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EDITORIAL COMMENT

Glass Half Empty?*

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In 1999, 1 of the coauthors of this editorial (P.R.K.), as a member of the Cardiorenal Drugs Advisory Committee of the Food and Drug Administration (FDA), served as the principal reviewer of the dofetilide new drug application (1). The dossier for the committee's open hearing was imposing, consisting of dozens of studies, some large and some small, that sought to demonstrate the safety and efficacy of dofetilide for patients with atrial fibrillation. After a long day of presentations and deliberations, the committee was asked to vote on the application. The majority believed that there was sufficient evidence of efficacy in patients with persistent but not with paroxysmal atrial fibrillation, but there was considerable angst regarding the safety of the drug. Although almost totally devoid of organ toxic side effects, and proven safe in patients with severe left ventricular dysfunction and ischemic heart disease (2,3), it clearly caused impressive QT prolongation and torsades de pointes (2,3). The committee transmitted their concern to the FDA Cardiorenal Division, which eventually approved the drug, but imposed some unusually harsh restrictions on its use that included mandatory physician education and registration, specialty pharmacy distribution, and inpatient initiation. The dose would not be titrated but rather selected on the basis of a complex scheme using renal function and QT measurements, and patients would be confined and monitored until steady state concentrations were attained and the QT interval was stabilized (4).

These draconian measures led to limited utilization in the United States and nonavailability in other areas of the world, much to the chagrin of the manufacturers and those in the arrhythmia community who were impressed with its obvious effectiveness and good tolerability. But, despite all of the restrictions and lack of promotion, dofetilide has survived in the electrophysiology community. It has become 1 of the most frequently used antiarrhythmic agents in the United States among rhythm specialists, and it has been adopted for use in patients after ablation or for those with heart failure and coronary artery disease, where its safety has been incontrovertibly established in large safety studies completed decades ago (2–4).

What accounts for dofetilide's amazing durability? The drug has never been promoted extensively, and has not been employed in large atrial fibrillation trials. It never gained traction in the general cardiology community, and it has not been approved in most parts of the world including Europe. We posit that the reason for its continued viability is a combination of clear effectiveness in patients who require cardioversion for preservation of sinus rhythm and, ironically enough, its relative safety (4).

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We would argue that the severe restrictions imposed on dofetilide at its approval nearly 2 decades ago made the drug successful, and the data from Anand et al. (5,6) in this issue of *JACC: Clinical Electrophysiology* supports this viewpoint. In their paper, a substantial percentage of patients who received dofetilide had the drug discontinued either because of QT prolongation or ventricular arrhythmia (5). The use of other drugs that prolong the QT interval was the only predictor of drug discontinuation. The authors bemoan the fact that the incidence of discontinuation is higher than that reported in clinical trials (5). We find that observation encouraging, because conservatism to preserve patient safety might be a better tactic in the "real world." Furthermore, these data add texture to the recommendation made years ago in dofetilide's package insert to avoid the concomitant use of drugs that not only increase drug levels but also exert their own effect on the QT interval.

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Missing from the Anand et al. (5) experience, and indeed from nearly all of the contemporary published data regarding dofetilide, is hard evidence that implementing this risk mitigation strategy actually affects patient outcomes. We are told that 20 deaths occurred during a nearly 4-year mean follow-up, including a numerically higher percentage of patients who had dofetilide discontinued compared with those discharged on the drug (5). We are not provided with any details regarding those deaths, including whether or not the patients who died were taking this or any other antiarrhythmic drug, and if the deaths were sudden and unexpected. Inspection of the Kaplan-Meier plot reveals that most of the deaths occurred years after discharge, arguing against a direct proarrhythmic effect. Because dofetilide is frequently used in practice for patients with a heavy burden of structural heart disease, as was true in this report, death during follow-up is hardly surprising. Without a control group in whom implementation standards were not applied, conclusions regarding the relative value of QT monitoring in the hospital are simply not tenable.

On the basis of data from Anand et al. (5) and many others, it is safe to conclude that dofetilide has established itself as an important drug for the management of patients with atrial fibrillation, but it clearly occupies a therapeutic niche. Although not reported in the present paper, most of the patients in our practice receive dofetilide when other drugs fail, cause intolerable side effects, or are fully contraindicated because of the nature of the underlying heart disease. It has been referred to as the "amiodarone alternative" in patients with heart failure and coronary artery disease, particularly in younger patients in whom the cumulative risk of years of treatment with amiodarone is simply not conscionable. Although a significant percentage of patients in the present series had "paroxysmal" atrial fibrillation, its efficacy in such patients is much less established than in populations with more persistent patterns. Given the wide overlap between these atrial fibrillation types, liberal use of the drug as put forward by Anand et al. (5) is hardly unreasonable.

Recently, the FDA announced that the Risk Evaluation and Mitigation Strategies program will no longer be required (7). The FDA reached this decision on the basis of the fact that the Risk Evaluation and Mitigation Strategies assessments had consistently demonstrated that prescribers were properly educated and aware of the risks associated with dofetilide, as well as the appropriate protocol for its initiation and monitoring as delineated in clinical practice guidelines. Appropriately, dofetilide will still be initiated in the in-hospital setting using renal function and the QT interval to select dose. In addition, dofetilide is now available in a generic formulation, which will hopefully affect its availability and cost. It will be interesting to see how much these 2 important changes influence the prescribing patterns of dofetilide, as well as its clinical safety.

We are indebted to Anand et al. (5) for making several important points about dofetilide, including the need for careful in-hospital observation during initiation, serial QT measurements during initial dosing, and scrupulous avoidance of concomitant medications that might increase the QT interval. We agree with their concern about the higher than expected rate of dofetilide discontinuation, but we think the glass is actually half full of good news about the appropriate and safe utilization of a powerful and effective drug for symptomatic patients afflicted with this common arrhythmia.

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