



Dronedaronone For Atrial Fibrillation: Unbridled Enthusiasm Or Just Another Small Step Forward?

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Introduction

In July 2009, the federal Food and Drug Administration (FDA) approved the marketing of dronedarone (Multaq, sanofi-aventis) for use in patients with atrial fibrillation (AF) or flutter (AFL) [with a requirement for a recent episode] that is paroxysmal or persistent – the latter having been converted to sinus rhythm or with conversion planned – who have, in addition to AF, certain “high-risk” markers for adverse outcomes that were derived from the enrollment criteria for the landmark ATHENA trial.¹ These markers include one or more of: age >70 yrs, hypertension, diabetes mellitus, prior cerebrovascular accident, left atrial size of 50 mm or larger, or LVEF <40%. Contraindications include class IV heart failure or symptomatic heart failure with a recent decompensation; second or third degree AV block without a functioning pacemaker; bradycardia < 50 bpm; concomitant use of a strong CYP3A inhibitor or a QT prolonging agent that may induce torsades de pointes; QTc Bazett interval of 500 ms or longer; or severe hepatic impairment.

This approval was the culmination of a developmental course that was detailed by Peter J. Zimetbaum, M.D. in his April 30, 2009 article in the *New England Journal of Medicine* entitled: Dronedaronone for Atrial Fibrillation – An Odyssey.² In this development process, dronedarone, an agent derived from amiodarone, with a similar but non-

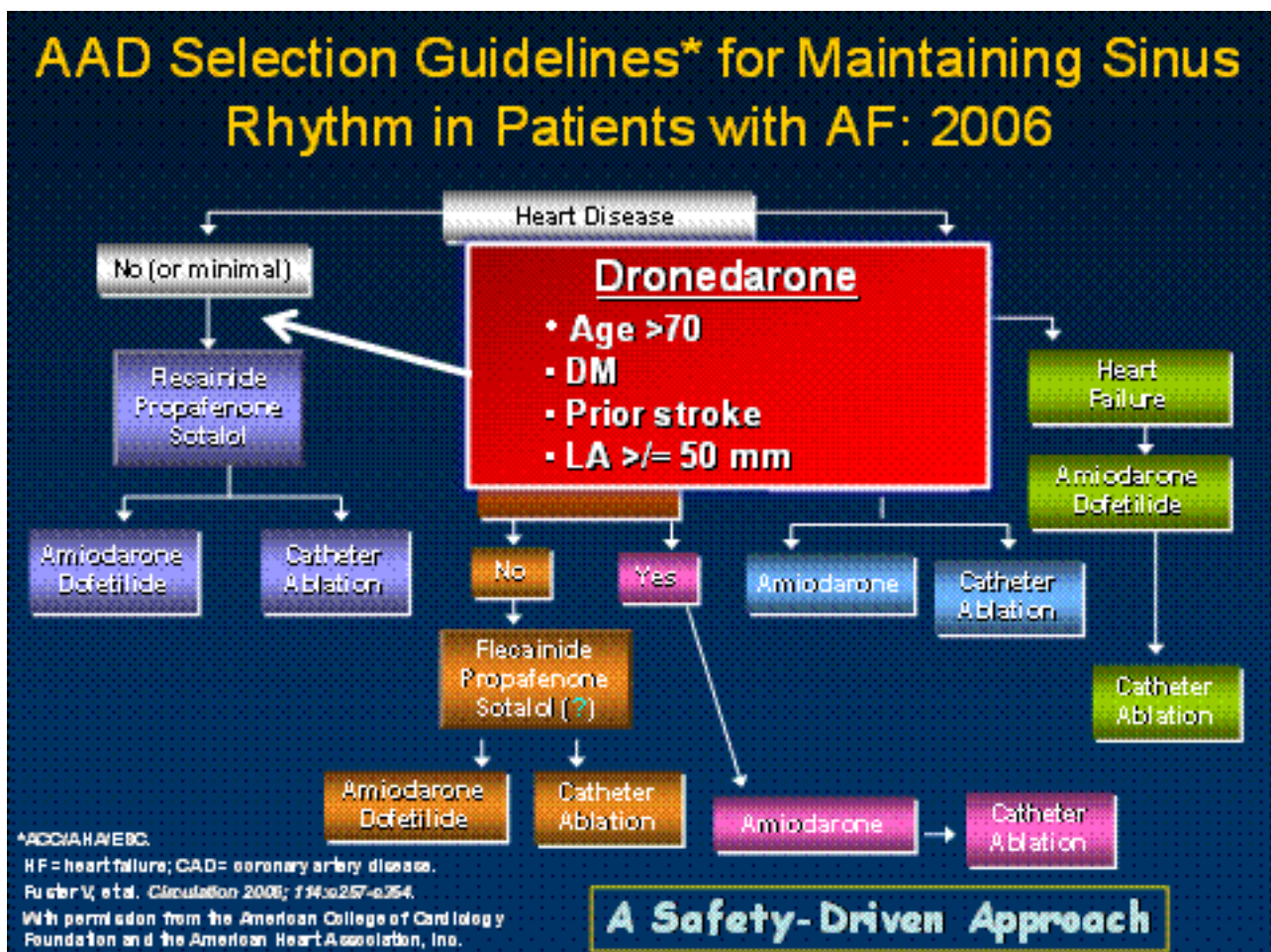
identical electrophysiologic profile, but with more user-friendly pharmacokinetics and an apparently much lower risk of toxicity – as was summarized in Dr. Zimetbaum’s manuscript-- was first proven superior to placebo in the suppression of atrial fibrillation in a mixed population of patients in the EURIDIS and ADONIS trials.³ In these trials dronedarone reduced the rate of recurrent AF from 75% to 64%; in addition, the ventricular rate during recurrences was reduced 12-15 bpm. The dose used was 400 mg bid – the only dose used in the pivotal trials for this agent, which is an outcome of its dose-ranging DAFNE trial [4] in which higher doses were poorly tolerated due mainly to diarrhea as well as appearing less effective. The prohibition against its use in class IV heart failure or heart failure with recent decompensation was the result of the premature termination of the ANDROMEDA trial⁵ – a mortality and morbidity trial in patients with LVEF 35% or lower and decompensated symptomatic heart failure – in which the trial was terminated early due to excess mortality and hospitalization risk on the active agent as compared to placebo. The requirement for additional cardiovascular risk markers in addition to AF/AFL and the specific indication for dronedarone – “to reduce the risk of cardiovascular hospitalization” in patients with AF or AFL with a recent episode “and associated cardiovascular risk factors” was derived from the dramatic findings in the ATHENA trial.¹ ATHENA demonstrated, in 4628 patients with

a recent episode of AF or AFL and specific associated risk markers including those identified above, that dronedarone, as compared to placebo, was associated with a lower risk of the composite endpoint of death from any cause and hospitalization due to cardiovascular events. There was a non-significant trend towards reduction of total mortality. The reduction in cardiovascular hospitalization was largely due to a reduction in AF/AFL events requiring hospitalization – but, of note, time to first AF recurrence, the number of AF recurrences, and similar measures of AF burden were not outcome events measured in this trial. The results were generally similar in all subgroups that were assessed, including a variety of commonly used cardiovascular drugs. Also reduced were acute coronary syndrome, and, as shown in a post-hoc analysis, presented at the 2008 European Society of Cardiology meetings by Dr. Hohnloser, stroke (independent of the use of anticoagulants).

Consequent to the approval of dronedarone, for the indication detailed above – which is not simply for the reduction of AF/AFL (i.e., for prolongation of the time to recurrence, the most common indication for drugs approved for the therapy of AF/AFL) – how are physicians likely to use this drug and what unknowns remain that may be necessary to learn in order to ultimately use dronedarone to its fullest and most appropriate potential. Perhaps the two major limitations at this point are the limited duration of long-term experience with the drug and limited comparative efficacy and tolerance/safety data. In the trials outlined in dronedarone’s “odyssey”² the duration of follow up was generally 1 year with the longest follow up for any patient approximating 3 years. Thus, while in these trials dronedarone appeared to be free of the pulmonary, thyroid, and other toxicities that plague the use of amiodarone, we have to recognize that longer exposure without events will truly be re-

Figure 1: A suggestion for the application of dronedarone to the ACC/AHA/ESC algorithm.

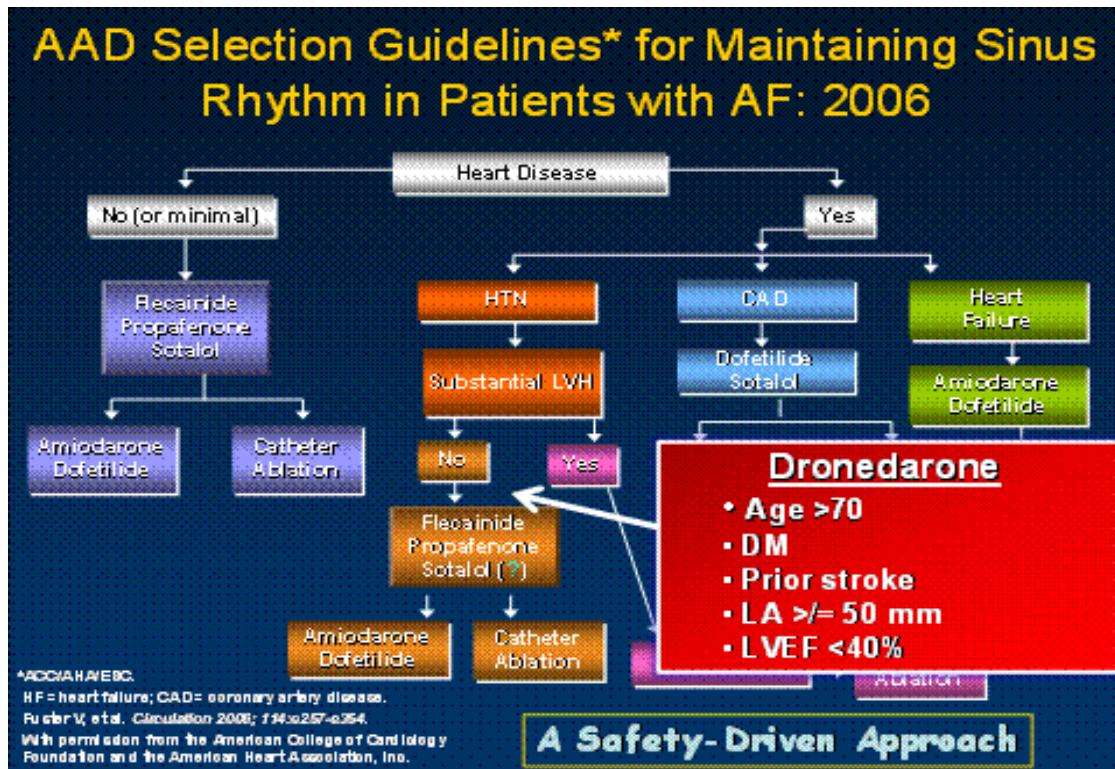
Panel 1: patients with no or minimal heart disease



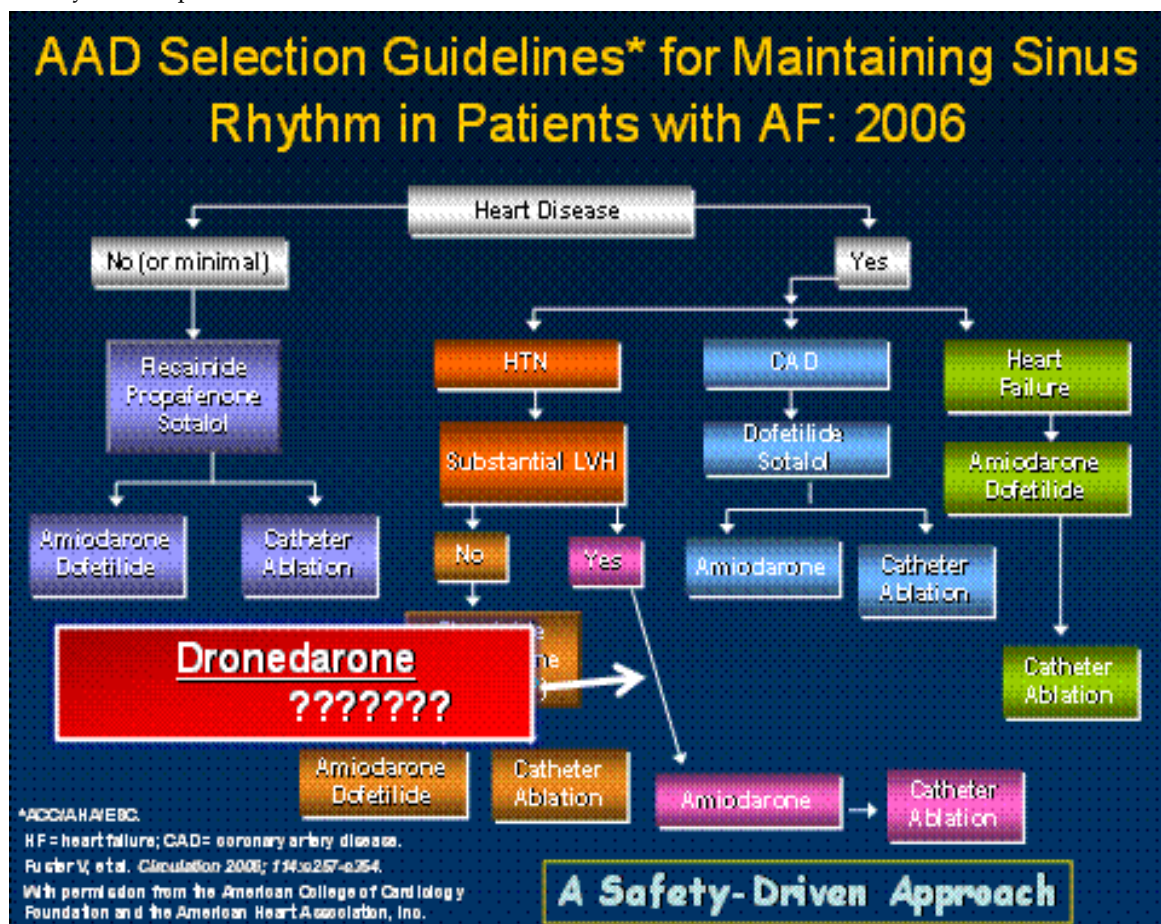
*ACC/AHA/ESC.
 HF = heart failure; CAD = coronary artery disease.
 Fuster V, et al. *Circulation* 2006; 114:e257-e254.
 With permission from the American College of Cardiology Foundation and the American Heart Association, Inc.

A Safety-Driven Approach

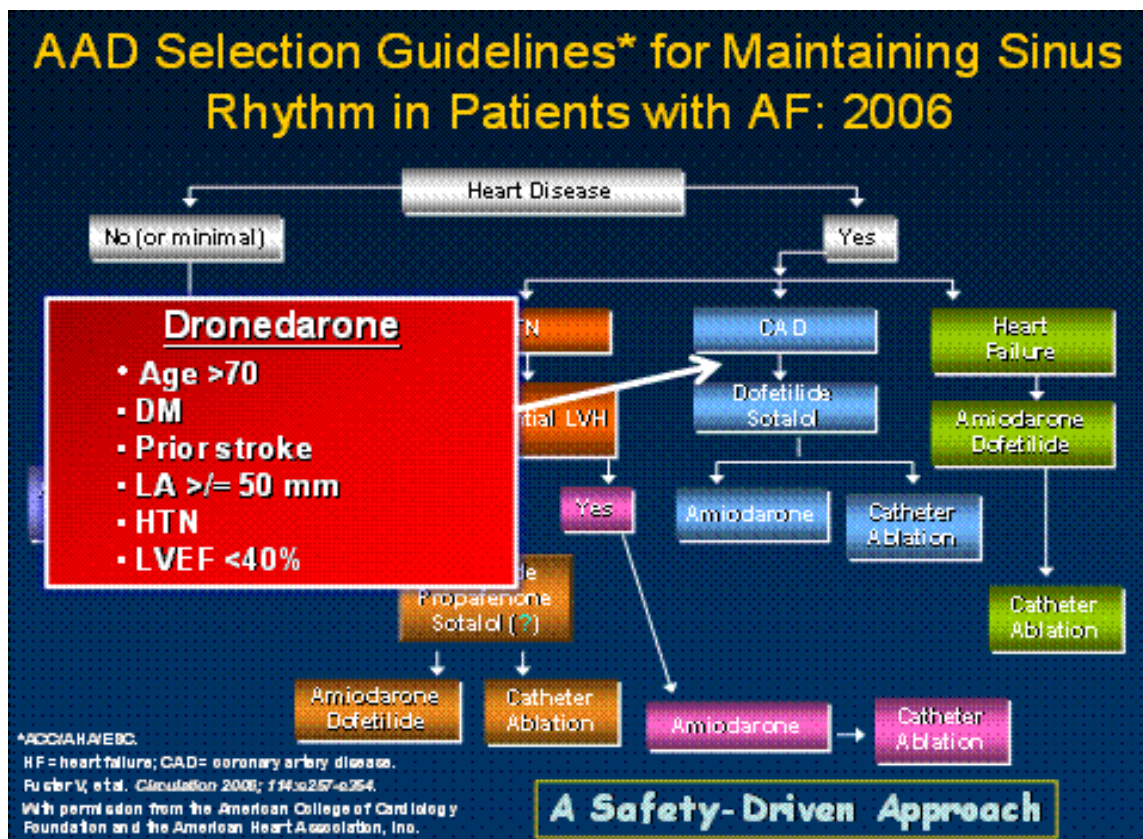
Panel 2: Patients with hypertension without significant hypertrophy



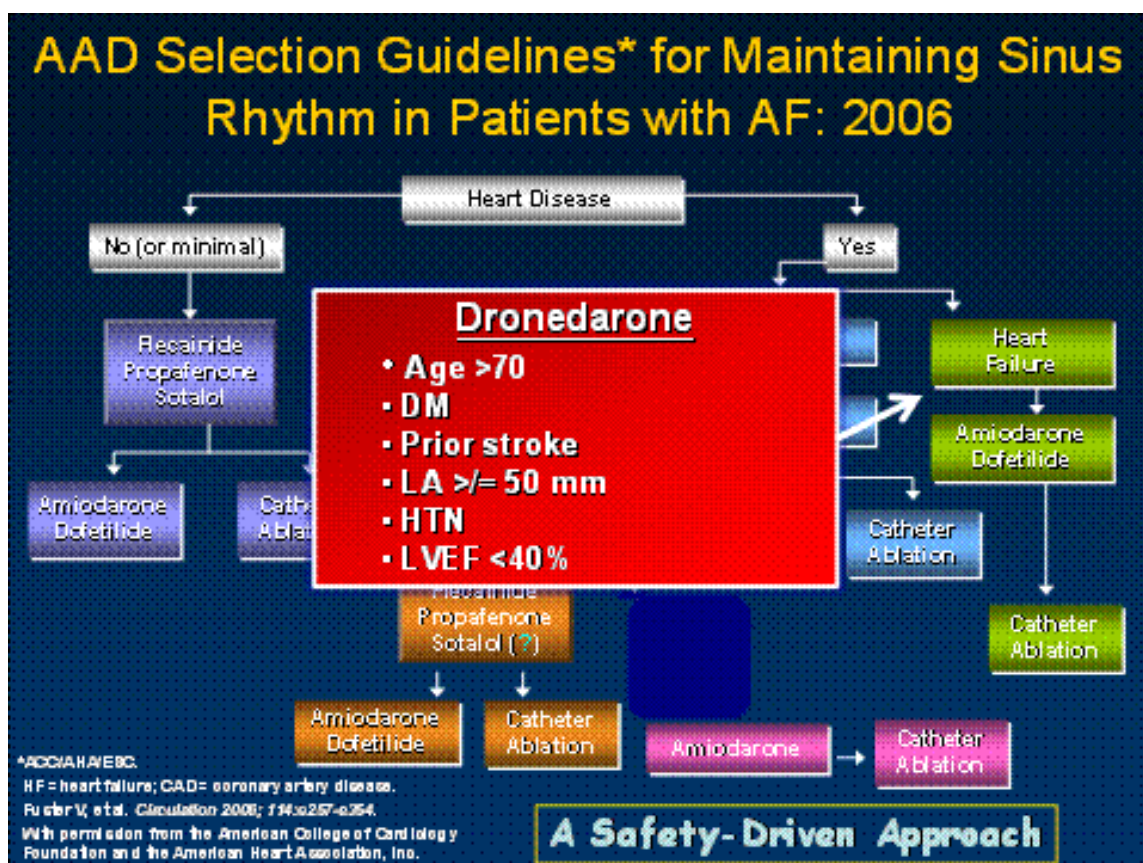
Panel 3: patients with hypertension with significant hypertrophy: here, there is no significant published data to indicate safety for the specific use of dronedaron



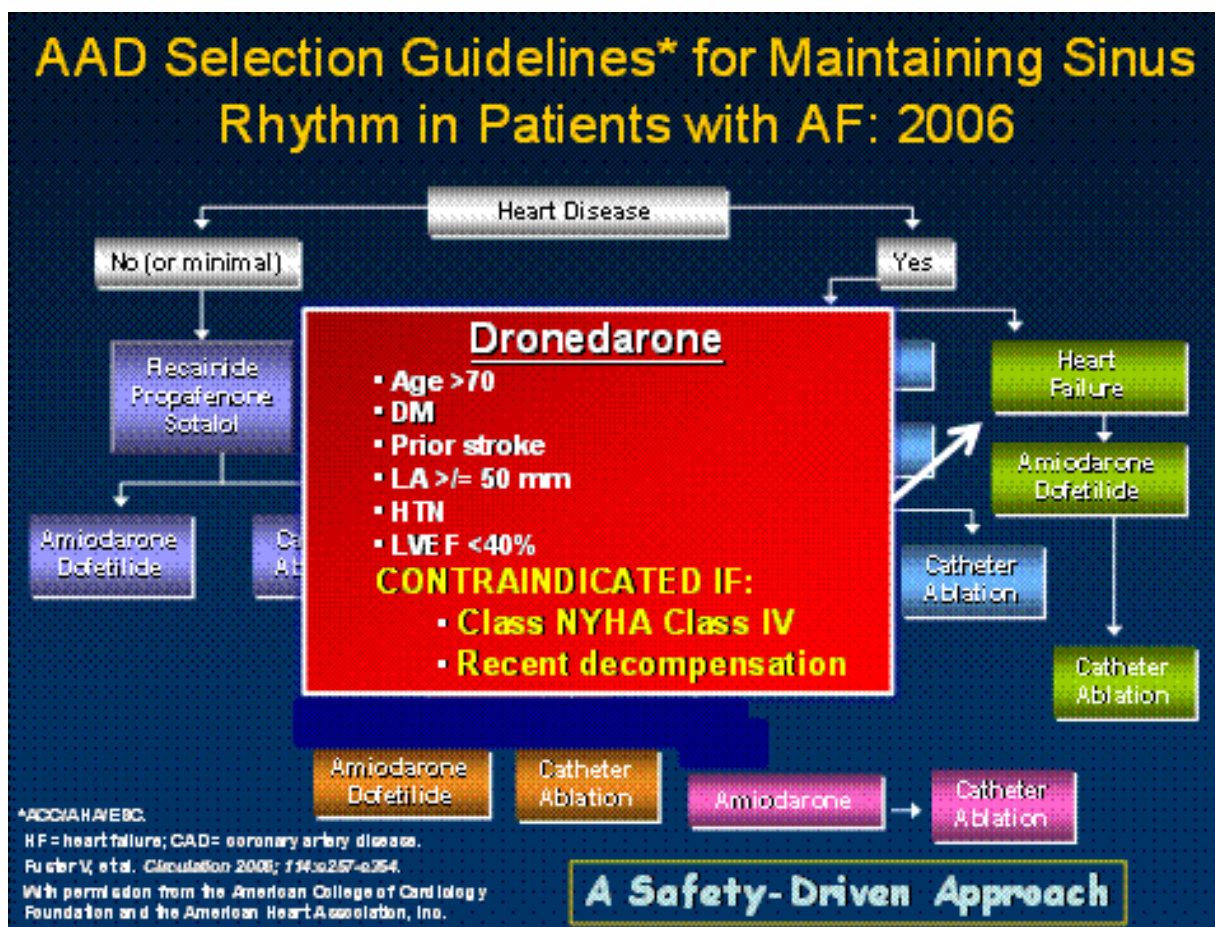
Panel 4: patients with coronary artery disease



Panel 5: patients with heart failure



Panel 6: patients with heart failure in whom dronedarone is contraindicated



quired to assure us fully as to its chronic safety profile. Recall that some of amiodarone's toxic profile is total dose and time-exposure dependent. Secondly, we have very limited comparative efficacy for dronedarone against other antiarrhythmic agents (AADs). The only such data that exists is that from the DIONYSOS trial² in which dronedarone and amiodarone were compared in a 500 patient trial of only 6 months duration in which dronedarone demonstrated lower efficacy against AF than did amiodarone, but fewer adverse effects and a lower rate of drug withdrawal. Hence, how it might perform against other AADs either in the suppression of AF/AFL or in a trial similar to ATHENA is unknown.

So, where does all this information leave the clinician who now must incorporate it into his or her armamentarium? One view might be that given the dramatic outcome events demonstrated in ATHENA, dronedarone should be the first AAD tried in AF/AFL patients with a recent arrhyth-

mic event and the associated cardiovascular risk profile that is part of the indication for this agent – it may be seen as unethical to do otherwise. Others may have less unbridled enthusiasm preferring to await longer-term safety data than currently exists and more comparative data than currently exists before taking such a strong stance. Personally, I find myself somewhere in between, but leaning towards the former and would propose that dronedarone has a role in each of the arms of the treatment algorithm outlined in the 2006 ACC/AHA/ESC guidelines⁶ as shown in the following figure that I have developed specifically for this manuscript.

References

1. Hohnloser SH, Crijns HJGM, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; 360:668-678.
2. Zimetbaum PJ. Dronedarone for atrial fibrillation – an odyssey. *N Engl J Med* 2009; 360:1811-1813.
3. Singh BN, Connolly SJ, Crijns HJGM, et al. Dronedarone for

maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007; 357:987-999.

4. Touboul P, Brugada J, Capucci A. et al. Dronedaron for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J*. 2003;24:1481-1487.

5. Kober L, Torp-Pedersen C, McMurray JJV, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; 358:2678-2687.

6. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006

guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice

guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J*. 2006; 27:1979-2030.