# Predictors of Stroke in Patients With Impaired Glucose Tolerance

## Results From the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research Trial

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***Background and Purpose***—Risk factors for stroke are well-established in general populations but sparsely studied in individuals with impaired glucose tolerance.

***Methods***—We identified predictors of stroke among participants with impaired glucose tolerance in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial. Cox proportional-hazard regression models were constructed using baseline variables, including the 2 medications studied, valsartan and nateglinide.

***Results***—Among 9306 participants, 237 experienced a stroke over 6.4 years. Predictors of stroke included classical risk factors such as existing cerebrovascular and coronary heart disease, higher pulse pressure, higher low-density lipoprotein cholesterol, older age, and atrial fibrillation. Other factors, including previous venous thromboembolism, higher waist circumference, lower estimated glomerular filtration rate, lower heart rate, and lower body mass index, provided additional important predictive information, yielding a C-index of 0.72. Glycemic measures were not predictive of stroke. Variables associated with stroke were similar in participants with no prior history of cerebrovascular disease at baseline.

***Conclusions***—The most powerful predictors of stroke in patients with impaired glucose tolerance included a combination of established risk factors and novel variables, such as previous venous thromboembolism and elevated waist circumference, allowing moderately effective identification of high-risk individuals. (***Stroke***. 2013;44:2590-2593.)

**Key Words:** impaired glucose tolerance ■ stroke

Individuals with impaired glucose tolerance (IGT) are at increased risk for developing type 2 diabetes mellitus (T2DM) and cardiovascular disease, including stroke.[1] Individuals with IGT exhibit many cardiovascular disease risk factors found in T2DM.[2] However, longitudinal studies of well-characterized IGT populations have not been available to examine predictors of stroke. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial (NAVIGATOR) provides the opportunity to establish the factors associated with increased risk of stroke in IGT.[3]

## Methods

NAVIGATOR was a multi-continental randomized, double-blind, placebo-controlled trial to determine whether treatment with nateglinide and valsartan, respectively (2×2 factorial design), would reduce progression to T2DM and incident cardiovascular events, respectively, in participants with IGT but not T2DM.[3] A total of 9306 participants were followed for a median of 6.4 years. Doses of nateglinide and valsartan could be adjusted based on side-effects but not glucose levels or blood pressure readings, respectively. Patients with IGT (2-hour postchallenge glucose value, 7.8–11.0 mmol/L and fasting glucose, 5.3–6.9 mmol/L) were eligible if they had ≥1 cardiovascular risk factor and were aged ≥55 years or established cardiovascular

**Table 1.    Baseline Characteristics of 9306 Participants With Impaired Glucose Tolerance in NAVIGATOR Stratified by Occurrence of Stroke**

| | Stroke During Trial | | |
| Variable | No (n=9069) | Yes (n=237) | P Value |
| --- | --- | --- | --- |
| Age (y) | 64 (7) | 66 (7) | <0.001 |
| Men | 4454 (49) | 141 (59) | 0.002 |
| Race | | | 0.16 |
|     Black | 225 (3) | 11 (5) | |
|     White | 7537 (83) | 197 (83) | |
|     Asian | 601 (7) | 12 (5) | |
|     Other | 706 (8) | 17 (7) | |
| Region | | | 0.22 |
|     North America | 2101 (23) | 45 (19) | |
|     Europe | 4783 (53) | 126 (53) | |
|     Asia | 540 (6) | 12 (5) | |
|     Latin America | 1359 (15) | 47 (20) | |
|     Other | 286 (3) | 7 (3) | |
| Current smoker | 994 (11) | 31 (13) | 0.30 |
| Medical history | | | |
|     Coronary heart disease* | 2528 (28) | 98 (41) | <0.001 |
|     Cerebrovascular disease† | 692 (8) | 44 (19) | <0.001 |
|     Peripheral arterial disease‡ | 292 (3) | 17 (7) | 0.001 |
|     Chronic obstructive pulmonary disease | 436 (5) | 15 (6) | 0.28 |
|     Heart failure | 317 (4) | 14 (6) | 0.05 |
|     Hypertension | 7031 (78) | 185 (78) | 0.85 |
|     Venous thromboembolism (pulmonary embolism/deep venous thrombosis) | 116 (1) | 13 (6) | <0.001 |
|     Family history of premature coronary heart disease | 1499 (17) | 45 (19) | 0.32 |
|     Family history of diabetes mellitus | 3456 (38) | 91 (38) | 0.93 |
| Clinical features | | | |
|     Weight (kg) | 83.6 (17.2) | 84.1 (17.1) | 0.58 |
|     Body mass index (kg/m²) | 30.5 (5.4) | 30.3 (5.6) | 0.41 |
|     Waist circumference (cm) | 101 (14) | 103 (13) | 0.003 |
|     Height (cm) | 165 (10) | 167 (10) | 0.07 |
|     Systolic blood pressure (mm Hg) | 140 (17) | 145 (20) | <0.001 |
|     Diastolic blood pressure (mm Hg) | 83 (10) | 83 (11) | 0.46 |
|     Pulse pressure (mm Hg) | 57 (14) | 62 (16) | <0.001 |
|     Left ventricular hypertrophy | 254 (3) | 14 (6) | 0.005 |
|     Heart rate (bpm) | 70 (11) | 69 (12) | 0.01 |
|     Atrial fibrillation or flutter | 336 (4) | 20 (8) | <0.001 |
| Laboratory | | | |
|     Fasting glucose (mmol/L) | 6.1 (0.5) | 6.1 (0.5) | 0.28 |
|     2-hour glucose (mmol/L) | 9.2 (0.9) | 9.2 (0.9) | 0.17 |
|     HbA1c (%) | 5.8 (0.4) | 5.9 (0.5) | 0.011 |
|     eGFR (mL min⁻¹ 1.73 m⁻²) | 81 (18) | 76 (20) | <0.001 |
|     Urine albumin/creatinine ratio (log units) | 0.1 (1.2) | 0.3 (1.2) | <0.001 |
|     LDL cholesterol (mmol/L) | 3.3 (1.0) | 3.3 (0.9) | 0.14 |
|     HDL cholesterol (mmol/L) | 1.3 (0.3) | 1.2 (0.3) | 0.11 |
|     Triglycerides (mmol/L) | 1.9 (1.1) | 2.0 (1.1) | 0.68 |
|     Hemoglobin (g/L) | 147 (13) | 146 (13) | 0.61 |
|     Sodium (mmol/L) | 142 (2) | 143 (3) | 0.64 |

n (%) or mean [SD]. Not listed but also included in models: potassium, white blood cells, platelet count, and randomized treatments with nateglinide and valsartan, respectively. eGFR indicates estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial.

*Previous myocardial infarction, angina, positive stress test, and coronary revascularization.

†Stroke and transient ischemic attack.

‡Limb or foot amputation, intermittent claudication, and limb arterial bypass procedure.

**Table 2. Predictors of Stroke in NAVIGATOR Participants in a Multivariable Cox Proportional-Hazard Stepwise Selection Model**

| Baseline Variable* | Hazard Ratio (95% CI) | P Value |
|---|---|---|
| Venous thromboembolism (pulmonary embolism/deep venous thrombosis) | 4.09 (2.32–7.22) | <0.001 |
| Cerebrovascular disease | 2.15 (1.54–3.01) | <0.001 |
| Pulse pressure (per 1 mm Hg) | 1.02 (1.01–1.03) | <0.001 |
| Waist circumference (per 10 cm) | 1.28 (1.13–1.46) | <0.001 |
| Coronary heart disease | 1.67 (1.28–2.19) | <0.001 |
| LDL cholesterol (per 1 mmol/L increase between 2.5 and 4.0 mmol/L) | 1.44 (1.15–1.80) | 0.001 |
| eGFR (per 1 mL min$^{-1}$ 1.73 m$^{-2}$ up to 70 mL min$^{-1}$ 1.73 m$^{-2}$) | 0.98 (0.96–0.99) | 0.006 |
| Heart rate (per bpm up to 70) | 0.97 (0.96–0.99) | 0.007 |
| Body mass index (per 1 kg/m²) | 0.96 (0.92–0.99) | 0.01 |
| Age (per 10 y) | 1.24 (1.02–1.51) | 0.034 |
| Atrial fibrillation | 1.65 (1.04–2.63) | 0.035 |
| Black vs all other races | 2.16 (1.01–4.65) | 0.049 |
| Valsartan vs no treatment | 0.80 (0.62–1.03) | 0.088 |
| Nateglinide vs no treatment | 0.88 (0.68–1.13) | 0.31 |

All candidate variables were entered into the model, including closely related groups of variables (for example systolic blood pressure, diastolic blood pressure, pulse pressure, and hypertension). CI indicates confidence interval; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; and NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial.

*Table includes all independent predictors+randomized treatment (listed above). The model also included other race comparisons (white vs all other races; Asian vs all other races), eGFR>70 mL min$^{-1}$ 1.73 m$^{-2}$, heart rate >70 bpm, and LDL cholesterol >4.0 mmol/L (comparisons nonsignificant in this model, data not shown).

disease and aged ≥50 years. Relevant qualifying cardiovascular disease risk factors are provided in previous publications.[3] The trial was approved by local ethics committees, and participants provided written informed consent. The end point of stroke was adjudicated by an independent committee and trial definitions are provided in Table I in the online-only Data Supplement.

Cox proportional-hazard regression models were developed for occurrence of stroke. Thirty-nine candidate variables were included in the forward model selection (P<0.05; Table 1). Randomized treatments (valsartan versus placebo and nateglinide versus placebo) and race were forced into the model. Discrimination ability was assessed with optimism-corrected C-statistics. P values <0.05 were considered statistically significant, and all P values were 2-sided. Analyses were conducted independently at the Duke Clinical Research Institute (Durham, NC) using SAS version 9.2 software (SAS Institute Inc, Cary, NC).

## Results

Stroke occurred in 237 of the 9306 NAVIGATOR participants during a median follow-up of 6.4 years (202 nonhemorrhagic strokes). Among subjects without history of cerebrovascular disease (n=8570), 193 (2.3%) experienced a stroke, compared with 44 (6.0%) out of 736 with a history of cerebrovascular disease.

Major independent predictors of stroke included previous venous thromboembolism (pulmonary embolism or deep venous thrombosis; the strongest predictor), previous cerebrovascular disease (stroke or transient ischemic attack), higher pulse pressure, and higher waist circumference (Table 2). Other independent predictors were previous coronary heart disease, higher low-density lipoprotein cholesterol, lower estimated glomerular filtration rate, lower heart rate (below a threshold of 70 bpm), lower body mass index, older age, the presence of atrial fibrillation, and black race versus all other races. No glycemic measure was associated with stroke.

The C-statistic for the prognostic model was 0.72. Results were similar in the 8570 patients without a history of stroke at baseline (C-statistic 0.72; Table II in the online-only Data Supplement).

Predictors of nonhemorrhagic stroke (202 events) were similar to predictors of all strokes. The variables most strongly associated with nonhemorrhagic stroke were cerebrovascular disease, previous venous thromboembolism, coronary heart disease, higher pulse pressure, and lower estimated glomerular filtration rate (Table III in the online-only Data Supplement).

## Discussion

In this study, we confirmed that most stroke risk factors in IGT were similar to those in both the general population and T2DM.[1,4]

Cigarette smoking, hypertension, age, T2DM, cholesterol, low high-density lipoprotein cholesterol, atrial fibrillation, and carotid stenosis are the recognized stroke risk factors.[4] Results from NAVIGATOR largely reflected this, although surprisingly current smoking status was not predictive of stroke. Prior venous thromboembolism (pulmonary embolism or deep venous thrombosis) emerged as the strongest stroke risk factor, but this remains unexplained. Sensitivity analyses limited to only nonhemorrhagic strokes and to the subset of participants with no history of cerebrovascular disease at baseline were largely similar to the main analysis. Measures of glycemia were not predictive of stroke, possibly reflecting the relatively narrow range of dysglycemia in NAVIGATOR.

In summary, independent predictors of stroke in patients with IGT included not only established risk factors, but also other important variables, such as previous venous thromboembolism and elevated waist circumference.

## Sources of Funding

## Disclosures

None.

## References

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# Stroke

American Heart Association

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**SUPPLEMENTAL MATERIAL**

Predictors of Stroke in Patients with Impaired Glucose Tolerance: Results from the NAVIGATOR Trial

**Supplemental Tables**

**Table I.** Definitions of non-fatal and fatal stroke as used in the NAVIGATOR trial

**Table II.** Predictors of stroke in NAVIGATOR participants with no prior history of cerebrovascular disease as identified in a multivariable Cox proportional hazard stepwise selection model (8570 participants with 193 events)

**Table III.** Predictors of non-hemorrhagic stroke in NAVIGATOR participants as identified in a multivariable Cox proportional hazard stepwise selection model (9306 participants with 202 events)

**Table I.** Definitions of non-fatal and fatal stroke as used in the NAVIGATOR trial

| DEFINITION | SUPPORTIVE DOCUMENTATION |
|---|---|
| **6.3.1 Stroke**<br><br>An acute neurological dysfunction of vascular origin (verified or presumed) with clinical signs and / or symptoms that persist for 24 hours or more.<br><br>Types of stroke:<br><br>1. *Hemorrhagic stroke*: acute neurological deficit with documentation of intracranial blood (intraparenchymal, intraventricular, subdural, or subarachnoid) preferably by neuroimaging (e.g. CT scan or MRI of the brain.) Evidence of hemorrhagic stroke can also be obtained from lumbar puncture, neurosurgery, or autopsy.<br><br>2. *Non-hemorrhagic stroke*: acute focal neurologic deficit that results from a thrombus or embolus without evidence of intracranial blood by neuroimaging (e.g. CT scan or MRI of the brain.<br><br>3. *Unknown type of stroke*: if the type of stroke could not be determined due to a lack of imaging or other diagnostic information (e.g. lumbar puncture, neurosurgery, or autopsy).<br><br>**6.3.2 Fatal Stroke**<br><br>Autopsy or brain imaging (CT or MRI) confirmed stroke and thought to be the primary cause of death. Cessation of life support measures (initiated by a direct consequence of the stroke) will be classified as death secondary to the stroke. | Summary of hospitalization (discharge summary)<br><br>Written clinical summary (if the clinical picture is not adequately covered in the hospital discharge summary)<br><br>Physical examination findings<br><br>Neurological consult report<br><br>CT scan or MRI (original or copy)<br><br>Report of computed tomography, MRI, angiography, or other diagnostic procedure<br><br>Autopsy report (if appropriate)<br><br>Surgical/Pathology report of brain |

**Table II.** Predictors of stroke in NAVIGATOR participants with no prior history of cerebrovascular disease as identified in a multivariable Cox proportional hazard stepwise selection model (8,570 participants with 193 events)

| Variable* | HR (95% CI) | P-Value |
|---|---|---|
| Venous thromboembolism (Pulmonary embolism/DVT) | 4.62 (2.54–8.38) | <0.001 |
| Waist circumference, per 10 cm | 1.36 (1.19–1.56) | <0.001 |
| Coronary heart disease | 1.85 (1.37–2.49) | <0.001 |
| LDL-cholesterol, per 1 mmol/L higher between 2.5 and 4.0 mmol/L | 1.58 (1.23–2.02) | <0.001 |
| Pulse pressure, per 1 mm Hg | 1.02 (1.01–1.03) | <0.001 |
| Age, per 10 yrs | 1.44 (1.16–1.77) | <0.001 |
| Heart rate, per 1 bpm up to 70 bpm | 0.97 (0.95–0.99) | 0.001 |
| Left ventricular hypertrophy | 2.33 (1.32–4.11) | 0.004 |
| BMI, per 1 kg/m$^2$ | 0.96 (0.92–0.99) | 0.02 |
| Black vs. all other races | 2.51 (1.11–5.71) | 0.03 |
| Valsartan vs. no treatment | 0.76 (0.57–1.01) | 0.06 |
| Nateglinide vs. no treatment | 0.83 (0.63–1.11) | 0.20 |

*Table includes all independent predictors plus randomized treatment (listed above). The model also included other race comparisons (white vs. all other races; Asian vs. all other races), heart rate >70bpm and LDL-cholesterol >4.0mmol/L (comparisons non-significant in this model, data not shown)

All candidate variables were entered into the model, including closely related groups of variables (for example systolic blood pressure, diastolic blood pressure, pulse pressure, and hypertension).

BMI indicates body mass index; bpm, beats per minute; CI, confidence interval; DVT, deep venous thrombosis; HR, hazard ratio; LDL, low-density lipoprotein.

**Table III.** Predictors of non-hemorrhagic stroke in NAVIGATOR participants as identified in a multivariable Cox proportional hazard stepwise selection model (9306 participants with 202 events)

| Variable* | HR (95% CI) | P-Value |
|---|---|---|
| Cerebrovascular disease | 2.43 (1.71-3.44) | <0.001 |
| Venous thromboembolism (Pulmonary embolism/DVT) | 3.57 (1.88-6.79) | <0.001 |
| Coronary heart disease | 1.69 (1.27-2.27) | <0.001 |
| Pulse pressure, per 1 mm Hg | 1.02 (1.01-1.03) | <0.001 |
| eGFR (per 1mL/min/1.73m$^2$ up to 70) | 0.97 (0.96-0.99) | <0.001 |
| LDL-cholesterol, per 1 mmol/L higher between 2.5 and 4.0 mmol/L | 1.46 (1.14-1.85) | 0.002 |
| Heart rate, per 1 bpm up to 70 bpm | 0.97 (0.95-0.99) | 0.006 |
| Waist circumference, per 10 cm | 1.15 (1.04-1.28) | 0.008 |
| Female vs. male | 0.67 (0.50-0.91) | 0.009 |
| Age, per 10 yrs | 1.30 (1.06-1.60) | 0.014 |
| Valsartan vs. no treatment | 0.75 (0.57-0.99) | 0.041 |
| Nateglinide vs. no treatment | 0.82 (0.62-1.08) | 0.15 |

*Table includes all independent predictors plus randomized treatment (listed above). The model also includes race, eGFR >70mL/min/1.73m$^2$, heart rate >70bpm and LDL-cholesterol >4.0mmol/L (comparisons non-significant in this model, data not shown)

All candidate variables were entered into the model, including closely related groups of variables (for example systolic blood pressure, diastolic blood pressure, pulse pressure, and hypertension).

eGFR indicates estimated glomerular filtration rate; bpm, beats per minute; CI, confidence interval; DVT, deep venous thrombosis; HR, hazard ratio; LDL, low-density lipoprotein.