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Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events

The NAVIGATOR Study Group*

ABSTRACT

BACKGROUND

The ability of short-acting insulin secretagogues to reduce the risk of diabetes or cardiovascular events in people with impaired glucose tolerance is unknown.

METHODS

In a double-blind, randomized clinical trial, we assigned 9306 participants with impaired glucose tolerance and either cardiovascular disease or cardiovascular risk factors to receive nateglinide (up to 60 mg three times daily) or placebo, in a 2-by-2 factorial design with valsartan or placebo, in addition to participation in a lifestyle modification program. We followed the participants for a median of 5.0 years for incident diabetes (and a median of 6.5 years for vital status). We evaluated the effect of nateglinide on the occurrence of three coprimary outcomes: the development of diabetes; a core cardiovascular outcome that was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; and an extended cardiovascular outcome that was a composite of the individual components of the core composite cardiovascular outcome, hospitalization for unstable angina, or arterial revascularization.

RESULTS

After adjustment for multiple testing, nateglinide, as compared with placebo, did not significantly reduce the cumulative incidence of diabetes (36% and 34%, respectively; hazard ratio, 1.07; 95% confidence interval [CI], 1.00 to 1.15; P=0.05), the core composite cardiovascular outcome (7.9% and 8.3%, respectively; hazard ratio, 0.94, 95% CI, 0.82 to 1.09; P=0.43), or the extended composite cardiovascular outcome (14.2% and 15.2%, respectively; hazard ratio, 0.93, 95% CI, 0.83 to 1.03; P=0.16). Nateglinide did, however, increase the risk of hypoglycemia.

CONCLUSIONS

Among persons with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors, assignment to nateglinide for 5 years did not reduce the incidence of diabetes or the coprimary composite cardiovascular outcomes. (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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Persons with impaired glucose tolerance are at increased risk for type 2 diabetes mellitus and cardiovascular disease[1-3]; therefore, treatments that might reduce the incidence of diabetes and associated cardiovascular disease and death are potentially important.[3] The risk of diabetes is reduced with lifestyle interventions that involve increasing physical activity and reducing weight [4-6] and with metformin,[6] acarbose,[7] or rosiglitazone[8] therapy, but no trials to date have been powered to consider cardiovascular outcomes.

Among persons with type 2 diabetes, reducing glycemia results in a small reduction in the risk of major macrovascular events.[9] Glucose levels after a glucose challenge, however, are more closely associated with cardiovascular risk than are fasting glucose levels,[2] suggesting that postprandial glycemia may be a distinct therapeutic target. Lowering postprandial glucose levels with the alpha-glucosidase inhibitor acarbose has been reported to decrease the risk of myocardial infarction among persons with impaired glucose tolerance.[10]

In a large, prospective study involving persons with impaired glucose tolerance and cardiovascular disease or cardiovascular risk factors, we evaluated an alternative postprandial glucose-lowering approach that used the short-acting insulin secretagogue nateglinide, in addition to a lifestyle modification program. The aim of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial[11] was to determine whether the risk of diabetes and cardiovascular events could be reduced in this population.

Methods

Study Oversight

The trial was approved by the ethics committee at each participating center, and all participants provided written informed consent. The study was sponsored by Novartis Pharma, was designed by the sponsor in collaboration with an academic executive committee, and was monitored by an independent data and safety monitoring committee (see Supplementary Appendix 1, available with the full text of this article at NEJM.org).[11] Data were collected, managed, and analyzed by the sponsor, with oversight by the executive committee, and analyses were replicated by an independent academic statistician from the London School of Hygiene and Tropical Medicine. The manuscript was prepared by the writing group (see Section 1 in Supplementary Appendix 1), whose members had unrestricted access to the data, and was revised subsequently by all the authors. All the authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data. The NAVIGATOR trial protocol is available in Supplementary Appendix 2.

Study Participants

Subjects were eligible for inclusion in the study if they had impaired glucose tolerance,[3] a fasting plasma glucose concentration 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 (in the case of subjects who were 55 years of age or older) or known cardiovascular disease (in the case of subjects who were 50 years of age or older) (Section 2 in Supplementary Appendix 1). Subjects were excluded if they had abnormal laboratory test results or concomitant conditions that could interfere with the assessment of the safety or efficacy of the study drug or if they had taken antidiabetic medication within the previous 5 years.[11]

Study Medication

Participants were randomly assigned, with the use of an interactive voice-response telephone system, to nateglinide, at a dose of 60 mg taken before meals three times daily, or placebo and, in a 2-by-2 factorial design, to valsartan or placebo. Both the participants and the investigators were unaware of the treatment assignments. Nateglinide was initially dispensed at a dose of 30 mg, with an increase to the full dose of 60 mg after 2 weeks. Reductions in the dose were permitted if there were side effects. The comparison of valsartan with placebo is reported elsewhere in this issue of the *Journal*.[12]

Lifestyle Modification

All subjects were required to participate in a study-specific lifestyle modification program that was designed to reduce the risk of diabetes (see Section 3 in Supplementary Appendix 1). The aim of the program was to help participants achieve and maintain a 5% weight loss, reduce the amount of saturated and total fats in their diets, and in-

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crease their physical activity to 150 minutes weekly.[5,6] To facilitate adherence, site personnel who were trained to administer the program provided materials to participants at each clinic visit and reinforcement through interim telephone contacts.

STUDY PROCEDURES

After the dose-adjustment phase, participants returned for study visits every 6 months. The fasting plasma glucose level was measured every 6 months for 3 years and annually thereafter. Oral glucose-tolerance tests were performed yearly. On the mornings of study visits, the administration of the study medication was delayed until after the glucose tests had been performed so that the glucose measurements would not be affected by the study drugs.

STUDY OUTCOMES

Initially, there were two coprimary outcomes: incident diabetes mellitus and an extended composite cardiovascular outcome (death from a cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina). A third coprimary core cardiovascular outcome (death from a cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure), which had initially been designated as a secondary outcome, was added, as described previously.[11,13]

Diabetes was considered to be present[14,15] if the participant had a fasting plasma glucose level of 126 mg per deciliter or more or a glucose level of 200 mg per deciliter (11.1 mmol per liter) or more 2 hours after a glucose challenge — confirmed by an oral glucose-tolerance test within 12 weeks after the elevated glucose value was recorded. The date of the onset of diabetes was considered to be the date of the first elevated glucose value. An independent committee, whose members were unaware of the treatment assignments, adjudicated cases in which diabetes was diagnosed by other means. Participants in whom diabetes developed could have open-label antidiabetic medication — with the exception of prandial glucose regulators — added to their regimen.

Deaths, hospitalizations, and potential cardiovascular events that did not result in hospitalization were adjudicated by an independent committee whose members were unaware of the treatment assignments. (Definitions of these outcomes are provided in Section 4 in Supplementary Appendix 1.)

STATISTICAL ANALYSIS

The targeted sample size of 9152 participants was determined on the basis of the estimated number of participants that would be needed to provide the power required for the valsartan-versus-placebo component of the study.[11,13] We estimated that diabetes would develop in at least 3000 of these participants, with the result that the study would have more than 99% power to detect a 25% reduction in the risk of incident diabetes.

Since the effects of the two drugs (nateglinide and valsartan) on the three coprimary outcomes were examined in a factorial manner, we adjusted for the three tests that were performed for each drug, but not across drugs. We report two-sided P values throughout, as well as protocol-specified one-sided values for the coprimary outcomes and their components. The 2.5% one-sided family-wise type I error rate for each drug was controlled with the use of a closed-testing procedure that initially assigned one fifth of the alpha to the diabetes outcome and four fifths to the two cardiovascular outcomes (since we anticipated that there would be more cases of diabetes than of cardiovascular outcomes). This allowed for the testing of each coprimary outcome even if the others did not differ significantly between the study groups but would usually require a two-sided P value of less than 0.01 for the difference in the diabetes outcome to be considered significant (Section 5 in Supplementary Appendix 1). An O'Brien–Fleming type of alpha spending approach accounted for the interim efficacy analysis that was performed in November 2005, when 30% of the target number of participants had had an extended cardiovascular outcome (one-sided alpha spent: 0.00004).[16]

Log-rank tests, stratified according to the presence or absence of a history of cardiovascular disease and to randomized assignment to valsartan or placebo, were used to compare the nateglinide and placebo groups with respect to the time to the first event in the extended or core cardiovascular outcome. A Cox discrete-time proportional-odds model[17] was used to assess incident diabetes, given the fixed-time schedule for glucose measurements. We also performed predefined analyses of the components of the composite cardiovascular outcome, exploratory outcomes (the time to death from all causes and the time to

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cardiovascular-related hospitalization), indexes of hyperglycemia, and body weight. We tested for a possible interaction between valsartan and nateglinide for each reported outcome. The effects of the study treatment were evaluated in prespecified subgroups (Section 6 in Supplementary Appendix 1).[11] Baseline characteristics of the participants, safety assessments, and additional measurements during the trial were compared with the use of summary statistics.

RESULTS

STUDY PARTICIPANTS

Of 43,502 participants who were screened at 806 centers in 40 countries, 9518 were randomly assigned to a study drug between January 4, 2002, and January 29, 2004. The most common reasons for exclusion were ineligibility (96.6%) and refusal to participate (2.5%). After randomization, 212 participants at 10 sites were excluded when the sites were closed owing to deficiencies in the adherence to Good Clinical Practice guidelines, leaving 9306 participants whose data were included in the final analyses (Fig. 1).

Among participants who were taking the study drug at 6 months, fewer people in the nateglinide group than in the placebo group were taking the full dose of the study drug (92.0% vs. 94.2%, P<0.001). At 1 year, 79.8% of the surviving participants in the nateglinide group and 80.8% of those in the placebo group were still receiving the study medication (P=0.26); the respective percentages were 74.7% and 75.9% at 3 years (P=0.20) and 69.9% and 71.0% at 5 years (P=0.28).

The baseline characteristics of the nateglinide and placebo groups did not differ significantly (Table 1). Of the 9306 participants, 3547 (38.1%) reported that a primary relative had diabetes and 2266 (24.3%) had known cardiovascular disease. There were no significant differences between the groups in concomitant treatments at baseline or at study end. At study end, less than 3% of the participants in whom diabetes had not developed were taking open-label glucose-lowering therapies.

FOLLOW-UP

The fasting plasma glucose level or the plasma glucose level 2 hours after a glucose challenge was measured at the closeout visit or during the final 6 months of the study in 80% of the surviving participants who had not withdrawn consent and in whom diabetes had not developed. A total of 609 participants in the nateglinide group (13.1%) and 602 in the placebo group (12.9%) were lost to follow-up or withdrew from the study; however, because many of these participants were lost to follow-up or withdrew consent late in the study, information on vital status was available for 95.7% of the possible follow-up time in both groups. The median follow-up time for data on vital status was 6.5 years, and the median follow-up times for data on the diabetes, extended cardiovascular, and core cardiovascular outcomes were 5.0, 6.3, and 6.4 years, respectively.

STUDY OUTCOMES

Coprimary Diabetes Outcome

Diabetes developed in 1674 participants in the nateglinide group (36.0%) and in 1580 participants in the placebo group (33.9%) (hazard ratio with nateglinide, 1.07; 95% confidence interval [CI], 1.00 to 1.15; P=0.05) (Table 2 and Fig. 2A). The effect of nateglinide on the progression of impaired glucose tolerance to diabetes was consistent across all prespecified subgroups except for subgroups specified according to sex and fasting plasma glucose level (Section 6A in Supplementary Appendix 1).

Coprimary Cardiovascular Outcomes

The extended composite cardiovascular outcome occurred in 658 participants in the nateglinide group (14.2%) and in 707 participants in the placebo group (15.2%) (hazard ratio with nateglinide, 0.93; 95% CI, 0.83 to 1.03; P=0.16 (Table 2 and Fig. 2B). The core composite cardiovascular outcome occurred in 365 participants in the nateglinide group (7.9%) and in 387 participants in the placebo group (8.3%) (hazard ratio with nateglinide, 0.94; 95% CI, 0.82 to 1.09; P=0.43) (Table 2 and Fig. 2C). Nateglinide treatment had no significant effect on the coprimary cardiovascular outcomes in any of the prespecified subgroups (Sections 6B and 6C in Supplementary Appendix 1).

Components of Primary Outcomes and Exploratory Outcomes

As shown in Table 2 and Figure 2D, there were no significant differences between the nateglinide and placebo groups with respect to the components of the extended cardiovascular composite outcome, including death from cardiovascular

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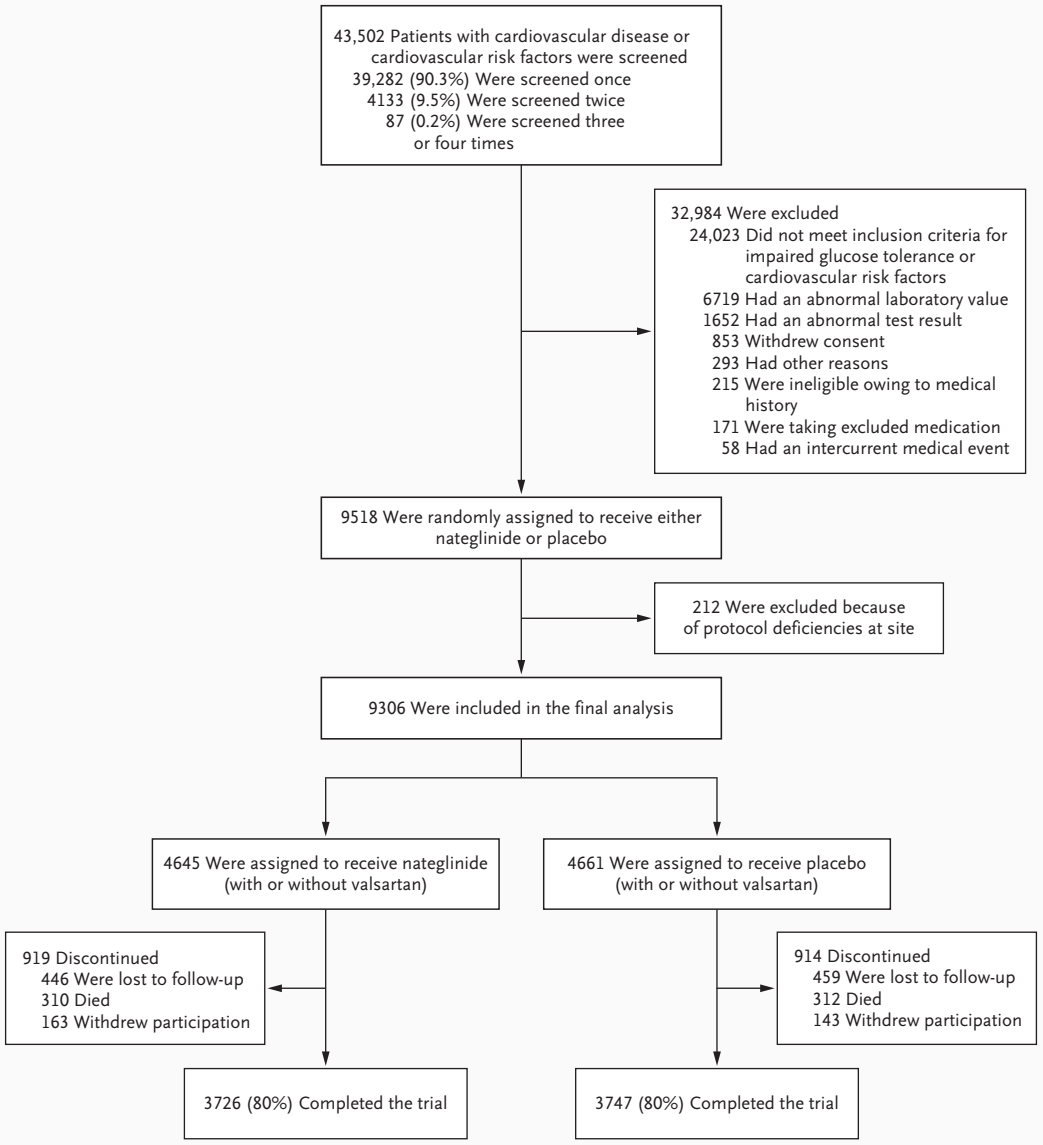

Figure 1. Enrollment and Follow-up of Study Participants.

causes, or with respect to the prespecified exploratory outcomes of hospitalization for a cardiovascular cause and death from any cause.

No interactions between nateglinide and valsartan were seen for any of the outcomes reported (Section 7 in Supplementary Appendix 1).

Glycemia

During the course of the study, participants in the nateglinide group had lower mean fasting plasma glucose levels than did those in the placebo group; the mean difference was 0.47 mg per deciliter (95% CI, 0.05 to 0.90) (0.03 mmol per liter [95% CI, 0.003 to 0.05]) (P=0.03) (Fig. 3A). However, glucose levels 2 hours after a glucose challenge were higher in the nateglinide group than in the placebo group; the mean difference was 4.37 mg per deciliter (95% CI, 2.80 to 5.93) (0.24 mmol per liter [95% CI, 0.16 to 0.33]) (P<0.001) (Fig. 3B).

In the two exploratory analyses we conducted, incident diabetes defined on the basis of fasting

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Table 1. Baseline Characteristics of the Trial Participants According to the Assigned Study Medication.*

Characteristic	Nateglinide (N=4645)	Placebo (N=4661)	P Value
Age — yr	63.7±6.8	63.8±6.9	0.68
Female sex — no. (%)	2368 (51.0)	2343 (50.3)	0.41
Race — no. (%)†			
White	3854 (83.0)	3880 (83.2)	0.71
Black	120 (2.6)	116 (2.5)	
Asian	310 (6.7)	303 (6.5)	
Other	361 (7.8)	362 (7.8)	
Weight — kg	83.6±17.2	83.6±17.2	0.96
Body-mass index‡	30.5±5.4	30.5±5.4	0.45
Waist circumference — cm§	101±14	101±14	0.72
Men	104±12	104±13	
Women	98±14	98±14	
Blood pressure while seated — mm Hg			
Systolic	139.8±17.5	139.5±17.4	0.30
Diastolic	82.6±10.3	82.5±10.2	0.79
Cardiovascular risk factors — no. (%)			
Any	4579 (98.6)	4607 (98.8)	0.22
Family history of premature heart disease	791 (17.0)	753 (16.2)	0.24
Current smoker	519 (11.2)	506 (10.9)	0.57
Hypertension	3608 (77.7)	3608 (77.4)	0.77
Left ventricular hypertrophy	135 (2.9)	133 (2.9)	0.83
Microalbuminuria	45 (1.0)	69 (1.5)	0.03
Reduced HDL cholesterol	443 (9.5)	449 (9.6)	0.89
Elevated non-HDL cholesterol	2047 (44.1)	2116 (45.4)	0.21
History of cardiovascular disease — no. (%)			
Any	1140 (24.5)	1126 (24.2)	0.38
Myocardial infarction	569 (12.2)	524 (11.2)	0.08
Angina or positive stress test	404 (8.7)	412 (8.8)	0.99
Percutaneous coronary intervention	190 (4.1)	172 (3.7)	0.26
Multivessel coronary-artery bypass grafting	194 (4.2)	186 (4.0)	0.61
Intermittent claudication	46 (1.0)	52 (1.1)	0.69
Peripheral arterial stenosis	16 (0.3)	38 (0.8)	0.003
Lower-limb angioplasty or bypass surgery	56 (1.2)	54 (1.2)	0.80
Nontraumatic leg or foot amputation	1 (<0.1)	6 (0.1)	0.06
Stroke	133 (2.9)	142 (3.0)	0.67
Family history of diabetes mellitus — no. (%)	1793 (38.6)	1754 (37.6)	0.33
Plasma glucose — mmol per liter			
Fasting	6.1±0.45	6.1±0.46	0.71
2 hr after glucose challenge	9.2±0.93	9.2±0.94	0.56
Glycated hemoglobin — %	5.8±0.45	5.8±0.48	0.06

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Table 1. (Continued.)

Characteristic	Nateglinide (N=4645)	Placebo (N=4661)	P Value
Metabolic syndrome — no. (%)¶	3897 (84.0)	3898 (83.6)	0.73
Lipids — mg/dl			
Total cholesterol	210±41	210±43	0.87
HDL cholesterol	50±13	50±13	0.43
LDL cholesterol	126±36	127±38	0.96
Triglycerides			0.76
Median	151	150	
Interquartile range	109–208	107–209	
Creatinine — mg/dl	0.9±0.2	0.9±0.2	0.25
Estimated GFR — ml/min/1.73 m^2‖	80.3±18.6	81.1±19.0	0.04
Estimated GFR <60 ml/min/1.73 m^2 — no. (%)	525 (11.3)	495 (10.6)	0.30
Ratio of urinary albumin (mg) to creatinine (g)			0.25
Median	7.1	7.1	
Interquartile range	4.5–14.1	4.5–14.8	
Medications — no. (%)**			
ACE inhibitor			
Baseline	330 (7.1)	346 (7.4)	0.42
Last study visit	729 (15.7)	745 (16.0)	0.64
Angiotensin-receptor blocker			
Baseline	20 (0.4)	27 (0.6)	0.31
Last study visit	317 (6.8)	311 (6.7)	0.75
Alpha-blocker			
Baseline	288 (6.2)	289 (6.2)	0.99
Last study visit	233 (5.0)	240 (5.1)	0.78
Aspirin or other antiplatelet drug			
Baseline	1712 (36.9)	1713 (36.8)	0.92
Last study visit	2119 (45.6)	2114 (45.4)	0.91
Beta-blocker			
Baseline	1872 (40.3)	1794 (38.5)	0.08
Last study visit	1913 (41.2)	1927 (41.3)	0.82
Calcium-channel blocker			
Baseline	1519 (32.7)	1493 (32.0)	0.49
Last study visit	1674 (36.0)	1720 (36.9)	0.39
Diuretic			
Baseline	1461 (31.5)	1499 (32.2)	0.48
Last study visit	1664 (35.8)	1755 (37.7)	0.07
Lipid-modulating drug			
Baseline	1797 (38.7)	1780 (38.2)	0.70
Last study visit	2301 (49.5)	2358 (50.6)	0.25

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Table 1. (Continued.)

Characteristic	Nateglinide (N=4645)	Placebo (N=4661)	P Value
Antidiabetic drug††			
Baseline	2 (<0.1)	5 (0.1)	0.26
Last study visit	651 (14.0)	670 (14.4)	0.61

* Plus–minus values are means ±SD. Cochran–Mantel–Haenszel tests were used in the analyses of categorical variables; F tests (variance ratio tests) were used in the analyses of continuous variables. Both tests were stratified according to valsartan or placebo assignment and presence or absence of a history of cardiovascular disease, except for cardiovascular disease and cardiovascular risk factors, for which stratification was according to age (<55 years vs. ≥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 is the weight in kilograms divided by the square of the height in meters.

§ Waist circumference was adjusted for sex.

¶ The metabolic syndrome was defined according to International Diabetes Federation consensus worldwide definition of the metabolic syndrome.[18]

‖ The estimated GFR was calculated with the use of the modified Modification of Diet in Renal Disease formula.[19]

** The last study visit was defined as the last time the investigator recorded that the patient had or had not been taking concomitant medication — either at the end-of-study visit or at the last recorded visit before the patient's death or withdrawal from the study.

†† Among participants who did not have progression to diabetes according to the protocol-specified criteria, 3.1% in the nateglinide group and 2.4% in the placebo group were taking antidiabetic medication. Among those who did have progression to diabetes, 33.3% and 37.7% in the two groups, respectively, were taking antidiabetic medication.

plasma glucose levels and adjudicated outcomes alone occurred in 775 of the participants in the nateglinide group (16.7%) and 877 of the participants in the placebo group (18.8%) (hazard ratio with nateglinide, 0.87; 95% CI, 0.79 to 0.96; P=0.005). In contrast, incident diabetes defined on the basis of plasma glucose levels 2 hours after a glucose challenge and adjudicated outcomes alone occurred in 981 of the participants in the nateglinide group (21.1%) and 819 of the participants in the placebo group (17.6%) (hazard ratio with nateglinide, 1.24; 95% CI, 1.13 to 1.36; P<0.001). Mean (±SD) glycated hemoglobin levels, measured at the time the diagnosis of diabetes was made, were lower in the nateglinide group than in the placebo group (6.1±0.6% vs. 6.3±0.6%, P<0.001).

Weight and Blood Pressure

There was a reduction in mean body weight during the study, with 10.1% of participants losing 5% of their baseline weight by 6 months, but the mean body weight was higher among participants in the nateglinide group than among those in the placebo group throughout the course of the study (mean difference, 0.35 kg; 95% CI, 0.22 to 0.48; P<0.001) (Fig. 3C). Mean waist circumference was also higher in the nateglinide group than in the placebo group (Fig. 3D). No significant between-group differences were seen in systolic or diastolic blood pressure (Fig. 3E and 3F).

ADVERSE EVENTS AND DISCONTINUATION OF THE STUDY DRUG

A total of 520 participants in the nateglinide group (11.2%) and 485 in the placebo group (10.4%) discontinued the study drug owing to an adverse event (P=0.23). Rates of adverse events did not differ significantly between the groups, except that more participants in the nateglinide group reported hypoglycemia (mostly mild events) (911 participants [19.6%], vs. 527 [11.3%] in the placebo group; P<0.001) (Section 8 in Supplementary Appendix 1).

DISCUSSION

In our study, the addition of nateglinide therapy to a lifestyle modification program did not reduce the risk of diabetes or cardiovascular events among subjects with impaired glucose tolerance and cardiovascular disease or cardiovascular risk factors. In two large-scale studies of lifestyle intervention, the rate of progression from impaired glucose tolerance to diabetes was reduced by

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Table 2. Rates of Coprimary Outcomes, Component Events, and Key Exploratory Outcomes.

Outcome	Nateglinide (N=4645)		Placebo (N=4661)		Absolute Hazard Difference*	Hazard Ratio† (95% CI)	P Value	
	Participants with Event	Event Rate	Participants with Event	Event Rate			Unadjusted One-Sided	Two-Sided
	no. (%)	*no. of events/ 1000 patient-yr**	*no. (%)*	*no. of events/ 1000 patient-yr**				
Coprimary outcomes								
Progression to diabetes‡	1674 (36.0)	86.4	1580 (33.9)	80.4	6.18 (0.47 to 11.90)	1.07 (1.00 to 1.15)	0.98	0.05
Extended composite cardiovascular outcome§	658 (14.2)	25.6	707 (15.2)	27.5	−0.61 (−3.01 to 1.79)	0.93 (0.83 to 1.03)	0.08	0.16
Core composite cardiovascular outcome¶	365 (7.9)	13.6	387 (8.3)	14.4	−0.29 (−2.08 to 1.49)	0.94 (0.82 to 1.09)	0.22	0.43
Component events of extended composite cardiovascular outcome								
Death from cardiovascular cause	126 (2.7)	4.4	118 (2.5)	4.1	0.59 (−0.34 to 1.52)	1.07 (0.83 to 1.38)	0.70	0.60
Fatal or nonfatal myocardial infarction‖	135 (2.9)	5.0	143 (3.1)	5.2	−0.21 (−1.20 to 0.79)	0.95 (0.75 to 1.20)	0.33	0.66
Fatal or nonfatal stroke**	111 (2.4)	4.1	126 (2.7)	4.6	−0.37 (−1.39 to 0.66)	0.89 (0.69 to 1.15)	0.18	0.36
Hospitalization for unstable angina	222 (4.8)	8.3	254 (5.4)	9.4	−0.55 (−1.81 to 0.70)	0.87 (0.73 to 1.05)	0.07	0.14
Hospitalization for heart failure	85 (1.8)	3.1	100 (2.1)	3.6	−0.27 (−1.14 to 0.59)	0.85 (0.64 to 1.14)	0.14	0.27
Arterial revascularization	332 (7.1)	12.5	315 (6.8)	11.8	0.84 (−0.68 to 2.36)	1.06 (0.91 to 1.24)	0.78	0.44
Exploratory outcomes								
Hospitalization for cardiovascular cause	883 (19.0)	35.6	882 (18.9)	35.4	1.78 (−1.17 to 4.74)	1.00 (0.91 to 1.09)		0.94
Death from any cause	310 (6.7)	10.9	312 (6.7)	11.0	0.28 (−1.32 to 1.89)	1.00 (0.85 to 1.17)		0.98

* The absolute hazard differences between nateglinide and placebo were estimated with the use of an exponential model with an additive treatment effect on the hazard scale, rather than the log-hazard scale, with different base hazards for those with or without a history of cardiovascular disease and with or without assignment to valsartan treatment.

† A Cox proportional-hazards (odds) model stratified according to randomized assignment to valsartan or placebo and presence or absence of a history of cardiovascular disease was used to estimate hazard ratios and 95% confidence intervals.

‡ Progression to diabetes was confirmed by laboratory measurements in 1587 participants in the nateglinide group (34.2%) and 1495 participants in the placebo group (32.1%) (hazard ratio in the nateglinide group, 1.08; 95% CI, 1.00 to 1.16; P=0.04). Progression to diabetes was determined by the adjudication committee in the case of 87 participants assigned to nateglinide (1.9%) and 85 assigned to placebo (1.8%).

§ The extended composite cardiovascular outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina, heart failure, or arterial revascularization.

¶ The core composite cardiovascular outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

‖ A total of 23 participants in the nateglinide group had a fatal myocardial infarction and 116 had one or more nonfatal myocardial infarctions. The corresponding numbers among participants assigned to placebo were 22 and 122, respectively.

** A total of 13 participants in the nateglinide group had a fatal stroke and 100 had at least one nonfatal stroke. The corresponding numbers among participants assigned to placebo were 16 and 110, respectively.

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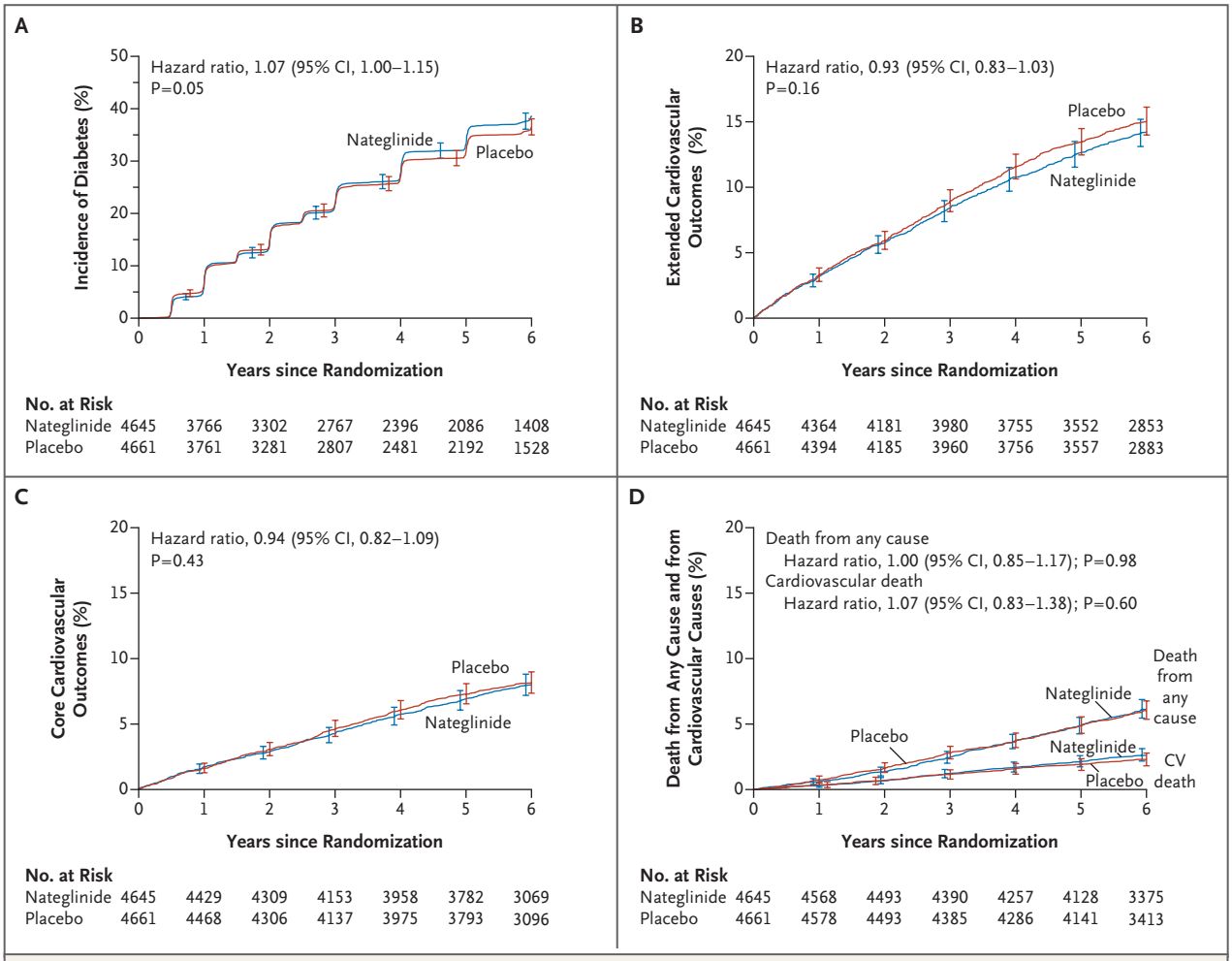

Figure 2. Kaplan–Meier Curves for the Coprimary and Two Exploratory Outcomes in the Nateglinide and Placebo Groups.

Panel A shows results for the coprimary outcome of incident diabetes, Panel B for the coprimary outcome of extended cardiovascular outcomes (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina, heart failure, or arterial revascularization), Panel C for the coprimary outcome of core cardiovascular outcomes (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure), and Panel D for death from any cause and death from cardiovascular causes. All P values are one-sided except for those for exploratory outcomes, which are two-sided. I bars indicate 95% confidence intervals.

58%.[5,6] Some pharmacologic interventions have also reduced the risk of diabetes: in the 3.3-year Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM; ClinicalTrials.gov number, NCT00629213), there was a 25% relative risk reduction with the alpha glucosidase inhibitor acarbose[7]; in the 2.8-year Diabetes Prevention Program (DPP; NCT00004992), there was a 31% reduction with the biguanide metformin[6]; and in the 3-year Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study (NCT00095654), there was a 62% reduction with the thiazolidinedione rosiglitazone.[8] The prevention or delay of diabetes with lifestyle intervention or metformin therapy can persist for up to 10 years.[20] However, a 3-year study of the second-generation sulfonylurea gliclazide, a long-acting insulin secretagogue, did not show any reduction in the progression from fasting hyperglycemia to diabetes.[21] In addition, no reduction was seen with the first-generation sulfonylurea tolbutamide in an intention-to-treat analysis of the 10-year follow-up data from the Malmöhus trial.[22]

The D-phenylalanine derivative nateglinide is a short-acting insulin secretagogue. When it is taken before meals, it reduces postprandial glucose excursions (i.e., increases above the premeal value) by enhancing early insulin secretion.[23] It

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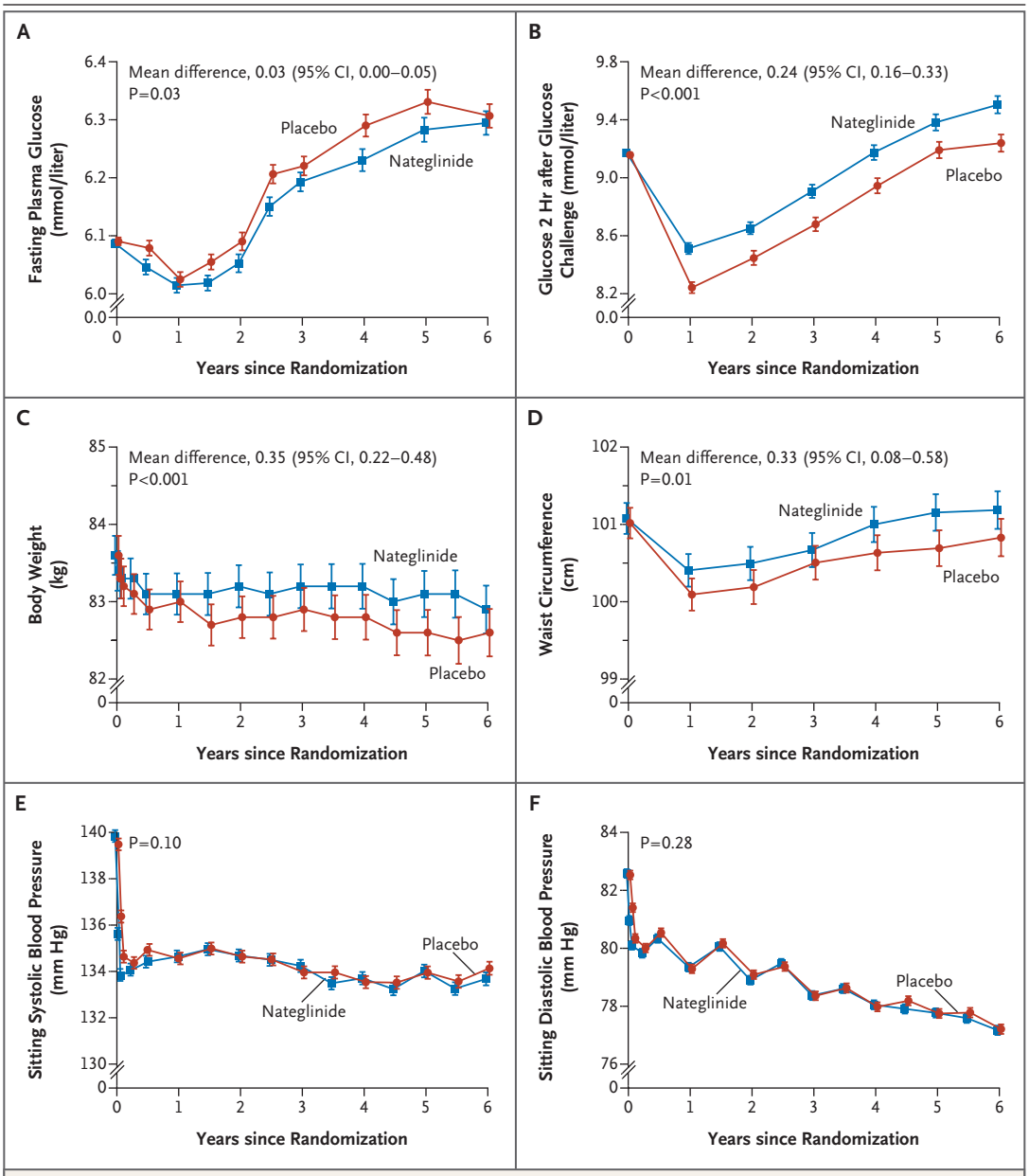

Figure 3. Changes in Mean Plasma Glucose Levels, Weight, Waist Circumference, and Blood Pressure in the Nateglinide and Placebo Groups over the Course of the Study.

To convert the values for glucose to milligrams per deciliter, divide by 0.05551. I bars indicate standard errors.

was hypothesized that nateglinide might reduce the risk of progression to diabetes by restoring a more physiologic insulin response to meals than that which occurs with sulfonylureas such as glyburide.[24] In addition, by diminishing postprandial hyperglycemia, nateglinide could have a favorable effect on the risk of cardiovascular events, given the independent significant association between elevated glucose levels after a glucose challenge and cardiovascular disease,[2] and given the reduced risk of myocardial infarction seen in the STOP-NIDDM trial.[10] We found that nateglinide offers no protection from the progression of impaired glucose tolerance to diabetes or from the progression of cardiovascular disease, and possibly raises glucose levels after a glucose challenge. A trial evaluating the effect of acarbose, an insulin-sparing agent, on cardiovascular out-

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comes among patients with impaired glucose tolerance and cardiovascular disease is under way.[25]

In a pilot study, glucose values 2 hours after a glucose challenge were significantly reduced when nateglinide was taken immediately before the test.[22] In the NAVIGATOR study, in which the study medication was withheld on mornings before oral glucose-tolerance testing, we observed elevated glucose values 2 hours after a glucose challenge. It is uncertain whether these elevated values reflect the immediate effect of withdrawal of nateglinide, which may be similar to the immediate effect of withdrawal of gliclazide,[21] or a long-term diminution in the beta-cell response to an acute glucose challenge. The former may be the case, since a 7-day study in which subjects ate a standardized test meal showed that postprandial glucose levels did not rebound above baseline values on the day that nateglinide was withdrawn.[26] In addition, glycated hemoglobin levels that were measured when diabetes developed were lower in the nateglinide group than in the placebo group, suggesting that the higher glucose values 2 hours after a glucose challenge that were seen after withdrawal of nateglinide may be a short-term rather than a long-term effect. Further interpretation might be aided by the assessment of markers of beta-cell function or insulin resistance, but peptide levels were not assayed, and samples from oral glucose-tolerance tests were not retained.

The lifestyle modification program seems to have had an effect, as evidenced by the weight loss in both study groups, but the mean body weight in the nateglinide group was 0.35 kg higher than that in the placebo group. The lower mean weight loss with nateglinide could be associated with a greater risk of diabetes, given the findings of the Diabetes Prevention Program, in which there was a 58% reduction in the risk of diabetes among the lifestyle-intervention subjects, who achieved a 5% weight loss over the course of 3 years[6]; however, formal modeling would be required to test this hypothesis.

Concerns about potential adverse cardiovascular effects of glucose-lowering agents, particularly in persons with cardiovascular disease or at high risk for cardiovascular disease, have led the Food and Drug Administration to require cardiovascular-outcome studies for new antidiabetic agents.[27] In this respect, nateglinide appears to be safe in persons with impaired glucose tolerance, although the risk of hypoglycemia is increased.

The results of the NAVIGATOR trial show that among persons with impaired glucose tolerance and cardiovascular disease or cardiovascular risk factors, assignment to nateglinide, at a dose of 60 mg three times daily, as compared with placebo, in addition to a lifestyle modification program, did not reduce the incidence of diabetes or cardiovascular outcomes.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org

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APPENDIX

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