

ORIGINAL ARTICLE

# Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events

The NAVIGATOR Study Group\*

## ABSTRACT

### BACKGROUND

It is not known whether drugs that block the renin–angiotensin system reduce the risk of diabetes and cardiovascular events in patients with impaired glucose tolerance.

### METHODS

In this double-blind, randomized clinical trial with a 2-by-2 factorial design, we assigned 9306 patients with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors to receive valsartan (up to 160 mg daily) or placebo (and nateglinide or placebo) in addition to lifestyle modification. We then followed the patients for a median of 5.0 years for the development of diabetes (6.5 years for vital status). We studied the effects of valsartan on the occurrence of three coprimary outcomes: the development of diabetes; an extended composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina; and a core composite outcome that excluded unstable angina and revascularization.

### RESULTS

The cumulative incidence of diabetes was 33.1% in the valsartan group, as compared with 36.8% in the placebo group (hazard ratio in the valsartan group, 0.86; 95% confidence interval [CI], 0.80 to 0.92;  $P < 0.001$ ). Valsartan, as compared with placebo, did not significantly reduce the incidence of either the extended cardiovascular outcome (14.5% vs. 14.8%; hazard ratio, 0.96; 95% CI, 0.86 to 1.07;  $P = 0.43$ ) or the core cardiovascular outcome (8.1% vs. 8.1%; hazard ratio, 0.99; 95% CI, 0.86 to 1.14;  $P = 0.85$ ).

### CONCLUSIONS

Among patients with impaired glucose tolerance and cardiovascular disease or risk factors, the use of valsartan for 5 years, along with lifestyle modification, led to a relative reduction of 14% in the incidence of diabetes but did not reduce the rate of cardiovascular events. (ClinicalTrials.gov number, NCT00097786.)

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\*The names of the investigators and members of the committees in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Study Group are listed in Supplementary Appendix 1, available with the full text of this article at NEJM.org.

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PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE have an increased risk of type 2 diabetes mellitus and cardiovascular disease.<sup>1-3</sup> Interventions that might reduce the incidence of diabetes and associated rates of death and complications from cardiovascular causes in such patients are therefore of importance.<sup>3</sup> Several trials have shown that lifestyle modification, including increased physical activity and weight loss, reduces the risk of diabetes, although these trials did not evaluate cardiovascular outcomes.<sup>3-8</sup> Certain drugs, including metformin, acarbose, and rosiglitazone, also reduce the incidence of diabetes, although their effect on cardiovascular events is uncertain.<sup>6,9,10</sup>

Another pharmacologic approach to reducing the risk of diabetes and cardiovascular disease is inhibition of the renin-angiotensin system. Some studies have shown that angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) may reduce the incidence of diabetes and the risk of cardiovascular events among patients with hypertension and other cardiovascular diseases.<sup>11-14</sup> In most of these studies, however, the incidence of diabetes was not the primary outcome of the trial, nor was it confirmed by systematic glucose measurement.<sup>15</sup>

A single trial, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study (ClinicalTrials.gov number, NCT00095654), attempted to prospectively and robustly ascertain the effect of an ACE inhibitor in a population at high risk for diabetes, although the study did not test this treatment in addition to lifestyle modification and was not powered to evaluate cardiovascular outcomes.<sup>16</sup> Ramipril did not reduce the incidence of diabetes, although plasma glucose levels measured 2 hours after an oral glucose load were significantly lower in the ramipril group.<sup>16</sup>

We conducted a large, prospective trial, called Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), to evaluate whether nateglinide, a blood glucose-lowering drug in the meglitinide class, or valsartan, an ARB, would reduce the risk of diabetes and cardiovascular events among patients with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors. This treatment was tested in addition to lifestyle

modification.<sup>17</sup> Here we report the results of the valsartan portion of the study; the results of the nateglinide portion are discussed elsewhere in this issue of the *Journal*.<sup>18</sup>

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## METHODS

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### STUDY PATIENTS

From January 2002 through January 2004, we recruited patients at 806 centers in 40 countries. All eligible patients had impaired glucose tolerance,<sup>3</sup> a fasting plasma glucose level of at least 95 mg per deciliter (5.3 mmol per liter) but less than 126 mg per deciliter (7.0 mmol per liter), and one or more cardiovascular risk factors (if 55 years of age or older) or known cardiovascular disease (if 50 years of age or older). A screening glucose-tolerance test was performed 2 hours after a 75-g oral glucose load to determine study eligibility. Impaired glucose tolerance was defined as a post-load plasma glucose level of at least 140 mg per deciliter (7.8 mmol per liter) but less than 200 mg per deciliter (11.1 mmol per liter).<sup>3</sup> (For details, see Section 2 in Supplementary Appendix 1, available with the full text of this article at NEJM.org.)

Exclusion criteria were laboratory abnormalities or conditions that could interfere with assessment of the safety or efficacy of a study drug, the use of an ACE inhibitor or ARB for the treatment of hypertension (although ACE inhibitors were allowed for other indications), and the use of an antidiabetic medication within the previous 5 years.<sup>17</sup>

The trial was approved by each center's ethics committee. All patients provided written informed consent.

### STUDY TREATMENT

We used a computerized, interactive voice-response telephone randomization system involving concealed study-group assignments to randomly assign patients to valsartan or matching placebo (and nateglinide or matching placebo) in a 2-by-2 factorial design. Randomization was stratified according to center, with a block size of eight within each center. Valsartan was started at a dose of 80 mg once daily, with an increase after 2 weeks to 160 mg once daily; dose reduction or interruption because of adverse events or for other clinical reasons was permitted.

**LIFESTYLE MODIFICATION**

All patients were required to participate in a study-specific lifestyle-intervention program that was designed to reduce the risk of diabetes. The objective of the intervention was to help patients achieve and maintain a 5% weight loss, reduce intake of saturated and total dietary fat, and increase physical activity to 150 minutes weekly (see Section 3 in Supplementary Appendix 1). Site personnel were trained to administer this program and provided materials designed to facilitate adherence at each clinic visit, with reinforcement and monitoring by telephone between study visits.

**STUDY PROCEDURES**

After the dose-adjustment phase, patients were seen every 6 months. Fasting plasma glucose levels were measured every 6 months for the first 3 years and then annually. Oral glucose tolerance tests were performed yearly. The morning dose of a study drug was delayed until after glucose levels had been measured.

**STUDY OUTCOMES***Coprimary Outcomes*

Initially, there were two coprimary outcomes: the incidence of diabetes and an extended cardiovascular outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina. A third coprimary core cardiovascular outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure), which was initially a secondary composite outcome, was added, as described previously.<sup>17,19</sup>

*Incidence of Diabetes*

Diabetes was defined as a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or more or a plasma glucose level of 200 mg per deciliter (11.1 mmol per liter) or more as measured 2 hours after an oral glucose load,<sup>20,21</sup> confirmed within 12 weeks by a glucose tolerance test. The date of onset of diabetes was defined as the date of the first diagnostic glucose value. An independent committee whose members were not aware of study-group assignments adjudicated the small number of cases in which patients received a diagnosis of diabetes or were started on an an-

tidiabetic drug without undergoing the study-specified laboratory investigations.

*Death, Hospitalization, and Other Cardiovascular Events*

An independent committee whose members were unaware of study-group assignments adjudicated the occurrence of death, hospitalization, and potential cardiovascular events that occurred in patients who were not hospitalized (for definitions of these events, see Section 4 in Supplementary Appendix 1).

**STUDY OVERSIGHT**

The trial was sponsored by Novartis Pharma and was designed in collaboration with an academic executive committee and monitored by an independent safety committee.<sup>17</sup> Data were collected, managed, and analyzed by the sponsor, with oversight from the executive committee, and the analyses were replicated by an independent academic statistician. The manuscript was prepared by a writing group, whose members had unrestricted access to the data, and was subsequently revised by all the authors. All authors decided to submit the manuscript for publication and assume responsibility for its accuracy and completeness. The trial protocol is available in Supplementary Appendix 2.

**STATISTICAL ANALYSIS**

On the assumption that the study would continue until the extended cardiovascular outcome occurred in 1774 patients in the placebo group, we anticipated a power of 90% to detect a 20% reduction in the hazard rate in the valsartan group, assuming subadditivity of the effects of valsartan and nateglinide and allowing for an annual discontinuation rate of 6.9%.<sup>17</sup> These calculations were revised after an updated meta-analysis of trials of renin-angiotensin blockers suggesting that the reduction in the hazard of the extended cardiovascular outcome was more likely to be 12% (providing a power of 64%) and 18% for the core cardiovascular outcome (providing a power of 74%, assuming the occurrence of 784 core events); the estimated power to show a reduction in at least one of the cardiovascular outcomes was 77%.<sup>17,19</sup>

While accumulating 1374 extended cardiovascular events, we anticipated that more than 3000 patients would have progression to diabetes, en-

asuring a power of more than 99% to detect a hazard reduction of 18%. Because we examined the effects of two drugs (valsartan and nateglinide) on three primary outcomes in a factorial manner, we adjusted for the three tests that were performed for each study drug (but not across drugs). Two-sided P values are given, with protocol-specified one-sided values for the coprimary outcomes and their components. The one-sided familywise type I error rate of 2.5% for each drug was controlled with the use of a closed-testing procedure, with one fifth of the alpha assigned to diabetes and four fifths to the two cardiovascular outcomes, since more cases of incident diabetes than cardiovascular events were anticipated. This allowed for testing of each primary outcome even if the other two outcomes did not show a significant result. An O'Brien–Fleming–type alpha spending approach accounted for the interim efficacy analysis performed with 30% of the target number of extended cardiovascular events (a one-sided alpha of 0.00004) in November 2005.<sup>22</sup> (For details, see Section 5 in Supplementary Appendix 1.)

Log-rank tests that were stratified according to a history of cardiovascular disease and nateglinide treatment were used to compare the valsartan and placebo groups for the time to a first event in the extended or core composite outcome. Given the fixed-time schedule for glucose measurement, a discrete time proportional-odds model was used for the incidence of diabetes. We also conducted predefined analyses of the components of the composite cardiovascular outcomes, time to death from any cause, time to cardiovascular-related hospitalization, indexes of hyperglycemia, and body weight. The possibility of interaction between valsartan and nateglinide was tested for each outcome reported. The effects of study treatment were evaluated in prespecified subgroups.<sup>17</sup> We compared baseline characteristics, safety, and other trial assessments using summary statistics.

## RESULTS

### STUDY PATIENTS

Of 43,502 patients who underwent screening, 9518 were randomly assigned to treatment. After randomization, 212 patients were excluded from the analysis, since 10 sites were closed because of deficiencies in meeting Good Clinical Practice guidelines, which left 9306 patients who could be evaluated (Fig. 1).

Among patients who were taking a study drug

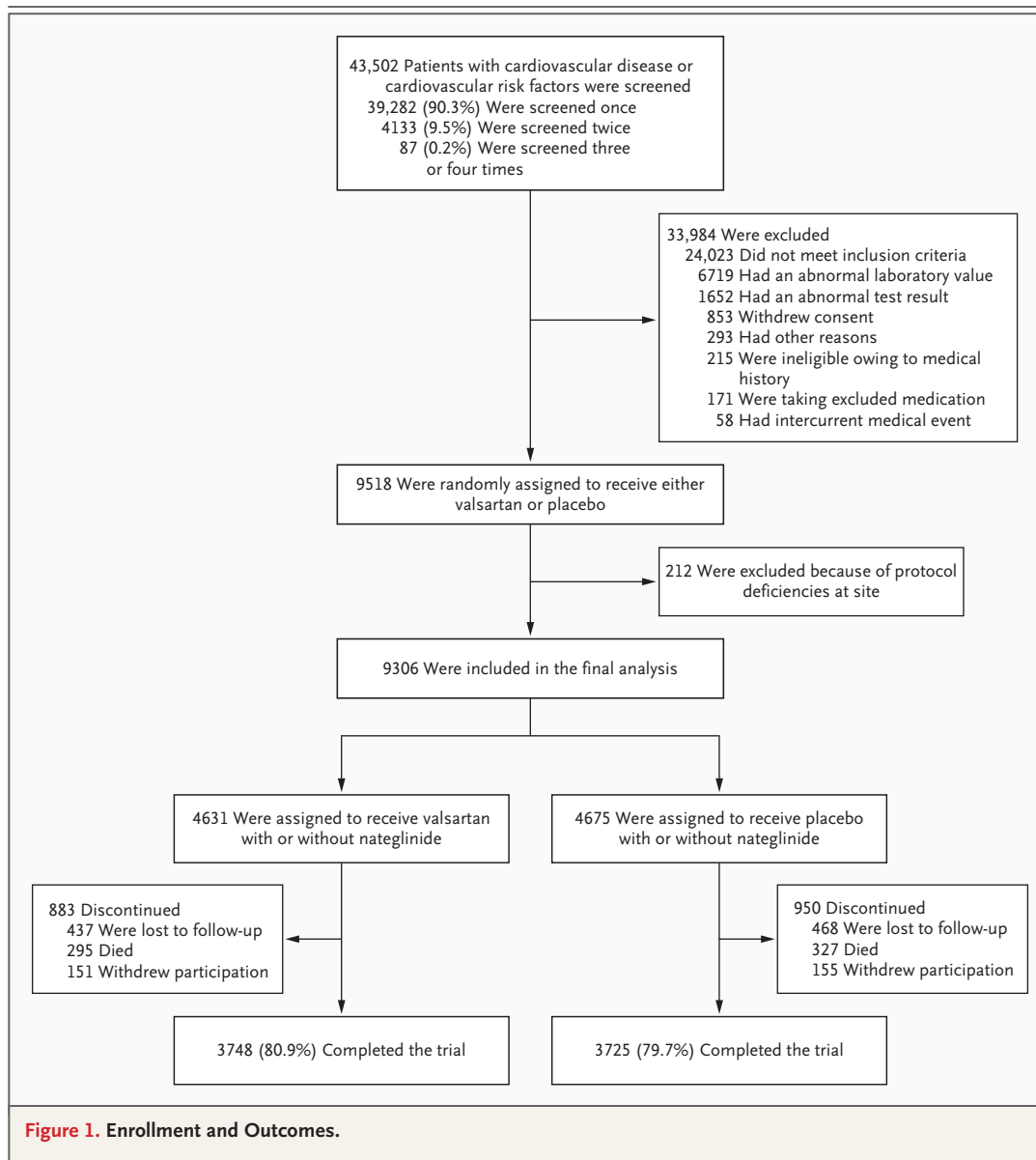
at 6 months, 91.1% of those who were assigned to receive valsartan were taking the higher dose (160 mg daily); this proportion was 94.6% in the placebo group ( $P<0.001$ ). At 1 year, 77.6% of patients in the valsartan group were taking a study drug, as compared with 79.2% of those in the placebo group ( $P=0.06$ ). The corresponding proportions in the valsartan group and the placebo group were 72.3 and 73.3% at 3 years ( $P=0.29$ ) and 66.2% and 66.7% at 5 years ( $P=0.59$ ).

Baseline characteristics were similar in the valsartan and placebo groups. Of the 9306 patients who were evaluated, 2266 (24.3%) had known cardiovascular disease, mainly coronary artery disease. Of the remainder who had cardiovascular risk factors only, 79.6% had a history of hypertension.

Patients with cardiovascular disease were treated more intensively at baseline than were those who had risk factors only: 21.5% received an ACE inhibitor, as compared with 2.7% of those with risk factors only; 75.8% received antiplatelet treatment, as compared with 24.2% of those with risk factors only; 61.7% received a beta-blocker, as compared with 32.2% of those with risk factors only; and 64.1% received lipid-modifying therapy, as compared with 30.2% of those with risk factors only.

The use of diuretics and calcium-channel blockers was similar in the two groups. The use of nonstudy cardiovascular treatments increased during follow-up (Table 1).<sup>23,24</sup> At the last study visit, 20.4% of patients in the valsartan group and 24.0% of those in the placebo group were receiving an open-label renin–angiotensin inhibitor ( $P<0.001$ ). In the placebo group, as compared with the valsartan group, 5.3% more patients were taking a diuretic, and 3.1% more were taking a beta-blocker ( $P<0.001$  for both comparisons).

Blood-pressure levels decreased more in the valsartan group than in the placebo group, with a mean ( $\pm$ SD) overall reduction in systolic pressure of  $6.3\pm 14.2$  mm Hg in the valsartan group, as compared with a reduction of  $3.8\pm 13.8$  mm Hg in the placebo group (between-group difference, 2.8 mm Hg; 95% confidence interval [CI], 2.4 to 3.2;  $P<0.001$ ) with adjustment for region, cardiovascular history, and nateglinide treatment (Fig. 2A). The mean reduction in diastolic pressure was  $4.4\pm 8.4$  mm Hg in the valsartan group, as compared with a reduction of  $3.0\pm 8.1$  mm Hg in the placebo group (difference, 1.4 mm Hg; 95% CI, 1.2 to 1.7;  $P<0.001$ ) (Fig. 2B). There was a small



decline in weight during follow-up that was slightly less in the valsartan group ( $0.31 \pm 3.9$  kg) than in the placebo group ( $0.60 \pm 4.0$  kg), a difference of 0.28 kg (95% CI, 0.12 to 0.44;  $P < 0.001$ ) (Fig. 2C). There was little change in waist circumference during the study, with an increase of  $0.08 \pm 6.5$  cm in the valsartan group, as compared with a decrease of  $0.16 \pm 6.5$  cm in the placebo group (difference, 0.20 cm; 95% CI,  $-0.05$  to 0.45;  $P = 0.12$ ) (Fig. 2D).

#### FOLLOW-UP

Among surviving patients who had not withdrawn consent and had not received a clinical diagnosis of

diabetes, 80% underwent measurement of fasting plasma glucose or plasma glucose 2 hours after an oral glucose load at the close-out visit or during the final 6 months of the study. The rate of loss to follow-up (including withdrawal of consent) was 12.7% in the valsartan group (588 patients) and 13.3% in the placebo group (623 patients). Because many discontinuations occurred late in the study, information on vital status was available for 96% of possible follow-up time in the two study groups. The median follow-up was 6.5 years for vital status, 6.4 years for the core cardiovascular outcome, 6.3 years for the extended cardiovascular outcome, and 5.0 years for the incidence of diabetes.

Characteristic	Valsartan (N=4631)	Placebo (N=4675)	P Value
Age — yr	63.7±6.8	63.8±6.8	0.27
Female sex — no. (%)	2314 (50.0)	2397 (51.3)	0.29
Race — no. (%)†			
White	3849 (83.1)	3885 (83.1)	0.96
Black	113 (2.4)	123 (2.6)	
Asian	298 (6.4)	315 (6.7)	
Other	371 (8.0)	352 (7.5)	
Weight — kg	83.5±17.4	83.8±17.1	0.38
Body-mass index‡	30.4±5.5	30.6±5.3	0.29
Waist circumference — cm			
All patients	101±14	101±14	0.36
Men	104±13	104±12	
Women	98±14	98±14	
Sitting blood pressure — mm Hg			
Systolic	139.4±17.8	139.9±17.1	0.21
Diastolic	82.5±10.4	82.6±10.1	0.93
Cardiovascular risk factors — no. (%)			
Any	4565 (98.6)	4621 (98.8)	0.26
Family history of premature heart disease	782 (16.9)	762 (16.3)	0.44
Current smoker	518 (11.2)	507 (10.8)	0.59
Hypertension	3581 (77.3)	3635 (77.8)	0.62
Left ventricular hypertrophy	133 (2.9)	135 (2.9)	0.97
Microalbuminuria	61 (1.3)	53 (1.1)	0.42
Reduced HDL cholesterol	459 (9.9)	433 (9.3)	0.28
Elevated non-HDL cholesterol	2066 (44.6)	2097 (44.9)	0.82
History of cardiovascular disease — no. (%)			
Any	1148 (24.8)	1118 (23.9)	0.30
Myocardial infarction	552 (11.9)	541 (11.6)	0.60
Angina or positive stress test	416 (9.0)	400 (8.6)	0.47
Percutaneous coronary intervention	190 (4.1)	172 (3.7)	0.29
Multivessel coronary-artery bypass grafting	182 (3.9)	198 (4.2)	0.46
Intermittent claudication	42 (0.9)	56 (1.2)	0.17
Peripheral-artery stenosis	32 (0.7)	22 (0.5)	0.16
Lower-limb angioplasty or bypass surgery	61 (1.3)	49 (1.0)	0.24
Nontraumatic leg or foot amputation	5 (0.1)	2 (<0.1)	0.25
Stroke of atherosclerotic origin	143 (3.1)	132 (2.8)	0.44
Family history of diabetes mellitus — no. (%)	1737 (37.5)	1810 (38.7)	0.25
Glycemic indexes			
Fasting plasma glucose — mmol/liter	6.1±0.45	6.1±0.45	0.55
Plasma glucose 2 hr after glucose load — mmol/liter	9.2±0.93	9.2±0.94	0.44
Glycated hemoglobin — %	5.79±0.47	5.82±0.46	0.08
Metabolic syndrome — no. (%)§	3825 (82.6)	3970 (85.0)	0.003

<b>Table 1. (Continued.)</b>			
<b>Characteristic</b>	<b>Valsartan (N = 4631)</b>	<b>Placebo (N = 4675)</b>	<b>P Value</b>
<b>Lipids — mg/dl</b>			
Total cholesterol	209±42	209±42	0.78
HDL cholesterol	50±14	50±13	0.67
LDL cholesterol	127±38	127±37	0.99
Triglycerides	177±104	117±104	0.25
Median	150	150	
Interquartile range	106–212	106–212	
Creatinine — mg/dl	0.9±0.2	0.9±0.2	0.29
<b>Estimated GFR¶</b>			
Mean — ml/min/1.73 m <sup>2</sup>	80.9±18.5	80.4±19.0	0.20
<60 ml/min/1.73 m <sup>2</sup> — no. (%)	499 (10.8)	521 (11.1)	0.53
<b>Ratio of urinary albumin (mg) to creatinine (g)</b>			
Median	0.8	0.8	
Interquartile range	0.5–1.6	0.5–1.7	
<b>Concomitant medication — no. (%)  </b>			
<b>ACE inhibitor</b>			
Baseline	351 (7.6)	325 (7.0)	0.36
Last study visit	688 (14.9)	786 (16.8)	0.005
<b>Angiotensin-receptor blocker</b>			
Baseline	10 (0.2)	20 (0.4)	0.07
Last study visit	212 (4.6)	266 (5.7)	0.02
<b>Alpha-blocker</b>			
Baseline	289 (6.2)	288 (6.2)	0.87
Last study visit	213 (4.6)	260 (5.6)	0.04
<b>Beta-blocker</b>			
Baseline	1863 (40.2)	1803 (38.6)	0.15
Last study visit	1840 (39.7)	2000 (42.8)	<0.001
<b>Calcium-channel blocker</b>			
Baseline	1483 (32.0)	1529 (32.7)	0.46
Last study visit	1537 (33.2)	1857 (39.7)	<0.001
<b>Diuretic</b>			
Baseline	1451 (31.3)	1509 (32.3)	0.36
Last study visit	1578 (34.1)	1841 (39.4)	<0.001
<b>Any antihypertensive drug</b>			
Baseline	3398 (73.4)	3418 (73.1)	0.90
Last study visit	3409 (73.6)	3696 (79.1)	<0.001
<b>Lipid-lowering drug**</b>			
Baseline	1782 (38.5)	1795 (38.4)	0.81
Last study visit	2298 (49.6)	2361 (50.5)	0.27
<b>Aspirin or other antiplatelet drug</b>			
Baseline	1729 (37.3)	1696 (36.3)	0.50
Last study visit	2103 (45.4)	2130 (45.6)	0.64

Characteristic	Valsartan (N = 4631)	Placebo (N = 4675)	P Value
Antidiabetic drug			
Baseline	1 (<0.1)	6 (0.1)	0.06
Last study visit	588 (12.7)	733 (15.7)	<0.001

\* Plus-minus values are means  $\pm$ SD. Cochran-Mantel-Haenszel tests were used for categorical variables; F tests (variance ratio tests) were used for continuous variables. Both tests were stratified according to the use or nonuse of the other study drug (nateglinide) and presence or absence of a history of cardiovascular disease, except for cardiovascular disease or risk factors, which were stratified according to age (<55 years or  $\geq$ 55 years). To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, GFR glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein.

† Race was reported by investigators.

‡ The body-mass index (the weight in kilograms divided by the square of the height in meters) was adjusted for sex.

§ The metabolic syndrome was defined according to the guidelines of the International Diabetes Federation.<sup>23</sup>

¶ The estimated glomerular filtration rate was calculated with the use of the modified formula from the Modification of Diet in Renal Disease study for traceable serum creatinine values as measured by isotope-dilution mass spectrometry.<sup>24</sup>

|| The last study visit was the last time point at which the investigator indicated whether the patient had been taking a concomitant medication. Such a visit was either the end-of-study visit or the last recorded visit before death or withdrawal from the study.

\*\* Statin use increased from 34 to 47% in the valsartan group and from 34 to 49% in the placebo group.

No interaction between valsartan and nateglinide was observed for any of the outcomes described (Section 6 in Supplementary Appendix 1).

## STUDY OUTCOMES

### *Coprietary Diabetes Outcome*

Diabetes mellitus developed in 1532 patients (33.1%) in the valsartan group and 1722 patients (36.8%) in the placebo group (Table 2 and Fig. 3). The hazard ratio for this outcome in the valsartan group, as compared with the placebo group, was 0.86 (95% CI, 0.80 to 0.92;  $P < 0.001$  in both one-sided and two-sided tests). The effect of valsartan on progression to diabetes was consistent across all prespecified subgroups (Section 7A in Supplementary Appendix 1). The proportion of patients who were taking an antidiabetic medication at their last study visit was smaller in the valsartan group than in the placebo group ( $P < 0.001$ ) (Table 1).

### *Glycemia*

During the study, the fasting plasma glucose level was reduced by a mean of 0.59 mg per deciliter (95% CI, 0.16 to 1.02) (0.03 mmol per liter [95% CI, 0.01 to 0.06]) in the valsartan group, as compared with the placebo group ( $P < 0.01$ ) (Fig. 2E). The plasma glucose level 2 hours after a glucose load was reduced by a mean of 3.15 mg per deci-

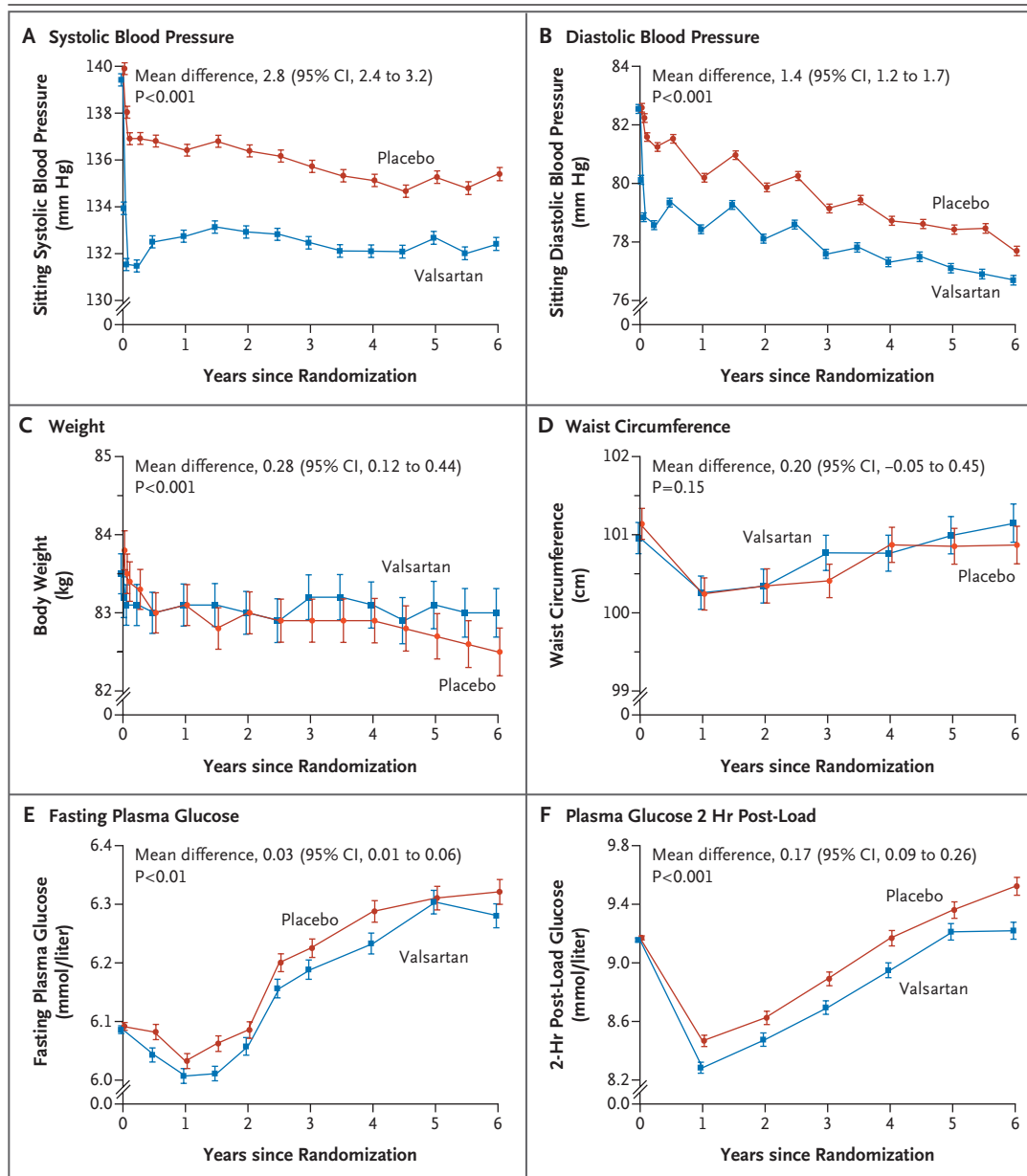
liter (95% CI, 1.58 to 4.72) (0.17 mmol per liter [95% CI, 0.09 to 0.26]) in the valsartan group ( $P < 0.001$ ) (Fig. 2F).

### *Coprietary Cardiovascular Outcomes*

The extended cardiovascular outcome occurred in 672 patients (14.5%) in the valsartan group and 693 patients (14.8%) in the placebo group (Table 2 and Fig. 3). The hazard ratio for this outcome in the valsartan group, as compared with the placebo group, was 0.96 (95% CI, 0.86 to 1.07;  $P = 0.22$  in a one-sided test;  $P = 0.43$  in a two-sided test). The core cardiovascular outcome occurred in 375 patients (8.1%) in the valsartan group and 377 patients (8.1%) in the placebo group (hazard ratio, 0.99; 95% CI, 0.86 to 1.14;  $P = 0.42$  in a one-sided test;  $P = 0.85$  in a two-sided test). The neutral effect of treatment was consistent for both outcomes across all prespecified subgroups (Sections 7B and 7C in Supplementary Appendix 1).

### *Exploratory Outcomes, Including Death*

There was no significant difference between the study groups with respect to any of the components of the extended cardiovascular outcome or the prespecified exploratory outcomes (Table 2). The numbers of deaths were 295 (6.4%) in the valsartan group and 327 (7.0%) in the placebo group ( $P = 0.17$ ).



**Figure 2. Changes in Blood Pressure, Weight, Waist Circumference, and Mean Plasma Glucose Levels.**

Shown are changes over 6 years of follow-up in sitting systolic blood pressure (Panel A), sitting diastolic blood pressure (Panel B), weight (Panel C), waist circumference (Panel D), fasting plasma glucose (Panel E), and plasma glucose measured 2 hours after an oral glucose load (Panel F). To convert the values for glucose to milligrams per deciliter, divide by 0.05551. The I bars indicate standard errors.

#### ADVERSE EVENTS AND DISCONTINUATION OF STUDY DRUG

Nasopharyngitis, back pain, and arthralgia were the most commonly reported individual adverse events (for a complete list, see Section 8 in Supplementary Appendix 1). There was no excess of renal dysfunction or hyperkalemia in the valsartan

group, but hypotension-related adverse events were more common in the valsartan group (occurring in 42.4% of patients) than in the placebo group (35.9%) (P<0.001). During the course of the study, 556 patients (12.0%) in the valsartan group and 531 (11.4%) in the placebo group discontinued the study drug because of an adverse event (P=0.33).

**Table 2. Coprimary Outcomes with Component Events and Key Exploratory Outcomes.\***

Outcome	Valsartan (N = 4631)		Placebo (N = 4675)		Absolute Hazard Difference†	Hazard Ratio (95% CI)‡	P Value§	
	Patients with Event no. (%)	Event Rate no./1000 patient-yr	Patients with Event no. (%)	Event Rate no./1000 patient-yr			One-Sided	Two-Sided
<b>Coprimary outcome</b>								
Progression to diabetes¶	1532 (33.1)	77.3	1722 (36.8)	89.7	-12.6 (-18.4 to -6.9)	0.86 (0.80 to 0.92)	<0.001	<0.001
Extended cardiovascular outcome	672 (14.5)	26.2	693 (14.8)	26.9	-0.6 (-3.0 to 1.8)	0.96 (0.86 to 1.07)	0.22	0.43
Core cardiovascular outcome	375 (8.1)	14.0	377 (8.1)	14.0	0.3 (-1.5 to 2.1)	0.99 (0.86 to 1.14)	0.42	0.85
<b>Components of composite cardiovascular outcomes</b>								
Death from a cardiovascular cause	128 (2.8)	4.5	116 (2.5)	4.1	0.6 (-0.3 to 1.5)	1.09 (0.85 to 1.40)	0.74	0.52
Fatal or nonfatal myocardial infarction	138 (3.0)	5.1	140 (3.0)	5.1	0.1 (-0.9 to 1.1)	0.97 (0.77 to 1.23)	0.41	0.83
Fatal or nonfatal stroke**	105 (2.3)	3.8	132 (2.8)	4.8	-0.9 (-1.9 to 0.2)	0.79 (0.61 to 1.02)	0.04	0.07
Hospitalization for unstable angina	242 (5.2)	9.1	234 (5.0)	8.7	0.5 (-0.7 to 1.8)	1.02 (0.86 to 1.23)	0.60	0.80
Hospitalization for heart failure	91 (2.0)	3.3	94 (2.0)	3.4	0.1 (-0.7 to 1.0)	0.97 (0.72 to 1.29)	0.41	0.81
Arterial revascularization	316 (6.8)	11.9	331 (7.1)	12.4	-0.2 (-1.7 to 1.4)	0.94 (0.80 to 1.10)	0.21	0.42
<b>Exploratory outcomes</b>								
Hospitalization for a cardiovascular reason	886 (19.1)	35.8	879 (18.8)	35.2	0.8 (-2.2 to 3.8)	1.00 (0.91 to 1.10)	NA	0.98
Death	295 (6.4)	10.4	327 (7.0)	11.5	-0.7 (-2.3 to 0.9)	0.90 (0.77 to 1.05)	NA	0.17

\* The coprimary outcomes were progression to diabetes, an extended cardiovascular outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina) and a core cardiovascular outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). NA denotes not applicable.

† To estimate the absolute hazard difference between valsartan and placebo, an exponential model with an additive treatment effect on the hazard scale (as opposed to the log hazard scale) and with different base hazards in each of the four strata of history of cardiovascular disease according to valsartan treatment was used.

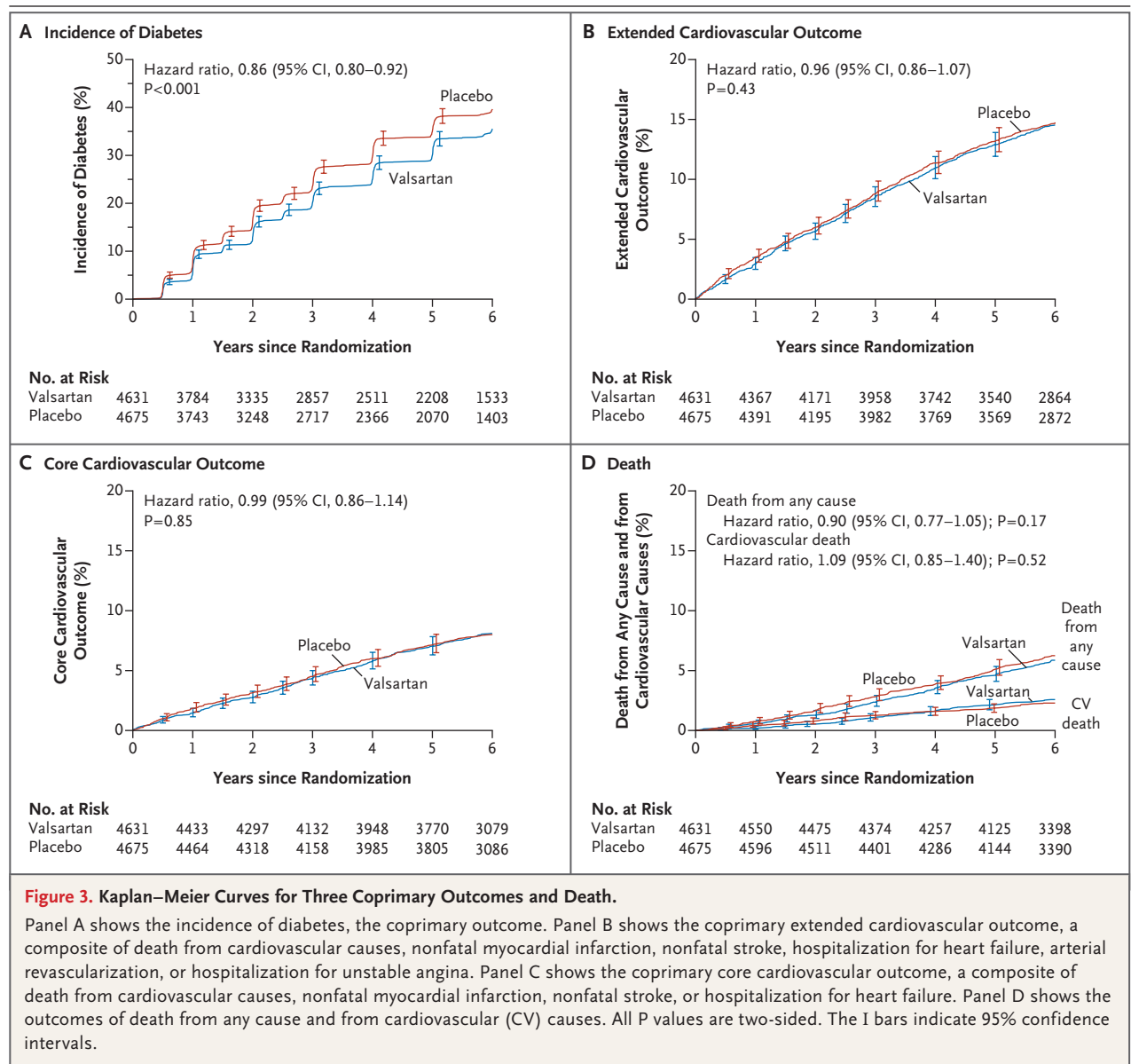
‡ A Cox proportional-hazards model that was stratified according to the other study treatment (nateginide) and the presence or absence of a history of cardiovascular disease was used to estimate hazard ratios and 95% confidence intervals.

§ Unadjusted one-sided and two-sided P values were calculated for coprimary outcomes, and two-sided P values were calculated for exploratory outcomes.

¶ Progression to diabetes was confirmed with the use of laboratory measurements in 1447 patients (31.2%) in the valsartan group and 1635 (35.0%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001 in both one-sided and two-sided tests). Progression to diabetes was determined by the adjudication committee in 85 patients (1.8%) in the valsartan group and 87 (1.9%) in the placebo group.

|| Fatal myocardial infarction occurred in 20 patients in the valsartan group and 25 in the placebo group. One or more nonfatal myocardial infarctions occurred in 119 patients in the valsartan group and 119 in the placebo group.

\*\* Fatal stroke occurred in 14 patients in the valsartan group and 15 in the placebo group. One or more nonfatal strokes occurred in 92 patients in the valsartan group and 118 in the placebo group.



**DISCUSSION**

When added to lifestyle intervention, a single daily dose of valsartan (up to 160 mg) reduced the risk of diabetes but not of cardiovascular events in patients with impaired glucose tolerance and established cardiovascular disease or risk factors. The relative reduction of 14% in the risk of diabetes in the valsartan group would translate into 38 fewer cases of diabetes per 1000 patients treated for 5 years, a reduction that was consistent across all subgroups that we examined.

The decline was smaller than that suggested by pooled analyses of previous trials of ACE inhibitors and ARBs, which suggested a risk reduction of 25 to 30%.<sup>11-15,25</sup> However, these trials differed from our study in that not all subjects had impaired glucose tolerance, ascertainment and other biases may have led to an overestimation of the effect of these drugs, and study treatment did not include lifestyle modification.<sup>26</sup> In addition, by the end of follow-up in our study, 24% of patients in the placebo group were taking an open-label ACE inhibitor or ARB, and many pa-

tients in the valsartan group had discontinued the study treatment, which probably reduced the observed effect of the drug.

Despite these factors, the effect of valsartan was greater than that of an ACE inhibitor in the only previous trial that had the development of diabetes or death as the prospectively defined primary outcome. In the DREAM study, there was a nonsignificant trend toward a reduction in the incidence of diabetes in the ramipril group, with 449 patients who had diabetes in the ramipril group, as compared with 489 in the placebo group (hazard ratio, 0.91; 95% CI, 0.80 to 1.03;  $P=0.15$ ), over a median follow-up period of 3 years.<sup>16</sup> The mechanism by which inhibitors of the renin-angiotensin system reduce the incidence of diabetes is unknown.<sup>27-30</sup>

Although indirect comparisons can be misleading, the effect of valsartan was smaller than that of lifestyle modification, which reduced the incidence of diabetes by 58% in two trials.<sup>5,6</sup> However, in these two studies, the patient populations differed from that in our study, and the study periods were shorter. In addition, we tested the effect of valsartan combined with lifestyle modification. The effect of valsartan was also smaller than that of acarbose, metformin, or rosiglitazone, medications that have a recognized glucose-lowering action, although none of these drugs were tested in addition to lifestyle modification or for as long as valsartan.

There are several possible reasons that valsartan did not improve cardiovascular outcomes, as expected. Our patients differed from those in previous trials of renin-angiotensin antagonists with cardiovascular outcomes in that all the patients had impaired glucose tolerance, only a minority (24%) had established cardiovascular disease, and blood pressure was relatively well controlled. The benefit of renin-angiotensin system blockade has

also been smaller in recent studies than observed historically, possibly because of greater use of other risk-reducing therapies.<sup>14,31-33</sup> The patients with cardiovascular disease in our study were extensively treated with such therapies, including an ACE inhibitor in 22% of patients at baseline, and the use of nonstudy therapies, including open-label ACE inhibitors and ARBs, increased during follow-up. These factors, coupled with the discontinuation of valsartan in a substantial proportion of patients, may have diluted any potential benefit of valsartan. Furthermore, lifestyle modification improves cardiovascular risk factors<sup>34</sup> and, in the long term, may also reduce the rate of cardiovascular events.<sup>35</sup> Finally, the most convincing evidence of improved cardiovascular outcomes with valsartan comes from trials in which patients received twice the daily dose that we used.<sup>36,37</sup>

Although lifestyle modification should remain the primary intervention to reduce the risk of diabetes in the general population, our findings may have implications for the treatment of hypertension, since the use of both thiazide diuretics and beta-blockers has been associated with an increased risk of diabetes.<sup>27-29</sup>

In conclusion, when added to a lifestyle intervention, valsartan at a daily dose of 160 mg reduced the risk of diabetes but did not affect cardiovascular outcomes in patients with impaired glucose tolerance. No safety concerns were identified.

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#### APPENDIX

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