Enalapril Reduces the Incidence of Diabetes in Patients With Chronic Heart Failure

Insight From the Studies Of Left Ventricular Dysfunction (SOLVD)

Emmanuelle Vermes, MD; Anique Ducharme, MD, MSc; Martial G. Bourassa, MD; Myriam Lessard; Michel White, MD; Jean-Claude Tardif, MD

Background—Diabetes mellitus is a predictor of morbidity and mortality in patients with heart failure. The effect of angiotensin-converting enzyme (ACE) inhibitors on the prevention of diabetes in patients with left ventricular dysfunction is unknown. The aim of this retrospective study was to assess the effect of the ACE inhibitor enalapril on the incidence of diabetes in the group of patients from the Montreal Heart Institute enrolled in the Studies of Left Ventricular Dysfunction (SOLVD).

Methods and Results—Clinical charts were evaluated for fasting plasma glucose (FPG) levels by blinded reviewers. A diagnosis of diabetes was made when a FPG ≥126 mg/dL (7 mmol/L) was found at 2 visits (follow-up, 2.9±1.0 years). Of the 391 patients enrolled at the Montreal Heart Institute, 291 were not diabetic (FPG <126 mg/dL without a history of diabetes), 153 of these were on enalapril and 138 were on placebo. Baseline characteristics were similar in the 2 groups. Forty patients developed diabetes during follow-up, 9 (5.9%) in the enalapril group and 31 (22.4%) in the placebo group (P<0.0001). By multivariate analysis, enalapril remained the most powerful predictor for risk reduction of developing diabetes (hazard ratio, 0.22; 95% confidence intervals, 0.10 to 0.46; P<0.0001). The effect of enalapril was striking in the subgroup of patients with impaired FPG (110 mg/dL [6.1 mmol/L] ≤ FPG <126 mg/dL) at baseline: 1 patient (3.3%) in the enalapril group versus 12 (48.0%) in the placebo group developed diabetes (P<0.0001).

Conclusions—Enalapril significantly reduces the incidence of diabetes in patients with left ventricular dysfunction, especially those with impaired FPG. (Circulation. 2003;107:1291-1296.)

Key Words: angiotensin inhibitors ■ diabetes mellitus ■ heart failure

Diabetes mellitus is a common comorbidity in patients with heart failure; it is present at baseline in 20% to 25% of the subjects enrolled in large randomized clinical trials.1–3 Furthermore, the presence of diabetes is an independent predictor of morbidity and mortality in these patients,4,5 almost doubling their incidence of death or hospitalization for cardiovascular reasons.5 Angiotensin-converting enzyme (ACE) inhibitors reduce mortality and the need for hospitalization and improve functional status in a wide array of heart failure patients (New York Heart Association class I to IV).2,6 In diabetic patients, ACE inhibitors prevent the development and progression of incipient or established nephropathy7,8 and delay the progression of diabetic retinopathy.9 Recently, the ACE inhibitor ramipril was demonstrated to reduce death, cardiovascular events (myocardial infarction and stroke), progression of diabetic nephropathy, and even the number of new cases of diabetes in high risk patients.10,11 However, there are no available data on the impact of long-term ACE inhibitor therapy on the incidence of diabetes in a cohort of patients with left ventricular dysfunction. Thus, to evaluate the effect of ACE inhibition on the development of diabetes in a heart failure population, we conducted a retrospective analysis of the Montreal Heart Institute patients who have been enrolled in the SOLVD trials (Studies Of Left Ventricular Dysfunction). The objective of the study was to assess the impact of the ACE inhibitor enalapril on the development of diabetes in patients with left ventricular dysfunction.

Methods

Study Population

The patients from the Montreal Heart Institute who were randomized in the SOLVD trials were included in this study. SOLVD was a multicenter, double-blind, randomized, placebo-controlled trial that assessed the effect of the ACE inhibitor enalapril on survival in patients with left ventricular dysfunction (ejection fraction ≤35%). The details of the trial have been described elsewhere.12 Briefly, the prevention trial included 4228 patients with asymptomatic left ventricular dysfunction, and the treatment trial randomized 2569 patients with congestive heart failure from June 1986 to August 1991. Patients were randomized to enalapril (5 to 20 mg/d) or placebo. Exclusion criteria included age >80 years, unstable angina pectoris, myocardial infarction in the previous month, severe pulmo-
nary disease, renal insufficiency (creatinine level >177 μmol/L [2 mg/dL]), and intolerance to ACE inhibitor or current ACE inhibitor use. Follow-up visits were scheduled 2 and 6 weeks after randomization and every 4 months until the end of the study, for a mean follow-up of 3.4 and 3.1 years for the treatment and prevention trials, respectively.

Data Collection and Definitions
Baseline characteristics, past medical history, and medication profiles at the time of enrollment into the SOLVD trials were obtained from the SOLVD databases. Fasting plasma glucose (FPG) was not collected for research purposes in the SOLVD trials. However, the follow-up of our patients in SOLVD involved regular blood samples, including FPG, at almost every research visit. Accordingly, the medical file of each patient was reviewed, and FPG results were collected. Chart reviewers were blinded to treatment allocation.

A diagnosis of new onset diabetes during the follow-up period was defined according to the American Diabetes Association criteria as a FPG ≥126 mg/dL (7.0 mmol/L) at 2 different visits. For the purpose of the present study, we did not include the visits in which FPG ≥126 mg/dL occurred during infection, trauma, or acute myocardial infarction. Participants with diabetes at baseline (history of diabetes or FPG ≥126 mg/dL at screening visit) were excluded. We further divided our study population among patients with impaired FPG at baseline (110 mg/dL [6.1 mmol/L] ≤FPG <126 mg/dL [7.0 mmol/L]) and those with normal FPG at baseline (FPG <110 mg/dL).

Statistical Analysis
The baseline characteristics of the 2 groups were compared using Student’ s t test for continuous variables and the χ² test for categorical variables. Incidence of diabetes in the 2 groups was compared with the χ² test. Time to occurrence of diabetes during the follow-up was analyzed with Kaplan-Meier curves and compared with the log-rank test. To analyze the effect of the treatment (enalapril) on development of diabetes, a Cox regression analysis was used to take into account the effect of potential confounding baseline variables (age, sex, current smoking, history of hypertension, and weight) and time-dependent variables (systolic blood pressure; diastolic blood pressure; and use of β-blockers, diuretics, calcium-channel blockers, antiplatelet agents, or antiarrhythmics). Cox proportional-hazard models were performed for each variable, with treatment (enalapril) forced in all models. Variables with a P=0.2 were included in a multivariate Cox proportional hazard model. For time-dependent variables, the last value before the occurrence of diabetes was taken; if the patient did not develop diabetes, the value at the last visit was taken.

Subgroup analyses were conducted with the χ² test. In the particular subgroup of patients with impaired FPG at baseline, Kaplan-Meier curves were performed. Preliminary assumptions were verified before all analyses. P<0.05 was considered significant. All analyses were performed using SAS version 8.2 (SAS Institute, Inc).

Results
Study Population
Among the 391 patients from the Montreal Heart Institute who were randomized in SOLVD (prevention and treatment arms), 80 had a diagnosis of diabetes at randomization and 20 had insufficient data regarding FPG. The remaining 291 patients constituted our study population: 198 were in the prevention arm and 93 were in the treatment arm. Of these 291 patients, 153 were randomized to enalapril and 138 to placebo. The mean follow-up of our patients was 2.9±1.0 years (range, 0.2 to 4.8 years). FPG samples were collected at almost every research visit (mean of 7.9±3.5 samples per patient) during the study follow-up.

Baseline Characteristics
The baseline characteristics of the 291 patients were well balanced between the 2 groups and are provided in Table 1. Most patients were men with NYHA class II symptoms and severe systolic dysfunction (mean ejection fraction of 26%) of ischemic cause. Approximately 20% of patients were receiving a β-blocker and 45% were treated with diuretics.

Development of Diabetes
Forty patients met the criteria for new-onset diabetes during the follow-up period, 9 (5.9%) in the enalapril group and 31 (22.4%) in the placebo group (relative risk [RR], 0.26; 0.0001). This represents an absolute risk reduction of 16.5%. During the follow-up, the probability of remaining free from diabetes was significantly higher with enalapril than with placebo (P<0.0001; Figure 1). By multivariate analysis using a Cox regression model (Table 2), enalapril treatment remained the most powerful variable associated with a decreased risk of developing diabetes (hazard ratio, 0.22; 95% confidence intervals, 0.10 to 0.46; P<0.0001). Age was the only other variable remaining in the model that was significantly related to the development of diabetes.

### Table 1. Baseline Patient Characteristics in the 2 Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Enalapril (n=153)</th>
<th>Placebo (n=138)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.1±10.1</td>
<td>56.8±10.0</td>
<td>0.581</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>90.9</td>
<td>93.5</td>
<td>0.406</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.9±10.7</td>
<td>76.0±12.0</td>
<td>0.510</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127.4±17.3</td>
<td>128.2±16.7</td>
<td>0.708</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.8±8.6</td>
<td>79.7±8.4</td>
<td>0.057</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74.5±10.2</td>
<td>75.0±11.0</td>
<td>0.741</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
<td></td>
<td>0.778</td>
</tr>
<tr>
<td>I</td>
<td>28.8</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>66.0</td>
<td>62.3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5.2</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>43.9</td>
<td>39.2</td>
<td>0.440</td>
</tr>
<tr>
<td>Past history, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>19.0</td>
<td>17.4</td>
<td>0.730</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>7.2</td>
<td>9.4</td>
<td>0.489</td>
</tr>
<tr>
<td>Previous MI</td>
<td>91.5</td>
<td>85.5</td>
<td>0.107</td>
</tr>
<tr>
<td>Primary cause of LV dysfunction, %</td>
<td></td>
<td></td>
<td>0.388</td>
</tr>
<tr>
<td>Ischemic</td>
<td>92.2</td>
<td>91.3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7.8</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>26.0±7.0</td>
<td>26.5±6.5</td>
<td>0.555</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.0±0.2</td>
<td>1.0±0.2</td>
<td>0.727</td>
</tr>
<tr>
<td>Drug therapy, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>45.8</td>
<td>42.8</td>
<td>0.607</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>18.3</td>
<td>21.7</td>
<td>0.463</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>37.9</td>
<td>45.9</td>
<td>0.266</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>43.8</td>
<td>37.7</td>
<td>0.289</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td>9.8</td>
<td>12.3</td>
<td>0.493</td>
</tr>
</tbody>
</table>

Data are presented as the mean±SD or percentages of patients. NYHA indicates New York heart association; MI, myocardial infarction; and LV, left ventricular.
We also examined the effect of enalapril in a subgroup of patients known to be at high risk for diabetes, ie, those with impaired FPG at baseline. Only 1 patient developed diabetes in the enalapril group compared with 12 patients in the placebo group, which represents an absolute risk reduction of 45% (Table 3). Kaplan-Meier curves for time to occurrence of diabetes in this subgroup of patients are shown in Figure 2. We further stratified the analysis according to baseline functional status by analyzing the effect of enalapril in the 2 arms of the trial (prevention and treatment). The beneficial effect of enalapril on the development of diabetes was significant, regardless of functional status at baseline (Table 3).

**Discussion**

We showed that, in nondiabetic patients with left ventricular systolic dysfunction, the ACE inhibitor enalapril markedly reduced the risk of developing diabetes. Although retrospective, our study deserves attention for several reasons. First, the baseline characteristics, including medications, were well balanced between the 2 groups. Second, even if these results are derived from a study that was published >10 years ago, the findings are still very relevant to current clinical practice. This is particularly true because the standard heart failure treatment now includes β-blockers, a class of drug that lowers mortality when combined with ACE inhibitors but seems to increase the risk of diabetes (perhaps except for carvedilol, which has been shown to have a favorable effect on insulin sensitivity compared with metoprolol). Furthermore, the prognosis of heart failure is worse when it is associated with diabetes.

Our study extends the beneficial effects of ACE inhibitors on the prevention of diabetes to all patients with left ventricular systolic dysfunction, whether symptomatic or not. Patients with impaired FPG were particularly likely to benefit. Other randomized trials, including CAPP (Captopril Prevention Project), have demonstrated a reduction in the relative risk of developing diabetes (RR=0.86; P=0.039) when an hypertensive population was treated with captopril compared...
with a \( \beta \)-blocker or a diuretic.\(^\text{16}\) Similar results were obtained in the LIFE (Losartan Intervention For Endpoint) trial,\(^\text{17}\) in which losartan was compared with atenolol in patients with hypertension (6% developed diabetes in the losartan group versus 8% with atenolol; \( \text{RR} = 0.75; P = 0.001 \)). Of note, 2 different levels of serum glucose were used to diagnose diabetes as the criteria evolved during that study.

Also, a nonsignificant 20% relative reduction in the incidence of diabetes was found in the recently presented Study on COgnition and Prognosis in the Elderly (SCOPE) when candesartan was compared with placebo (L. Hansson, MD, University of Uppsala, Sweden, unpublished data, 2002); however, \( \beta \)-blockers were used more frequently in the placebo group than in the candesartan group. From these studies, it cannot be concluded whether these findings were the result of a beneficial effect of captopril, losartan, or candesartan or a detrimental effect of \( \beta \)-blockers on diabetes. The Heart Outcomes Prevention Evaluation (HOPE) study has demonstrated a reduction in the number of new cases of diabetes with ramipril.\(^\text{11}\) Although the development of diabetes was not a predetermined end point in HOPE, Yusuf et al\(^\text{11}\) have shown, with a treatment period of 4.5 years, that ramipril reduced the relative risk of developing diabetes by 34% (3.6% in ramipril group versus 5.4% in placebo group; \( \text{RR} = 0.66; P < 0.001 \)) in a cohort of high-risk patients with no evidence of left ventricular dysfunction. The incidence of diabetes observed in the placebo group of our study (22.4%) is much higher than in that of the HOPE study (5.4%).

This can be explained by many factors, including the fact that we used a strict biochemical definition of diabetes (with FPG level), whereas the diagnosis in HOPE was based on the patients' self-report of newly diagnosed diabetes, thus resulting in an underestimation of the true incidence in that trial. Second, the severity of the underlying disease (established left ventricular dysfunction in SOLVD) may also contribute to the difference in incidence in these trials. Indeed, the neurohormonal activation encountered in heart failure can both increase peripheral insulin resistance and decrease insulin secretion, thus leading to impaired glucose handling,\(^\text{19}\) which favors the development of diabetes.\(^\text{19}\) The difference in the incidence of diabetes between both trials is even more striking considering that the follow-up was much longer in HOPE than in our study (4.5 years versus 2.9 years).

The mechanisms by which ACE inhibition exerts its protective effect against diabetes are not completely understood. ACE inhibitors not only block the conversion of

<table>
<thead>
<tr>
<th>Baseline FPG</th>
<th>Enalapril, ( n (%) )</th>
<th>Placebo, ( n (%) )</th>
<th>Absolute Risk Reduction, %</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG (( n = 55 ))</td>
<td>1(3.3)</td>
<td>12(48.0)</td>
<td>44.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>NFG (( n = 236 ))</td>
<td>8(6.6)</td>
<td>19(7.3)</td>
<td>10.7</td>
<td>0.011</td>
</tr>
<tr>
<td>Arm of the trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention (( n = 198 ))</td>
<td>6(6.0)</td>
<td>19(19.4)</td>
<td>13.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Treatment (( n = 93 ))</td>
<td>3(5.7)</td>
<td>12(30.0)</td>
<td>24.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Total population (( n = 291 ))</td>
<td>9(5.9)</td>
<td>31(22.4)</td>
<td>16.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

IFG indicates impaired FPG; NFG, normal FPG.

Figure 2. Kaplan-Meier curves for the time to occurrence of diabetes in the subgroup of 55 patients with impaired FPG at baseline in the enalapril (solid line) and placebo (dotted line) groups (\( P < 0.0001 \)).
angiotensin I to angiotensin II, but also increase bradykinin levels through inhibition of kininase II-mediated degradation.20,21 In hypertensive rats, Tomiyama and coworkers22 have shown improved insulin sensitivity with enalapril through an increase in endogenous kinins. The higher kinin levels lead to increased production of prostaglandins (PGE, and PGE₂) and nitric oxide, which improve muscle sensitivity to insulin23–25 and exercise-induced glucose metabolism,26 resulting in enhanced insulin-mediated glucose uptake. Furthermore, the peripheral vasodilatory actions of ACE inhibitors (through diverse mechanisms, including prostaglandin and nitric oxide) lead to an improvement in skeletal muscle blood flow, the primary target for insulin action and an important determinant of glucose uptake.27 Clinical evidence supporting this effect has been provided by Morel and coworkers,28 who have shown improved insulin sensitivity when enalapril was given for 12 weeks to 14 obese, hypertensive, and dyslipidemic patients. A similar effect has also been reported with captopril.29 Finally, ACE inhibitors inhibit the vasoconstrictive effect of angiotensin II in the pancreas and increases islet blood flow,30 which could improve insulin release by β-cells. These experimental and clinical studies all support our findings and suggest that ACE inhibition increases insulin sensitivity, skeletal muscle glucose transport, and pancreatic blood flow, which probably all contribute to the prevention of diabetes mellitus.

Clinical Implications
Diabetes mellitus is a major risk factor for cardiovascular events, increasing morbidity and mortality in heart failure patients. The lower incidence of diabetes found in heart failure patients treated with the ACE inhibitor enalapril should lead to improved long-term cardiovascular prognosis in this population. Because β-blockers seem to increase the risk of hyperglycemia and subsequent diabetes, combined therapy with an ACE inhibitor could attenuate this adverse effect of β-blockade. With an absolute risk reduction of 16.5% with enalapril in the present study, it is necessary to treat 6 patients with left ventricular dysfunction for 2.9 years to prevent one new case of diabetes.

Limitations
The present analysis was not a prespecified end point of the SOLVD trials, and FPG levels were not measured as an integral part of the trials. Nevertheless, FPG samples were measured serially for clinical purposes, and their results were carefully reviewed. Our results reflect the true incidence of diabetes in patients with left ventricular dysfunction, using strict and modern diagnosis criteria of diabetes. Our findings will nevertheless require confirmation from prospectively designed studies that will measure not only FPG but also glucose intolerance. Also, lipid profiles were not collected prospectively and thus could not be included in the multivariate analysis.

Conclusion
The ACE inhibitor enalapril markedly reduces the risk of developing diabetes mellitus in patients with left ventricular dysfunction. This beneficial effect is even more striking in patients with impaired FPG.

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