

## Editorial: Advances in The Therapy of Atrial Fibrillation: Incrementally Progressive But Not Without Missteps

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**Abstract:** Advances in the therapy of atrial fibrillation (AF) have not come easily or quickly, despite the recognized need for significantly better antiarrhythmic agents for AF termination and prevention as well as for more user-friendly anticoagulants for the prevention of emboli in patients with AF. Rather, the road has been only slowly progressive and bumpy. This manuscript will introduce the recent issues with dronedarone, the complex development story for vernakalant, and the appearance of the new oral anticoagulants. Each of these three considerations will then be explored in more depth by the invited experts for this “mini-Thematic issue” in Current Cardiology Reviews.

**Keywords:** Atrial fibrillation, antiarrhythmic drugs, anticoagulants, dronedarone, vernakalant, factor Xa and direct thrombin inhibitors.

Advances in the therapy of atrial fibrillation (AF) have not come easily or quickly, despite the recognized need for significantly better antiarrhythmic agents for AF termination and prevention as well as for more user-friendly anticoagulants for the prevention of emboli in patients with AF. Rather, the road has been only slowly progressive and bumpy.

In the United States, approximately two decades passed between the approval of dofetilide and the approval of dronedarone, without the appearance of even one other oral antiarrhythmic drug (AAD) for AF in between. Then, following dronedarone’s approval and steady increase in use, PALLAS [1], a post-marketing trial aimed at an additional indication, abruptly altered the drug’s safety profile, which seemed to be clear beforehand. It has taken a significant period of time after the trial’s publication for the underpinnings of the PALLAS results [1] to begin to become apparent. Notably, they appear to include an underlying significant history of heart failure in most of the patients enrolled, with periods of decompensation, and the role of higher digoxin levels that develop in patients given dronedarone. Approximately 70% of patients in PALLAS had AF of over 2 year’s duration and approximately the same percentage had heart failure sufficiently severe to warrant hospitalization in the prior year – though not in the prior month. Advanced structural heart disease, worsened ventricular function and its consequences while on dronedarone rather than on placebo during periods of decompensation, and adverse dronedarone-digoxin interactions were likely major factors in the outcome results in PALLAS. Notably, the PALLAS results resembled the adverse outcomes in the dronedarone heart failure study, ANDROMEDA [2], more than they did the beneficial

outcomes in the less-advanced heart disease dronedarone AF trial, ATHENA [3], from which the concept for the PALLAS trial actually derived. For example, the hazard ratios in ATHENA, PALLAS, and ANDROMEDA respectively were: 1.0, 1.9, and 2.3 for total mortality and 0.76, 1.92, and 2.13 for cardiovascular hospitalization or total mortality and the percentage of patients with a heart failure history was approximately 20%, 70%, and 100% (with the severity being least in ATHENA). Understanding such issues will help clinicians use dronedarone more effectively and safely. These will be discussed in more detail in the accompanying manuscript by Drs. Naccarelli and Kowey. Dronedarone is now indicated for the reduction of AF in patients with non-permanent AF who do not have heart failure. In this usage, dronedarone can be effective and may have some distinct advantages over other agents.

Juxtaposed to the development of dronedarone, another new antiarrhythmic agent, vernakalant, was also ongoing. Its intravenous (IV) form (for terminating AF) was developed first; the oral congener (for the prevention of AF) lagged behind. As to its current status in the U.S., a certain former New York Yankee catcher might say: “you don’t have what you can’t have because everyone else has it”.

Several pivotal trials involving over 700 patients examined the profile of IV vernakalant for the conversion of AF [4]. These revealed efficacy and safety sufficient to result in approval of intravenous vernakalant in multiple countries for this purpose. Conversion rates for recent onset AF of over 50% (versus <5% with placebo) with an average time to conversion of 8 to 11 minutes were demonstrated. Interestingly, the drug does not work for atrial flutter.

Despite vernakalant’s approval for pharmacologic cardioversion of AF in multiple countries ex-U.S., the FDA viewed the results differently than did their European counterparts. Rather than approve vernakalant for the conversion of AF, the FDA requested an additional larger trial to further

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examine vernakalant's safety. Following one death in a South American patient of uncertain relationship to the drug, this study was put on hold, resulting in a drug now available in Europe that American clinicians do not have. Will we ever, or will we not? The rest of this story is still to be told. More details concerning vernakalant's path to approval (and non-approval) can be found in the accompanying manuscript by Dr. A. John Camm.

Finally, there is the issue of anticoagulation – a therapy required for the majority of patients with AF. In this arena, the concern has not been drugs with less than desirable efficacy (something we have not been able to say about AADs). The vitamin K antagonists (VKA), such as warfarin, are highly effective for reducing stroke and systemic embolism (SSE) and the risk of death in patients with AF who are at increased risk for SSE [5]. Rather, VKAs are inconvenient to use, both from the standpoint of the patient and the prescriber. They are also associated with a risk of bleeding, which, if intracranial, can be fatal. Accordingly, in practice, despite its high efficacy, warfarin has been used in only 40-60% of patients at risk in almost all reports, and, when used, it is used inadequately about half of the time (as determined by a time in the therapeutic range for the INR of only about 50-60% in most published series).

Now after over 5 decades of VKAs without an orally administered alternative, suddenly, within the period of only a couple of years, we have multiple new FDA approved agents to reduce SSE in at-risk patients with “nonvalvular” AF (NVAf): dabigatran, rivaroxaban, and apixaban – with more still in development (including edoxaban, whose pivotal trial data were presented in 2013). These agents target either thrombin inhibition or reducing thrombin production. Moreover, they have been demonstrated to be as effective as or more effective than warfarin with similar or lower bleeding risks and a dramatically lower risk of intracranial bleeding [6-8], no food interactions, fewer drug interactions, and no requirement for coagulation test monitoring to guide their essentially fixed dosing regimens. Some would suggest that these agents replace VKAs in all patients with NVAf who require anticoagulation to prevent SSE. Should they? If so, how is the clinician to choose among them for any given patient (or are they entirely interchangeable)? The path leading to the approval of these agents as well as many considerations regarding their use are detailed in the accompanying manuscript by Drs. Halperin and Dorian.

For this issue of *Current Cardiology Reviews*, I was given the privilege and opportunity to assemble a group of true experts in the fields of antiarrhythmics, anticoagulants, and drug development and to request of them that they ex-

plore the above stories and questions in more detail for the clinician reader. Drs. Naccarelli and Kowey will discuss the most recent data with dronedarone and then opine for the reader how best to use this agent. Dr. Camm will detail and clarify the vernakalant story and perhaps give us a clue to its future. And, Drs. Halperin and Dorian will highlight the details of the pivotal trials of our exciting new oral anticoagulants and provide guidance as to the proper use of and selection factors for these agents.

It is my hope that upon completion of this issue of *Current Cardiology Reviews* that the reader will have both a better understanding of some of the pitfalls in drug development as well as a better understanding regarding the optimal use of our newest therapeutic drugs for the ever increasing number of patients with atrial fibrillation.

## CONFLICT OF INTEREST

The author reports the following conflict of interest: investigator for, consultant for, and/or speaker on behalf of Sanofi, Merck, Boehringer Ingelheim, Janssen, Pfizer, Bristol Myers Squibb.

## ACKNOWLEDGEMENTS

Declared none.

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