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Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure

An analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme

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Aims To determine whether the risk of adverse cardiovascular (CV) outcomes associated with diabetes differs in patients with low and preserved ejection fraction (EF) heart failure (HF).

Methods and results We analysed outcomes in the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) programme which randomized 7599 patients with symptomatic HF and a broad range of EF. The prevalence of diabetes was 28.3% in patients with preserved EF (>40%) and 28.5% in those with low EF (≤40%). Diabetes was associated with a greater relative risk of CV death or HF hospitalization in patients with preserved EF [hazard ratio (HR) 2.0 (1.70–2.36)] than in patients with low EF [HR 1.60 (1.44–1.77); interaction test $P = 0.0009$]. For all-cause mortality, the risk conferred by diabetes was similar in both low and preserved EF groups. The effect of candesartan in reducing CV morbidity and mortality outcomes was not modified by having diabetes at baseline ($P = 0.09$ test for interaction).

Conclusion Diabetes was an independent predictor of CV morbidity and mortality in patients with HF, regardless of EF. The relative risk of CV death or HF hospitalization conferred by diabetes was significantly greater in patients with preserved when compared with those with low EF HF.

Keywords Heart failure • Diabetes

Introduction

The prevalence of diabetes is high in patients with heart failure (HF) and its presence is associated with a worse outcome.[1] The prognostic importance of diabetes in patients with HF has, however, been established, primarily, in populations with a low, left ventricular ejection fraction (EF). In these patients, diabetes is associated with more symptoms, greater morbidity, and increased mortality.[2–4] Up to 50% of patients with HF, however, have preserved EF.[5] Less is known of the prevalence, associations, and prognostic importance of diabetes in patients with HF and preserved EF. The Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) programme assessed the efficacy of candesartan in a broad spectrum of

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patients having HF. We examined the relationship of diabetes to morbidity and mortality in patients with HF and both low and preserved EF enrolled in the CHARM programme.

Methods

The design and primary results of the CHARM programme have previously been reported in detail.[6,7] Briefly, 7599 patients with symptomatic chronic HF [New York Heart Association (NYHA) class II–IV] with a serum creatinine <265 μmol/L (<3 mg/dL), serum potassium <5.5 mmol/L, who were not taking an angiotensin receptor blocker, and who had no critical aortic, mitral stenosis, recent myocardial infarction (<4 weeks), stroke, or heart surgery were studied. They were randomized to placebo or candesartan (target dose was 32 mg once daily, mean dose achieved was 24 mg). Patients were enrolled in one of three parallel concurrent trials, dependent on EF and treatment with an angiotensin-converting enzyme (ACE) inhibitor. CHARM-Alternative ($n = 2028$) enrolled patients with an EF ≤40% (hereafter referred to as low EF) previously intolerant of an ACE-inhibitor. CHARM-Added ($n = 2548$) included patients with an EF ≤40% treated with an ACE-inhibitor. CHARM-Preserved ($n = 3023$) included patients with an EF >40% (hereafter referred to as preserved EF). The primary outcome of the individual component trials was cardiovascular (CV) death or admission to hospital with worsening HF. The primary outcome of the overall programme was all-cause mortality. The median duration of follow-up was 37.7 months.

Whether patients had diabetes or not was reported by the investigators at baseline. Blood chemistry and haematology were measured systematically using a central laboratory in the subset of 2675 patients enrolled from North America. In this subset, glomerular filtration rate was estimated (eGFR) using the simplified modification of diet in renal disease (MDRD) equation.

Statistical analysis

Baseline characteristics of patients with and without diabetes were summarized by mean (standard deviation) for continuous variables and by frequency (percentage) for categorical variables. Statistical tests were two-sided and a *P*-value of ≤0.05 was taken as the level of significance. All analyses were done by intention to treat. Hazard ratios (HRs) were calculated using Cox-proportional hazards models. The influence of diabetes on outcomes was assessed after adjusting for the following 32 co-variates: age, gender, NYHA class, left ventricular EF, heart rate, systolic and diastolic blood pressures, body mass index, HF hospitalization, previous myocardial infarction, current angina, stroke, hypertension, atrial fibrillation, pacemaker, current smoker, percutaneous coronary intervention, coronary artery bypass grafting, implantable cardioverter defibrillator, previous cancer, ACE-inhibitors, β-blocker, diuretics, digoxin, calcium antagonists, other vasodilators, oral anticoagulants, antiarrhythmic agents, aspirin, other antiplatelets, treatment group, and lipid-lowering agents.[7] Tests for an interaction between diabetes and study group (low vs. preserved EF) were carried out for each individual outcome, prior to the other variables being entered into the model.

Results

The prevalence of diabetes was 28.5% and was similar in patients with preserved EF (28.3%) and low EF (28.5%) [*Table 1*]. There were notable differences in both baseline characteristics and outcomes between diabetics and non-diabetics.

Baseline characteristics

Demographics

Baseline characteristics of patients with and without diabetes are shown in *Table 1*. The differences between diabetics and non-diabetics were amplified when EF category was considered—the most striking contrasts were between low EF HF patients with diabetes and preserved EF HF patients without diabetes (columns 4 and 5 in *Table 1*).

HF patients with diabetes were more often females and of non-European ethnicity than HF patients without diabetes.

Diabetic patients were more likely to be overweight or obese than non-diabetics. They were also less likely to be current smokers. They were more likely to have an investigator designated ischaemic or hypertensive aetiology of HF than non-diabetics (and less likely to have idiopathic dilated cardiomyopathy).

Functional class, signs, and symptoms

Patients with diabetes had more signs and symptoms of HF and worse NYHA functional status than non-diabetics in both the low and preserved EF groups. The highest rates of symptoms and signs (and greatest proportion of III/IV vs. II NYHA functional class) were seen in patients with a low EF and diabetes and the lowest rates (and proportion) in patients with preserved EF without diabetes.

Medical history

Regardless of EF, patients with diabetes had a higher prevalence of hypertension, myocardial infarction, coronary artery bypass grafting, and stroke than patients without diabetes. The prevalence of hypertension in patients with preserved EF and diabetes (79%) was nearly double that in patients with low EF and no diabetes (44.0%).

Blood chemistry, haematology, and renal function

Diabetic patients had a slightly lower mean haemoglobin concentration and slightly lower eGFR than non-diabetics.

Treatment

Diabetic patients had higher rates of treatment with most CV drugs than non-diabetics, with the highest rates of use being in patients with a low EF and diabetes and the lowest rates in patients with preserved EF without diabetes (with the notable exception of calcium channel blockers).

About half of diabetic patients (50.7%) were treated with oral diabetic therapy and a third with insulin (32.7%).

Outcomes

The unadjusted rates of death and hospitalization from all causes were significantly higher in diabetic patients when compared with those in non-diabetics (*Table 2* and *Figures 1–4*). After adjustment for 32 co-variates, diabetes at baseline remained an independent predictor of the main primary and secondary outcomes, regardless of EF (*Figure 4*). The effect of diabetes on outcomes was not modified by sex or aetiology of HF.

Diabetes at baseline was associated with a higher risk of CV as well as non-CV death (*Table 2*). The risk of each of the major modes of CV death was also increased in diabetic, compared to non-diabetic, patients (*Table 2*).

Table 1 Baseline characteristics

Variable	Overall (n = 7599)		PEF (n = 3023)		LEF (n = 4576)	
	Diabetes mellitus (DM)	No DM	DM	No DM	DM	No DM
N	2163 (28.5%)	5436	857 (28.3%)	2166	1306 (28.5%)	3270
Demographics						
Age (years)	65.8 (10.0)	66.0 (11.4)	66.6 (10.0)	67.4 (11.5)	65.3 (9.9)	65.1 (11.4)
Male (%)	66.7	69.1	57.4	60.9	72.7	74.6
Female (%)	33.3	30.9	43.6	39.1	27.3	25.4
Non-European origin	329 (15.2%)	400 (7.4%)	131 (15.3%)	125 (5.8%)	198 (15.2%)	275 (8.4%)
Physiologic measure						
Body mass index (mean, kg/m^2)	29.8 (5.9)	27.6 (5.1)	31.2 (6.3)	28.4 (5.3)	29.0 (5.5)	27.1 (4.9)
Underweight (<18.5)	12 (0.6%)	69 (1.3%)	3 (0.4%)	20 (0.9%)	9 (0.7%)	49 (1.5%)
Normal (18.5–24.9)	407 (18.8%)	1640 (30.2%)	115 (13.4%)	558 (25.8%)	292 (22.4%)	1082 (33.1%)
Overweight (25.0–29.9)	811 (37.5%)	2242 (41.2%)	302 (35.2%)	877 (40.5%)	509 (39.0%)	1365 (41.7%)
Obese (≥30.0)	923 (42.7%)	1464 (26.9%)	436 (50.9%)	699 (32.3%)	487 (37.3%)	765 (23.4%)
Heart rate (beats/min)	74.4 (12.5)	72.3 (13.2)	72.5 (11.7)	70.9 (12.7)	75.7 (12.8)	73.2 (13.4)
Systolic blood pressure (mmHg)	131.9 (19.2)	130.5 (19.1)	137.4 (18.3)	135.7 (18.5)	128.3 (19.0)	127.0 (18.8)
Diastolic blood pressure (mmHg)	75.7 (10.7)	77.0 (10.8)	76.3 (11.0)	78.4 (10.5)	75.3 (10.5)	76.1 (10.8)
Left ventricular ejection fraction (%)	38.6	39.0	53.9	54.1	28.5	29.0
Aetiology of heart failure						
Ischaemic heart disease	1426 (66.0%)	3255 (59.9%)	502 (58.6%)	1204 (55.6%)	924 (70.8)	2051 (62.7%)
Idiopathic dilated cardiomyopathy	294 (13.6%)	1033 (19.0%)	66 (7.7%)	197 (9.1%)	228 (17.5%)	836 (25.6%)
Hypertension	312 (14.4%)	669 (12.3%)	219 (25.6%)	465 (21.5%)	93 (7.1%)	204 (6.2%)
NYHA functional class						
NYHA (mean)	2.7 (0.5)	2.5 (0.5)	2.5 (0.6)	2.4 (0.5)	2.7 (0.5)	2.7 (0.5)
II	814 (37.6%)	2602 (47.9%)	428 (49.9%)	1408 (65.0%)	386 (29.6%)	1194 (36.5%)
III	1273 (58.9%)	2712 (49.9%)	405 (47.3%)	735 (33.9%)	868 (66.5%)	1977 (60.5%)
IV	76 (3.5%)	122 (2.2%)	24 (2.8%)	23 (1.1%)	52 (4.0%)	99 (3.0%)
Clinical features at baseline						
Peripheral oedema	1467 (67.8%)	2977 (54.8%)	583 (68.0%)	1143 (52.8%)	884 (67.7%)	1834 (56.1%)
Orthopnoea	1392 (64.4%)	2686 (49.4%)	512 (59.7%)	928 (42.8%)	880 (67.4%)	1758 (53.8%)
Paroxysmal nocturnal dyspnoea	1150 (53.2%)	2269 (41.7%)	426 (49.7%)	741 (34.2%)	724 (55.4%)	1528 (46.7%)
Jugular venous pressure > 6 cm	765 (35.4%)	1509 (27.8%)	257 (30.0%)	451 (20.8%)	508 (38.9%)	1058 (32.4%)
Rest dyspnoea	1259 (58.2%)	2708 (49.8%)	450 (52.5%)	909 (42.0%)	809 (61.9%)	1799 (55.0%)
Third heart sound	682 (31.5%)	1462 (26.9%)	186 (21.7%)	330 (15.2%)	496 (38.0%)	1132 (34.6%)
Pulmonary crackles-basilar	1463 (67.6%)	3252 (59.8%)	523 (61.0%)	1147 (53.0%)	940 (72.0%)	2105 (64.4%)

Continued

Table 1 *Continued*

Variable	Overall ($n = 7599$)		PEF ($n = 3023$)		LEF ($n = 4576$)	
	Diabetes mellitus (DM)	No DM	DM	No DM	DM	No DM
Medical history						
Hypertension	1481 (68.5%)	2705 (49.8%)	678 (79.1%)	1265 (58.4%)	803 (61.5%)	1440 (44.0%)
Prior myocardial infection	1215 (56.2%)	2789 (51.3%)	401 (46.8%)	939 (43.4%)	814 (62.3%)	1850 (56.6%)
Current angina pectoris	539 (24.9%)	1269 (23.3%)	250 (29.2%)	582 (26.9%)	289 (22.1%)	687 (21.0%)
Prior coronary artery bypass grafting	624 (34.8%)	1167 (21.5%)	229 (26.7%)	425 (19.6%)	395 (30.2%)	742 (22.7%)
Stroke	237 (11.0%)	426 (7.8%)	101 (11.8%)	167 (7.7%)	136 (10.4%)	259 (7.9%)
Atrial fibrillation	562 (26.0%)	1521 (28.0%)	224 (26.1%)	657 (30.0%)	338 (25.9%)	864 (26.4%)
Cancer	139 (6.4%)	374 (6.9%)	65 (7.6%)	161 (7.4%)	74 (5.7%)	213 (6.5%)
Pacemaker	183 (8.5%)	454 (8.4%)	60 (7.0%)	161 (7.4%)	123 (9.4%)	293 (9.0%)
Implantable cardioverter defibrillator	44 (2.0%)	147 (2.7%)	6 (0.7%)	17 (0.8%)	38 (2.9%)	130 (4.0%)
Current smoker	264 (12.2%)	850 (15.6%)	91 (10.6%)	318 (14.7%)	173 (13.2%)	532 (16.3%)
Biochemistry and haematology						
Modification of diet in renal disease equation to estimate glomerular filtration rate (ml/mm/1.73 m^2)	66.1 (26.4) ($N = 996$)	71.8 (25.6) ($N = 1679$)	67.2 (27.1) ($N = 435$)	72.9 (25.1) ($N = 651$)	65.3 (25.8) ($N = 561$)	71.2 (25.8) ($N = 1028$)
Haemoglobin (g/dL)	13.3 (1.7) ($N = 992$)	13.8 (1.6) ($N = 1657$)	13.1 (1.7) ($N = 433$)	13.6 (1.6) ($N = 635$)	13.4 (1.7) ($N = 559$)	13.8 (1.5) ($N = 1022$)
Cardiovascular medication						
Angiotensin-converting enzyme inhibitors	1019 (47.1%)	2106 (38.7%)	261 (30.5%)	315 (14.5%)	758 (58.0%)	1791 (54.8%)
Beta-blocker	1249 (57.7%)	2954 (54.3%)	490 (57.2%)	1194 (55.1%)	759 (58.1%)	1760 (53.8%)
Diuretics	1923 (88.9%)	4363 (80.3%)	717 (83.7%)	1542 (71.2%)	1206 (92.3%)	2821 (86.3%)
Long-acting nitrates	838 (38.7%)	1743 (32.1%)	316 (36.9%)	688 (31.8%)	522 (40.0%)	1055 (32.3%)
Spironolactone	398 (18.4%)	874 (16.1%)	117 (13.7%)	235 (10.8%)	281 (21.5%)	639 (19.5%)
Digitalis glycoside	1036 (47.9%)	2218 (40.8%)	269 (31.4%)	573 (26.5%)	767 (58.7%)	1645 (50.3%)
Calcium channel blocker	507 (23.4%)	1035 (19.0%)	304 (35.5%)	640 (29.5%)	203 (15.5%)	395 (12.1%)
Lipid-lowering drug	1046 (48.4%)	2107 (38.8%)	418 (48.8%)	844 (39.0%)	628 (48.1%)	1263 (38.6%)
Oral anticoagulant	634 (29.3%)	1704 (31.3%)	200 (23.3%)	548 (25.3%)	434 (33.2%)	1156 (35.4%)
Diabetes treatment						
Diet only	358 (16.6%)		151 (17.6%)		207 (15.8%)	
Insulin	707 (32.7%)		295 (34.4%)		412 (31.5%)	
Oral therapy	1096 (50.7%)		410 (47.8%)		686 (52.5%)	
Unknown	2 (0.1%)		1 (0.1%)		1 (0.1%)	
Age of diabetes onset (years)	54.1 (15.1)		54.6 (15.2)		53.7 (15.0)	

Table 2 Rates of death and admission to hospital per 1000 patient years of follow-up by diabetic status (*P*-values for univariate comparisons)

Variable	All patients			Preserved EF			Low EF		
	Diabetes ($n = 2163$)	No diabetes (5436)	*P*-value	Diabetes ($n = 857$)	No diabetes (2166)	*P*-value	Diabetes ($n = 1306$)	No diabetes (3270)	*P*-value
Death									
Total	681	1150		185	296		496	854	
All causes	116.3	72.9	<0.001	77.4	46.0	<0.001	143.1	91.4	<0.001
Cardiovascular	94.4	57.5	<0.001	58.6	31.1	<0.001	119.1	75.7	<0.001
Heart failure	30.7	18.3	<0.001	16.3	9.8	0.011	40.7	24.2	<0.001
Sudden	40.0	25.9	<0.001	23.8	12.0	<0.001	51.1	35.5	<0.001
Myocardial infarction	8.0	4.1	<0.001	5.0	1.4	0.003	10.1	5.9	0.013
Stroke	6.1	3.4	0.005	5.9	3.0	0.048	6.3	3.6	0.046
Other cardiovascular	9.6	5.8	0.003	7.5	5.0	0.14	11.0	6.4	0.009
Non-cardiovascular	21.9	15.4	0.001	18.8	14.9	0.18	23.9	15.7	0.002
Hospital admissions (first)									
Total	1531	3266		606	1228		925	2038	
All causes	473.4	327.2	<0.001	466.6	296.3	<0.001	477.9	349.1	<0.001
Cardiovascular	306.5	207.4	<0.001	284.8	177.1	<0.001	321.8	229.2	<0.001
Heart failure	139.3	68.2	<0.001	116.6	45.9	<0.001	155.4	84.3	<0.001
Myocardial infarction	13.0	7.8	0.001	14.1	7.2	0.004	12.3	8.2	0.041
Stroke	14.0	9.2	0.002	15.7	9.4	0.014	12.9	9.0	0.058
Other cardiovascular	211.8	159.4	<0.001	200.5	137.1	<0.001	219.7	175.0	<0.001
Non-cardiovascular	222.9	152.7	<0.001	221.1	146.7	<0.001	224.2	156.8	<0.001
CV death or hospital admission for CV cause									
Total	1361	2708		492	924		869	1784	
	345.1	231.4	<0.001	302.6	189.4	<0.001	374.8	261.4	<0.001

The same was true for CV hospitalizations. Of note, however, patients with preserved EF HF (which generally had better outcomes than those with reduced EF HF) and diabetes had a higher rate of CV hospitalization than patients with reduced EF HF, without diabetes (284.8 vs. 229.2 admissions to hospital per 1000 years of patient follow-up). This was also the case for hospitalization for HF and myocardial infarction separately (*Table 2*).

The effect of candesartan in reducing CV morbidity and mortality outcomes was not modified by having diabetes at baseline ($P = 0.09$ test for interaction).

Interaction between diabetes and left ventricular ejection fraction

CV death and HF hospitalization

Diabetes was associated with an increased risk of the combined primary outcome of CV death or HF hospitalization in patients with both low and preserved EF HF (*Figure 3*). In patients with low EF, diabetes was an independent predictor of CV death or HF hospitalization with an HR of 1.60 (1.44–1.77, $P < 0.0001$). The magnitude of the risk was even greater in patients with preserved EF, where diabetes was associated with a doubling of the risk of CV death or HF hospitalization [HR 2.0 (1.70–2.36, $P < 0.0001$)]. There was a statistically significant ($P = 0.0009$) interaction between diabetes at baseline and EF with respect to this outcome.

Diabetes was an independent risk factor for each component of this combined outcome in patients with both low and preserved EF HF. The adjusted HR for HF hospitalization in diabetics compared with non-diabetics was 1.64 (1.44–1.86, $P < 0.0001$) in patients with low EF and 2.04 (1.68–2.47, $P < 0.0001$) in patients with preserved EF HF. That diabetes confers a greater risk for HF hospitalization in those with preserved EF than in those with low EF was confirmed by the interaction test ($P = 0.0029$). In absolute terms, patients with preserved EF and diabetes had a greater rate of HF hospitalization than those with low EF without diabetes (116.6 vs. 84.3 admissions to hospital per 1000 years of patient follow-up).

In the low EF group, the rates of CV death per 1000 years of patient follow-up were 119.1 and 75.7 for diabetics and

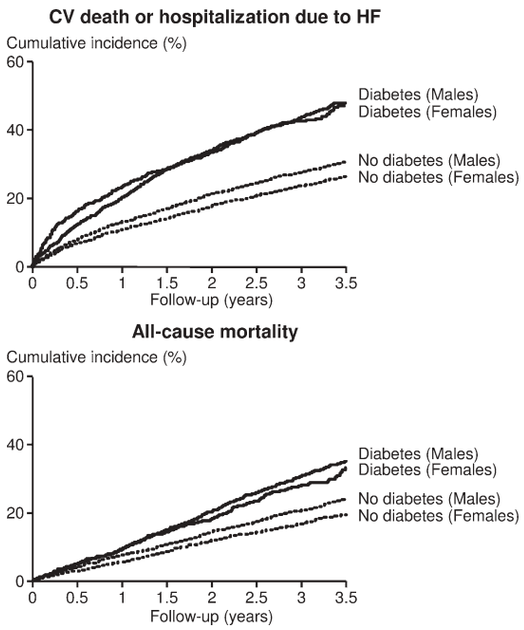

Figure 1 Outcomes in diabetic and non-diabetic patients based on sex. The cumulative incidence of cardiovascular death or heart failure hospitalization and all-cause mortality in diabetic and non-diabetic patient based on sex are shown. CV, cardiovascular; HF, heart failure

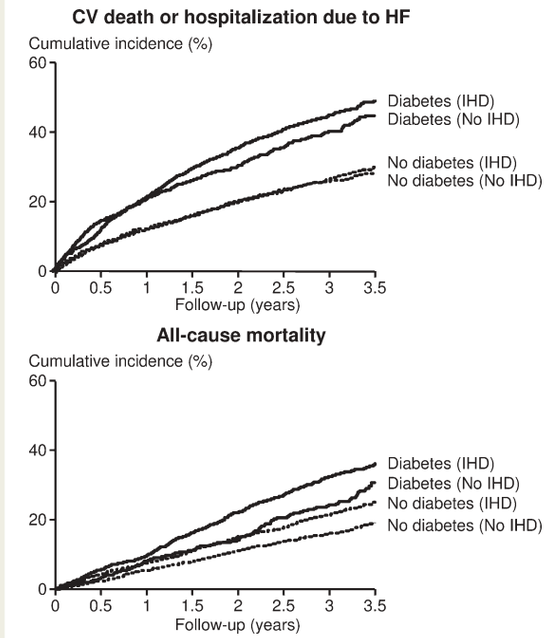

Figure 2 Outcomes in diabetic and non-diabetic patients based on aetiology (ischaemic vs. non-ischaemic). The cumulative incidence of cardiovascular death or heart failure hospitalization and all-cause mortality in diabetic and non-diabetic patients based on aetiology of heart failure are shown. CV, cardiovascular; HF, heart failure; IHD, investigator designated ischaemic heart disease aetiology

non-diabetics, respectively [adjusted HR 1.54 (1.35–1.75, $P < 0.0001$)]. In those with preserved EF, the rates were 58.6 for diabetics and 31.1 for non-diabetics [adjusted HR 1.93 (1.52–2.45, $P < 0.0001$)]. The test for interaction was not, however, significant for this outcome.

All-cause mortality

In the low EF population, the absolute rates of death from any cause per 1000 years of patient follow-up were 143.1 in diabetics and 91.4 in non-diabetics [adjusted HR 1.55 (1.38–1.74, $P < 0.0001$)]. In those with preserved EF, the rates were lower at 77.4 and 46.0 for diabetics and non-diabetics, respectively [adjusted HR 1.84 (1.51–2.26, $P < 0.0001$)]. Again, the test for interaction was not significant for this outcome.

Discussion

This study reports the prevalence of diabetes in large and contemporary cohorts of patients with chronic symptomatic HF and either low or preserved EF, enrolled using common inclusion and exclusion criteria in the same centres in a single comprehensive programme comprised of three concurrent trials. We also described the characteristics of those patients. We have confirmed and extended previous work by demonstrating that diabetes was an independent predictor of morbidity and mortality in both low and preserved EF HF. A novel finding was that diabetes conferred a greater increase in relative risk (and similar substantial increase in absolute risk) of the primary outcome of CV death or HF hospitalization in preserved EF HF when compared with low EF HF.

The prevalence of diabetes in patients with low EF HF in our study (28.5%) was similar to that reported in prior low EF HF trials.[8,9] Only three large HF clinical trials have included patients with preserved EF.[10,11] The prevalence of diabetes in our preserved EF patients (28.3%) was similar to that in the Digitalis Investigator Group study PEF cohort (28.8%) and the Irbesartan in Heart Failure with Preserved Systolic Function trial (I-PRESERVE, 27%).[12] The prevalence of diabetes was, however, somewhat lower in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF, 20%) study.

Previous studies have found that patients with low EF HF and diabetes have worse symptoms, more impaired exercise capacity,[13] and greater pulmonary dysfunction[14] than those with low EF without diabetes. We believe that ours is the first study to extend those findings to patients with HF and preserved EF.

Our analysis also extends previous work by demonstrating that diabetes is not only an important independent predictor of morbidity and mortality in patients with low EF, but also in patients with preserved EF. In particular, we found that diabetes was associated with an increased risk of CV death or HF hospitalization in those with low and preserved EF HF. Furthermore, the relative risk conferred by diabetes was statistically significantly greater in patients with preserved EF than in those with low EF, and the

increase in absolute risk was similarly large. The increase in events in patients with preserved EF and diabetes was primarily driven by an increased risk of HF hospitalization, with 27.8% hospitalized for HF compared with 12.9% of patients without diabetes. This risk related to diabetes in those with preserved EF was so marked that patients with preserved EF HF and diabetes had a greater rate of HF hospitalization than patients with low EF HF and no diabetes (27.8 vs. 21.7%).

Although the relative and absolute risks of both CV and all-cause mortality were higher in diabetics compared with non-diabetics with both types of HF, we did not find a statistically significant interaction between diabetes and EF for either of these outcomes.

Why was diabetes associated with a greater risk of HF hospitalization in patients with preserved but not low EF HF? Competing risks may have played a role because patients with preserved EF had a lesser risk of death and, therefore, had greater time at risk for HF hospitalization. In other words, an increased risk of HF hospitalization in low EF patients may not have been seen because their high rate of early death concealed the 'effect' of diabetes on hospitalization. However, diabetic patients with preserved EF were at much greater risk than those without diabetes, even when the risk of HF hospitalization was expressed per 1000 patient years of follow-up.

Alternatively, in some patients with HF and preserved EF, diabetes may be the primary cause of cardiac dysfunction and in others, it may play a more important role than in patients with low EF HF. There are numerous pathophysiologic processes in diabetics that are thought to alter the myocardium resulting in inefficient, ineffective, contraction (e.g. collagen cross-linking secondary to advanced glycation end-products, disorders in calcium transport, and induction of the foetal gene programme).[15–18] It is possible that these processes have a more detrimental effect on cardiac function in a heart where the primary problem is impaired diastolic filling than in a heart where the main problem is systolic dysfunction. The other vascular and non-vascular effects of diabetes such as decreased arterial compliance, worse endothelial function, renal angiopathy, and autonomic dysfunction may also be relatively more

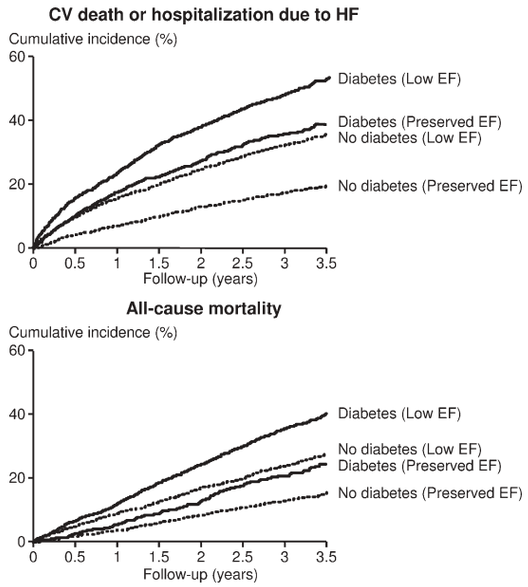

Figure 3 Outcomes in diabetic and non-diabetic patients based on ejection fraction category (low vs. preserved). The cumulative incidence of cardiovascular death or heart failure hospitalization and all-cause mortality in diabetic and non-diabetic patients based on ejection fraction category. CV, cardiovascular; EF, ejection fraction; HF, heart failure

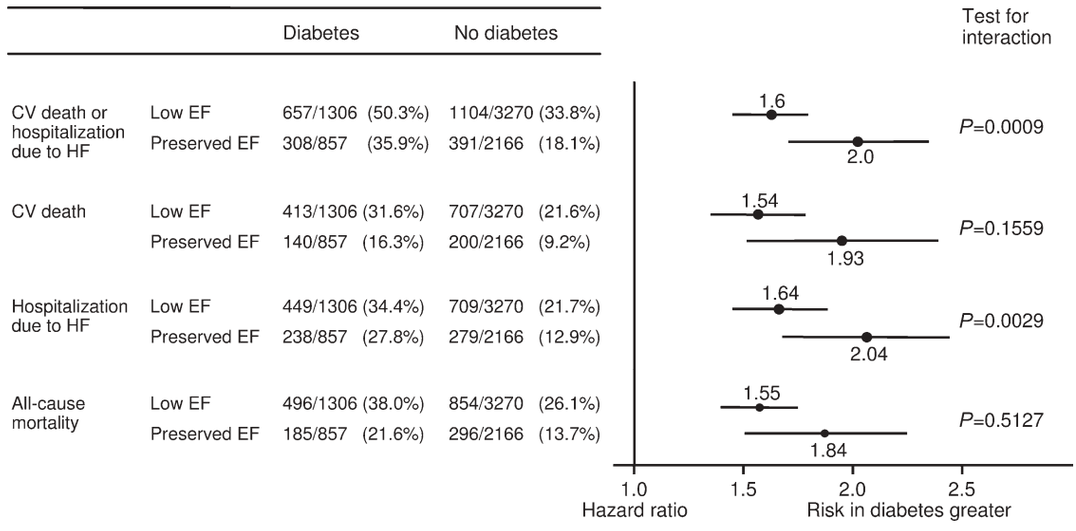

Figure 4 Risk of different outcomes associated with diabetes. Hazard ratios shown are adjusted for 32 baseline co-variates. Horizontal bars represent the 95% confidence intervals. CV, cardiovascular; EF, ejection fraction; HF, heart failure

important in patients with predominantly diastolic dysfunction. For example, these patients may be more sensitive to increases in preload and reductions in diastolic filling time due to increases in heart rate. Alternatively, diabetes has previously been identified as an independent predictor of the development of atrial fibrillation and a prior analysis from CHARM found that atrial fibrillation was associated with a greater increase in the risk of CV death and HF hospitalization in patients with preserved EF than in those with low EF HF.[19] Development of atrial fibrillation and loss of atrial contribution to diastolic filling may result in a greater likelihood of cardiac decompensation in patients with diastolic than systolic dysfunction. Diabetes may also interact with other risk factors, e.g. hypertension, which is particularly prevalent in patients with preserved EF, to amplify risk.

Previous studies examining diabetes in patients with HF had suggested that the increased risk associated with diabetes was confined to patients with ischaemic aetiology[3,20] and females.[21] We did not find any interaction between diabetes and sex or aetiology of HF. Results from these previous cohorts may well have been influenced by small patient numbers.

One limitation of this study is that the diagnosis of diabetes was reported by investigators and did not require systematic documentation using standardized diagnostic criteria. Its prevalence is, therefore, likely to have been underestimated. A previous study examining insulin and glucose abnormalities in HF patients enrolled in a clinical trial identified that 8% were undiagnosed diabetics.[2] It should also be noted that this is a selected population, and as such it has a higher proportion of males and a lower mean age than a community HF population. However, unlike community populations it was highly characterized, permitting extensive multivariable analysis. We did not collect data on use of glitazones which can cause HF hospitalization but these drugs were not widely used (especially outside the USA from where most CHARM patients came) during the period of recruitment of this study (1999–2001).

In conclusion, we report the effect of diabetes on CV morbidity as well as mortality in a large cohort of concurrently enrolled patients with both preserved and low EF HF treated with contemporary medications. We found diabetes to be an independent predictor of CV morbidity and mortality in patients with chronic symptomatic HF, in those with preserved and low EF HF. The relative risk of CV death or hospitalization due to HF conferred by diabetes was significantly greater in those with preserved when compared with low EF HF, and the increase in absolute risk was substantial and similar in both types of HF.

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CLINICAL VIGNETTE

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Contribution of organized thrombus to in-stent restenosis after sirolimus-eluting stent implantation: optical coherence tomography findings

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A 58-year-old man with hypercholesterolaemia and diabetes mellitus was admitted for exertional angina pectoris. Coronary angiography showed a 90% stenosis in the mid-right coronary artery (Panel A) and optical coherence tomography (OCT: LightLabTM) was performed to assess plaque morphology. OCT revealed diffusely bordered signal poor region with overlying signal-rich band at the culprit site (L indicates lipid core in Panel B). Two sirolimus-eluting stents (CypherTM; 3.0 × 33 and 3.0 × 33 mm) were deployed in the culprit lesion and excellent angiographic results were obtained (Panel C). The final intravascular ultrasound also demonstrated the well-expanded and apposed stents with no plaque protrusion. The patient was prescribed aspirin 100 mg and ticlopidin 200 mg orally daily for 1 year. Twelve months follow-up coronary angiography showed a 99% stenosis with contrast filling defect in the stents (Panel D). At this site, OCT revealed a low-backscattering projections irregular mass protruding into the lumen (white arrows in Panel E) with some microchannels (white arrowheads in Panel F). This finding may suggest that organized thrombus was the main component of restenotic tissue 12 months after sirolimus-eluting stent implantation.

Stent fracture and suboptimal stent expansion are thought to be the mechanism of restenosis after sirolimus-eluting stent implantation. Our images suggest that intra-stent thrombus accumulation may represent a new potential mechanism of restenosis after sirolimus-eluting stent implantation. OCT, which is a new high-resolution (approximately 10 μm) imaging modality, may be a useful tool for assessing the mechanism of restenosis after drug-eluting deployment.