International Variation in Outcomes Among People with Cardiovascular Disease or Cardiovascular Risk Factors and Impaired Glucose Tolerance: Insights from the NAVIGATOR Trial

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Background—Regional differences in risk of diabetes mellitus and cardiovascular outcomes in people with impaired glucose tolerance are poorly characterized. Our objective was to evaluate regional variation in risk of new-onset diabetes mellitus, cardiovascular outcomes, and treatment effects in participants from the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial.

Methods and Results—NAVIGATOR randomized people with impaired glucose tolerance and cardiovascular risk factors or with established cardiovascular disease to valsartan (or placebo) and to nateglinide (or placebo) with a median 5-year follow-up. Data from the 9306 participants were categorized by 5 regions: Asia (n=552); Europe (n=4909); Latin America (n=1406); North America (n=2146); and Australia, New Zealand, and South Africa (n=293). Analyzed outcomes included new-onset diabetes mellitus; cardiovascular death; a composite cardiovascular outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; and treatment effects of valsartan and nateglinide. Respective unadjusted 5-year risks for new-onset diabetes mellitus, cardiovascular death, and the composite cardiovascular outcome were 33%, 0.4%, and 4% for Asia; 34%, 2%, and 6% for Europe; 37%, 4%, and 8% for Latin America; 38%, 2%, and 6% for North America; and 32%, 4%, and 8% for Australia, New Zealand, and South Africa. After adjustment, compared with North America, European participants had a lower risk of new-onset diabetes mellitus (hazard ratio 0.86, 95% CI 0.78–0.94; *P*=0.001), whereas Latin American participants had a higher risk of cardiovascular death (hazard ratio 2.68, 95% CI 1.82–3.96; *P*<0.0001) and the composite cardiovascular outcome (hazard ratio 1.48, 95% CI 1.15–1.92; *P*=0.003). No differential interactions between treatment and geographic location were identified.

Conclusions—Major regional differences regarding the risk of new-onset diabetes mellitus and cardiovascular outcomes in NAVIGATOR participants were identified. These differences should be taken into account when planning global trials.

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Key Words: cardiovascular disease • diabetes mellitus • risk factor

T he prevalence of diabetes mellitus is increasing globally, especially in low-income countries.[1] The global prevalence of patients with impaired fasting glucose or impaired glucose tolerance (IGT) is also rapidly increasing. It is projected that >470 million adults globally will develop impaired fasting glucose or IGT by 2030.[1,2] People with IGT have an increased risk of developing type 2 diabetes mellitus and cardiovascular disease.[3,4] Interventions that might reduce the conversion from IGT to diabetes mellitus and reduce the associated rates of death and complications from cardiovascular causes are highly desirable. Several trials have shown that lifestyle modification[5] and pharmacological therapy,

including metformin,[6] acarbose,[7] and rosiglitazone,[8] reduce the incidence of diabetes mellitus. Examination of regional registries suggests differences in the conversion from IGT to diabetes mellitus,[9–11] yet variable methodology, length of follow-up, and differences in collected data limit comparisons between regions. Furthermore, it is unclear whether international geographic location influences the risk of cardiovascular outcomes or response to treatments in people with IGT.

The NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial assessed whether nateglinide, a short-acting insulin secretagogue, or valsartan, an angiotensin receptor blocker, could reduce the risk of new-onset diabetes mellitus and/or cardiovascular events among people with IGT and established cardiovascular disease or cardiovascular risk factors.[12,13] The NAVIGATOR trial recruited from 40 countries, providing an opportunity to evaluate the potential role of regional differences in outcomes. Using NAVIGATOR data, we aimed to assess the association between international geographic location and the risk of new-onset diabetes mellitus, cardiovascular death, a composite cardiovascular outcome, and treatment effects of valsartan and nateglinide.

Methods

Study Population and Trial Design

The study design, participant characteristics, and outcomes of the NAVIGATOR study have been published.[12–14] Briefly, NAVIGATOR was a prospective multicenter randomized controlled trial with a 2×2 factorial design that included 9306 patients with IGT and established cardiovascular disease or cardiovascular risk factors. Participants were assigned randomly to receive valsartan (up to 160 mg daily) or placebo and, simultaneously, nateglinide (up to 60 mg 3 times daily) or placebo, in addition to lifestyle modification. Men and women with IGT and ≥1 cardiovascular risk factor (aged ≥55 years) or with known cardiovascular disease (aged ≥50 years) were eligible for participation in NAVIGATOR. Exclusion criteria included laboratory abnormalities or conditions that could interfere with assessment of the safety or efficacy of a study drug, the use of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker for the treatment of hypertension, and the use of an antidiabetic medication within the previous 5 years. Participants were followed prospectively for a median of 5 years for the occurrence of 3 coprimary outcomes: (1) new-onset diabetes mellitus; (2) a core cardiovascular outcome that was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; and (3) an extended cardiovascular outcome that was a composite of the individual components of the core

composite outcome plus either hospitalization for unstable angina or arterial revascularization. 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. Valsartan (but not nateglinide) reduced the incidence of diabetes mellitus by 14%. Neither valsartan nor nateglinide reduced the risk of the other coprimary end points. The NAVIGATOR trial was approved by the appropriate institutional review boards, and all participants provided written informed consent.

For this study, data from all 9306 NAVIGATOR trial participants were analyzed and divided into the following 5 regions: Asia; Europe; Latin America; North America; and Australia, New Zealand, and South Africa (AU/NZ/SAf). Four major outcomes based on international geographic location were evaluated: (1) development of diabetes mellitus; (2) cardiovascular death; (3) a composite cardiovascular outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke; and (4) differential treatment response to valsartan or nateglinide.

Statistical Analysis

Continuous baseline variables were summarized as medians with 25th and 75th percentiles, and categorical factors and the number of participants with a characteristic per region were summarized as percentages. Between-group comparisons of continuous measures were performed using Kruskal–Wallis tests. Categorical factors were compared using Pearson chi-square or Fisher exact tests. The event rates at 5 years by region were summarized using Kaplan–Meier rates and compared using log-rank tests.

Multivariable Cox proportional hazards regression models were developed previously to determine factors associated with NAVIGATOR outcomes.[15] Region was included as a covariate in these models, with North America as the reference group. For the development of diabetes mellitus, adjustments were made for age; sex; body mass index (in kg/m^2); systolic blood pressure; family history of diabetes mellitus; the composite of history of myocardial infarction, unstable angina, coronary revascularization, stroke, or heart failure; fasting glucose; 2-hour glucose on oral glucose tolerance testing; hemoglobin A1c; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; platelet count; and hemoglobin concentration. Cardiovascular death risk was adjusted for age; sex; renal dysfunction; the composite of history of myocardial infarction, unstable angina, or coronary revascularization; current smoking; ECG; ECG interpretation; the composite of stroke, transient ischemic attack, or history of cerebrovascular disease; log urinary albumin:creatinine ratio; peripheral arterial disease; history of

heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; atrial fibrillation; and estimated glomerular filtration rate. The composite cardiovascular outcome was adjusted for age; sex; race; the composite of history of myocardial infarction, unstable angina, or coronary revascularization; current smoking; ECG interpretation; the composite of stroke, transient ischemic attack, or history of cerebrovascular disease; log urinary albumin:creatinine ratio; history of pulmonary embolism or deep vein thrombosis; low-density lipoprotein cholesterol; peripheral arterial disease; history of heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; pulse pressure; waist circumference; atrial fibrillation; serum sodium; and estimated glomerular filtration rate. To adjust for country-specific measures of wealth and poverty, we conducted a sensitivity analysis adjusting for gross domestic product as a continuous variable in addition to the variables mentioned previously. We conducted an additional secondary analysis after excluding patients with baseline ACEI use to remove those with potentially dual ACEI and angiotensin receptor blocker treatment (351 patients at baseline and 460 patients at the end of 4 years). Single imputation was implemented by creating a monotone missing pattern using the Markov chain Monte Carlo method and then by completing each data set by regression models for monotone missing. The proportional hazards assumption was tested by plotting the Schoenfeld residuals by time and then testing for a nonzero slope; there were no violations, so we reported the single hazard ratio (HR) as an average over time. Because this was a hypothesis-generating analysis, we did not make any adjustments for multiple hypothesis testing.

Possible regional differences in treatment effects for valsartan versus placebo and for nateglinide versus placebo were evaluated, with potential interactions between treatment and region tested for each outcome in adjusted Cox proportional hazards regression models. Missing data were handled by single imputation. SAS 8.3–9.3 (SAS Institute, Cary, NC) was used for all analyses.

Results

Baseline characteristics by region for the 9306 NAVIGATOR participants are shown in Table 1. In total, 4909 (53%) patients were enrolled from Europe, 2146 (23%) from North America, 1406 (15%) from Latin America, 552 (6%) from Asia, and 293 (3%) from AU/NZ/SAf. The distributions of participants recruited per country are provided in Table 2.

Baseline Demographics and Medical History

Latin America had the highest proportion of female participants (59.6%), whereas AU/NZ/SAf had the lowest (47.8%).

Europe had the highest proportion of current smokers (12.7%), and Asia had the lowest (7.2%). North America had the highest proportion of black participants (8.5%), and Asia had the lowest (0.0%). Participants in Europe also had the highest systolic (141 mm Hg) and diastolic (84 mm Hg) blood pressures. Participants in North America had the highest body mass index (31.5 kg/m^2), the largest waist circumference (104 cm), and the most frequent family history of diabetes mellitus (51.9%). AU/NZ/SAf had the highest rate of baseline cardiovascular disease (composite of myocardial infarction, unstable angina, coronary revascularization, history of stroke, and history of heart failure) at 34.5%, followed by Europe at 34.3%. Latin America had the lowest rate of baseline cardiovascular disease (25.2%). Participants from Asia had the lowest body mass index (25.8) and systolic blood pressure (131 mm Hg).

Medication Use and Laboratory Findings

Lipid-lowering medication and aspirin use was highest in North America (54.5% and 46.8%, respectively) and lowest in Asia (24.5% and 25.9%, respectively). ACEI use was highest in AU/NZ/SAf (9.9%), followed by North America (9.3%). Beta blocker and diuretic use was highest in Latin America (42.7% and 36.0%, respectively). Calcium channel blocker use was highest in Asia (46.9%). Europe had the highest low-density lipoprotein cholesterol (3.4 mmol/L) and total cholesterol (5.5 mmol/L), whereas North America had the lowest (2.8 and 5.0 mmol/L, respectively). Europe had the highest high-density lipoprotein cholesterol (1.28 mmol/L), whereas Asia had the lowest (1.11 mmol/L). Latin America had the highest triglyceride levels (1.9 mmol/L) and the highest estimated glomerular filtration rate (82.1 mL/min per 1.73 m^2). Fasting glucose was highest in Latin America and Europe (both 6.1 mmol/L). Hemoglobin A1c appeared to be uniform across regions (5.8%), although it was numerically higher in AU/NZ/SAf (6%).

Outcomes

New-onset diabetes mellitus

The incidence and risk of new-onset diabetes mellitus at 5 years varied significantly among the 5 regions (Tables 3 and 4). North America had the highest unadjusted rate (38%), whereas AU/NZ/SAf had the lowest (32%). In the multivariable Cox model, risk of new-onset diabetes mellitus was lower in Europe (HR 0.86, 95% CI 0.78–0.94; *P*=0.001) and AU/NZ/SAf (HR 0.75, 95% CI 0.61–0.93; *P*=0.009) compared with North America (Figure 1, Table 5). The results were similar in the sensitivity analysis, which included adjustment for gross domestic product (HR 0.79, 95% CI 0.67–0.92; *P*=0.003)

Table 1. Baseline Characteristics by Region From the 9306 Participants in NAVIGATOR

Characteristic	Total N=9306 (100%)	Asia n=552 (6%)	Europe n=4909 (53%)	Latin America n=1406 (15%)	North America n=2146 (23%)	AU/NZ/SAf n=293 (3%)	P value
Age at screening, y	63.0 (58.0–69.0)	63.0 (58.0–68.0)	63.0 (58.0–68.0)	64.0 (58.0–70.0)	63.0 (58.0–69.0)	62.0 (58.0–67.0)	0.0035
Female	4711/9306 (50.6)	275/552 (49.8)	2368/4909 (48.2)	838/1406 (59.6)	1090/2146 (50.8)	140/293 (47.8)	<0.0001
Pooled race group-original							<0.0001
White	7734/9306 (83.1)	1/552 (0.2)	4872/4909 (99.2)	860/1406 (61.2)	1770/2146 (82.5)	231/293 (78.8)	
Black	236/9306 (2.5)	0/552 (0.0)	13/4909 (0.3)	35/1406 (2.5)	183/2146 (8.5)	5/293 (1.7)	
Oriental	613/9306 (6.6)	547/552 (99.1)	11/4909 (0.2)	4/1406 (0.3)	20/2146 (0.9)	31/293 (10.6)	
Other	723/9306 (7.8)	4/552 (0.7)	13/4909 (0.3)	507/1406 (36.1)	173/2146 (8.1)	26/293 (8.9)	
Current smoker	1025/9306 (11.0)	40/552 (7.2)	623/4909 (12.7)	121/1406 (8.6)	212/2146 (9.9)	29/293 (9.9)	<0.0001
BMI, kg/m^2	29.7 (26.8–33.3)	25.8 (23.8–27.8)	29.5 (26.9–32.9)	29.7 (26.8–33.2)	31.5 (28.0–35.7)	29.4 (26.9–33.1)	<0.0001
Height, cm	165.0 (158.0–173.0)	161.0 (155.0–166.0)	166.0 (159.0–173.0)	160.0 (153.0–167.0)	168.0 (160.0–175.0)	168.0 (161.0–174.0)	<0.0001
Weight, kg	82.0 (71.5–93.5)	67.0 (60.0–74.2)	82.3 (73.0–92.8)	76.8 (67.1–86.7)	89.5 (78.0–102.7)	83.4 (73.0–95.0)	<0.0001
Waist circumference, cm	100.0 (92.0–109.0)	89.0 (83.0–95.0)	100.0 (92.0–108.0)	100.0 (93.0–108.0)	104.0 (95.0–114.0)	102.0 (94.0–109.0)	<0.0001
Systolic BP, mm Hg	140.0 (128.0–150.0)	131.3 (120.0–142.5)	141.0 (130.5–152.5)	140.0 (130.0–150.0)	134.0 (123.0–145.0)	136.5 (125.0–147.5)	<0.0001
Diastolic BP, mm Hg	82.0 (76.0–90.0)	80.0 (73.0–88.0)	83.5 (78.0–90.0)	83.0 (79.0–90.0)	79.0 (72.0–84.0)	81.0 (75.0–88.5)	<0.0001
Pulse, bpm	70.0 (63.0–77.0)	72.0 (66.0–79.5)	70.0 (62.0–76.0)	70.0 (64.0–78.0)	68.0 (63.0–76.0)	68.0 (62.0–76.0)	<0.0001
Family history of diabetes	3547/9306 (38.1)	130/552 (23.6)	1594/4909 (32.5)	569/1406 (40.5)	1113/2146 (51.9)	141/293 (48.1)	<0.0001
Family history of premature CHD	1544/9306 (16.6)	35/552 (6.3)	794/4909 (16.2)	208/1406 (14.8)	434/2146 (20.2)	73/293 (24.9)	<0.0001
History of cardiovascular disease*	2933/9306 (31.5)	146/552 (26.4)	1684/4909 (34.3)	355/1406 (25.2)	647/2146 (30.1)	101/293 (34.5)	<0.0001
Renal dysfunction	90/9306 (1.0)	7/552 (1.3)	31/4909 (0.6)	5/1406 (0.4)	46/2146 (2.1)	1/293 (0.3)	<0.0001
Atrial fibrillation/flutter	356/9306 (3.8)	16/552 (2.9)	212/4909 (4.3)	46/1406 (3.3)	75/2146 (3.5)	7/293 (2.4)	0.0921
Pulmonary embolism/deep vein thrombosis	129/9306 (1.4)	1/552 (0.2)	77/4909 (1.6)	5/1406 (0.4)	41/2146 (1.9)	5/293 (1.7)	0.0002
COPD/emphysema/chronic bronchitis	451/9306 (4.8)	22/552 (4.0)	229/4909 (4.7)	37/1406 (2.6)	149/2146 (6.9)	14/293 (4.8)	<0.0001
ECG interpretation							<0.0001
Normal	4525/9306 (48.6)	325/552 (58.9)	2491/4909 (50.7)	611/1406 (43.5)	934/2146 (43.5)	164/293 (56.0)	
Clinically insignificant abnormality	3326/9306 (35.7)	120/552 (21.7)	1650/4909 (33.6)	446/1406 (31.7)	1020/2146 (47.5)	90/293 (30.7)	
Clinically significant abnormality	1455/9306 (15.6)	107/552 (19.4)	768/4909 (15.6)	349/1406 (24.8)	192/2146 (8.9)	39/293 (13.3)	

Table 1. Continued

Characteristic	Total N=9306 (100%)	Asia n=552 (6%)	Europe n=4909 (53%)	Latin America n=1406 (15%)	North America n=2146 (23%)	AU/NZ/SAf n=293 (3%)	P value
Laboratory							
Hemoglobin, g/L	147.0 (138.0–155.0)	142.0 (135.0–152.0)	147.0 (139.0–155.0)	147.0 (138.0–156.0)	145.0 (137.0–154.0)	150.0 (140.0–158.0)	<0.0001
2-Hour glucose, mmol/L	9.00 (8.40–9.90)	9.20 (8.40–10.10)	9.00 (8.30–9.90)	9.10 (8.40–9.90)	9.10 (8.40–10.00)	9.10 (8.40–9.90)	<0.0001
Fasting glucose, mmol/L	6.10 (5.70–6.40)	5.90 (5.60–6.30)	6.10 (5.80–6.50)	6.10 (5.70–6.40)	6.00 (5.70–6.40)	6.00 (5.60–6.30)	<0.0001
Hemoglobin A1c, %	5.8 (5.5–6.1)	5.8 (5.4–6.2)	5.8 (5.5–6.1)	5.8 (5.6–6.1)	5.8 (5.6–6.1)	6.0 (5.7–6.3)	<0.0001
HDL, mmol/L	1.24 (1.03–1.47)	1.11 (0.93–1.35)	1.28 (1.07–1.52)	1.19 (1.01–1.42)	1.22 (1.03–1.45)	1.23 (1.07–1.44)	<0.0001
LDL, mmol/L	3.22 (2.59–3.90)	3.30 (2.77–3.94)	3.37 (2.76–4.06)	3.21 (2.64–3.83)	2.82 (2.30–3.49)	2.99 (2.43–3.66)	<0.0001
Total cholesterol, mmol/L	5.36 (4.67–6.10)	5.26 (4.66–5.91)	5.51 (4.82–6.27)	5.38 (4.71–6.10)	5.04 (4.40–5.79)	5.13 (4.44–5.80)	<0.0001
Triglycerides, mmol/L	1.69 (1.22–2.36)	1.61 (1.14–2.08)	1.60 (1.16–2.22)	1.86 (1.35–2.55)	1.84 (1.33–2.60)	1.62 (1.24–2.19)	<0.0001
eGFR, mL/min/1.73 m^2	79.8 (68.7–91.2)	84.0 (70.6–96.8)	78.6 (68.6–90.0)	82.1 (68.9–96.1)	81.7 (68.3–95.1)	79.2 (67.9–90.5)	<0.0001
Log of albumin:creatinine ratio, mg/mmoL	−0.20 (0.67–0.56)	0.14 (0.45–0.88)	−0.20 (0.67–0.54)	−0.14 (0.65–0.63)	−0.29 (0.71–0.43)	−0.20 (0.63–0.49)	<0.0001
Sodium, mmol/L	142.0 (141.0–144.0)	144.0 (142.0–146.0)	142.0 (140.0–143.0)	143.0 (142.0–145.0)	143.0 (141.0–144.0)	142.0 (141.0–143.0)	<0.0001
Potassium, mmol/L	4.3 (4.1–4.6)	4.2 (4.0–4.5)	4.3 (4.1–4.6)	4.4 (4.1–4.7)	4.3 (4.1–4.6)	4.3 (4.1–4.6)	<0.0001
WBCs, 10^9/L	6.7 (5.7–7.9)	5.9 (5.1–6.9)	6.8 (5.8–8.0)	6.7 (5.7–7.8)	6.7 (5.7–8.0)	6.6 (5.5–7.6)	<0.0001
Platelets, 10^9/L	252.0 (212.0–295.0)	217.0 (181.0–259.0)	254.0 (214.0–296.0)	257.0 (217.0–304.0)	251.0 (212.0–295.0)	253.0 (225.0–297.0)	<0.0001
Baseline medication use							
Alpha blocker	577/9306 (6.2)	29/552 (5.3)	349/4909 (7.1)	33/1406 (2.3)	152/2146 (7.1)	14/293 (4.8)	<0.0001
ACEI	676/9306 (7.3)	3/552 (0.5)	384/4909 (7.8)	61/1406 (4.3)	199/2146 (9.3)	29/293 (9.9)	<0.0001
Antihypertensives	6816/9306 (73.2)	402/552 (72.8)	3566/4909 (72.6)	1168/1406 (83.1)	1488/2146 (69.3)	192/293 (65.5)	<0.0001
Angiotensin II receptor blocker	30/9306 (0.3)	1/552 (0.2)	15/4909 (0.3)	2/1406 (0.1)	11/2146 (0.5)	1/293 (0.3)	0.3733
Aspirin	3425/9306 (36.8)	143/552 (25.9)	1702/4909 (34.7)	451/1406 (32.1)	1004/2146 (46.8)	125/293 (42.7)	<0.0001
Beta blocker	3666/9306 (39.4)	200/552 (36.2)	2030/4909 (41.4)	600/1406 (42.7)	744/2146 (34.7)	92/293 (31.4)	<0.0001
Calcium channel blocker	3012/9306 (32.4)	259/552 (46.9)	1519/4909 (30.9)	556/1406 (39.5)	611/2146 (28.5)	67/293 (22.9)	<0.0001
Diuretic	2960/9306 (31.8)	114/552 (20.7)	1518/4909 (30.9)	506/1406 (36.0)	731/2146 (34.1)	91/293 (31.1)	<0.0001
Lipid-lowering agent	3577/9306 (38.4)	135/552 (24.5)	1723/4909 (35.1)	400/1406 (28.4)	1170/2146 (54.5)	149/293 (50.9)	<0.0001

Data presented as n/N (%) or median (25th–75th percentiles). *P* value compares across all categories. ACEI indicates angiotensin-converting enzyme inhibitor; AU/NZ/SAf, Australia, New Zealand, and South Africa; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; WBC, white blood cell.

*Cardiovascular disease composite refers to a composite of myocardial infarction, unstable angina, coronary revascularization, history of stroke, and history of heart failure.

Table 2. Enrollment by Country

Characteristic	Total=9306
Asia	552 (5.93%)
China (mainland)	301 (3.23%)
Hong Kong	65 (0.70%)
Malaysia	51 (0.55%)
Singapore	9 (0.10%)
Taiwan	126 (1.35%)
Europe	4909 (52.75%)
Austria	71 (0.76%)
Belgium	45 (0.48%)
Czech Republic	60 (0.64%)
Denmark	239 (2.57%)
Finland	247 (2.65%)
France	114 (1.23%)
Germany	137 (1.47%)
Greece	22 (0.24%)
Hungary	215 (2.31%)
Italy	668 (7.18%)
Netherlands	205 (2.20%)
Norway	37 (0.40%)
Poland	339 (3.64%)
Russia	634 (6.81%)
Slovakia	66 (0.71%)
Spain	124 (1.33%)
Sweden	94 (1.01%)
Switzerland	30 (0.32%)
Turkey	76 (0.82%)
United Kingdom	1486 (15.97%)
Latin America	1406 (15.11%)
Argentina	720 (7.74%)
Brazil	328 (3.52%)
Chile	30 (0.32%)
Colombia	85 (0.91%)
Ecuador	24 (0.26%)
Guatemala	52 (0.56%)
Mexico	100 (1.07%)
Peru	52 (0.56%)
Uruguay	15 (0.16%)
North America	2146 (23.06%)
Canada	340 (3.65%)
United States (including Puerto Rico)	1806 (19.41%)

Table 2. Continued

Characteristic	Total=9306
Other	293 (3.15%)
Australia	107 (1.15%)
New Zealand	33 (0.35%)
South Africa	153 (1.64%)

(Table 6). Furthermore, the removal of patients with ACEI use did not significantly alter the results (HR 0.88, 95% CI 0.79–0.97; *P*=0.009) (Table 7).

Cardiovascular death and the composite cardiovascular outcome

The unadjusted incidence of cardiovascular death at 5 years differed significantly among the regions studied (Table 3). Latin America had the highest incidence at 3.6%, whereas Asia had the lowest at 0.4%. AU/NZ/SAf had the highest rate of the composite cardiovascular outcome at 7.9%, followed by Latin America at 7.6%. In the adjusted model (Figure 2, Table 5), risk of cardiovascular death was higher in Latin America (HR 2.68, 95% CI 1.82–3.96; *P*<0.0001) and AU/NZ/SAf (HR 2.32, 95% CI 1.22–4.40; *P*=0.01) compared with North America (Figure 3). In the adjusted model for the composite cardiovascular outcome, compared with North America, only Latin America continued to demonstrate an increased risk (HR 1.48, 95% CI 1.15–1.92, *P*=0.003). Using the sensitivity analysis after adjustment for gross domestic product, a similar magnitude of risk was seen in Latin America in both the composite outcome (HR 1.51, 95% CI 0.93–2.44; *P*=0.09) and cardiovascular death (HR 2.84, 95% CI 1.21–6.67; *P*=0.02) (Table 6). Results were similar after excluding patients who were on an ACEI at baseline (Table 7).

Differential Treatment Effect Among Regions for Valsartan and Nateglinide

There were no significant interactions for valsartan or nateglinide with region with respect to new-onset diabetes mellitus (*P*=0.11 and *P*=0.80, respectively), cardiovascular death (*P*=0.94 and *P*=0.07, respectively), or the composite cardiovascular outcome (*P*=0.99 and *P*=0.48, respectively).

Discussion

In this study, compared with North America, Europe and AU/NZ/SAf had lower risks of new-onset diabetes mellitus, whereas Latin America had higher risks of cardiovascular

Table 3. Unadjusted 5-Year Event Rate Based on Outcome and Region

Region	Development of Diabetes Mellitus, %	Cardiovascular Death	Composite of Cardiovascular Death, MI, and Stroke
	% (95% CI)		
Asia (n=552)	33 (29–38)	0.36 (0.09–1.44)	4.04 (2.68–6.07)
Europe (n=4909)	34 (32–35)	1.67 (1.34–2.08)	5.53 (4.91–6.23)
Latin America (n=1406)	37 (35–40)	3.63 (2.75–4.77)	7.61 (6.32–9.16)
North America (n=2146)	38 (36–40)	1.93 (1.42–2.64)	5.90 (4.93–7.05)
Australia, New Zealand, and South Africa (n=293)	32 (26–38)	3.58 (1.94–6.54)	7.94 (5.3–11.81)
Log-rank*	<0.001	<0.001	0.02

MI indicates myocardial infarction.
*Log-rank compares incidence among the regions.

death and the composite cardiovascular outcome after multivariable adjustment. No regional differences in treatment effects for valsartan or nateglinide were identified.

Differences in Clinical Trial Participants

Global clinical trials are increasingly used to reduce costs, to enroll participants rapidly, to ensure timely completion, to provide global applicability, and to satisfy regulatory requirements. Potential problems, however, include regional differences in patient characteristics, medical practice patterns, and health care policies that may influence outcomes and ultimately limit generalizability.[16] As seen in our study, despite stringent inclusion and exclusion criteria, baseline characteristics demonstrated significant variation by region. Such variation has been seen previously in cardiovascular trials ranging from heart failure to atrial fibrillation.[16] Potential reasons for these variations in baseline characteristics include differences in study trial conduct, interpretation of inclusion and exclusion criteria, ascertainment of outcomes, differences in the demographics of patients available to be recruited, and investigator preferences in recruiting patients.

Even within geographic regions, there is likely significant heterogeneity by country. In our study, Europe had the highest

low-density lipoprotein cholesterol and total cholesterol levels compared with other geographic regions. Countries such as Russia, Poland, Slovakia, and Hungary have some of the highest out-of-pocket health expenditures, rank low on the World Health Organization health system performance index, and have the highest total cholesterol levels globally.[17] In our study, 1254 patients were enrolled from these countries (25.5% of all patients enrolled in Europe). In comparison, the United Kingdom, Finland, and Denmark have some of the lowest out-of-pocket health expenditures, have higher World Health Organization health system performance index metrics, and have some of the lowest total cholesterol levels globally.[17] Such regional differences in participant demographics reflect the need for careful selection of countries to participate in cardiovascular clinical trials, as differences in baseline clinical characteristics and therapies may influence trial results.

International Variation in Progression to Diabetes Mellitus

Externally validated risk-prediction models use factors such as age, sex, ethnicity, body mass index, waist circumference, family history of diabetes mellitus, systolic blood pressure,

Table 4. Unadjusted HRs for the Development of Outcomes Based on Regions

Country	Development of Diabetes Mellitus	Cardiovascular Death	Composite of Cardiovascular Death, MI, and Stroke
	HR (95% CI); *P* Value		
Asia vs North America	0.76 (0.65–0.89); <0.001	0.47 (0.21–1.04); 0.06	0.71 (0.48–1.06); 0.09
Europe vs North America	0.84 (0.78–0.92); <0.001	0.90 (0.64–1.25); 0.52	0.94 (0.77–1.15); 0.56
Latin America vs North America	0.93 (0.84–1.04); 0.21	1.89 (1.31–2.72); <0.001	1.24 (0.97–1.57); 0.08
Australia, New Zealand, South Africa vs North America	0.80 (0.64–0.98); 0.03	1.73 (0.92–3.24); 0.09	1.27 (0.83–1.94); 0.28

HR indicates hazard ratio; MI, myocardial infarction.
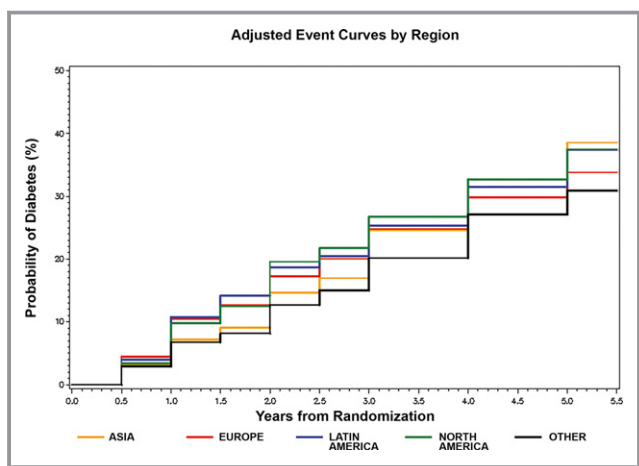
Figure 1. Adjusted event curves for incidence of diabetes mellitus by region. Other indicates Australia, New Zealand, and South Africa.

and high-density lipoprotein cholesterol, among other factors, to predict the risk of developing diabetes mellitus.[18] Despite the prespecified inclusion and exclusion criteria, the significant variability in the baseline characteristics of patients enrolled based on geographic region combined with unmeasured and unrecognized social, physical activity participation, health care delivery, and genetic factors likely contributes to the different risks of diabetes mellitus that we described. Compared with North America, the risk of diabetes mellitus development appears to be lowest in European patients. As seen in our study, a higher prevalence of risk factors such as obesity, waist circumference, and family history of diabetes mellitus in North America compared with Europe[11] may be a major driver of this increased risk of conversion from the

prediabetic state to full diabetes mellitus.[11,19] In addition, lower numbers of higher-risk minority groups, such as black patients in the European region (0.3%) compared with the North America region (8.5%), may also contribute significantly to the lower risk of progression to diabetes mellitus.[19]

International Variation in NAVIGATOR Trial Outcomes

International variation in clinical trial outcomes are likely due to a complex interplay of patient baseline characteristics (eg, race, genetics, nutritional status, education, and medication adherence), regional medical culture, and processes of care.[16] Developing regions, such as Latin America, are experiencing a growing burden of cardiovascular disease[20] and related risk factors such as type 2 diabetes mellitus.[21] These findings may result from deficits in preventive strategies, genetic factors, exposure to Western countries' high-fat diets, and increasing prevalence of sedentary behaviors.[21] The PURE (Prospective Urban and Rural Epidemiological) study, which enrolled 156 424 persons across 17 countries, identified that although the burden of cardiovascular risk factors may be lower in low- to middle-income countries, the risk of cardiovascular events was much higher.[20] This may reflect superior control of risk factors and more frequent use of proven pharmacological therapies and revascularization in high-income countries.[20] Differences in cardiovascular outcomes based on regions have been shown in patients with diabetes mellitus.[22] Our findings support this concept, as patients in Latin America used fewer therapies for prevention of cardiovascular events, such as aspirin (32% versus 47% in North America and 35% in Europe), lipid-lowering therapies

Table 5. Adjusted HRs for the Development of Outcomes Based on Regions

Country	Development of Diabetes Mellitus* HR (95% CI); *P* Value	Cardiovascular Death† 	Composite of Cardiovascular Death, MI, and Stroke‡
Asia vs North America	0.93 (0.79–1.10); 0.41	0.66 (0.30–1.47); 0.31	0.90 (0.59–1.37); 0.63
Europe vs North America	0.86 (0.78–0.94); 0.001	1.05 (0.74–1.48); 0.80	0.92 (0.74–1.14); 0.44
Latin America vs North America	0.95 (0.85–1.06); 0.37	2.68 (1.82–3.96); <0.0001	1.48 (1.15–1.92); 0.003
Australia, New Zealand, South Africa vs North America	0.75 (0.61–0.93); 0.009	2.32 (1.22–4.40); 0.01	1.40 (0.91–2.15); 0.13

HR indicates hazard ratio; MI, myocardial infarction.

*Adjusted for age sex; body mass index; systolic blood pressure; family history of diabetes mellitus; the composite of history of MI, unstable angina, coronary revascularization, stroke, or heart failure; fasting glucose; 2-hour glucose on oral glucose tolerance test; hemoglobin A1c; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; platelet count; and hemoglobin concentration.

†Adjusted for age; sex; renal dysfunction; the composite of history of MI, unstable angina, or coronary revascularization; current smoking; ECG interpretation; the composite of stroke, transient ischemic attack, or history of cardiovascular disease; log urinary albumin:creatinine ratio; peripheral arterial disease; history of heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; atrial fibrillation; and estimated glomerular filtration rate.

‡Adjusted for age; sex; race; the composite of history of MI, unstable angina, or coronary revascularization; current smoking; ECG interpretation; the composite of stroke, transient ischemic attack, or history of cardiovascular disease; log urinary albumin:creatinine ratio; history of pulmonary embolism or deep vein thrombosis; low-density lipoprotein cholesterol; peripheral arterial disease; history of heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; pulse pressure; waist circumference; atrial fibrillation; serum sodium; and estimated glomerular filtration rate.

Table 6. Sensitivity Analysis With Multivariable Adjustment Including Gross Domestic Product for the Development of Outcomes Based on Regions

Country	Development of Diabetes Mellitus*	Cardiovascular Death[†]	Composite of Cardiovascular Death, MI, and Stroke[‡]
	HR (95% CI); *P* Value		
Asia vs North America	0.85 (0.69–1.06); 0.15	0.70 (0.24–2.04); 0.51	0.92 (0.52–1.61); 0.76
Europe vs North America	0.79 (0.67–0.92); 0.003	1.11 (0.51–2.41); 0.80	0.93 (0.61–1.44); 0.75
Latin America vs North America	0.86 (0.72–1.04); 0.11	2.84 (1.21–6.67); 0.02	1.51 (0.93–2.45); 0.09
Australia, New Zealand, South Africa vs North America	0.68 (0.53–0.88); 0.004	2.46 (0.92–6.62); 0.07	1.42 (0.79–2.58); 0.24

HR indicates hazard ratio; MI, myocardial infarction.

*Adjusted for age sex; body mass index; systolic blood pressure; family history of diabetes mellitus; the composite of history of MI, unstable angina, coronary revascularization, stroke, or heart failure; fasting glucose; 2-hour glucose on oral glucose tolerance test; hemoglobin A1c; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; platelet count; and hemoglobin concentration.

[†]Adjusted for age; sex; renal dysfunction; the composite of history of MI, unstable angina, or coronary revascularization; current smoking; ECG interpretation; the composite of stroke, transient ischemic attack, or history of CV disease; log urinary albumin:creatinine ratio; peripheral arterial disease; history of heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; atrial fibrillation; and estimated glomerular filtration rate.

[‡]Adjusted for age; sex; race; the composite of history of MI, unstable angina, or coronary revascularization; current smoking; ECG interpretation; the composite of stroke, transient ischemic attack, or history of CV disease; log urinary albumin:creatinine ratio; history of pulmonary embolism or deep vein thrombosis; low-density lipoprotein cholesterol; peripheral arterial disease; history of heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; pulse pressure; waist circumference; atrial fibrillation; serum sodium; and estimated glomerular filtration rate.

(28% versus 55% in North America and 35% in Europe), and ACEIs (4% versus 9% in North America and 8% in Europe). These variations in outcomes have significant implications for future global clinical trials because regions will have to be selected carefully based on expected event rates.

Therapeutic Treatment Effect Based on Geographic Location

This analysis suggests that there were no regional differences in treatment effects for valsartan or nateglinide. Our results suggest that the impact of valsartan in reducing progression to diabetes mellitus—despite the differences in baseline therapies, background drug treatment, patient characteristics, and risk of outcomes—is independent of geographic region. This has important implications for hypertension management in regions such as Latin America, which has a high risk of conversion from prediabetes to diabetes mellitus. NAVIGATOR data show that antihypertensive use is highest in Latin America and that use of beta blockers and thiazide diuretics is common. These drugs can increase risk of progression to diabetes mellitus,[23] and so angiotensin receptor blocker agents could be considered as preferred antihypertension management for people with IGT in Latin America.

Table 7. Sensitivity Analysis After Removing Patients With Baseline Angiotensin-Converting Enzyme Inhibitor for the Development of Outcomes Based on Regions
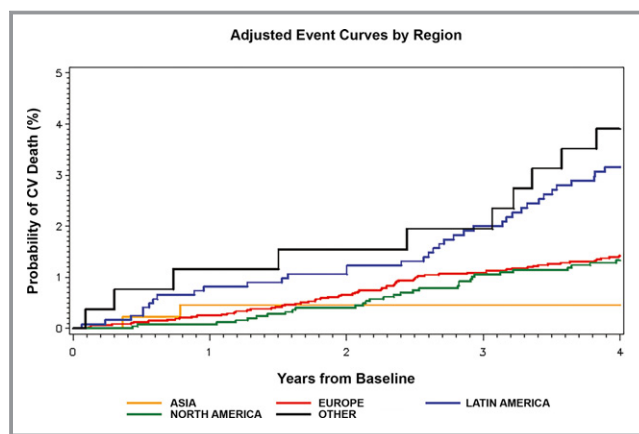
Country	Development of Diabetes Mellitus*	Cardiovascular Death[†]	Composite of Cardiovascular Death, MI, and Stroke[‡]
	HR (95% CI); *P* Value		
Asia vs North America	0.93 (0.78–1.11); 0.42	0.52 (0.22–1.24); 0.14	0.85 (0.55–1.31); 0.46
Europe vs North America	0.88 (0.79–0.97); 0.009	0.97 (0.66–1.42); 0.86	0.88 (0.69–1.11); 0.28
Latin America vs North America	0.95 (0.84–1.06); 0.35	2.27 (1.48–3.49); 0.0002	1.36 (1.03–1.80); 0.03
Australia, New Zealand, South Africa vs North America	0.73 (0.58–0.92); 0.007	2.01 (0.97–4.17); 0.06	1.16 (0.70–1.91); 0.56

HR indicates hazard ratio; MI, myocardial infarction.

*Adjusted for age sex; body mass index; systolic blood pressure; family history of diabetes mellitus; the composite of history of MI, unstable angina, coronary revascularization, stroke, or heart failure; fasting glucose; 2-hour glucose on oral glucose tolerance test; hemoglobin A1c; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; platelet count; and hemoglobin concentration.

[†]Adjusted for age; sex; renal dysfunction; the composite of history of MI, unstable angina, or coronary revascularization; current smoking; ECG interpretation; the composite of stroke, transient ischemic attack, or history of CV disease; log urinary albumin:creatinine ratio; peripheral arterial disease; history of heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; atrial fibrillation; and estimated glomerular filtration rate.

[‡]Adjusted for age; sex; race; the composite of history of MI, unstable angina, or coronary revascularization; current smoking; ECG interpretation; the composite of stroke, transient ischemic attack, or history of CV disease; log urinary albumin:creatinine ratio; history of pulmonary embolism or deep vein thrombosis; low-density lipoprotein cholesterol; peripheral arterial disease; history of heart failure; hemoglobin concentration; chronic obstructive pulmonary disease; pulse pressure; waist circumference; atrial fibrillation; serum sodium; and estimated glomerular filtration rate.

Figure 2. Adjusted event curves for cardiovascular death by region. Other indicates Australia, New Zealand, and South Africa.

Study Limitations

Our study has some limitations. Because these data were collected in the context of a clinical trial, with prespecified inclusion and exclusion criteria, they may not accurately reflect the regions' real-world populations. In addition, these are post hoc analyses and are subject to the limitations of such analyses. Despite statistical adjustments, unmeasured confounders may still be present. With the available data, we were only able to adjust for current history of smoking and not cumulative smoking history. Detailed demographic information regarding race (beyond white, black, Asian, and others) was unavailable. A causal relationship between geographic region and outcomes cannot be determined. Furthermore, there is likely significant variation among practice pattern, health care delivery, and participant characteristics, even within a given region. Our analysis focuses on baseline characteristics and does not account for changes in risk factors or background drug treatment throughout the
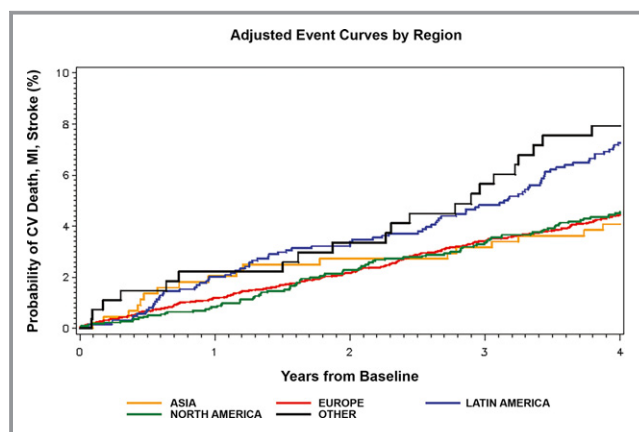
duration of the trial. In addition, the AU/NZ/SAf region reflects a geographically heterogeneous population with small numbers of patients and events, and hence any interpretation of risk in this group should be viewed with caution. However, the strength of our analysis arises from several factors: (1) the NAVIGATOR study is one of the largest trials in patients with IGT and cardiovascular risk factors; (2) the event rate allows for comprehensive multivariable adjustment; and (3) the well-phenotyped patients in this clinical trial provide the ability to adjust for important clinical, demographic, and biochemical variables. Furthermore, our sensitivity analysis, which adjusted for gross domestic product (a country's measure of wealth and poverty), verified our key findings that the risk of progression to diabetes mellitus was lowest in Europe and the risk of cardiovascular death was highest in Latin America. In addition, removing patients with baseline ACEI use did not change results.

Conclusion

Our analysis of the NAVIGATOR trial demonstrated that geographic regions significantly influence the risk of diabetes mellitus and cardiovascular outcomes in patients with IGT. Important differences in baseline risk factors among regions existed. Differences in the risk of development of diabetes mellitus and adverse cardiovascular events based on geographic region must be considered when conducting international trials in patients with IGT. The use of angiotensin receptor blocker agents as antihypertensive therapy in patients with IGT could be considered in regions with high risk of progression to diabetes mellitus. Future studies to identify causal factors contributing to the differential risk of diabetes mellitus progression and cardiovascular outcomes based on geographic region are needed.

Disclosures

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Figure 3. Adjusted event curve for cardiovascular death, myocardial infarction (MI), and stroke by region. Other indicates Australia, New Zealand, and South Africa.

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