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The Effect of Diabetes on Outcomes of Patients With Advanced Heart Failure in the BEST Trial

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OBJECTIVES This was a retrospective analysis to determine the effect of diabetes on outcome in patients with advanced heart failure (HF), and to determine the effect of beta-blockade in patients with HF with and without diabetes mellitus.

BACKGROUND In chronic HF the impact on clinical outcomes and therapeutic response of the prevalent comorbid condition diabetes mellitus has not been extensively investigated.

METHODS We assessed the impact of diabetes on prognosis and effectiveness of beta-blocker therapy with bucindolol in patients with HF enrolled in the Beta-Blocker Evaluation of Survival Trial (BEST). We conducted a retrospective analysis to examine the prognosis of patients with advanced HF with and without diabetes, and the effect of beta-blocker therapy on mortality and HF progression or myocardial infarction (MI). The database was the 2,708 patients with advanced HF (36% with diabetes and 64% without diabetes) who were randomized to the beta-blocker bucindolol or placebo in BEST and followed for mortality, hospitalization, and MI for an average of two years.

RESULTS Patients with diabetes had more severe chronic HF and more coronary risk factors than patients without diabetes. Diabetes was independently associated with increased mortality in patients with ischemic cardiomyopathy (adjusted hazard ratio 1.33, 95% confidence interval 1.12 to 1.58, $p = 0.001$), but not in those with a nonischemic etiology (adjusted hazard ratio 0.98, 95% confidence interval 0.74 to 1.30, $p = 0.89$). Compared with patients without diabetes, in diabetic patients beta-blocker therapy was at least as effective in reducing death or HF hospitalizations, total hospitalizations, HF hospitalizations, and MI. Ventricular function and physiologic responses to beta-blockade were similar in patients with and without diabetes.

CONCLUSIONS Diabetes worsens prognosis in patients with advanced HF, but this worsening appears to be limited to patients with ischemic cardiomyopathy. In advanced HF beta-blockade is effective in reducing major clinical end points in patients with and without diabetes. (J Am Coll Cardiol 2003;42:914–22) © 2003 by the American College of Cardiology Foundation

Diabetes mellitus is associated with increases in most adverse cardiovascular events including myocardial infarction (MI), chronic heart failure (HF) and stroke (1,2). Diabetes is also associated with structural and metabolic abnormalities that can adversely affect myocardial function (3–10). However, the impact of diabetes on the natural history of HF has not been extensively investigated. A single previous study (11) has reported a worsened prognosis in mild-moderate HF populations with diabetes, and those data suggested the effect is limited to patients with ischemic as compared with nonischemic cardiomyopathy. Moreover, the impact of diabetes has not been examined in subjects with more advanced HF who are also on contemporary HF therapy such as angiotensin-converting enzyme inhibitors and beta-blockers.

A number of compensatory mechanisms are activated in response to HF that serve the purpose of initially stabilizing cardiac performance, but which eventually contribute to progressive left ventricular dysfunction and remodeling (12). Inhibition of this so-called neurohormonal response is now a well-accepted treatment paradigm, and beta-blockers are an established component of this therapeutic approach. However, the adverse effects of the diabetic process or unwanted metabolic effects of anti-adrenergic therapy could add a pathophysiologic burden that might be sufficient to abrogate the clinical benefits of beta-blocker treatment in HF patients with diabetes.

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Abbreviations and Acronyms

BEST = Beta-Blocker Evaluation of Survival Trial
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NYHA = New York Heart Association
RVEF = right ventricular ejection fraction

The Beta-Blocker Evaluation of Survival Trial (BEST) investigated beta-blockade with bucindolol for treatment of patients with advanced HF, and the primary outcomes have been reported previously (13). In clinical practice beta-blockers have been used with reluctance in diabetic subjects because of the fear of adverse effects including effects on insulin resistance and, in particular, fear of hypoglycemia in subjects receiving insulin. We analyzed the BEST database to investigate the prognosis of patients with advanced HF with and without diabetes, and to assess the effect of beta-blocker therapy.

METHODS

Study objectives. This was a retrospective analysis to determine the effect of diabetes on outcome in patients with advanced HF, and to examine the effect of beta-blockade in HF patients with and without diabetes mellitus.

Study design. The main BEST results have been described previously (13). The trial was stopped prematurely on the recommendation of the Data and Safety Monitoring Board on the basis of the "totality of evidence derived from BEST and other studies" (13). Specifically, the data in BEST subpopulations (class III, non-African-American patients) that had been investigated in other large and recently reported survival trials (14,15) were consistent with a beta-blocker-related reduction in mortality (13,16), and this, coupled with concern about loss of equipoise in an increasing number of BEST trial investigators (13) prompted the stopping recommendation.

All patients had a left ventricular ejection fraction (LVEF) $\geq$0.35, and were in New York Heart Association (NYHA) functional class III or IV. Patients were required to be on optimal medical therapy including, if tolerated, an angiotensin-converting enzyme inhibitor for at least one month. Randomization to bucindolol or to a matched placebo was stratified at each clinical site by: 1) etiology of HF (ischemic or nonischemic cardiomyopathy), 2) LVEF $>$0.20 or $\leq$0.20, 3) gender, and 4) race (black vs. nonblack). Ischemic cardiomyopathy HF etiology was defined as significant ($\geq$70% narrowing in a major epicardial vessel) coronary artery disease by angiography or evidence of previous MI. In BEST 2,708 patients were enrolled, with a mean follow-up of two years (13).

Patients were considered to have diabetes if they had a documented history of diabetes mellitus at baseline. Data were gathered on Diabetes History Case Report Forms for childhood ($<$18 years) versus adult onset of diabetes, type of treatment received (insulin, oral hypoglycemic, or dietary only), and whether the patient had documented end-organ disease (retinopathy, neuropathy, or nephropathy). Hypoglycemia, hyperglycemia, or weight gain as adverse events was determined from protocol-defined Adverse Medical Events Forms.

Treatment and follow-up. Patients were initiated on study medication at 3 mg twice daily, and then uptitrated on bucindolol or placebo weekly as tolerated, to a maximum dose of 50 mg twice daily for patients weighing $<$75 kg and 100 mg twice daily for patients weighing $\geq$75 kg (13). Patients were examined at three, six, and 12 months following randomization and at six-month intervals thereafter. Electrocardiogram, chest X-ray, ventricular function, plasma norepinephrine, and laboratory measurements were evaluated at baseline and repeated three and 12 months after randomization (13). Ventricular function was assessed by radionuclide ventriculography (13).

End points. The primary end point of BEST was all-cause mortality. Secondary end points included 1) cardiovascular mortality (defined as mortality due to pump failure, sudden death, and ischemic events), 2) total hospitalizations, 3) hospitalizations due to HF, 4) the combination of death or heart transplantation, 5) LVEF at three and 12 months, and 6) MI (13). For the current analysis, the additional combined end point of death (from any cause) or HF hospitalization was examined. An end points committee blinded to the treatment assignment centrally adjudicated cause of death and MI.

Statistical methods. Continuous data are reported as means and standard deviations or medians, with intergroup comparisons performed by *t* or Wilcoxon rank-sum tests unless otherwise noted. Categorical data are reported as proportions, with intergroup comparisons by the chi-square or Fisher's exact test. Cumulative time to event curves including the combined end point of death or HF hospitalization were constructed using Kaplan-Meier methods, and differences between groups were evaluated using the log-rank test. Cox proportional hazards regression was used to examine the effects of diabetes, etiology of HF, and treatment with bucindolol in the presence of prespecified covariates. All analyses were conducted using the intention-to-treat principle. A p value of 0.05 was used to indicate statistical significance.

RESULTS

Baseline clinical characteristics. Table 1 summarizes clinical characteristics by diabetic status. Generally, patients with diabetes had more adverse prognostic indicators than patients without diabetes reflected by a slightly older age, more class IV patients, more ischemic cardiomyopathy etiology, more Blacks, more vascular disease, a higher baseline heart rate, and a higher creatinine level. However, a few baseline parameters were more favorable in patients

Table 1. Baseline Patient Clinical Characteristics by Diabetic Status

Characteristic	Diabetes (n = 964)	No Diabetes (n = 1,744)	p Value
Demographics			
Age (yrs) mean (range)	61 ± 10.4 (23–88)	60 ± 13.3 (19–93)	< 0.0001
Men	750 (78%)	1,365 (78%)	0.78
Body mass index (kg/m^2)	29 ± 6.1	27 ± 5.9	< 0.0001
Median CHF duration (months)	39.5	36	0.002
Current smoker	136 (14%)	338 (19%)	0.001
NYHA class III	865 (90%)	1,617 (93%)	0.007
Ischemic etiology	645 (67%)	942 (54%)	< 0.0001
Black not Hispanic	244 (25%)	383 (22%)	0.048
Cardiovascular history			
Hypertension	672 (70%)	924 (53%)	< 0.0001
Hyperlipidemia	498 (52%)	672 (39%)	< 0.0001
History of MI	460 (48%)	684 (39%)	< 0.0001
Peripheral vascular disease	237 (25%)	204 (12%)	< 0.0001
Coronary bypass surgery	309 (32%)	473 (27%)	0.007
Coronary angioplasty/PTCA/DCA	170 (18%)	253 (15%)	0.032
Hemodynamics/ventricular function			
Heart rate (beats/min)	83 ± 12.7	81 ± 13.4	< 0.0001
Blood pressure (mm Hg)			
Systolic	120 ± 19.0	116 ± 17.3	< 0.0001
Diastolic	72 ± 11.1	71 ± 11.3	0.06
LVEF (× 100)	23.4 ± 7.0	22.8 ± 7.4	0.023
RVEF (× 100)	34.4 ± 13.5	35.1 ± 13.5	0.26
Atrial fibrillation	82 (9%)	221 (13%)	0.001
Creatinine (mg/dl)	1.3 ± 0.4	1.2 ± 0.4	> 0.0001
Neurohormonal status			
Plasma norepinephrine (pg/ml)			
Median	401	453	< 0.0001
Mean	476 ± 329	537 ± 351	

CHF = congestive heart failure; DCA = directional coronary atherectomy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction.

with diabetes, including a higher body mass index, lower incidence of smokers, a higher systolic blood pressure, and a lower plasma norepinephrine.

Prognostic impact of diabetes. We examined the effect of diabetes mellitus on outcomes in a multivariate analysis (Table 2). The final model included NYHA functional class, LVEF, systolic blood pressure, etiology of HF, age, race, gender, body mass index, cholesterol, creatinine, treatment group assignment (bucindolol and placebo), and whether taking diuretics or vasodilators at baseline. After adjusting for other known risk factors, diabetes was associated with an increased risk of death, cardiovascular death, pump failure death, and HF hospitalization. Additionally, in patients with diabetes insulin therapy was a significant predictor of cardiovascular mortality both in univariable (hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.08 to 1.70) and multivariable (HR 1.30, 95% CI 1.03 to 1.65) analyses.

Effect of ischemic cardiomyopathy HF etiology on survival. In patients with an ischemic cardiomyopathy etiology of HF, diabetes conferred an increased risk for a number of adverse cardiovascular events including all-cause death, cardiovascular death, pump failure death and the combined end point of death or HF hospitalization (Table 3). There

Table 2. Prognostic Impact of Diabetes Mellitus for Primary and Secondary Outcomes Adjusted for Risk Factors (Overall and by Ischemic Versus Nonischemic Etiology of Cardiomyopathy)

End Point	Diabetes (n = 964)	No Diabetes (n = 1,744)	HR*	(95% CI)	p Value	# Events
All-cause death	347 (36%)	513 (29%)	1.22	(1.06–1.41)	0.007	845
CV death	301 (31%)	430 (25%)	1.26	(1.08–1.47)	0.004	720
Pump failure death	117 (12%)	145 (8%)	1.50	(1.15–1.94)	0.002	258
Sudden death	153 (16%)	232 (13%)	1.16	(0.93–1.43)	0.19	380
HF hospitalization	405 (42%)	640 (37%)	1.16	(1.02–1.32)	0.027	1,026
HF hospitalization + death	559 (58%)	862 (49%)	1.19	(1.06–1.33)	0.003	1,398

Hazard ratios (HR) compare diabetics to nondiabetics. *Hazard ratios and 95% confidence intervals (CI) adjusted for baseline creatinine, left ventricular ejection fraction, New York Heart Association functional class, systolic blood pressure, age, etiology of heart failure, cholesterol, body mass index, diuretics, gender, vasodilators, race, and randomization to bucindolol or placebo.
CV = cardiovascular; HF = heart failure.

Table 3. Effect of Diabetes vs. No Diabetes on Clinical End Points in Ischemic or Nonischemic Cardiomyopathy

	Ischemic Etiology (n = 1,562)			Nonischemic Etiology (n = 1,099)		
End Point	HR†	(95% CI)	p Value	HR*	(95% CI)	p Value
All-cause death	1.33	(1.12–1.58)	0.001	0.98	(0.74–1.30)	0.89
CV death	1.36	(1.14–1.64)	0.0009	1.01	(0.74–1.38)	0.95
Pump failure death	1.44	(1.06–1.94)	0.019	1.64	(0.99–2.74)	0.056
Sudden death	1.28	(0.99–1.64)	0.058	0.90	(0.59–1.38)	0.64
HF hospitalization	1.14	(0.97–1.34)	0.113	1.23	(0.98–1.54)	0.074
HF hospitalization + death	1.19	(1.04–1.37)	0.011	1.18	(0.97–1.44)	0.10

*Hazard ratios (HR) for patients with diabetes vs. non-diabetic patients and 95% confidence intervals (CI) adjusted for baseline creatinine, left ventricular ejection fraction, New York Heart Association functional class, systolic blood pressure, age, cholesterol, body mass index, diuretics, gender, vasodilators, race, and randomization to bucindolol or placebo.
HF = heart failure; CV = cardiovascular.

were also nonsignificant trends towards a diabetes-conferred increased risk of sudden death and HF hospitalization in this subgroup. In contrast, in patients with nonischemic etiology, diabetes was not a predictor for all-cause death, cardiovascular death, or sudden death. However, there were strong nonsignificant trends for an increase in risk for pump failure death, HF hospitalization, and death or HF hospitalization in patients with versus those without diabetes in the nonischemic group.

Figure 1 shows the survival of patients according to HF etiology and diabetes status. In patients with a non-ischemic etiology, survival is comparable in patients with vs. those without diabetes (log rank p value 0.85, 12-month respective rates of 88.8% and 88.4%), and better than in ischemic cardiomyopathy (respective 12-month rates of 77.4% and 83.2% in patients with and without diabetes). Therefore, ischemic cardiomyopathy patients with diabetes had the greatest risk for mortality, which at 12 months was respectively 34% or 101% higher than in patients with nondiabetic ischemic or diabetic nonischemic cardiomyopathy.

Effect of beta-blocker therapy in diabetics. Baseline characteristics by treatment group in patients with diabetes were comparable to those without diabetes (data not shown). Treatment outcomes by diabetes status are given in Table 4

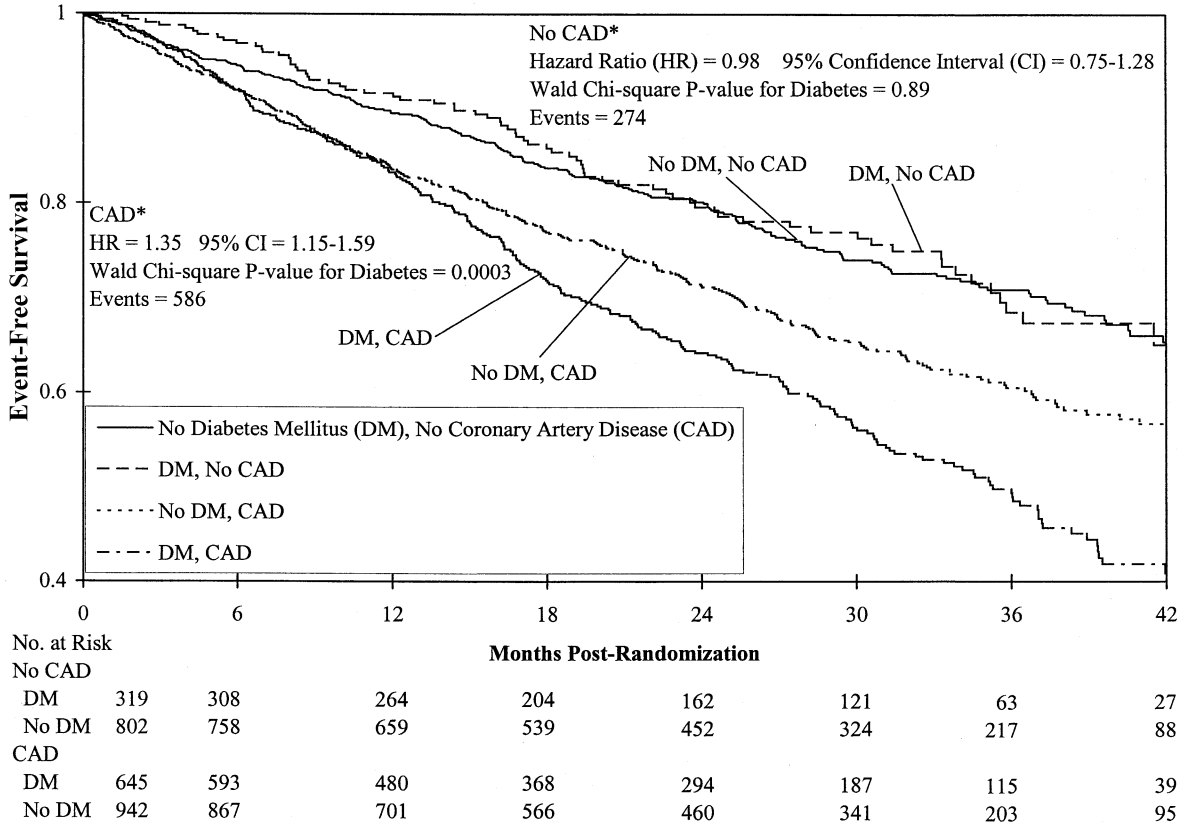


Figure 1. Survival of patients according to diabetic and coronary artery disease status in the entire cohort (placebo or bucindolol treatment). Hazard ratio (HR) and 95% confidence interval compare diabetics to nondiabetics. Estimates are adjusted for treatment group assignment. CAD = coronary artery disease (ischemic cardiomyopathy); DM = diabetes mellitus.

Table 4. Primary and Secondary End Points by Diabetic Status and Treatment Group*

End Point	Diabetes: Placebo (n = 465)	Diabetes: Bucindolol (n = 499)	HR*	95% CI	p Value†
Primary end point					
Death§	172 (37%)	175 (35%)	0.91	0.74–1.13	0.40
Secondary end points					
Cardiovascular death‡	153 (33%)	148 (30%)	0.87	0.70–1.09	0.23
Sudden death	76 (16%)	77 (15%)	0.91	0.67–1.25	0.57
Pump failure death	63 (14%)	54 (11%)	0.77	0.54–1.11	0.16
Myocardial infarction death	4 (1%)	7 (1%)	1.57	0.46–5.37	0.47
Other	10 (2%)	10 (2%)	0.90	0.37–2.16	0.81
Noncardiovascular death	13 (3%)	20 (4%)	1.36	0.68–2.74	0.39
Heart transplantation	6 (1%)	5 (1%)	0.76	0.23–2.50	0.65
Death or transplantation‡	175 (38%)	177 (35%)	0.91	0.74–1.12	0.39
Hospitalization (all-cause)	326 (70%)	330 (66%)	0.85	0.73–0.99	0.039
HF hospitalization†	216 (46%)	189 (38%)	0.72	0.60–0.88	0.001
Death or HF hospitalization†	288 (62%)	271 (54%)	0.77	0.65–0.91	0.002
Myocardial infarction‡	20 (4%)	12 (2%)	0.52	0.26–1.07	0.069
Death or myocardial infarction‡	181 (39%)	180 (36%)	0.87	0.71–1.08	0.20

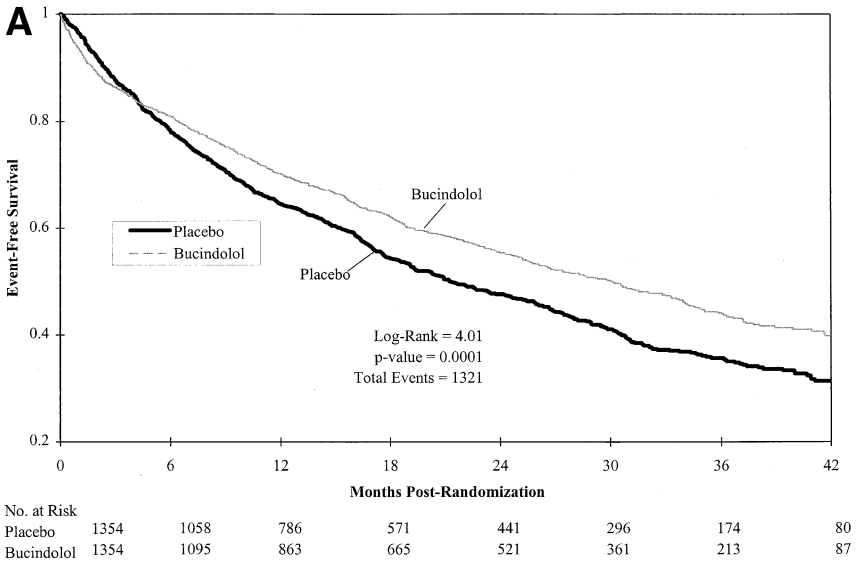
End Point	No Diabetes: Placebo (n = 889)	No Diabetes: Bucindolol (n = 855)	HR*	95% CI	p Value†
Primary end point					
Death§	277 (31%)	236 (28%)	0.87	0.73–1.03	0.1134
Secondary end points					
Cardiovascular death‡	236 (27%)	194 (23%)	0.84	0.69–1.02	0.0698
Sudden death	127 (14%)	105 (12%)	0.85	0.66–1.10	0.2096
Pump failure	77 (9%)	68 (8%)	0.90	0.65–1.24	0.5097
Death					
Myocardial infarction death	9 (1%)	3 (0%)	0.34	0.09–1.27	0.0924
Other	23 (3%)	18 (2%)	0.79	0.43–1.47	0.4612
Noncardiovascular death	29 (3%)	31 (4%)	1.09	0.66–1.81	0.7416
Heart transplantation	35 (4%)	24 (3%)	0.69	0.41–1.16	0.1569
Death or transplantation§	305 (34%)	254 (30%)	0.84	0.71–0.99	0.0388
Hospitalization (all-cause)	549 (62%)	499 (58%)	0.95	0.84–1.08	0.4270
HF hospitalization†	353 (40%)	287 (34%)	0.81	0.69–0.95	0.0078
Death or HF hospitalization†	473 (53%)	389 (45%)	0.82	0.71–0.93	0.0030
Myocardial infarction‡	21 (2%)	12 (1%)	0.58	0.29–1.18	0.1306
Death or myocardial infarction‡	283 (32%)	239 (28%)	0.86	0.72–1.02	0.0806

*Hazard ratios (HR) compare bucindolol to placebo-treated patients. †$p < 0.001$ bucindolol vs. placebo, entire cohort; ‡$p \leq 0.05$ bucindolol vs. placebo, entire cohort; §$p \leq 0.10$ bucindolol vs. placebo, entire cohort. P values reported are unadjusted. Overall values reported compare the overall treatment group comparisons (bucindolol vs. placebo).
CI = confidence interval, HF = heart failure.

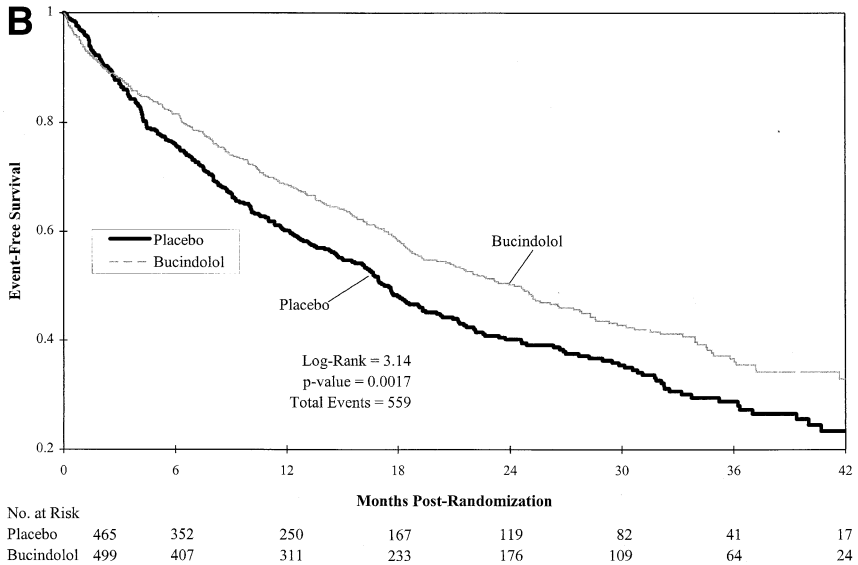
and Figure 2. As shown in Table 4, in patients with diabetes treatment with bucindolol was associated with a reduction in total hospitalizations, HF hospitalizations, and the combined end point of death or HF hospitalization. In patients without diabetes bucindolol therapy was associated with a reduction in the end points of death or cardiac transplantation, HF hospitalizations, and death or HF hospitalization. These end points plus cardiovascular deaths, MI, and death or MI were reduced by bucindolol in the entire cohort. Although the occurrence of MI was low in the BEST patients, the incidence was reduced by 48% in diabetics and by 42% in nondiabetics. In the entire cohort the reduction in MI was by 43% (hazard ratio 0.57 [0.34. 0.94], p = 0.024), and 57 of the 65 total MIs were in ischemic cardiomyopathy patients.

Figure 2 gives the substantial (at 12 months of follow-up a reduction in relative risk by 20.8%, 24.5%, and 20.0% in the total cohort, in diabetic patients, and in patients without diabetes, respectively) reduction in the combined end point of death or HF hospitalization associated with bucindolol therapy.

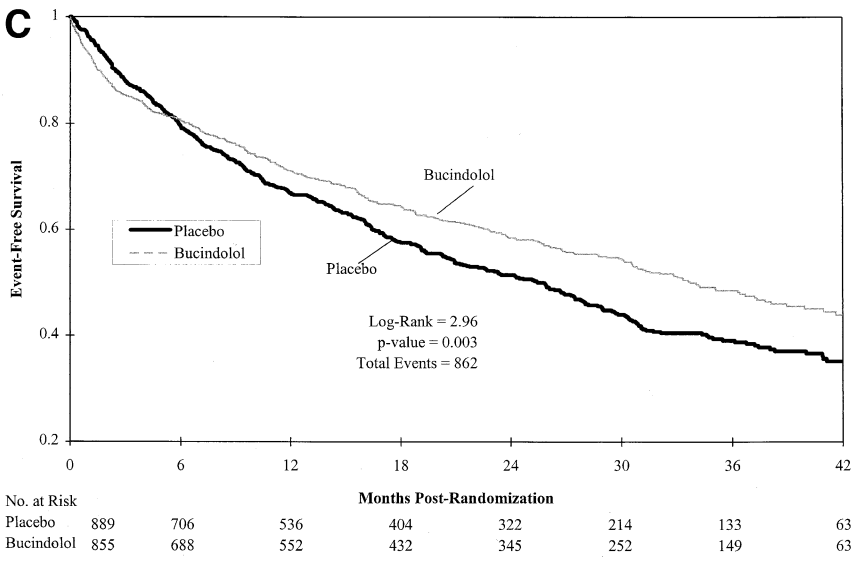
As shown in Table 5, a number of parameters that have prognostic importance were improved with bucindolol therapy. In both patients with and without diabetes, at three and 12 months of follow-up increases in both left and right ventricular ejection fractions (RVEF) were higher in bucindolol- compared with placebo-treated patients. In patients treated with bucindolol the improvement in LVEF was similar in patients with and without diabetes. At 12 months the bucindolol-associated increase in RVEF in patients without diabetes was slightly greater than the change in diabetic patients, which was only a trend com-



No. at Risk								
Placebo	1354	1058	786	571	441	296	174	80
Bucindolol	1354	1095	863	665	521	361	213	87



No. at Risk								
Placebo	465	352	250	167	119	82	41	17
Bucindolol	499	407	311	233	176	109	64	24



No. at Risk								
Placebo	889	706	536	404	322	214	133	63
Bucindolol	855	688	552	432	345	252	149	63

Figure 2. Effect of bucindolol or placebo treatment on the combined end point of death or heart failure hospitalization, in the entire cohort **(A),** diabetics **(B)**, and nondiabetics **(C)**.

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Table 5. Treatment Effects on Nonclinical End Points in Diabetics and Nondiabetics (± SD)

Parameter	Diabetes, Treatment Group		No Diabetes, Treatment Group	
	Placebo (n = 465)	Bucindolol (n = 499)	Placebo (n = 889)	Bucindolol (n = 855)
Δ LVEF 3 months (EF × 100)*	2.2 ± 6.9	5.7 ± 8.3†	2.0 ± 6.9	5.4 ± 7.5†
Δ LVEF 12 months (EF × 100)*	3.2 ± 8.3	6.7 ± 10.0†	3.3 ± 8.9	7.6 ± 10.0†
Δ RVEF 3 months (EF × 100)*	1.9 ± 10.9	4.1 ± 10.2‡	1.2 ± 11.3	4.4 ± 11.9†
Δ RVEF 12 months (EF × 100)*	3.1 ± 12.6	5.1 ± 12.4§	1.9 ± 12.6	6.3 ± 12.9†
Δ Heart rate 3 months (beats/min)	−1.2 ± 12.2	−10.0 ± 12.4†	−1.3 ± 13.3	−9.0 ± 13.4†
Δ Heart rate 12 months (beats/min)	−1.5 ± 13.8	−9.0 ± 13.9†	−2.4 ± 13.3	−8.3 ± 13.8†
Δ Norepinephrine 3 months (pg/ml)	15.0 ± 287	−79.1 ± 346	33.6 ± 307	−67.8 ± 344†
Δ Norepinephrine 12 months (pg/ml)	36.6 ± 310	−9.9 ± 295	49.0 ± 309	−29.2 ± 303†

*Δ = change from baseline. †$p < 0.001$ bucindolol vs. placebo, entire cohort; ‡$p \leq 0.05$ bucindolol vs. placebo, entire cohort; §$p \leq 0.10$ bucindolol vs. placebo, entire cohort. EF = ejection fraction; other abbreviations as in Table 1.

pared to the placebo change. Reduction in heart rate was much greater at 3 and 12 months in bucindolol-treated patients, and the degrees of reduction were similar in patients with and without diabetes. Plasma norepinephrine levels decreased in bucindolol-treated patients at three months, to a similar degree in patients with and without diabetes. At 12 months the reduction in norepinephrine was significant in patients without diabetes, and only a nonsignificant trend in patients with diabetes in the bucindolol groups.

In terms of reported adverse events, irrespective of treatment assignment, patients with diabetes versus those without diabetes had significantly more weight gain (38% vs. 30%), hyperglycemia (36% vs. 5%), hypoglycemia (14% vs. 1%), elevated creatinine levels (12% vs. 8%), syncope (12% vs. 9%), kidney failure (9% vs. 5%), MI (7% vs. 3%), and cerebrovascular accident (4% vs. 3%). However, treatment with bucindolol was generally not associated with more adverse events in either patients with diabetes or those without. The exceptions were: bradycardia, which in patients with diabetes or no diabetes respectively was reported in 11% and 12% of bucindolol-treated compared to 5% ($p < 0.001$ and 5% ($p < 0.001$) in placebo-treated patients; and presyncope, which was reported at an increased incidence with bucindolol treatment only in patients with diabetes (7% of bucindolol-treated patients vs. 4% of placebo patients, $p = 0.024$). Myocardial infarction reported as an adverse event (as opposed to adjudicated MI given in Table 4) was reduced in bucindolol- versus placebo-treated diabetic (from respective incidences of 10% to 5%, $p = 0.005$) and nondiabetic (from respective incidences of 5% to 2%, $p = 0.02$) patients.

Importantly, neither hyperglycemia nor hypoglycemia was reported at a significantly higher frequency in bucindolol- versus placebo-treated patients with diabetes. However, among diabetic subjects on insulin therapy, bucindolol was associated with an increase in hypoglycemia (28% bucindolol vs. 18% placebo, $p = 0.017$); there was no difference in hypoglycemia among subjects with diabetes who were not on insulin therapy (7% bucindolol vs. 8% placebo, p = NS).

DISCUSSION

Diabetes is a common condition with increasing prevalence in the U.S. The diabetes prevalence in BEST of 36% compares to 20% to 37% reported in other HF clinical trials (17–22), and the large number of patients with diabetes in BEST allowed us to compare outcomes in them to those in BEST patients without diabetes. The main findings of this study are that in an advanced HF population, 1) the prognostic effect of diabetes on mortality is confined to those with an ischemic cardiomyopathy etiology, and 2) the clinical and physiologic benefits of beta-blockade are similar in patients with and without diabetes. In addition, for the first time in a chronic HF clinical trial a beta-blocker was shown to reduce the incidence of MI, a finding that has implications for many diabetic patients with HF.

Beta-blockade was administered to patients with advanced HF (NYHA class III and IV) in the form of the third generation compound bucindolol, which blocks $beta_1$ and $beta_2$-adrenergic receptors, has mild vasodilator properties that contribute to its good tolerability, has potent sympatholytic properties that were confirmed in the BEST trial (13), and on the basis of in vivo (23) and in vitro (24–26) data has no intrinsic sympathomimetic activity in functioning human ventricular myocardium. In BEST bucindolol produced a reduction in mortality in patients (class III, non–African-American) (13) that heretofore were the predominant subpopulations investigated in other beta-blocker mortality trials, and in this population bucindolol's efficacy was similar (16) to that of metoprolol CR/XL in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) (14) and bisoprolol in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) (15).

On multivariable analysis, diabetes was strongly and independently associated with increased mortality. In the entire cohort diabetes was a predictor of cardiovascular death, and specifically pump failure, but not sudden death. Consistent with an adverse effect of diabetes on pump function, HF hospitalizations were increased in diabetic patients compared to those without diabetes. Mechanisms by which diabetes might contribute to progression of LV

dysfunction are well described (27,28), and an attractive hypothesis for the adverse effect of diabetes on mortality is that diabetes confers an additional myopathic risk in subjects with established secondary dilated cardiomyopathies. However, this additional risk appears to be confined to ischemic cardiomyopathy, inasmuch as diabetes did not confer additional mortality risk in patients with nonischemic cardiomyopathy. In BEST the use of insulin was associated with increased cardiovascular mortality that may have been a direct consequence of insulin therapy or, more likely, insulin use was a marker of more severe cardiovascular effects of diabetes.

In contrast to the lack of an effect on sudden death by diabetes in the entire cohort, there was a nearly significant trend for an increase in diabetes-conferred sudden death risk in the ischemic cardiomyopathy subgroup, with a hazard ratio of 1.28 (0.99 to 1.64) compared to a hazard ratio of <1.0 in patients with nonischemic cardiomyopathy with diabetes. These data contributed to the overall increase in all-cause (by 33%) and cardiovascular mortality (by 36%) risks conferred by the presence of diabetes in patients with ischemic cardiomyopathy, compared to patients with nonischemic cardiomyopathy who were not at increased risk for total or cardiovascular death in patients with versus those without diabetes. A potential explanation for the differential effect of diabetes on mortality risk in ischemic versus nonischemic cardiomyopathy patients is the well-known accumulation of risk factors for coronary artery disease (29), which may have increased the risk of ischemia-related sudden death in patients with ischemic cardiomyopathy. That the etiology of HF appears to be an important determinant of prognosis in patients with HF and diabetes agrees with previous observations in the SOLVD patient population (11), which had less advanced HF than patients enrolled in BEST. Therefore, our results confirm and extend those from SOLVD, and the reinforcing findings of these two studies highlight the need to consider a more aggressive treatment approach in diabetic patients with ischemic cardiomyopathy.

The effect of diabetes on myopathic mechanisms or myocardial ischemia could influence the response of HF patients to beta-blockade. However, our data do not suggest a differential response to beta-blockers in diabetics versus nondiabetics. Diabetes did not influence the effect of beta-blockade on adrenergically related parameters thought to contribute to the therapeutic response to beta-blockade, including heart rate, LVEF or RVEF, and plasma norepinephrine. Importantly, there was no differential sympatholytic effect of bucindolol in diabetic versus nondiabetic patients; such effects likely contributed to less desirable treatment effects in the Class IV and black subpopulations of BEST (30). Another way in which the presence of diabetes could influence the response to beta-blockade would be to enhance the anti-ischemic properties of beta-blockers. Indeed, in this study we demonstrate for the first time in a beta-blocker trial in chronic HF a reduction in MI. In BEST MI was an adjudicated secondary end point, and it was reduced in bucindolol-treated patients by $>40\%$ ($p < 0.05$) in the entire BEST Cohort. However, the overall prevalence of clinically evident MI was low in BEST (4% and 2% in placebo-treated diabetic and nondiabetic patients, respectively), and this small absolute differential prevalence was not high enough to have influenced the treatment effect of bucindolol in patients with versus those without diabetes. Therefore, in BEST, beta-adrenergic blockade as a treatment for advanced chronic HF was equally effective in patients with and without diabetes.

The combined end point of death or HF hospitalizations is probably the most sensitive major indicator of clinical efficacy of HF treatment, because it combines two high prevalence end points that may be directly influenced by therapy that favorably alters HF natural history. Our data demonstrate that bucindolol was effective in reducing the prevalence of this combined end point, with highly statistically significant reductions by 21% in the entire cohort, 24% in diabetic patients, and 20% in non-diabetics. These data support the ideas that in an advanced HF population bucindolol therapy is overall efficacious, and there is no difference in beta-blocker response between patients with and those without diabetes. Regarding the latter point, the data suggest that HF patients with diabetes derive benefit from beta-blockade despite the additional cardiovascular disease burden conferred by this pervasive disorder. A similar conclusion has been reached with the third-generation beta-blocker carvedilol in another HF clinical trial database, albeit with a smaller sample size and a more limited analysis (31). However, until more data are available with other beta-blockers it would be prudent to consider the effects reported in this study as drug-specific rather than a class effect.

Hypoglycemia is more frequent in patients with diabetes who are receiving insulin treatment, and in BEST Trial patients with diabetes bucindolol treatment was associated with increased hypoglycemia only in patients who were receiving insulin therapy. Hyperglycemia was not increased in patients with diabetes treated with bucindolol. These data suggest that beta-blockade with bucindolol does not worsen insulin sensitivity, and in fact may have increased it. In this regard, in the setting of hypertension other vasodilating beta-blockers also have not worsened insulin sensitivity, in contrast to $beta_1$-receptor selective blockers (32). Bucindolol was also associated with a slight increase in presyncope in diabetic patients, probably due to an aggravation in autonomic dysfunction known to accompany diabetes. However, overall bucindolol appeared to have a very acceptable safety profile in patients with advanced HF and diabetes.

In conclusion, diabetes worsens prognosis in patients with HF, but this worsening appears to be limited to patients with an ischemic cardiomyopathy etiology. The third-generation beta-blocker bucindolol was equally effective in reducing the combined end point of death or HF

hospitalization and other clinical end points in patients with, compared to those without diabetes. Finally, in BEST beta-blockade with bucindolol lowered the incidence of MI, and this beneficial property might be important in HF patient populations exhibiting a greater degree of active ischemia.

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