Over the past decade, several large, randomized trials have allowed us to better define the appropriate population for primary prevention implantable cardioverter-defibrillator (ICD) placement, saving thousands of lives every year. MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) have demonstrated a survival benefit of 31% and 23% over 20 and 45.5 months follow-up, respectively.1,2 However, our selection criteria that are mostly based on left ventricular ejection fraction (LVEF) of limited specificity. Long-term follow-up data show that only 35% of patients ever receive an appropriate shock for ventricular tachycardia (VT) and ventricular fibrillation (VF) during a 3-year follow-up.3

Apart from the imaging data, the baseline serum level of high-sensitivity C-reactive protein (hsCRP) was also independently associated with the primary outcome in the multivariate analysis. CRP measurements in the middle and highest tertile conferred a 2.4- and 2.8-fold risk of the primary outcome ($P$=0.07 and $P$=0.03, respectively). When combining the MRI gray zone data and the hsCRP results, the investigators found that the 18% of patients with the lowest tertile in both had only a 0.7%/year event rate. Inversely, the patient group with the highest tertile for both had an event rate of 16.1%/year for appropriate ICD shock or cardiac death.

This work raises several important points. A test that could identify a subset of patients with an event rate low enough that the patients may not benefit from ICD implantation would be of high clinical impact. Complications associated with device implantation and subsequent follow-up, such as infections, lead fractures, or inappropriate shocks, can result in significant morbidity and increased mortality. Additionally, given the current constraints on the healthcare budget, potentially eliminating 18% of the ~130 000 ICDs placed in 2010 in the United States alone could result in a cost savings of ~$500 to $700 million per year.

**Substrate and Triggers**

It is a generally accepted paradigm that in the structurally abnormal heart, both substrate and triggers are required for the genesis of ventricular arrhythmias.5 Myocardial scar is the arrhythmogenic substrate in ischemic cardiomyopathy and has been recently recognized in most nonischemic cardiomyopathies. The interposition of fibroblasts and myocardial cells create spatial heterogeneity and anisotropy, resulting in slow conduction, fixed and functional conduction block, and abnormal excitability as well as in dispersion of refractoriness, which favors reentrant arrhythmias as the preeminent tachycardia mechanism. This substrate is modulated by a variety of transient factors, such as ischemia, autonomic tone, electrolyte disturbances, or drugs, with complex effects on action potential duration, membrane properties, calcium handling, and cellular coupling. Although conceptually understood, the complexity of these interactions makes the quantification of a specific arrhythmic risk for an individual patient very challenging.

Nevertheless, numerous clinical, imaging, proteomic, and genetic markers have been evaluated over the past 3 decades to predict patient characteristics associated with high and low risk of SCD. ECG-derived markers have been the most common used in assessing abnormal autonomic modulation (heart rate variability, heart rate turbulence, or heart rate recovery), indices of abnormal impulse conduction (signal-averaged ECG, QRS fractionation), or abnormal repolarization (T-wave alternans, QT-interval dynamicty).6 Cardiac
imaging was used early on to visualize not only the arrhythmogenic substrate of myocardial scar, but also the potential triggers. In a large cohort of 1926 patients, myocardial scar diagnosed based on 201TI single-photon emission CT results was associated with an increased rate of cardiovascular death. Using MRI, Bello et al demonstrated that in 48 patients with ischemic cardiomyopathy, infarct size and morphology was a better predictor of inducible ventricular arrhythmias than LVEF.

Triggers such as myocardial ischemia were shown to correlate in 5183 patients who underwent stress and rest single-photon emission CT imaging, with increased risk of cardiac death. Similarly, PET imaging demonstrated an increased mortality in patients with ischemic cardiomyopathy and hibernating versus nonhibernating myocardium (50% versus 8%, $P=0.007$). Revascularization was especially beneficial in patients with a >7% mismatch.

Recently, methyldobenzylguanidine, a norepinephrine analog used to visualize the sympathetic postganglionic presynaptic fibers, has been used to better characterize cardiac innervations and arrhythmia risk. The prospective, multicenter ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) trial demonstrated in 961 patients with heart failure (66% ischemic) that a heart-to-mediastinum uptake ratio of <1.6 resulted in a ~3-fold increase of arrhythmic events after 24 months of follow-up.

Over the past 5 years, the gray zone has emerged as a new concept to further characterize the VT substrate, building on the superb soft tissue resolution of CMR. It represents a natural extension of the binary concept of gadolinium-enhanced scar imaging in which scar, because of its increased volume of distribution and higher gadolinium concentration, appears white, whereas normal myocardium with fewer gadolinium molecules per volume units has a black appearance. As discussed previously, the most proarrhythmic substrate, however, is believed to contain bundles of viable myocardium intermixed with fibrous tissue, which frequently is located at the scar border zone. CMR signals in this area would be expected to represent a mixture of white (scar) and black (viable myocardium), hence the term gray zone.

Indeed, gray zone areas have been associated in patients with mild to moderate ischemic cardiomyopathy (LVEF, 44±17%) by an increased all-cause (hazard ratio, 1.42) and cardiovascular (hazard ratio, 1.49) mortality. In severe ischemic cardiomyopathy (mean LVEF, <30%), the gray zone was the only predictive factor for inducibility of monomorphic VT and the strongest predictor for appropriate ICD therapy during 8.5 months of follow-up. Consistently, the gray zone outperformed LVEF or scar core and total scar as a predictive factor.

It is important to note that each of these studies used a different algorithm to define the gray zone. Comparative data among the different algorithms is scant. A study by de Haan et al compared the 3 methods in 55 patients undergoing ICD implantation for severe ischemic cardiomyopathy (LVEF, 25±7%). The overall scar size was comparable among the methods, but the SD-based method by Yan et al resulted in the largest scar core measurement, whereas the full-width half-maximum method described by Schmidt et al (and used in Wu et al) yielded the largest gray zone. Indeed, the gray zone mass (in grams) varied by a factor >5 among the methods. Interestingly, receiver operating characteristic curves suggest a comparable predictive value of all 3 methods for the occurrence of VF or sustained VT >150 beats/minute during a 2-year follow-up. Surprisingly, this study did not demonstrate an additional predictive value of the gray zone over the total scar mass.

It is important to note that some inherent MRI properties, such as partial volume effects, will affect the gray zone measurement. Partial volume effect refers to a loss of signal intensity in small regions because of the technical limited resolution of today’s CMR systems. Indeed, changing the CMR spatial resolution in infarcted rat hearts to the clinically achievable settings increased the gray zone by a factor of 2.

Despite these limitations, it appears that with appropriate expertise, biologically meaningful signals can be extracted from the gray zone data using today’s technology. Indeed, several animal and human studies have recently started to evaluate the gray zone as an area for targeted ablation.

Despite all the previous work on predictive markers for SCD, it is noteworthy that not a single one has led to a significant change in selection criteria for primary prevention ICDs. One of the reasons is that these markers frequently result in hazard ratios of 1.5 to 3, which are statistically significant but do not reach enough clinical significance to withhold or extend ICD therapy. Given these limitations as well as the complexity of ventricular arrhythmogenesis, it is likely that a combination of multiple risk markers may prove superior to a single test when predicting VT/VF or cardiac death.

Wu et al tested the combination with hsCRP, a cytokine-triggered acute-phase reactant. CRP is synthesized in the liver in response to a wide variety of acute and chronic inflammatory conditions, such as infections, rheumatic and inflammatory diseases, malignancy, or tissue injury or necrosis. Although multiple studies have established a strong link of hsCRP with coronary artery disease and heart failure, several ad hoc analyses have also suggested an increased risk of SCD independent of ischemia or infarction. Because a genetically elevated CRP is not correlated with adverse cardiovascular outcome, it is likely to be a marker of an underlying proinflammatory process. A single, elevated baseline hsCRP level may indicate a higher risk for future coronary artery disease, asymptomatic LV dysfunction, or a diffuse process of inflammation marked as isolated areas of myocardial fibrosis at autopsy. Other possible pathways mentioned by Wu et al include chronically elevated proinflammatory cytokines in the setting of sympathetic nervous system activation and matrix metalloproteinase activation.

Wu et al found that patients with the lowest tertile of gray zone and hsCRP demonstrated only a yearly event rate of 0.7%. Although this is still higher than the 0.1%/year SCD rate in the general population, a clinical benefit from ICD implantation might be difficult to prove in such a subgroup, especially when considering unavoidable complications.

Identifying the most suitable biomarker may be challenging, and new candidates, such as soluble ST2 or highsensitivity troponin, will continue to emerge.
(C-reactive Protein Assessment After Myocardial Infarction to Guide Implantation of Defibrillator), the first prospective, multicenter trial to evaluate hsCRP and SCD, failed to demonstrate a significant correlation in 300 patients with ischemic cardiomyopathy during a 2-year follow-up.\(^1\) Interestingly, the biomarker analysis in CAMI-GUIDE showed a positive association of ventricular arrhythmias with N-terminal pro-brain natriuretic peptide, which also demonstrated a significant correlation in the multivariate analysis in Wu et al.\(^4\) The concept chosen by the investigators to combine a substrate marker (gray zone) with a marker that may reflect part of the triggering pathway (biomarker) represents a very plausible and promising approach.

A few points should be considered before testing this hypothesis in a prospective trial. The study is the first to extend the concept of the gray zone to patients with nonischemic cardiomyopathy. Although scar-related reentrant arrhythmias appear to be the predominant mechanism (and primary end point rates or subgroup comparisons were similar between patients with and without ischemia), further validation of the gray zone concept is needed in this patient population. This would also better characterize the still wide CIs the authors report.

The quality of biomarker measurements will be relatively comparable between different centers once commercial test kits become available. However, the technical complexity may make the correct gray zone assessment more challenging in less-experienced centers.

It is also important to note that a normal renal function was an inclusion criterion in the trial (creatinine clearance of $\geq 60$ mL/min for the latter half of the study), which may not apply to all of the heart failure population. Indeed, patients with significant renal dysfunction (creatinine $>2.5$ mg/dL) did not benefit from ICD placement in the MADIT II population.\(^2\)

Twenty-seven percent of patients received a biventricular device. Although the proportion of resynchronization therapy was similar in both groups, the well-established arrhythmia-modulating effects will need to be taken into consideration.

Like in almost all other studies, risk markers for ventricular arrhythmias and cardiac death were only determined at the beginning of the study. However, the arrhythmogenic substrate and triggers are dynamic, and an individual at low risk may evolve to an intermediate- or even high-risk patient later in life. This might be an explanation for the failure of some previous noninvasive risk stratification trials. Questions about how long of a low-risk interval such markers can predict and whether repeat tests may be required undoubtedly will be topics of future studies.

Finally, this important study outlines avenues to improve on our current patient selection and sets the stage for a prospective multicenter trial, which ultimately will be needed for confirmation. The search for the Holy Grail continues from the past millennium. Wu and colleagues give us hope that we are on the right path.

**Disclosures**

None.

**References**


**KEY WORDS:** Editorials ■ biological markers ■ magnetic resonance imaging ■ sudden cardiac death ■ tachycardia ventricular ■ implantable cardioverter-defibrillators
Pursuing the "Holy Grail"
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doi: 10.1161/CIRCIMAGING.112.972935
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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