The Hemoglobin A₁c Level as a Progressive Risk Factor for Cardiovascular Death, Hospitalization for Heart Failure, or Death in Patients With Chronic Heart Failure

An Analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program

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**Background:** A progressive relationship between hemoglobin A₁c (HbA₁c) levels and cardiovascular (CV) events has been observed in persons with and without diabetes. To our knowledge, the nature of such a relationship in patients with symptomatic chronic heart failure (HF) has not been studied.

**Methods:** A total of 2412 participants (907 with prior diabetes) in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program with at least 1 HbA₁c level were followed up for a median of 34 months. The incidence of the primary outcome (CV death or HF hospitalization), CV death, and total mortality was calculated according to eighths of the usual HbA₁c level ranging from 5.8% or less to greater than 8.6%. Adjusted and unadjusted hazard ratios per 1% rise in HbA₁c levels were also calculated.

**Results:** A total of 99.6% of eligible participants were followed up until they developed an outcome or the study finished. The risk of the primary composite outcome, CV death, hospitalization for worsening HF, and total mortality rose progressively with higher levels of usual HbA₁c (P for trend <.001). After age and sex were adjusted for, hazards of these outcomes per 1% higher HbA₁c level were 1.25 (95% confidence interval [CI] 1.20-1.31), 1.24 (95% CI, 1.17-1.31), 1.25 (95% CI, 1.19-1.31), and 1.22 (95% CI, 1.16-1.29), respectively. This relationship was evident in patients with and without diabetes and with reduced or preserved ejection fraction and persisted after adjustment for diabetes, other risk factors, and allocation to candesartan.

**Conclusion:** In diabetic and nondiabetic patients with symptomatic chronic HF, the HbA₁c level is an independent progressive risk factor for CV death, hospitalization for HF, and total mortality.

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**Diabetes** is a metabolic disorder characterized by hyperglycemia and is well established as a strong independent risk factor for cardiovascular (CV) events; indeed, diabetes confers a CV risk that is comparable to an age increase of 15 years. The exact reasons for this relationship remain unknown; however, they include the strong association between diabetes and other established CV risk factors, such as hypertension, dyslipidemia, and renal insufficiency. Moreover, a growing body of epidemiologic evidence now implicates elevated glucose levels themselves as important determinants of CV disease, and biologic evidence suggests that this relationship may be mediated by (1) a direct effect of the elevated glucose levels; (2) insufficient insulin effect due to the relative or absolute lack of insulin that permits the glucose levels to rise; (3) insulin resistance; (4) an antecedent problem that increases both the risk of diabetes and the risk of CV events; or (5) some combination of these factors.

Glycated hemoglobin (HbA₁c) levels reflect ambient glucose levels over a 2- to 3-month period and are routinely measured in people with diabetes to assess response to glucose-lowering therapies. Epidemiologic studies have shown that HbA₁c is a progressive risk factor for ischemic CV events and CV death in patients with diabetes and in individuals in the general population and that this relationship is independent of the presence or absence of
diabetes. However, few studies have assessed the relationship between HbA1c levels and CV events in persons with chronic symptomatic heart failure (HF). Because patients with this condition already have damaged myocardial tissue, the heart may be particularly susceptible to any toxic effects of an elevated glucose level.

The Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program consisted of 3 international placebo-controlled trials in patients with symptomatic chronic HF in which candesartan reduced the risk of CV death or hospitalization for worsening HF over a median follow-up of 38 months. The HbA1c levels were measured in a subset of CHARM participants both at baseline and during the trial in a central laboratory; these measurements provide a unique opportunity for evaluation of the relationship between HbA1c levels and CV outcomes in patients with chronic HF.

METHODS

The design and results of the CHARM trials are described elsewhere. Briefly, patients with symptomatic chronic HF (New York Heart Association Class II-IV) who (1) had a serum creatinine level of less than 3 mg/dL (<265 µmol/L), (2) had a serum potassium level of less than 5.5 mEq/L (<5.5 mmol/L), (3) were not taking an angiotensin receptor blocker, and (4) had no critical aortic or mitral stenosis or recent myocardial infarction, stroke, or heart surgery were included in the study. The patients were divided into those with (1) a left ventricular ejection fraction (LVEF) greater than 40%; (2) an LVEF less than or equal to 40% and who were taking an angiotensin-converting enzyme (ACE) inhibitor; and (3) an LVEF less than or equal to 40% and who were not receiving an ACE inhibitor because of intolerance. Within each of the component trials, patients were randomly allocated to treatment with candesartan (up to 32 mg/d) or matching placebo between March 1999 and March 2001.

The primary outcome of the entire program was death from any cause, and the primary composite outcome for the 3 component trials was CV death or hospitalization for worsening HF. All end points were independently blindly adjudicated. Deaths were considered to be CV unless another clear cause was apparent. A hospitalization for worsening HF was defined as an unplanned admission necessitated by HF and requiring therapy with inotropic diuretics.

Participants in North America underwent laboratory assessments, including measurement of HbA1c levels, at baseline, at 6 weeks, at 14 months, and annually thereafter. Hemoglobin A1c levels were measured in the central core laboratory with a Diabetes Control and Complications Trial/traceable assay using an automated, high-performance liquid chromatography analyzer (Biorad Variant Analyzer; GMI Inc, Ramsey, Minnesota); the normal value for this assay was less than 6.3%. Serum creatinine levels were assessed by spectrophotometry using an automated chemistry analyzer (Olympus Chemistry Analyzer; Olympus America Inc, Center Valley, Pennsylvania); urinary albumin levels were assessed by a competitive radioimmunoassay (Diagnostic Products Corp, Los Angeles, California); and urinary creatinine levels were assessed by a colorimetric kinetic Jaffe method using a random-access analytical system (Cobas Integra Instrument; Roche Diagnostic Systems, Branchburg, New Jersey). The estimated glomerular filtration rate was calculated as previously reported. Diabetic status was based on self-report.

The statistical analyses were restricted to the North American participants in whom HbA1c levels were available through a central laboratory as part of a planned examination of the relationship between HbA1c levels and CV outcomes. Usual HbA1c levels were used to reduce regression-dilution bias and were calculated as the mean of all of the available HbA1c levels during treatment until the primary outcome occurred. Characteristics of participants divided according to eighths of usual HbA1c levels were compared using a Cochran-Armitage test for categorical variables and linear regression for continuous variables. Division into eighths was done to ensure that the groups clearly spanned a broad range of glycemia that included the normoglycemic range, while containing sufficient numbers of participants to estimate the incidence of the outcome. Cox proportional hazards models were used to analyze the prospective relationship between usual HbA1c levels and (1) primary outcome of CV death or hospitalization for worsening HF, (2) CV death, (3) hospitalization for worsening HF, and (4) all-cause death. Proportionality was assessed by inspection. Independent variables that were added to the models included age, sex, LVEF, body mass index, natural logarithm of the baseline urinary albumin-creatinine ratio, estimated glomerular filtration rate, systolic blood pressure, treatment allocation, current or past smoker, or use of ACE inhibitors, diuretics, β-blockers, spironolactone, calcium channel blockers, or aspirin. Survival curves for each eighth of HbA1c were compared using log-rank tests.

RESULTS

A total of 2412 of 2743 participants (87.9%) in North America had at least 1 HbA1c level available (mean, 2.3 measurements). Their mean age was 65.8 years; 33.0% were women; and 37.6% had a history of diabetes. These and the other characteristics of the cohort divided according to eighths of usual HbA1c levels are shown in Table 1. There was a significant progressive relationship between rising eighths of HbA1c levels and the proportion of patients with a history of diabetes; hypertension; CV disease; previous hospitalization for HF; baseline New York Heart Association classification III or IV; use of diuretics, ACE inhibitors, or vasodilators; and mean body mass index, systolic blood pressure, heart rate, serum creatinine levels, and the natural logarithm of the urinary albumin-creatinine ratio (P for trend <.001 for all except ACE inhibitors and systolic blood pressure, for which P = .002 and P = .01, respectively).

Final event status was available for 2402 of the 2412 participants (99.6%) with a baseline HbA1c measurement after a median follow-up period of 36.7 months. The risk of the primary outcome (CV death or hospitalization for worsening HF) rose progressively with eighths of HbA1c levels. Indeed, the proportion of patients with an HbA1c level in the highest HbA1c eighth (ie, >8.6%) who had a primary outcome (50.7%), CV death alone (25.8%), hospitalization for worsening HF (36.2%), or death from any cause (31.9%) was 2 to 3 times higher than in patients whose HbA1c level was 5.8% or less (P for trend <.001 across eighths of HbA1c). Figure 1 illustrates the progressive rise in the proportion of individuals who developed these outcomes in subgroups characterized by progressively increasing eighths of HbA1c levels (P <.001).

After adjustment for age and sex in the Cox model, the hazard of the primary composite outcome, CV death, hospitalization for worsening HF, and all-cause death in-
The relationship observed in individuals without previous diabetes. Finally, the reduction of the primary composite outcome by candesartan vs placebo was independent of all of these variables, including the HbA1c level (hazard ratio, 0.85; 95% CI, 0.74–0.97; P = .01).

This analysis of HbA1c data collected during the CHARM program shows that in individuals who have a diagnosis of symptomatic chronic HF, the HbA1c level is strongly associated with classic risk factors for CV events and is itself a strong and independent risk factor for future CV events and death. Figures 2 and 3 also show that this relationship is as (or possibly more) relevant for individuals without diabetes as it is for individuals with a history of diabetes. Therefore, in this population, for every 1% increase in the level of HbA1c, the risk of CV events or death increases by approximately 25%.

These findings extend those from previous analyses of the link between HbA1c levels and CV events that were conducted in the general population14,21 and in patients with newly diagnosed diabetes,22 in patients with established diabetes,9 and in patients with diabetes and other CV risk factors.21 They are also consistent with analyses of the link between fasting plasma glucose levels and CV events in non-diabetic individuals with previous CV events15 and between fasting or postload glucose levels and CV events4,6 in volunteers from the general population.
These data are limited by the fact that HbA1c levels were only measured in North American CHARM participants. However, there is no reason to believe that a similar relationship would not be found in the other participants or in other similar populations. Moreover, (1) HbA1c levels were measured centrally in 99.3% of all eligible participants; (2) outcomes were prospectively collected and blindly adjudicated; and (3) there was a 99.6% follow-up rate by study end. These data are also limited by the determination of diabetes status on the basis of self-report and the

![Figure 1. The proportion of patients who developed the primary composite outcome (cardiovascular (CV) death or hospitalization for worsening heart failure (HF)), CV death, HF, or death according to eighths of usual hemoglobin A1c (HbA1c) levels is shown (\(P\) for trend <.001). Error bars indicate 95% confidence intervals.](image)

Table 2. Independent Effect of Hemoglobin A1c (HbA1c) Levels on Outcomes

<table>
<thead>
<tr>
<th>Independent Effect of Usual HbA1c After Controlling for Age, Sex, and . . .</th>
<th>Risk Per 1% Higher Usual HbA1c Levels, HR (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CV Death or Worsening HF</td>
</tr>
<tr>
<td>Nothing else</td>
<td>1.25 (1.20-1.31)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.17 (1.11-1.24)</td>
</tr>
<tr>
<td>EF</td>
<td>1.24 (1.19-1.30)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.26 (1.21-1.31)</td>
</tr>
<tr>
<td>Log ACR</td>
<td>1.19 (1.13-1.24)</td>
</tr>
<tr>
<td>eGFR</td>
<td>1.22 (1.17-1.27)</td>
</tr>
<tr>
<td>Log ACR and eGFR</td>
<td>1.18 (1.12-1.23)</td>
</tr>
<tr>
<td>SBP</td>
<td>1.26 (1.21-1.32)</td>
</tr>
<tr>
<td>Smoking and drugs(^b)</td>
<td>1.28 (1.20-1.36)</td>
</tr>
<tr>
<td>EF, BMI, log ACR, and SBP</td>
<td>1.17 (1.12-1.23)</td>
</tr>
<tr>
<td>EF, BMI, log ACR, SBP, and diabetes</td>
<td>1.14 (1.07-1.21)</td>
</tr>
<tr>
<td>Drug allocation to candesartan or placebo</td>
<td>1.25 (1.20-1.31)</td>
</tr>
<tr>
<td>Drug allocation to candesartan or placebo, smoking, and drugs(^b)</td>
<td>1.24 (1.19-1.30)</td>
</tr>
<tr>
<td>EF, BMI, Log ACR, SBP, drug allocation to candesartan or placebo, smoking, drugs,(^b) and diabetes</td>
<td>1.14 (1.07-1.21)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; log ACR, natural logarithm of urinary albumin-creatinine ratio; SBP, systolic blood pressure.

\(a\) All values are statistically significant at \(P<.001\).

\(b\) Drugs refers to angiotensin-converting enzyme inhibitors, diuretics, \(\beta\)-blockers, spironolactone, calcium channel blockers, and aspirin.
lack of standardized testing to detect undiagnosed diabetes. Therefore, the reported prevalence of diabetes and the contribution of diabetes status to the risk of clinical outcomes may have been underestimated.

Despite the above-mentioned limitations, the addition of these findings to the growing body of evidence noted above confirms the existence of an independent link between various indices of glycemia and CV outcomes in low-, moderate-, and high-risk individuals. Reasons for this relationship remain unclear. However, exposure of cells to higher levels of glucose than are required to satisfy normal energy requirements leads to increased concentrations of metabolites and activation of metabolic pathways that have been linked to endothelial cell dysfunction and atherosclerosis. These pathways include increased hexosamine pathway flux, activation of protein kinase C, production of advanced glycation end products, and production of reactive oxygen species by the mitochondria. Alternatively, or in addition, the higher glucose levels are a marker of insufficient insulin effect, and this insufficient effect, or the underlying insulin resistance, may promote atherosclerosis.

Current proven therapies for HF focus on reducing neurohumoral activation (eg, ACE inhibitors, angiotensin receptor blockade, aldosterone antagonists, and β-blockers) or increasing contractility (eg, digoxin). These data suggest that it is worth exploring glucose lowering as an additional method of reducing HF-related mortality and morbidity. Finally, they support but do not prove the hypothesis that glucose lowering or the prevention of an increase in glucose levels may reduce CV events. This hypothesis is currently being tested in a number of large international clinical trials.

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Figure 2. The hazard ratios (HRs) (adjusted for age and sex) and 95% confidence intervals (CIs) of the primary composite outcome, cardiovascular (CV) death, hospitalization for worsening heart failure (HF), or death (per 1% higher usual hemoglobin A1c [HbA1c] levels) are shown for all participants, for those with diabetes, and for those with no history of diabetes.

Figure 3. The hazard ratios (HRs) (adjusted for age, sex, urinary albumin levels, ejection fraction, body mass index, drug allocation, smoking, and drug use) and 95% confidence intervals (CIs) of the primary composite outcome, cardiovascular death, hospitalization for worsening heart failure (HF), or death (per 1% higher usual hemoglobin A1c [HbA1c] levels) are shown for all participants, for those with diabetes, and for those with no history of diabetes.
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