

# Antiarrhythmic Drug Therapy for Atrial Fibrillation



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## KEYWORDS

- Atrial fibrillation • Cardioversion • Antiarrhythmic • Pharmacologic therapy • Rhythm control
- Rate control • Upstream therapy • Prevention

## KEY POINTS

- Atrial fibrillation (AF) is a complex disease, requiring better understanding in a multifaceted approach.
- Better research is needed to develop, subclassify, and identify new therapeutic targets, which hold the promise that precise therapies aimed at preventing or reversing AF will be developed.
- Antiarrhythmic therapeutic strategies for AF should be focused on controlling pathophysiologic remodeling, with better prevention and disease-modifying strategies.

Atrial fibrillation (AF) is the most common arrhythmia, and its incidence increases with advanced age. About 1% of patients with AF are younger than 60 years, 12% are between 75 and 85 years, and one-third of patients with AF are older than 80 years.<sup>1-3</sup> It is estimated that there are 3 million AF cases, and prevalence is expected to reach 7 million by 2050.<sup>4,5</sup> Incidence rates of AF vary among different races. Individuals of European descent have lifetime risk of 20% to 25% of developing AF after the 40 years of age.<sup>6</sup> Although risk factors for developing AF are more prevalent in African Americans, their incidence seems to be lower than whites.<sup>7</sup>

AF is associated with a 3-fold to 5-fold increased risk of stroke, and stroke caused by AF has significantly higher mortality and

morbidity than without AF. There is a 3-fold increase in the risk of heart failure (HF),<sup>8</sup> 2-fold increased risk of dementia, and higher mortality associated with AF. There are more than 470,000 hospitalizations in the United States with the primary diagnosis of AF, and it is estimated to cause 100,000 deaths per year. AF, besides being one of the leading causes of mortality and morbidity, adds \$26 billion to costs in the US health system annually.<sup>9</sup>

Treatment of AF is multifold but revolves around 1 essential consideration: whether or not to attempt to restore sinus rhythm or to treat AF by controlling ventricular rate only. This decision depends on symptom severity, age of the patient, underlying heart disease, and other comorbidities, which may limit therapeutic options.

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AF can be classified as paroxysmal, persistent, and permanent. The term lone AF refers to the finding of AF in patients without obvious structural heart disease. Paroxysmal AF terminates spontaneously or with intervention within 7 days of onset. Persistent AF lasts longer than 7 days, requiring electrical or chemical cardioversion. Long-standing persistent AF is continuous AF for longer than 12 months. Permanent AF describes continuous AF that has failed cardioversion, and the patient and clinician have jointly decided to not pursue restoring or maintaining sinus rhythm. Nonvalvular AF is AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.<sup>10</sup>

Symptoms of AF can vary and are individual. They range from fatigue, shortness of breath, palpitations, syncope, hypotension, and HF, with the most common symptom being fatigue. Some of the symptoms may abate with slowing of the heart rate with the use of atrioventricular (AV) nodal blocking agents. Symptom resolution may not be achieved in some patients, who continue to feel fatigued and have exercise intolerance despite adequate heart rate control, which is attributed to the loss of atrial mechanical function. Patients with underlying diastolic dysfunction and left ventricular hypertrophy are particularly sensitive to the loss of AV synchrony. For patients with no deterioration of functional status in AF, rate control may be sufficient. On the other hand, patients with clear functional decline and exacerbation of symptoms may benefit from the rhythm control strategy.

## RHYTHM VERSUS RATE CONTROL

Several studies have assessed rhythm versus rate control strategies. The 2 largest trials, AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation), failed to show any significant benefit in choosing the rhythm control strategy.<sup>11,12</sup> Similar findings were seen in the PIAF (Pharmacological Intervention in Atrial Fibrillation) and STAF (Strategies of Treatment of Atrial Fibrillation) trials.<sup>13,14</sup>

The AFFIRM trial enrolled patients with persistent and paroxysmal AF randomly assigned to rate or rhythm control strategy. There were no significant differences in overall mortality, with a trend toward increase mortality in the rhythm control group. There was also a trend toward more ischemic strokes in rhythm control groups; however, this was mainly in patients who were not adequately anticoagulated.<sup>12</sup>

An AFFIRM substudy analyzing on-treatment analysis<sup>15</sup> showed that the presence of sinus

rhythm was associated with a lower risk of mortality, suggesting that adverse effect of antiarrhythmic drugs (AAD) overcomes the potential benefit of sinus rhythm restoration.

The RACE trial<sup>11</sup> randomized only patients with persistent AF, and all patients were anticoagulated irrespective of previous electric cardioversion efforts into rate or rhythm control groups. After a mean follow-up of 2.3 years, the rate control strategy was noninferior to rhythm control for the prevention of death or morbidity. A substudy of the AFFIRM trial<sup>16</sup> looked at exercise tolerance within the rhythm control and rate control strategies for AF and performed serial 6-minute walk tests on 245 patients. There was improvement in walking distance in both groups. Roy and colleagues<sup>17</sup> in 2008 analyzed rhythm versus rate controlled strategy for AF with patients with HF in the AF-CHF trial. This trial enrolled 1376 patients with left ventricular ejection fraction (LVEF) of 35% or less and found no clinically significant differences between the 2 groups in terms of cardiovascular death, all-cause death, stroke, or worsening HF.

Most of the studies evaluating issue of rhythm versus rate control treatment of AF are applicable to patient's age older than 60 years and younger than 80 years but still failed to show mortality benefit with the rhythm control strategy.<sup>11-14,18</sup> This lack of superiority is partly linked to AAD side effects as well as excess stroke risk in patients in whom anticoagulation was discontinued. Although younger (<60 years) and older (>80 years) are not well represented in these studies, the results are still applicable. In the last decade, there has been an increase in the use of rhythm control strategies, which is largely driven by an increase in AF ablations.<sup>19</sup> For younger symptomatic patients with AF without significant underlying heart disease, who are not adequately represented in the earlier studies, restoration of sinus rhythm is still considered a valid approach, because the long-term implications of permanent AF are unknown.

## RHYTHM CONTROL

AAD have been available for nearly 100 years and remain a cornerstone in AF therapy.<sup>20</sup> The role of AAD is not only to reduce the arrhythmia burden (frequency and duration of AF) but also to reduce hospitalization associated with AF. Despite the side effects associated with most of the antiarrhythmic pharmacotherapy for AF, AAD are still widely prescribed medications for AF.

### Pharmacologic Cardioversion

Chemical cardioversion can be achieved with oral as well as intravenous (IV) AAD. Once the decision

to restore sinus rhythm by electric or pharmacologic means is made, duration of AF is an important factor. Patients with duration of AF onset less than 48 hours have a spontaneous conversion rate of 60% in the first 24 hours.<sup>21</sup> Attempting pharmacologic or electrical cardioversion in AF of less than 48 hours duration allows easier restoration of sinus rhythm, increased long-term success rate, and shorter length of stay. Success of sinus rhythm restoration with pharmacologic agents varies by the choice of AAD used; however, average success rate is about 50% in the first 90 minutes from the time of drug administration. The success rate of electrical cardioversion is higher, ranging between 75% and 93%, but requires general anesthesia or conscious sedation and an 8-hour fasting period.<sup>22</sup> Once AF duration is greater than 7 days, pharmacologic cardioversion is less effective, and therefore, electric cardioversion is favored. Both strategies require adequate anticoagulation before cardioversion and for a period of 4 to 6 weeks after. Risk of thromboembolism without anticoagulation is similar with either of the cardioversion strategies.

### ***Decision to Maintain Sinus Rhythm***

Reversible causes of AF should be treated before initiating AAD therapy. Multiple studies evaluated short-term and long-term outcomes associated with rate control compared with rhythm control in patients with AF.<sup>11-14,18</sup> Once the decision of rhythm control is made, choice of agent must be individualized, considering side effect profile of the AAD and the potential benefit for a particular patient. Even after successful electrical cardioversion, risk of AF recurrence is high in untreated patients, with relapse rates of 71% to 84% at 1 year. This risk can be reduced by 30% to 50% with the use of AAD.<sup>23</sup>

### ***Available AAD Choices***

Over the last 20 to 25 years, AAD have been used for the management and treatment of multiple cardiac arrhythmias. AAD therapy for AF has evolved and involves complex classification, effect on multiple ion channels and adrenergic receptors, with multitude of cardiac and noncardiac side effects.

Most of the AAD used for AF exert their effect as membrane stabilizers or sodium channel blockers and potassium channel blockers. Quinidine and disopyramide have intermediate sodium channel blocking properties and show use dependence, which means the dominant effect of the drug of sodium channel blockade is seen at rapid heart rates. These agents also affect potassium channel ( $I_{Kr}$ ) at normal or slower heart rates and at lower

concentrations, and therefore show reverse use dependence for potassium channel blockade. Propafenone and flecainide have the slowest dissociation from sodium channels, causing more bound drug concentration with a greater degree of slowing conduction at rapid heart rates and, as a result, more use dependence. Potassium channel blockers prolong the action potential duration and refractory period. Sotalol and dofetilide cause reverse use dependence by a potassium channel blocking effect, prolonging repolarization at slower heart rates. Amiodarone and dronedarone affect multiple channels, including sodium, potassium, and calcium.

Many AAD have active metabolites, with pharmacologic action different from the parent compound. Procainamide, a class IA AAD, blocks sodium channels, but its major metabolite *N*-acetylprocainamide blocks outward potassium current with little or no effect on sodium channels and behaves like a class III antiarrhythmic agent. Likewise, the class IC agent propafenone is metabolized to 5-hydroxypropafenone, which lacks the  $\beta$ -blocker properties of the parent compound. Therefore, when prescribing, it is prudent to know the active metabolites of AAD.

#### ***Quinidine***

Quinidine is one of the oldest known AAD and is rarely used for AF, because of its proarrhythmic and noncardiovascular side effects. The effect of quinidine on  $I_{to}$  current has generated interest as a potential therapy for Brugada syndrome and idiopathic ventricular fibrillation.<sup>23</sup>

#### ***Disopyramide***

Disopyramide is a class IA sodium channel blocker with additive anticholinergic, negative inotropic, and vagolytic properties. Anticholinergic effects led to its recommendation for use in patients with vagally mediated AF.<sup>24</sup> Negative inotropy makes disopyramide beneficial in treating AF with hypertrophic obstructive cardiomyopathy (HOCM). The same property precludes its use in left ventricular systolic dysfunction.<sup>25</sup> It is rarely used and makes up 1% to 2% of annual AAD prescriptions in the United States.<sup>20</sup>

#### ***Flecainide and propafenone***

Class IC agents can convert AF into slow atrial flutter, which may conduct 1:1 and can cause hemodynamic compromise. Therefore, it is recommended to coadminister AV nodal blocking agents with class IC agents, although not necessarily in all patients. These agents cause lengthening of the PR segment and prolong the QRS duration up to 25% from baseline. These drugs should be used with caution in patients with

underlying conduction delay or bundle branch blocks. Propafenone is metabolized by the liver P-450 system into 2 major active metabolites, 5-hydroxypropafenone and *N*-depropylpropafenone. The active metabolites are eliminated renally and cannot be cleared by hemodialysis. The dosage of propafenone needs to be reduced in patients with severe hepatic and renal insufficiency. CYP2D6 is genetically absent in 7% of the patients (poor metabolizers) and is inhibited by tricyclic antidepressants, fluoxetine, and quinidine. These drug interactions and genetic poor metabolism can lead to excess drug levels and enhance  $\beta$ -blocker and calcium channel blocker properties of parent propafenone.<sup>26</sup>

These agents are considered for patients in AF without underlying structural heart disease. They both are well tolerated and have a low risk of toxicity. Both flecainide and propafenone are proarrhythmic and have negative inotropic properties and are therefore contraindicated in patients with left ventricular systolic dysfunction and ischemic heart disease.<sup>27</sup> RAFT (Rhythm Atrial Fibrillation Trial) randomized 523 patients into 3 sustained release propafenone dose groups (225 mg, 325 mg, and 425 mg twice a day, respectively) and followed them for 39 weeks. At the end of the study period, the recurrence rate of AF was 69% in the placebo group, higher than all tested doses of propafenone (52% in 225 mg, 42% in 325 mg, and 30% in 425 mg groups).<sup>28</sup> Similar findings were observed in ERAFT (European Rhythm/Rytmnorm Atrial Fibrillation Trial).<sup>29</sup>

Flecainide may cause mild neurologic side effects, like headache and tremors. Propafenone can cause gastrointestinal symptoms, such as nausea, and should be avoided in chronic obstructive pulmonary disease.

### **Sotalol**

Sotalol is a potassium channel blocker ( $I_{Kr}$ ) with nonselective  $\beta$ -blocker properties. It is not used for cardioversion but can be used to prevent AF recurrence. In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial and Canadian Trial of Atrial Fibrillation studies, sotalol significantly reduced rates of AF compared with placebo with sinus rhythm maintenance at 1-year ranges between 30% and 50%.<sup>21,29,30</sup> Sotalol never showed benefit over amiodarone in preventing AF recurrence. Sotalol has near 100% renal excretion and should be used with caution in patients with chronic kidney disease or with unstable renal functions. Sotalol prolongs the QT interval and can cause torsades de pointes (TDP). It should not be used in patients who have significant left ventricular hypertrophy and HF. It is usually started

as an 80 mg twice a day regimen, unless creatinine clearance is between 30 and 60 mL/min, in which case it should be once a day.<sup>31</sup> The dose should be uptitrated, with careful attention paid to the corrected QT interval. The usual dose range is 160 mg to 480 mg a day, in divided doses. Most experts recommend starting sotalol in the inpatient setting with electrocardiographic (ECG) monitoring.

### **Dofetilide**

Dofetilide is a class III AAD and a potassium channel blocker ( $I_{Kr}$ ). It inhibits the delayed rectifier potassium current and increases the atrial and ventricular effective refractory period, without causing negative inotropy. Its peak plasma concentration is achieved 2 to 3 hours after oral administration. Dofetilide is effective for sinus rhythm maintenance and for restoring sinus rhythm. The corrected QT interval lengthens in a dose-related linear pattern. Safety of dofetilide has been well studied in different settings. The DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) trial involved 2 large randomized control trials, DIAMOND-CHF and DIAMOND-AF.<sup>28,32</sup> DIAMOND-CHF enrolled 1518 patients, looking at mortality as a primary endpoint in patients with severe left ventricular systolic dysfunction receiving dofetilide or placebo. After a median follow-up of 18 months, there was no difference in survival between the 2 groups (41% vs 42%). DIAMOND-AF was a substudy of 506 patients with HF with baseline AF or atrial flutter and showed that 44% in the dofetilide group converted to sinus rhythm compared with 14% in the placebo group. After 1 year, 79% patients in the dofetilide group remained in sinus rhythm compared with 42% in the placebo. Incidence of TDP was 3.3% in DIAMOND-CHF, and 76% occurred within the first 3 days of initiating dofetilide; however, risk of TDP was reduced by dose adjusting dofetilide based on creatinine clearance.<sup>32</sup> Because of the increased risk of TDP with renal clearance, dofetilide requires mandatory inpatient ECG monitoring. Dofetilide by its QT prolonging effect and property of reverse use dependence promotes the development of the Ashman phenomenon in patients with AF.<sup>33</sup>

The SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) study<sup>34</sup> evaluated the safety and efficacy of dofetilide in 325 patients with persistent AF. The trial showed that 58% of patients maintained sinus rhythm at 1 year compared with 25% with placebo, with a lower incidence of TDP (0.8%) compared with the DIAMOND-AF study. In this trial, dofetilide dose was reduced for impaired renal functions and for corrected QT prolongation more than

15% from the baseline. It is approved in the United States, but not in Europe, for paroxysmal AF with a mandatory loading period of 3 days (or 5 doses) in hospital. Because of the complex dosing regimen and safety concerns of dofetilide, the US Food and Drug Administration (FDA) has restricted its prescription to registered physicians, nurses, and pharmacists who have completed specific training in the use of the drug. Dofetilide has shown reasonable safety in patients after myocardial infarction as well.<sup>32</sup>

### **Amiodarone**

Amiodarone is the most effective AAD in preventing recurrence of paroxysmal as well as persistent AF.<sup>22,30,35</sup> Although it is not approved by the FDA for AF, it is still the most commonly prescribed AAD for AF, representing 45% of annual US drug prescriptions.<sup>20</sup> It is a complex iodinated compound, with action on multiple ion channels ( $I_{Na}$ ,  $I_{Kur}$ ,  $I_{to}$ ,  $I_{CaL}$ ,  $I_{KACH}$ , and  $I_f$ ) and nonselective inhibition of  $\alpha$  and  $\beta$  receptors.

In SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial), 665 patients with persistent AF were randomized to receive amiodarone, sotalol, or placebo and were followed for 1 to 4.5 years. Recurrence rates at 1 year were 48%, 68%, and 87% in the amiodarone, sotalol, and placebo treated groups, respectively. There were higher bleeding rates in the amiodarone group, which is likely because of its interaction with warfarin.<sup>29</sup> Similar results were found in the Canadian Trial of Atrial Fibrillation, in which 403 patients were assigned to amiodarone, sotalol, or propafenone. After a mean follow-up of 16 months, the recurrence rate of AF in patients treated with amiodarone was 35%, compared with 63% in the sotalol or propafenone treated group. In a Veterans Affairs (VA) health system study,<sup>36</sup> amiodarone facilitated conversion to and maintenance of sinus rhythm in patients with left ventricular systolic dysfunction and decreased mortality in patients who remained in sinus rhythm, with no overall worsening of HF.

A study from Europe<sup>37</sup> compared the treatment of various AAD (amiodarone, sotalol, propafenone, dronedarone, and flecainide) for the treatment of AF or atrial flutter and found the largest reduction of AF recurrence in patients receiving amiodarone, but this benefit came at the expense of higher adverse effects and treatment withdrawals. In SCD HeFT (Sudden Cardiac Death in Heart Failure Trial),<sup>38</sup> amiodarone treatment was associated with more noncardiac deaths in patients with New York Heart Association (NYHA) class III HF.

Amiodarone is an iodine-rich lipid-soluble compound, with variable but generally poor bioavailability. Higher lipid solubility leads to extracardiac

accumulation of amiodarone in fat, muscles, liver, skin, and lungs, causing multiple potential toxicities. Amiodarone should be avoided in younger patients, in whom other AAD can be useful (because of cumulative toxicity). Pulmonary toxicity of amiodarone is dose related and can be fatal. Amiodarone may be used as the initial AAD of choice in patients with left ventricular systolic dysfunction, left ventricular hypertrophy, and coronary artery disease (CAD) or previous myocardial infarction. Patients on chronic amiodarone therapy should be annually screened for the end organ damage (eg, liver, thyroid, lung, and eye). The most common cardiovascular effects is bradycardia, with the highest risk of pacemaker in women.<sup>39</sup> QT interval prolongation is common, but rarely associated with TDP ( $\leq 0.5\%$ ).<sup>40</sup> Amiodarone is loaded in 600-mg to 1200-mg daily doses to a load of up to 10 g, before reducing the dose to a maintenance regimen of 200 mg or less a day. IV amiodarone does not have the same electrophysiologic effects as oral amiodarone. Use of oral amiodarone is associated with benefit of effective rate control, frequently eliminating the need for other drugs to control ventricular rates. Administration of the drug with food minimizes gastrointestinal side effects; however, grapefruit juice can inhibit amiodarone metabolism and can cause increased drug levels.<sup>41</sup> There is an increased risk of myositis when amiodarone is combined with a CYP3A4 substrate like simvastatin, which should be used at a dose of no more than 20 mg per day in patients treated with amiodarone. Amiodarone can also potentiate the anticoagulant effect of warfarin and inhibits *P*-glycoprotein transport, resulting in reduced digoxin clearance. Amiodarone is weakly effective for AF conversion into sinus rhythm.<sup>24,42</sup>

### **Dronedarone**

Dronedarone is an amiodaronelike substance without the iodine moiety, which may be responsible for fewer extracardiac side effects than amiodarone.<sup>43</sup> Like amiodarone, dronedarone also carries complex antiarrhythmic properties, spanning all classes of Vaughan Williams classification. It inhibits sodium current  $I_{Na}$ , potassium current  $I_{Kr}$  and  $I_{KACH}$  and *L*-type calcium current, and carries  $\alpha$ -receptor-blocking and  $\beta$ -receptor-blocking properties. Dronedarone prolongs the action potential in the atria and ventricles, with no major reverse use dependence.

The DAFNE (Dronedarone Atrial Fibrillation Study After Electrical Cardioversion) study<sup>44</sup> was formulated to study the most suitable dose of dronedarone for the prevention of AF after cardioversion. This trial showed that an 800-mg daily dose



of dronedarone was the optimal dose. Extracardiac (thyroid, pulmonary, ocular, hepatic toxic) or proarrhythmic effects were not seen at any of the studied doses. EURIDIS (European Trial In Atrial Fibrillation or Flutter Patients Receiving Dronedaron for the Maintenance of Sinus Rhythm) and ADONIS (American-Australian Trial with Dronedaron in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm) studied patients treated with dronedarone for AF and atrial flutter in maintaining sinus rhythm. These trials found that a dose of dronedarone of 400 mg twice a day was effective in preventing symptomatic and asymptomatic AF recurrences. The adverse events reported in both of these trials were similar in the dronedarone and placebo group, with more gastrointestinal toxicity associated with dronedarone.<sup>44</sup> Dronedaron was also tested in patients with symptomatic permanent AF for its effect on heart rate control. Dronedaron significantly reduced resting and maximal exercise heart rates compared with placebo.<sup>45</sup>

In the ATHENA trial,<sup>46</sup> patients with paroxysmal or persistent AF or atrial flutter with risk factors of thromboembolism, dronedaron reduced the combined end point of death and cardiovascular complications. This effect was largely seen by reducing hospitalization for AF. ANDROMEDA (Antiarrhythmic Trial with Dronedaron in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease)<sup>47</sup> evaluated tolerability of dronedaron in high-risk patients with HF and ventricular dysfunction in a double-blind, placebo-controlled fashion. The study was terminated prematurely because of excess risk of death in patients receiving dronedaron. The PALLAS trials<sup>48</sup> evaluated patients with persistent AF and found that dronedaron increases the combined end point of stroke, cardiovascular death, and hospitalization. As a result of these trials, dronedaron is contraindicated in patients with recent decompensated HF, depressed left ventricular function, or with NYHA class III or IV HF symptoms. It should be given for prevention of AF only to patients in whom sinus rhythm is already restored.

Dronedaron does not interact with warfarin. It increases serum creatinine levels through impaired tubular secretion, without an effect on renal function. Dronedaron, like amiodaron, interacts with P450 glycoprotein and CYP3A4 and therefore causes increase in digoxin levels and simvastatin induce myositis. There is generally a 10% risk of gastrointestinal side effects with the use of dronedaron. Like with warfarin, grapefruit juice increases dronedaron levels and should be avoided. The FDA has issued a warning to monitor liver function tests with the use of dronedaron,

based on a few recent case reports of liver failure that occurred within 6 months of the start of dronedaron.<sup>49</sup>

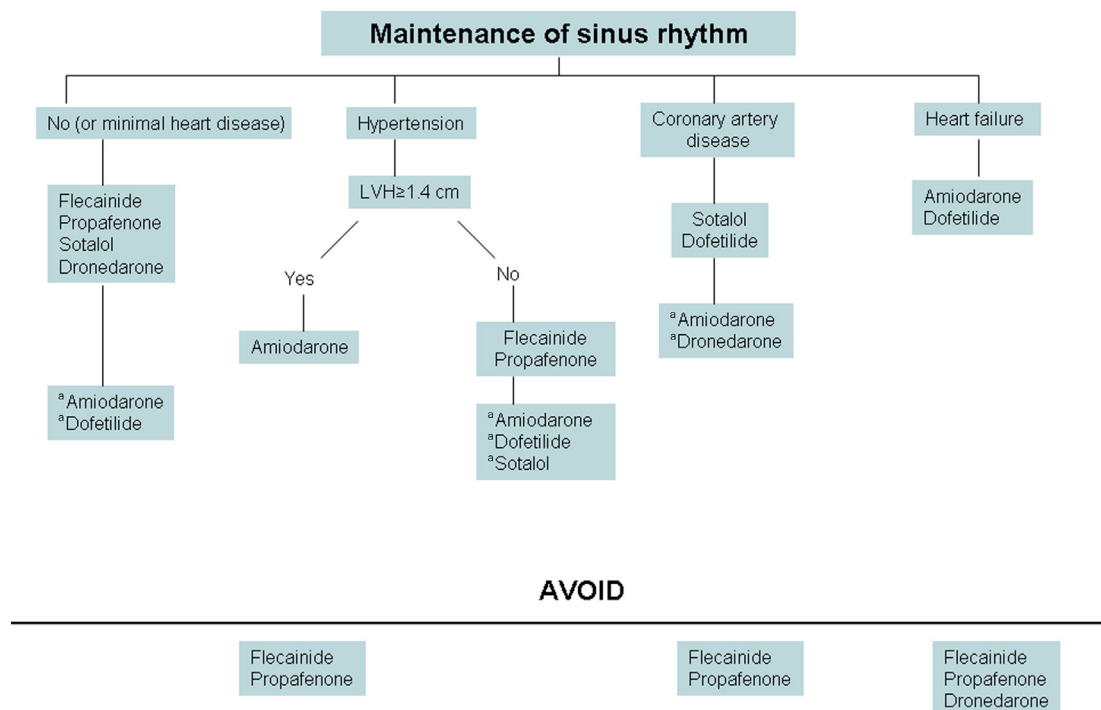
After the start of dronedaron therapy, rhythm should be monitored at least every 3 to 6 months. Dronedaron may be considered as a rhythm control agent in patients without HF and when extracardiac side effects of amiodaron need to be avoided. Dronedaron should be avoided in patients with permanent AF.

### ***Ibutilide***

Ibutilide is an IV  $I_{Kr}$  blocker, which also enhances late inward sodium current.<sup>50</sup> It is metabolized by the cytochrome P450 isoenzyme of the liver other than CYP3A4 and CYP2D6, and its plasma concentration constitutes less than 10% of the administered ibutilide, with most of the drug (82% of a 0.01-mg/kg dose) quickly excreted in urine. After administration, it restores sinus rhythm in 50% of patients, with an average conversion time of less than 30 minutes. It converts atrial flutter, with a higher rate of success than AF,<sup>51</sup> and pretreatment with IV magnesium sulfate improves the efficacy of electrical cardioversion.<sup>52</sup> It prolongs the QT interval with a risk of TDP, and, therefore, ibutilide infusion must be carried out in the inpatient setting, with continuous monitoring of the ECG for greater than 4 hours after administration. Ibutilide should be avoided in patients with hypokalemia, baseline prolonged QT, and depressed left ventricular function (<30%), because of increased risk of proarrhythmia.<sup>52</sup> IV magnesium pretreatment may decrease the risk of proarrhythmia.<sup>53</sup>

### ***Common Rules in AAD Selection***

Selection of antiarrhythmic agents is based on the presence or absence of underlying cardiac disease (Fig. 1) and the cardiac or noncardiac toxicity profile of a chosen drug (Table 1) as well as contraindications and drug-drug interactions. Other factors that may play a role in AAD selection are risk of associated bradyarrhythmias, risk of QT prolongation and TDP, and renal or hepatic dysfunction. Class I antiarrhythmic agents are contraindicated in patients with marked left ventricular hypertrophy, CAD, or congestive HF, because of the risk of ventricular arrhythmia. In patients without underlying structural heart disease, almost all AAD can be selected; however, flecainide, propafenone, or sotalol are preferred first-line agents. Dronedaron can be used as a first-line maintenance therapy for AF in patients without structural heart disease, but because of the excess mortality in patients with HF and stroke in persistent AF, its market share is restricted. Among class III drugs, dofetilide and sotalol are



**Fig. 1.** Algorithm for AAD selection for maintenance of sinus rhythm. <sup>a</sup> Second-line drug therapy. LVH, left ventricular hypertrophy.

associated with QT prolongation and should be avoided in patients with marked left ventricular hypertrophy. Disopyramide, because of its negative inotropic properties, is ideal for patients with HOCM, particularly if they already have a pacemaker or implantable cardioverter defibrillator.<sup>25</sup> In patients with congestive HF, only amiodarone and dofetilide are safe for use (see Fig. 1).

Our goal should be to use AAD in reducing AF symptoms. Occasional AF recurrences on AAD are expected and do not necessarily mean discontinuation of therapy. AAD for rhythm control should not be continued when AF becomes permanent. See Table 1 for AAD dosage, side effects, and major drug-drug interactions.

### OUTPATIENT VERSUS INPATIENT START OF ANTIARRHYTHMIC THERAPY

For paroxysmal AF, inpatient versus outpatient initiation of AAD therapy is an important consideration. Outpatient start of AAD is always desirable for patients, because it is less cumbersome and financially more feasible. Some controversy exists regarding the safety of outpatient start of AAD. This caution primarily relates to concerns of QT prolongation and risk of TDP, particular at the time of conversion from AF to sinus rhythm.<sup>54</sup> In patients with infrequent, and reasonably well-tolerated, symptomatic episodes of AF, the pill in

the pocket approach uses self-administration of a single dose of a drug shortly after the start of palpitations, therefore terminating an AF episode early and reducing the need for emergency room visits, hospitalization, and direct cardioversion. Flecainide and propafenone have been studied for this approach, and the expected effect is usually seen in 3 to 4 hours after administration.<sup>55</sup> However, this approach requires absence of any structural heart disease at baseline.<sup>56</sup>

Sotalol causes QT prolongation and may cause proarrhythmia. There is evidence of outpatient start of sotalol in patients with nearly no underlying structural heart disease with normal electrolytes and baseline QT interval of less than 450 milliseconds.<sup>57</sup> However, the package insert of sotalol has a black box warning against starting the medication in the outpatient setting. Patients treated with sotalol should be hospitalized with ECG monitoring if medication is to be initiated while the patient is in AF.<sup>58</sup> Data for outpatient AAD are strong for amiodarone and dronedarone. The decision to start AAD in an inpatient or outpatient setting should be carefully individualized.

### UPSTREAM THERAPY FOR AF

The concept of upstream therapy is the use of drugs that can prevent atrial electric and mechanical remodeling, thereby reducing the likelihood of

**Table 1**

Currently available drugs for treatment of atrial fibrillation according to the Vaughan-Williams classification, their mechanism of action, and their main adverse effects

<b>AAD</b>	<b>Dose/Metabolism</b>	<b>Drug Interactions/ Pharmacokinetics</b>	<b>Cardiovascular Toxicity</b>	<b>Noncardiovascular Toxicity</b>
<b>Vaughan Williams Class IA</b>				
Quinidine	324–648 mg every 8 h; hepatic CYP3A4 (70%), renal (30%)	Inhibits P450: ↑ digoxin levels Inhibits CYP2D6: ↑ tricyclic antidepressant and metoprolol	QRS prolongation with toxic doses, TDP (non-dose-related)	Rash, thrombocytopenia, cinchonism, pruritus
Disopyramide	Immediate release: 100–200 mg once every 6 h Extended release: 200–400 mg once every 12 h; renal/hepatic CYP3A4; reduced dose for renal and hepatic dysfunction	Metabolized with CYP3A4: caution with inhibitors (verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (rifampin, phenobarbital, phenytoin)	TDP, congestive HF	Anticholinergic side effects: narrow angle glaucoma, dry mouth, constipation, urinary retention, blurry vision
<b>Vaughan Williams Class IC</b>				
Flecainide	50–200 mg every 12 h; renal/hepatic CYP2D6	Metabolized by CYP2D6 (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%–10% of population) and renal excretion (dual impairment can increase plasma concentration)	Atrial flutter with 1:1 conduction, can unmask Brugada type ST elevation, contraindicated with CAD, ventricular tachycardia	Dizziness, headache, visual blurring
Propafenone	150–300 every 8 h or sustained release 225–425 twice a day; hepatic	Metabolized by CYP2D6 (inhibitors include quinidine, fluoxetine, tricyclics); genetically absent in 7%–10% of population—poor metabolizers have β blockade Inhibits P-glycoprotein: increases digoxin concentration Inhibits CYP2C9: increases warfarin concentration	Atrial flutter with 1:1 conduction, can unmask Brugada type ST elevation, contraindicated with CAD, ventricular tachycardia	Metallic taste, dizziness



Vaughan Williams Class III				
Sotalol	40–160 mg once every 12 h; renal	None	TDP, bradycardia	Bronchospasm
Dofetilide	CrCl $\geq$ 60 (500 $\mu$ g twice a day), CrCl 40–60 (250 $\mu$ g twice a day), CrCl 20–39 (125 $\mu$ g twice a day), CrCl <20 (not recommended); renal/hepatic CYP3A4	Metabolized by CYP3A: verapamil, hydrochlorothiazide, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol are contraindicated; discontinue amiodarone at least 3 mo before initiation	TDP	None
Amiodarone	Half-life 50 days; oral: load 10 g over 7–10 d, 400–600 mg daily in divided doses for 2–4 wk; maintenance typically 100–200 mg every day IV: load 150–300 mg over 10 min; then 1 mg/min for 6 h; then 0.5 mg/min for 18 h or change to oral dosing; after 24 h, consider decreasing dose to 0.25 mg/min; hepatic	Inhibits most CYPs to cause drug interaction: increase concentrations of warfarin, statins, many other drugs Inhibits P-glycoprotein: increase digoxin concentration	Bradycardia	Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates); hepatitis; thyroid (hypothyroidism or hyperthyroidism); photosensitivity; skin discoloration with chronic high dose; nausea; ataxia; tremor; alopecia
Dronedarone	400 mg every 12 h; renal, hepatic	Metabolized by CYP3A: caution with inhibitors (verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (rifampin, phenobarbital, phenytoin) Inhibits CYP3A, CYP2D6, P-glycoprotein: increase concentrations of some statins, sirolimus, tacrolimus, $\beta$ -blockers, digoxin	Bradycardia, avoid in congestive HF and permanent AF	Anorexia; nausea, liver failure
Ibutilide	IV 1 mg over 10 min; second dose 1 mg after 10 min if necessary; hepatic	No known drug interactions	TDP	Nausea

Abbreviation: CrCl: creatinine clearance.

AF. These drugs might arrest or delay the cellular process leading to AF either before (primary prevention) or after (secondary prevention) the development of AF. **Table 2** gives a summary of upstream therapy.

### **Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers**

Atrial tissue remodeling may contribute to the initiation and continuation of AF, especially in the population with HF. There are several studies, both in humans and animals, that have shown that inhibition of the renin angiotensin-aldosterone system (RAAS) may help prevent AF.<sup>59,60</sup> This finding could be because of the pleiotropic effects of RAAS blockade, which include prevention of left atrial dilatation and atrial fibrosis, slowing of atrial dilatation, and reduction of inflammation.<sup>61,62</sup>

Data for angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) for primary prevention (hypertensive heart disease without significant structural heart disease) are robust; however, secondary prevention has not been well shown.<sup>60,63,64</sup> A substudy of the Trandolapril Cardiac Evaluation trial<sup>65</sup> analyzed patients who had sinus rhythm at the time of randomization. After 2 to 4 years of follow-up, patients treated with trandolapril had significantly less AF compared with placebo. ACE-i have also been associated with reduced AF after myocardial infarction in patients with reduced LVEF.<sup>66,67</sup> Aldosterone inhibitors were compared with ACE-i in a randomized fashion, and they conferred the same reduction in AF recurrence rate in patients with paroxysmal AF.<sup>68</sup> A meta-analysis of AF studies<sup>60</sup> showed ACE-i and ARB use may be effective in reducing AF in patients with HF, and those with hypertension and left ventricular hypertrophy. However, the included retrospective studies were not designed to determine AF reduction as a primary outcome.

The ANTIPAF (Angiotensin II Antagonist in Paroxysmal Atrial Fibrillation) trial<sup>69</sup> is a prospective, randomized, placebo-controlled trial analyzing AF burden in patients with documented paroxysmal AF without baseline structural heart disease. In this trial, 430 patients received olmesartan 40 mg or placebo, and after 1 year of follow-up, ARB therapy failed to show any reduction in the primary outcome (ie, AF burden).

As per recent 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines and the Heart Rhythm Society (HRS) AF guidelines,<sup>10</sup> upstream ACE-i and ARB are class IIa recommendations for primary prevention of new onset AF in patients with HF, and class IIb for primary prevention of new onset AF in the setting of hypertension.

### **3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitors/Statins**

Statins are known to have pleiotropic effects and may exert positive effects on AF by reducing inflammation by pathways other than 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibition.<sup>70,71</sup> Animal data show that simvastatin reduces electrical remodeling, atrial fibrosis by decreasing fibroblast proliferation, and reduces AF duration.<sup>72,73</sup> Most of the data evaluating statin effects on AF are retrospective and conflicting. Young-Xu and colleagues<sup>74</sup> studied 449 patients with chronic stable CAD, treated with any statin, followed for an average 5 years and showed a significant reduction in the risk of developing AF (odds ratio: 0.48; 95% confidence interval: 0.28–20.83). However, similar results were not seen in a VA study,<sup>75</sup> which looked at 5417 patients who received statin therapy (any brand) in a similar patient profile with CAD and failed to show any reduction in AF recurrence after 4.8 years of follow-up. Smaller randomized prospective studies have shown benefit of statins in reducing AF episodes; however, similar benefits are still to

**Table 2**  
Upstream drug therapy for AF and its proposed mechanisms

Mechanism	Drugs/Agents	Effect on Atrial Fibrillation
RAAS inhibition	1. ACE-i/ARB	Inhibition of atrial fibrosis, remodeling, and antiinflammatory effect
	2. Aldosterone	Inhibition of atrial fibrosis, antiinflammatory effect
HMG-CoA reductase	Statins	Antiinflammatory effect, pleiotropic effects
Antiinflammatory drugs	1. Steroids	Antiinflammatory
	2. $\omega$ -3 PUFA	Unclear, may be direct antiarrhythmic effect

**Abbreviations:**  $\omega$ -3 PUFA,  $\omega$ -3 polyunsaturated fatty acids; ACE-i, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; RAAS, renin angiotensin-aldosterone system.

be determined in a larger prospective trial, PAFRIOSIES (Paroxysmal Atrial Fibrillation: Role of Inflammation, Oxidative Stress Injury and Effect of Statins) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00321802) Identifier: NCT00321802), which is under way and awaiting results. Data are still unclear in regard to the effects of statins on clinical outcomes in AF. The clearest prospective data of statin in AF prevention are in the postoperative setting.<sup>76</sup> The ARMYDA-3 (Atorvastatin for Reduction of Myocardial Damage During Angioplasty 3) study<sup>77</sup> randomized 200 patients undergoing cardiothoracic surgery to receive either atorvastatin or placebo starting 7 days preoperatively. Atorvastatin showed a significant reduction in postoperative AF (POAF) versus placebo ( $P = .003$ ) and significantly shorter length of hospital stay ( $P = .001$ ).

Statin therapy may be reasonable for primary prevention of new onset AF in patients with CAD, but its routine use in preventing AF is not recommended.

### **Antiinflammatory Agents**

Inflammation associated with or without postoperative setting has a clear association with AF.<sup>78,79</sup> The levels of inflammatory markers like C-reactive protein (CRP) are increased in patients with AF compared with sinus rhythm.<sup>80</sup> Inflammation seems to be involved in the early phase of electrical remodeling. However, it is not clear if inflammation is a precursor of AF and electrical remodeling or a marker of ongoing electrical remodeling.

- Corticosteroids: data for steroid use and reduction in AF burden and recurrence are sparse. Most of the steroid data evaluated steroids for POAF.<sup>81</sup> Studies evaluating beneficial effects of steroids in POAF are small or meta-analyses of smaller studies with heterogeneous patient pools.<sup>82–85</sup> The risk of long-term steroid use warrants their cautious prophylactic use. Judicious use of steroids for AF prevention and reduction of AF burden is not recommended.
- $\omega$ -3 polyunsaturated fatty acid (PUFA): Li and colleagues<sup>86</sup> reported that  $\omega$ -3 PUFA inhibits transient outward ( $I_{to}$ ), ultrarapid delayed rectifier potassium currents ( $I_{Kur}$ ) and voltage gate sodium channel ( $I_{Na}$ ) in human atrial myocyte, which may be responsible for decrease in AF with the use of  $\omega$ -3 PUFA. Initial studies evaluated the use of  $\omega$ -3 PUFA in sudden cardiac death and concluded with disappointing results. At the same time, a proof of concept open-label study showed a remarkable 65% reduction in AF occurrence after coronary

artery bypass graft,<sup>87</sup> and a search for antiarrhythmic effects of  $\omega$ -3 PUFA in atrial tachyarrhythmias began. Despite positive results of  $\omega$ -3 PUFA in various animal studies, similar results in large robust designed POAF trials and postelectrical cardioversion studies could not be replicated.<sup>88,89</sup> Kowey and colleagues<sup>90</sup> evaluated the safety and efficacy of  $\omega$ -3 PUFA in a randomized, double-blind, placebo-controlled design in patients with paroxysmal or persistent AF without underlying structural heart disease. After 6 months of follow-up, there was no significant benefit of  $\omega$ -3 PUFA in preventing recurrence of symptomatic AF in both AF strata.

### **Aldosterone Antagonists**

Aldosterone is known to play an important role in angiotensin II-mediated inflammation and fibrosis. There is also a higher incidence of AF in patients with primary hyperaldosteronism. In an experimental model of HF, spironolactone and eplerenone decreased atrial fibrosis and vulnerability to AF. A substudy of the eplerenone in patients with mild systolic HF (EMPHASIS) trial showed that eplerenone treatment can prevent the first AF or atrial flutter episode. After 2 years of observation, 2.7% patients treated with eplerenone compared with 4.5% treated with placebo developed new AF.<sup>91</sup> The SPIR-AF trial evaluated the antiarrhythmic effect of spironolactone compared with ACE-i in 164 patients with an average 4-year recurrent AF history. It is a prospective, randomized 12-month trial, with 4 treatment arms: group A, spironolactone, enalapril, and a  $\beta$ -blocker; group B, spironolactone and a  $\beta$ -blocker; group C, enalapril plus a  $\beta$ -blocker; and group D, a  $\beta$ -blocker alone. There was a significant reduction in the incidences of symptomatic AF in both groups treated with spironolactone (group A and group B) ( $P \leq .001$ ), at 3, 6, 9 and 12 months of treatment. However, no significant difference was seen in AF recurrences between group A and B.<sup>68</sup> Aldosterone antagonist treatment may be a simple and valuable additional option in the population with HF along with other approved antiarrhythmic agents for AF prevention. More robust data, especially in primary prevention, are required before recommending its upstream use (see [Table 2](#)).

### **FUTURE PHARMACOLOGIC THERAPY**

Current AAD bring success with associated safety issues with their use, which has stimulated the development of AF pharmacologic agents in 2

directions: modification of existing compounds and designing drugs with new targets.

### ***Vernakalant***

Vernakalant is a complex class III electrophysiologic agent with the use-dependent or rate-dependent sodium inhibition and broad potassium channel inhibition ( $I_{to}$ ,  $I_{KACH}$ , and  $I_{Kur}$ ).<sup>92,93</sup> It has shown good safety both in animal studies as well as in initial phase 1 to 3 trials.<sup>24,94,95</sup> It is more effective in conversion of AF than atrial flutter, particularly if administered within 7 days of arrhythmia onset and AF of shorter duration. A phase 3 superiority study of Vernakalant Versus Amiodarone in Subjects With Recent Onset Atrial Fibrillation (AVRO), randomized 234 patients for AF conversion into an IV vernakalant and IV amiodarone strategy in a double-blind fashion. Conversion from AF to sinus rhythm within the first 90 minutes (primary end point) was achieved in 60 of 116 (51.7%) patients treated with vernakalant compared with 6 of 116 (5.2%) patients treated with amiodarone ( $P < .0001$ ). Vernakalant showed efficacy superior to amiodarone for acute conversion of recent onset AF.<sup>24</sup> The IV formulation can cause hypotension and shock and is therefore not approved in the United States. An IV form is available in Europe, and an oral formulation is in development.

### ***Ranolazine***

Ranolazine is a new drug approved for refractory chronic angina. Preclinical data showed that as well as being anti-ischemic, ranolazine also reduced supraventricular arrhythmia, including AF. It blocks several ion channels, including peak and late  $I_{Na}$ ,  $I_{CaL}$ , and  $I_{Kr}$ . Inhibition of  $I_{Na}$  with ranolazine or vernakalant may reduce the risk of TDP associated with  $I_{Kr}$  inhibition. It is still to be determined if combination of ranolazine or vernakalant with  $I_{Kr}$  blockers (sotalol or dofetilide) decreases the risk of TDP.

Nonclinical studies showed that dronedarone in combination with ranolazine works synergistically, which is likely caused by a multichannel ion effect, resulting in inhibition of peak and late  $I_{Na}$ ,  $I_{KACH}$ , and  $I_{Kr}$  in atrial myocyte. A synergistic effect of low-dose dronedarone with ranolazine was studied in a recently presented phase 2 study (HARMONY trial, [ClinicalTrials.gov](http://ClinicalTrials.gov) Identifier: NCT01522651), evaluating AF reduction with the combination drug. After a 12-week treatment, in patients treated with ranolazine/dronedarone 750 mg/150 mg twice a day and 750 mg/225 mg twice a day, there was a 45% and 59% AF reduction, respectively ( $P = .072$  and  $P = .008$ ), versus placebo.<sup>96</sup> These results

are consistent with preclinical findings of a synergistic effect when these therapies are used in combination.

### ***Miscellaneous***

Atrial tissue has a predominance of  $I_{Kur}$  and  $I_{KACH}$ , and therefore, inhibiting these ion channels selectively prolongs action potential duration in the atria. AVE0118 selectively blocks the  $I_{Kur}$  and showed some efficacy in the early phase of development.<sup>97</sup> Tertiapin-Q is a nonselective inhibitor of  $I_{KACH}$  and is derived from honeybee. Tertiapin-Q terminated AF in a vagally induced AF model, as well as reducing AF inducibility.<sup>98,99</sup> NTC-801 is the only available selective  $I_{KACH}$  inhibitor.<sup>100</sup> There are still limited human data of specific potassium channel blockers, but there is promise for future growth in AAD development for AF. Oral vanoxerine was initially in clinical development for Parkinson disease, but recent preclinical data showed its prominent antiarrhythmic effects.

### **SUMMARY**

AF is a complex disease, requiring better understanding and a multifaceted approach. Research is needed to develop, subclassify, and identify new therapeutic targets, with promise that precise therapies aimed at preventing or reversing AF will be developed. Antiarrhythmic therapeutic strategies for AF should be focused on controlling pathophysiologic remodeling, with better prevention and disease-modifying strategies. Large randomized controlled trials are required in order to develop improved clinically relevant guidelines for AF.<sup>101</sup>

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