

Should We Limit Antiarrhythmic Drug Choice in Patients With Left Ventricular Hypertrophy?

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Potential Conflicts; Gerald V. Naccarelli MD (Consultant: Milestone, Sanofi, InCarda Therapeutics, Acesion, Glaxo Smith Kline); Peter R. Kowey MD (Consultant: Sanofi, Acesion, InCarda Therapeutics)

Left ventricular hypertrophy (LVH) occurs commonly in cardiac and hypertensive patients and those with structural heart disease and is associated with an increased risk of atrial fibrillation (AF), ventricular arrhythmias and sudden death (1,2). Over the years, guidelines have cautioned against using class III antiarrhythmic drugs in patients with LVH due to a presumed increased risk of torsade de pointes and death (3). This concern was based on electrophysiological studies demonstrating that hypertrophied cells have longer action potentials and are more likely to develop phase 2 after-depolarizations that could trigger a ventricular tachyarrhythmia (4-6). In contrast, Gillis et al (7) reported that an increased dispersion of ventricular action potential duration occurs in the rabbit model of LVH and that dofetilide did not significantly increase action potential duration in hypertrophied versus control hearts. In a cat model study of LVH, Kowey et al (8) reported that blockade of the voltage dependent potassium current, but not the slow inward calcium current, narrows the dispersion of recovery of excitability and could protect against the development of ventricular fibrillation.

Clinical trials and real-world data have reported findings that are less concerning. In this issue, Wann et al (9) report on a retrospective analysis of 359 patients with AF and LVH > 1.4 cm. treated with dofetilide compared to a propensity matched control group without a history of antiarrhythmic drug therapy. In this study, 32% of patients treated with dofetilide had LV wall thickness > 1.5 cm. The primary outcome of all-cause mortality occurred in 7% of dofetilide patients versus 12% in the control group (pNS) over a 3-year follow-up period. Total all-cause hospitalizations were higher in the control group (p = 0.005), but AF hospitalizations were similar. These data are consistent with Abraham et al (10) in which dofetilide caused torsade de pointes in 5/429 (1.1%) with LVH and 12/958 (1.2%) without LVH.

Given theoretic concerns that LVH increases the dispersion of refractoriness and the fact that class III antiarrhythmic drugs, such as dofetilide and sotalol, prolong the QT interval, guidelines have not recommended the use of these drugs and have favored drugs such as amiodarone and dronedarone (11). However, Chung et al (12) reported that amiodarone was associated with a lower survival compared to non-amiodarone drugs such as the class IC agent's flecainide and propafenone.

Complicating these recommendations is that the guideline definition of LVH started arbitrarily at > 1.4 cm. then moved to > 1.5 cm. without any data to support the initial recommendation or change. Newer guidelines have left the definition of meaningful LVH as undefined. Fortunately, most patients treated with antiarrhythmic drugs with LVH by echocardiographic criteria have LV wall thicknesses less than 1.4 cm. The complexity of the defining LVH by echocardiographic criteria has been well-documented and can include LV mass measurements in addition to LV wall thickness (13). To complicate things further, LV remodeling can occur. LVH can be present with or without coronary artery disease, electrolyte disturbances and clinical heart failure all of which increases the risk of ventricular arrhythmias. In all patients with hypertension and LVH, strict control of blood pressure may lead to regression of LVH and atrial and ventricular arrhythmias and is an important part of the treatment of such patients (14).

A small case series of patients with hypertrophic cardiomyopathy, treated with dofetilide, that demonstrated no significant proarrhythmia (15) support Wann's findings. More relevant risk factors for torsade de pointes during dofetilide dosing include overdosing, renal function, systolic heart failure, female gender, QTc prolongation from baseline, hypokalemia, or hypomagnesemia (10).

We conclude that antiarrhythmic agent choice does not have to be altered in patients with LVH except in patients with the distinct syndrome of hypertrophic cardiomyopathy, for whom more data are needed. Large clinical trials, such as ATHENA, have been helpful in collecting data in patients with hypertension and LVH

(16). Antiarrhythmic choice should follow guideline recommendations based on the absence or presence of structural heart diseases, ischemic heart disease and systolic heart failure although the overuse of amiodarone ignoring guideline recommendations continues to be an issue (17). Antiarrhythmic drugs with a minimal risk of causing torsade de pointes, such as dronedarone and amiodarone, continue to have a role in such patients.

There is little evidence that class IC and III antiarrhythmic drugs should be excluded in such patients. Furthermore, in patients without other evidence of structural heart disease, class IC drugs are safe and effective (18). The DIAMOND-HF trial demonstrated that dofetilide has neutral effects on mortality in systolic heart failure patients (19). Recent data reported that dofetilide was as effective as amiodarone in suppressing AF recurrences (20). Dofetilide and sotalol can be used with caution in patients with LVH with inpatient telemetry to monitor for any proarrhythmic activity. Other pharmacologic principles such as avoiding important drug interactions, dosing based on food effects and renal function, and maintaining electrolytes in the normal range all have importance.

We believe that antiarrhythmic drug choices should not be limited by inference or extrapolation. Careful patient and antiarrhythmic drug selection, based on validated clinical trial data, will permit the use of a wider variety of drugs to treat arrhythmias that plague our patients with LVH.

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