Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator

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BACKGROUND Limited data regarding the effect of right ventricular pacing (RVP) on long-term survival following implantable cardioverter-defibrillator (ICD) implantation are available.

OBJECTIVE The purpose of this study was to evaluate the effect of RVP on the long-term survival benefit of primary ICD therapy.

METHODS Mortality data were obtained for all patients enrolled in the Multicenter Automatic Defibrillator Trial-II (MADIT-II) during an extended follow-up period of 8 years. The cumulative percent RVP during the trial was categorized as low (≤50% [n = 369]) and high (>50% [n = 198]). The benefit of ICD versus non-ICD therapy (n = 490) was evaluated in the two pacing categories during the early (0–3 years) and late (4–8 years) phases of the extended follow-up period.

RESULTS During the early phase of the extended follow-up period, ICD therapy was associated with similar benefits in the low-RVP and high-RVP subgroups (hazard ratio [HR] = 0.35 and 0.38, respectively, $P < .001$ for both). In contrast, during the late phase, the long-term survival benefit of the ICD was maintained among patients with low RVP (HR = 0.60, $P < .001$) and attenuated among those with the high RVP (HR = 0.89, $P = .45$). An increased risk for late mortality associated with high versus low RVP was evident only among patients without left bundle branch [LBBB] at enrollment (HR = 1.63, $P = .002$).

CONCLUSION Among ICD recipients, high RVP is associated with a significant increase in the risk of long-term mortality and with attenuated device efficacy. The deleterious effects of RVP are pronounced mainly in non-LBBB patients, suggesting a possible role for combined cardiac resynchronization–defibrillator therapy in this population.

KEYWORDS Heart failure; Implantable cardioverter-defibrillator; Right ventricular pacing

ABBREVIATIONS **DAVID** = Dual Chamber and VVI Implantable Defibrillator; **HF** = heart failure; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **LBBB** = left bundle branch block; **LV** = left ventricle; **LVEF** = left ventricular ejection fraction; **MADIT-II** = Multicenter Automatic Defibrillator Implantation Trial-II; **NYHA** = New York Heart Association; **RVP** = right ventricular pacing

Introduction

Right ventricular pacing (RVP) causes a iatrogenic left bundle branch block (LBBB) conduction disturbance and is associated with ventricular dyssynchrony and left ventricular (LV) functional deterioration among both patients with good LV function[1,2] and patients with poor LV function.[3,4] Frequent RVP contributes to an increased incidence and severity of heart failure (HF).[5,6] The deleterious consequences of RVP are also evident among patients with a primary prevention indication for an implantable cardioverter-defibrillator (ICD), as demonstrated in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial[7] and the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II).[8] We recently showed that patients who received dual-chamber devices in MADIT-II did not derive a significant survival benefit from the ICD during

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long-term follow-up,[9] suggesting a possible detrimental effect of increased cumulative percent RVP among dual-chamber pacemaker recipients. However, currently no data regarding the effect of RVP on long-term mortality among patients who receive an ICD for primary prevention are available.

The present study was performed in the MADIT-II population and was designed to (1) evaluate the effect of high RVP on long-term mortality among ICD recipients and (2) relate the long-term effects of RVP to QRS morphology. Because patients with LBBB already have a ventricular dyssynchrony similar to that associated with RVP, we hypothesized that the long-term deleterious effects of high RVP will be more pronounced among ICD recipients who did not have LBBB at the time of enrollment in the trial.

Methods

MADIT-II extended 8-year follow-up

MADIT-II enrolled 1,232 patients with a myocardial infarction 1 month or more before entry into the study and left ventricular ejection fraction (LVEF) ≤30%. Patients were randomly assigned in a 3:2 ratio to receive either an implanted defibrillator or non-ICD conventional medical therapy. Details of the design, methods, and results of MADIT-II have been previously reported.[10] The protocol was approved by the institutional review board at each participating organization, and each patient provided written informed consent before enrollment. Data acquisition and follow-up of MADIT-II were performed between July 1997 and December 2001. For the current long-term outcome study, we acquired post-trial mortality data for all study participants through March 2009. For patients who were enrolled in US centers (n = 1,123), information was acquired from the US National Death Registry. For study participants who were enrolled in non-US centers (n = 109), information was acquired from the enrolling centers through hospital records and death registries. The original MADIT-II publication was based primarily on the 0 through 4-year trial period, with median follow-up of 1.5 years (interquartile range 0.8–2.5 years) and total follow-up of 2,070 patient-years. The newly acquired long-term data comprise a median follow-up of 7.6 years (interquartile range 3.5–9.0 years) and total follow-up of 7,815 patient-years during an 8-year period after enrollment. Data regarding cross-over between allocated treatment arms were recorded for all study participants during the study and after trial closure. Among the 742 patients randomized to ICD therapy, 22 patients did not receive an ICD after randomization, and 13 had the ICD extracted during trial. Among the 490 study participants who were allocated to non-ICD conventional medical therapy, 27 patients crossed over to the ICD arm during trial. Study patients who survived to trial closure without an ICD (n = 390) were offered the device provided by the study sponsors. One hundred forty (36%) patients consented and received an ICD within 4 months after trial closure, whereas 250 (64%) patients did not agree to receive an ICD at study end. Limited available information indicates that there were relatively minor changes between treatment arms (<5%) during the subsequent post-trial follow-up period.

ICD data analysis

Among 720 patients who received an ICD during the study, 56% received a single-chamber ICD with the back-up pacing rate programmed at VVI 40 to 50, and 44% received a dual-chamber ICD with the pacing programmed at DDD 60 to 70. The implanted devices included the VENTAK AV series, the VENTAK Mini series, and the VENTAK Prizm series (Guidant Corp., St. Paul, MN, USA). No investigational devices were used during MADIT-II. All ICDs were routinely interrogated at the local investigative site, and data were stored on computer disk. At each ICD interrogation, the number of ventricular paced beats over the total number of beats was calculated for the life of the device and was termed *cumulative percent RVP*. The cumulative percent RVP variable was dichotomized at 0%–50% (low RVP group) and 51%–100% (high RVP group), justified by distribution of the data.[8] Programming of the ICD with regard to back-up bradycardia pacing parameters, including mode, rate, and AV interval, was not predefined by the MADIT-II protocol and was left to the discretion of the local investigator.

Study design and endpoints

Information on the cumulative rate of RVP during the trial was available for 567 (79%) of the ICD-treated patients. Thus, patients were categorized into three subgroups : low RVP (≤50% pacing, n = 369), high RVP (>50% pacing, n = 198), and no ICD (n = 490). We excluded from analysis 153 ICD patients with unknown RVP data and 22 patients who were randomized to the ICD arm but did not receive an ICD after randomization.

The long-term benefit of the ICD by percent RVP was evaluated during the early (0–3 years), and late (4–8 years) phases of the extended follow-up period and by QRS morphology at enrollment.

Statistical analysis

Characteristics of study patients were compared by Wilcoxon rank sum, Chi-square, or Fisher exact test, as appropriate. The probability of all-cause mortality by treatment group and by percent RVP, with follow-up censored upon change in treatment arm, was graphically displayed according to the Kaplan-Meier method, with comparison of cumulative events by log rank test. Cox proportional hazards regression modeling was used to evaluate the independent contribution of the ICD and percent RVP to the occurrence of all-cause mortality during 8-year follow-up, with follow-up censored upon change in treatment arm. Outcomes were further assessed during the early (0–3 years) and late (4–8 years) phases of the extended follow-up period by including a treatment-by-time interaction term in the multivariate models. Prespecified covariates in the multivariate models included age >70 years, New York Heart Associ-