Registry data on implantation of ICD is not necessarily reflective of an arrhythmic event

Dear Editor,

It was with great interest that we read the article by Leif Friberg who used Swedish national registry data to assess the relationship between antiarrhythmic drugs (AADs) administered to patients with atrial fibrillation and incident ventricular arrhythmias and mortality.[1] As a secondary measure, the study used the unambiguous end point of total mortality, which demonstrated that dronedarone and flecainide were the 2 drugs that performed better than any other antiarrhythmic drug using sotalol as a reference. Although the limitations of using registry data are well understood and acknowledged and selection of the healthiest AF patients for rhythm control using flecainide is likely to explain the result, it is nevertheless reassuring that real-life dronedarone safety data do not contradict the safety information reported in controlled clinical trials.

With this unquestionable result in place, the introduction of the combined arrhythmic end point, which included ICD implantation, as the primary end point introduces unnecessary uncertainty in the interpretation of the study findings. In contemporary cardiology practice, the vast majority of patients receiving ICD implants are patients with heart failure receiving ICD for primary prevention of sudden death, that is, patients who have not had sustained ventricular arrhythmias prior to ICD implantation.

According to the Swedish ICD & Pacemaker registry accessible through https://www.pacemakerregistret.se, during the period of 2010-2016, which corresponds to the study period analyzed in the article, 9,435 patients underwent their first ICD implantation, of whom 5,911 (63%) received it for primary prevention of sudden death. Although being the lowest in 2010 (53%), the proportion of primary prevention ICDs remained relatively stable during the rest of the study period, gradually increasing from 61% in 2011 to 69% in 2016.

On the other hand, the actual incidence of ventricular arrhythmias in primary prevention ICD recipients is low. Our group has studied the incidence of appropriate ICD therapies in the Swedish primary prevention ICD cohort[2,3] and reported that the annual rate of first appropriate ICD therapy (shock or ATP) does not exceed 6%. The vast majority of primary prevention ICD recipients remained arrhythmia-free, and even those who received appropriate therapies cannot be considered equivalent to survivors of sustained ventricular arrhythmias.

Because the Swedish Patient Register does not distinguish primary from secondary prevention ICD implantation, the inclusion of ICD implantation in the primary study end point will undoubtedly lead to an increase in the number of nonarrhythmic events quantified as ventricular arrhythmias. This would arguably be of lesser importance if the ICD implantation contribution to the composite end point would have been low. However, of all primary end point events presented per AAD group, ICD implantation at any time was reported in 30 of 163 (18%) events observed in the sotalol group, 156 of 281 (56%) in amiodarone, 6 of 26 (23%) in dronedarone, 3 of 63 (5%) in flecainide, and 6 of 22 (27%) in disopyramide group, which compare to 1,693 of 5,531 (30%) in patients not treated with AAD. Although these percentages do not necessarily reflect the real contribution of ICD implantation to the time-dependent primary arrhythmic end point, which is likely to be lower, it is highly probable that the exclusion of ICD implantations from the composite end point would affect the study results and, perhaps, not support the conclusion claiming uniqueness of dronedarone as a rhythm-control AAD. ICD implantation rates expectedly differ between the compared AAD groups because primary prevention ICD implantation may be an indicator of left ventricular dysfunction, which impacts the selection of AAD.

Dronedarone has been shown to be a safe AAD for rhythm control in patients with AF without heart failure. Inclusion of ICD implantation, likely consisting mostly of events not related to ventricular arrhythmia occurrence but rather being an indicator of heart failure (or perhaps more precisely of low left ventricular ejection fraction), in the main study end point brings confusion and complicates interpretation of the study findings.

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Pyotr G Platonov, MD, PhD
Fredrik Holmqvist, MD, PhD
Department of Cardiology
Clinical Sciences
Lund University
22185 Lund, Sweden
E-mail: Pyotr.Platonov@med.lu.se

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