Are we at the Goal Line with the Novel Oral Anticoagulants and Have We Reached the End of the Line for Dronedarone and Vernakalant – or is There More to Come?

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Abstract: The authors of this Mini-Hot-Topic collection of review manuscripts have provided an outstanding review of the development and current status of several of our most recently developed agents in the fight against atrial fibrillation (AF). They have also given the readers a glimpse into the difficulty of drug development and the contrasts that can exist with the same product in different geographies. For their efforts they have my deepest appreciation. It is my hope that these articles will assist those of you who are clinicians in your care of patients and those of you who are investigators in your appreciation of the drug development process and its hurdles. More specifically, this Mini-Hot-Topic symposium has reviewed for you: (1) the evidence supporting the new novel oral anticoagulants (NOACs) as first-line therapy for prevention of stroke and systemic embolism in patients with “nonvalvular” atrial fibrillation (NVAF); (2) the winding path taken by dronedarone in reaching its current place in our antiarrhythmic armamentarium – in which it still has a role; and (3) the contrasting decisions made with respect to the marketing of vernakalant in Europe versus the United States. Now, in this last manuscript of the collection, I will echo for emphasis some of their highlights and I will also bring you further up to date with respect to a possible future role for dronedarone, as hinted at by the HARMONY trial.

Keywords: Atrial fibrillation, anticoagulation, antiarrhythmic drugs, dronedarone, NOACs, ranolazine, vernakalant.

INTRODUCTION

As invited guest Editor for this Mini-Hot-Topic collection of review manuscripts, I have had the honor of having a collection of world-experts in the pharmacologic management of atrial fibrillation (AF) assemble for you, the readers, a timely collection of manuscripts that describe not only where we are with the newest antiarrhythmic and anticoagulant agents for the management of AF, but also that tell some of the behind-the-scenes story of how we got here and why it can be so difficult. It is my hope that for those of you who are clinicians, you will find these articles of assistance in your management of patients, and for those of you who are interested in the development process concerning new pharmaceutical agents, that you will have learned about a few of the many hurdles that must be overcome for a new agent to reach the market and find its correct place in our therapeutic armamentarium. Often the latter becomes clear only when a product is used in a larger number and wider variety of patients after-market than were included in the development program that resulted in the release of that product to the marketplace.

Moreover, I trust that the conclusions reached and elucidated in the manuscripts in this collection will resonate with your personal experiences and opinions – though I recognize that we each have experiences and opinions of our own that can color our reception of those opined by others.

For myself, I might even have stated the conclusions reached by Drs. Halperin and Dorian, a bit more strongly. That is, *for patients with nonvalvular AF (NVAF)*, as defined in the pivotal trials that led to the approval of the now available new novel oral anticoagulants (NOACs), I can no longer find a reason to start a vitamin K antagonist (VKA) as my agent of choice for anticoagulation (aside, possibly, from cost) as I stated in a recent editorial in the Journal of Atrial Fibrillation (JAFIB) [1]. In their pivotal trials, as well as in the many follow-up reports in the literature involving post-marketing observations on large numbers of patients (such as those noted in the FDA mini-sentinel reports that are available on its website [www.fda.gov], the NOACs have proven themselves to be as effective or more effective than VKAs in reducing/preventing stroke and systemic embolism (SSE) and as safe or safer than the VKAs with respect to fatal bleeds, life-threatening bleeds, and intra-cranial bleeding (our most feared adverse events from anticoagulation). Simultaneously, they are more convenient for both patients and physicians alike, given their minimal to no dietary interactions, their relatively few drug-drug interactions (as compared with the VKAs), their lack of need for anticoagulant test monitoring, and the similar handling of bleeding events to that applied to VKAs. While some might argue that vitamin K can be effective in reversing the effect of VKAs but not the NOACs when a patient bleeds, the time course of vitamin K effect is not substantially different than the time course of elimination of the NOACs when their dosing is discontinued. And within this decade, we expect, rapidly-acting intravenously-administered antidotes to the NOACs will become available. As regards cost, my JAFIB editorial

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does provide some insight into ways for patients to functionally reduce the differences in pricing.

With respect to our antiarrhythmic drug (AAD) options, and to dronedarone in particular, I think Drs. Naccarelli and Kowey provided an excellent summary. At present, I continue to consider dronedarone as a first-line option in AF patients who require rhythm control when they have neither permanent AF nor heart failure nor bradycardic rates (in the absence of a permanent pacemaker), nor hepatic dysfunction nor a history of pulmonary toxicity with amiodarone. Its efficacy is modest, but as Drs. Naccarelli and Kowey noted, its toxicity and proarrhythmic potential is low, especially as compared to torsades de pointes risk with typical class III AADs and the toxicity profile of amiodarone. Of greatest interest, however, may be the role of dronedarone in doses lower than are now commercially available in combination with modest dose ranolazine. At the time Drs. Naccarelli and Kowey wrote their manuscript, the HARMONY trial was just beginning. At the time of my writing this editorial, it has been completed and presented [2]. At the recently-completed Heart Rhythm Society annual scientific sessions held in San Francisco, California, in May 2014, Dr. Kowey presented the HARMONY results on behalf of the steering committee and the investigators. The combination of reduced-dosage dronedarone with reduced-dosage ranolazine showed significant efficacy in reducing AF burden in the patients enrolled and excellent tolerance, sufficiently so that there are now planned two large-scale pivotal phase 3 trials aimed at eventually bringing a combined compound to market – so “stay tuned”. The dronedarone story is not yet over.

Finally, with respect to vernakalant, the future seems far “fuzzier” at this point than with either the NOACs or with dronedarone. At present, no additional trials are open and enrolling, for either the intravenous product or the United

States, or for the oral product. So, our European readers, take note that for now, and perhaps for the long-term, you have an effective and rapidly-acting agent for the conversion of atrial fibrillation, with in my opinion, a reasonable safety profile *if used as directed and in the population indicated* that we in the U.S. do not have. Use it carefully but do not fear it. Also, recall with interest, vernakalant is not effective for atrial flutter – only for atrial fibrillation. Whether this is because of a degree of not only atrial selectivity, but also atrium-selectivity [right versus left] (as some of the investigational “atrial selective agents” have demonstrated) or some other factor(s) remains to be determined. Hopefully at some future time, we will learn more about this interesting propensity and more of us will have the opportunity to use it in our practices.

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.

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Declared none.

REFERENCES

- [1] Reiffel JA. The new novel oral anticoagulants (NOACs) in patients with atrial fibrillation: dogma, dilemmas, and decisions on dosing. *JAFIB* 2014; 6(5): 6-9.
- [2] Kowey PR, Reiffel JA, Camm AJC. The HARMONY trial. Presented at the late-breaking trials section of the Heart Rhythm Society, San Francisco, CA, Saturday May 10, 2014.