American perspective: Comparing the AHA/ACC and ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

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The “Guidelines in Review” series in this issue of the Journal of Nuclear Cardiology focuses on the comparison of the AHA/ACC and ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.¹ In spite of the fact that the AHA/ACC guidelines were published in 2006² (to be updated in the near future) and the ESC guidelines in 2015,³ there are relatively minor differences between their recommendations. This is true even after incorporating recommendations on sudden death prevention from more recent AHA/ACC guidelines on heart failure,⁴ implantable electronic devices,⁵ and congenital heart disease.⁶ The most substantive difference between the two guidelines relates to implantation of a primary prevention implantable cardiac defibrillator (ICD). Both the AHA/ACC and ESC guidelines recommend consideration of an ICD in patients without other life-limiting comorbidities having ischemic and nonischemic class II and III congestive heart failures and a left ventricular ejection fraction (LVEF) less than or equal to 35%. This recommendation is based on several well-designed randomized

clinical trials.^{7,8} The AHA/ACC guidelines also continue to recommend that primary prevention ICD therapy be considered in patients with functional class I congestive heart failure and a LVEF less than or equal to 30%. The latter recommendation is based on a single study, the MADIT II trial.⁷ Both guidelines are consonant in underscoring the importance of evaluating patients for underlying coronary artery disease.

What is most notable from an imaging standpoint is that despite a difference of almost a decade in the publication of these two sets of guidelines, there has been no real evolution of methods for risk stratification beyond the assessment of LVEF. LVEF in itself has no pathophysiological basis for arrhythmogenesis (for ICD implantation) or ‘dyssynchrony’ (for resynchronization therapy). It is a simple ratio of end-systolic and end-diastolic volumes. While LVEF remains the “gold standard” to define the risk of sudden cardiac arrest (SCA) among patients with cardiomyopathy, there is a general lack of specifics on how it should actually be quantified in any of the guidelines, and many clinical decisions are still based on the subjective echocardiographic assessment of ventricular function.

It needs to be emphasized that the clinical trials that form the basis of these guidelines allowed LVEF to be assessed from any imaging modality. This is a significant limitation of contemporary management, as it is well known that there are substantial variations in LVEF estimates between modalities. Studies have shown overestimation or underestimation of LVEF by invasive ventriculography and echocardiography, when using magnetic resonance imaging (MRI) as the gold standard.⁹ Similar differences have also been reported comparing LVEF measurements by cardiac MRI vs

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high-resolution gated single photon emission computed tomography (SPECT),¹⁰ and by equilibrium radionuclide angiocardiology (ERNA) vs gated blood-pool SPECT.¹¹ The lack of agreement in LVEF among different modalities may to some extent contribute to variations in clinical benefit from device therapy.

Variability in LVEF may become a particularly critical problem in evaluating patients with a reduced LVEF, who undergo serial imaging to determine whether a reduction in LVEF below 35% persists after instituting optimal medical therapy. Examples of ranges reported for interreader and test–retest variability in the assessment of LVEF by various imaging modalities are presented in the Table 1. The data presented are very humbling, and provide insight into the degree of error when risk is based on our current standard. In addition, we assume that those with a nondilated LV and a LVEF <35% carry the same risk as those with dilated LV and LVEF <35% which may not be the case. In this regard, quantitation of diastolic LV volume may be a more accurate measure of LV remodeling and has been shown in some studies to predict the risk of SCA.^{12,13}

Advanced myocardial imaging modalities to identify the myocardial substrate responsible for arrhythmogenesis using cardiac MRI (scar volume and

gray zone)¹⁴ and radionuclide imaging approaches to assess myocardial sympathetic innervation (using ¹²³I-meta-iodobenzylguanidine [I-123 mIBG] and ¹¹C-hydroxyephedrine)¹⁵ have been studied in many patients, and are discussed as emerging approaches in the guidelines. While characterizing the myocardial substrate has been suggested to be useful in identifying the risk of arrhythmic events, there are currently no specific recommendations on their clinical use.

Why has advanced imaging not been incorporated into the guidelines to help direct selection of patients for primary prevention of SCA? Perhaps this should not be that much surprising as it may not be unlike the long history of promising electrocardiographic and electrophysiological predictors that have subsequently been demonstrated to provide no incremental improvement in risk prediction over the last 40 years.¹⁶ Aside from inducible ventricular tachycardia (VT) at electrophysiological testing in post-myocardial infarction patients with an ejection fraction <40%,¹⁷ none of the EKG markers have demonstrated a predictive value that adds significantly to the measurement of the ejection fraction when evaluated in a prospective fashion. In terms of studies evaluating advanced imaging modalities to predict lethal ventricular arrhythmias, there is a lack of clarity in most of the available data regarding a modality's ability to predict cause-specific mortality from SCA.

Much of our early experience with risk prediction has been based on findings from retrospective studies that have well-recognized limitations. While there are some larger prospective studies of gadolinium-enhanced cardiac MRI¹⁸ and I-123 mIBG¹⁹ in patient groups at risk of sudden death, all are observational and have substantive methodological issues that limit implementing them into risk prediction for SCA. First, almost all studies have employed composite endpoints that include many outcomes that are unrelated to arrhythmic death. Many studies evaluating the prognostic impact of advanced imaging include death from heart failure as well as sudden death although competing risk analyses are beginning to emerge.²⁰ Some studies have included heart failure hospitalization and progression of heart failure in the composite endpoints. These would be relevant in evaluating cardiac resynchronization outcomes, but would not inform patient selection for primary prevention ICD therapy since they have no bearing on the ability of the imaging technique to predict death from lethal arrhythmias. Second, with rare exception, arrhythmic events include all appropriate device therapies administered via an ICD (e.g., anti-tachycardia pacing, shock for brief VT, and shock for VT at all heart rates). With the conventional device programming, this approach greatly overestimates SCA

Table 1. Range of reported variability (coefficient of variation) in measurements of left ventricular ejection fraction among imaging modalities

Imaging modality	Coefficient of variation (%)
Echocardiography ²⁴	
2D echo biplane	9.4
2D echo biplane with contrast	11
2D echo triplane	11.6
2D echo triplane with contrast	13.8
3D echo	4.4
3D echo with contrast	8.4
Radionuclide imaging	
ERNA	3–5 ^{11,25}
Gated SPECT TI-201	10 ²⁶
Gated SPECT Tc-99 m	5–8 ^{26,27}
Gated blood-pool SPECT	4 ¹¹
Cardiac MRI	4–7.5 ^{28,29}

2D, 2-dimensional; 3D, 3-dimensional; echo, echocardiography; ERNA, equilibrium radionuclide ventriculography; SPECT, single photon emission computed tomography; TI-201, thallium; Tc-99m, technetium-99m; MRI, magnetic resonance imaging

events (perhaps by as much as threefold). Recent studies with less-aggressive device programming have demonstrated a high frequency of self-terminating VTs.²¹ Third, many advanced imaging studies have pooled patients with ischemic and nonischemic cardiomyopathy. Aside from the rates of SCA being higher in ischemic vs nonischemic cardiomyopathy (and controversy about the value of a primary prevention ICD in nonischemic cardiomyopathy),²² the underlying pathological substrate leading to lethal arrhythmias may be fundamentally different. For example, substrate factors that differ in CAD include localization of myocardial scar in the subendocardium vs midwall in nonischemic cardiomyopathy, regional sympathetic denervation from ischemia and infarction vs global myocardial sympathetic denervation from sympathetic activation in nonischemic cardiomyopathy, and the role of regional ischemia as a potential trigger of arrhythmias in CAD.

Although practice guidelines are continually being updated and refined, a final concern in incorporating more robust risk stratification is related to how one would go about implementing a new risk-prediction algorithm (e.g., using advanced imaging, biomarkers, and even emerging EKG predictors) to stratify SCA risk in patients that currently qualify for a primary prevention ICD based solely on a depressed LVEF. Here, there seem to be two approaches to generate the clinical evidence required to change current practice. Both would require multicenter clinical trials. One approach would be to conduct a noninferiority trial of optimal medical therapy with or without ICD implantation in the low-risk population. It would require acceptance of a prespecified rate of SCA that would define the margin. Because of the anticipated low event rate, the trial would need to be very large. For example, a study to detect a 5% absolute difference in the occurrence of SCA between those with and without an ICD over 5 years of follow-up (<1%/year difference with vs without an ICD), at a power of 90% and error of 5%, will need to enroll approximately 3600 patients. Alternatively, a pragmatic multicenter observational trial could be employed in primary prevention ICD recipients with agreement on ICD programming and a consensus regarding device-detected arrhythmias resulting in ICD shocks that best correlate with risk for SCA. After risk stratification at entry, the incidence of device therapy for the SCA equivalent arrhythmia would be the primary endpoint. Such an approach has been employed in the single-center PAR-EPET study where ICD shock for VT >240 beats per minute was used as the SCA equivalent.¹² With either approach, thorny issues come up and center around defining what is an acceptably low level of SCA events. This may ultimately center around a cost-benefit analysis of the number of patients needed to treat in order to

save a life. This is not unlike the argument to withhold ICD implantation for primary prevention in patients with advanced heart failure or other noncardiac competing risks of death where preventing SCA does not meaningfully impact long-term survival.

SCA remains a leading cause of mortality in the general population; yet, over the last 20 years, the rate of arrhythmic death in the heart failure population has declined with the broad implementation of angiotensin-converting inhibitors, beta blockers, and aldosterone antagonists in patients with heart failure.²³ While there is general agreement among the cardiology community about the need to better target patients for primary prevention ICDs, consensus in refining the guidelines and implementing new risk-stratification approaches employing advanced imaging as well as other biomarkers will require continued joint collaboration among the imaging, electrophysiological, and clinical cardiology communities on an international basis.

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