Effect of Cardiac Resynchronization on Morbidity and Mortality of Diabetic Patients With Severe Heart Failure

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Diabetes is a well-known and important risk factor for heart disease, including heart failure (1–4). Despite improvements in pharmacologic treatment, many patients with heart failure have severe and persistent symptoms, and their prognosis remains poor (5,6). While most recent data indicate a higher mortality rate in diabetic patients with heart failure compared with nondiabetic patients (7–9), it is unresolved whether this effect might be limited to patients with ischemic heart disease and/or patients on insulin therapy (10–13).

Cardiac resynchronization therapy (CRT) reduces symptoms and improves left ventricular function and prognosis in many patients with moderate-to-severe heart failure due to systolic dysfunction and cardiac dyssynchrony (14–19). The pathophysiology underlying heart failure in diabetic patients differs from that in nondiabetic patients and is generally considered more progressive. Thus, direct and indirect effects of diabetes on myopathic mechanisms might influence the response of heart failure patients to CRT. We conducted an analysis of the 813 participants of the Cardiac Resynchronisation in Heart Failure (CARE-HF) trial to determine the effect of CRT on the risk of complications and death in diabetic compared with nondiabetic heart failure patients. We also tested the hypothesis that diabetes has a prognostic impact in patients with heart failure.

RESEARCH DESIGN AND METHODS

— The CARE-HF trial (14,20–22) investigated the effects of cardiac resynchronization on morbidity and mortality in patients receiving standard pharmacologic therapy for left ventricular systolic dysfunction, with markers of cardiac dyssynchrony, and symptomatic heart failure. For the purposes of the present analysis, we studied the impact of diabetes by stratifying patients into those with and without a history of diabetes. The impact of treatment with insulin or oral hypoglycemic agents was also evaluated. Data on the duration of diabetes and quality of diabetes control (i.e., A1C) were not available. Patients with a history of myocardial infarction, revascularization, or angiographically documented coronary heart disease were considered to have ischemic heart disease. The primary end point of this analysis was all-cause mortality until the end of the study extension period at 36.4 months (22). Further end points were those of the main trial, death, or unplanned hospitalization for a major cardiovascular event (20). Statistical analysis was performed as previously reported (14,22,23).

RESULTS

— Of the participants, 207 (25.5%) had a history of diabetes. At baseline, 85 (10.5%) patients were receiving insulin, 90 (11.1%) were receiving oral hypoglycemic agents, and 45 (5.5%) were on diet only. Baseline variables were similar in patients assigned to CRT or control (14,21). Patients with diabetes more often had a history of hypertension and had a higher BMI, but New York Heart Association functional class, ejection fraction, renal function, NH_2-terminal pro-brain natriuretic peptide, and C-reactive protein levels were similar compared with nondiabetic patients (online appendix table [available at http://dx.doi.org/10.2337/dc06-2035]).

By the end of the extension period, 181 (29.9%) nondiabetic and 74 (35.9%) diabetic patients had died (hazard ratio [HR] 1.30 [95% CI 0.99–1.70], $P = 0.06$). CRT reduced all-cause mortality in diabetic and nondiabetic patients to a similar extent (1.026, [0.59–1.78], P for interaction = 0.93), and the effect was also independent of the therapy used to treat diabetes. CRT also reduced other end points regardless of the presence or absence of diabetes (Table 1).

The prevalence of diabetes was 30.4 and 22.4% in patients with and without ischemic heart disease, respectively. Patients with diabetes tended to have a higher death rate in both the ischemic (HR 1.23 [95% CI 0.86–1.75], $P = 0.26$) and nonischemic (1.29 [0.85–1.96], $P = 0.24$) groups. More diabetic patients on insulin (42 of 85, 49.4%) than on oral hypoglycemics alone (17 of 77, 22.1%) and on diet only (15 of 45, 33.3%; $P = 0.0004$ for the interaction term of insulin vs. other treatments for diabetes) died. However, there was no interaction between insulin use and the effects of CRT. Insulin use was associated with an increased mortality rate in patients with (1.48 [1.03–2.25], $P = 0.012$) and without (2.84 [1.75–4.62], $P < 0.0001$) ischemic heart disease. In an exploratory analysis (24) to examine whether the risks associated with insulin could be explained by renal function or ischemic history, including glomerular filtration rate as a nonlinear restricted cubic spline, in-

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Received for publication 2 October 2006 and accepted in revised form 9 December 2006.

N.F. and J.G.F.C. have received research grants from Medtronic, Inc. M.M. is an employee of Medtronic Bakken Research Center.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/dc06-2035.

Abbreviations: CARE-HF, Cardiac Resynchronisation in Heart Failure; CRT, cardiac resynchronization therapy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-2035. Clinical trial reg. no. NCT00170300, clinicaltrials.gov.

Table1 —*Study outcomes stratified according to the presence or absence of diabetes*

Outcome	Diabetic patients		Nondiabetic patients		*P* (interaction between CRT and diabetes)
	Medical therapy	Medication + CRT	Medical therapy	Medication + CRT	
n	101	106	303	303	
End points					
Death from any cause or unplanned hospitalization for a cardiovascular event	64 (63.4)	43 (40.6)	160 (53.0)	116 (38.3)	0.39
Death from any cause or unplanned hospitalization with worsening heart failure	54 (53.5)	35 (33.0)	137 (45.4)	83 (27.4)	0.91
Other serious adverse events					
Myocardial infarction	30 (29.7)	43 (40.6)	100 (33.1)	106 (35.0)	0.24
Stroke, transient ischemic attack	3 (3.0)	3 (2.8)	6 (2.0)	3 (1.0)	0.55
Continuous outcome					
NYHA class at 18 months	3.13 (2.88–3.37)	2.52 (2.24–2.80)	2.86 (2.72–3.01)	2.29 (2.15–2.43)	0.95
Minnesota Living with Heart Failure score at 18 months	42.9 (38.3–47.4)	32.1 (27.6–36.7)	38.5 (36.0–41.1)	32.3 (29.9–34.7)	0.14
EuroQoL EQ-5D score at 3 months	0.62 (0.56–0.69)	0.69 (0.62–0.75)	0.67 (0.63–0.70)	0.74 (0.71–0.77)	0.82
Left ventricular ejection fraction at 18 months (%)	27.7 (25.6–29.7)	34.6 (32.2–37.0)	28.1 (27.0–29.3)	34.5 (33.0–35.9)	0.76
Left ventricular end-systolic volume index at 18 months (ml/m^2)	108.3 (97.2–119.4)	83.5 (73.6–93.3)	119.9 (111.9–127.9)	89.2 (80.7–97.8)	0.61
NH_2-terminal pro-brain natriuretic peptide at 18 months (pg/ml)	2,514 (1,293–3,736)	2,383 (1,097–3,668)	3,561 (2,822–4,301)	2,309 (1,755–2,864)	0.25

Data are *n* (%) or means (95% CI). NYHA, New York Heart Association.

sulin use remained a significant predictor of mortality (1.66 [1.12–2.08], $P = 0.01$).

CONCLUSIONS — Patients with heart failure who also have diabetes are more likely to have morbid events (25) and have a higher mortality rate (7–9). Some studies (8) indicate that the adverse effect of diabetes on outcome is independent of heart failure etiology; others (10–12) suggest that increased mortality is limited to patients with ischemic heart disease. These studies did not, however, assess the relationship between insulin use and clinical outcome. Recent data suggest that insulin use rather than diabetes is the marker of adverse prognosis in patients with systolic heart failure. Patients not treated with insulin may be at little or no increased risk (9,13). Insulin may be acting as a marker of more severe and/or longer duration of diabetes and, therefore, patients more prone to micro- and macrovascular complications of diabetes. The CARE-HF data are consistent with the concept that it is insulin use or requirement rather than diagnosis of diabetes that are associated with worse outcome. Appropriate randomized controlled trials are required to determine whether insulin is a marker or mediator of a worse outcome.

Given the worse prognosis of patients with both heart failure and diabetes, it is of particular interest to improve outcome in this population. While the benefits of medical therapy for heart failure appear similar in patients with and without diabetes (26–29), the effect of diabetes on myopathic mechanisms and on the progression of cardiac dysfunction might influence the response of heart failure patients to CRT. This analysis of CARE-HF does not suggest a differential response to cardiac resynchronization in diabetic versus nondiabetic patients. Diabetes, regardless of the therapy used to treat it and the presence of coronary artery disease, did not influence the beneficial effect of CRT on any end point.

In conclusion, patients with advanced heart failure and diabetes treated with insulin have a markedly worse prognosis. CRT was equally effective in reducing mortality and in improving other clinical outcomes in diabetic patients compared with those without diabetes.

Acknowledgments — We thank the CARE-HF Study team for their work on the CARE-HF trial.

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