Diabetes, Fasting Glucose Levels, and Risk of Ischemic Stroke and Vascular Events: Findings from the Northern Manhattan Study (NOMAS)

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**Background:** There is insufficient randomized trial data to support evidence-based recommendations for tight control of fasting blood glucose (FBG) among diabetics in primary stroke prevention. We explored the relationship between FBG among diabetics and risk of ischemic stroke in a multi-ethnic prospective cohort.

**Methods:** Medical/social data and FBG were collected on 3298 stroke-free community residents: mean age was 69 years ±10 yrs; 63% were women; 21% white, 24% black, 53% Hispanic; 6.5 yrs follow-up. Baseline FBG levels were categorized: 1) *Elevated FBG,* history of diabetes and FBG ≥ 126 mg/dl (7.0 mmol/l); 2) *Target FBG,* history of diabetes and FBG < 126 mg/dl (7.0mmol/l); or, 3) *no diabetes/reference group.* Cox models calculated hazard ratios (HR) and 95% confidence intervals (95% CI) for ischemic stroke and vascular events.

**Results:** In NOMAS, 572 reported a history of diabetes and 59% (n=338) had elevated FBG. Elevated FBG among diabetics was associated with female gender (p 0.04), Medicaid (p = 0.01) or no insurance (p=0.03). We detected 190 ischemic strokes and 585 vascular events. Diabetics with elevated FBG [HR 2.7, 95% CI 2.0 – 3.8] were at increased risk of stroke, but those with target FBG levels[HR 1.2, 95% CI 0.7 – 2.1] were not, even after adjustment. A similar relationship existed for vascular events: elevated FBG [HR 2.0, 95% CI 1.6 – 2.5]; target FBG [HR 1.3, 95% CI 0.9 – 1.8].

**Conclusions:** This prospective cohort study provides evidence for the benefits of tighter glucose control for primary stroke prevention.
Diabetes mellitus is a major public health problem. In the US today, over 18.2 million people have been diagnosed with diabetes. The prevalence of diabetes increases with age, and certain populations, including minority groups, may be more vulnerable. According to the American Diabetes Association, one out of every four African American and Hispanic individuals over 65 years of age is a diabetic. Additionally it is estimated that another 10-15% of the US population has elevated blood glucose levels, and may be considered “pre-diabetic”. Diabetes mellitus is a major risk factor for cardiovascular disease and is associated with a more than 2-fold risk of cardiovascular outcomes including incident MI and mortality. 1, 2 Similarly, diabetes has been associated with an increased risk of stroke with relative risks ranging from 1.8 to 6. 3-5

Despite the public health significance of diabetes, there is a paucity of data which emphasizes tight control of fasting blood glucose as a stroke prevention measure. According to the American Heart Association “Guidelines for the Primary Prevention of Stroke”, there is insufficient randomized trial data to support glycemic control among diabetics as a stroke prevention measure. 6 American Heart recommendations based on the United Kingdom Prospective Diabetes Study (UKPDS) support glycemic control among diabetes to “reduce microvascular complications, nephropathy, and retinopathy, as well as peripheral neuropathy.” 6, 7 In the UKPDS, tight glycemic control of a prospective cohort of newly diagnosed diabetics did not significantly reduce stroke risk. 7

The current obesity epidemic and associated increasing prevalence of diabetes, especially among minority populations, warrants further investigation of whether tight control of FBG is associated with decreased stroke risk. The aim of this study was to explore the relationship between FBG levels among diabetics and the risk of ischemic stroke as well as other vascular events in a multi-ethnic prospective cohort.

METHODS

The Northern Manhattan Study (NOMAS) is a prospective population-based cohort study designed to study incidence, risk factors, and prognosis of stroke in a multi-ethnic urban community. Based in Northern Manhattan, an area of approximately 260,000 people, with 104,000 aged over 39 years of age, this study has a unique race-ethnic distribution of approximately 63% Hispanic, 20% black and 15% white. Methodology for NOMAS has been described previously and is summarized briefly below. 8

Selection of Prospective Cohort: A total of 3298 subjects were recruited and enrolled between 1993 and 2001. Participants were eligible if they (1) had never been diagnosed with a stroke, (2) were age ≥ 40 years, and (3) resided for at least 3 months in a household with a telephone in Northern Manhattan. Subjects were identified by random digit dialing utilizing dual frame sampling and bilingual interviews conducted. 9 The telephone response rate was 91% (9% refused to be screened), and 87% of those eligible indicated willingness to participate. This study was approved by the local governing institutional review board and written consent was obtained.

Baseline Evaluation: Subjects were recruited from the telephone sample to have an in-person baseline interview and assessment. The enrollment response rate was 75% with an overall response rate of 68% (telephone response x enrollment response). Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System regarding medical history. 10 Race-ethnicity was based upon self-identification.
**Glucose levels:** To examine the impact of FBG on stroke risk among diabetics we divided baseline FBG levels into three categories: 1) Elevated FBG - a history of diabetes and fasting blood glucose \( \geq 126 \text{ mg/dl (7.0 mmol/l)} \); 2) Target FBG - a history of diabetes and fasting blood glucose \(< 126 \text{ mg/dl (7.0mmol/l)} \); or, 3) no diabetes/reference group. The non diabetes group included those with no history of diabetes. Fasting serum glucose was measured according to standard procedures using a glucose dehydrogenase method. 11

**Other Baseline Assessments:** Hypertension was defined as either systolic blood pressure levels \( \geq 140 \text{ mmHg} \), diastolic blood pressure \( \geq 90 \text{ mmHg} \) or history of hypertension. Cardiac disease included history of angina, MI, coronary artery disease or valvular heart disease. Obesity was defined using body mass index. Smoking was categorized as none, former and current smoker. Moderate alcohol use was defined as current drinking of more than one drink per month and less than or equal to 2 drinks per day. Physical activity was defined as engaging in leisure activity versus not over the 10 days prior to baseline enrollment. Social resources were defined by educational level and health insurance status. Education was dichotomized into those who had completed high school versus those who had not. Health insurance was separated into three mutually exclusive groups: a) individuals who had Medicaid or Medicaid/Medicare or no insurance, b) individuals who had private insurance or private/Medicare, and c) individuals with Medicare only. (Reference group) We combined the no insurance group with the Medicaid group based on a similar risk ratio in these groups, as well as the very low prevalence (7%) of non insured in this cohort.

**Annual Prospective Follow-up:** Subjects were screened annually by telephone interview to determine any change in vital status, detect neurological and cardiac symptoms and events, review any interval hospitalizations, review risk factor status, changes in medication, and determine changes in functional status. Phone assessment served as a screen for events. The telephone interview simple stroke question (Since your last visit have you been diagnosed with a stroke?”) had a sensitivity of 92% and specificity of 95%. Moreover, a 10% random sample of the cohort was followed annually in-person for 5 years to evaluate for any telephone false negatives and evaluate for serial change in baseline measures. In between follow-up interviews, subjects and family members were reminded to notify us in the event of stroke, MI or death.

Subjects who screened positive by telephone were scheduled for an in-person assessment. All affirmative responses to neurological symptoms and conditions required a review and examination by the study neurologists. Additionally ongoing hospital surveillance of admission and discharge ICD-9 codes provided data on mortality and morbidity that may not have been captured during annual telephone follow-up.

**Outcome Classifications (Ischemic Stroke, MI, Vascular Death):** For these analyses, two outcome measures were: 1) first ischemic stroke, and 2) first vascular event, defined as either first ischemic stroke or first MI or vascular death.

Stroke was defined as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.” 12 Subjects who are hospitalized for stroke at CPMC have systematic evaluations during their hospitalization which includes standard diagnostic tests: admission serological studies, head CT, carotid duplex Doppler, transcranial Doppler, echocardiography, electrocardiography, magnetic resonance
imaging and angiography. The diagnostic evaluation by neurologists at non-Northern Manhattan hospitals is difficult to control, but any participant who needs vascular non-invasive testing can have these done as part of their in-person follow-up visit at CPMC. Subjects who are suspected of having a stroke and have not had a prior diagnostic evaluation have one done either through their primary care physicians, the CPMC neurology clinic or the Clinical Research Center. If a patient has been hospitalized, then medical records will be reviewed to verify any details.

Over 98% of these stroke outcomes had at least one form of imaging, predominately a CT. Although our surveillance system captured both hemorrhagic and ischemic stroke, for the purposes of this study we are reporting only on ischemic stroke outcomes. Hemorrhagic stroke accounted for 9% of all stroke and we did not have the power to examine this stroke subtype separately. Over 70% of the stroke cases were hospitalized at the Columbia University Medical Center.

Myocardial infarction was defined by criteria adapted from the Lipid Research Clinics Coronary Primary Prevention Trial and required at least 2 of the 3 following criteria: (a) ischemic cardiac pain determined to be typical angina; (b) cardiac enzyme abnormalities defined as abnormal CPK-MB fraction or Troponin values; and (c) EKG abnormalities.

For subjects who died, the date of death was recorded along with cause of death. Deaths were classified as vascular or non-vascular based on information obtained from the family and physicians and validated with medical records and death certificate. Causes of vascular death included ischemic stroke, MI, heart failure, pulmonary embolus, cardiac arrhythmia, and other vascular causes. Nonvascular causes of death included accident, cancer, pulmonary (pneumonia, chronic obstructive pulmonary disease, etc) and other nonvascular causes. All vascular outcomes were reviewed and validated in a similar manner to stroke outcomes by our team of three study cardiologists.

**Statistical Analyses:** The prevalence of socio-demographic, conventional vascular risk factors and other baseline variables was calculated. Kaplan-Meier curves of survival free of ischemic stroke and survival free of vascular events (ischemic stroke, MI or vascular death) were calculated (online appendix figure 1 [available at http://care.diabetesjournals.org]). Cox proportional regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for ischemic stroke and all vascular events (stroke, MI and vascular death). Time to first event among stroke and vascular outcomes (ischemic stroke, MI or vascular death) were analyzed as outcomes with censoring at the time to either non-vascular event or last follow-up.

Additionally, we performed a separate cross sectional analysis among those with diabetes to identify factors associated with elevated FBG versus target FBG levels (online appendix figure 2). Age, gender, race-ethnicity, education, and insurance status were considered as socio-demographic factors, and models were adjusted for hypertension, obesity, dyslipidemia, cardiac disease, smoking, physical inactivity, and alcohol consumption.

**RESULTS**

A cohort of 3,298 community residents was enrolled. At baseline, mean age was 69 years ±10 yrs; 63% were women; 21% white, 24% black and 53% were Hispanic. Over 18% (N= 572) of the cohort had reported a diagnosis of diabetes. Among those with diabetes, 19% were diet controlled, 55% were on oral hypoglycemics, and 26% were on insulin at baseline interview.

Control of FBG diabetics was poor with over 59% (338) of individuals with
diabetes having fasting blood glucose levels $\geq 126$mg/dl. Elevated FGB levels were similar among whites, black and Hispanic diabetics. The mean duration of diabetes in the cohort was 12 years with a median of 8 years. There was no difference in the duration of diabetes among those with target FGB levels (mean 11.3 years, median 8 years) versus elevated FGB levels (mean 12 years, median 8 years). Likewise, the use of oral hypoglycemic agents and insulin among diabetics was not statistically different between diabetics with poor control of fasting glucose versus those with better fasting glucose levels.

During a mean of 6.5 years of follow-up, 190 ischemic strokes and 585 vascular events were detected. Among the diabetic group, 62 ischemic stroke events were documented (14 in the controlled diabetic group and 48 in the uncontrolled group). In a multivariable Cox model with no diabetes as the reference, elevated fasting blood glucose levels [HR 2.7, 95% CI 1.9-3.8] were significantly associated with increased risk of stroke, while target fasting blood glucose levels [HR 1.2, 95% CI 0.7-2.1] did not significantly increase stroke risk after adjusting for age, race-ethnicity, gender, insurance status, education, HTN, CAD, lipid levels, obesity, physical inactivity, ETOH, and smoking. A similar relationship existed for risk of any vascular events: elevated FGB [HR 2.0, 95% CI 1.6-2.5]; target FGB [HR 1.3, 95% CI 0.9-1.8]. In a separate analysis to determine if the effect of elevated FGB was significantly different from target FGB, we found that they were significantly different $p=0.3$.

We further explored the dose response model for levels of fasting blood glucose for ischemic stroke, vascular death and any vascular event. We found that FGB levels $\geq 126$ but $< 150$ were associated with a HR 4.1 95% CI 2.3-7.2 and FGB levels $\geq 150$ were associated with an HR or 2.7 95% CI 1.8-3.9, after controlling for age, race-ethnicity, gender, education, and physical activity.

In separate analysis, we explored factors associated with elevated versus target FGB levels. Three dimensions of factors were examined: demographics, risk factors and social resources. In multivariable analyses, elevated FGB was significantly greater among women ($p=0.04$), those with Medicaid ($p=0.01$) or no insurance ($p=0.03$). Vascular risk burden or prevalence of risk factors was not significantly associated with elevated versus target FGB levels among those with diabetes.

**DISCUSSION**

In our multi-ethnic prospective community-based stroke free cohort, we report a strong relationship between elevated FGB levels among diabetics (fasting blood glucose $\geq 126$ mg/dl (7.0mmol/l) and increased risk of incident ischemic stroke as well as vascular events after adjustment for socio-demographics and vascular risk factors. The increased risk associated with elevated FGB was similar whether fasting glucose was 126-150 mg/dl or above. In our cohort, risk of ischemic stroke among a diabetic population with FGB levels within target range was associated with a lower and non significant risk of stroke and vascular events. Furthermore, there was a significantly different relationship in stroke risk between those with elevated FGB levels and target FGB levels. Few studies have examined the relationship between control of FGB levels and ischemic stroke risk, and most include stroke as a combined outcome with cardiovascular disease. In a meta-analysis, chronic hyperglycemia defined by a 1 point increase in glycosylated hemoglobin was found to be associated with a pooled relative risk of 1.18 95% CI 1.10-1.26 for all vascular endpoints, and a pooled relative risk of 1.15 95% CI 1.08 - 1.23 for stroke. Similarly, in a nested sample from the ARIC cohort,
Elevated baseline HbA1c was reported to be an independent predictor of cardiovascular outcomes [RR 1.1, (95% CI 1.1 – 1.20) per 1-percentage point increase in HbA1c]. In a registry cohort of Finnish diabetic patients, both high plasma glucose levels (> 13.4 mmol/l) and elevated HbA1c > 10.7% were strongly associated with increased risk of prevalent stroke. In the large prospective ARIC study which examined the relationship between FBG levels and risk of ischemic stroke, relative risks were compared among two definitions of diabetes. Poor glycemic control defined as a fasting glucose ≥ 140 mg/dl or history of diabetes conferred a 2.2 fold risk (95% CI 1.6-3.2) of ischemic stroke, and poor glycemic control defined by a history of diabetes or fasting glucose ≥ 126 mg/dl was associated with a HR 1.9 (95% CI 1.3 – 2.7) for ischemic stoke. However, the ARIC study did not examine the impact of elevated glucose levels among diabetics. While there appears to be a dose response relationship between the glucose levels and outcomes in the lower glucose group compared to the mid range and high range group, the relative risks in the mid-range group and the high range group are similar. Indeed the confidence intervals are almost identical. Further the mid-range group (n=73) is small. Nevertheless, the lack of dose response between the two upper glucose groups may suggest that damage to organ systems begins in the midlevel group. Other studies have reported that FBG level is an independent risk factor for coronary heart disease among non-diabetic populations. In ARIC, the relationship between FBG levels and ischemic stroke among non diabetics demonstrated a slightly increased risk but failed to reach significance. We found similar results.

Only a few randomized trials have been conducted to examine whether tight FBG control leads to better vascular outcomes, and these trials have been criticized for small numbers and insufficient follow-up. The University Group Diabetes Program (UGDP) found no significant benefit of tight glycemic control among 400 diabetics. This study, however, suggested that two agents (tolbutamide and phenformin) utilized for glycemic control might actually be associated with increased cardiovascular mortality. Another trial of 153 type 2 diabetic men assigned to intensive versus conventional therapy demonstrated no difference in cardiovascular events during 22 months of follow-up.

The largest randomized clinical trial examining the relationship between vascular outcomes and tight glycemic control among type 2 diabetics was the United Kingdom Prospective Diabetes Study (UKPDS). In the UKPDS, intensive glycemic control reduced the relative risk of any diabetes-related endpoint by 12% and microvascular complications by 25%. However, tight glycemic control was not significantly associated with decreased risk of stroke (HR 1.1 (0.8 – 1.5) among 5102 diabetics randomized to conventional (diet controlled only) versus intensive treatment regiments (chlorpropamide, glyburide, insulin or metformin among obese subjects). Strengths of the UKPDS included meticulous, serial measurement of glycemic control using HbA1C techniques. One limitation of UKPDS was its definition of stroke as “a major stroke with symptoms or signs lasting 1 month or longer”. This outcome criteria may have led to an under identification of stroke cases, especially those of small vessel etiology. Additionally, the short follow-up period associated with clinical trials may underestimate the “control effect”, while a FBG in an observational study may be an effective indicator of control over many years. Further, because of the “intent to treat” nature of the trial, over 80% of the control group required one or more of the therapies reserved...
for the intensive intervention regiment. The NOMAS cutoff for glycemic control was 126 mg/dl (7.0mmol/l) which was actually higher than target glucose levels in UKPDS. Finally, in UKPDS, none of the monotherapies were capable of maintaining target “control” glucose levels of < 108 mg/dl (<6.0mmol/l). 7

In a separate analysis, we also examined associations between FBG levels and vascular and social risk factors. We report that health insurance type is an independent predictor of elevated FBG levels among our diabetic patients. Indeed, FBG targets may be difficult to achieve in clinical practice settings where continuity of care and adherence to treatment is not emphasized. Other studies have found similar results. In a retrospective design of newly treated diabetics captured through an administrative claims database, female gender, PPO insurance plans and use of insulin was associated with early non-adherence as well as treatment discontinuation. 19 In a small cross-sectional study, lower family SES, and lower rate of health insurance but not education, or ethnicity were associated with higher HBA1C levels. 20 UKPDS found little difference by race-ethnicity in glycemic control. 21 In our study, despite differences in the prevalence of diabetes by race-ethnicity, there were no significant differences in elevated versus target glucose levels between whites, blacks and Hispanics.

The inclusion of a large multi-ethnic, elderly, heterogeneous cohort with similar geographical access to the medical center is generalizable to other multi-ethnic urban populations and allows for more valid comparisons across race-ethnic categories. Other strengths include a prospective population-based design where both baseline exposures and outcomes were well documented. Our aggressive follow-up strategies have resulted in less than 1% loss to follow-up. Study participants were seen in-person at both study entry and follow-up to document outcome events. One potential limitation in our results is that ascertainment of outcomes might differ by diabetic control status. It is possible that poor controlled patients may be identified earlier due to outer related co-morbidities. Overall, 54% of our outcome information was obtained through CPMC daily admissions information and there was no difference in the proportion of controlled and uncontrolled diabetics identified this way. Similarly, the proportion of outcome events reported during follow-up of patient and family report (43%) did not differ by diabetic control status. Finally 3% of outcomes were picked up through screening and examination with no difference by diabetic control status.

An important limitation was our use of a single sample of fasting glucose to define baseline glycemic control. However, given its use in previous epidemiologic studies, and our lack of HbA1C, we felt this measurement of FBG has a reasonable utility. 4 Most studies have used HbA1C as the indicator of better versus poor long term regulation of plasma glucose. Indeed, glycosylated hemoglobin is thought to reflect long-term glycemic control and may be a more accurate and stable measure than fasting glucose levels. 22 Theoretically, HbA1C reflects the average fasting glucose level throughout the 3 month cycle of the erythrocyte. In reality, the measure of HbA1C is actually a weighted average with more recent glucose levels contributing more than earlier levels. Studies also indicate that fasting plasma glucose levels may underestimate HbA1C levels especially at higher HA1C levels. 23 Indeed, there may be a systematic bias towards incorrectly assigning persons with a higher HbA1C as having a lower FBG (better control) which would bias results towards the null hypothesis. Hence, the effect on FBG on risk of incident stroke may be larger than what it observed.
Other limitations of this study include our inability to capture micro vascular endpoints, as well as our non-specific identification of therapies for glycemic control.

A number of issues remain unresolved regarding elevated versus targeted FBG among diabetics. Data from this and other prospective studies provide evidence that targeted FBG levels among diabetes are associated with a reduction of macro-vascular risk including ischemic stroke and other vascular events. Ongoing rigorous clinical trials such as ACCORD a study of over 10,000 adults with diabetes will ultimately provide conclusive evidence regarding the importance of glycemic control in preventing macro vascular disease including ischemic stroke.

ACKNOWLEDGEMENTS

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REFERENCES


### Table 1. Baseline Socio-demographic Characteristics of the Northern Manhattan Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>Overall N=3298</th>
<th>Prevalence, % Mean ± SD</th>
<th>Non-Diabetics N=2724</th>
<th>Diabetics N= 574</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>69±10</td>
<td>69 ± 11</td>
<td>68 ± 8</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Men</td>
<td>1224(37)</td>
<td>1008(37)</td>
<td>216(38)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>White</td>
<td>691(21)</td>
<td>624(23)</td>
<td>67(12)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>803(25)</td>
<td>647(24)</td>
<td>156(28)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Hisp</td>
<td>1725(54)</td>
<td>1384(52)</td>
<td>341(60)</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Completed high school</td>
<td>1511(46)</td>
<td>1304(48)</td>
<td>206(36)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Medicaid only</td>
<td>1432(44)</td>
<td>1123(41)</td>
<td>309(55)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2425(74)</td>
<td>1939(71)</td>
<td>486(85)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Any physical activity</td>
<td>1943(59)</td>
<td>1627(60)</td>
<td>316(55)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>787(24)</td>
<td>608(22)</td>
<td>179(31)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Current Smoking</td>
<td>508(15)</td>
<td>419(15)</td>
<td>89(16)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mild/Moderate Alcohol</td>
<td>1074(33)</td>
<td>944(35)</td>
<td>130(23)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 29</td>
<td>1124 (34)</td>
<td>884 (32)</td>
<td>240(42)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL &lt; 35</td>
<td>741(22)</td>
<td>581(21)</td>
<td>160(28)</td>
<td></td>
<td>0.0005</td>
</tr>
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</table>
Table 2. Adjusted hazard ratios of ischemic stroke and vascular events by level of glucose among diabetics

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=2621)</td>
<td>Glucose &lt; 126 mg/l (n=214)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>Referent</td>
<td>1.8 (1.0 - 3.1)</td>
</tr>
<tr>
<td>Vascular Death</td>
<td>Referent</td>
<td>1.4 (0.9 – 2.2)</td>
</tr>
<tr>
<td>Any Vascular Event</td>
<td>Referent</td>
<td>1.6 (1.2 – 2.3)</td>
</tr>
</tbody>
</table>

All Models adjusted for age, race-ethnicity, gender, education, and physical activity.