



# Drug Therapy in Atrial Fibrillation Management: Where Do We Stand in 2010?

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## Abstract

Atrial fibrillation (AF) is a commonly encountered arrhythmia in our daily practice. Every year a huge bulk of data is published about different management strategies, new antiarrhythmic drugs, anticoagulation protocols and ablation procedures in these patients. In this review article, we discuss different management strategies and new antiarrhythmic drugs as well as those commonly used. We will also have a brief look at anticoagulation in AF.

We try to introduce the most recent publications in this field and we think that this review article may not only give information about the current state of antiarrhythmic therapy of AF, it may also show some progresses that we may anticipate in the near future. New drugs are promising in the management of AF because of better safety profile and also acceptable efficacy. A comparison between the catheter ablation procedure and antiarrhythmic therapy is beyond the scope of this article.

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## Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia. The prevalence of AF increases with age<sup>1-3</sup> and it tends to occur more frequently in men; the reason for the latter is not clear yet.<sup>4</sup>

In addition to the structural heart disease, hypertension and obesity also play very important roles in the AF development. Alcohol consumption, fatty acid intake, inflammation, and oxidative stresses may predispose the development of AF.<sup>5</sup> Approximately one third of patients have no evidence of cardiac involvement.<sup>6</sup> AF is classified into first onset, paroxysmal, persistent, and permanent based on its pattern of evolution and response to treatment.<sup>7</sup>

The direct cost of AF on the National Health Service was 244-531 million Euros (0.6-1.2% of overall health care expenditure) in the UK in 1995.<sup>8</sup>

There are several management options for patients with

AF which are evolving rapidly. The aim of the present review article is to explain the current state of drug therapy as well as new drugs used in the AF management.

## Pathogenesis

The development and maintenance of AF depend on several factors, amongst which atrial re-entry and sustained ectopic atrial activities are the most important.<sup>6</sup>

Cardiac diseases can initiate atrial remodeling and create an irreversible substrate, after which enhanced ectopy and re-entry are facilitated.<sup>9</sup>

Atrial fibrosis and structural remodeling are common findings in long-lasting AF;<sup>10</sup> and when they happen, maintenance of sinus rhythm becomes more difficult.<sup>11</sup>

Elevated levels of matrix metalloproteinase and longer duration of AF may contribute to difficulty in the conversion

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of the AF rhythm.<sup>12</sup>

## ***AF Management***

Although AF is a benign disease, it is associated with increased morbidity. Of great significance are heart failure and stroke.<sup>13</sup> Indeed, the risk of stroke significantly increases in AF (23.3% life-time risk in patients between 80 and 89 years of age).<sup>14</sup>

AF management creates a high economic burden because of the concomitant presence of heart failure, coronary artery disease, hypertension, and the need for frequent hospitalizations. Expensive antiarrhythmic drugs and interventional procedures are other important factors that raise the costs of AF care.<sup>15</sup>

Four major aspects should be considered in the AF management: I- Symptom control by slowing ventricular response during paroxysmal or persistent AF and long-term rate control in permanent AF, II- Cardioversion to sinus rhythm, III- Maintenance of sinus rhythm after successful cardioversion, and IV- Prevention of complications and thromboembolic events.<sup>15</sup> The first three objects are related but anticoagulation is a different aspect in the AF management.<sup>16</sup>

In cases where there is a treatable cause for AF (endocrine disease, inflammation, cardiac surgery, etc.), there may be no need for the long-term management of AF except when treating the underlying condition.<sup>16</sup>

Monotherapy with digoxin maybe a good option for old patients and ventricular rate response is an acceptable index for the evaluation of response to therapy.<sup>17</sup> Be that as it may, digoxin is not an ideal drug for this purpose because it works well in lowering ventricular response at rest but with less effect during exertion. Adding a beta blocker or calcium antagonist may be useful, but in older patients it should be done cautiously.<sup>17</sup>

## ***Rhythm versus Rate Control***

In order to prevent the complications and symptoms of AF, two main strategies exist: I - Rhythm control: converting the patient's rhythm to sinus and maintaining the sinus rhythm, and II - Rate control: slowing the ventricular response rate without insisting on conversion to sinus rhythm.<sup>18</sup>

From a theoretical point of view, converting AF into sinus rhythm is the best option.<sup>6</sup> Nonetheless; the most important trials reported in the existing literature thus far have mentioned no significant difference in terms of quality of life and other outcomes between the two strategies. It seems that the side effects of antiarrhythmic agents (pro-arrhythmia) in the long term, poor efficacy of drugs in the maintenance of sinus rhythm, and inappropriate discontinuation of anticoagulants

in the patients who still have AF episodes can interfere with good results in the rhythm-control arm.<sup>16</sup> Therefore, many experts believe that rhythm control with safe antiarrhythmic drugs or catheter ablation will play an important role in the AF management.

Antiarrhythmic agents from class IA, IC, and III can be effective; and by using less toxic drugs, the risk of tachycardia-mediated cardiomyopathy can also be lowered.<sup>19, 20</sup>

The main agents for slowing ventricular response in AF are beta blockers, calcium channel blockers, and digoxin.<sup>17</sup> In the AFFIRM study, there was no survival difference between rate-control and rhythm-control strategies. In addition, the lower risk of adverse drug effects in the rate-control arm conferred some advantages in this arm. A post-hoc analysis of the AFFIRM data proved that there was no significant benefit in the rhythm-control group versus the rate-control group in patients with AF and left ventricular dysfunction.<sup>21</sup>

The RACE study showed that for the prevention of cardiovascular mortality and morbidity in AF, rhythm control was not superior to rate control.<sup>22</sup> A later analysis of the RACE data showed that the rhythm-control strategy in AF patients with hypertension was associated with increased cardiovascular morbidity and mortality; accordingly, the rate-control strategy was deemed superior.<sup>23</sup>

In the PIAF trial, clinical outcomes were similar between the rate-control group and the rhythm-control group but exercise tolerance was better in the rhythm-control arm.<sup>24</sup>

The STAF study showed no difference between the two main strategies of the AF management in all end-points except for hospitalization.<sup>25</sup>

The HOT CAFÉ study demonstrated that rate control was similar to rhythm control with respect to AF mortality and morbidity such as stroke, thromboembolic events, and bleeding.<sup>26</sup>

Guedon-Moreau et al. posited that the management of paroxysmal AF with flecainide was associated with improved quality of life.<sup>27</sup>

Serial cardioversion in heart failure patients is correlated with poor outcome compared with normal left ventricular ejection fraction patients.<sup>28</sup>

The rhythm-control strategy is more popular than the rate-control strategy worldwide. Still, it seems that in patients with recurrent AF after cardioversion, slowing the ventricular response may be the choice and first step. Those with long-standing AF or previous failure of antiarrhythmic drugs should be selected for the rate-control strategy.<sup>29</sup>

## ***Antiarrhythmic Drugs***

Class III antiarrhythmic agents have an important role as a part of cardioversion strategy and maintaining sinus rhythm. Amiodarone, which is the hallmark drug in this group, is a relatively safe and effective drug but frequent adverse effects

have been reported with its long-term use.<sup>30</sup>

It is the most frequently used antiarrhythmic drug for AF treatment in that it prolongs the repolarization in the atria and ventricles.<sup>31</sup> The elimination half-life of amiodarone is 30-55 days.<sup>32</sup> It may give rise to thyroid dysfunction, pulmonary fibrosis, dermatological changes, and ophthalmic involvement.<sup>31</sup>

Roy et al. posited that low-dose amiodarone (< 600 mg daily) was more effective than sotalol or propanolone for the prevention of AF. In their study, the recurrence rate of AF in a 16-month follow-up period was 35% in the amiodarone group versus 63% in the other group.<sup>33</sup>

Some other studies have also shown similar success rates (50-70%) in achieving and maintaining sinus rhythm for amiodarone.<sup>34, 35</sup>

Cardioversion rate for class IC and III drugs is approximately 60-80% in AF episodes lasting less than 48 hours.<sup>13</sup>

Dronedaron is a benzofuran-derivate of amiodarone with the same electropharmacological profile<sup>36</sup> but without side effects on the pulmonary system.<sup>37</sup> It has a shorter half-life than amiodarone (1 - 2 days).<sup>32</sup> By blocking multiple channels and having some antiadrenergic properties, it prolongs action potential duration and, therefore, reduces the heart rate. Additionally, it has low risk of Torsade de pointes.<sup>6</sup>

The EURIDIS and ADONIS trials showed that 400mg dronedaron orally, twice daily, was more effective than placebo in slowing the ventricular response and maintaining sinus rhythm in AF patients.<sup>38</sup>

The ANDROMEDA study was terminated prematurely because of increased mortality due to the worsening of heart failure in the dronedaron group.<sup>39</sup> Therefore, dronedaron is contraindicated in patients with moderate to severe heart failure.<sup>6</sup>

The ATHENA trial supported the idea that dronedaron could reduce both primary and secondary end-points. The median time to the recurrence of AF was prolonged with this drug.<sup>40</sup>

Dronedaron can reduce the rate of death or hospitalization in AF patients.<sup>40</sup>

Data from the DIONYSOS trial suggested higher tolerability for dronedaron than that for amiodarone but less efficacy.<sup>6</sup>

Budiodarone (ATI-2042) is another analogue of amiodarone. Its half-life is 7 hours and is administered orally up to 1200 mg daily. Even in low doses, it can be effective in the reduction of AF episodes and the duration of the mean episode.<sup>41</sup> This drug is undergoing phase II trials.<sup>42</sup>

Celivarone is another analogue of amiodarone and is still under investigation. It can be consumed both by oral and intravenous (IV) routes and can act similarly to all categories of antiarrhythmic agents. It is effective in the management of hypokalemic and vagotonic AF. In experimental animal models, it was at least as potent as amiodarone and dronedaron.<sup>43</sup>

Ibutilide is a class III antiarrhythmic agent that can convert AF to sinus rhythm more rapidly than can procainamide or sotalol. Its dosage is 0.008 mg/kg over 10 minutes. It has been shown that ibutilide has no significant advantage compared with amiodarone for the conversion of AF but severe hypotension was not seen with ibutilide.<sup>44</sup>

For acute AF, conversion to sinus rhythm with ibutilide is about 59%, but there is 1.7% risk of polymorphic ventricular tachycardia with this drug. As a result, it is advised to keep the patients receiving ibutilide under monitoring for at least 24 hours after the infusion of this drug.<sup>45</sup>

Dofetilide is another class III antiarrhythmic drug that can be used for maintaining sinus rhythm in congestive heart failure patients with AF. The DIAMOND CHF trial showed that it could reduce hospitalization due to heart failure. Heart failure worsening was reduced by 25%.<sup>46</sup>

Dofetilide is known to be more effective in patients with persistent AF compared with those with paroxysmal AF, and significant proarrhythmic adverse effects can occur even with close monitoring.<sup>47</sup>

Ranolazine is an antianginal agent that can block several ion channels and consequently increase the QT interval modestly (2 - 6 millisecond). This agent has higher affinity for sodium channels in the atria than in the ventricles. Phase III human trial is planned for this agent.<sup>48</sup>

Azimilide is also a class III antiarrhythmic drug with the dosage of 100 - 125 mg daily orally and a half-life of 4 days. A trial demonstrated that azimilide was a safe and effective drug for the management of AF in patients with left ventricular dysfunction after myocardial infarction.<sup>49</sup>

Tedisamil is another drug from class III family. It can prolong action potential in the atria more than ventricles and its half-life is 8 - 13 hours. It has a rapid onset of action and can convert AF to sinus rhythm in the majority of patients by 30 - 40 minutes following an IV injection (0.4 - 0.6 mg/kg).<sup>50</sup>

Impaired conduction between myocytes is associated with increased risk of AF, and this effect is more prominent in patients with heart failure and mitral insufficiency. Rotigoptide can improve cell-to-cell conduction by the augmentation of the gap junction conductance. In an animal model, rotigoptide was effective in the management of AF associated with mitral regurgitation or ischemia but was not effective in the presence of heart failure or atrial enlargement.<sup>51</sup>

Introduction of drugs with selective affinity for channels that specifically contribute in atrial repolarization is an interesting aspect in the AF management. These drugs are called atrial repolarization delaying agents.<sup>42</sup>

By the application of these agents, the proarrhythmic effect of traditional drugs can be minimized.<sup>42</sup>

Inhibition of ultra rapid delayed rectifier potassium current (Ik<sub>ur</sub>) is an example for atrium-selective approach because this channel is located exclusively in the atria.<sup>52</sup>



Sodium channel characteristics are different between the atrium and ventricle, and selective sodium channel blocking is another specific strategy for the management of AF.<sup>53</sup>

Vernakalant is an atrial-selective agent that can block sodium and potassium channels in the atrium and has little effect on the other channels.<sup>54</sup> Vernakalant prolongs the atrial-effective refractory period.<sup>55</sup>

Roy et al. showed that an IV administration of RSD1235 (Vernakalant) was effective in the termination of recent onset AF (50-60% vs 4 - 5% compared with placebo).<sup>56, 57</sup> The drug is infused at 2.25 - 4.5 mg/kg in 35 minutes.<sup>56</sup>

This drug has a small effect on sinus node recovery time (SNRT), atrioventricular node (AVN) refractoriness, and intraventricular conduction.<sup>55</sup>

Phase II trials have shown that oral vernakalant 300 - 600 mg twice daily can effectively maintain sinus rhythm compared with placebo, and earlier studies demonstrated that this drug was very effective for converting new AF to sinus rhythm.<sup>58</sup>

Sneezing, nausea, dysgeusia, paresthesia, and hypotension are amongst the adverse effects that can be seen with vernakalant. Sinus arrest, atrioventricular dissociation, and ventricular fibrillation are the other effects that have been reported.<sup>58</sup>

AZD7009 is another agent that can block delayed rectifier potassium current (I<sub>kr</sub>), sodium current (I<sub>Na</sub>), and ultra rapid rectifier delayed potassium current (I<sub>kur</sub>).<sup>59</sup>

In animal studies, it has been shown that this drug has a predominant atrial electrophysiological effect.<sup>60</sup>

It is a highly effective agent in terminating AF/AFL and maintaining sinus rhythm in animal models.<sup>59</sup>

AZD7009 can increase the atrial-effective refractory period more in the dilated atrium rather than the normal-sized atrium (probably due to I<sub>Na</sub> inhibition). Therefore, it is effective in converting persistent AF to sinus rhythm.<sup>61</sup>

Nifekalant is an I<sub>kr</sub> blocker that is used for the acute treatment of refractory ventricular tachycardia. It can prolong the atrial refractory period and can terminate atrial flutter in 75% of patients within one hour but it is not a suitable agent for converting AF to sinus rhythm.<sup>62</sup>

As was mentioned before, atrial fibrosis has a central role in pathological changes contributed to AF.<sup>63</sup>

Upstream therapy can interfere with this phenomenon. Renin angiotensin system (RAS) inhibitors, statins, and omega-3 fatty acids are the drugs used to prevent atrial fibrosis.<sup>6</sup>

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may be effective in AF prevention in patients with hypertension, left ventricular hypertrophy, and congestive heart failure, as well as in post-myocardial infarction patients with depressed left ventricular function.<sup>42</sup>

Kalus et al. demonstrated that the use of ARBs and ACEIs for at least three months before cardiothoracic surgery could

decrease the incidence of post-operative AF.<sup>64</sup>

Serotonin (5HT<sub>4</sub>) receptor blockers (RS - 100302, SB - 207266, and CVT - 150) have no ventricular side effect and can be promising agents in the AF management because the infusion of serotonin can cause AF.<sup>42</sup>

## ***Atrial Fibrillation and Thromboembolism***

Atrial fibrillation can predispose clot formation in the left atrium and consequently ischemic stroke and extra cranial thromboembolism.<sup>65, 66</sup>

If AF persists for two days, left atrium thrombosis could be seen in 5 - 14% of patients.<sup>67</sup> It might, subsequently, become fragmented and embolize to the peripheral atrial system.<sup>68</sup>

Most thromboembolic events are manifested in the brain, but other organs can also be affected and contribute to mortality and morbidity. The annual incidence rates of ischemic stroke, acute mesenteric ischemia, and acute limb ischemia are 2.3% (lethality 30%), 0.14 (lethality 70%), and 0.4% (lethality 16%), respectively. Thromboembolic events can be reduced by warfarin and aspirin in guideline-adherent antithrombotic therapy. If thromboembolic events occur, restoring perfusion and limiting the tissue ischemia are the treatment of choice. The major goal is, however, preventing these events. In patients with valvular heart disease or high-risk individuals (according to the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>VAS<sub>C</sub> scoring), warfarin is the drug of choice. In low-risk conditions, aspirin can be used.<sup>69</sup>

Warfarin needs frequent dose adjustment because it has multiple interactions with food and drugs, and it requires frequent laboratory monitoring. Therefore, the rates of discontinuation are high. That is why many patients may receive inadequate anticoagulation.

Dabigatran is a new, potent, direct and competitive inhibitor of thrombin. Its half-life is 12 to 17 hours, and it does not require regular monitoring. Connolly et al. demonstrated that AF patients receiving Dabigatran 110 mg twice daily had similar rates of stroke and systemic embolism compared with those using warfarin, but with lower rates of major bleeding. At a dose of 150 mg twice daily, the rate of stroke and systemic embolism is lower but the rate of major bleeding is similar to warfarin.<sup>70</sup>

## ***Conclusion***

In conjunction with catheter ablation, which is a rapidly growing modality in the AF management, drug therapy of AF still has a pivotal role and is subject to striking changes and new developments. Our new concepts about the mechanisms of AF and its triggers, substrates, atrial remodeling, and related ionic channels have led investigators towards newly developed drugs which may probably be more effective



and with fewer side effects. Atrial selective antiarrhythmic drugs, new class III antiarrhythmics, and new anticoagulants are most mentionable amongst these drugs.

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