Valsartan Improves β-Cell Function and Insulin Sensitivity in Subjects With Impaired Glucose Metabolism

A randomized controlled trial

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OBJECTIVE—Recently, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research Trial demonstrated that treatment with the angiotensin receptor blocker (ARB) valsartan for 5 years resulted in a relative reduction of 14% in the incidence of type 2 diabetes in subjects with impaired glucose metabolism (IGM). We investigated whether improvements in β-cell function and/or insulin sensitivity underlie these preventive effects of the ARB valsartan in the onset of type 2 diabetes.

RESEARCH DESIGN AND METHODS—In this randomized controlled, double-blind, two-center study, the effects of 26 weeks of valsartan (320 mg daily; n = 40) or placebo (n = 39) on β-cell function and insulin sensitivity were assessed in subjects with impaired fasting glucose and/or impaired glucose tolerance, using a combined hyperinsulinemic-euglycemic and hyper-glycemic clamp with subsequent arginine stimulation and a 2-h 75-g oral glucose tolerance test (OGTT). Treatment effects were analyzed using ANCOVA, adjusting for center, glucometabolic status, and sex.

RESULTS—Valsartan increased first-phase (P = 0.028) and second-phase (P = 0.002) glucose-stimulated insulin secretion compared with placebo, whereas the enhanced arginine-stimulated insulin secretion was comparable between groups (P = 0.25). In addition, valsartan increased the OGTT-derived insulinogenic index (representing first-phase insulin secretion after an oral glucose load; P = 0.027). Clamp-derived insulin sensitivity was significantly increased with valsartan compared with placebo (P = 0.049). Valsartan treatment significantly decreased systolic and diastolic blood pressure compared with placebo (P < 0.001). BMI remained unchanged in both treatment groups (P = 0.89).

CONCLUSIONS—Twenty-six weeks of valsartan treatment increased glucose-stimulated insulin release and insulin sensitivity in normotensive subjects with IGM. These findings may partly explain the beneficial effects of valsartan in the reduced incidence of type 2 diabetes.

Diabetes Care 34:845–851, 2011

The association between insulin resistance, type 2 diabetes, and inappropriate activation of the renin-angiotensin system (RAS) has been described extensively (1,2). These relationships are not solely attributed to systemic RAS components, which mainly are derived from the kidney, liver, and lung. Additional activation of local RAS in adipocytes and the pancreas also may contribute to impaired insulin sensitivity and β-cell function (3,4). Recent trials (5,6) have suggested that RAS inhibition with angiotensin II receptor blockers (ARBs) or ACE inhibitors may reduce the incidence of new-onset type 2 diabetes. However, these studies mainly were performed in hypertensive patients, and the onset of type 2 diabetes was not a prespecified end point. More recently, the large-scaled, prospective Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial addressed the potential of the ARB valsartan to protect individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) against type 2 diabetes and cardiovascular disease (7). After a treatment period of 5 years, valsartan decreased the onset of type 2 diabetes by 14%. However, the underlying mechanisms are incompletely understood.

One of the underlying mechanisms may involve a positive effect of RAS blockers on insulin sensitivity (8). In part, these effects may be a result of hemodynamic changes, increasing skeletal muscle blood flow, with augmented glucose and insulin delivery to insulin-sensitive tissues (4). In addition, RAS blockade may exert direct effects on skeletal muscle and adipose tissue, such as increased adipocyte differentiation (9), which may increase insulin-induced glucose uptake in skeletal muscle (3,4). Furthermore, treatment with an ARB or ACE inhibitor may directly affect β-cell function. In vitro, blocking the RAS with an ACE inhibitor or ARB prevented the deleterious effects of hyperglycemia on β-cell function (10,11). In vivo, however, limited information regarding the effect of RAS blockade on β-cell function is available. Short-term treatment (6 weeks) with valsartan had no effect on β-cell function (12), whereas Suzuki et al. (13) demonstrated that 3 months of treatment with the ARB candesartan increased first-phase insulin secretion, assessed during an oral glucose tolerance test (OGTT).

We hypothesized that both improvement of insulin sensitivity and β-cell function may underlie the protective effect of ARB intervention in the development of type 2 diabetes in subjects with impaired glucose metabolism (IGM). We tested this hypothesis by conducting a randomized controlled trial in which individuals with IGM were randomly assigned...
to receive either valsartan (320 mg once daily) or placebo for 26 weeks. Insulin sensitivity and various aspects of β-cell function were assessed using both the gold standard hyperinsulinemic-euglycemic and hyperglycemic clamp as well as an OGTT.

**RESEARCH DESIGN AND METHODS**—In this randomized controlled, double-blind study (Vrije Universiteit Medical Center, Maastricht University Medical Center, the Netherlands), patients with IFG and/or IGT were randomly assigned to valsartan (n = 40) or placebo (n = 39). Patients received 160 mg valsartan or placebo once daily for 2 weeks. Thereafter, the dosage was doubled to 320 mg q.d. valsartan or placebo for the subsequent 24 weeks. Before and after 26 weeks of treatment, we performed a combined hyperinsulinemic-euglycemic and hyperglycemic clamp with arginine stimulation and a 2-h 75-g OGTT.

The primary end point was the effect of valsartan versus placebo on clamp-measured β-cell function. The secondary end point was the effect of valsartan versus placebo on clamp-measured insulin sensitivity, blood pressure, fasting plasma glucose (FPG), HbA1c, fasting plasma insulin (FPI), body weight, waist, safety, and tolerability.

Participants were recruited by advertisements in newspapers. After obtaining written informed consent, 259 subjects underwent a screening OGTT. Subjects with IFG (FPG ≥ 6.1 and < 7.0 mmol/L or FPG ≥ 5.6 and < 7.0 mmol/L and a family history of type 2 diabetes) and/or IGT (2-h plasma glucose level ≥ 7.8–11.0 mmol/L) were eligible. Individuals only were allowed to use lipid-lowering medication (statins). Subjects with a blood pressure > 140/90 mmHg were treated with 5 mg amlodipine. If blood pressure persisted > 140/90 mmHg, amlodipine was increased to 10 mg, followed by 12.5 mg hydrochlorothiazide and/or 25 mg cavedilol. Subjects with blood pressure < 140/90 mmHg were included in the study. A total of 43 subjects with IFG (51% male), 11 subjects with IGT (46% male), and 25 subjects with IFG/IGT (56% male) were enrolled. Exclusion criteria were excess alcohol intake, hepatitis and/or pancreatitis, abnormal liver and renal function tests, and recent changes in weight (≥ 5% change). The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee.

**Clamp**

A hyperinsulinemic-euglycemic and hyperglycemic clamp with arginine stimulation was performed to assess insulin sensitivity and secretion. During the hyperinsulinemic-euglycemic clamp, the insulin infusion rate was maintained at 40 mU·min⁻¹·m² body surface area. After an hour resting period, the hyperglycemic clamp was started by giving a glucose bolus, which increased the blood glucose concentration to 15.0 mmol/L. Steady-state blood glucose concentrations at 15.0 mmol/L were sustained with a variable 20% glucose infusion for 80 min. Thereafter, 5.0 g arginine was administered to measure maximum insulin secretion at a steady-state blood glucose concentration of 15.0 mmol/L.

**OGTT and blood pressure**

A 75-g 2-h OGTT was performed. Blood samples were obtained at seven time points to determine glucose and insulin. Blood pressure was measured using an Omron 705 CP (Omron; Shiojiko Horikawa, Shimogyo-ku, Japan) on the non-dominant arm, after a 15-min rest.

**Biochemical analyses**

Glucose concentrations were determined using a hexokinase method (Gluco-quant; Roche Diagnostics, Mannheim, Germany). HbA1c was measured by cation-exchange chromatography (reference values: 4.3–6.1%; Menarini Diagnostics, Florence, Italy). Serum insulin concentrations were quantified using immunometric assays (Advia; Centaur; Siemens Medical Solutions Diagnostics, Deerfield, IL). The intra-assay precision for insulin ranged from 3% to 4% over a mean range of 0.02–1.5 nmol/L.

**Calculations**

**Hyperinsulinemic-euglycemic clamp.** Insulin sensitivity was defined as the glucose infusion rate (M value, mg·min⁻¹·kg⁻¹) during the last 30 min of the hyperinsulinemic-euglycemic clamp, with a steady-state blood glucose concentration of 5.0 mmol/L. The M value was used because correction for steady-state insulin concentrations (M/I) did not alter the results.

**Hyperglycemic clamp.** First-phase insulin secretion was calculated as the insulin area under the curve (AUC; pmol·min⁻¹·L⁻¹) during the first 10 min after the glucose bolus, increasing glucose levels to 15.0 mmol/L. Second-phase insulin secretion was calculated as the insulin AUC during 70 min after first-phase insulin secretion. Arginine-stimulated acute insulin response (AIRarg) was calculated as the insulin AUC during the first 10 min after the arginine bolus and administered at t = 80 min during the hyperglycemic clamp. The disposition index (mg·L⁻¹·kg⁻¹·min⁻¹·L⁻¹) was calculated as the ratio of the increment of insulin 30 min after the oral glucose load to the increment of blood glucose concentration over the first 30 min [(I30 – I0)/G30 – G0]. Insulin sensitivity was calculated using the insulin sensitivity index composite (ISIcomp: 10,000/ (yG0 · I0 · Gmean · tmean)). The mean arterial pressure (MAP) was calculated as diastolic blood pressure + [1/3 · (systolic blood pressure – diastolic blood pressure)].

**Statistical analysis**

The primary end point was change in first-phase glucose-stimulated insulin secretion after 26 weeks of treatment with valsartan or placebo, which was calculated as the AUC of insulin and/or C-peptide over the first 10 min of the hyperglycemic clamp. We assumed a decline in AUC first-phase insulin secretion of 2.5% in subjects with IFG or IGT (14) and an improvement of β-cell function by valsartan of 10% (SD 50%). A sample size of 68 subjects would provide 80% power to detect a 10% increase in valsartan compared with placebo, taking into account correction for confounders. Assuming a drop-out rate of 20%, 80 subjects needed to be included.

Treatment effects were assessed by ANCOVA, with adjustment for center, sex, glucometabolic status (i.e., IFG and/or IGT), and baseline measurement. Univariate correlations (Spearman ρ) were used to examine associations with changes in insulin sensitivity and insulin secretion. All statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS, Chicago, IL). P < 0.05 was considered statistically significant. Data are expressed as means ± SEM or, in the case of skewed distributions, as median (interquartile range) for numerical variables and as proportions for categorical variables.

**RESULTS**

**Subject characteristics**

Baseline characteristics of the study population randomly assigned to valsartan or...
placebo are listed in Fig. 1. The valsartan group included 52% subjects with IFG and 48% subjects with IFG/IGT, and the placebo group included 56% subjects with IFG and 44% subjects with IFG/IGT. The study medication was well tolerated; there were no serious adverse events. All randomly assigned individuals completed the study. A total of 15% of subjects randomly assigned to valsartan used antihypertensive agents compared with 28% of subjects in the placebo group ($P = 0.15$). At 26 weeks, valsartan, relative to placebo, resulted in a significant reduction in systolic and diastolic blood pressure (Table 1) and MAP ($-8.4 \pm 1.6$ mmHg vs. $-1.7 \pm 1.0$ mmHg, $P < 0.001$, respectively). Furthermore, 2-h postload glucose tended to increase after placebo treatment compared with valsartan treatment ($P = 0.09$). Twenty-six weeks of treatment had no effect on BMI, waist circumference, FPG, HbA1C, FPI, and lipid metabolism (Table 1).

**β-Cell function**
At baseline, there were no differences in insulin secretion between the two treatment groups (first phase: $2.4 \pm 0.3$ vs. $2.6 \pm 0.4$ nmol $\cdot$ min$^{-1} \cdot$ L$^{-1}$, $P = 0.66$; second phase: $21.7 \pm 1.8$ vs. $27.2 \pm 2.9$ nmol $\cdot$ min$^{-1} \cdot$ L$^{-1}$, $P = 0.13$; arginine stimulated: $20.0 \pm 1.6$ vs. $24.7 \pm 2.1$ nmol $\cdot$ min$^{-1} \cdot$ L$^{-1}$, $P = 0.10$; valsartan vs. placebo, respectively) At 26 weeks, valsartan versus placebo increased first- and second-phase glucose-stimulated insulin secretion during the hyperglycemic clamp, whereas arginine-stimulated insulin secretion was comparable between groups (Fig. 2). The disposition index tended to be increased after valsartan treatment compared with placebo, although this did not reach statistical significance ($5 \pm 14$ vs. $-30 \pm 18$ [nmol $\cdot$ min$^{-1} \cdot$ L$^{-1}$] $\times$ [mg $\cdot$ kg$^{-1} \cdot$ min$^{-1}$], $P = 0.12$, respectively). In accordance with clamp-measured β-cell function, valsartan treatment significantly increased the insulinogenic index, reflecting an increased first-phase insulin secretion during the OGTT (Fig. 2).

**Insulin sensitivity**
Twenty-six-week valsartan treatment significantly increased clamp-derived insulin sensitivity compared with placebo (Fig. 3). There were no between-group differences in insulin plasma levels during the hyperinsulinemic-euglycemic clamp. Correcting the $M$ value for prevailing insulin levels did not alter the results. Interestingly, the difference in OGTT-derived insulin sensitivity did not reach statistical significance (Fig. 3).

**Determinants of insulin sensitivity and β-cell function**
The change in clamp-derived insulin sensitivity was inversely correlated with the change in MAP ($r = -0.30$, $P = 0.02$). However, no significant correlations were found between MAP and β-cell function parameters (first-phase insulin secretion: $r = -0.028$, $P = 0.82$; second-phase insulin secretion: $r = -0.006$, $P = 0.96$; IGI$_{O_G T T}$: $r = -0.08$, $P = 0.51$). No other determinants were detected that could explain the change in insulin sensitivity and β-cell function.

**CONCLUSIONS**—The current study demonstrated that 26 weeks of valsartan treatment improved various aspects of β-cell function and insulin sensitivity, compared with placebo, in individuals with IGM. Importantly, all subjects had blood pressure values within the normal range at baseline, with or without concomitant antihypertensive therapy.

Recently, the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial (15) and the NAVIGATOR trial specifically addressed the effect of prolonged ACE inhibitor and ARB treatment on incident type 2 diabetes in large populations of individuals with IGM. In the DREAM trial, 15 mg q.d. ramipril, given for 3 years, nonsignificantly reduced the incidence of type 2 diabetes by 9%. During this relatively short intervention period, individuals treated with ramipril were more likely to revert from IGM to normoglycemia, and their postload glucose levels were significantly reduced compared with placebo (15). In the NAVIGATOR trial, 160 mg q.d. valsartan, given for 5 years, not only reduced fasting and postload glucose after an OGTT but also reduced the incidence of type 2 diabetes by 14% (11). However, in these trials no underlying mechanisms were addressed. Our data, obtained in a comparable high-risk population, suggest that improvement in β-cell function, as well as in insulin sensitivity, may contribute to the effect of ARBs to reduce the incidence of type 2 diabetes.

Previously, short-term (6 weeks) low doses of valsartan (80 mg q.d.) did not affect clamp-measured β-cell function in subjects with IGT (12). In contrast, other studies (13) found increased OGTT-derived first-phase insulin secretion after 3 months of candesartan treatment (8 mg q.d.) in subjects with IGT and hypertension. Our study is the first to...
Valsartan in the PRESERVE study

Table 1—Valsartan-induced changes in glucometabolic variables

| Variable                        | Valsartan          | Placebo           | P     |
|---------------------------------|--------------------|-------------------|-------|
| n                               | 40                 | 39                |       |
| BMI (kg/m²)                     |                    |                   |       |
| Baseline                        | 29.8 ± 0.6         | 29.5 ± 0.8        |       |
| Post-treatment                  | 29.9 ± 0.7         | 29.7 ± 0.8        |       |
| Change                          | 0.16 ± 0.15        | 0.15 ± 0.12       | 0.89  |
| Waist (cm)                      |                    |                   |       |
| Baseline                        | 101.8 ± 1.7        | 102.4 ± 2.0       |       |
| Post-treatment                  | 102.3 ± 1.9        | 102.8 ± 2.0       |       |
| Change                          | 0.7 ± 0.7          | 0.2 ± 0.5         | 0.56  |
| Systolic blood pressure (mmHg)  |                    |                   |       |
| Baseline                        | 131 ± 1.6          | 130 ± 1.8         |       |
| Post-treatment                  | 117 ± 1.9          | 127 ± 2.0         |       |
| Change                          | −12.91 ± 2.1       | −1.38 ± 1.2       | <0.001|
| Diastolic blood pressure (mmHg) |                    |                   |       |
| Baseline                        | 83 ± 1.2           | 83 ± 0.9          |       |
| Post-treatment                  | 75 ± 1.3           | 81 ± 1.2          |       |
| Change                          | −7.24 ± 1.4        | −0.69 ± 1.1       | <0.001|
| FPG (mmol/L)                    |                    |                   |       |
| Baseline                        | 6.4 ± 0.1          | 6.3 ± 0.1         |       |
| Post-treatment                  | 6.3 ± 0.1          | 6.3 ± 0.1         |       |
| Change                          | −0.2 ± 0.1         | 0 ± 0.1           | 0.56  |
| 2-h Postload glucose (mmol/L)   |                    |                   |       |
| Baseline                        | 8.4 ± 0.4          | 8.1 ± 0.4         |       |
| Post-treatment                  | 8.5 ± 0.5          | 8.9 ± 0.4         |       |
| Change                          | 0.1 ± 0.4          | 0.8 ± 0.2         | 0.09  |
| HbA₁c (%)                       |                    |                   |       |
| Baseline                        | 6.0 ± 0.1          | 5.9 ± 0.1         |       |
| Post-treatment                  | 5.9 ± 0.1          | 5.9 ± 0.1         |       |
| Change                          | −0.05 ± 0.02       | 0.05 ± 0.01       | 0.32  |
| FPI (pmol/L)                    |                    |                   |       |
| Baseline                        | 90.4 ± 8.0         | 87.4 ± 8.3        |       |
| Post-treatment                  | 90.2 ± 7.7         | 91.0 ± 9.0        |       |
| Change                          | −0.5 ± 3.6         | 3.6 ± 4.3         | 0.83  |
| Total fasting cholesterol (mmol/L)|                  |                   |       |
| Baseline                        | 5.4 ± 0.14         | 5.3 ± 0.17        |       |
| Post-treatment                  | 5.4 ± 0.12         | 5.2 ± 0.17        |       |
| Change                          | −0.01 ± 0.1        | −0.11 ± 0.12      | 0.33  |
| HDL cholesterol (mmol/L)        |                    |                   |       |
| Baseline                        | 1.26 ± 0.06        | 1.26 ± 0.06       |       |
| Post-treatment                  | 1.23 ± 0.06        | 1.26 ± 0.06       |       |
| Change                          | −0.03 ± 0.03       | 0.01 ± 0.02       | 0.31  |
| LDL cholesterol (mmol/L)        |                    |                   |       |
| Baseline                        | 3.49 ± 0.12        | 3.37 ± 0.13       |       |
| Post-treatment                  | 3.44 ± 0.13        | 3.26 ± 0.11       |       |
| Change                          | −0.04 ± 0.08       | −0.11 ± 0.08      | 0.31  |
| Triglycerides (mmol/L)          |                    |                   |       |
| Baseline                        | 1.46 ± 0.12        | 1.43 ± 0.11       |       |
| Post-treatment                  | 1.61 ± 0.11        | 1.58 ± 0.15       |       |
| Change                          | 0.10 ± 0.09        | 0.15 ± 0.08       | 0.70  |

Data are means ± SE unless otherwise indicated.

simultaneously measure the effects of 26 weeks of high-dose valsartan treatment on multiple aspects of β-cell function using the hyperglycemic clamp method. We found an increase in clamp-measured glucose-stimulated insulin secretion, with no alterations in arginine-stimulated insulin secretion. Furthermore, similar to Suzuki et al. (13), the insulinogenic index, reflecting first-phase insulin secretion during an OGTT, increased with valsartan compared with placebo. The discrepant findings between the current study and the study of Bokhari et al. (12), who did not find an effect on clamp-measured β-cell function after ARB treatment, may be explained by differences in exposure time and the used dosage.

In the current study, and in the study of Suzuki et al. (13), treatment-related alterations in clamp- and OGTT-derived β-cell function were unrelated to changes in blood pressure, suggesting that valsartan may directly affect pancreatic islets, thereby increasing insulin secretion. Molecular mechanisms explaining this observation have been addressed in vitro and in vivo rodent studies (10,11). In the pancreas, a local RAS is present, with the expression and localization of angiotensinogen and AT₁ receptors particularly localized in the islets and endothelial cells of the pancreatic vasculature (16). A relationship between RAS activation and hyperglycemia was assessed in vitro, where exposure to high glucose concentrations upregulated RAS components in rodent and human pancreatic β-cells (10). Glucose-induced RAS activation resulted in increased reactive oxygen species production, tissue inflammation, and increased cell proliferation and apoptosis (11). Furthermore, RAS blockade prevented these deleterious effects of hyperglycemia on β-cell function (10).

In addition to improvements in β-cell function, we found that valsartan relative to placebo increased insulin sensitivity, as assessed with the hyperinsulinemic-euglycemic clamp. However, the observed increase of OGTT-derived insulin sensitivity (ISclamp) after valsartan treatment did not reach statistical significance. After an OGTT, there is a great intra- and intersubject variability in glucose uptake and hepatic glucose production. Therefore, although OGTT-derived insulin sensitivity may take into account more physiological contributing mechanisms, the variability by far exceeds that of clamp-measured insulin sensitivity (17). Clamp-measured insulin sensitivity provides an accurate estimate of whole-body insulin sensitivity, which is largely determined by skeletal muscle because the used insulin levels almost fully suppress endogenous glucose production (18). Several mechanisms may underlie the valsartan-induced improvement in peripheral insulin sensitivity. First,
angiotensin II (AngII) decreases skeletal-muscle blood flow in humans (19). Accordingly, RAS blockade resulted in increased forearm blood flow (20), thereby increasing glucose and insulin delivery to skeletal muscle, which may lead to increased glucose utilization. Second, in rodents, AngII directly inhibited insulin signaling in skeletal muscle (2), which was counteracted by ARB treatment (2,3). Finally, AngII may increase the number of large insulin-resistant adipocytes via inhibition of adipocyte differentiation. RAS blockade reduced adipocyte size and improved adipose tissue function.
in human adipocytes (9) and in rodents (21). The underlying mechanisms of improved insulin sensitivity need to be investigated in future studies in humans.

The effect of ARB treatment on insulin sensitivity might differ among the various compounds. Hsueh et al. (22) recently showed that telmisartan (160 mg q.d., 16 weeks of treatment) did not affect insulin sensitivity in obese, hypertensive, normoglycemic individuals. Ideally, a head-to-head comparison of different ARBs in a randomized controlled trial is needed to address the issue of whether improvement in insulin sensitivity is a class effect of ARBs or is confined to specific agents. Furthermore, conflicting results have been published regarding the protective effect of ARBs in addition to blood pressure medication known to induce type 2 diabetes (23,24). Therefore, the glucometabolic benefits of ARBs might depend on the agent that is used, the study population (a priori risk), concomitant medication, and the duration of exposure.

Despite changes in insulin secretion and action, there were no significant changes in FPG, FPI, and HbA1c. A trend toward improvement in 2-h postload glucose was observed in the valsartan group. This lack of changes in clinical variables of glucose metabolism is in line with previous studies (8) and is likely to be a result of the treatment duration of these studies, which all last <6 months. Although physiological differences have been described in the underlying defects of IFG and/or IGT, in general, subjects with IFG and/or IGT already are characterized by impaired insulin sensitivity and β-cell function (25). This study was not powered to measure the effect of valsartan in individuals with IFG and IFG/IGT separately. Furthermore, we were not able to detect a delay in the onset of type 2 diabetes, as seen in large clinical studies. This might be a result of the treatment time and limited power, although a high dose of valsartan was used.

In conclusion, the current study demonstrates that 26 weeks of treatment with valsartan significantly improved glucose-stimulated insulin release and insulin sensitivity in subjects with IGM. These findings may partly explain the beneficial role of valsartan in lowering the risk of incident type 2 diabetes in comparable, high-risk populations. However, the mechanisms underlying the valsartan-induced improvements in β-cell function and insulin sensitivity remain to be established and warrant further investigation.

Acknowledgments—This work was supported by an investigator-initiated study grant from Novartis Pharma.

Through M.D., the Vrije University Medical Center received research grants from Amylin, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Novo Nordisk, sanofi-aventis, and Takeda; consultancy fees from Eli Lilly, Merck, Novo Nordisk, sanofi-aventis, and speaker fees from Eli Lilly, Merck, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

N.J.v.d.Z. and C.C.M.M. researched data and wrote the manuscript. G.H.G. contributed to discussion and reviewed the manuscript. M.M.H.H., E.E.B., and M.D. reviewed the manuscript.

Parts of this study were presented in abstract form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010.

The authors thank Jeannette Boerop, Diabetes Center, Department of Internal Medicine, Vrije University Medical Center, Amsterdam, the Netherlands, for her excellent practical support.

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