

# Predictors of Development of Diabetes in Patients With Chronic Heart Failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Program

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 FOR THE CANDESARTAN IN HEART FAILURE  
 ASSESSMENT OF REDUCTION IN  
 MORTALITY AND MORBIDITY  
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CHF severity or drug-associated diabetes risk. Identifying patients with CHF at risk of diabetes through simple criteria appears possible and could enable targeted preventative measures.

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**OBJECTIVE** — The purpose of this study was to identify predictors of incident diabetes during follow-up of nondiabetic patients with chronic heart failure (CHF) in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program.

**RESEARCH DESIGN AND METHODS** — A total of 1,620 nondiabetic patients had full baseline datasets. We compared baseline demographic, medication, and laboratory data for patients who did or did not develop diabetes and conducted logistic regression and receiver operator characteristic curve analyses.

**RESULTS** — Over a median period of 2.8 years, 126 of the 1,620 patients (7.8%) developed diabetes. In multiple logistic regression analysis, the following baseline characteristics were independently associated with incident diabetes in decreasing order of significance by stepwise selection: higher A1C (odds ratio [OR] 1.78 per 1 SD increase;  $P < 0.0001$ ), higher BMI (OR 1.64 per 1 SD increase;  $P < 0.0001$ ), lipid-lowering therapy (OR 2.05;  $P = 0.0005$ ), lower serum creatinine concentration (OR 0.68 per 1 SD increase;  $P = 0.0018$ ), diuretic therapy (OR 4.81;  $P = 0.003$ ), digoxin therapy (OR 1.65;  $P = 0.022$ ), higher serum alanine aminotransferase concentration (OR 1.15 per 1 SD increase;  $P = 0.027$ ), and lower age (OR 0.81 per 1 SD increase;  $P = 0.048$ ). Using receiver operating characteristic curve analysis, A1C and BMI yielded areas under the curve of 0.723 and 0.712, respectively, increasing to 0.788 when combined. Addition of other variables independently associated with diabetes risk minimally improved prediction of diabetes.

**CONCLUSIONS** — In nondiabetic patients with CHF in CHARM, A1C and BMI were the strongest predictors of the development of diabetes. Other minor predictors in part reflected

**D** iabetes and chronic heart failure (CHF) often coexist in patients (1). The prevalence of diabetes in patients with CHF is substantial, typically 20–30% in clinical trials (1). Although caution should be exercised in extrapolating from these data, the prevalence appears substantially higher than that in the general population. Furthermore, diabetes is itself a well-recognized risk factor for the development of CHF (1,2). When diabetes is present in patients with CHF, it is associated with complications such as increased hospitalization (3), and diabetes is also an independent predictor of cardiovascular morbidity and mortality in heart failure (4). It is therefore plausible, although unproven, that approaches to reduce incident diabetes in CHF may have benefits in such patients.

Strong predictors of diabetes in the general population are well established and include the following: 1) measures of adiposity (5) such as BMI, waist circumference, and waist-to-hip ratio (typically with an area under the receiver operating characteristic curve [AUC-ROC] 0.66–0.73); 2) dysglycemia measures demonstrated by either abnormal fasting or postload glucose measures (AUC-ROC 0.73–0.77) (6), or elevated A1C, a marker of cumulative glucose exposure (7,8); 3) combinations of measures of obesity and dysglycemia (9); and 4) risk scores or questionnaires such as the Cambridge Diabetes Risk Score (10), which combines age, sex, BMI, history of antihypertensive or steroid medication, family history, and smoking history to estimate risk of diabetes (0.80).

Analysis of data from the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM)

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program has already shown a reduction in the incidence of diabetes in patients with CHF treated with the angiotensin II receptor blocker (ARB) candesartan (11). Whereas data on the rate of development of CHF in diabetes are widely available, there is no published evidence regarding potential predictors of incident diabetes in CHF. In this study we investigated which characteristics were associated with development of diabetes in patients with CHF using data from the CHARM program. Such data are novel and may be of value in predicting those with an elevated risk of diabetes and therefore help improve targeting of preventative measures, if applicable.

**RESEARCH DESIGN AND METHODS**

Detailed descriptions of the methods and results of the CHARM program have been published previously (12–15). In brief, the CHARM program consisted of three parallel trials with complementary populations of patients with symptomatic CHF: 1) CHARM Alternative: left ventricular ejection fraction (LVEF) ≤0.40 and prior intolerance to an ACE inhibitor; 2) CHARM Added: LVEF ≤0.40 and receiving an ACE inhibitor already; and 3) CHARM Preserved: LVEF >0.40, whether or not already receiving an ACE inhibitor.

A total of 7,601 (7,599 with data) patients were randomly assigned, of whom 2,163 were already known to have diabetes, as reported by the investigators at the time of randomization, a prevalence of 28.5%. In North America, 2,743 patients were recruited, of whom 1,722 patients were not diabetic and 1,021 were diabetic at baseline (prevalence of 37.2%). Complete datasets were defined as datasets for patients that contained all baseline demographic and clinical data, information regarding baseline drug therapies, and all blood results and randomization data (as in Table 1). Only the North American patients had blood samples analyzed for full laboratory result sets via a central core facility, including A1C, at baseline. Of the 1,722 nondiabetic patients, complete datasets were available for 1,620 patients, and their data were analyzed in this report; missing data were almost exclusively missing laboratory data.

In CHARM, patients were randomly assigned to receive either candesartan or placebo. Patients received the study drug in incremental doses (up to a maximum of 32 mg candesartan once daily as tolerated) or matching placebo. Patients were followed

**Table 1—Baseline characteristics of the 1,620 North American patients with full core laboratory datasets in CHARM with no medical history of diabetes at baseline, grouped by those who did and did not develop diabetes during the trials**

	No diabetes during trials	Diabetes during trials
All patients	1,494 (92.2)	126 (7.8)
Age (years)	66.4 ± 12.0	61.5 ± 12.3
Sex (% male)	1,008 (67.5)	82 (65.1)
BMI (kg/m <sup>2</sup> )	28.2 ± 5.9	32.4 ± 6.2
Smoking habit		
Nonsmoker	451 (30.2)	38 (30.2)
Previous smoker	804 (53.8)	73 (57.9)
Current smoker	239 (16.0)	15 (11.9)
SBP (mmHg)	127 ± 19	130 ± 19
History of prior myocardial infarction	763 (51.1)	59 (46.8)
History of hypertension	915 (61.2)	85 (67.5)
NYHA class		
II	600 (40.2)	45 (35.7)
III	860 (57.6)	78 (61.9)
IX	34 (2.3)	3 (2.4)
LVEF	0.38 ± 0.2	0.36 ± 0.2
Drug therapy		
ACE inhibitors	636 (42.6)	62 (49.2)
β-Blocker	791 (52.9)	80 (63.5)
Diuretic therapy	1,235 (82.7)	122 (96.8)
Long-acting nitrates	380 (25.4)	25 (19.8)
Spironolactone	215 (14.4)	27 (21.4)
Digoxin	766 (51.3)	82 (65.1)
Calcium channel blocker	353 (23.6)	30 (23.8)
Lipid-lowering drug	670 (44.8)	69 (54.8)
Oral anticoagulant	484 (32.4)	36 (28.6)
Laboratory results		
A1C (%)	6.2 ± 0.7	6.8 ± 0.9
Creatinine (μmol/l)	100 ± 35	91 ± 26
Potassium (mmol/l)	4.4 ± 0.4	4.3 ± 0.4
Sodium (mmol/l)	141 ± 3	140 ± 3
ALT (units/l)	18 (13–25)	23 (16–33)
AST (units/l)	20 (16–25)	20 (17–26)
Alkaline phosphatase (units/l)	79 (65–97)	85.5 (69–106)
Bilirubin total (μmol/l)	10.0 (6.8–13.7)	10.3 (8.0–12.0)
Bilirubin direct (μmol/l)	2.0 (1.7–4.0)	2.0 (1.7–3.4)
Hemoglobin (mmol/l)	8.5 ± 1.0	8.6 ± 0.8
Hematocrit (%)	41.2 ± 4.6	41.5 ± 3.7
Red cell count (10 <sup>12</sup> /l)	4.5 ± 0.5	4.6 ± 0.5
MCV (fl)	92.6 ± 5.9	91.2 ± 5.3
MCH (pg)	30.9 ± 2.4	30.5 ± 2.0
MCHC (mmol/l)	20.7 ± 0.7	20.8 ± 0.7
White cell count (10 <sup>9</sup> /l)	7.1 ± 2.1	7.6 ± 2.1
Eosinophils (%)	2.7 (1.7–4.1)	2.5 (1.6–3.4)
Lymphocytes (%)	25.8 ± 8.6	26.8 ± 8.4
Basophils (%)	0.3 (0.2–0.5)	0.3 (0.2–0.6)
Neutrophils (%)	63.9 ± 9.5	63.5 ± 9.5
Neutrophils band (%)	1 (0–3)	0.5 (0–1)
Monocytes (%)	6.7 ± 2.7	6.6 ± 2.4
Treatment randomization		
Candesartan	751 (50.3)	54 (42.9)

Data are means ± SD, n (%), or median (interquartile range). AST, aspartate aminotransferase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; NYHA, New York Heart Association Classification of heart failure; SBP, systolic blood pressure.

up at 2, 4, and 6 weeks; at 6 months; and then every 4 months until the end of the program. All patients provided written informed consent, and the protocol was approved by the ethics committee at each participating institution. A1C was measured in the central core laboratory on an automated high-performance liquid chromatography analyzer (Bio-Rad Variant Analyzer; GMI, Ramsey, MN) using a Diabetes Control and Complications Trial-aligned assay. The upper limit of normal for the assay was quoted as 6.5%.

### Diagnosis of diabetes

Investigators were asked to report the occurrence of a new diagnosis of diabetes for all patients at the end of the trials. Fasting blood tests were not performed as part of the CHARM program, and formal tests for diabetes were not done. Details of diagnoses of diabetes (date of diagnosis, details of the criteria for diagnosis, hypoglycemic medication prescribed, and lifestyle modifications prescribed) during the study were documented on case report forms at the closing study visit as described previously based on reporting by investigators (11). Diagnoses of diabetes were based on fasting plasma glucose  $\geq 7$  mmol/l (126 mg/dl), 2-h oral glucose tolerance tests (OGTTs) or a random glucose  $\geq 11.1$  mmol/l (200 mg/dl), or doctor diagnosis of diabetes with treatment specification. At baseline and throughout the program, physicians were free to prescribe various treatments, including other cardiovascular drugs (other than ARBs) or glucose-lowering drugs. Although the development of diabetes was a prespecified outcome in CHARM, potential predictors of diabetes were not prespecified. Results are presented to allow comparison of all pertinent or potentially relevant characteristics between patients who did and did not develop diabetes.

### Statistical methods

All variables measured were considered as possible predictors of diabetes. We chose this fully inclusive method because there is little prior information on the range of parameters potentially relevant to diabetes risk in a population with CHF. Univariate and multiple logistic regressions were carried out to identify those variables associated with the development of diabetes. For multiple logistic regression, two methods were used: multiple logistic regression including only those associations with  $P < 0.10$  on univariate logistic regression and, as an additional check given the large number of parameters

identified as potentially relevant, a forward-backward stepwise selection process. The forward-backward selection procedure starts with estimating an intercept for the model, followed by a forward selection step. In this step the score  $\chi^2$  statistic for each of the considered factors not yet included in the model is computed. If the effect with the largest statistic is significant at a prespecified entry significance level, the corresponding factor is added to the model. This is followed by a backward selection step. In this step, parameters for the complete model, as specified after the previous step, are estimated. The least significant factor that does not meet a prespecified significance level is removed. The backward selection step is repeated until no factor is removed. The forward step is then repeated and followed by one or more backward elimination steps. The selection process terminates if no further factor can be added or if the factor just entered is the only factor removed in the subsequent backward elimination. The odds ratios (ORs) and 95% CIs comparing treatment groups were calculated for the overall data. For the purposes of estimating diabetes predictive power, AUC-ROC analysis was used in a stepwise mode, with the AUC-ROC reported at each step in the selection process.

**RESULTS** — During the CHARM program, 365 (6.7%) of the 5,436 initially nondiabetic patients developed diabetes. This equates to an incidence of  $\sim 21.4$  cases per 1,000 patients per year. For the 1,620 patients with full datasets, i.e., those that are the subject of this report, median follow-up was 2.8 years and during this time 126 (7.8%) developed diabetes, an incidence of  $\sim 27.8$  cases per 1,000 patients per year. New diagnoses of diabetes were made as follows: 78 (62%) from fasting glucose values, 7 (6%) from OGTT, 5 (4%) from a combination of fasting glucose and OGTT, and 36 (29%) for whom no specific criteria were noted on the case report forms. Median follow-up for those who did not develop diabetes ( $n = 1,494$ ) during the study was 2.8 years compared with 3.1 years for those who did. Baseline characteristics of the 1,620 patients who did and did not develop diabetes over the course of the study are displayed in Table 1.

### Univariate associations with incident diabetes

The following baseline parameters showed significant positive associations

with the development of diabetes in univariate logistic regression at baseline (in decreasing order of significance by Wald  $\chi^2$  statistic) (Table 2): higher A1C, higher BMI, lower age, diuretic therapy, digoxin therapy, lower serum creatinine concentration, lower serum potassium, lower mean corpuscular volume, higher red cell count,  $\beta$ -blocker therapy, higher white cell count, lipid-lowering therapy, spironolactone therapy, lower mean corpuscular hemoglobin, higher serum alanine aminotransferase (ALT) concentration, lower serum sodium concentration, and lower eosinophil percentage. BMI was split into quartiles which showed that incident diabetes increased in a linear fashion and therefore analyzing BMI as a continuous variable was appropriate (data not shown). A1C (Wald  $\chi^2$  statistic 58.8) and BMI (Wald  $\chi^2$  statistic 52.7) were statistically the strongest predictors in this analysis by some margin. Expressed per unit change, an increase in A1C of 1% was associated with an increased OR for incident diabetes of 2.30 (95% CI 1.86–2.84) and an increase in BMI of 1 kg/m<sup>2</sup> was associated with an increased OR for incident diabetes of 1.10 (1.07–1.13). Expressed per SD, ORs for incident diabetes were 1.79 (1.54–2.08) and 1.78 (1.53–2.09) for increases of 1 SD in A1C and BMI, respectively. Those with BMI  $\geq 28$  kg/m<sup>2</sup> were 4.29 (2.79–6.61) times more likely to develop diabetes and those aged  $\geq 67$  years were 60% less likely to develop diabetes (OR 0.39 [95% CI 0.27–0.58]).

### Independent predictors of incident diabetes

Those characteristics associated with the development of diabetes in univariate logistic regression ( $P < 0.10$ ) were incorporated into a multiple logistic regression model (Table 2). The following baseline characteristics showed significant positive associations in decreasing order of significance: higher A1C, higher BMI, lipid-lowering therapy, lower serum creatinine concentration, diuretic therapy, higher serum ALT concentration, and digoxin therapy. The independent associations of higher A1C, higher BMI, and use of lipid-lowering therapy with incident diabetes were highly significant ( $P < 0.001$ ). Using the forward-backward stepwise selection method of multiple logistic regression, with the prespecified significance level for entering and keeping factors in the model set to 0.05, the following parameters showed indepen-

Table 2—Baseline characteristics associated with the development of diabetes in CHARM as analyzed by univariate and multiple logistic regression analyses

	Univariate logistic regression			Multiple logistic regression*		
	Wald $\chi^2$	P	OR (95% CI)	Wald $\chi^2$	P	OR (95% CI)
A1C (per %)	58.8	<0.0001	2.30 (1.86–2.84)	43.9	<0.0001	2.20 (1.74–2.78)
BMI (per kg/m <sup>2</sup> )	52.7	<0.0001	1.10 (1.07–1.13)	24.7	<0.0001	1.09 (1.05–1.12)
Age (per year)	19.0	<0.0001	0.97 (0.96–0.98)	1.3	0.25	0.99 (0.97–1.01)
Diuretics at baseline (yes vs. no)	13.1	0.0003	6.39 (2.34–17.46)	6.9	0.008	4.17 (1.44–12.05)
Digoxin (yes vs. no)	8.7	0.003	1.77 (1.21–2.59)	5.9	0.016	1.73 (1.11–2.69)
Creatinine (per $\mu\text{mol/l}$ )	8.5	0.004	0.99 (0.98–1.00)	8.6	0.003	0.99 (0.98–1.00)
Potassium (per mmol/l)	8.2	0.004	0.53 (0.34–0.82)	3.3	0.07	0.63 (0.39–1.04)
MCV (per fL)	7.4	0.007	0.96 (0.93–0.99)	0.9	0.34	0.96 (0.89–1.04)
Red cell count (per $10^{12}/\text{l}$ )	5.7	0.02	1.53 (1.08–2.18)	0.0	0.97	1.01 (0.65–1.57)
$\beta$ -Blocker (yes vs. no)	5.1	0.02	1.55 (1.06–2.25)	3.6	0.06	1.50 (0.99–2.27)
White cell count (per $10^9/\text{l}$ )	5.1	0.02	1.09 (1.01–1.18)	0.1	0.75	0.99 (0.90–1.08)
Lipid-lowering therapy (yes vs. no)	4.6	0.03	1.49 (1.03–2.15)	12.8	0.0003	2.12 (1.41–3.20)
Spironolactone (yes vs. no)	4.5	0.03	1.62 (1.04–2.54)	1.3	0.25	1.35 (0.81–2.23)
MCH (per pg)	4.4	0.04	0.92 (0.85–1.00)	0.2	0.64	1.04 (0.87–1.25)
ALT (per units/l)	4.3	0.04	1.01 (1.00–1.02)	6.0	0.015	1.01 (1.00–1.02)
Sodium (per mmol/l)	3.9	0.048	0.94 (0.89–1.00)	0.7	0.41	0.97 (0.91–1.04)
Eosinophils (per %)	3.9	0.049	0.91 (0.83–1.00)	2.5	0.12	0.91 (0.81–1.02)
Candesartan therapy (placebo vs. candesartan)	2.5	0.11	1.35 (0.93–1.95)			
ACE inhibitors (yes vs. no)	2.1	0.15	1.31 (0.91–1.88)			
Bilirubin direct (per $\mu\text{mol/l}$ )	2.0	0.16	0.94 (0.86–1.03)			
Long-acting nitrates (yes vs. no)	1.9	0.17	0.73 (0.46–1.14)			
SBP (per mmHg)	1.9	0.17	1.01 (1.00–1.02)			
Medical history: hypertension (yes vs. no)	1.9	0.17	1.31 (0.89–1.93)			
Lymphocytes (per %)	1.6	0.21	1.01 (0.99–1.03)			
Ejection fraction	1.5	0.22	0.48 (0.15–1.54)			
MCHC (per mmol/l)	1.3	0.25	1.16 (0.90–1.48)			
Basophils (per %)	1.2	0.27	1.32 (0.81–2.15)			
Hemoglobin (per mmol/l)	1.2	0.28	1.11 (0.92–1.35)			
NYHA (III or IV vs. I or II)	1.0	0.33	1.21 (0.83–1.76)			
Medical history: prior myocardial infarction (yes vs. no)	0.8	0.36	0.84 (0.59–1.21)			
Alkaline phosphatase (per units/l)	0.8	0.38	1.00 (1.00–1.01)			
Oral anticoagulant therapy (yes vs. no)	0.8	0.38	0.84 (0.56–1.25)			
Hematocrit (%)	0.7	0.41	1.02 (0.98–1.06)			
AST (per units/l)	0.6	0.44	1.00 (1.00–1.01)			
Bilirubin total (per $\mu\text{mol/l}$ )	0.6	0.44	0.99 (0.96–1.02)			
Sex (female vs. male)	0.3	0.58	1.11 (0.76–1.63)			
Neutrophils (per %)	0.3	0.60	1.00 (0.98–1.01)			
Monocytes (per %)	0.1	0.73	0.99 (0.92–1.06)			
Calcium channel blocker (yes vs. no)	0.002	0.96	1.01 (0.66–1.55)			
Smoking habit (current or past vs. none)	0.000	0.99	1.00 (0.67–1.49)			

\*Only factors with  $P < 0.10$  on univariate logistic regression were included in this multiple factor logistic regression. AST, aspartate aminotransferase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; NYHA, New York Heart Association Classification of heart failure; SBP, systolic blood pressure.

dent and significant associations with an increased risk of developing diabetes (in decreasing order of significance) (Table 3): higher A1C, higher BMI, lipid-lowering therapy, lower serum creatinine concentration, diuretic therapy, digoxin therapy, higher serum ALT concentration, and younger age. The two methods of statistical analysis therefore identified

the same independent predictors of diabetes. Expressed per unit change, an increase in A1C of 1% was associated with an increased OR for incident diabetes of 2.28 (95% CI 1.82–2.85) and an increase in BMI of 1 kg/m<sup>2</sup> was associated with an increased OR for incident diabetes of 1.09 (1.05–1.12). Expressed per SD, ORs for incident diabetes were 1.78 (1.52–2.08)

and 1.64 (1.36–1.98), respectively, for increases of 1 SD in A1C and BMI.

**Assessing predictive ability of baseline parameters for diabetes**

AUC-ROC for A1C alone was 0.72. The optimal point for prediction of diabetes was at an A1C of 6.5%, which yielded a sensitivity of 0.63 and specificity of 0.70.

**Table 3—Multiple logistic regression of baseline characteristics with stepwise selection of all effects predicting the development of diabetes in CHF**

	Wald $\chi^2$	P	OR (95% CIs)
A1C	51.6	<0.0001	1.78 (1.52–2.08)
BMI	26.6	<0.0001	1.64 (1.36–1.98)
Lipid-lowering therapy	12.1	0.0005	2.05 (1.37–3.07)
Serum creatinine	9.7	0.0018	0.68 (0.54–0.87)
Diuretic therapy	8.6	0.0033	4.81 (1.69–13.69)
Digoxin therapy	5.2	0.0221	1.65 (1.08–2.54)
ALT	4.9	0.0269	1.15 (1.02–1.31)
Age	3.9	0.0476	0.81 (0.65–1.00)

ORs are expressed per 1 SD change in age, BMI, ALT, A1C, and creatinine.

AUC-ROC for BMI alone was 0.71. The optimal point for diabetes prediction was at a BMI of 29.1 kg/m<sup>2</sup>, which yielded a sensitivity of 0.73 and a specificity of 0.63. Of the other factors associated with incident diabetes, serum ALT gave the best AUC-ROC of 0.63 on univariate analysis. Predictive performance was moderately improved by the addition of BMI to A1C in a multivariate model. The AUC-ROC for BMI and A1C combined was 0.79 with a sensitivity of 0.73 and specificity of 0.72 for predicting incident diabetes. Adding other elements associated with future diabetes (digoxin, diuretics and lipid-lowering therapies, lower age, lower serum creatinine, and higher ALT concentrations) to the model improved AUC-ROC progressively, although by relatively small amounts, to a maximum of 0.82.

**CONCLUSIONS**— Analysis of data from the CHARM program confirmed the high general prevalence and incidence of diabetes in patients with CHF. An estimated incidence of 21–28 cases per 1,000 patients per year (mean age 66 years) contrasts with the incidence of diabetes of 16.8 cases per 1,000 population per year (age 65–79 years) and 11.2 cases per 1,000 population per year (age 45–64 years) from the National Health and Nutrition Examination Survey (NHANES) in 2003 (16) in which self-reporting of diabetes was used. Data available from 1,620 of these patients in CHARM, of whom 126 developed diabetes, showed that the two most powerful independent predictors of diabetes in the program were A1C, a measure of dysglycemia, and BMI. Both gave AUC-ROCs very similar to those expected in the general population. Given the worse outcomes of CHF events described in patients with diabetes, the ability to better identify individuals at risk of

diabetes may allow the clinician to take steps to reduce this risk with resultant better clinical outcomes. In view of evidence that A1C is a predictor of cardiovascular death, hospitalization, and total mortality in not only diabetic but also nondiabetic patients with CHF (17), its measurement in patients with CHF may have clinical potential, and future studies that include fasting glucose will allow further assessment of this. This is on the background of emerging support for the use of A1C as part of a screening strategy for diabetes (18).

The independent associations of certain characteristics with the development of diabetes, namely use of lipid-lowering therapy, use of digoxin, and lower serum creatinine concentration, plus the strong association of diuretic use at baseline require further examination and explanation. With regard to baseline therapies, there is contradictory evidence on statin therapy and risk for incident diabetes (19), which suggests that the association found may reflect either ischemic heart disease, itself associated with insulin resistance, or underlying lipid abnormalities, which may predict diabetes (hypertriglyceridemia and low HDL cholesterol) rather than any statin treatment effect. We are not aware of any data suggesting that digoxin therapy influences the development of diabetes. One possibility is that patients receiving both digoxin and diuretic therapies have more severe CHF requiring more intensive therapy, and, therefore, these are serving as proxies of CHF severity. There is evidence that worse CHF predicts diabetes (20,21), although, interestingly, LVEF did not predict diabetes in the present analysis. Further studies are needed to examine these issues. Furthermore, there are powerful data from the field of hypertension showing an increased incidence

of diabetes on diuretic therapy (22) relative to both placebo and other antihypertensive agents. The proportions of patients taking loop and thiazide diuretics in CHARM were not available. Those receiving multiple medications may have had blood samples for biochemical analyses taken more often outside the trial, thereby increasing the chance of detecting diabetes if fasting glucose analyses were also performed. As shown in CHARM (12) and elsewhere, the use of ACE inhibitors and ARBs leads to a rise in serum creatinine concentration, and so this finding may reflect confounding effects of treatments on diabetes risk rather than any direct association between renal function and diabetes risk. In addition, lower creatinine concentrations could partially reflect reduced muscle mass and thus a biologically plausible mechanism linking lower creatinine levels to elevated higher diabetes risk.

The increase in risk of diabetes per unit increase in serum ALT was admittedly modest and of uncertain clinical significance in this analysis; furthermore, elevation in serum ALT may occur as a result of hepatic congestion in CHF. However, it should be recognized that the association between serum ALT and risk of diabetes concurs with findings in the general population. Serum ALT, a hepatocellular enzyme, is a reasonable marker of fat accumulation in the liver in nonalcoholic fatty liver disease (23). Nonalcoholic fatty liver disease is itself a condition strongly linked to insulin resistance, type 2 diabetes, and obesity. Serum ALT has previously been shown to predict diabetes in different populations, including hypercholesterolemic men in Scotland (24) and a general population cohort in Japan (25), but to our knowledge this is the first evidence of any association in patients with CHF. This finding implies that liver fat is relevant to the pathogenesis of diabetes in patients with CHF, as it is in individuals without CHF.

The finding that younger age was an independent predictor of diabetes was unexpected. It may simply be that younger patients with CHF have a longer survival time and consequently a greater chance to develop diabetes. An alternative explanation is that younger patients with CHF may represent a slightly different phenotype with higher BMI and higher risk of diabetes compared with that of older patients. There are data to support this suggestion; in a substudy of 2,107 patients in CHARM, the prevalence of

obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) was four times higher in patients with CHF aged <50 years than in patients aged  $\geq 80$  years (data not shown). Irrespective of the above findings, it should be noted that age did not significantly improve AUC-ROC for prediction beyond other measures.

The strengths of the present analysis are the number of incident cases of diabetes and number of patients included in the program, together with excellent baseline phenotyping. There are also potential weaknesses that must be highlighted. Given that identifying predictors of diabetes was not a predetermined outcome of the CHARM program, these findings must be treated as post hoc. In addition, all data are limited to North American patients. Ideally, the diagnoses of diabetes would have been carried out uniformly under controlled circumstances in all patients, although pragmatic factors, as occurs in clinical practice, dictated otherwise. We cannot, therefore, exclude the possibility that patients with undiagnosed diabetes at baseline were included in our analysis. It would also have been preferable to measure and include fasting glucose results and serum lipids, particularly serum triglycerides, but the patients were nonfasting and so these parameters were not available. Finally, potentially useful data such as family history of diabetes were not available. Nevertheless, the results provide the first comprehensive examination of predictors of diabetes in patients with CHF and provide a useful framework for further study.

In summary, the strongest predictors of development of diabetes in patients with CHF in the CHARM program were A1C and BMI, in line with prior observations in the general population. Other minor independent predictors of diabetes in part reflected CHF severity or drug-associated diabetes risk, but their addition did not substantially improve prediction of diabetes. Our findings suggest that simple predictors would serve well to identify those patients with CHF at elevated risk for developing type 2 diabetes. Identification of high-risk individuals may allow application of approaches that reduce progression to diabetes in patients with CHF and potentially result in better clinical outcomes.

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**References**

1. MacDonald MR, Petrie MC, Hawkins NM, et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J* 2008;29:1224–1240
2. Nichols GA, Gullion CM, Koro CE, et al. The incidence of congestive heart failure in type 2 diabetes. *Diabetes Care* 2004;27:1879–1884
3. Held C, Gerstein HC, Yusuf S, et al. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. *Circulation* 2007;115:1371–1375
4. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure. *Eur Heart J* 2008;29:1377–1385
5. Stevens J, Couper D, Pankow J, et al. Sensitivity and specificity of anthropometrics for the prediction of diabetes in a biracial cohort. *Obes Res* 2001;9:696–705
6. Dankner R, Abdul-Ghani MA, Gerber Y, et al. Predicting the 20-year diabetes incidence rate. *Diabetes Metab Res Rev* 2007;23:551–558
7. Pradhan AD, Rifai N, Buring JE, et al. Hemoglobin a1c predicts diabetes but not cardiovascular disease in nondiabetic women. *Am J Med* 2007;120:720–727
8. Little RR, England JD, Wiedmeyer HM, et al. Glycated hemoglobin predicts progression to diabetes-mellitus in Pima-Indians with impaired glucose-tolerance. *Diabetologia* 1994;37:252–256
9. Norberg M, Eriksson JW, Lindahl B, et al. A combination of HbA1c, fasting glucose and BMI is effective in screening for individuals at risk of future type 2 diabetes: OGTT is not needed. *J Intern Med* 2006;260:263–271
10. Griffin SJ, Little PS, Hales CN, et al. Diabetes risk score: towards earlier detection of type 2 diabetes in general practice. *Diabetes Metab Res Rev* 2000;16:164–171
11. Yusuf S, Ostergren JB, Gerstein HC, et al. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005;112:48–53
12. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759–766
13. McMurray JJV, Ostergren J, Swedberg K, et al. Effects of candesartan in patients

with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767–771

14. Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772–776
15. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;362:777–781
16. Geiss LS, Pan LP, Cadwell B, et al. Changes in incidence of diabetes in US adults, 1997–2003. *Am J Prev Med* 2006;30:371–377
17. Gerstein HC, Swedberg K, Carlsson J, et al. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure. *Arch Intern Med* 2008;168:1699–1704
18. Saudek CD, Herman WH, Sacks DB, et al. A new look at screening and diagnosing diabetes mellitus. *J Clin Endocrinol Metab* 2008;93:2447–2453
19. Jick SS, Bradbury BD. Statins and newly diagnosed diabetes. *Br J Clin Pharmacol* 2004;58:303–309
20. Tenenbaum A, Motro M, Fisman EZ, et al. Functional class in patients with heart failure is associated with the development of diabetes. *Am J Med* 2003;114:271–275
21. Amato L, Paolisso G, Cacciatore F, et al. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. *Diabetes Metab* 1997;23:213–218
22. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of anti hypertensive drugs: a network meta-analysis. *Lancet* 2007;369:201–207
23. Preiss D, Sattar N. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. *Clin Sci (Lond)* 2008;115:141–150
24. Sattar N, Scherbakova O, Ford I, et al. Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the West of Scotland Coronary Prevention Study. *Diabetes* 2004;53:2855–2860
25. Doi Y, Kubo M, Yonemoto K, et al. Liver enzymes as a predictor for incident diabetes in a Japanese population: the Hisayama study. *Obesity* 2007;15:1841–1850