Obtaining Optimal Results with Flecainide and Propafenone

Written by Toni Rizzo

The role of flecainide and propafenone for treating atrial fibrillation (AF) was reviewed by Girish M. Nair, MD, McMaster University, Hamilton, Ontario, Canada. These class 1C antiarrhythmic drugs (AADs) are used widely in clinical management of atrial arrhythmias.

Flecainide and propafenone have a role in the first-line management of AF in patients without structural damage or ion channelopathies. In what is commonly referred to as the "Pill-in-the-Pocket" study [Alboni P et al. *N Engl J Med* 2004], both flecainide and propafenone were effective to terminate paroxymal AF, although 5% of patients experienced major side effects, including symptomatic bradycardia and transient atrial flutter (AFL), leading to premature study discontinuation. Freemantle et al. [*Europace* 2011] demonstrated that flecainide and propafenone are effective for preventing recurrent AF in patients with paroxysmal or persistent AF without structural cardiac disease or ion channelopathies. Analysis of several studies of flecainide and propafenone showed that both agents reduce AF recurrence after cardioversion [Lafuente-Lafuente C et al. *Cochrane Database Syst Rev* 2012].

Flecainide also has a role in managing maternal and fetal supraventricular arrhythmia. These agents are contraindicated in patients with heart failure (HF) or left ventricular (LV) systolic dysfunction, coronary artery disease, cardiomyopathy, or ion channel defects. Both agents are reasonably well tolerated during long-term therapy in most patients without these contraindications.

Sotalol, Dofetilide, and Amiodarone for AF

Gerald V. Naccarelli, MD, Penn State Hershey Heart and Vascular Institute, Hershey, Pennsylvania, USA, reviewed the effectiveness and side effects of the potassium channel blockers sotalol, dofetilide, and amiodarone for AF.

Sotalol (120 mg BID) significantly improves recurrence-free survival in patients with AF (log-rank p=0.036) [Benditt DG et al. *Am J Cardiol* 1999]. Sotalol has negative inotropic potential, owing to its β-blocking properties. This negative effect is minimal; however, because action potential lengthening may enhance cardiac contractility. Cardiac side effects include symptomatic hypotension. Torsade de pointes (TDP) is the most common proarrhythmia; TDP is minimized to <2% with a total daily dose ≤320 mg/day and QTc ≤525 ms.

Dofetilide (500 µg) significantly converted patients to normal sinus rhythm versus placebo in the European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide study [EMERALD; Greenbaum RA et al. *Circulation* 1998] (p=0.001) and the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide study [SAFIRE-D; Singh S et al. *Circulation* 2000] (p<0.001). Dofetilide has no effect on blood pressure, PR interval, or QRS width and no influence on cardiac conduction velocity or sinus node function in patients with or without structural heart disease or with pre-existing conduction and/or sinus node abnormalities. Dofetilide decreases the defibrillation threshold and has no negative inotropic effects.

In a study that compared amiodarone, propafenone, and sotalol, significantly more patients who received amiodarone were recurrence-free at 600 days of follow-up (p<0.001) [Roy D et al. *N Engl J Med* 2000]. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial [SAFE-T] reported a median time to AF recurrence with amiodarone of 487 days versus 74 days with sotalol and 6 days with placebo (amiodarone p<0.001 versus sotalol and placebo; sotalol p<0.001 versus placebo) [Singh BN et al. *N Engl J Med* 2005]. TDP occurs rarely with amiodarone. Amiodarone is associated with a 3% to 7% incidence of pulmonary toxicity and increased mortality; by 3 years, 45% of patients had continued with amiodarone.

Dronedarone

L. Brent Mitchell, MD, Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada, reviewed results of the American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm [ADONIS; NCT00259376], the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm [EURIDIS; NCT00259428], and A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation [ATHENA; NCT00174785], contrasting the favorable findings in these 3 studies with the negative findings in the more recently reported Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy [PALLAS; NCT01151137].

The ADONIS and EURIDIS trials compared dronedarone with placebo in low-risk patients with nonpermanent AF or atrial flutter (AFL; n=1237) [Singh BN et al. *N Engl J Med* 2007]. The time to first AF/AFL recurrence was significantly longer with dronedarone (HR, 0.75; 95% CI, 0.65 to 0.87; p<0.001), as was the time to first cardiovascular

(CV) hospitalization or death (HR, 0.73; 95% CI, 0.57 to 0.93; p=0.001). The ATHENA trial of dronedarone versus placebo in patients with persistent or paroxysmal AF and at least 1 risk factor for CV hospitalization reported reduced incidences of CV hospitalization/death (HR, 0.76; 95% CI, 0.69 to 0.84; p <0.001), CV death (HR, 0.71; 95% CI, 0.51 to 0.98; p=0.03), and stroke events (HR, 0.66; 95% CI, 0.46 to 0.96; p=0.027) [Connolly SJ et al. *Circulation* 2009]. The incidence of CV hospitalization/death in the subgroup of patients with permanent AF was not significantly lower versus placebo (HR, 0.74; p=0.096).

The PALLAS trial compared dronedarone versus placebo in patients only with permanent AF/AFL [Connolly SJ et al. *N Engl J Med* 2011]. The study was terminated early for apparent harm, owing to a significantly increased incidence of CV events (HR, 2.29; 95% CI, 1.34 to 3.94; p=0.002). Dronedarone also increased all-cause mortality/HF hospitalization and all-cause mortality in patients with congestive heart failure (CHF) in the Antiarrhythmic Trial With Dronaderone in Moderate to Severe CHF Evaluating Morbidity Decrease [ANDROMEDA; NCT00696631].

Dronedarone improved outcomes in low-risk patients with nonpermanent AF/AFL in the ADONIS/EURIDIS studies and in moderate-risk patients with nonpermanent AF or AFL in the ATHENA trial. In contrast, in the PALLAS trial, dronedarone increased adverse CV outcomes in patients at high-risk with permanent AF or AFL.

Dr. Mitchell concluded that dronedarone should not be used in patients with permanent AF or AFL, a history of HF, or reduced LV ejection fraction. Dronedarone should be used with caution in patients who are taking digoxin. Close monitoring of digoxin levels is recommended, since dronedarone inhibits p-glycoprotein, resulting in increased serum digoxin concentration.

Personalized Medicine for AF

John Camm, MD, St. George's University of London, England, United Kingdom, reviewed pharmacogenomic data on AADs in patients with AF. Lubitz et al. [*Circ Arrhythm Electrophysiol* 2010] identified a number of candidate genes that are associated with AF, while Kandoi et al. [*Indian Pacing Electrophysiol J* 2012] identified genes that are associated with the action of several AADs. Several studies have found associations between gene variants and response to AADs, recurrent arrhythmias, and proarrhythmias (Table 1).

Various AF guidelines recommend the use of specific AADs, based on a patient's underlying condition, with respect to efficacy and safety. For example, the European Society of Cardiology guidelines recommend amiodarone, dronedarone, flecainide, propafenone, or sotalol in patients with underlying heart disease. Amiodarone is most effective, but because of its toxicity, it should be used when other AADs have failed or are contraindicated. In patients with severe HF or recently unstable New York Heart Association Class II HF, amiodarone should be the drug of choice.

Table 1. Pharmacogenomic Studies in AF.

Study	Result
β1-adrenergic receptor polymorphism: Success of rate control in AF [Parvez B. *J Am Coll Cardiol* 2012]	• AF patients with *ArgGly389* β1-adrenergic receptor polymorphism required lowest doses of rate-control drugs versus wild-type and *Ser49Gly* carriers
ACE genotype: Response of recurrent AF to AAD [Darbar D. *Heart Rhythm* 2007]	• ACE deletion allele associated with increased ACE activity and adverse outcomes • Lone AF and *DD/ID* genotypes highly significant predictors of drug therapy failure
4q25 variants: AF recurrence after ablation [Husser D. *J Am Coll Cardiol* 2010]	• AF recurrence at 6 months significantly higher with any 4q25 variant (p=0.007)
Gene-drug interactions mediating proarrhythmia [Roden DM. *Cardiovasc Res* 2005]	• Digitalis toxicity: MDR1 polymorphisms linked to increased blood level to digitalis-mediated arrhythmias; RyR2, ANK2, CASQ2 loss of function may predispose to digitalis-mediated arrhythmias • TDP: CYP2D6 Poor metabolizers increased risk for thioridazine-related TDP; KCNQ1, KCNH2 (HERG), KCNE1, SCN5A-subclinical congenital long QT syndrome mutations predispose to TDP; SCN5A, S1102Y-Y allele confers increased risk in African-Americans • Sodium channel blocker toxicity: Poor metabolizers at increased risk for flecainide-related adverse events; ultrarapid metabolizer at increased risk for encainide-related toxicity; SCN5A–VF during drug challenge

AAD=antiarrhythmic drug; ACE=angiotensin-converting enzyme; AF=atrial fibrillation; TDP=torsade de pointes.

Pharmacogenetic testing may identify individuals with a high risk of idiosyncratic reactions, those who are poor metabolizers and taking prodrugs (lack of efficacy), those who are rapid metabolizers and taking prodrugs (safety), and variations that are associated with no response. Some drugs in one class can be excluded in some patients because of frequent adverse effects or lack of efficacy. Selecting the best drug for each patient is controversial. Important economic benefits may result for the most frequently selected drug. Pharmacodynamic gene variations require balancing risk versus benefit and safety versus efficacy. Matching individual genetic profiles and many different drugs may be difficult.