



Outcomes of Cardiac Resynchronization Therapy With or Without Defibrillation in Patients With Nonischemic Cardiomyopathy

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ABSTRACT

BACKGROUND Recent studies have cast doubt on the benefit of cardiac resynchronization therapy (CRT) with defibrillation (CRT-D) versus pacing (CRT-P) for patients with nonischemic cardiomyopathy (NICM). Left ventricular myocardial scar portends poor clinical outcomes.

OBJECTIVES The aim of this study was to determine whether CRT-D is superior to CRT-P in patients with NICM either with (+) or without (–) left ventricular midwall fibrosis (MWF), detected by cardiac magnetic resonance.

METHODS Clinical events were quantified in patients with NICM who were +MWF (n = 68) or –MWF (n = 184) who underwent cardiac magnetic resonance prior to CRT device implantation.

RESULTS In the total study population, +MWF emerged as an independent predictor of total mortality (adjusted hazard ratio [aHR]: 2.31; 95% confidence interval [CI]: 1.45 to 3.68), total mortality or heart failure hospitalization (aHR: 2.02; 95% CI: 1.32 to 3.09), total mortality or hospitalization for major adverse cardiac events (aHR: 2.02; 95% CI: 1.32 to 3.07), death from pump failure (aHR: 1.95; 95% CI: 1.11 to 3.41), and sudden cardiac death (aHR: 3.75; 95% CI: 1.26 to 11.2) over a maximum follow-up period of 14 years (median 3.8 years [interquartile range: 2.0 to 6.1 years] for +MWF and 4.6 years [interquartile range: 2.4 to 8.3 years] for –MWF). In separate analyses of +MWF and –MWF, total mortality (aHR: 0.23; 95% CI: 0.07 to 0.75), total mortality or heart failure hospitalization (aHR: 0.32; 95% CI: 0.12 to 0.82), and total mortality or hospitalization for major adverse cardiac events (aHR: 0.30; 95% CI: 0.12 to 0.78) were lower after CRT-D than after CRT-P in +MWF but not in –MWF.

CONCLUSIONS In patients with NICM, CRT-D was superior to CRT-P in +MWF but not –MWF. These findings have implications for the choice of device therapy in patients with NICM. (J Am Coll Cardiol 2017;70:1216–27)
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Cardiac resynchronization therapy (CRT) is a standard treatment for patients with heart failure (HF), impaired left ventricular (LV) systolic function, and a prolonged QRS duration (1,2). Although CRT-pacing (CRT-P) prevents pump failure by correcting LV dyssynchrony, the addition of defibrillation (CRT-D) leads to a greater treatment

effect by preventing sudden cardiac death (SCD) from ventricular arrhythmias (2,3).

It is well recognized that the clinical outcome of CRT is influenced by the underlying etiology of HF. Nonischemic cardiomyopathy (NICM) is associated with a better LV reverse remodeling response (4) and better clinical outcomes after CRT (5). Because NICM



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is associated with a lower background risk for ventricular arrhythmias than ischemic cardiomyopathy, the benefit of CRT-D over CRT-P has been questioned. In this respect, most of the evidence in favor of defibrillation in patients with NICM comes from studies evaluating patients with single- or dual-chamber implantable cardioverter-defibrillators (ICD) rather than CRT-D devices. Both CAT (Cardiomyopathy Trial) (6) and AMIOVIRT (Amiodarone Versus Implantable Cardioverter-Defibrillator Trial) (7) used single- and dual-chamber ICDs, but neither trial showed any survival benefit from ICDs in patients with NICM. Importantly, these studies involved small numbers of patients (each about 100). In the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) study (8), in which 458 patients with NICM were randomized to medical therapy or a single-chamber ICD, ICD therapy did not reduce total mortality, despite a significant reduction in SCD. A subgroup analysis of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), including patients with NICM, also failed to show a significant reduction in mortality from ICD therapy (9). In the recent DANISH (Defibrillator Implantation in Patients With Nonischemic Systolic Heart Failure) study, ICDs did not reduce total mortality in patients with NICM (10). These studies cast doubt on the relative benefit of CRT-D versus CRT-P in patients with NICM.

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All clinical outcome studies of ICDs in NICM (6-9,11), including DANISH (10), have defined NICM on the basis of findings from echocardiography, coronary angiography, and/or nuclear imaging. These imaging modalities, however, do not provide tissue characterization. In this regard, LV midwall fibrosis (MWF) is a specific form of myocardial scar found in approximately 30% of patients with NICM (Figure 1). It is now recognized that MWF, detected using cardiac magnetic resonance (CMR) imaging, portends a poor outcome in the general NICM population (12-15) and in CRT-P recipients (16). Increasing evidence supports a link between MWF and ventricular arrhythmias (12-14,17). On this basis, we hypothesized that the relative benefit of CRT-D over CRT-P is influenced by MWF.

METHODS

Patients were recruited from 2 centers (Good Hope Hospital and Queen Elizabeth Hospital, Birmingham, United Kingdom). All patients underwent successful CRT device implantation and pre-implantation CMR

from July 2002 to January 2017. Some patients were included in a previous study (16). The present study extended to a larger group and a longer follow-up period.

The diagnosis of HF was made on the basis of clinical features plus echocardiographic evidence of LV systolic dysfunction. The diagnosis of NICM was made if LV dysfunction was associated with either no myocardial scar or with MWF (14). Exclusion criteria included a history of myocardial infarction, coronary revascularization, or diagnosis of ischemic cardiomyopathy on the basis of other investigations (e.g., nuclear imaging); ischemic pattern of scar on CMR; a diagnosis of hypertrophic or restrictive cardiomyopathy, primary valvular disease, sarcoidosis, amyloidosis, or myocarditis made on the basis of CMR or another investigation (e.g., echocardiography, cardiac biopsy, and/or positron emission tomography); and NICM and scar patterns other than MWF (patchy or subepicardial). The study was approved by the local ethics committee or the local clinical audit departments and conformed with the Declaration of Helsinki.

DEVICE THERAPY. In the United Kingdom, the National Institute of Clinical Excellence guidelines in 2007 recommended CRT-P rather than CRT-D for patients with NICM and indications for CRT. With a subsequent guideline change in 2014 recommending CRT-D for NICM (18), the proportion of CRT-D recipients increased thereafter.

Device implantation was undertaken using standard transvenous techniques under local anesthesia and intravenous sedation. After implantation, patients were followed at dedicated device therapy clinics. Before 2013, patients in sinus rhythm underwent transmitral Doppler-directed optimization of atrioventricular delay using an iterative technique prior to discharge and at every scheduled visit thereafter. After 2013, routine echocardiographic optimization was abandoned and undertaken only in the case of symptomatic nonresponders. Backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR with an interventricular delay of 0 to 4 ms, according to manufacturer instructions. In the case of patients in permanent atrial fibrillation, right ventricular and LV leads were implanted and a CRT generator was used, plugging the atrial port and programming to a ventricular triggered mode. Atrioventricular junction ablation was undertaken according to physicians' decision.

ABBREVIATIONS AND ACRONYMS

aHR	= adjusted hazard ratio
CI	= confidence interval
CMR	= cardiac magnetic resonance
CRT	= cardiac resynchronization therapy
CRT-D	= cardiac resynchronization therapy-defibrillation
CRT-P	= cardiac resynchronization therapy-pacing
HF	= heart failure
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
IQR	= interquartile range
LV	= left ventricular
MACE	= major adverse cardiac event
MWF	= midwall fibrosis
NICM	= nonischemic cardiomyopathy
NYHA	= New York Heart Association
SCD	= sudden cardiac death

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