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Risk Stratification in Nonischemic Dilated Cardiomyopathy in the Era of Personalized Medicine:

Can Cardiac Magnetic Resonance With Late Gadolinium Imaging "Enhance" Our Strategy? *

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The mortality benefit of implantable cardioverter-defibrillators (ICD) in ischemic cardiomyopathy has been well established by a number of large clinical trials (1,2). However, data for patients with nonischemic cardiomyopathy (NICM) are less definitive. Although a number of trials have demonstrated a reduction in sudden cardiac death (SCD), individual trials have not consistently demonstrated a reduction in overall mortality with ICD therapy for patients with NICM (3,4). Although multiple recent meta-analyses have shown a mortality benefit in pooled analyses, skepticism about the role of ICDs in NICM has recently been rekindled by the DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) trial (5). This study demonstrated no significant differences in overall mortality with ICD implantation between patients with NICM and those with left ventricular ejection fraction (LVEF) ≤35%, the current guideline threshold for ICD candidacy (6).

These data raise the question of whether assessment of LVEF alone is an adequate prognostic tool with which to determine which patients with NICM would most benefit from ICD therapy. LVEF is frequently dynamic in NICM. In 1 study, 41% of patients had improvements in LVEF by at least 10% over a 4-year follow-up period, but this rate was sustained in only 64% of these patients (7). Another study found that 26% of patients with primary prevention devices no longer met the LVEF cutoff value for ICD implantation at the

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time of first generator change (8). There is clearly a need for tools that can more precisely stratify risk in patients with NICM. Cardiac magnetic resonance (CMR) imaging using late gadolinium enhancement (LGE) to accurately identify myocardial fibrosis could meet this need.

Indeed scar tissue, as assessed by LGE, has already been associated with prognosis; earlier meta-analyses have identified LGE as a predictor of SCD and overall mortality in heart failure (HF) due to NICM. A 2014 meta-analysis by Kuruvilla et al. (9) combined data from 1,488 patients across 9 studies and found increased mortality (odds ratio [OR]: 3.27), HF hospitalization (OR: 2.91), and SCD or aborted SCD (OR: 5.32) (9). In 2017, an updated meta-analysis of patients with dilated NICM published by Di Marco et al. (10), including 2,948 patients across 29 studies, demonstrated OR of 4.30 of a ventricular arrhythmic event. LGE has been identified as a risk factor for adverse cardiovascular events in specific cardiomyopathies as well, predicting all-cause mortality, cardiac death, and SCD in patients with hypertrophic cardiomyopathy and cardiac sarcoidosis (11–14).

In this issue of *iJACC*, Becker et al. (15) performed the most contemporary and comprehensive appraisal to date of the prognostic utility of LGE in patients with HF and NICM. They aggregated data from 4,554 patients across 34 studies and demonstrated that the presence of LGE is associated with increased cardiovascular mortality (OR: 3.40), ventricular arrhythmic events (OR: 4.52) and hospital readmission for HF (OR: 2.66). A subset of studies quantified the extent of LGE, allowing for an estimate of the pooled hazard ratios of mortality and major arrhythmic events as a function of the amount of LV myocardium subtended by LGE. Additionally, in 5 studies (n = 305) with available data, the absence of LGE was correlated with reverse remodeling (OR: 0.15).

These results are largely consistent with the 2 previous meta-analyses of this topic with similar ORs for SCD, mortality, and HF hospitalizations. The current analysis includes newer studies, presumably reflecting contemporary guideline-directed medical therapy, confirming that LGE continues to portend more SCD, higher rates of hospitalization, and increased mortality in patients with NICM. Additionally, the authors demonstrated a linear relationship between extent of LGE (as a percent of LV myocardium) and OR of SCD and mortality, and showed that the absence of scar tissue by CMR predicts reverse remodeling, potentially identifying patients who may have a significant improvement in LVEF.

This meta-analysis is well executed, comprehensive, and timely. Of course, the present work is subject to the same limitations that commonly arise with meta-analyses. There were differences in the inclusion criteria of individual studies, and the definition of dilated cardiomyopathy (typically defined as LV systolic dysfunction and LV enlargement) was applied loosely: some studies simply included patients with HF and LVEF <50%. There was also significant variability in the methods used to identify and quantify the extent of LGE. Both of these factors likely explain the significant heterogeneity for some patients-level data, the effects of important covariates, including the LVEF of individual subjects, could not be explored.

This meta-analysis raises 2 important questions which CMR could help answer: first, are there with an LVEF >35% with extensive scarring who would benefit from ICD therapy? Some answers will come from CMR GUIDE HF (Cardiovascular Magnetic Resonance GUIDEd management of mild-moderate left ventricular systolic Heart Failure), an ongoing randomized trial of ICD implantation for patients with HF and intermediate-range LVEF (36% to 50%) and LGE (16). Second, are there patients with an LVEF <35% who would not likely benefit from ICD therapy? In an era of precision medicine, shared decision making, and escalating costs of medical care, it may be time to move beyond LVEF alone as the sole imaging parameter to assess risk of SCD and cardiovascular death in NICM. The use of LGE could provide a more precise assessment of risk, leading to more individualized decision making.

Where do we go from here for CMR, NICM, and ICD implantation? More than 30 papers and 3 meta-analyses have shown similar increases in mortality with LGE in NICM. Whether this risk can be modified by implantation of a primary prevention ICD is still unknown. Although a clinical trial of CMR-guided ICD implantation in NICM patients is currently under way, it excludes patients with an EF <35%. Another sensible step would be a multicenter, prospective registry in this NICM population. Such a registry could incorporate common definitions of clinically relevant endpoints and use standardized imaging and quantification protocols. Furthermore, other important CMR features that may provide independent stratification, such as native T1 mapping and extracellular volume should be studied. In the era of personalized medicine, CMR imaging with LGE has the potential to fulfill the tripartite goal of noninvasive imaging: to deliver diagnosis, to secure prognosis, and to affect management (17).

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