Response to Letter Regarding Article, “Combined Cardiac Magnetic Resonance Imaging and C-Reactive Protein Levels Identify a Cohort at Low Risk for Defibrillator Firings and Death”

We thank Dr Obeyesekere for his interest in our work. His letter highlights the importance of identifying low-risk individuals currently receiving implantable cardioverter-defibrillators (ICDs) and the difficulties in identifying particularly high-risk patients. However, to impact current clinical ICD implantation decision making, it is critical to identify patient subsets who do not derive benefit from the device, i.e., those with a low risk of arrhythmic outcomes.¹ Our study in patients receiving clinically indicated primary prevention ICDs reported the value of gray zone (GZ) and high-sensitivity C-reactive protein (hsCRP) in identifying a low-risk subgroup with a 0.7%/year rate of appropriate firings or cardiac death. Although there have been prior studies of risk models aimed at identifying low-risk groups, an acceptable threshold of risk below which ICD therapy can be safely withheld remains to be established. In the MADIT-II substudy, a low-risk subgroup identified by 5 clinical factors had an 8% crude mortality rate at 2 years.²³ In our study, the lowest tertile GZ-hsCRP cohort had 0% crude mortality rate at 2 years, and no patient had an appropriate firing or cardiac death at 2 years, suggesting that combined cardiovascular magnetic resonance and hsCRP identifies a subgroup at an even lower risk than that identified in the MADIT-II report.

Dr Obeyesekere questioned whether GZ contributes to nonarrhythmic death. GZ could mechanistically contribute to worse left ventricular remodeling and heart failure through its effects on differential wall stress properties compared with the stiff, adjacent core regions. In analyzing the association of GZ and hsCRP with heart failure outcomes (heart failure hospitalization or heart failure deaths, n=41), there were nonsignificant trends (P=0.13 for GZ; P=0.08 for hsCRP), suggesting some degree of contribution.

Distinguishing between arrhythmic and nonarrhythmic cardiac causes of death is difficult. We defined cardiac deaths as including both arrhythmic and nonarrhythmic causes. As stated in the Limitations section, we used cardiac mortality as an end point because of the inherent difficulty in further attributing causality.³ Of the 15 cardiac deaths, 2 were definite sudden arrhythmic deaths (1 of whom had a prior ICD firing), leaving 13 that were undetermined. In analyzing the association between GZ and hsCRP with these outcomes, as requested by Dr Obeyesekere, we found that both GZ and hsCRP strongly predicted the arrhythmic end point (ICD firings or sudden arrhythmic death, n=31; P=0.007 for GZ and P=0.02 for hsCRP) but did not predict undetermined death (n=15, P=0.45 for GZ and P=0.23 for hsCRP), many of which were presumably nonarrhythmic within the limitations of the sample size.

We acknowledge Dr Obeyesekere’s comment that ICD programming favoring therapy can result in therapy for arrhythmias that may not have been life threatening, and thus including appropriate firings as an end point may overestimate the survival benefit of ICD therapy. However, it is more important to avoid underestimation of arrhythmic events in the low-risk cohort when defining a low-risk threshold.

In summary, the findings in the original article and these additional analyses support the contribution of GZ and hsCRP in predicting arrhythmic outcomes in patients receiving primary prevention ICDs under current guideline recommendations.

Disclosures

None.

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