JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN
COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 69, NO. 16, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.02.042

Implantable Cardioverter-Defibrillators With Versus Without Resynchronization Therapy in Patients With a QRS Duration >180 ms

Varun Sundaram, MD,[a,b] Jayakumar Sahadevan, MD,[a,c] Albert L. Waldo, MD, PhD, (Hon),[a] George J. Stukenborg, PhD,[d] Yogesh N.V. Reddy, MD,[e] Samuel J. Asirvatham, MD,[e] Judith A. Mackall, MD,[a] Anselma Intini, MD,[c] Brigid Wilson, PhD,[c] Daniel I. Simon, MD,[a] Kenneth C. Bilchick, MD[d]

ABSTRACT

BACKGROUND More than 20% of Medicare beneficiaries receiving cardiac resynchronization therapy defibrillators (CRT-D) have a very wide (≥180 ms) QRS complex duration (QRSD). Outcomes of CRT-D in these patients are not well-established because they have been underrepresented in clinical trials.

OBJECTIVES This study examined outcomes in patients with CRT-D in a very wide QRSD with left bundle branch block (LBBB) versus those without LBBB.

METHODS Medicare patients from the Implantable Cardioverter Defibrillator Registry (January 1, 2005, through April 30, 2006) with a CRT-D and confirmed Class I or IIa indications for CRT-D were matched to implantable cardioverter-defibrillator (ICD) patients without CRT despite having Class I or IIa indications for CRT. Mortality and heart failure hospitalizations longer than 4 years with CRT-D versus standard ICDs based on a QRSD and morphology were analyzed.

RESULTS We analyzed 24,960 patients. Among those with LBBB, patients with a QRSD ≥180 ms had a greater adjusted survival benefit with CRT-D versus standard ICD (hazard ration [HR] for death: 0.65; 95% confidence interval [CI]: 0.59 to 0.72) compared with those having a QRSD 120 to 149 ms (HR: 0.85; 95% CI: 0.80 to 0.92) and 150 to 179 ms (HR: 0.87; 95% CI: 0.81 to 0.93). CRT-D versus ICD was associated with an improvement in survival in those with LBBB and a QRSD ≥180 ms (adjusted HR for death: 0.78; 95% CI: 0.68 to 0.91), but not in those with LBBB and a QRSD 150 to 179 ms (adjusted HR for death: 1.06; 95% CI: 0.95 to 1.19).

CONCLUSIONS Improvements in both survival and heart failure hospitalizations with CRT-D were greatest in patients with a QRSD ≥180 ms with or without LBBB, whereas patients with a QRSD 150 to 179 ms without LBBB had no improvement in survival with CRT-D, and those with a QRSD 150 to 179 ms and LBBB had only a modest improvement. (J Am Coll Cardiol 2017;69:2026–36) Published by Elsevier on behalf of the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio; [b]Royal Brompton and Harefield Hospitals, National Heart and Lung Institute, Imperial College, London, United Kingdom; [c]Department of Medicine, Louis Stokes Veteran Affairs Medical Center, Cleveland, Ohio; [d]Division of Cardiovascular Medicine, University of Virginia Health System, Charlottesville, Virginia; and the [e]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota. Dr. Sahadevan is supported by Ohio Third Frontier and the Clinical and Translational Science Collaborative grants. Dr. Waldo has received a research contract from and served as a consultant to Gilead Sciences; consulted on a clinical trial steering committee for Atricure; consulted for Milestone Pharmaceuticals and Biosense-Webster; served on a scientific advisory board for Daiichi-Sankyo; served on a trial steering committee for St. Jude Medical; and served as a speaker for Bristol-Myers Squibb and Pfizer. Dr. Reddy is supported by T32 HL007111 from the National Institutes of Health. Dr. Mackall has served as a consultant for and undertaken clinical research for St. Jude Medical. Dr. Bilchick is supported by grant R03 HL135463 from the National Institutes of Health. Drs. Sundaram and Sahadevan contributed equally to this work.

Manuscript received December 5, 2016; revised manuscript received February 2, 2017, accepted February 10, 2017.

Cardiac resynchronization therapy defibrillators (CRT-Ds) have been associated with marked reductions in mortality and heart failure (HF) hospitalizations in patients with heart failure and reduced ejection fraction (HFrEF) (1-3). However, 30% of patients meeting current CRT criteria do not achieve CRT response (4). Based on data from randomized clinical trials, patients with a pre-CRT QRS complex duration (QRSD) ≥150 ms benefit more than those with a QRSD of 120 to 149 ms (5). Furthermore, patients with left bundle branch block (LBBB) and a QRSD ≥150 ms have a stronger guideline-based indication for CRT-D (Class I) than patients with a QRSD 120 to 149 ms, whereas patients without LBBB and a QRSD ≥150 ms have a Class IIa indication for CRT-D (6). According to guideline-based recommendations (6), patients with LBBB and a very wide QRSD (VWQRSD) (≥180 ms) have a Class I indication for CRT-D and patients without LBBB who have a QRSD ≥180 ms have a Class IIa indication for CRT-D. However, these groups have not been well-studied because they have been underrepresented in CRT clinical trials (3,7).

SEE PAGE 2037

A QRSD ≥120 ms can be due to either conduction block in the bundle branches, electrical uncoupling in the ventricular myocardium, or a combination of both. Electrical uncoupling in HF results from altered expression of connexins that assemble gap junctions (8). Gap junctions are critical in regulating conduction of electrical impulses within the myocardium. Decreased expression and/or disruption of gap junctions decrease the conduction velocity in the myocardium (9), leading to a wide QRSD on the electrocardiogram.

It has been shown from actual heart and computer simulation studies that with true LBBB, the QRSD is in the range of 140 ms (10); with true right bundle branch block (RBBB), the QRSD is even less. Using a realistic computer model of the human heart and torso, Potse et al. (11) demonstrated that by decreasing electrical coupling by 50% in the absence of LBBB, the QRSD increased from 90 to 120 ms; in the presence of LBBB with electrical uncoupling, the QRSD increased from 140 to 190 ms. It is also possible that a QRSD could be prolonged beyond 140 ms in the presence of left ventricular dilatation with LBBB. In the presence of significant electrical uncoupling, the benefits of CRT may be negated by slow and dispersed conduction during pacing (12). Based on these considerations, we hypothesized that 1 reason for nonresponsiveness to CRT may be the presence of significant electrical uncoupling; therefore, patients with a VWQRSD (≥180 ms) would have less favorable outcomes than patients with a moderately wide QRSD (150 to 179 ms), and different outcomes depending on bundle branch block morphology (BBB).

To evaluate outcomes in patients with a VWQRSD, we stratified patients by a QRSD and compared long-term outcomes among 24,960 Medicare patients identified in the Implantable Cardioverter Defibrillator Registry (ICDR) who received CRT-D with those of a propensity-matched control cohort receiving standard implantable cardioverter-defibrillators (ICDs) that had an indication for CRT-D.

METHODS

DATA SOURCES. Records were obtained for patients with CRT-Ds and standard ICDs from the original ICDR maintained by the Iowa Foundation for Medical Care under contract with Medicare from January 2005 and to April 2006 (13,14). During this period, all health care providers implanting devices funded by Medicare were required to enter patient information including demographics, history, clinical investigations, and device information into a patient registry. This Medicare ICDR was maintained by the Iowa Foundation for Medical Care through April 2006 and constitutes a distinct dataset.

COHORT COMPOSTION. Patients were classified on the basis of whether they had CRT-D or ICD devices implanted. Patients with CRT-D or a standard ICD who had an accepted Class I or Class IIa recommendation for CRT-D as per the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines were included in the analysis. All patients were required to have a left ventricular ejection fraction ≤0.35 and New York Heart Association functional class II to IV HF. In addition, patients with LBBB were required to have a QRSD ≥120 ms, and patients without LBBB were required to have a QRSD ≥150 ms. Patients without LBBB and a QRSD of 120 to 149 ms were not included in our analysis because they do not meet Class I or Class IIa recommendations for CRT-D placement. All patients with ICDs were required to meet the same criteria for inclusion as those with CRT-D.

OUTCOME DATA AND LINKAGE. Medicare hospital claims files, program eligibility records, and dates of death were also obtained for these patients for the period from ICD implantation through at least the end of 2009. Registry records were matched to Medicare eligibility and utilization data using patients' social

ABBREVIATIONS AND ACRONYMS

BBB = bundle branch block

CI = confidence interval

CRT-D = cardiac resynchronization therapy defibrillator

HF = heart failure

HFH = heart failure hospitalization

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

ICDR = Implantable Cardioverter Defibrillator Registry

IVCD = intraventricular conduction delay

LBBB = left bundle branch block

QRSD = QRS complex duration

RBBB = right bundle branch block

VWQRSD = very wide QRS complex duration