Impact of New-Onset Diabetes Mellitus on Cardiac Outcomes in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial Population

Tonje A. Aksnes, Sverre E. Kjeldsen, Morten Rostrup, Per Omvik, Tsushung A. Hua, Stevo Julius

Abstract—There has been a lot of interest about new-onset diabetes mellitus in recent hypertension trials, but the implications of diabetes development on cardiac outcomes have not been known. In the Valsartan Antihypertensive Long-Term Use Evaluation trial, 15 245 high-risk patients were followed for an average of 4.2 years. At baseline, 5250 patients were diabetic by the 1999 World Health Organization criteria, and among the 9995 nondiabetic patients, 1298 patients developed diabetes during follow-up. We have investigated the influence of diabetes development on outcomes in the Valsartan Antihypertensive Long-Term Use Evaluation trial. The patients with diabetes at baseline and new-onset diabetes were compared with patients who did not develop diabetes by a Cox regression model with adjustment for prespecified covariates (age, diabetes status, left ventricular hypertrophy, baseline coronary heart disease, and randomized study treatment). Patients with diabetes at baseline had the highest cardiac morbidity defined as myocardial infarction and heart failure with a hazard ratio of 2.20 (95% CI: 1.95 to 2.49). The patients with new-onset diabetes had significantly higher cardiac morbidity, especially more congestive heart failure, than those without diabetes, with a hazard ratio of 1.43 (95% CI: 1.16 to 1.77). This indicates that patients who develop diabetes during antihypertensive treatment have cardiac morbidity intermediate between diabetic subjects and those subjects who never had diabetes and that it is of importance to find these patients at risk of diabetes development and optimize lifestyle and medical treatment. (Hypertension. 2007;50:467-473.)

Key Words: congestive heart failure ■ diabetes mellitus ■ hypertension ■ morbidity ■ myocardial infarction ■ stroke

There has been a lot of interest in the development of diabetes mellitus in recent hypertension trials, because differences in new-onset diabetes between “old” and “new” antihypertensive treatments have been seen. Blockers of the renin-angiotensin system have seemed to be especially favorable in preventing or delaying diabetes development. Although it is well established that the coexistence of diabetes and hypertension portends a 2- to 3-fold higher risk of cardiovascular disease,1 surprisingly few data exist on the prognostic impact of new-onset diabetes in initially nondiabetic patients, and the implications have been debated.2 Some observational studies have reported the impact of new-onset diabetes in hypertensive subjects,3,4 but the cohorts are small and the number of end points limited.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial5–7 compared cardiac outcomes between the angiotensin II receptor blocker valsartan and the calcium channel blocker amlodipine in a population of hypertensive patients recruited according to a specific predefined age- and risk factor-dependent algorithm.5 There were no differences seen between the 2 treatment regimens either in the primary composite cardiac end point or in all-cause mortality.7,8 However, for 1 of the prespecified secondary end points, new-onset diabetes mellitus, there was a significant 23% lower risk in the valsartan group compared with the amlodipine group.7,9 A total of 1298 patients developed diabetes during the course of the VALUE trial. Thus, the present study aimed to investigate the impact of new-onset diabetes on cardiac outcomes in the VALUE trial population. There is a known elevated risk of cardiovascular disease before the clinical diagnosis of type 2 diabetes,10 and we prespecified to investigate cardiovascular events in this high-risk patient group.
Methods

Study Design
The VALUE trial was an investigator-designed, prospective, multicenter, double-blind, randomized, active-control, parallel group trial. The primary objective was, for the same level of achieved blood pressure, to compare the long-term effects on the incidence of cardiovascular morbidity and mortality between antihypertensive treatment with valsartan and amiodipine. Patients were followed for 4 to 6 years (average follow-up: 4.2 years) with regular visits, and upward-titration of medication was implemented in 5 predefined steps to reach a goal blood pressure of <140/90 mm Hg. The study was approved by all of the concerned ethics committees and conducted in accordance with the Declaration of Helsinki. All of the patients gave written, informed consent, and the study had an independent data and safety monitoring board.

Patients
A total of 15,245 eligible patients in 31 countries were randomly assigned into the VALUE trial. The trial included patients ≥50 years of age who were treated (92%) or untreated for essential hypertension. Previously untreated patients were included if they had a mean sitting blood pressure between 160 and 210 mm Hg (inclusive) and a mean sitting diastolic blood pressure ≤95 mm Hg or a mean sitting diastolic blood pressure between 95 and 115 mm Hg (inclusive) and a mean sitting systolic blood pressure <210 mm Hg. For patients already on antihypertensive treatment, the mean sitting blood pressure should not exceed 210 mm Hg systolic and 115 mm Hg diastolic, but there was no lower limit. Additional inclusion criteria were the presence of predefined combinations of cardiovascular risk factors and/or disease factors according to an algorithm based on age and gender. The qualifying risk factors included diabetes mellitus, cigarette smoking, hypercholesterolemia, proteinuria, serum creatinine >150 μmol/L, and left ventricular hypertrophy without strain on ECG using Cornell11–14 or Sokolow-Lyon criteria.15 The qualifying disease factors included documented history of myocardial infarction or significant coronary heart disease (eg, documented on arteriogram), peripheral vascular disease, cerebral stroke or transient ischemic attack, or the presence of left ventricular hypertrophy with strain on ECG. Women aged 50 to 59 years had to have ≥1 disease factor and 2 risk factors, whereas men in the same age group only had to have 1 disease factor or 3 risk factors to enter into the trial. For men and women 60 to 69 years, ≥2 risk factors or 1 disease factor were required, and for patients above the age of 70 years, only 1 risk factor or 1 disease factor was required for randomization. We have divided the 15,245 patients in the VALUE trial into 3 prespecified groups, patients with diabetes at baseline, patients who developed diabetes during the average 4.2 years of the trial, and patients without diabetes both at baseline and at the end of the trial, and compared the impact on cardiac outcomes.

Study End Points
The VALUE trial was end-point driven and continued until 1450 patients experienced the primary cardiac end point defined as time to first cardiac event (a composite of sudden cardiac death, fatal and nonfatal myocardial infarction, death during or after percutaneous transluminal coronary angioplasty or coronary artery bypass graft, death associated with recent myocardial infarction on autopsy, heart failure requiring hospital management or death because of heart failure, and emergency procedures to prevent myocardial infarction). Prespecified secondary end points were fatal and nonfatal myocardial infarction, fatal and nonfatal heart failure, and fatal and nonfatal stroke. Analyses of all-cause mortality and new-onset diabetes mellitus were also prespecified. Only time to the first cardiac event was considered in the composite primary end point. For secondary analyses, only the first event was counted in each category, but a single patient could have multiple first events across all of the event categories. An end point committee, blinded to therapy allocation, reviewed the clinical records of all of the cardiovascular events reported and rejected 379 submitted cardiac morbidity cases (19%) and 314 strokes (30%).

Diabetes mellitus was at the outset of the trial defined as the use of antidiabetic treatment or by the 1985 World Health Organization (WHO) criteria (fasting glucose ≥7.8 mmol/L [140 mg/dL] in ≥2 separate occasions). In 1999, during the course of the study, WHO changed the definition of diabetes mellitus to a fasting blood glucose of ≥7.0 mmol/L (126 mg/dL) and/or blood glucose ≥11.1 mmol/L (200 mg/dL) 2 hours after oral intake of 75 g of glucose in venous plasma or serum (≥12.2 mmol/L [220 mg/dL]) if capillary blood. During the blinded phase of the trial, the working classification of new-onset diabetes was redefined to adhere to the WHO 1999 criteria, and this protocol was prespecified in a study newsletter. The criteria for diagnosing new-onset diabetes in the initially nondiabetic population were information about new diabetes reported by investigators as an adverse event during the trial, use of antidiabetic drugs in study reports, and/or a fasting glucose concentration ≥7.0 mmol/L (126 mg/dL) in a venous blood sample drawn at study end and analyzed in a central laboratory. This article

| TABLE 1. Baseline Variables by the 3 Groups Presented by Mean±SD and a P Value for Overall Trend |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Baseline Variable | Never DM (8697) | New-Onset DM (1298) | Baseline DM (5250) | Overall P Value |
| Age, y | 67.5±8.3 | 65.6±8.0* | 67.1±7.9† | <0.0001 |
| Gender, male | 57.8 | 63.1%† | 55.9%‡ | <0.0001 |
| BMI, kg/m² | 27.7±4.6 | 29.6±5.1* | 29.9±5.4* | <0.0001 |
| SBP, mm Hg | 153.9±19.0 | 154.4±19.0 | 156.0±18.9* | <0.0001 |
| DBP, mm Hg | 87.8±10.8 | 87.9±10.8 | 86.9±10.8* | <0.0001 |
| HR, bpm | 71.1±10.5 | 72.9±11.1* | 74.2±10.8* | <0.0001 |
| Creatinine, μmol/L | 101.5±23.5 | 100.2±22.4‡ | 100.4±24.4* | 0.0072 |
| Glucose, mmol/L (mg/dL) | 5.38±0.60 (96.8±10.8) | 5.88±0.67 (108.5±12.1) | 9.25±3.26 (166.5±58.7) | <0.0001 |
| Hemoglobin, g/L | 140.8±13.0 | 140.3±12.5* | 140.3±14.2‡ | <0.0001 |
| Potassium, mmol/L | 4.36±0.45 | 4.32±0.44‡ | 4.43±0.46* | <0.0001 |
| Total cholesterol, mmol/L | 5.76±1.18 | 5.65±1.17† | 5.58±1.17* | <0.0001 |
| Uric acid, μmol/L | 375.5±93.2 | 393.7±93.3* | 363.9±97.5* | <0.0001 |

Pairwise comparisons are performed with the never-diabetes mellitus group as a comparator. DBP indicates diastolic blood pressure; DM, diabetes mellitus; HR, heart rate; SBP, systolic blood pressure.

*P<0.0001; †P<0.001; ‡0.001<P<0.01; §0.01<P<0.05.
TABLE 2. End Points by the 3 Groups

<table>
<thead>
<tr>
<th>End Point</th>
<th>Never DM (8697)</th>
<th>New-Onset DM (1298)</th>
<th>Baseline DM (5250)</th>
<th>Total (15 245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>724 (8.3)</td>
<td>120 (9.2)</td>
<td>755 (14.4)</td>
<td>1599</td>
</tr>
<tr>
<td>Cardiac morbidity</td>
<td>489 (5.6)</td>
<td>107 (8.2)</td>
<td>568 (10.8)</td>
<td>1164</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>318 (3.7)</td>
<td>65 (5.0)</td>
<td>299 (5.7)</td>
<td>682</td>
</tr>
<tr>
<td>Heart failure</td>
<td>283 (3.3)</td>
<td>59 (4.6)</td>
<td>412 (7.9)</td>
<td>754</td>
</tr>
</tbody>
</table>

Mortality

<table>
<thead>
<tr>
<th>End Point</th>
<th>Never DM (10.2)</th>
<th>New-Onset DM (78)</th>
<th>Baseline DM (692)</th>
<th>Total (1659)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>889 (10.2)</td>
<td>78 (6.0)</td>
<td>692 (13.2)</td>
<td>1659</td>
</tr>
<tr>
<td>Cardiac</td>
<td>302 (3.5)</td>
<td>20 (1.5)</td>
<td>286 (5.5)</td>
<td>608</td>
</tr>
<tr>
<td>Stroke</td>
<td>320 (3.7)</td>
<td>49 (3.8)</td>
<td>234 (4.5)</td>
<td>603</td>
</tr>
</tbody>
</table>

Data are n (%). DM indicates diabetes mellitus.

TABLE 3. Differences in Hazard Ratios Among Patients Without Diabetes (HR=1), Patients With New-Onset Diabetes, and Patients With Diabetes at Baseline

<table>
<thead>
<tr>
<th>End Point</th>
<th>New-Onset DM</th>
<th>Baseline DM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>1.10 (0.90 to 1.33)</td>
<td>1.98 (1.78 to 2.19)</td>
<td>0.3447 &lt;0.0001</td>
</tr>
<tr>
<td>Cardiac morbidity</td>
<td>1.43 (1.16 to 1.77)</td>
<td>2.20 (1.95 to 2.49)</td>
<td>0.0008 &lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.30 (0.99 to 1.70)</td>
<td>1.73 (1.48 to 2.03)</td>
<td>0.0567 &lt;0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.41 (1.06 to 1.87)</td>
<td>2.79 (2.40 to 3.25)</td>
<td>0.0168 &lt;0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>0.61 (0.48 to 0.77)</td>
<td>1.41 (1.28 to 1.56)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.44 (0.28 to 0.70)</td>
<td>1.76 (1.50 to 2.07)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.04 (0.77 to 1.41)</td>
<td>1.27 (1.07 to 1.50)</td>
<td>0.0065</td>
</tr>
</tbody>
</table>

95% CIs are shown in parentheses. A hazard ratio >1 favors patients without diabetes. DM indicates diabetes mellitus. Results were derived from a Cox model adjusted for prespecified variables: age, diabetes status, left ventricular hypertrophy, coronary heart disease, and randomized study treatment (valsartan and amiodipine).
There was a highly significant increased hazard ratio of 1.98 between the baseline diabetic subjects and the patients without diabetes in the prespecified analysis. The patients who developed new-onset diabetes during the course of the trial showed a trend toward higher event rate of the primary end point, but the hazard ratio was not significantly different from the patients who did not develop diabetes (Table 3).

Cardiac Morbidity
The patients with diabetes at baseline had significantly more myocardial infarction (both fatal and nonfatal) compared with the patients without diabetes as shown in Table 3. There was also a trend toward more myocardial infarction in the patients with new-onset diabetes as shown by Figure 1, but it did not achieve statistical significance as shown in Table 3.

There was a significant increase of congestive heart failure in patients with diabetes, both at baseline and new-onset, compared with those without diabetes, as shown in Figure 2, with a hazard ratio of 2.79 and 1.41, respectively.

When looking at cardiac morbidity as a whole, the patients with new-onset diabetes had significantly higher cardiac morbidity compared with those without diabetes, as shown in Figure 3.

Mortality
There was a significantly increased hazard ratio of 1.41 in all-cause mortality between patients with diabetes at baseline and patients without diabetes, as shown in Table 3. Among the nondiabetic patients at outset of the trial, there was a significantly lower all-cause mortality rate among the patients with new-onset diabetes compared with the patients without diabetes, with a hazard ratio of 0.61. Regarding cardiac mortality, there was a similar picture. There was a highly significant increase in cardiac deaths among the patients with diabetes at baseline compared with patients without diabetes, and a significant decrease among the patients with new-onset diabetes.

Stroke
There was an increased event rate of stroke (fatal and nonfatal) in the patients with diabetes at baseline, but no difference in stroke was found between patients with new-onset diabetes and patients without diabetes, as shown in Table 3.

Blood Pressure and Heart Rate at the End of the Trial
The mean blood pressure in the patients without diabetes was 137.8 ± 16.2/78.9 ± 9.5 mm Hg at study end, whereas in the patients with new-onset diabetes it was 138.1 ± 15.8/78.9 ± 9.1 mm Hg, and in the patients with diabetes at baseline it was 139.7 ± 16.8/77.8 ± 9.5 mm Hg (P for trend < 0.0001). Heart rate at the end of the trial was 70.0 ± 10.9, 70.7 ± 10.5, and 72.5 ± 11.4 bpm in the patients without diabetes, those with new-onset diabetes, and those who were diabetic at baseline, respectively.

Baseline and In-Trial Drug Use
The use of cardiovascular drugs both at baseline and in trial is shown in Table 4. The patients with new-onset diabetes used more aspirin and more statin than the patients without diabetes throughout the trial. More in-trial use of β-blockers, diuretics, and a combination of β-blocker and diuretics was observed for patients with new-onset diabetes. More patients randomized to amlodipine developed diabetes during follow-up as discussed elsewhere.9

Discussion
We found that patients with diabetes at baseline had 2-times greater cardiac morbidity and mortality than patients without
diabetes. The patients with new-onset diabetes had significantly higher cardiac morbidity defined as myocardial infarction and congestive heart failure compared with those without diabetes.

There was a relatively high incidence of new-onset diabetes (3.1% per year) in the VALUE trial compared with other hypertension trials like the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2.6% per year),19 the Captopril Prevention Project (1.1% per year),20 the Losartan Intervention For Endpoint reduction in hypertension study (1.5% per year),21 and the Nordic Diltiazem Study (1.0% per year),22 but this can be related to different diagnosis criteria of new-onset diabetes and the high-risk population in the VALUE trial.

The average age at randomization was marginally lower in the patients with new-onset diabetes, and this may be because of selection, as the potential of developing diabetes may only be in the youngest age groups in these high-risk patients. The elderly could also qualify with less risk factors, and this may also have decreased the risk of developing diabetes in the oldest age groups. As expected, because of risk, there was a higher proportion of males and nonwhites in patients with new-onset diabetes compared with the patients without diabetes, and the body mass index and fasting glucose level at baseline was higher among the diabetic patients.

Prevention of diabetes development is a priority in patients at high risk of developing the disease, whether or not they have established hypertension.23,24 In recent hypertension trials, new-onset diabetes has been an end point, but the prognostic importance has not been settled. Observational studies reporting cardiovascular risk in patients with new-onset diabetes have shown that many years of observation were needed before the prognostic curves separated from people without diabetes.3,25 Because in a typical hypertension outcome trial the average follow-up is ≈5 years, the average duration of new-onset diabetes is only ≈2.5 years, and the impact of the diabetes on cardiovascular outcomes will be underestimated.

In our results, despite the short time of observation, we found a significant increased risk of cardiac morbidity in patients with new-onset diabetes compared with patients without diabetes during the average 4.2 years of follow-up in our prespecified analyses. The hazard ratio of total cardiac morbidity was a significant 1.43 for new-onset diabetes compared with patients without diabetes, and congestive heart failure was the main contributor to the difference seen. The increased risk of cardiac morbidity in the patients with new-onset diabetes emphasizes the need for aggressive management of cardiovascular risk factors in individuals at increased risk of developing diabetes. A retrospective analysis from the Nurses Health Study even showed that there is an elevated risk of cardiovascular disease (myocardial infarction and stroke) >15 years before the clinical diagnosis of type 2 diabetes.10

All-cause and cardiac mortality in the patients with new-onset diabetes were lower than in the patients without diabetes. This is because of the data collection, as deaths in the new-onset diabetes group could only occur after the time of the diabetes diagnosis, but in the other 2 groups (baseline diabetes and never diabetes), deaths could be counted throughout the trial. On the other hand, when looking at these observational data of patients with new-onset diabetes during the whole trial period, the in-trial extensive attention to the patients’ diabetes may also have reduced mortality, as the investigators may have treated the new-onset diabetic patients with greater care, indicating that these are high-risk patients.
There was more use of aspirin, β-blocker, diuretics, and statin in the patients with new-onset diabetes as shown in Table 4, and this may at least explain some of the decreased mortality seen in these patients.

Some observational studies have reported the impact of new-onset diabetes on cardiac outcomes in hypertensive subjects. In the up to 16 years of follow-up of 795 initially untreated hypertensive patients in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale Study, occurrence of new diabetes portends a risk for subsequent cardiovascular disease that was not dissimilar from that of previously known diabetes, with a adjusted relative risk of 2.92 (95% CI: 1.33 to 6.41; \( P = 0.007 \)) compared with the group persistently free of diabetes.\(^3\) However, this was a rather small cohort study with only 63 cardiovascular events in their analysis. In the 18 years of follow-up of the Multiple Risk Factor Intervention Trial, 1246 new cases of diabetes were recorded among the initial 11 645 high-risk, middle-aged men without cardiovascular disease and diabetes at baseline.\(^25\) The adjusted hazard ratio for total mortality compared with the patients without diabetes and cardiovascular disease was 2.75 (\( P < 0.0001 \)) for the patients developing both cardiovascular disease and diabetes and 1.49 (\( P < 0.0001 \)) for the patients with diabetes only. This implicates an increased mortality risk with new diabetes and a more than added effect in combination with cardiovascular disease, which is more to be expected compared with the apparent decreased mortality rate seen in the patients with new-onset diabetes from the VALUE trial. In a another longitudinal study of 686 middle-aged hypertensive men followed for 15 years, patients with diabetes at entry had double the coronary risk of nondiabetic patients (relative risk: 2.12; 95% CI: 1.11 to 4.07).\(^4\) Diabetes developed in 1.3% of participants per year, and these subjects were \( \sim 1.5 \) times (range: 0.37 to 6.00) as likely to have coronary heart disease as those without diabetes, which is at the same level as seen in the VALUE trial, although this excess risk was not statistically significant.

On the contrary, the 14-year follow-up of the patients from the SHEP Study showed that diabetes development during the 4.3 years of diuretic therapy of the Systolic Hypertension in the Elderly Program study did not have significant association with cardiovascular or total mortality rate.\(^26\) However, these long-term results were retrospective, achieved in elderly patients, and the authors used an administrative database to adjudicate vital status and cause of death, which may diminish the impact of the results. Because the SHEP Study was placebo controlled, the results can also be interpreted as a favorable effect of better blood pressure control per se. This indicates that any treatment is better than no treatment or control, even when a nonmetabolically optimal therapy is used.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial investigators have recently published their results of patients with incident or new-onset diabetes.\(^27\) Although only 53.2% of their initial 18 411 nondiabetic patients had satisfactory follow-up to be included in this posthoc analysis, they found a statistically significant increased hazard ratio for coronary heart disease in patients with incident diabetes (hazard ratio: 1.64; 95% CI: 1.15 to 2.33) but not for mortality and other end points.\(^27\)

The VALUE trial has some limitations when evaluating the impact of new-onset diabetes, as the patients are hypertensive subjects with a relatively high cardiovascular risk. The study also enrolled patients of mainly white origin (91%); therefore, caution is needed when extrapolating from our results into other ethnic groups. The mortality data must be evaluated with caution because of the relatively small absolute number of deaths in the new-onset diabetes group, and as these patients with new-onset diabetes had shorter follow-up time because mortality events could only be counted after the diabetes diagnosis. This also influences the primary end point rate, because it includes mortality data. In case of morbidity, we have included all of the clinical events during the whole trial period for the patients in the prespecified new-onset diabetes group; also events happened before the actual diagnosis of new-onset diabetes. This is supported by the Nurses Health Study in which the risk of cardiovascular disease is increased long before the clinical diagnosis of diabetes.\(^10\)

Perspectives

In the high-risk hypertensive VALUE population, patients with diabetes mellitus at baseline had higher cardiac morbidity and mortality than patients without diabetes. Patients who developed diabetes during the average follow-up of 4.2 years of the trial had higher cardiac morbidity. This indicates that these patients who develop diabetes during antihypertensive treatment have cardiac morbidity intermediate between diabetics and never diabetics and that it is of importance to find these patients at risk of diabetes development and to optimize lifestyle and medical treatment.

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Disclosures

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References


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