

inhibitors and direct thrombin inhibitors whose serum concentrations can be increased by dronedarone. Dronedarone may also interact with warfarin (largely, in my experience via speeding transit time, sometime with frank diarrhea, thus reducing vitamin K availability for absorption) with a resultant increase in prothrombin times.

Clinical Trials Regarding the use of Dronedarone for Atrial Fibrillation

Dronedarone has been widely studied with several completed trials relevant to AF therapy. The phase 2, prospective, double-blind, placebo-controlled, dose-ranging Dronedarone Atrial Fibrillation study after Electrical Cardioversion (DAFNE) study resulted in the single clinical dosing regimen of only 400 mg bid. DAFNE enrolled patients undergoing cardioversion for AF,⁴ most of whom had been in AF for 2-4 months. Average left ventricular ejection fraction (LVEF) was >50%; average LA size 45 mm. The primary endpoint was time to AF recurrence. After pharmacologic or electrical cardioversion, 199 patients were followed for 6 months. Although the study showed a significant increase in time (60 days) before AF recurrence on 400 mg bid of dronedarone versus 5 days in the placebo group, higher doses were not more effective by intent to treat analysis. Rather, doses of 600 mg bid and 800 mg bid were less effective (for probably multiple and complex reasons). At 400 mg bid, the QT interval was not prolonged, and there was no evidence of organ toxicity. Discontinuation was excessive at higher doses, mostly due to GI symptoms. All trials subsequent to DAFNE have used only the 400 mg bid dosing regimen.

Following DAFNE, a series of phase 3 and phase 4 trials ensued. The EUROpean trial in atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS) and the American-Australian trial with Dronedarone In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS) were pivotal double-blind, randomized, placebo-controlled phase III trials using identical protocols that enrolled patients with paroxysmal AF (PAF) or persistent AF that had been cardioverted.⁵ The data from these trials was pooled for publication. EURIDIS enrolled patients in Europe and ADONIS in North America, South Africa, and Australia;

1,237 patients were enrolled. In both trials patients were in NSR at the time of randomization and received dronedarone 400 mg bid or placebo. Exclusions included: conduction abnormalities, bradycardia, renal insufficiency, and severe heart failure (HF). The average age was 63 years. The average LVEF was >59% but patients with low EF were not excluded. In both trials, approximately 17% of patients had mild HF (NYHA class I or II), most had a history of hypertension, 21% had coronary artery disease (CAD), and 56% were on beta-blockers. The primary end point was time to AF or AFL recurrence detected by scheduled ECGs and transtelephonic monitoring. Follow up was one year. The median time to recurrence of AF or AFL in ADONIS was 158 days compared to 59 for placebo, and in EURIDIS 96 days versus 41 for placebo. In both trials, if AF did recur, the ventricular rate was significantly (about 10-15 bpm) slower with dronedarone compared to placebo, though still averaging approximately 105 bpm. This same degree of rate-slowing effect was also demonstrated as the primary efficacy endpoint in the ERATO trial which was performed specifically to assess the effect of dronedarone on ventricular rate control in patients with permanent AF.⁶ In EURIDIS and ADONIS the relative risk of the post-hoc combined end point of hospitalization or death was significantly improved with dronedarone, RR = 0.73, p=0.01, and there was a trend towards reduced mortality. The rate of adverse effects was similar to placebo, and there was no evidence of proarrhythmia or organ toxicity during these short trials. The absolute rate of serious cardiac adverse effects was in fact slightly lower in the dronedarone group than in the placebo group.

Subsequent to EURIDIS and ADONIS, the AN-DROMEDA (Antiarrhythmic trial with Dronedarone in Moderate to severe CHF Evaluating morbidity Decrease)⁹ was performed as a regulatory agency request. ANDROMEDA was a trial of dronedarone who had moderately severe or severe HF (recent episode of NYHA class IV HF or class III HF with recent (1 month) severe decompensation and LVEF <35%), a group with a high baseline mortality rate and high risk of TdP. AF was not a requirement for enrollment and only the minority of patients had it. ANDROMEDA was planned primarily as a safety trial. Six hundred twenty-seven patients were enrolled, average age 69 years. The primary end point was death or hospitalization

for HF. It was hoped that this study would confirm the absence of adverse events in a high-risk group of patients and perhaps demonstrate a benefit in reducing the morbidity and mortality of HF in these patients. However, worsened hospitalization/mortality (RR 1.38, CI 0.918 – 2.088, $p=0.118$) was noted prior to study completion and the trial was stopped prematurely. No TdP was observed. There are multiple possible contributors to these results but they were not further assessed by additional specific studies.

Subsequent to ANDROMEDA regulatory agencies determined that approval for AF could not be given unless an additional large trial were performed in patients who had both AF and significant structural heart disease or other high risk factors – but not severe advanced HF. Accordingly, ATHENA (A Trial With Dronedaron to Prevent Hospitalization or Death in Patients With Atrial Fibrillation) was then performed. ATHENA was a multinational, double-blind, placebo-controlled prospective randomized outcome study of 4,628 high-risk patients with AF that was conducted to provide further data on dronedarone's efficacy and safety profile in sicker patients.¹⁰ Patients had paroxysmal and/or persistent AF. Enrollment was limited to patients aged 70-75 years (after an initial period allowing younger patients as well) with one or more high-risk markers (hypertension, diabetes, prior CVA, left atrium size >50 mm, or LVEF <40%) or to patients older than age 75 with or without additional risk markers. Class IV heart failure was excluded. ATHENA patients had a mean age of 72 years (19% <65, 42% age >75), 53% male, 6% lone AF, 60% structural heart disease (86% hypertension, 30% coronary artery disease, 16% valvular disease, 6% non-ischemic cardiomyopathy). LVEF was <45% in 12% of patients and <35% in 4% of patients. Twenty nine percent had a history of heart failure (mostly class II).

Dramatically, in ATHENA, the primary end point, all-cause mortality combined with cardiovascular hospitalization, was reduced by 24% ($p<0.001$). Total mortality had a trend (16% reduction) towards improvement ($p=0.176$); first cardiovascular hospitalization was reduced 25% ($P<0.001$); and cardiovascular mortality was reduced by 29% ($p=0.034$).¹⁰ Also reduced was arrhythmic death.

The decrease in hospitalization was mainly due to a reduction in hospitalization for AF related events ($p<0.001$). Also noted was a reduction in hospitalization for acute coronary syndrome ($p=0.030$). Discontinuation rates were approximately 30% in both the dronedarone and the placebo arms. Discontinuation for “adverse events” was 12.7% for dronedarone (mainly for GI symptoms) and 8.2% for placebo (mainly for AF recurrence). There was no excess withdrawal of ACE-inhibitors or ARBs (in contrast to ANDROMEDA). There were not signals of organ toxicity.

These striking results, in which an antiarrhythmic drug shown effective for AF reduction was now also shown effective in decreasing cardiovascular mortality, cardiovascular hospitalization (and arrhythmic death) were exciting and so far novel in the antiarrhythmic world. 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. Contraindications include class IV heart failure or symptomatic heart failure with a recent decompensation (patients with NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic); 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 or history of adverse hepatic reaction on amiodarone. 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 trial. European regulators gave similar approval later in the same year (although it was also approved for rate control as well as for rhythm control).

Perhaps the two major informational limitations at this point were the limited duration of long-term experience with the drug and limited comparative

efficacy and tolerance/safety data. The only direct comparative data that exists is that from the subsequently performed DIONYSOS trial¹¹ 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. With post marketing observations, efficacy continues to appear modest and tolerance reasonable. However, as noted above, rare cases of serious hepatic toxicity have been reported, as have occasional observations of pulmonary changes (that have not been found to be definitively causative, unlike amiodarone). Diarrhea and lesser changes in bowel habit and symptoms remain the major complaints of patients given dronedarone.

Following the above trials, one more important trial was completed – PALLAS.¹² PALLAS was performed in follow up to some intriguing additional, post-hoc observations made from ATHENA. In ATHENA, patients in the dronedarone arm had a 7.5% absolute reduction in the primary outcome event, which was largely driven by reduction in hospitalization due to AF and other cardiovascular events as was noted above. However, additional post hoc analysis suggested a reduction in stroke, which had not previously been shown by an AAD, as well as reductions in acute coronary syndrome and death from cardiac arrhythmia in the dronedarone arm.^{10,13} ATHENA also demonstrated a lower incidence of the development of permanent AF on dronedarone than on placebo (not unexpected for an AAD). Interestingly, in a post-hoc analysis, patients who went into permanent AF also had lower event rates on dronedarone than on placebo similar to those in the trial as a whole. Whether similar outcomes could truly be extended to patients with permanent AF was then tested prospectively in the PALLAS trial. The rationale to study such patients was thus based on the hypothesis of a pleiotropic effect of dronedarone on vascular outcomes that was independent of its antiarrhythmic drug effect as was derived from the post-hoc analysis in ATHENA noted above. PALLAS enrolled patients who were at least 65 years old with at least a 6 month history of permanent AF and risk factors

for major vascular events. The trial was prospective, randomized, double-blind using 400 mg bid of dronedarone and a matching placebo. Notably, almost 70% of patients that enrolled in PALLAS had been in permanent AF for at least 2 years and almost 70% had a history of HF, with most having been hospitalized for it in the prior year (but not in the prior month). One third of the PALLAS patients were taking digoxin and 84% were receiving a vitamin K antagonist.

In stark contrast to ATHENA, PALLAS was terminated after less than one year due to an approximately doubling of the rates of heart failure, stroke, and cardiovascular mortality in patients taking dronedarone in contrast to placebo.¹² Why such discordant results between ATHENA and PALLAS? Both trials employed the same drug and dosing regimen of 400 mg bid and tested similar composite endpoints, and both were multi-center, international trials. Population-related differences are likely the key contributing factor. The PALLAS population was distinct from the ATHENA population as permanent AF was an enrollment exclusion criterion in ATHENA, while PALLAS enrolled entirely patients with permanent AF. Indeed, in PALLAS, at four months follow-up, AF was still present in 96.3% vs. 98.2% of patients randomized to dronedarone vs. placebo, a statistically significant but clinically small difference. When the trial populations are closely examined it becomes clearly apparent that the PALLAS subjects in many ways more closely resembled those of ANDROMEDA (in which dronedarone showed harm) than it did those of ATHENA (in which dronedarone showed benefit independent of the issue of permanent AF). As noted above, approximately 70% of PALLAS subjects had a history of heart failure (NYHA I-III), as did 100% in ANDROMEDA (NYHA III-IV) in contrast to 22% in ATHENA (NYHA II-III) and most of these 70% had been hospitalized with heart failure in the prior year, perhaps raising questions about the stability of their heart disease, (though hospitalization in the prior month was an exclusion that differs them from ANDROMEDA patients). Hospitalization for acute worsened HF was rare in the demographics of ATHENA. Importantly, dronedarone is contraindicated in patients with recent acute decompensated heart failure. Moreover, classification of patients by baseline NYHA

status may not be sufficient to understand the PALLAS results. Heart failure is a dynamic syndrome and stable heart failure at enrollment need not predict stability throughout a trial. Increased risk from disease-drug interaction may become manifest only during episodes of disease instability and may do so disproportionately on a drug rather than on placebo. In HF, this might include the development of decompensated HF with a resultant decrease in end-organ perfusion causing secondarily significant drug-drug and drug-patient interactions that may only be apparent at such times. Dronedaronone is a substrate for P-glycoprotein and increases digoxin levels. Reduced renal perfusion during acute HF could further increase digoxin levels and possibly potentiate its risk. Digoxin elevations in HF would not be as great on placebo. Notably, then, digoxin levels were one third higher in the dronedaronone group in PALLAS, raising the risk for digoxin toxic arrhythmias both at baseline and especially during episodes of acute HF. Dronedaronone, as noted early in this manuscript, can increase dabigatran levels and can increase INR in patients taking warfarin. A further additive interaction with warfarin and/or bleeding risk on any anticoagulant might be expected if hepatic dysfunction and congestion significant enough to disturb coagulation protein synthesis were to occur during episodes of HF. Of important note, hemorrhagic strokes in PALLAS were significantly more frequent in the dronedaronone arm than on placebo, and the hazard ratio for dronedaronone compared to placebo was 2.23 vs 1.31 in the subgroup of patients receiving anticoagulation (although INR levels at the time were not reported). Dronedaronone also decreases mean heart rate compared to placebo both during sinus rhythm and during AF.¹⁴ In patients with advanced heart failure, arrhythmic death is frequently due to bradycardic pulseless electrical activity.¹⁵ A drug such as dronedaronone that increases bradycardia or that lowers blood pressure while reducing inotropy might increase mortality risk in such patients during acute HF whereas placebo would not. Moreover, the relatively mild negative inotropic effect of sodium and calcium channel blockade of dronedaronone may not be important in stable patients, but could rationally be so during acute HF – and would worsen it disproportionately in dronedaronone as compared to placebo patients. Finally, in contrast to the events assessed in the ATHENA patients who went on to

first develop permanent AF during the one year of therapy, over 70% of patients in PALLAS had documented permanent AF for 2 years or more; and, in general, the longer AF persists, the more advanced SHD is likely to be present. Accordingly, the population differences between ADONIS, EURIDIS, ATHENA, ANDROMEDA, and PALLAS clearly had to have contributed to dramatically different safety outcomes in PALLAS as compared to ATHENA whereas the dronedaronone dosing was the same.

To better assess the above hypothetical contributors to the PALLAS results, it would be interesting to see an analysis limited to the 30% of patients without a history of heart failure, and whose left ventricular ejection fraction was preserved, and who were not taking digoxin. However, since PALLAS was terminated after a median follow-up of 3.5 months and less than one third of target enrollment, the statistical power of subgroup analyses for the primary and secondary endpoint would likely be too limited to discern differences between groups. Nonetheless, such an analysis, if possible, would clarify the issue as to whether simply the presence of permanent AF was of any importance to the results observed.

In the aftermath of PALLAS, dronedaronone's place in the AHA/ACC/HRS¹⁶ and other guidelines for AF rhythm control was modified. Dronedaronone is now listed as a first-line option to suppress AF in patients without structural heart disease and in those with structural heart disease – excluding those with heart failure (and those with LVH, for which data is limited). In Europe, dronedaronone is no longer indicated for rate control. Accordingly, dronedaronone is contraindicated in heart failure as well as in permanent AF. Patients on dronedaronone are now supposed to undergo some form of rhythm assessment at least quarterly, with discontinuation if the patient has developed permanent AF.

What is Next for Dronedaronone?

Perhaps the next chapter in the use of dronedaronone for AF will come as a component of a combination regimen. Work in the basic electrophysiology lab [Belardinelli and Zeng, 2012, personal communication] has demonstrated that dronedaronone

rone's effect on calcium channel inhibition (which is likely its major contributor to intolerance in heart failure) is dose related and can be avoided with lower concentrations of the drug than are achieved with the 400 mg bid dose in man. Additionally, basic and animal lab studies have shown a remarkable synergistic effect on AF suppression when combined with ranolazine.¹⁷ Ranolazine itself has been shown in small clinical studies and case reports¹⁸⁻²¹ to have AF suppression and AF termination efficacy. In the basic and animal labs noted above, both dronedarone and ranolazine can suppress AF in a highly inducible model in about 20-30% of subjects, but when combined, suppression approaches 90%. Ranolazine in its clinical trials has been free of organ toxicity, has constipation (in contrast to the diarrhea that can occur with dronedarone) and vague dizziness as its major adverse effects, and can suppress rather than induce torsade de pointes. These observations have led a group of investigators, working with Gilead (the manufacturer of ranolazine) to initiate a clinical trial of low and moderate dose ranolazine combined with reduced dose dronedarone in which the effect of the combination on AF burden is being assessed. This trial, HARMONY, is currently enrolling patients with implanted pacemakers capable of rhythm interrogation using a placebo-controlled dose-ranging design. If substantial efficacy and tolerance are demonstrated, larger phase 3 trials are expected to follow using one or more of the doses being tested in this trial (which are not the doses clinically available for either of the commercially available agents).

Clinical Implications

Dronedarone is a clinically useful multichannel blocker that has a place in clinical practice for the reduction of / prevention of recurrent symptomatic atrial fibrillation in patients with neither permanent AF nor heart failure. These latter two circumstances are clinical contraindications for its use. Dronedarone's relative lack of toxicity or proarrhythmia make it a reasonable first-line agent when its use is indicated; and, it can be used in the absence of or presence of structural heart disease (so long as LV failure is absent). Dronedarone is less effective than amiodarone. No direct comparative data exists for its relative potency versus other standard antiarrhythmic drugs. Be-

cause of selection bias that goes into clinical trials of new antiarrhythmic agents – including a typical history of prior drug failures antecedent to clinical trial enrollment for a new antiarrhythmic drug, comparison of its efficacy data in ADONIS/EURIDIS to that obtained in trials of older antiarrhythmics would likely be misleading. There is enticing data that both its efficacy for suppressing AF as well as its tolerance and its safety with respect to heart failure may be enhanced when used in doses lower than that which are presently available commercially in combination with ranolazine. The ongoing HARMONY trial will shed more light on this promise. If positive in a manner consistent with the basic laboratory's data on such a combination, dronedarone's use could rise dramatically.

Conclusions

Dronedarone is a useful first-line agent for reducing AF recurrence in patients with non-permanent AF, in the absence of underlying heart failure, which is a contraindication to its use. In patients with clinical markers of risk such as those used as inclusion factors in the ATHENA trial, dronedarone may also reduce the likelihood of hospitalization – something not yet shown with any other antiarrhythmic agent in AF patients. Although dronedarone does slow the ventricular rate in AF, it is not indicated for this purpose; hence it has no role in patients who have or who develop permanent AF. Dronedarone should be taken with food to enhance its pharmacokinetics and minimize its potential for gastrointestinal symptoms. Dronedarone is less effective than amiodarone but also has lower rates of discontinuation and of organ toxicity. Aside from amiodarone, dronedarone has not been directly compared to any other antiarrhythmic agent in head to head trials. Dronedarone has relatively few drug interactions, when compared with those associated with amiodarone or dofetilide; however, the potential for increasing the effects of warfarin and the new oral anticoagulants does exist and their dosing may need to be adjusted if dronedarone is begun in patients taking them. When used appropriately, dronedarone has proven a helpful addition to our therapeutic armamentarium for AF.

Disclosures

Dr. Reiffel has been an investigator in several of the dronedarone clinical trials (ADONIS, ATHENA) and has provided consultation services to its manufacturer, Sanofi, in addition to serving on its Speaker's Bureau.

References

- Gautier P, Guillemare E, Marion A, Bertrand JP, Tourneur Y, Nisato D. Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. *J Cardiovasc Pharmacol* 2003;41(2):191-202.
- Lalevee N, Nargeot J, Barrere-Lemaire S, Gautier P, Richard S. Effects of amiodarone and dronedarone on voltage-dependent sodium current in human cardiomyocytes. *J Cardiovasc Electro-physiol* 2003;14(8):885-90.
- Sun W, Sarma JS, Singh BN. Chronic and acute effects of dronedarone on the action potential of rabbit atrial muscle preparations: comparison with amiodarone. *J Cardiovasc Pharmacol* 2002;39(5):677-84.
- Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J* 2003;24(16):1481-7.
- Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;357(10):987-99.
- Davy J. Efficacy and safety of dronedARone for The cOntrol of ventricular rate. AHA 2005 Scientific Sessions 2005:abstract 2737.
- Sablayrolles S, Le Grand B. Drug evaluation: dronedarone, a novel non-iodinated anti-arrhythmic agent. *Curr Opin Investig Drugs* 2006;7(9):842-9.
- Dale KM, White CM. Dronedarone: an amiodarone analog for the treatment of atrial fibrillation and atrial flutter. *Ann Pharmacother* 2007;41(4):599-605
- 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.
- 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.
- Piccini JP, Hasselblad V, Peterson ED et al. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2009; 54: 1089-95.
- Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. *N Eng J Med* 2011; 365:2268-76.
- Connolly SJ, Crijns HJ, Torp-Pedersen C, van Eickels M, Gaudin C, Page RL, et al. Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation* 2009; 120:1174-80.
- Page RL, Connolly SJ, Crijns HJ, van Eickels M, Gaudin C, Torp-Pedersen C, et al. Rhythm- and rate-controlling effects of dronedarone in patients with atrial fibrillation (from the ATHENA trial). *Am J Cardiol* 2011; 107:1019-22.
- Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989; 80:1675-80.
- Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American heart Association Task Force on practice guidelines. *Circulation* 2011; 123: e269-367.
- Burashnikov A, Sicouri S, Di Diego JM et al. Synergistic effect of the combination of ranolazine and dronedarone to suppress atrial fibrillation. *J Am Coll Cardiol* 2012; 56:1216-24.
- Murdock DK, Reiffel JA, Kaliebe J, Larrain G. The conversion of paroxysmal or initial onset atrial fibrillation with oral ranolazine: implications for a new "pill-in-pocket" approach in structural heart disease. *JAFIB* 2010; 2:705-710.
- Reiffel, JA. The power of one: a highly detailed, log-based, case example that clearly demonstrates the effective use of ranolazine for the control of progressive atrial fibrillation. *JAFIB* 2010; 2:810-813.
- Biviano A, Goa C, Reiffel JA. The use of ranolazine in the management of recurrent atrial fibrillation after percutaneous radiofrequency ablation: a case report and review of the literature. *JAFIB* 2012; 5 (2): 1-4.
- Miles RH, Passman R, Murdock DK. Comparison of effectiveness and safety of ranolazine versus amiodarone for preventing atrial fibrillation after coronary artery bypass grafting. *Am J Cardio* 2011; 108:673-6.