An ECG index of myocardial scar enhances prediction of defibrillator shocks: An analysis of the Sudden Cardiac Death in Heart Failure Trial

David G. Strauss, MD, PhD,*† Jeanne E. Poole, MD,‡ Galen S. Wagner, MD,§ Ronald H. Selvester, MD,‖ Julie M. Miller, MD,* Jill Anderson, RN,‡ George Johnson, B.S.E.E.,§ Steven E. McNulty, MS,§ Daniel B. Mark, MD, MPH,§ Kerry L. Lee, PhD,§ Gust H. Bardy, MD,‡ Katherine C. Wu, MD*

From the Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD, †Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD, ‡Seattle Institute for Cardiac Research, Seattle, WA, §Duke Clinical Research Institute, Durham, NC, ‖Memorial Hospital Research Center, Long Beach, CA.

BACKGROUND Only a minority of patients receiving implantable cardioverter-defibrillators (ICDs) for the primary prevention of sudden death receive appropriate shocks, yet almost as many are subjected to inappropriate shocks and device complications. Identifying and quantifying myocardial scar, which forms the substrate for ventricular tachyarrhythmias, may improve risk stratification.

OBJECTIVE This study sought to determine whether the absence of myocardial scar detected by novel 12-lead electrocardiographic (ECG) Selvester QRS scoring criteria identifies patients with low risk for appropriate ICD shocks.

METHODS We applied QRS scoring to 797 patients from the ICD arm of the Sudden Cardiac Death in Heart Failure Trial. Patients were followed up for a median of 45.5 months for ventricular tachycardia/fibrillation treated by the ICD or sudden tachyarrhythmic death (combined group referred to as VT/VF).

RESULTS Increasing QRS score scar size predicted higher rates of VT/VF. Patients with no scar (QRS score = 0) represented a particularly low-risk cohort with 48% fewer VT/VF events than the rest of the population (absolute difference 11%; hazard ratio 0.52, 95% confidence interval 0.31 to 0.88). QRS score scar absence versus presence remained a significant prognostic factor after controlling for 10 clinically relevant variables. Combining QRS score (scar absence versus presence) with ejection fraction ($\geq$25% versus $<$25%) distinguished low-, middle-, and high-risk subgroups with 73% fewer VT/VF events in the low-risk versus high-risk group (absolute difference 22%; hazard ratio = 0.27, 95% confidence interval 0.12 to 0.62).

CONCLUSION Patients with no scar by QRS scoring have significantly fewer VT/VF events. This inexpensive 12-lead ECG tool provides unique, incremental prognostic information and should be considered in risk-stratifying algorithms for selecting patients for ICDs.

KEYWORDS Sudden death; Defibrillation; Electrocardiography; Electrophysiology; Tachyarrhythmias

ABBREVIATIONS **ECG** = electrocardiogram; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **LAFB** = left anterior fascicular block; **LBBB** = left bundle branch block; **LVEF** = left ventricular ejection fraction; **MADIT-II** = Multicenter Automatic Defibrillator Implantation Trial II; **MRI** = magnetic resonance imaging; **NYHA** = New York Heart Association; **RBBB** = right bundle branch block; **SCD-HeFT** = Sudden Cardiac Death in Heart Failure Trial; **VT/VF** = ventricular tachycardia and ventricular fibrillation

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Introduction

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) demonstrated that implantation of a cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) significantly decreased mortality in patients with reduced left ventricular ejection fraction (LVEF).[1,2] However, only a minority of patients

Dr. Strauss was supported by the Sarnoff Cardiovascular Research Foundation (Great Falls, VA) for work at Johns Hopkins, and has subsequently moved to the U.S. Food and Drug Administration. Views expressed do not represent those of the FDA. Dr. Wu and Dr. Miller were supported by the Donald W. Reynolds Cardiovascular Research Center at Johns Hopkins University (Baltimore, MD), and Dr. Miller was supported by the Doris Duke Charitable Foundation (New York, NY). The main SCD-HeFT study was supported by grants (UO1 HL55766, UO1 HL55297, and UO1 HL55496) from the NHLBI, National Institutes of Health, and by Medtronic, Wyeth–Ayerst Laboratories, and Knoll Pharmaceuticals. Dr. Poole has received speaking fees from Medtronic, Boston Scientific and St. Jude Medical, and a research grant from Biotronik. Dr. Wagner has received research support from Physio-Control and Welch-Allyn. Dr. Mark has received research support from Abbott Laboratories, Abbott Vascular Business, Abiomed, and Acorn Cardiovascular. Dr. Bardy has received research grants from St. Jude Medical, is a consultant for Phillips Medical and Cardiac Sciences, and is a board member and has equity and intellectual property in Cameron Health Inc. This study is registered at http://www.clinicaltrials.gov – identifier NCT00000609. **Address reprint requests and correspondence:** Dr. Katherine C. Wu, Division of Cardiology, Johns Hopkins Hospital, 600 North Wolfe Street, Carnegie 568, Baltimore, MD 21287. E-mail address:kwu@jhmi.edu. (Received August 19, 2010; accepted September 22, 2010.)

1547-5271/$ -see front matter © 2011 Heart Rhythm Society. All rights reserved. doi:10.1016/j.hrthm.2010.09.071

receive appropriate ICD shocks for ventricular tachyarrhythmias, whereas almost as many patients receive inappropriate shocks, which are associated with increased mortality.[3,4] Furthermore, patients are subjected to device-related complications.[5] Finally, under current implantation guidelines the extent to which ICDs are cost effective is controversial.[6] Better risk stratification of potential ICD candidates could improve the cost effectiveness of this therapy if device placement is avoided in those unlikely to benefit, and instead, specifically targeted to those in whom maximal benefit is expected.[6-8] For this purpose, a widely available, inexpensive, noninvasive diagnostic tool that facilitates mass screening would be most ideal.

Ventricular tachycardia and fibrillation (VT/VF) leading to SCD result from the interaction of abnormal myocardial anatomic/functional substrate and electrophysiological triggering events.[9] Although reduced LVEF is a risk factor for arrhythmogenesis, it is not synonymous with the structural myocardial damage needed to support arrhythmic circuits.[9,10] Regions of prior myocardial infarction are potentially arrhythmogenic, irrespective of LVEF, as are myocardial scars in nonischemic cardiomyopathies.[11,12] Characterization of the myocardial substrate (scar) as a risk predictor has not been investigated in published, large, randomized, ICD clinical trials. Recent observational studies have used contrast-enhanced magnetic resonance imaging (MRI) to identify and quantify myocardial scar. MRI scar presence and characteristics predict inducibility of arrhythmias by programmed stimulation[13-15] and prognosis.[16-19] Although MRI analysis of myocardial scar is a promising risk-stratifying tool for arrhythmias, it is costly and not commonly available. In contrast, the 12-lead electrocardiogram (ECG) is inexpensive and universally available, and can be readily used to perform Selvester QRS scoring, which estimates infarct/scar size by quantifying changes in Q-, R- and S-wave durations, amplitudes, and morphologies.[20]

The Selvester QRS score consists of 32 total possible points, with each point reflecting myocardial infarction involving 3% of the left ventricle (LV).[20] With training, the score can be performed in 2 to 5 minutes, and multiple automated versions have been developed with further implementation for widespread use underway.[20-24] Prior studies with QRS scoring excluded ECG confounding factors such as the presence of ventricular hypertrophy and bundle branch blocks, which were thought to preclude accurate electrocardiographic infarct diagnosis. However, modified QRS scoring systems for use in the presence of confounders were created based on computer simulation and recently validated in comparison with MRI scar size and shown to predict the substrate for arrhythmias defined by inducibility of monomorphic VT during programmed stimulation.[25]

The current study was performed to test the hypothesis that the absence of scar by 12-lead ECG QRS scoring identifies patients with a low risk of ICD shocks for sustained VT/VF or sudden tachyarrhythmic death in SCD-HeFT.

Methods

Study patients

The main SCD-HeFT study enrolled patients with New York Heart Association (NYHA) class II or III heart failure with LVEF $\leq$35%.[1] The study was approved by an institutional review committee, and all subjects gave informed consent. Notably, heart failure etiology was defined as ischemic if patients had $\geq$75% narrowing in $\geq$1 major coronary artery or a history of infarction. Patients without these criteria were defined as nonischemic. Patients were randomly assigned to 1 of 3 arms: single-chamber ICD (n = 829), amiodarone (n = 845), or placebo (n = 847). We retrospectively performed QRS scoring on the baseline, predevice 12-lead ECGs of the patients randomized to ICD. Of these patients, 18 of 829 (2%) did not receive an ICD and were excluded from analysis.

12-Lead ECG protocol

All patients received baseline 12-lead ECGs, before randomization.[1] Standard 12-lead ECGs (10 mm/mV and 25 mm/s) were sent to the ECG QRS scoring core laboratory for analysis. There were no uniform ECG filter settings. Analysis was performed blinded to all clinical and ICD data except for age and gender, which are considered when performing QRS scoring. A single investigator analyzed all ECGs using a standardized protocol with quality control by 2 additional investigators. The QRS score analysis protocol has been reported previously[20,25] (and is included in the Online-Appendix). Briefly, ECGs were first classified by primary ventricular conduction/hypertrophy type: left bundle branch block (LBBB), left anterior fascicular block (LAFB), left ventricular hypertrophy, right bundle branch block (RBBB), RBBB+LAFB, or no confounders. The QRS scoring system for the appropriate conduction/hypertrophy type was then applied, which involves measurements of Q-, R-, and S-wave amplitudes, durations, amplitude ratios, and notches in 10 of the 12 standard ECG leads (excluding leads III and aVR). No patients had ventricular pacing or pre-excitation, which would preclude QRS scoring.

ICD protocol, electrogram classification, and death classification

The ICD implantation protocol, device settings, and electrogram core laboratory protocol have been reported previously in detail.[3] By design, the ICDs in SCD-HeFT were restricted to single-lead devices with a detection rate of $\geq$188 beats/min and no antitachycardia pacing programmed.[1,3] Bradycardia pacing was set to 50 beats/min with a hysteresis of 34 beats/min. Recorded ICD data were sent to the SCD-HeFT ICD electrogram core laboratory for review at 3-month follow-up visits, after known ICD therapy, and when possible, after patient deaths.[3] Two members of the committee, blinded to all patient data, classified each

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