

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 hyperglycemic 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.

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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

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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

RESEARCH DESIGN AND METHODS—In this randomized controlled, double-blind study (Vrije University 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), HbA_{1c}, 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 – 11.1 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 carvedilol. 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 ($\geq 5\%$ 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 $40 \text{ mU} \cdot \text{min}^{-1} \cdot \text{m}^2$ 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 secretory capacity 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; Shiokoji 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). HbA_{1c} 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, $\text{mg} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) 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; $\text{pmol} \cdot \text{min}^{-1} \cdot \text{L}^{-1}$) 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 (AIR_{arg}) 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 ($\text{mg} \cdot \text{L} / (\text{nmol} \cdot \text{kg})$, correcting insulin secretion for insulin sensitivity, was calculated by multiplying first- and second-phase glucose-stimulated insulin secretion with the M value.

OGTT. First-phase glucose-stimulated insulin secretion (the insulinogenic index) 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 $[(I_{30} - I_0) / (G_{30} - G_0)]$. Insulin sensitivity was calculated using the insulin sensitivity index composite ($\text{ISI}_{\text{comp}}: 10,000 / \sqrt{G_0 \cdot I_0 \cdot G_{\text{mean}} \cdot I_{\text{mean}}}$). The mean arterial pressure (MAP) was calculated as diastolic blood pressure + $[1/3 \cdot (\text{systolic blood pressure} - \text{diastolic blood pressure})]$.

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 \pm 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 ± 1.6 mmHg vs. -1.7 ± 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, HbA_{1c}, 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 ± 0.3 vs. 2.6 ± 0.4 nmol \cdot min⁻¹ \cdot L⁻¹, $P = 0.66$; second phase: 21.7 ± 1.8 vs. 27.2 ± 2.9 nmol \cdot min⁻¹ \cdot L⁻¹, $P = 0.13$; arginine stimulated: 20.0 ± 1.6 vs. 24.7 ± 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 ± 14 vs. -30 ± 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_{OGTT}: $r = -0.08$, $P = 0.51$). 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

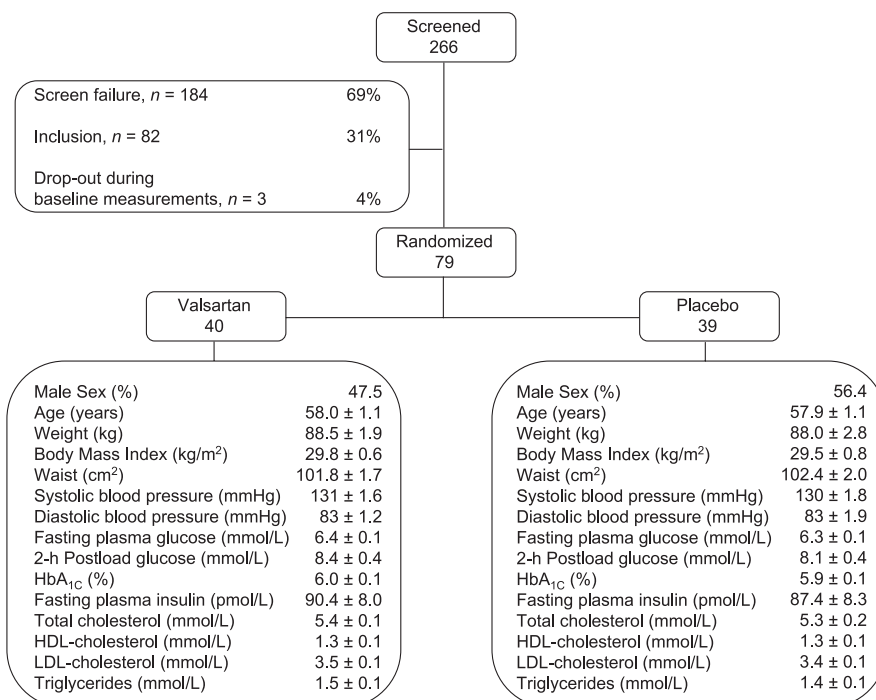


Figure 1—Inclusion flowchart and baseline characteristics of the study population. Data represent means \pm SE.

Table 1—Valsartan-induced changes in glucometabolic variables

	Valsartan	Placebo	P
n	40	39	
BMI (kg/m ²)			
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
HbA _{1c} (%)			
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 ± 5.6	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 in 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 (ISI_{comp}) 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,

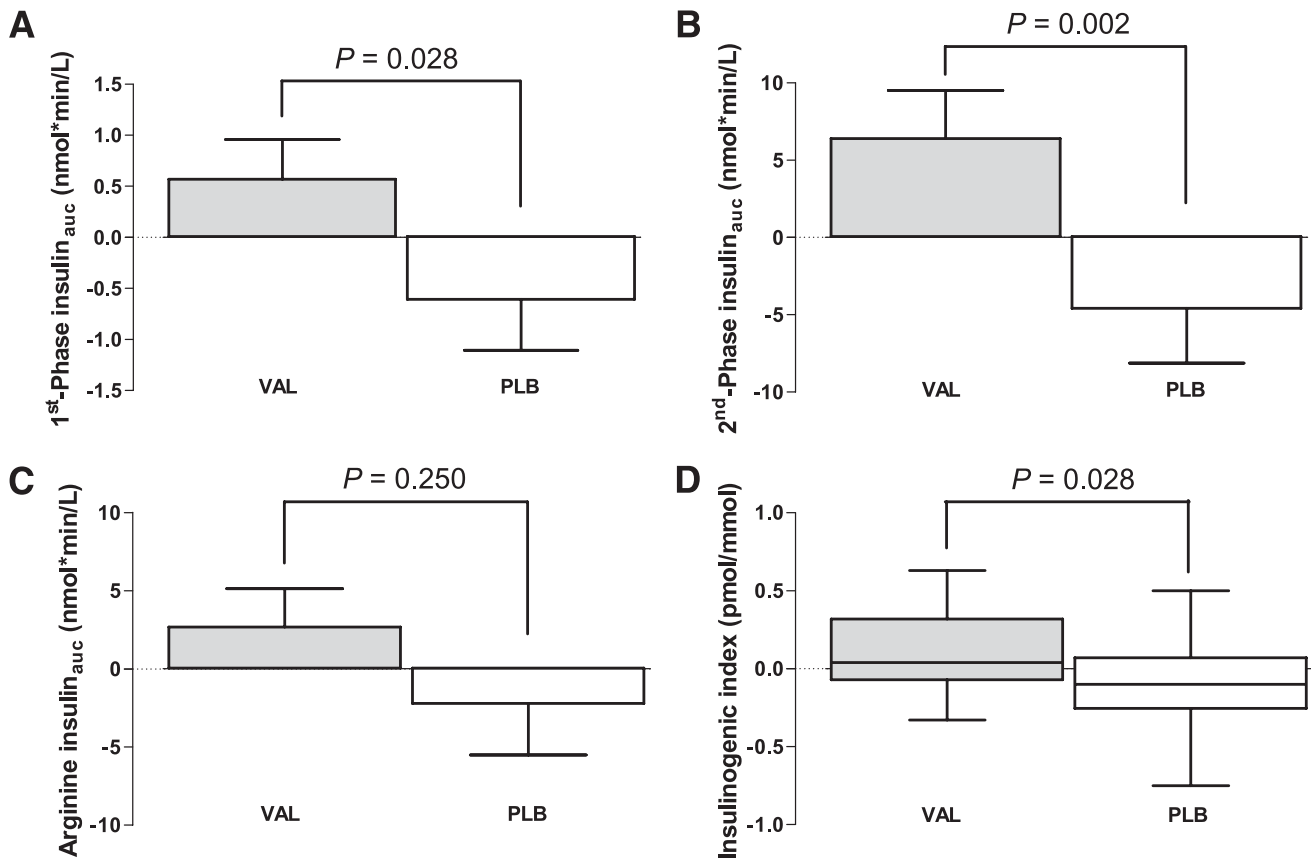


Figure 2—Effect of 26 weeks of valsartan (VAL) on clamp- and OGTT-derived measures of β -cell function. Changes in AUC first-phase (A) and second-phase (B) glucose-stimulated insulin secretion and combined hyperglycemia and arginine-stimulated insulin secretion (C) and insulinogenic index (D) at 26 weeks of valsartan (■) or placebo (PLB) (□). Data represent means \pm SE or, in the case of nonnormally distributed data, medians (interquartile range).

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

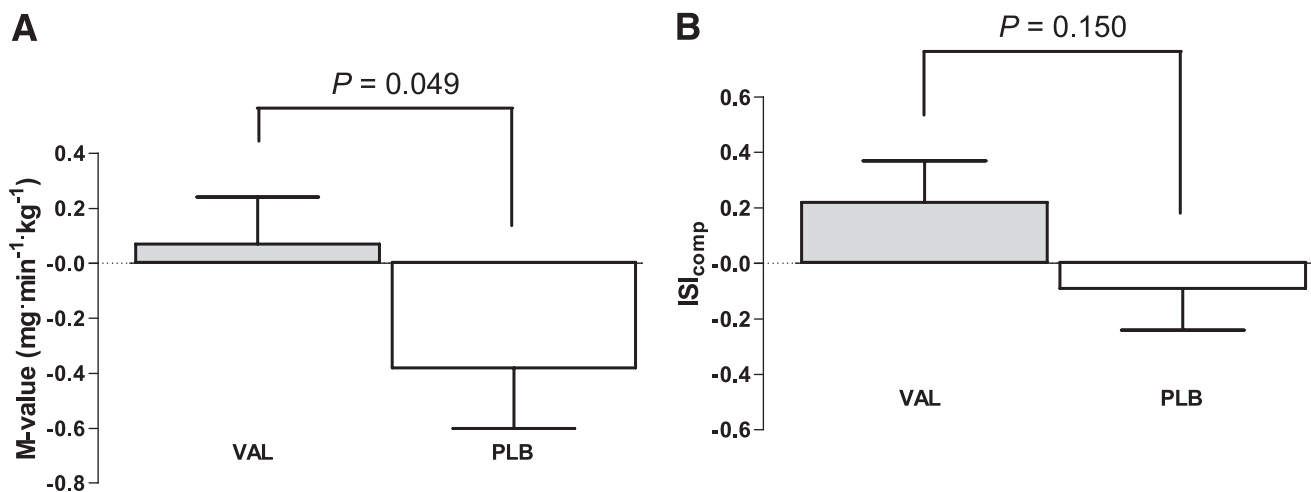


Figure 3—Effect of 26 weeks of valsartan (VAL) treatment on clamp- and OGTT-derived insulin sensitivity. Changes in clamp-derived insulin sensitivity (A) and OGTT-derived insulin sensitivity (B) at 26 weeks of valsartan (■) or placebo (PLB) (□). Data represent means \pm SE.

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 HbA_{1c}. 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 pathophysiological 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.

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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.

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References

1. Lastra-Lastra G, Sowers JR, Restrepo-Erazo K, Manrique-Acevedo C, Lastra-González G. Role of aldosterone and angiotensin II in insulin resistance: an update. *Clin Endocrinol (Oxf)* 2009;71:1–6
2. Velloso LA, Folli F, Sun XJ, White MF, Saad MJ, Kahn CR. Cross-talk between the insulin and angiotensin signaling systems. *Proc Natl Acad Sci USA* 1996;93:12490–12495
3. Shiuchi T, Iwai M, Li HS, et al. Angiotensin II type-1 receptor blocker valsartan enhances insulin sensitivity in skeletal muscles of diabetic mice. *Hypertension* 2004;43:1003–1010
4. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. *Diabetologia* 1998;41:127–133
5. Julius S, Kjeldsen SE, Weber M, et al.; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022–2031
6. Jandeleit-Dahm KA, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J Hypertens* 2005;23:463–473
7. McMurray JJ, Holman RR, Haffner SM, et al.; NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1477–1490

8. Fogari R, Preti P, Zoppi A, et al. Effect of valsartan addition to amlodipine on insulin sensitivity in overweight-obese hypertensive patients. *Intern Med* 2008;47:1851–1857
9. Janke J, Engeli S, Gorzelnik K, Luft FC, Sharma AM. Mature adipocytes inhibit in vitro differentiation of human preadipocytes via angiotensin type 1 receptors. *Diabetes* 2002;51:1699–1707
10. Lupi R, Del Guerra S, Bugliani M, et al. The direct effects of the angiotensin-converting enzyme inhibitors, zofenoprilat and enalaprilat, on isolated human pancreatic islets. *Eur J Endocrinol* 2006;154:355–361
11. Tikellis C, Wookey PJ, Candido R, Andrikopoulos S, Thomas MC, Cooper ME. Improved islet morphology after blockade of the renin-angiotensin system in the ZDF rat. *Diabetes* 2004;53:989–997
12. Bokhari S, Israelian Z, Schmidt J, Brinton E, Meyer C. Effects of angiotensin II type 1 receptor blockade on β -cell function in humans. *Diabetes Care* 2007;30:181
13. Suzuki K, Nakagawa O, Aizawa Y. Improved early-phase insulin response after candesartan treatment in hypertensive patients with impaired glucose tolerance. *Clin Exp Hypertens* 2008;30:309–314
14. Walker M, Mari A, Jayapaul MK, Bennett SM, Ferrannini E. Impaired beta cell glucose sensitivity and whole-body insulin sensitivity as predictors of hyperglycaemia in non-diabetic subjects. *Diabetologia* 2005;48:2470–2476
15. Bosch J, Yusuf S, Gerstein HC, et al.; DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006;355:1551–1562
16. Leung PS, Carlsson PO. Pancreatic islet renin angiotensin system: its novel roles in islet function and in diabetes mellitus. *Pancreas* 2005;30:293–298
17. Pacini G, Mari A. Methods for clinical assessment of insulin sensitivity and beta-cell function. *Best Pract Res Clin Endocrinol Metab* 2003;17:305–322
18. DeFronzo RA, Tobin JD, Andres R. Glucoseclamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;237:E214–E223
19. Goossens GH, Blaak EE, Saris WH, van Baak MA. Angiotensin II-induced effects on adipose and skeletal muscle tissue blood flow and lipolysis in normal-weight and obese subjects. *J Clin Endocrinol Metab* 2004;89:2690–2696
20. Kodama J, Katayama S, Tanaka K, Itabashi A, Kawazu S, Ishii J. Effect of captopril on glucose concentration. Possible role of augmented postprandial forearm blood flow. *Diabetes Care* 1990;13:1109–1111
21. Furuhashi M, Ura N, Takizawa H, et al. Blockade of the renin-angiotensin system

- decreases adipocyte size with improvement in insulin sensitivity. *J Hypertens* 2004;22:1977–1982
22. Hsueh W, Davidai G, Henry R, Mudaliar S. Telmisartan effects on insulin resistance in obese or overweight adults without diabetes or hypertension. *J Clin Hypertens (Greenwich)* 2010;12:746–752
23. Sowers JR, Raji L, Jialal I, et al. Angiotensin receptor blocker/diuretic combination preserves insulin responses in obese hypertensives. *J Hypertens* 2010;28:1761–1769
24. Bakris G, Molitch M, Hewkin A, et al.; STAR Investigators. Differences in glucose tolerance between fixed-dose antihypertensive drug combinations in people with metabolic syndrome. *Diabetes Care* 2006;29:2592–2597
25. Meyer C, Pimenta W, Woerle HJ, et al. Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. *Diabetes Care* 2006;29:1909–1914