Glucose Levels Predict Hospitalization for Congestive Heart Failure in Patients at High Cardiovascular Risk

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Background—Patients with diabetes mellitus (DM) are at high risk of developing congestive heart failure (CHF). However, the relationships between glucose levels and CHF in people with or without a history of DM have not been well characterized.

Methods and Results—We evaluated the associations between fasting plasma glucose and risk of hospitalization for CHF during follow-up in patients at high cardiovascular risk and without CHF enrolled in a large-scale clinical trials program. Baseline fasting plasma glucose levels were assessed in 31 546 high-risk subjects with ≥1 coronary, peripheral, or cerebrovascular disease or DM with end-organ damage who are participating in 2 ongoing parallel trials evaluating the effects of telmisartan, ramipril, or their combination (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET]; n=25 620) and the effects of telmisartan against placebo in angiotensin-converting enzyme–intolerant patients (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease [TRANSCEND]; n=5926). Interim analyses blinded for randomized treatment were performed to compare baseline fasting plasma glucose with the adjusted CHF event rate at a mean follow-up of 886 days. Multivariable Cox regression models were performed, and associations were reported as hazard ratios and 95% confidence intervals. Among all subjects (mean age, 67 years; 69% men), of whom 11 708 (37%) had known DM and 1006 (3.2%) had newly diagnosed DM at baseline, 668 patients were hospitalized for CHF during follow-up. After adjustment for age and sex, a 1-mmol/L-higher fasting plasma glucose was associated with a 1.10-fold-increased risk of CHF hospitalization (95% confidence interval, 1.08 to 1.12; P<0.0001). The association persisted after adjustment for age, sex, smoking, previous myocardial infarction, hypertension, waist-to-hip ratio, creatinine, DM, and use of aspirin, β-blockers, or statins (hazard ratio, 1.05; 95% confidence interval, 1.02 to 1.08; P<0.001).

Conclusions—Fasting plasma glucose is an independent predictor of hospitalization for CHF in high-risk subjects. These data provide theoretical support for potential direct beneficial effects of glucose lowering in reducing the risk of CHF and suggests the need for specific studies targeted at this issue. (Circulation. 2007;115:1371-1375.)

Key Words: cardiovascular diseases ■ clinical trials ■ glucose ■ heart failure ■ risk factors

Congestive heart failure (CHF) is a serious condition, with a 4- to 8-fold-increased risk of death compared with the general population. Patients with diabetes mellitus (DM) are at high risk of CHF, particularly in the presence of comorbid hypertension, coronary artery disease, smoking, and left ventricular hypertrophy. In such patients, high glucose levels also may increase the risk of CHF as a result of several potential mechanisms.

Growing evidence indicates that dysglycemia is a risk factor for cardiovascular (CV) disease regardless of DM status, but the relationship between the glucose levels and the risk of CHF remains poorly characterized. Recently, the Reykjavik study of a population-based cohort (n=19 381) showed strong associations between glucometabolic perturbations and prevalent CHF and incident morbidity and mortality during follow-up of an average of 21.3 years. However, the association of glucose abnormalities with the development of CHF was not assessed in that study, and there are few other reports specifically assessing the role of glycemic control and CHF. Therefore, the aim of this report was to evaluate associations of baseline fasting plasma glucose (FPG) and hospitalization for CHF events in a broad population-based cohort.
range of patients at high risk of CV disease who were free of symptomatic CHF at entry into a large-scale randomized trials program evaluating the benefits of various degrees of renin-angiotensin system blockade in the prevention of CV disease.

**Methods**

Subjects included in these analyses are from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) studies, 2 parallel randomized controlled trials, the details of which are given elsewhere. In brief, these trials were designed to determine the effects of an angiotensin receptor blocker (telmisartan) and an angiotensin-converting enzyme inhibitor (ramipril) alone and in combination (ONTARGET; n=25 620) and of telmisartan compared with placebo in patients intolerant to angiotensin-converting enzyme inhibitors (TRANSCEND; n=5926) on reducing the composite end point of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for CHF. Secondary outcomes were newly diagnosed CHF, revascularization procedures, newly diagnosed DM, development of dementia/cognitive decline, nephropathy, and new onset of atrial fibrillation. Subjects were included if they were at high risk for CV disease, defined by an age ≥55 years and a history of symptomatic CV disease or DM with evidence of major end-organ damage. Key exclusion criteria included symptomatic CHF, significant valvular disease, and uncontrolled hypertension. After a 1-month active run-in phase and randomization, subjects were followed up at 6 weeks, 3 months, 6 months, and then every 6 months thereafter for an average of 4.5 years. At baseline, FPG was collected after an overnight fast and assessed by standard routine biochemistry analyses at each local hospital site.

Hospitalization for CHF was defined as admission to hospital or attendance at an acute healthcare facility for administration of inotropic or diuretic treatment, escalation of diuretic doses, and/or inotropes. All events were reviewed by an independent adjudication committee.

**Statistical Analysis**

These 2 studies make up a large cohort with a high number of accumulated events (2882 primary). Baseline FPG levels were related to the incident CV disease event rates using data blinded to randomized allocation of treatment. Subjects were categorized using available criteria into groups based on FPG and DM status: low normal (FPG <5.0 mmol/L), the median of subjects without impaired FPG; high normal (FPG ≥5.0 mmol/L), impaired fasting glucose (FPG, 5.6 to 6.9 mmol/L), new DM (FPG ≥7.0 mmol/L), or previously diagnosed DM. Multivariable analyses with 3 Cox regression models were used to explore associations between FPG levels and the rate of hospitalization for CHF and, to account for competing risks also, the composite of hospitalization for CHF/CV death. These models adjusted for age and sex; age, sex, smoking, previous MI, DM status, hypertension, and use of medication (aspirin, β-blockers, and statins); and all factors in the previous model plus creatinine and waist-to-hip ratio. Continuous variables are expressed as mean ± SD and categorical variables as number (percent). Data are reported as the estimated hazard ratios (HRs) and 95% confidence intervals (CIs) (with a value of P <0.05 considered statistically significant). All data were analyzed with the Statistical Analysis Software, version 8.2 (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Table 1 shows the baseline characteristics for all subjects and by groups based on FPG levels. Among this predominantly middle-aged high-risk group, most had experienced ≥1 prior coronary (MI, stable angina, previous revascularization procedure), peripheral (intermittent claudication or peripheral artery surgery/angioplasty), or cerebrovascular event. Three patients without DM were on metformin for other reasons but did not fulfill the criteria for DM. More than a third (n=11 708) had known type 2 DM, and 3.2% (1006) had newly diagnosed DM on the basis of an FPG of ≥7.0 mmol/L at entry into one of the trials. All groups had creatinine levels within normal limits.

CV risk factors were evenly distributed over the 5 groups, except for hypertension, which was more common in the DM group. Overall, patients with DM had less previous CV disease in terms of MI, stable/unstable angina, and previous coronary revascularization because a proportion of these people were included on the basis of only the primary criteria of DM with end-organ damage. Most subjects were on optimal concomitant medications for secondary prevention of CV disease with frequent use of β-blockers, aspirin, angiotensin-converting enzyme inhibitors, and statins. However, patients with known DM were less frequently treated with aspirin, β-blockers, and statins.

During a mean follow-up of 886 days, there were 2882 primary events (1067 CV deaths, 926 MI, 823 strokes, and 668 hospitalizations for CHF).

**Classes of Dysglycemia and Risk of CHF Hospitalization**

As noted in the Figure, higher categories of dysglycemia predicted a higher incidence of CHF hospitalization (log-rank P <0.001). Compared with people with low FPG (<5.0 mmol/L), the HR of CHF hospitalization rose from 1.09 (95% CI, 0.8 to 1.50) to 2.56 (95% CI, 1.98 to 3.31) with progressively higher categories of dysglycemia in the regression models that adjusted for age and sex (model 1) and for multiple other CHF risk factors (models 2 and 3; Table 2; P for trend <0.0001).

**FPG and Risk of CHF Hospitalization**

When baseline FPG was analyzed as a continuous variable, a 1-mmol/L rise in FPG predicted a 1.10-fold-increased risk of incident CHF hospitalization (95% CI, 1.08 to 1.12; P <0.0001). This association was attenuated but remained significant even after adjustment for DM status and other CV risk factors (Table 3; P <0.001). The association between FPG and hospitalization for CHF was present both among those with known or newly diagnosed DM and in those without DM (P for interaction =0.23). In patients without known DM, the HR was 1.23 (95% CI, 1.03 to 1.47) in models 1 and 2 and was slightly attenuated in model 3. In patients with known DM, the HR was 1.04 (95% CI, 1.01 to 1.07; P <0.01) in all 3 models (Table 3).

**FPG and Risk of CHF Hospitalization/CV Death**

For each increment of 1 mmol/L glucose, the HR for the combined end point of hospitalization for CHF/CV death in all patients was 1.09 (95% CI, 1.07 to 1.10; P <0.001) in model 1 (Table 3). The results remained unchanged in models 2 and 3. The association between FPG and the risk of hospitalization for CHF/CV death was present among both
patients with (HR, 1.05; 95% CI, 1.03 to 1.07) and without (HR, 1.03; 95% CI, 0.93 to 1.15) known DM in the fully adjusted model (P for interaction/H11005 0.66; Table 3).

**Discussion**

In this large, prospective, 2.4-year follow-up of a cohort of people at high risk of CV disease with and without a history of DM, the FPG was a modest but significant independent risk factor for incident CHF hospitalization and the combined end point of CHF/CV death. Moreover, these associations persisted after adjustment for DM status, and the absence of a significant interaction between patients with and without known DM suggests that the degree of dysglycemia, and not the diagnosis of DM per se, is the key determinant of the relationship. These findings for CHF are consistent with a previous study that showed that an abnormal response of the 2-hour glucose value on the standard oral glucose tolerance test was an independent predictor of CHF in a prospective population-based cohort of elderly men.14 Our data also are consistent with accumulating evidence showing that elevated glucose is a progressive risk factor for CV disease outcomes even with levels below the threshold for a diagnosis of DM15,16 and that an elevated FPG is associated with higher mortality in healthy subjects11 and in those with established CHF without known DM.17 Finally, we believe our results extend previous knowledge about the utility of FPG as a risk factor for CHF in people at high risk of CV disease but without known DM.

**Potential Mechanisms**

Several potential explanations exist for the observed relationship between FPG and CHF. First, people with glucose
intolerance have a higher left ventricular mass and wall thickness than people who are normoglycemic, possibly because of the formation of advanced glycosylation end products in the myocardium, leading to myocardial stiffness. These are well-known risk factors and possibly key components of the development of overt CHF. Second, the previously described relationship between dysglycemia and CV disease risk suggests that individuals with higher FPG levels have more underlying coronary artery disease. Hyperglycemia may have unfavorable effects on the heart by inducing inflammation, modulating nitric oxide metabolism, and increasing oxidative stress, factors that are involved in the development of atherosclerosis and therefore later lead to greater damage to and dysfunction of the myocardium. Third, high FPG levels have been shown to induce activation of signaling involved in endothelial apoptosis. Fourth, hyperglycemic individuals are hyperinsulinemic, and the high insulin levels may promote increased ventricular mass and decreased cardiac output. Fifth, hyperglycemic individuals also are insulin resistant, which is an independent predictor of incident CHF after accounting for diabetes or obesity. Finally, activation of the sympathetic nervous system, either by the high insulin level or possibly secondary to glucose-induced diuresis, may promote CHF.

Despite its large sample size and acceptable power, this analysis has some limitations. Because this is an ongoing randomized trials program, we cannot fully exclude the possibility that the randomized treatment may have had an impact on outcome. Furthermore, factors such as blood pressure and glucose control and information on time since the diagnosis of DM were not available. Left ventricular function is a major determinant of the development of CHF, and information on this parameter was not required at study entry. Data on left ventricular function were collected at randomization as a recall of information during the last 12 months and were limited to a subgroup of patients.

The present study represents a large and unique cohort with a relatively long period of follow-up and a large number of CHF events, thus providing a suitable setting and high statistical power to explore the significance of glucose on the development of CHF. Although we have shown that FPG independently predicts hospitalization for CHF, whether glucose lowering reduces the risk of CHF requires study in prospective, randomized studies designed specifically for this purpose.

**Sources of Funding**
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<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Normal (≤median) (n=5136)</th>
<th>Normal (&gt;median) (n=6298)</th>
<th>IFG (n=6650)</th>
<th>New DM (n=1006)</th>
<th>DM (n=11708)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1* HR (95% CI)</td>
<td>1.00</td>
<td>1.09 (0.80–1.40)</td>
<td>1.33 (0.99–1.79)</td>
<td>1.88 (1.18–2.99)</td>
<td>2.56 (1.98–3.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2† HR (95% CI)</td>
<td>1.00</td>
<td>1.10 (0.81–1.51)</td>
<td>1.31 (0.97–1.77)</td>
<td>1.83 (1.15–2.92)</td>
<td>2.79 (2.15–3.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 3‡ HR (95% CI)</td>
<td>1.00</td>
<td>1.07 (0.78–1.46)</td>
<td>1.24 (0.92–1.68)</td>
<td>1.74 (1.09–2.76)</td>
<td>2.59 (1.99–3.36)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Low normal, FPG <5.0 mmol/L; high normal, 5.0 mmol/L>FPG<5.6 mmol/L; impaired fasting glucose (IFG), FPG, 5.6 to 6.9 mmol/L; new DM or previously diagnosed DM, FPG >7.0 mmol/L.

Adjustments as follows: *for age and sex; †for age, sex, smoking, previous MI, hypertension, aspirin, β-blockers, and statins; and ‡for age, sex, smoking, previous MI, hypertension, creatinine, waist-to-hip ratio, aspirin, β-blockers, and statins.
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Disclosures

Dr Gerstein has received a research grant for studies on insulin to reduce cardiovascular events and is a consultant for Sanofi-Aventis. The other authors report no conflicts.

References

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