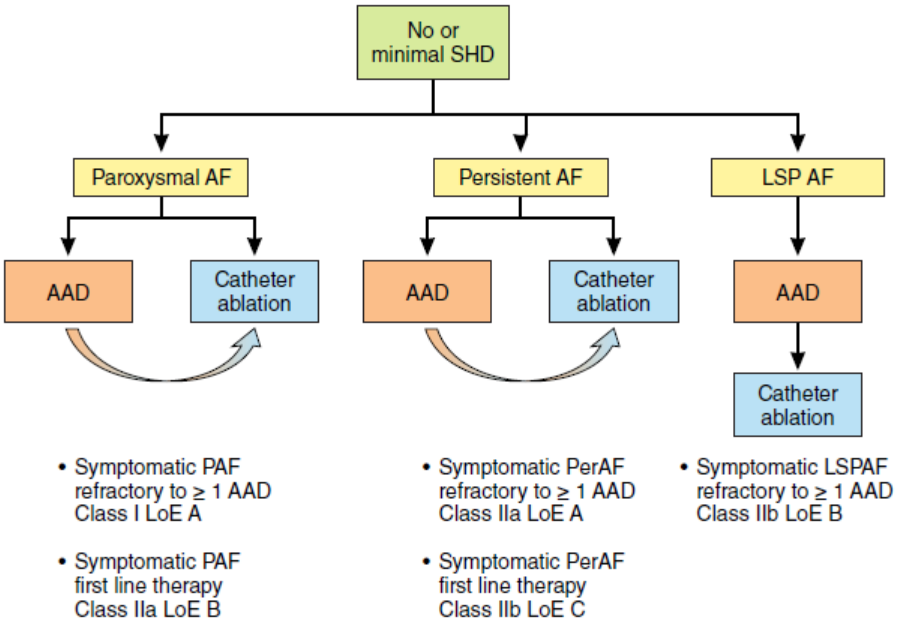
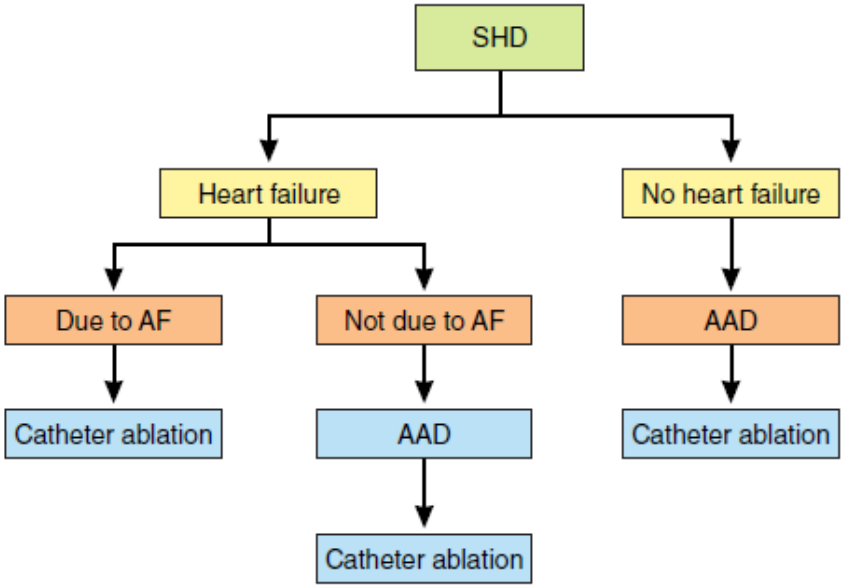


Figure 4. Treatment options for individuals with structural heart disease (SHD) (From Link et al, Circulation. 2016).



The latest AF ablation Guidelines were updated in the US in 2014[1] and in Europe in 2012 (Table 3).[5] For patients with symptomatic paroxysmal AF, the latest AHA/ACC recommendations give a class I recommendation (is useful) for catheter ablation in paroxysmal AF patients who have failed or are intolerant of class I or III antiarrhythmic agents.[1] These same

Guidelines give a IIa recommendation (is reasonable) for those symptomatic paroxysmal AF patients who wish to pursue ablation as an initial rhythm strategy, and symptomatic persistent AF patients who have failed or are intolerant to a class I or III antiarrhythmic agent. For patients with long-standing persistent AF, the recommendation drops to a IIb (may be considered) and this recommendation is irrespective of whether they have failed or are intolerant of Class I or III antiarrhythmic agents or wish to pursue ablation as an initial strategy. Importantly, these Guidelines give a class III: harm warning for pursuing AF ablation for the sole purpose of discontinuing anticoagulation. The European Society of Cardiology (ESC) guidelines for paroxysmal AF are remarkably similar.[5] Paroxysmal AF patients who fail antiarrhythmic agents are given a class I indication. It is an IIa indication for paroxysmal AF patients who prefer ablation prior to antiarrhythmic agent. The 2012 ESC guidelines did not change the 2010 recommendations for ablation of persistent AF, which remained IIa if patients are resistant to antiarrhythmic agents and IIb as initial strategy.[23]

Table 3. US and European Guidelines for ablation of AF (From Link et al, Circulation. 2016).

	US Guidelines	European Guidelines
Paroxysmal, failed AAD	I	I
Paroxysmal, initial strategy	IIa	IIa
Persistent, failed AAD	IIa	IIa
Persistent, initial strategy	IIb	IIb
Long-standing persistent (>12 mo)	IIb	IIb
Heart failure	IIb	IIb
Sole purpose of discontinuation of anticoagulation	III: harm	

AAD indicates antiarrhythmic drugs; and AF, atrial fibrillation. I=benefit>>>risk, should be performed; IIa=benefit>>risk, is reasonable; IIb=benefit≥risk, may be considered; and III=no benefit or harm.

While most trials have an endpoint of AF recurrence, there are some that hypothesize that AF ablation will ultimately reduce mortality and stroke incidence. The results of CABANA (catheter ablation versus antiarrhythmic drug therapy for atrial fibrillation) and EAST (Early therapy of atrial fibrillation for stroke prevention study) testing this hypothesis are highly anticipated.

CONCLUSION

The management of AF has undergone revolutionary changes over the last 2 decades. Expanding options for treatment include direct anticoagulants and ablation. Patient selection for ablation has evolved from healthy individuals with paroxysmal AF to those individuals with persistent AF and those with underlying heart disease such as mitral regurgitation and chronic heart failure.

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