CLINICAL RESEARCH STUDY

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Venous Thromboembolism and Cardiovascular Risk: Results from the NAVIGATOR Trial

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ABSTRACT

BACKGROUND: Contemporary studies suggest an association between venous thromboembolism and a higher incidence of major cardiovascular events, mostly attributed to arterial atherothrombosis. Using data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, we assessed the association of venous thromboembolism with major cardiovascular events.

METHODS: In NAVIGATOR, patients with impaired glucose tolerance were randomly allocated to receive valsartan or placebo and nateglinide or placebo in addition to lifestyle modification. Baseline characteristics and prior history of venous thromboembolism were assessed. After adjusting for important baseline covariates, Cox proportional hazards regression models were used to assess the association between venous thromboembolism and major cardiovascular outcomes.

RESULTS: Of the 9306 patients enrolled, 129 (1.4%) had a history of venous thromboembolism. Patients with venous thromboembolism were older, more frequently white and female, and had a higher body mass index. Patients with venous thromboembolism had higher 5-year event rates for the composite of death, myocardial infarction, and stroke, as compared with patients without venous thromboembolism (10.7% vs 5.9%; $P < .001$; adjusted hazard ratio 2.12; 95% confidence interval, 1.36-3.31; $P = .001$).

CONCLUSION: In patients with impaired glucose tolerance at high risk for cardiovascular events, the prevalence of venous thromboembolism was rare but associated with worse long-term cardiovascular outcomes, including arterial events. Venous thromboembolism is a marker of risk, and attention should be paid to this high-risk group of patients.

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In the past, venous thromboembolism and arterial thrombosis were considered distinct entities. However, contemporary data have suggested an association between venous thromboembolism and a higher incidence of major cardiovascular events.[1-6] The hypothesis that venous thromboembolism and atherosclerosis share common pathways is still controversial, but cumulative evidence suggests this relationship exists.[1-8] A recent meta-analysis combining the results of 6 cohort studies demonstrated the high risk for adverse cardiovascular events in patients with unprovoked venous thromboembolism.[9] Despite recent data, few studies have tested this association in a more controlled setting such as a randomized clinical trial with a large sample size. Moreover, there is some uncertainty about the magnitude of the association between venous thromboembolism and major cardiovascular events. The Nateglinide and Valsartan in Impaired Glucose

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Tolerance Outcomes Research (NAVIGATOR) study was a double-blind, randomized clinical trial testing the effects of nateglinide and valsartan on the incidence of diabetes and a composite of cardiovascular events.[10-12] Using data from NAVIGATOR, we assessed the association of venous thromboembolism with major cardiovascular events.

METHODS

Study Population and Trial Design

The study design, patient characteristics, and outcomes of the NAVIGATOR study have been published.[10-13] Briefly, NAVIGATOR was a prospective, multicenter, randomized trial with a 2×2 factorial design that included 9306 patients with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors. Patients were randomly assigned to receive valsartan (up to 160 mg daily) or placebo and nateglinide or placebo, in addition to lifestyle modification. Men and women with impaired glucose tolerance and one or more cardiovascular risk factors (age $\geq$55 years) or with known cardiovascular disease (age $\geq$50 years) were eligible for participation in NAVIGATOR. The exclusion criteria were laboratory abnormalities or conditions that could interfere with assessment of the safety or efficacy of a study drug, the use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for the treatment of hypertension, and the use of an antidiabetic medication within the previous 5 years. Patients were followed prospectively for a median of 5.0 years for the occurrence of 3 co-primary outcomes: 1) development of diabetes; 2) an extended composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina; and 3) a core composite outcome that excluded unstable angina and revascularization. An independent committee whose members were unaware of study group assignments adjudicated the occurrence of outcomes. All patients (N = 9306) from NAVIGATOR were included in the analyses.

All patients gave written informed consent and the trial was approved by ethics committees at all participating centers.

Venous Thromboembolism

Venous thromboembolism was reported at baseline by the investigator in the form of free text and included the following terms: pulmonary embolism, vena cava filter insertion, venous thrombosis, and deep vein thrombosis. Baseline characteristics and a prior history of venous thromboembolism were assessed.

CLINICAL SIGNIFICANCE

- In patients with impaired glucose tolerance at high risk for cardiovascular events, the prevalence of venous thromboembolism was rare but associated with worse long-term cardiovascular outcomes, including arterial events.
- Venous thromboembolism is a marker of risk, and attention should be paid to this high-risk group of patients.

Statistical Analysis

Baseline patient characteristics are summarized by patients with and without venous thromboembolism. Continuous variables are reported as medians with 25th and 75th quartiles and compared using the Wilcoxon rank-sum test. Categorical variables are reported as frequencies and percentages and compared using Pearson chi-squared or Fisher's exact tests. Adjusted Cox proportional hazards regression models were used to assess the association of venous thromboembolism with the following 2 outcomes: model 1 considered the composite of cardiovascular death, myocardial infarction, and stroke; and model 2 considered the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, hospitalization for unstable angina, or arterial revascularization (extended cardiovascular endpoint). The adjusted variables came from the previously developed baseline models for those 2 outcomes. The proportional hazards assumptions have been tested for venous thromboembolism and are satisfied for both outcomes. The adjusted survival curves were displayed by patients with and without venous thromboembolism for 2 outcomes; the event rates at 5 years were summarized.

Missing data were handled by the single imputation method (because the covariates had a small amount of missing values). All statistical tests were 2-sided, and the criterion for statistical significance was $P < .05$. All statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Clinical Characteristics

Of the 9306 patients included in NAVIGATOR, 129 (1.4%) had a previous history of venous thromboembolism. Baseline characteristics according to venous thromboembolism are shown in Table 1. Patients with venous thromboembolism were older; more frequently white, female, and from Europe and North America; and had higher body mass index and waist circumference. In addition, chronic obstructive pulmonary disease was more common in patients with a previous history of venous thromboembolism.

Table 1 illustrates the baseline laboratory characteristics according to venous thromboembolism. Patients with a previous diagnosis of venous thromboembolism had slightly higher levels of glycated hemoglobin and high-density lipoprotein, while triglyceride levels were somewhat lower in this group when compared with patients without venous thromboembolism.