Effects of Candesartan on the Development of a New Diagnosis of Diabetes Mellitus in Patients With Heart Failure

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Background—Diabetes is a risk factor for heart failure, and both conditions are increasing. Identifying treatments that prevent both conditions will be clinically important. We previously reported that candesartan (an angiotensin receptor blocker) reduces cardiovascular mortality and heart failure hospitalizations in heart failure patients (CHARM: Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity Program).

Methods and Results—We assessed the impact of candesartan versus placebo on the development of diabetes, a predefined secondary outcome in a randomized, controlled, double-blind study involving 5436 of the 7601 patients with heart failure, irrespective of ejection fraction, who did not have a diagnosis of diabetes at entry into the trial. Patients received candesartan (target of 32 mg once daily) or matching placebo for 2 to 4 years. One hundred sixty-three (6.0%) individuals in the candesartan group developed diabetes, as compared with 202 (7.4%) in the placebo group (hazard ratio [HR], 0.78 with a 95% confidence interval [CI] of 0.64 to 0.96; P=0.020). The composite end point of death or diabetes occurred in 692 (25.2%) and 779 (28.6%), respectively, in the candesartan and placebo groups (HR, 0.86; 95% CI, 0.78 to 0.95; P=0.004). The results were not statistically heterogeneous in the various subgroups examined, although the apparent magnitude of benefit appeared to be smaller among those treated concomitantly with angiotensin-converting enzyme inhibitors at trial entry (HR, 0.88; 95% CI, 0.65 to 1.20) compared with those not receiving these drugs (HR, 0.71; 95% CI, 0.53 to 0.93; P for heterogeneity, 0.28).

Conclusions—The angiotensin receptor blocker candesartan appears to prevent diabetes in heart failure patients, suggesting that the renin-angiotensin axis is implicated in glucose regulation. (Circulation. 2005;112:48-53.)

Key Words: renin ■ diabetes mellitus ■ prevention ■ heart failure ■ glucose

Type 2 diabetes mellitus (DM) is an important and common risk factor for the development of heart failure and for subsequent prognosis. This could be related to the established link between diabetes and either left ventricular hypertrophy, coronary artery disease, or other risk factors (eg, hypertension or obesity) with heart failure. Both DM and heart failure are increasing and are associated with high rates of mortality and morbidity compared with unaffected individuals. Both conditions lead to substantial economic costs to society. Preventing DM may prevent or delay the development of many of its complications (eg, atherosclerotic vascular disease or renal dysfunction). Recent evidence suggests that lifestyle modification by weight loss and some glucose-lowering drugs (eg, metformin or acarbose) can reduce the risk of DM in high-risk individuals. A complementary approach may be to prevent DM by blocking the renin-angiotensin-aldosterone system. Recent retrospective analysis of the HOPE (Heart Outcomes Prevention Evaluation) and ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) and data from a single center in the SOLVD (Studies of Left Ventricular Dysfunction) trials suggest that angiotensin-converting enzyme (ACE) inhibitors (ramipril and enalapril, respectively) may reduce the risk of DM in individuals with atherosclerosis or heart failure. Data from the LIFE (Losartan Intervention for End-point Reduction) study suggest that losartan, an angiotensin receptor blocker (ARB), may reduce the risk of new DM compared with atenolol, a β-adrenergic blocker, in patients with hypertension and left ventricular hypertrophy. However, it is unclear whether this difference was caused by a lower rate of DM with losartan or an increased rate of DM with atenolol. That angiotensin type 1 receptor blockade has
A real effect in preventing DM is suggested by recent findings from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE), in which valsartan significantly reduced the new incidence of DM in comparison with amlodipine, a drug that is considered to be metabolically neutral.

In the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Program, we prospectively specified that we would perform a secondary analysis of the effects of candesartan compared with placebo with respect to preventing the development of DM (and of DM plus all-cause mortality) in a broad range of patients with heart failure.

**Methods**

Detailed descriptions of the methods and results of the CHARM program have been published previously. In brief, the CHARM program consisted of 3 parallel trials involving complementary populations of patients with symptomatic heart failure. Those with a low ejection fraction (<0.40) and with prior intolerance to an ACE inhibitor were included in the CHARM Alternative trial, and those receiving an ACE inhibitor were included in the CHARM Added trial. Those with an ejection fraction ≥0.40 and heart failure were enrolled into the CHARM Preserved trial (whether or not they were receiving an ACE inhibitor). Overall, 7601 patients were randomized, of whom 2163 were known to have DM as reported by the investigators at randomization, and 5436 were not known to have DM at baseline (Figure 1). This latter group of patients forms the basis for this report. Patients were randomized to receive either candesartan (n=2715) or placebo (n=2721). 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 up at 2, 4, and 6 weeks; 6 months; and then every 4 months until the study end. The investigators were asked to report the occurrence of a new diagnosis of DM for all patients at the end of the trial. If a diagnosis of DM was reported after randomization, the date of diagnosis, details of the criteria used (fasting plasma glucose ≥7 mmol/L [126 mg/dL], fasting blood glucose ≥6.1 mmol/L [110 mg/dL], 2-hour [oral glucose tolerance test] or a random glucose ≥11.1 mmol/L [200 mg/dL]), hypoglycemic medication prescribed, and lifestyle modifications prescribed were recorded on the case record forms. The planned minimum follow-up was 2 years with a maximum of 4 years, with the median being 3.1 years. At baseline and throughout the study, physicians were free to prescribe various treatments, including other cardiovascular drugs (other than ARBs) or glucose-lowering drugs.

The prespecified outcomes for this report were the development of DM alone or as a composite with all-cause mortality (to avoid the problem of competing risk). All analyses were based on an intention-to-treat approach with the Wald statistic in a Cox proportional-hazards model and displayed by Kaplan-Meier plots according to treatment allocation. The hazard ratios (HRs) and 95% confidence intervals (CIs) comparing treatments, stratified by trial, were calculated for the overall data. The results in a few key subgroups are also presented, along with the tests of heterogeneity based on the Cox regression model to evaluate whether the effects of candesartan varied in the subgroups. All patients provided written, informed consent, and the protocol was approved by the ethics committee at each participating institution.

**Results**

The characteristics of the 5436 patients who were not known to have DM at baseline are provided in Table 1 and were well balanced between the groups allocated to candesartan or placebo. Of note, 68% of patients had a body mass index ≥25 kg/m², 50% were hypertensive, 55% were taking β-blockers, 80% were taking diuretics, and 39% were receiving ACE inhibitors.
The proportion of patients receiving the study drug at 14 months was 86.0% and 89.5% and at 26 months, was 82.4% and 86.7% in the active and placebo groups, respectively. Of those taking the study medication, the mean dose used at the last visit was 24.5 mg/d in the candesartan group and 28.0 mg in the placebo group.

Overall, there were 163 (6.0%) individuals who reported a new diagnosis of DM in the candesartan group compared with 202 (7.4%) in the placebo group (HR, 0.78; 95% CI, 0.64 to 0.96; \( P = 0.020 \)) (Figure 2). The composite of new DM or death occurred in 692 (25.2%) patients in the candesartan group compared with 779 (28.6%) in the placebo group (HR, 0.86; 95% CI, 0.78 to 0.95; \( P = 0.004 \)). The difference in new DM was most marked in patients with preserved ejection fraction, with a favorable trend in the Alternative trial (wherein candesartan was compared with placebo in the absence of an ACE inhibitor) and little apparent benefit in the Added trial (wherein candesartan or placebo was added to an ACE inhibitor). However, the 95% CIs of these estimates overlap, and there was no statistically significant heterogeneity. Examining the results on the composite of death or development of DM in various subgroups also provided no evidence of statistical heterogeneity across the 3 component trials (Figures 3 and 4).

### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Candesartan (n=2715)</th>
<th>Placebo (n=2721)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>66±11</td>
<td>66±12</td>
</tr>
<tr>
<td>Age &gt;75 years, %</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Male, %</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>White, %</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Previous smokers, %</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>&lt;25, %</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>≥25 to &lt;30, %</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>≥30, %</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130±19</td>
<td>131±19</td>
</tr>
</tbody>
</table>

NYHA class, %

- II: 48 (23%)
- III/IV: 52 (29%)

Hypertension, %

- 50 (29%)

Previous myocardial infarction, %

- 48 (28%)

Baseline medication, %

- Any diuretic: 80 (47%)
- Thiazide diuretic: 12 (7%)
- \( \beta \)-Blocker: 54 (31%)
- ACE inhibitor: 39 (23%)

BMI indicates body mass index.

Proportions are in percent or mean±SD.

DM was most marked in patients with preserved ejection fraction, with a favorable trend in the Alternative trial (wherein candesartan was compared with placebo in the absence of an ACE inhibitor) and little apparent benefit in the Added trial (wherein candesartan or placebo was added to an ACE inhibitor). However, the 95% CIs of these estimates overlap, and there was no statistically significant heterogeneity. Examining the results on the composite of death or development of DM in various subgroups also provided no evidence of statistical heterogeneity across the 3 component trials (Figures 3 and 4).

**Figure 2.** Effects of candesartan compared with placebo on incidence of DM.

**Figure 3.** Results of candesartan in various subgroups. BMI indicates body mass index; MI, myocardial infarction; low., low-;

**Figure 4.** Results in each of 3 component trials.
TABLE 2. Previous Studies Evaluating ACE Inhibitors and ARBs on Development of Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE5</td>
<td>0.66 (0.51–0.85)</td>
</tr>
<tr>
<td>CAPP20</td>
<td>0.79 (0.67–0.94)</td>
</tr>
<tr>
<td>SOLVD7</td>
<td>0.22 (0.10–0.46)</td>
</tr>
<tr>
<td>ALLHAT6</td>
<td>0.83 (0.66–1.04)</td>
</tr>
<tr>
<td>ARBs</td>
<td>0.70 (0.57–0.86)</td>
</tr>
<tr>
<td>LIFE3</td>
<td>0.75 (0.63–0.88)</td>
</tr>
<tr>
<td>SCOPE27</td>
<td>0.80 (0.62–1.03)</td>
</tr>
<tr>
<td>ALPINE28</td>
<td>0.13 (0.02–0.99)</td>
</tr>
<tr>
<td>VALUE9</td>
<td>0.77 (0.69–0.86)</td>
</tr>
</tbody>
</table>

*Based on data from only 1 center of 23 in the trial and thus may be open to biases.
†Comparator could be diabetogenic.

Results by Diagnostic Criteria and Hypoglycemic Treatment

DM was diagnosed by the patient’s physician on the basis of a fasting glucose sample in 130 patients allocated to placebo compared with 112 in the candesartan group and by an oral glucose tolerance test in 25 placebo patients compared with 21 candesartan patients. No criteria for the diagnosis of DM were specified on the case report forms provided for 47 placebo patients and 30 candesartan patients. DM was treated with insulin or an oral hypoglycemic drug in 151 placebo patients compared with 117 candesartan patients and with dietary modification alone in 51 placebo patients and 45 candesartan patients. In 1 patient with candesartan treatment, information on treatment for DM was missing.

Subgroups

The benefits of candesartan in preventing DM were seen in those with a high or low body mass index and in those receiving or not receiving β-blockers or diuretics (Figures 3 and 4). Similar benefits were observed in those in New York Heart Association (NYHA) classes II and III. Although the magnitude of benefit appeared to be smaller in those receiving a concomitant ACE inhibitor (HR, 0.88; 95% CI, 0.65 to 1.20) compared with those not on it (HR, 0.71; 95% CI, 0.53 to 0.65), these differences were not heterogeneous from each other (P for interaction, 0.28). The effect was most marked in patients with left ventricular ejection fractions >40% (the CHARM Preserved trial), but there was no significant heterogeneity in effect between the trials in the program (P for heterogeneity, 0.14).

Impact of Postrandomization Differences in Drugs

There was a higher proportion of patients in the placebo group receiving a diuretic (76.5% placebo versus 72.6% candesartan), a β-blocker (64.3% versus 60.0%), or an ACE inhibitor (38.1% versus 34.3%) by the end of the trial. Adjusting for these differences did not affect the overall impact of candesartan in preventing DM.

Impact of Baseline Potassium and Changes in Potassium Levels

Potassium levels were available for 2743 patients involved in North America. The impact on reducing the rates of DM was similar in those with potassium values equal to or below and above the median (HR, 0.725; 95% CI, 0.47 to 1.11; HR, 0.81; 95% CI, 0.45 to 1.47, respectively; P for interaction, 0.81). There was a small decrease in potassium levels (~0.028; SD, ~0.497) in the placebo group and an increase (+0.144; SD, +0.544) in the candesartan group (P<0.0001). However, adjusting for this difference in potassium (with the use of time-dependent covariate analysis) between the 2 groups did not alter the impact of candesartan on the development of DM.

Impact of Postrandomization Differences in Hospitalization

Because candesartan reduced the risk of hospitalizations (during which patients are likely to be investigated more intensively), we examined whether the difference in new diagnoses of DM could be explained by differences in the rates of hospitalization. The rates of development of DM were similarly affected by candesartan in those with (58 versus 74; HR, 0.76; 95% CI, 0.54 to 1.06) versus those without (105 versus 128; HR, 0.79; 95% CI, 0.61 to 1.02) an interim hospitalization.

Discussion

Our study demonstrates that candesartan, an ARB, appears to prevent the development of DM in patients with heart failure and no previous diagnosis of this condition. This effect was consistently observed in all subgroups examined, with no evidence of heterogeneity among the 3 component trials in this program. It appears that the magnitude of the effect may have been smaller in those receiving concomitant ACE inhibitors. Although the relative attenuation of the effects of preventing DM among those receiving concomitant ACE inhibitor is not conclusive (the test for interaction is not significant), it is nevertheless plausible, as the mechanisms of action of ARBs and ACE inhibitors have considerable overlap. The reduction in DM was observed in those with varying severities of heart failure symptoms; those with varying levels of left ventricular ejection fraction; and those with different levels of body mass index, blood pressure, potassium, and concomitant drugs such as β-blockers or diuretics (which may affect glycemic levels). The difference in DM is not explained by differences in the rates of hospitalizations, thereby excluding the possibility of detection biases.

Recent studies implicate angiotensin II (A-II) in the growth and development of adipose tissue. Angiotensinogen is induced early in the adipogenic differentiation of preadipocytes and is highly expressed in mature adipocytes. A-II inhibits the adipogenic differentiation of preadipocytes, and blockade of the angiotensin receptor enhances the response of preadipocytes to insulin. Increased expression of both A-II and ACE has been demonstrated in subcutaneous, abdominal, adipose tissue of overweight and obese individuals. Reducing the levels of A-II with either an ACE inhibitor or blunting the actions of A-II with ARBs could facilitate differentiation...
of preadipocytes to mature adipocytes and subsequently increase lipid storage capacity in adipose tissue. Such an effect may reduce intramyocellular and hepatic fat and thereby improve insulin sensitivity. ARBs may also improve insulin sensitivity by raising adiponectin levels and by increasing the serine phosphorylation of insulin receptors, insulin receptor substrate-1, and phosphatidylinositol 3-kinase. It is also possible that ACE inhibitors and ARBs increase blood flow to the pancreas and skeletal muscle or improve insulin sensitivity or secretion by increasing potassium levels. Some ARBs have been demonstrated to have an agonist effect on the peroxisome proliferator–activated receptor-γ enzyme, and this may also play an additional role in reducing glucose levels and the risk of DM.

Our clinical observation of a reduction in the development of DM with candesartan, an ARB, is supported by several previous studies of ACE inhibitors or ARBs (Table 2). In the HOPE study, ramipril reduced the risk of new DM in those with atherosclerosis. Similar observations have been made with enalapril in SOLVD in patients with low ejection fractions. In the LIFE study, losartan reduced the development of DM compared with a β-blocker; thus, that study is not able to differentiate between a protective effect of an ARB or an adverse effect of a β-blocker on the development of DM. In the ALLHAT study of patients with hypertension, lisinopril reduced the rates of new DM compared with amlodipine (which has a neutral effect) and thiazides (which have an adverse effect on DM rates). Our observation in CHARM, wherein candesartan was compared with placebo, indicates that the benefits are likely mediated through blocking the effects of A-II. In the absence of concomitant therapy with an ACE inhibitor, there is an approximate one-third relative risk reduction in DM with candesartan, which is similar to the benefits of ramipril compared with placebo, when used alone in the HOPE study. Therefore, although CHARM is the only study that directly assessed the effects of an ARB against a placebo, the collective experience from several trials with different comparator groups provides persuasive and coherent evidence that ACE inhibitors and ARBs prevent DM. Recently, our finding has also gained persuasive and coherent evidence that ACE inhibitors and ARBs prevent DM. Furthermore, the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End-point Trial) study is evaluating the relative impact of ramipril versus telmisartan versus their combination in >25 000 individuals (two thirds of whom do not have DM) in preventing DM, as well as a range of vascular complications.

Whereas prevention of DM should be fundamentally approached by reducing weight and increasing activity, the observations that ACE inhibitors and ARBs prevent the development of DM has implications for certain populations (such as heart failure, after myocardial infarction, vascular disease, or hypertension) in whom such drugs have already been shown to reduce major vascular events. In such populations, preventing DM by blocking the renin-angiotensin-aldosterone system is likely to confer additional clinical benefits by reducing some of the risks associated with DM (such as renal and vascular damage), especially during prolonged treatment (up to 10 years), which is well beyond the time frame of current trials (usually 2 to 5 years). This suggests that the clinical benefits observed during the planned follow-up of current trials of a few years may be an underestimate of the full benefits that may accrue from longer treatment. Supportive evidence for this hypothesis stems from the extended follow-up of SOLVD and the 7-year follow-up of the HOPE study.

There are a few limitations of our study. First, we relied on the clinical diagnosis of DM, rather than on serial testing of blood glucose levels or performing an oral glucose tolerance test. However, because this was a blinded study, no material biases in comparing candesartan versus placebo groups would be expected to occur. However, we may have underestimated the absolute rates of DM (and hence, the absolute benefits). Second, our population consisted of patients with heart failure, which is an intensely “diabetogenic” state. Therefore, further studies with ARBs to evaluate their impact in preventing DM in other high-risk populations are required.

In conclusion, we have demonstrated that candesartan reduces the risk of developing DM. This benefit occurs in addition to reductions in cardiovascular mortality and hospitalizations for heart failure, improvement in functional status (according to NYHA classification), and prevention of atrial fibrillation. These benefits of candesartan in preventing multiple adverse outcomes in this high-risk population provide persuasive evidence of the clinical benefits of ARBs in patients with heart failure.

Acknowledgments
The CHARM program was funded by AstraZeneca, which was responsible for data collection and analysis. The Study Executive Committee, consisting of all authors (except H. Gerstein and J. Probstfield), supervised the management of the study and were primarily responsible for the interpretation of the data, preparation, review, and approval of the manuscript.

Disclosure
Dr Yusuf has received research grants, has served on speakers’ bureaus and/or received honoraria, and has served as a consultant to

subjects With Cardiovascular Disease) study, which has evaluated telmisartan in patients with impaired fasting glucose or impaired glucose tolerance and vascular disease. Furthermore, the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End-point Trial) study is evaluating the relative impact of ramipril versus telmisartan versus their combination in >25 000 individuals (two thirds of whom do not have DM) in preventing DM, as well as a range of vascular complications.

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Disclosure
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several pharmaceutical companies, including AstraZeneca. Dr Pfeffer has received a research grant from, has served on the speakers’ bureau of and/or received honoraria from, and has consulted for AstraZeneca. Dr Olofsson is employed by AstraZeneca. Dr Swedberg has received research grants or other research support, has served on speakers’ bureaus and/or received honoraria, and has served as a consultant. Dr Östergren has received a research grant from AstraZeneca; has served on the speakers’ bureaus of and/or received honoraria from AstraZeneca, Merck, Aventis, and Novartis; and has served as a consultant to AstraZeneca, Pfizer, Aventis, and Novartis. Dr Gerstein is the principal investigator in a trial of ACEI to prevent diabetes and has received research support for CHARM CI, a substudy to prevent albuminuria. Dr Granger has received a research grant from and has served as a consultant to AstraZeneca. Dr Probstfield has received research grants from King, Wyeth, and Boehringer; has served on the speakers’ bureaus of and/or received honoraria from King, Wyeth, and Pfizer; and has served as a consultant to King. Dr McMurray has received research grants or other research support from, served on the speakers’ bureaus of and/or received honoraria from, and consulted for AstraZeneca and Takeda.

References

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