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ORIGINAL RESEARCH

Hyperglycemia, Risk of Subsequent Stroke, and Efficacy of Dual Antiplatelet Therapy: A Post Hoc Analysis of the POINT Trial

Brian Mac Grory, MB BCh BAO, MRCP; Jonathan P. Piccini, MD, MHS; Shadi Yaghi, MD; Sven Poli, MD; Adam De Havenon, MD; Sara K. Rostanski, MD; Martin Weiss, MD; Ying Xian, MD, PhD; S. Claiborne Johnston, MD, PhD; Wuwei Feng, MD, MS

BACKGROUND: One-quarter of all strokes are subsequent events. It is not known whether higher levels of blood glucose are associated with an increased risk of subsequent stroke after high-risk transient ischemic attack or minor ischemic stroke.

METHODS AND RESULTS: We performed a secondary analysis of the POINT (Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial to evaluate the relationship between serum glucose hyperglycemia (≥180 mg/dL) versus normoglycemia (<180 mg/dL) before enrollment in the trial and outcomes at 90 days. The primary end point was subsequent ischemic stroke modeled by a multivariable Cox model with adjustment for age, sex, race, ethnicity, study treatment assignment, index event, and key comorbidities. Of 4878 patients included in this study, 267 had a recurrent stroke. There was a higher hazard of subsequent stroke in patients with hyperglycemia compared with normoglycemia (adjusted hazard ratio [HR], 1.50 [95% CI, 1.05–2.14]). Treatment with dual antiplatelet therapy was not associated with a reduced hazard of subsequent stroke in patients with hyperglycemia (HR, 1.18 [95% CI, 0.69–2.03]), though the wide confidence interval does not exclude a treatment effect. When modeled as a continuous variable, there was evidence of a nonlinear association between serum glucose and the hazard of subsequent stroke (P<0.001).

CONCLUSIONS: Hyperglycemia on presentation is associated with an increased risk of subsequent ischemic stroke after high-risk transient ischemic attack or minor stroke. A rapid, simple assay of serum glucose may be a useful biomarker to identify patients at particularly high risk of subsequent ischemic stroke.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT0099102.

Key Words: antithrombotic therapy ■ clinical trial ■ diabetes ■ hyperglycemia ■ ischemic stroke

Every ischemic stroke represents a critical opportunity to prevent another, potentially more severe, stroke. The risk of subsequent stroke is as high as 17% in the 90 days following the index event, but this risk is front-loaded within the first 7 days.[1] For this reason, there is a need to incorporate dynamic physiological metrics into risk stratification schemes, and not simply long-term risk factors. Serum glucose is an intriguing potential predictor of recurrent stroke risk, because it is already assessed in the majority of patients with acute stroke using widely available, low-cost assays.

Hyperglycemia, an elevation in serum glucose, is associated with an increase in lesion volume[2,3] and worse functional outcomes[3–8] after acute ischemic stroke. Several studies[9,10] have shown that a history of diabetes is associated with subsequent stroke after transient ischemic attack (TIA) or minor ischemic

Correspondence to: Brian Mac Grory, MB BCh BAO, MRCP, Department of Neurology, Duke University School of Medicine, Durham, NC 27710. E-mail: brian.macgrory@duke.edu

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CLINICAL PERSPECTIVE

What Is New?

- This study demonstrates that higher serum glucose on admission is associated with an increased risk of subsequent stroke after a high-risk transient ischemic attack or minor stroke.

What Are the Clinical Implications?

- People with high serum glucose may be at higher risk of future stroke and may benefit from particularly cautious monitoring and follow-up.

Nonstandard Abbreviations and Acronyms

CHANCE	Clopidogel in High-Risk Patients With Acute Nondisabling Events
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
SHINE	Stroke Hyperglycemia Insulin Network Effort

stroke. One prior study[11] suggested that stress hyperglycemia (serum glucose indexed against glycosylated albumin) was associated with subsequent stroke. However, it is not known whether serum glucose itself is associated with subsequent stroke risk.

The objective of this study was to determine whether serum glucose measured on presentation to the emergency department is associated with the risk of subsequent ischemic stroke within 90 days after a high-risk TIA or minor ischemic stroke. We hypothesized that elevated admission serum glucose is associated with a higher risk of subsequent stroke.

METHODS

This research is based on the National Institute of Neurological Disorders and Stroke's archived clinical research data sets (POINT [Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial], S. Claiborne Johnston [U01/NS062835]). The data supporting this study are available upon request from the National Institute of Neurological Disorders and Stroke Clinical Research Liaison (CRLiaison@ninds.nih.gov). The code supporting this analysis and the STrengthening the Reporting of OBservational studies in Epidemiology checklist for observational research[12] are included in Data S1. Because this study was performed using a deidentified, publicly available data set, it was deemed exempt from further review by the institutional review board of Duke University School of Medicine (number 00108046).

Study Design

We performed a secondary analysis using data from the POINT (Registration URL: https://www.clinicaltrials.gov; Unique identifier: NCT00991029).[13] The POINT compared clopidogrel/aspirin to aspirin alone with respect to the primary outcome of a composite of subsequent ischemic stroke, myocardial infarction, or vascular death within 90 days of randomization. It enrolled 4881 patients aged 18 years or older who presented with a high-risk TIA (ABCD^2 score ≥4) or acute minor ischemic stroke (National Institutes of Health Stroke Scale score ≤3) between May 2010 and December 2017 at 269 hospitals. Patients were excluded if they received intravenous tissue-type plasminogen activator, mechanical thrombectomy, had an indication for anticoagulation, or were planned for carotid endarterectomy.

Exposure

The independent variable in this analysis was hyperglycemia. This was defined as a random serum glucose on presentation ≥180 mg/dL (10 mmol/L). The threshold of 180 mg/dL was chosen a priori based on (1) the upper bound of the active control arm of the SHINE (Stroke Hyperglycemia Insulin Network Effort) trial[14] and (2) the upper bound of the serum glucose range recommended from the *2019 Guidelines for the Early Management of Acute Ischemic Stroke*.[15] Serum glucose was assayed on presentation per trial protocol and documented before a determination was made on eligibility for the trial. It was recorded in millimoles per liter or milligrams per deciliter and stored pro forma by study investigators. We excluded patients in whom serum glucose level was unavailable.

End Points

The primary end point of this analysis was subsequent ischemic stroke. This was collected as a secondary outcome in POINT and defined as acute, focal infarction of the brain or retina as evidenced by (1) rapid onset of a new, focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a nonischemic cause; or (2) rapid worsening of an existing focal neurological deficit that was judged by the investigator as attributed to new infarction.[13] Subsequent ischemic stroke was adjudicated by 2 neurologists based on study outcome visits complemented by neuroimaging and medical record review. Secondary end points for this study included major hemorrhage and a composite of subsequent ischemic stroke, myocardial infarction, and death. All definitions used in this article are per the POINT protocol.[13]

Power Calculations

Because this study was performed on a data set of fixed size, sample size calculations were not performed in advance of data analysis. Instead, we calculated study power across a range of postulated hazard ratios and group proportions. With the known 267 ischemic stroke events in the data set and assuming 15% of subjects in the exposure (hyperglycemia) group, a Cox proportional hazards regression model would have 99% power to detect a hazard ratio (HR) of 2 between the groups, at an α of 0.05. We determined the study was likely to be adequately powered with study power in the extreme cases ranging from 61% (10% exposed; HR, 1.5) to 99.9% (25% exposed; HR, 2.5). Power calculations were performed using the powerSurvEpi package in R (version 4.03; R Foundation for Statistical Computing, Vienna, Austria).

Statistical Analysis

Our study sample was described using descriptive statistics with mean±SD or median±interquartile range as appropriate for continuous variables and frequencies/counts for categorical variables. Patients with or without hyperglycemia were compared on univariate analysis using the Student *t* test or Mann-Whitney test for continuous variables and the χ^2 or Fisher exact test for categorical variables, as appropriate. We compared the rate of subsequent ischemic stroke between patients with and without hyperglycemia on presentation using Kaplan-Meier statistics. The log-rank test was used to compare survival curves between groups.

We constructed a Cox proportional hazards regression model to calculate HRs for the primary end point between those with and without admission hyperglycemia. We adjusted for known predictors of subsequent stroke by including age, biological sex, hypertension, diabetes, coronary artery disease, congestive cardiac failure, tobacco exposure, valvular heart disease, carotid disease, treatment assignment (clopidogrel/aspirin versus placebo/aspirin based on the intent-to-treat analysis), and index event classification (high-risk TIA or acute minor ischemic stroke). Additionally, we chose to include both race and ethnicity in multivariable modeling because each are known to predict subsequent stroke.[16,17] We tested the assumption of proportional hazards by inspection of Schoenfeld residuals plots. We fitted models containing the interaction terms hyperglycemia*clopidogrel and hyperglycemia*final adjudicated cause. No adjustment was performed in the clopidogrel interaction analysis because we expected equal distribution of covariates across groups. We reported the HRs with 95% CIs for clopidogrel within the stratifications of hyperglycemia or no hyperglycemia and for hyperglycemia within the subdivisions of diabetes or no diabetes and minor stroke or other adjudicated cause. These analyses were repeated for the secondary end points of major hemorrhage and the composite outcome of ischemic stroke, myocardial infarction, or vascular death.

Sensitivity/Subgroup Analyses

We performed several further analyses:

1. We used a continuous measurement of admission serum glucose as the independent variable within a fully adjusted proportional hazards regression model. To explore the potential for nonlinearity between glucose and subsequent stroke, glucose was modeled as a restricted cubic spline. We chose 5 knots within the restricted cubic spline function at the 5%, 27.5%, 50%, 72.5%, and 95% percentiles. We then performed proportional hazards regression modeling with adjustment for the same covariates as in our primary analysis. We tested for nonlinearity using a likelihood ratio test. The relative hazards of subsequent ischemic stroke were graphed.
2. We created a logistic regression model incorporating all covariates within our primary analysis, and we created a propensity score[18] to predict hyperglycemia versus normoglycemia. Using a caliper of 0.05, we matched hyperglycemic patients on a 1:1 ratio with a propensity-score matched patient without hyperglycemia and replicated our primary analysis restricted to this subgroup.
3. We replicated the main analysis substituting “acute infarction on an imaging study that was attributed to the index event” for “final diagnosis of index event based on symptoms, signs, and imaging data.”
4. We performed subgroup analyses restricted to (1) patients with minor stroke as the index event and (2) patients with TIA as the index event.

All hypothesis testing was 2-sided, and the threshold for statistical significance was set at α=0.05. We did not perform imputation for missing data. Statistical analyses were performed using R (version 4.03).

RESULTS

Patient Characteristics

Overall, 4878 patients were included in this analysis after 3 patients without recorded serum glucose values were excluded. The mean age of subjects in this analysis was 64.6±13.1 years, 45% were women, and 594 (12.2%) were hyperglycemic on presentation. Nine hundred sixty-six (19.8%) patients were Black

and 387 (7.9%) were Hispanic. Patients with hyperglycemia on presentation were more likely to be Hispanic (12.3% versus 7.3%, *P*<0.001) and to have hypertension (83.5% versus 67.1%, *P*<0.001), diabetes (85.7% versus 19.4%, *P*<0.001), congestive cardiac failure (4.5% versus 2.3%, *P*=0.002), coronary artery disease (13.1% versus 9.8%, *P*=0.01), or an index event consistent with minor ischemic stroke (56.7% versus 45.9%, *P*<0.001). Key demographic and clinical characteristics of the study population are presented in Table 1.

Study End Points

During 90 days of follow-up, 267 out of 4878 patients had a subsequent ischemic stroke. The cumulative incidence of subsequent ischemic stroke was 9.7% (95% CI, 7.2%–12.2%) in patients with hyperglycemia and 5.2% (95% CI, 4.5%–5.8%) in normoglycemic patients (*P*<0.001 by the log-rank test) (Figure 1). The hazard of subsequent ischemic stroke was higher among patients with hyperglycemia than among normoglycemic patients (HR, 1.88 [95% CI, 1.39–2.53]; *P*<0.001) in an unadjusted proportional hazards regression model (Table 2). In a fully adjusted model (including age, biological sex, race, ethnicity, treatment assignment, index event classification, and vascular risk factors as covariates), a significant association remained between admission hyperglycemia and subsequent ischemic stroke (HR, 1.5 [95% CI, 1.05–2.14]; *P*=0.01). There was no significant association between hyperglycemia and major hemorrhage in a model adjusted for age, biological sex, race, ethnicity, treatment assignment, final adjudicated cause, and hypertension (HR, 0.47 [95% CI, 0.11–1.99]; *P*=0.31). There was a significant association between hyperglycemia and the composite of ischemic stroke, myocardial infarction, or vascular death (HR, 1.55 [95% CI, 1.10–2.20]; *P*=0.01).

Interaction Analyses

In patients with hyperglycemia, treatment with dual antiplatelet therapy was not associated with a reduced

Table 1. Demographics and Key Clinical Characteristics of Patients Included in This Study

	All, N=4878	Hyperglycemia, n=594	Normoglycemia, n=4284	*P* value
Demographics				
Age, y, mean±SD	64.6±13.1	62.6±11.5	64.8±13.3	<0.001
Women	2194 (45%)	248 (41.8%)	1946 (45.4%)	0.1
Black*	966 (19.8%)	123 (20.7%)	843 (19.7%)	0.59
Hispanic†	387 (7.9%)	73 (12.3%)	314 (7.3%)	<0.001
Comorbidities				
Hypertension‡	3371 (69.1%)	496 (83.5%)	2875 (67.1%)	<0.001
Diabetes§	1340 (27.5%)	509 (85.7%)	831 (19.4%)	<0.001
Congestive cardiac failure‖	126 (2.6%)	27 (4.5%)	99 (2.3%)	0.002
Atrial fibrillation¶	49 (1%)	4 (0.7%)	45 (1.1%)	0.52
Coronary artery disease#	497 (10.2%)	78 (13.1%)	419 (9.8%)	0.01
Valvular disease**	83 (1.7%)	8 (1.3%)	75 (1.8%)	0.59
Carotid disease††	208 (4.3%)	31 (5.2%)	177 (4.1%)	0.26
Active smoking‡‡	1003 (20.6%)	109 (18.4%)	894 (20.9%)	0.17
Index stroke§§	2304 (47.2%)	337 (56.7%)	1967 (45.9%)	<0.001
Assigned to clopidogrel	2430 (49.8%)	307 (51.7%)	2123 (49.6%)	0.35
Subsequent stroke	267 (5.5%)	54 (9.1%)	213 (5%)	<0.001

POINT indicates Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke.

*Other racial groups represented in this sample included 3555 (72.9%) White patients, 144 (3%) Asian patients, 23 (0.5%) American Indian/Alaskan Native patients, 15 (0.3%) Native Hawaiian patients, 9 (0.2%) patients of >1 race, 26 (0.5%) patients labeled as "other," and 140 (2.9%) patients who were "unknown/not reported." Within the POINT study, the 140 "unknown" patients were not included in the denominator, hence the discrepancy between the percentages reported between that study and the present one.

†There were 230 patients labeled as being of unknown ethnicity.

‡There were 21 patients labeled as unknown hypertension status.

§There were 9 patients missing data on diabetes.

‖There were 7 patients labeled as unknown congestive cardiac failure status.

¶There were 4 patients labeled as unknown atrial fibrillation status.

#There were 12 patients labeled as unknown coronary artery disease status.

**There were 12 patients labeled as unknown valvular disease status.

††There were 32 patients labeled as unknown carotid disease status.

‡‡There were 4 patients missing data on smoking status.

§§There were 3 patients who had missing data on index event (minor stroke vs transient ischemic attack).

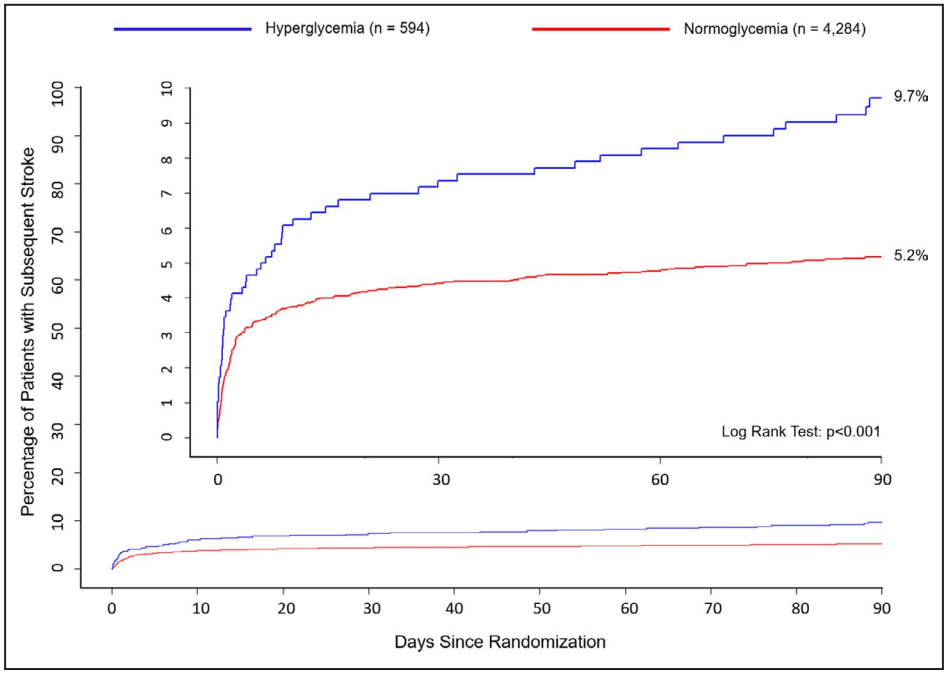

Figure 1. Kaplan-Meier curves depicting cumulative risk of subsequent ischemic stroke in patients with and without hyperglycemia.

hazard of subsequent ischemic stroke in an unadjusted Cox model (HR, 1.18 [95% CI, 0.69–2.03]). In patients with normoglycemia, treatment with dual antiplatelet therapy was associated with a lower hazard of subsequent ischemic stroke (HR, 0.63 [95% CI, 0.48–0.83]). The *P* value for interaction was 0.04. We observed similar results for the composite end point of stroke, myocardial infarction, and vascular death (Table 3). The low number of major hemorrhages observed in this sample did not permit an interaction analysis. There was no significant interaction between hyperglycemia and final adjudicated cause (minor stroke versus TIA) on these end points (Table S1).

Table 2. Association Between Hyperglycemia and Subsequent Ischemic Stroke

Model	HR* (95% CI)
1. Unadjusted	1.87 (1.39–2.53)
2. Model 1+age, biological sex, race, and ethnicity	1.93 (1.43–2.61)
3. Model 2+treatment assignment† and index event‡	1.77 (1.31–2.39)
4. Model 3+vascular risk factors§ (excluding diabetes)	1.71 (1.26–2.32)
5. Model 4+vascular risk factors (including diabetes)	1.5 (1.05–2.14)

HR indicates hazard ratio.
*HR is for the comparison of hyperglycemia vs normoglycemia.
†Treatment assignment includes aspirin/clopidogrel compared with aspirin/placebo (on intention-to-treat basis).
‡Index event denotes minor ischemic stroke compared with high-risk transient ischemic attack/other diagnosis.
§Vascular risk factors include hypertension, congestive cardiac failure, atrial fibrillation, coronary artery disease, valvular disease, carotid disease, and active smoking.

Sensitivity Analyses

Incorporating Serum Glucose as a Continuous Variable

There was evidence of a nonlinear relationship between serum glucose and subsequent stroke risk (*P*<0.001). Figure 2 assesses glucose as a restricted cubic spline rather than as a categorical variable. The restricted cubic spline for the risk of subsequent stroke was positively sloped with a gradual inflection in the 100 to 150 mg/dL range with a plateau at approximately 200 mg/dL.

Propensity Score–Matched Cohort

We compared the hazard of subsequent stroke between 554 (out of 594) patients with hyperglycemia and 554 propensity score–matched controls with normoglycemia. The association with subsequent stroke was not evident in this analysis (HR, 1.42 [95% CI, 0.92–2.12]). There was satisfactory matching of propensity scores across groups (Figure S1).

Alternative Definition of Index Event

Incorporating "acute infarction on an imaging study that was attributed to the index event" instead of final adjudicated cause, the association with subsequent stroke persisted (adjusted HR, 1.47 [95% CI, 1.03–2.11]; *P*=0.03).

Table 3. Association Between Treatment Assignment (Clopidgrel Versus Placebo) and Key Study End Points in Patients With and Without Hyperglycemia

Outcome	Aspirin/clopidogel, n=2430	Aspirin/placebo, n=2448	HR (95% CI)*	*P* value	*P* value for interaction
Ischemic stroke					
<180 mg/dL	82/2123	131/2161	0.63 (0.48–0.83)	<0.001	0.04
≥180 mg/dL	30/307	24/287	1.18 (0.84–02.03)	0.50	
Major hemorrhage					
<180 mg/dL	21/2123	10/2161	2.14 (1.01–4.54)	<0.05	…
≥180 mg/dL	2/307	0/287	…	…	
Primary end point†					
<180 mg/dL	89/2123	134/2161	0.67 (0.51–0.87)	0.003	0.06
≥180 mg/dL	32/207	26/287	1.17 (0.70–1.96)	0.55	

HRs are for the association between clopidogrel and the end point within the <180 mg/dL and ≥180 mg/dL strata. The interaction term is derived from a model including all patients in the study sample, which includes the term clopidogrel*hyperglycemia. HR indicates hazard ratio.

*Unadjusted HR.

†Subsequent ischemic stroke, myocardial infarction, ischemic vascular death.

Subgroup Analyses

In the 2327 patients whose index event was a TIA, there was a higher hazard of subsequent stroke in an unadjusted model (HR, 2.35 [95% CI, 1.28–4.31]) but a nonsignificant association in a fully adjusted model (HR, 1.67 [95% CI, 0.83–3.35]). In the 2304 patients whose index event was an acute minor ischemic stroke, there was a higher hazard of subsequent stroke in an unadjusted model (HR, 1.5 [95% CI, 1.05–2.15]) but not in a fully adjusted model (HR, 1.48 [95% CI, 0.95–2.29]).

DISCUSSION

We found that patients with hyperglycemia had a higher risk of subsequent ischemic stroke than patients with normoglycemia within the POINT clinical trial. The association between hyperglycemia and subsequent ischemic stroke persisted even after adjustment for demographics and clinical covariates that are known to predict subsequent stroke. The benefits of clopidogrel/aspirin were not apparent in the small subgroup of patients with hyperglycemia, with an interaction observed between clopidogrel and serum glucose on subsequent stroke.

There are several possible explanations for this association. First, hyperglycemia on presentation may be a marker of undiagnosed or poorly controlled diabetes, signifying a population known to be at high risk of subsequent stroke. Second, hyperglycemia may act as a surrogate for overall illness[19,20] and thus a marker of an inflammatory prothrombotic state. Third, it increases the likelihood of developing infection, itself a risk factor

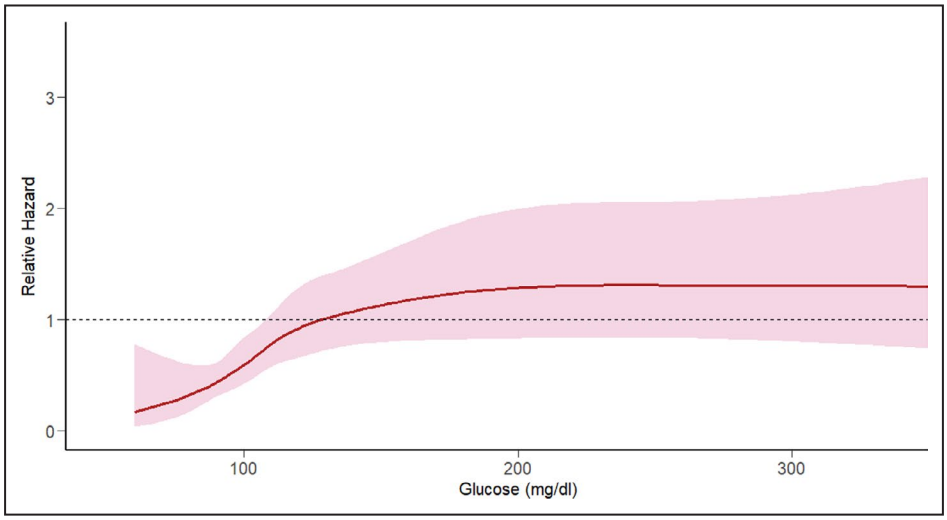

Figure 2. Relative hazard of subsequent ischemic stroke modeled on serum glucose as a restricted cubic spline and adjusted for all covariates used in the primary analysis.

for stroke[21]; thus, hyperglycemia may act as an intermediate step in the development of subsequent stroke. Fourth, there may be a causal relationship between hyperglycemia and stroke. There are several mechanisms described linking transient short-term hyperglycemia with thrombus formation.[22,23] In subjects with and without diabetes, there is a linear correlation between fasting serum glucose and coagulation factor VII.[22] In healthy individuals, elevated thrombin–antithrombin complex and tissue factor are observed after only 3 hours of induced hyperglycemia and further accentuated by an induced inflammatory response.[24] Transient hyperglycemia is typically followed by transient hyperinsulinemia in healthy subjects, and this combined elevation of serum glucose and insulin have been shown to have an additive effect on enhancing circulating tissue factor and other components of the coagulation system.[25] Acute hyperglycemia also has deleterious effects on the vascular endothelium, and increased extracellular glucose increases the propensity to platelet activation and endothelial dysfunction.[26–28] The mechanisms linking hyperglycemia to thrombus formation independent of platelet function may explain the apparent lack of effect of dual antiplatelet therapy in the subgroup of patients with hyperglycemia, although given the low number, this may also represent a type I error.

One previous study[11] examined glycemic control as a predictor of subsequent stroke in the CHANCE (Clopidogel in High-Risk Patients With Acute Nondisabling Events) trial.[29] Using the glucose/glycosylated albumin ratio they found that patients in the highest quartile had an HR of 1.46 (95% CI, 1.06–2.01) of subsequent stroke compared with patients in the lowest quartile. This study was performed in an exclusively Chinese population and relied on 2 separate assays (serum glucose and glycosylated albumin), calculation of a ratio, then classification into quartiles. The current study overcomes the limitations inherent in this prior study by (1) focusing on 1 simple, rapid measurement of serum glucose, and (2) testing our hypothesis in a population more diverse and representative with respect to race, ethnicity, and national origin.

Currently, direct serum glucose measurements are not incorporated in stroke risk classification schemes. However, the presence/absence of diabetes is included in scores used to predict subsequent stroke after TIA[9,10] and risk of stroke in atrial fibrillation.[30] Subsequent stroke risk may be estimated based on imaging characteristics or cause classification.[31] The ABCD2[9] and California[10] scores aim to predict the risk of stroke after an index TIA at 7 and 90 days, respectively, by combining data on vascular risk factors and characteristics of the presenting stroke. However, there is a heightened risk of stroke within a short period of time after the index event,[1] which suggests that more short-term, dynamic factors are likely at play. Serum glucose may be a useful measure for identifying patients at high-risk of early recurrence. By contrast, assay of glycosylated hemoglobin is reflective only of glycemic control over a period of approximately 2.5 months.[32] Additionally, measurement of serum glucose can be performed rapidly, is inexpensive, and does not require calculation. For this reason, its use is proposed in 2 scoring systems for predicting hemorrhage after intravenous tissue plasminogen activator (IV tissue-type plasminogen activator) use (the TAG[33] and SEDAN scores[34]).

The SHINE trial[14] randomized 1151 patients with hyperglycemia on presentation to either intensive therapy via continuous intravenous insulin infusion (target glucose 80–130 mg/dL) or standard therapy (target glucose 80–179 mg/dL) via an insulin sliding scale administered subcutaneously. There was no difference in the primary outcome (proportion of patients with a favorable score on the modified Rankin Scale at 90 days) between the 2 groups and more episodes of hypoglycemia in the intensive versus standard therapy groups (11.2% versus 3.2%). Subsequent ischemic stroke was not ascertained as a secondary outcome in this trial, but there were an equivalent number of ischemic strokes (16) reported across each arm as a serious adverse event. Although not specifically designed to test the hypothesis that control of serum glucose reduced the risk of subsequent stroke, the results suggest that elevated serum glucose may be a marker of overall sickness/illness severity and not a target for therapy itself.

There are limitations inherent in this study. First, because this is a secondary analysis of data already collected from a well-phenotyped clinical trial population with high-risk TIA or acute minor ischemic stroke, our results should be used for hypothesis generation only. Second, the subgroup of patients with hyperglycemia was small (12.2% of the study sample), which limits our power to observe true effects. In particular, our finding that dual antiplatelet therapy was not associated with a reduced risk of subsequent stroke should be interpreted with caution and should not be evoked as a reason to deviate from guideline-based care in this population (the most recent American Heart Association stroke secondary prevention guidelines advocate for the use of dual antiplatelet therapy for 21 to 90 days for patients with noncardioembolic minor ischemic stroke or high-risk TIA[35]). Third, the POINT excluded patients who received IV tissue-type plasminogen activator, underwent mechanical thrombectomy, had an indication for anticoagulation, or were planned for a revascularization procedure, and so our results may not apply to these groups of patients. Fourth, hypo- or hyperglycemia can cause acute, focal neurological deficits. Although abnormalities in serum

glucose were not listed as exclusion criteria for POINT, the trial protocol did require that the study investigator believed the primary reason for the presenting neurological deficit to be focal brain ischemia. Thus, it is possible that some patients with hypo- or hyperglycemia and concurrent stroke were erroneously excluded from the trial. Finally, glucose levels were not taken with reference to the time of a patient's last meal and thus are classified as random levels.

CONCLUSIONS

There was a higher rate of subsequent ischemic stroke and no clear benefit to dual antiplatelet therapy in patients with hyperglycemia on admission. This study may provide further support for developing innovative secondary prevention strategies in this high-risk patient population.

ARTICLE INFORMATION

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Affiliations

Department of Neurology (B.M.G., M.W., Y.X., W.F.); and Division of Cardiology, Department of Medicine (J.P.P.), Duke University School of Medicine, Durham, NC; Duke Clinical Research Institute, Durham, NC (J.P.P., Y.X.); Department of Neurology, Warren Alpert Medical School of Brown University, Providence, RI (S.Y.); Department of Neurology & Stroke and Hertie Institute for Clinical Brain Research, Eberhard Karls University Tübingen, Tübingen, Germany (S.P.); Department of Neurology, Yale University School of Medicine, New Haven, CT (A.D.H.); Department of Neurology, NYU Grossman School of Medicine, New York, NY (S.K.R.); and Dean's Office, Dell Medical School, The University of Texas at Austin, Austin, TX (S.C.J.).

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Supplemental Material

Data S1
Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4 & 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4 & 5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	20
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8&9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	9

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10 & 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13 & 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Data S1.

```
#R Script for Exploratory analysis of POINT, Mac Grory et al. 2021.

#CONTENTS:
#0. General points and power calculations
#1. Input, inspection and merging of data
#2. Variables of interest
#3. Cleaning up variables of interest
#4. Recharacterizing variables
#5. Descriptive statistics
#6. Inferential statistics
#7. Table 1 ***TABLE 1***
#8. Kaplan-Meier curves ***FIGURE 1***
#9. Cox proportional hazards modelling
#--A. Unadjusted modelling
#--B. Adjusted modelling ***TABLE 2***
#--C. Interaction analyses
#1. Subgroup Analyses
#--1. Minor stroke only - KM/UA/A
#--2. TIA only - KM/UA/A
#--2. DAPT only - KM/UA/A ***TABLE 3***
#--2. SAPT only - KM/UA/A
#11. Sensitivity Analyses
#--11.1. Glucose as continuous variable ***FIGURE 2***
#--11.2. Propensity score-matched analysis
#12. Final sensivity analysis - infarct on imaging instead of adjudicated etiology

#0. General points

#Running lines 1-495 creates analysis dataset

#Packages:
library(powerSurvEpi)
library(haven)
library(dplyr)
library(doBy)
library(reshape)
library(table1)
library(survival)
library(survminer)
library(survMisc)
library(ggpubr)
library(ggplot2)
library(MatchIt)
library(ipw)
library(rms)
library(splines)
library(pROC)
library(coxphw)
library(Hmisc)
```

```
library('mgcv')
library(visreg)

#We did not "attach" data at any point to maintain clarity given the multiple datasets that were created in the course of the analysis.

#The POINT dataset is comprised of the following individual data files, stored as separate .SAS files:
#Form00 - Eligibility Form
#Form01 - Demographics
#Form02 - ABCD2 Score
#Form03 - Modified Rankin Scale
#Form04 - NIH Stroke Scale
#Form05 - Medical History
#Form06 - Prior Medications
#Form07 - Index TIA/Stroke Symptoms
#Form08 - Vital Signs
#Form10 - Randomization Form
#Form11 - Head CT/MRI Scan
#Form12 - Electrocardiogram
#Form13 - Carotid Imaging Results
#Form14 - Questionnaire for Verifying Stroke Free Status
#Form15 - Morisky Quesionnaire
#Form16 - Study Drug Compliance
#Form17 - End of Study
#Form18 - Concomitant Medications
#Form19 - SAE/Clinical Outcome Reporting Form
#Form20 - Final Diagnosis
#Form22 - Anciliary Biomarker study
#Pointoutcomes - All endpoints from both intention to treat and per protocol analysis

#Power Calculations
powerCT.default0(0.10,
        267,
        1.5,
        alpha = 0.05)

powerCT.default0(0.10,
        267,
        2,
        alpha = 0.05)

powerCT.default0(0.10,
        267,
        2.5,
        alpha = 0.05)

powerCT.default0(0.15,
        267,
        1.5,
```

```
        alpha = 0.05)

powerCT.default0(0.15,
        267,
        2,
        alpha = 0.05)

powerCT.default0(0.15,
        267,
        2.5,
        alpha = 0.05)

powerCT.default0(0.25,
        267,
        1.5,
        alpha = 0.05)

powerCT.default0(0.25,
        267,
        2,
        alpha = 0.05)

powerCT.default0(0.25,
        267,
        2.5,
        alpha = 0.05)


#1. Input, inspection and merging of data
#We required variables stored in "Form00", "Form 01", "Form02", "Form05", "Form20", and "pointoutcomes" for this study.
#The datasets of interest were loaded in to R as follows:
#OFFICE
form00 <- read_sas("C:/Users/bcm39/Desktop/POINT Sub-study/POINT DATA/POINT Datasets/form00.sas7bdat", NULL)
form01 <- read_sas("C:/Users/bcm39/Desktop/POINT Sub-study/POINT DATA/POINT Datasets/form01.sas7bdat", NULL)
form02 <- read_sas("C:/Users/bcm39/Desktop/POINT Sub-study/POINT DATA/POINT Datasets/form02.sas7bdat", NULL)
form05 <- read_sas("C:/Users/bcm39/Desktop/POINT Sub-study/POINT DATA/POINT Datasets/form05.sas7bdat", NULL)
form20 <- read_sas("C:/Users/bcm39/Desktop/POINT Sub-study/POINT DATA/POINT Datasets/form20.sas7bdat", NULL)
pointoutcomes <- read_sas("C:/Users/bcm39/Desktop/POINT Sub-study/POINT DATA/POINT
Datasets/pointoutcomes.sas7bdat", NULL)

#HOME
#form00 <- read_sas("POINT/POINT Datasets/form00.sas7bdat", NULL)
#form01 <- read_sas("POINT/POINT Datasets/form01.sas7bdat", NULL)
#form02 <- read_sas("POINT/POINT Datasets/form02.sas7bdat", NULL)
#form05 <- read_sas("POINT/POINT Datasets/form05.sas7bdat", NULL)
#form20 <- read_sas("POINT/POINT Datasets/form20.sas7bdat", NULL)
#pointoutcomes <- read_sas("POINT/POINT Datasets/pointoutcomes.sas7bdat", NULL)
```

```
#We visually inspected the data files before analysis
#View(form00)
#View(form01)
#View(form02)
#View(form05)
#View(form20)
#View(pointoutcomes)

#Then examined their structure
str(form00)
str(form01)
str(form02)
str(form05)
str(form20)
str(pointoutcomes)

#File merging
#Files were merged using "subject_id" as the linkage variable
merge1 <- left_join(form00, form01, by = "subject_id", copy = FALSE)
merge2 <- left_join(merge1, form02, by = "subject_id", copy = FALSE)
merge3 <- left_join(merge2, form05, by = "subject_id", copy = FALSE)
merge4 <- left_join(merge3, form20, by = "subject_id", copy = FALSE)
data <- left_join(merge4, pointoutcomes, by = "subject_id", copy = FALSE)

#For this project, there were 4,881 observation units or less in each data file and thus we did not need to rearrange from skinny to fat dataframes

#We manually inspected the new analysis data set
#View(data)


#2. Variables of interest
data$age #Age (Form 00)
data$F00Q28 #Serum glucose (Form 00)
data$F00Q48 #Glucose units (Form 00)
data$GENDER #Gender (Form01)
data$RACE #Race (Form 01)
data$ABCD2 #ABCD2 Score (Form 02)
data$F05Q01 #Congestive Heart Failure (Form 05)
data$F05Q02 #Atrial Fibrillation (Form 05)
data$F05Q03 #Ischemic Heart Disease (Form 05)
data$F05Q04 #Valvular Heart Disease (Form 05)
data$F05Q05 #Carotid stenosis/Endarterectomy/Stent/Angioplasty (Form 05)
data$F05Q06 #Hypertension (Form 05)
data$F05Q07 #Diabetes Mellitus (Form 05)
data$Smoke #Smoking status (Form 05)
data$F20Q01 #Final diagnosis of TIA (1) vs. Minor Stroke (2) (Form 20)
data$tx #Treatment assignment (from ITT analysis) - A: Placebo, B=Clopidogrel
data$itt_outcome_type4#Subsequent ischemic stroke (pointoutcomes)
```

```
data$itt_outcome_type4_days #Days from randomization to event (pointoutcomes)
data$F20Q04 #Infarct on imaging attributable to index event


#3. Cleaning up variables of interest
#Age (Form 00)
#Manual inspection:
data$age
summary(data$age)
sum(is.na(data$age)==FALSE)
sum(is.na(data$age)==TRUE)
#Age was initially stored as a factor.
table(data$age)
#There were also 73 patients with >89 listed as their age.
#For the purposes of this analysis we assigned the age 90 to them.
data$age[data$age==">89"] <- 90
table(data$age)
#We did this prior to conversion to a numeric variable to avoid introducing NAs
data$age <- as.numeric(data$age)
table(data$age)
summary(data$age)
hist(data$age)
sum(is.na(data$age)==FALSE)
sum(is.na(data$age)==TRUE)

#Serum glucose (Form 00)
data$F00Q28
str(data$F00Q28)
#Glucose is already stored as a numeric variable
sum(is.na(data$F00Q28)==FALSE)
sum(is.na(data$F00Q28)==TRUE)
#3 Subjects have missing information for this variable
#We will remove them from the analysis dataset
data[is.na(data$F00Q28),]
nrow(data)
data <- data[!(is.na(data$F00Q28)),]
nrow(data) #3 subjects have been excluded from this analysis
summary(data$F00Q28)
hist(data$F00Q28)
#Around 500 people have implausibly low glucose readings from inspecting the histogram
table(data$F00Q48)
#595 people have glucose stored in a different unit, explaining these apparently low readings
#From the data dictionary, serum glucose was stored in two units - mg/dl and mmol/L
#Before proceeding further with the analysis, we had to harmonize units
#Convert 2(mmol/L) to 1 (mg/dL)
#Conversion factor = 18.0182
data$F00Q28[data$F00Q48 == 2] <- (data$F00Q28[data$F00Q48 == 2]*18.0182)
hist(data$F00Q28)
str(data$F00Q28)
```

```
sort(data$F00Q28, decreasing=FALSE)
data$glucose <- data$F00Q28
#There remains one person with an implausible low glucose reading of 7.8
#However, on the basis of the information contained in the dataset, I cannot definitively state this is not real
#If this was a mmol/L measurement, it would still be below the threshold of 180mg/dl
#So for the main analyses this subject will still be classed as "not hypoglycemic"
#We then created a dummy variable (entitled "hyperglycemia")
#We dichotomized patients in to >= 180 ("1") or <180 ("0")
data$hyperglycemia <- ifelse(data$glucose >=180, "1", "0")
str(data$hyperglycemia)
plot(data$hyperglycemia,data$glucose)
sum(is.na(data$hyperglycemia))

#Gender (Form01)
data$GENDER
str(data$GENDER)
sum(is.na(data$GENDER)==TRUE)
data$GENDER <- as.factor(data$GENDER)
str(data$GENDER)
table(data$GENDER)
data$female <- data$GENDER
table(data$female)

#Ethnicity (Form 01)
#0 - Hispanic/Latino; 1 - Not hispanic or latino; 3 - Unknown
#We altered this to a dichotomous variable where subjects are classed as 1 (Hispanic/Latino) or 2(Not hispanic/latino)
data$ETHNIC
sum(is.na(data$ETHNIC)==FALSE)
sum(is.na(data$ETHNIC)==TRUE)
table(data$ETHNIC)
data$ETHNIC[data$ETHNIC==3] <- "1"
data$ETHNIC[data$ETHNIC==1] <- "2"
data$ETHNIC[data$ETHNIC==0] <- "1"
data$ETHNIC[data$ETHNIC==2] <- "0"
table(data$ETHNIC)
str(data$ETHNIC)
data$hispanic <- data$ETHNIC
data$hispanic <- as.factor(data$hispanic)
table(data$hispanic)
str(data$hispanic)

#Race (Form 01)
#0 - American Indian/Alaskan Native, 1 - Asian, 2 - Black/African American, 3 - Native Hawaiian, 4 - White, 5 - More than one race, 98 - Other, 99 - Unknown/not reported
str(data$RACE)
table(data$RACE)
sum(is.na(data$ETHNIC)==FALSE)
sum(is.na(data$ETHNIC)==TRUE)
#We altered this to a dichotomous variable where subjects are classed as "Black" or "Non-Black"
```

```
data$RACE[data$RACE==1] <- "0"
data$RACE[data$RACE==3] <- "0"
data$RACE[data$RACE==4] <- "0"
data$RACE[data$RACE==5] <- "0"
data$RACE[data$RACE==98] <- "0"
data$RACE[data$RACE==99] <- "0"
data$RACE[data$RACE==2] <- "1"
data$black <- data$RACE
str(data$black)
data$black <- as.factor(data$black)
str(data$black)
table(data$black)

#ABCD2 Score (Form 02)
data$ABCD2
str(data$ABCD2)
table(data$ABCD2)
sum(is.na(data$ABCD2[data$F20Q01==2]))
#1594 missing
sum(is.na(data$ABCD2[data$F20Q01==98]))
#132 missing
sum(is.na(data$ABCD2[data$F20Q01==1]))
#422 missing
#Very high volume of missing data in this variable, even among patients whose final adjudicated etiology was TIA so we chose to exclude it.

#Congestive Heart Failure (Form 05)
data$F05Q01
sum(is.na(data$F05Q01)==FALSE)
sum(is.na(data$F05Q01)==TRUE)
table(data$F05Q01)
#7 patients had "Unknown" CHF status
str(data$F05Q01)
data$F05Q01[data$F05Q01==2] <- "0"
table(data$F05Q01)
str(data$F05Q01)
data$F05Q01 <- as.factor(data$F05Q01)
str(data$F05Q01)
data$chf <- data$F05Q01
str(data$chf)

#Atrial Fibrillation (Form 05)
data$F05Q02
sum(is.na(data$F05Q02)==FALSE)
sum(is.na(data$F05Q02)==TRUE)
table(data$F05Q02)
#14 patients had "Unknown" AF status
str(data$F05Q02)
data$F05Q02[data$F05Q02==2] <- "0"
```

```
table(data$F05Q02)
str(data$F05Q02)
data$F05Q02 <- as.factor(data$F05Q02)
str(data$F05Q02)
data$af <- data$F05Q02
str(data$af)

#Ischemic Heart Disease (Form 05)
data$F05Q03
sum(is.na(data$F05Q03)==FALSE)
sum(is.na(data$F05Q03)==TRUE)
table(data$F05Q03)
#12 patients had "Unknown" CHF status
str(data$F05Q03)
data$F05Q03[data$F05Q03==2] <- "0"
table(data$F05Q03)
str(data$F05Q03)
data$F05Q03 <- as.factor(data$F05Q03)
str(data$F05Q03)
data$cad <- data$F05Q03
str(data$cad)

#Valvular Heart Disease (Form 05)
data$F05Q04
sum(is.na(data$F05Q04)==FALSE)
sum(is.na(data$F05Q04)==TRUE)
table(data$F05Q04)
#12 patients had "Unknown" Valvular heart disease status
str(data$F05Q04)
data$F05Q04[data$F05Q04==2] <- "0"
table(data$F05Q04)
str(data$F05Q04)
data$F05Q04 <- as.factor(data$F05Q04)
str(data$F05Q04)
data$valvedisease <- data$F05Q04
str(data$valvedisease)

#Carotid stenosis/Endarterectomy/Stent/Angioplasty (Form 05)
data$F05Q05
sum(is.na(data$F05Q05)==FALSE)
sum(is.na(data$F05Q05)==TRUE)
table(data$F05Q05)
#32 patients had "Unknown" carotid stenosis/endarterectomy/stent/angioplasty
str(data$F05Q05)
data$F05Q05[data$F05Q05==2] <- "0"
table(data$F05Q05)
str(data$F05Q05)
data$F05Q05 <- as.factor(data$F05Q05)
str(data$F05Q05)
```

```
data$carotiddisease <- data$F05Q05
str(data$carotiddisease)

#Hypertension (Form 05)
data$F05Q06
sum(is.na(data$F05Q06)==FALSE)
sum(is.na(data$F05Q06)==TRUE)
table(data$F05Q06)
#21 patients were "Unknown" hypertension status
str(data$F05Q06)
data$F05Q06[data$F05Q06==2] <- "0"
table(data$F05Q06)
str(data$F05Q06)
data$F05Q06 <- as.factor(data$F05Q06)
str(data$F05Q06)
data$htn <- data$F05Q06
str(data$htn)

#Diabetes Mellitus (Form 05)
data$F05Q07
sum(is.na(data$F05Q07)==FALSE)
sum(is.na(data$F05Q07)==TRUE)
table(data$F05Q07)
#9 patients were "Unknown" diabetes mellitus status
str(data$F05Q07)
data$F05Q07[data$F05Q07==2] <- "0"
table(data$F05Q07)
str(data$F05Q07)
data$F05Q07 <- as.factor(data$F05Q07)
str(data$F05Q07)
data$diabetes <- data$F05Q07
str(data$diabetes)

#Smoking status (Form 05)
data$smoke
str(data$smoke)
sum(is.na(data$smoke)==FALSE)
sum(is.na(data$smoke)==TRUE)
#4 patients had missing data on smoking
table(data$smoke)
#We considered active smoking as smoking (1) and past/never smoking as not smoking (0)
data$smoke[data$smoke==1] <- "0"
data$smoke[data$smoke==2] <- "1"
table(data$smoke)
str(data$smoke)
#The 4 patients had missing data on smoking were classified as "not smoking"
data$smoke[is.na(data$smoke)] <- "0"
data$smoke <- as.factor(data$smoke)
sum(is.na(data$smoke)==TRUE)
```

```
str(data$smoke)
data$smoking <- data$smoke
str(data$smoking)

#Final diagnosis of TIA (1) vs. Minor Stroke (2) (Form 20)
data$F20Q01
sum(is.na(data$F20Q01)==FALSE)
sum(is.na(data$F20Q01)==TRUE)
#3 patients had missing data
table(data$F20Q01)
str(data$F20Q01)
data$F20Q01[data$F20Q01==1] <- "0"
data$F20Q01[data$F20Q01==98] <- "0"
data$F20Q01[data$F20Q01==2] <- "1"
sum(is.na(data$F20Q01)==TRUE)
data$F20Q01[is.na(data$F20Q01)] <- 0
data$F20Q01 <- as.factor(data$F20Q01)
data$minorstroke <- data$F20Q01
table(data$minorstroke)
str(data$minorstroke)

#Treatment assignment (from ITT analysis) - A: Placebo, B=Clopidogrel
table(data$tx)
str(data$tx)
sum(is.na(data$tx)==FALSE)
sum(is.na(data$tx)==TRUE)
#No missing data on treatment assignment
data$tx[data$tx=="B"] <- "1"
data$tx[data$tx=="A"] <- "0"
table(data$tx)
str(data$tx)
data$tx <- as.factor(data$tx)
table(data$tx)
str(data$tx)
data$dapt <- data$tx
str(data$dapt)

#Subsequent ischemic stroke (pointoutcomes)
data$itt_outcome_type4
sum(is.na(data$itt_outcome_type4)==FALSE)
sum(is.na(data$itt_outcome_type4)==TRUE)
#No missing data on subsequent ischemic stroke
table(data$itt_outcome_type4)
str(data$itt_outcome_type4)
data$itt_outcome_type4 <- as.factor(data$itt_outcome_type4)
table(data$itt_outcome_type4)
str(data$itt_outcome_type4)
data$stroke <- data$itt_outcome_type4
str(data$stroke)
```

```
#Days from randomization to event (pointoutcomes)
data$itt_outcome_type4_days
str(data$itt_outcome_type4_days)
sum(is.na(data$itt_outcome_type4_days)==FALSE)
sum(is.na(data$itt_outcome_type4_days)==TRUE)
#No missing data on time to subsequent ischemic stroke
table(data$itt_outcome_type4_days)
data$itt_outcome_type4_days <- as.numeric(data$itt_outcome_type4_days)
str(data$itt_outcome_type4_days)
data$days <- data$itt_outcome_type4_days
str(data$days)


#4. Recharacterizing variables

data$age #Age (Form 00) --> NUMERIC
data$glucose #Serum glucose (Form 00) --> NUMERIC
data$hyperglycemia #Hyperglycemia (dummy variable) --> CHARACTER
data$female #Female sex (Form 00) --> FACTOR
data$black #Race (Form 01) --> FACTOR
data$hispanic #ETHNIC (Form 01) --> FACTOR
data$chf #Congestive Heart Failure (Form 05) --> FACTOR
data$af #Atrial Fibrillation (Form 05) --> FACTOR
data$cad #Ischemic Heart Disease (Form 05) --> FACTOR
data$valvedisease #Valvular Heart Disease (Form 05) --> FACTOR
data$carotiddisease #Carotid stenosis/Endarterectomy/Stent/Angioplasty (Form 05) --> FACTOR
data$htn #Hypertension (Form 05) --> FACTOR
data$diabetes #Diabetes Mellitus (Form 05) --> FACTOR
data$smoking #Smoking status (Form 05) --> FACTOR
data$minorstroke #Final diagnosis of TIA (1) vs. Minor Stroke (2) (Form 20) --> FACTOR
data$dapt #Treatment assignment (from ITT analysis) - A: Placebo, B=Clopidogrel --> FACTOR
data$stroke #Subsequent ischemic stroke (pointoutcomes) --> FACTOR
data$days #Days from randomization to event (pointoutcomes) --> NUMERIC

#data$age <- as.numeric(data$age)
#data$GENDER <- as.factor(data$GENDER)
#data$F05Q01 <- as.numeric(data$F05Q02)
#data$F05Q02 <- as.numeric(data$F05Q02)
#data$F05Q03 <- as.numeric(data$F05Q03)
#data$F05Q06 <- as.numeric(data$F05Q06)
#data$smoke <- as.numeric(data$smoke)
#data$itt_outcome_type4_days <- as.numeric(data$itt_outcome_type4_days)
#data$itt_outcome_type4 <- as.numeric(data$itt_outcome_type4)


#5. Descriptive statistics
#Age
summary(data$age [data$hyperglycemia == 1],)
```

```
summary(data$age [data$hyperglycemia == 0],)
mean(data$age, na.rm=TRUE)
sd(data$age, na.rm=TRUE)
#Sex
table(data$female)
table(data$female [data$hyperglycemia == 1])
table(data$female [data$hyperglycemia == 0])
#Race
table(data$black)
table(data$black [data$hyperglycemia == 1])
table(data$black [data$hyperglycemia == 0])
#Ethnicity
table(data$hispanic)
table(data$hispanic [data$hyperglycemia == 1])
table(data$hispanic [data$hyperglycemia == 0])
#Hypertension
table(data$htn)
table(data$htn [data$hyperglycemia == 1])
table(data$htn [data$hyperglycemia == 0])
#Diabetes mellitus
table(data$diabetes)
table(data$diabetes [data$hyperglycemia == 1])
table(data$diabetes [data$hyperglycemia == 0])
#Atrial fibrillation
table(data$af)
table(data$af [data$hyperglycemia == 1])
table(data$af [data$hyperglycemia == 0])
#CAD
table(data$cad)
table(data$cad [data$hyperglycemia == 1])
table(data$cad [data$hyperglycemia == 0])
#CHF
table(data$chf)
table(data$chf [data$hyperglycemia == 1])
table(data$chf [data$hyperglycemia == 0])
#Tobacco use
table(data$smoking)
table(data$smoking [data$hyperglycemia == 1])
table(data$smoking [data$hyperglycemia == 0])
#Index stroke
table(data$minorstroke)
table(data$minorstroke [data$hyperglycemia == 1])
table(data$minorstroke [data$hyperglycemia == 0])
#Treatment assignment
table(data$dapt)
table(data$dapt [data$hyperglycemia == 1])
table(data$dapt [data$hyperglycemia == 0])
```

```
#6. Creating table 1
table.data <- data

# Nice website with some advanced features https://benjaminrich.github.io/table1/vignettes/table1-examples.html
table.data$female <- factor(table.data$female, labels = c("Male","Female"))
table.data$black <- factor(table.data$black, labels = c("Non-Black","Black"))
table.data$hispanic <- factor(table.data$hispanic, labels = c("Non-Hispanic","Hispanic"))
table.data$hyperglycemia <- factor(table.data$hyperglycemia, labels = c("Normoglycemic","Hyperglycemic"))
label(table.data$age) <- "Age"
label(table.data$female) <- "Sex"
label(table.data$black) <- "Race"
label(table.data$hispanic) <- "Ethnicity"
label(table.data$htn) <- "Hypertension"
label(table.data$diabetes) <- "Diabetes Mellitus"
label(table.data$chf) <- "Congestive Heart Failure"
label(table.data$af) <- "Atrial Fibrillation"
label(table.data$cad) <- "Coronary Artery Disease"
label(table.data$valvedisease) <- "Valve Disease"
label(table.data$carotiddisease) <- "Carotid Disease"
label(table.data$smoking) <- "Smoking (active)"
label(table.data$minorstroke) <- "Minor Stroke"
label(table.data$dapt) <- "Dual Anti-platelet Therapy"
label(table.data$stroke) <- "Subsequent Stroke"
label(table.data$hyperglycemia) <- "Hyperglycemia"

# Creating table 1, comparing characteristics between the two groups
table1(~ table.data$age + table.data$female + table.data$black + table.data$hispanic + table.data$htn +
table.data$diabetes +
        table.data$chf + table.data$af + table.data$cad + table.data$valvedisease +
        table.data$carotiddisease + table.data$smoking + table.data$minorstroke +
        table.data$dapt + table.data$stroke| table.data$hyperglycemia, data=table.data,
        topclass="Rtable1-grid Rtable1-shade Rtable1-times")


#7. Inferential statistics
#A. Comparing continuous variables with a t-test
hist(data$age[data$hyperglycemia==0])
hist(data$age[data$hyperglycemia==1])
t.test(data$age~data$hyperglycemia, data=data, var.equal=TRUE, conf.level=0.95)

#7B. Comparing categorical variables with a Chi Squared test
x <- table(data$female, data$hyperglycemia)
chisq.test(x)
x <- table(data$black, data$hyperglycemia)
chisq.test(x)
x <- table(data$hispanic, data$hyperglycemia)
chisq.test(x)
x <- table(data$htn, data$hyperglycemia)
chisq.test(x)
```

```
x <- table(data$diabetes, data$hyperglycemia)
chisq.test(x)
x <- table(data$chf, data$hyperglycemia)
chisq.test(x)
x <- table(data$af, data$hyperglycemia)
chisq.test(x)
x <- table(data$cad, data$hyperglycemia)
chisq.test(x)
x <- table(data$valvedisease, data$hyperglycemia)
chisq.test(x)
x <- table(data$carotiddisease, data$hyperglycemia)
chisq.test(x)
x <- table(data$smoking, data$hyperglycemia)
chisq.test(x)
x <- table(data$minorstroke, data$hyperglycemia)
chisq.test(x)
x <- table(data$dapt, data$hyperglycemia)
chisq.test(x)
x <- table(data$stroke, data$hyperglycemia)
chisq.test(x)


#8. Kaplan-Meier curves for Main Analysis
time <- data$days
event <- data$stroke
event <- as.numeric(event)
#Changing property of hyperglycemia variable as a way of troubleshooting
data$hyperglycemia <- as.numeric(data$hyperglycemia)
group <- data$hyperglycemia
summary(time)
summary(event)
summary(group)
kmsurvival <- survfit(Surv(time,event) ~ 1, conf.type="none")
summary (kmsurvival)
#Getting estimates with 95% CIs for each group at 90 days
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.943
#Upper CI
1-0.936
#Lower CI
1-0.95
#Getting estimates with 95% CIs for hyperglycemia group
hyperglycemicgroup <- data[data$hyperglycemia ==1,]
time <- hyperglycemicgroup$days
event <- hyperglycemicgroup$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1, conf.type="none")
```

```
summary (kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.903
#Upper CI
1-0.878
#Lower CI
1-0.928
#Getting estimates with 95% CIs for normoglycemia group
normoglycemicgroup <- data[data$hyperglycemia ==0,]
time <- normoglycemicgroup$days
event <- normoglycemicgroup$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.948
#Upper CI
1-0.942
#Lower CI
1-0.955
#kmsurvivalestimate <- survfit(Surv(time,event) ~ group)
#summary (kmsurvivalestimate, times=90)
#Curve for all patients in database
plot(kmsurvival)
#Curve stratified based on serum glucose (hyperglycemic or normoglycemic)
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
plot(kmsurvival, fun="event", conf.type = "log")
####Repeat of graph with 4 lines 444444444444##################
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
plot(kmsurvival, fun="event", conf.type = "log")
#Better way to incoporate graphics
#ggsurvplot(fit.km, data = ovarian2,
#          risk.table = TRUE,
#         surv.median.line = "hv")
#Comparing curves using the log Rank test
time <- data$days
event <- data$stroke
event <- as.numeric(event)
#Changing property of hyperglycemia variable as a way of troubleshooting
data$hyperglycemia <- as.numeric(data$hyperglycemia)
group <- data$hyperglycemia
survdiff(Surv(time,event) ~ group + data$diabetes, data=data)
```

```
#NB event has to be numeric and not a factor

#We then created an annotated and labelled figure with two components
#A. A large, labelled graph
plot(kmsurvival, fun="event", xlab="Days Since Randomization", ylab="Proportion of Patients With Subsequent Stroke",
lwd=1, ylim=c(0,1), col=c("red","blue"))
box (lwd=2)
axis(side=1, at = c(0,10,20,30,40,50,60,70,80,90))
axis(side=2, at = c(0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9,1))
legend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#B. A small insert with less conspicious labelling and a smaller y access to magnify the area of interest
plot(kmsurvival, fun="event", col=c("red","blue"))
legend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#We went on to do further manipulation of both graphs as follows:
#LARGE GRAPH
plot(kmsurvival, fun="event", col=c("red","red", "blue", "blue"), lwd=1, lty=c(1,5,1,5), ylim = c(0,1))
box(lwd=2)
axis(side=1, at = c(0,10,20,30,40,50,60,70,80,90))
axis(side=2, at = c(0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9,1))
legend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#INSERT
plot(kmsurvival, fun="event", col=c("red", "blue"), lwd=2, ylim = c(0,0.14), axes = TRUE)
box(lwd=2)
axis(side=1, at = c(0,30,60,90))
axis(side=2, at = c(0,0.01,0.02,0.03,0.04,0.05,0.06,0.07,0.08,0.09,0.1,0.11,0.12,0.13))
slegend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)


#9. Cox proportional hazards modeling
#A. Unadjusted Cox Model
time <- data$days
event <- data$stroke
group <- data$hyperglycemia
summary(time)
summary(event)
summary(group)
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ group, data=data, method="breslow")
summary(coxph)

#B. Adjusted Cox Model
#MODEl 1 - unadjusted
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia, method="breslow")
summary(coxph)

#MODEL 2 - Model 1 + Age, sex, race, ethnicity
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female, method="breslow")
```

```
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black + data$hispanic,
method="breslow")
summary(coxph)

#MODEL 3 - Model 2 + treatment assignment and index event
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black + data$hispanic +
data$dapt + data$minorstroke, method="breslow")
summary(coxph)

#MODEL 4 - Model 3 + vascular risk factors (excluding diabetes mellitus)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black + data$hispanic +
data$dapt + data$minorstroke + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking, method="breslow")
summary(coxph)

#MODEL 5 - Model 4 + vascular risk factors (including diabetes mellitus)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black + data$hispanic +
data$dapt + data$minorstroke + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking + data$diabetes, method="breslow")
summary(coxph)

#MODEL 5 with major hemorrhage as outcome
#Major hemorrhage is itt_outcome_type11 in point outcomes
#Time to major hemorrhage is itt_outcome_type11_days in point outcomes
time <- data$itt_outcome_type11_days
event <- data$itt_outcome_type11
group <- data$hyperglycemia
summary(time)
summary(event)
summary(group)
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black + data$hispanic +
data$dapt + data$minorstroke + data$htn, method="breslow")
summary(coxph)

#MODEL 5 with composite as outcome
#Composite is itt_outcome_type1 in point outcomes
#Time to composite is itt_outcome_type1_days in point outcomes
time <- data$itt_outcome_type1_days
event <- data$itt_outcome_type1
group <- data$hyperglycemia
summary(time)
summary(event)
summary(group)
event <- as.numeric(event)
```

```
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black + data$hispanic +
data$dapt + data$minorstroke + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking + data$diabetes, method="breslow")
summary(coxph)

#C. Interaction Analyses
hyperglycemicgroup <- data[data$hyperglycemia ==1,]
normoglycemicgroup <- data[data$hyperglycemia ==0,]
#1---> Hyperglycemia and DAPT
#OUTCOME 1 - subsequent stroke
table(hyperglycemicgroup$stroke, hyperglycemicgroup$dapt)
table(normoglycemicgroup$stroke, normoglycemicgroup$dapt)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$dapt, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$dapt, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$dapt + data$hyperglycemia*data$dapt, data=data,
method="breslow")
summary(coxph)

#Outcome 2 - major hemorrhage
#Major hemorrhage is itt_outcome_type11 in point outcomes
#Time to major hemorrhage is itt_outcome_type11_days in point outcomes
table(hyperglycemicgroup$itt_outcome_type11, hyperglycemicgroup$dapt)
table(normoglycemicgroup$itt_outcome_type11, normoglycemicgroup$dapt)
#In whole sample
time <- data$itt_outcome_type11_days
event <- data$itt_outcome_type11
group <- data$hyperglycemia
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$dapt, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$dapt, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$dapt + data$hyperglycemia*data$dapt, data=data,
method="breslow")
summary(coxph)
#In hyperglycemic group - Major hemorrhage/DAPT
time <- hyperglycemicgroup$itt_outcome_type11_days
event <- hyperglycemicgroup$itt_outcome_type11
group <- data$dapt
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ hyperglycemicgroup$dapt, data=hyperglycemicgroup, method="breslow")
summary(coxph)
#Won't work as 0 events in SAPT group
```

```
#In normoglycemic group - Major hemorrhage/DAPT
time <- normoglycemicgroup$itt_outcome_type11_days
event <- normoglycemicgroup$itt_outcome_type11
group <- data$dapt
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ normoglycemicgroup$dapt, data=normoglycemicgroup, method="breslow")
summary(coxph)

#Outcome 3 - subsequent ischemic stroke, myocardial infarction or vascular death
#Composite is itt_outcome_type1 in point outcomes
#Time to composite is itt_outcome_type1_days in point outcomes
table(hyperglycemicgroup$itt_outcome_type1, hyperglycemicgroup$dapt)
table(normoglycemicgroup$itt_outcome_type1, normoglycemicgroup$dapt)
#In whole sample
time <- data$itt_outcome_type1_days
event <- data$itt_outcome_type1
group <- data$hyperglycemia
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ group, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$dapt, data=data, method="breslow")
summary(coxph)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$dapt + data$hyperglycemia*data$dapt, data=data,
method="breslow")
summary(coxph)
#In hyperglycemic group
time <- hyperglycemicgroup$itt_outcome_type1_days
event <- hyperglycemicgroup$itt_outcome_type1
group <- hyperglycemicgroup$dapt
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ hyperglycemicgroup$dapt, data=hyperglycemicgroup, method="breslow")
summary(coxph)
#In normoglycemic group
time <- normoglycemicgroup$itt_outcome_type1_days
event <- normoglycemicgroup$itt_outcome_type1
group <- normoglycemicgroup$dapt
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ normoglycemicgroup$dapt, data=normoglycemicgroup, method="breslow")
summary(coxph)

#2---> Hyperglycemia and Stroke/TIA
hyperglycemicgroup <- data[data$hyperglycemia ==1,]
normoglycemicgroup <- data[data$hyperglycemia ==0,]
minorstroke <- data[data$minorstroke ==1,]
tiaother <- data[data$minorstroke ==0,]

#####################################################
```

```
#Hyperglycemia and Stroke/TIA interaction analysis
#OUTCOME 1 - subsequent stroke
table(minorstroke$stroke, minorstroke$hyperglycemia)
table(tiaother$stroke, tiaother$hyperglycemia)
#Whole sample
time <- data$days
event <- data$stroke
group <- data$hyperglycemia
summary(time)
summary(event)
summary(group)
event <- as.numeric(event)
#Unadjusted main analysis
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia, data=data, method="breslow")
summary(coxph)
#Model with hyperglycemia and stroke/tia
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$minorstroke, data=data, method="breslow")
summary(coxph)
#Otherwise unadjusted model with interaction term of hyperglycemia*minorstroke
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$minorstroke + data$hyperglycemia*data$minorstroke,
data=data, method="breslow")
summary(coxph)
#Adjusted model including interaction term of stroke/tia*hyperglycemia
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$minorstroke + data$hyperglycemia*data$minorstroke +
data$age + data$female + data$black + data$hispanic + data$dapt + data$htn + data$chf + data$af + data$cad +
data$valvedisease + data$carotiddisease + data$smoking + data$diabetes, method="breslow")
summary(coxph)
#Hyperglycemic group
time <- hyperglycemicgroup$days
event <- hyperglycemicgroup$stroke
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ hyperglycemicgroup$minorstroke + hyperglycemicgroup$age +
hyperglycemicgroup$female + hyperglycemicgroup$black + hyperglycemicgroup$hispanic + hyperglycemicgroup$dapt +
hyperglycemicgroup$htn + hyperglycemicgroup$chf + hyperglycemicgroup$af + hyperglycemicgroup$cad +
hyperglycemicgroup$valvedisease + hyperglycemicgroup$carotiddisease + hyperglycemicgroup$smoking +
hyperglycemicgroup$diabetes, method="breslow")
summary(coxph)
#Normoglycemic group
time <- normoglycemicgroup$days
event <- normoglycemicgroup$stroke
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ normoglycemicgroup$minorstroke + normoglycemicgroup$age +
normoglycemicgroup$female + normoglycemicgroup$black + normoglycemicgroup$hispanic +
normoglycemicgroup$dapt + normoglycemicgroup$htn + normoglycemicgroup$chf + normoglycemicgroup$af +
normoglycemicgroup$cad + normoglycemicgroup$valvedisease + normoglycemicgroup$carotiddisease +
normoglycemicgroup$smoking + normoglycemicgroup$diabetes, method="breslow")
summary(coxph)

#Hyperglycemia and Stroke/TIA interaction analysis
```

```
#OUTCOME 2 - major hemorrhage
#Major hemorrhage is itt_outcome_type11 in point outcomes
#Time to major hemorrhage is itt_outcome_type11_days in point outcomes
table(hyperglycemicgroup$itt_outcome_type11, hyperglycemicgroup$minorstroke)
table(normoglycemicgroup$itt_outcome_type11, normoglycemicgroup$minorstroke)
#In whole sample - Interation analysis not possible given 0 hemorrhages in hyperglycemia/minor stroke group
#In normoglycemic group - Major hemorrhage/minorstroke-TIA
time <- normoglycemicgroup$itt_outcome_type11_days
event <- normoglycemicgroup$itt_outcome_type11
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ normoglycemicgroup$minorstroke, method="breslow", data=normoglycemicgroup)
summary(coxph)
#Could only adjust for age, sex, race, ethnicity, treatment assignment and hypertension
coxph <- coxph(Surv(time,event) ~ normoglycemicgroup$minorstroke + normoglycemicgroup$age +
normoglycemicgroup$female + normoglycemicgroup$black + normoglycemicgroup$hispanic +
normoglycemicgroup$dapt + normoglycemicgroup$htn, method="breslow", data=normoglycemicgroup)
summary(coxph)

#Hyperglycemia and Stroke/TIA interaction analysis
#OUTCOME 3 - subsequent ischemic stroke, myocardial infarction or vascular death
#Composite is itt_outcome_type1 in point outcomes
#Time to composite is itt_outcome_type1_days in point outcomes
table(hyperglycemicgroup$itt_outcome_type1, hyperglycemicgroup$minorstroke)
table(normoglycemicgroup$itt_outcome_type1, normoglycemicgroup$minorstroke)
#In whole sample
time <- data$itt_outcome_type1_days
event <- data$itt_outcome_type1
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$minorstroke + data$hyperglycemia*data$minorstroke +
data$age + data$female + data$black + data$hispanic + data$dapt + data$htn + data$chf + data$af + data$cad +
data$valvedisease + data$carotiddisease + data$smoking + data$diabetes, method="breslow")
summary(coxph)
#In hyperglycemic group
time <- hyperglycemicgroup$itt_outcome_type1_days
event <- hyperglycemicgroup$itt_outcome_type1
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ hyperglycemicgroup$minorstroke + hyperglycemicgroup$age +
hyperglycemicgroup$female + hyperglycemicgroup$black + hyperglycemicgroup$hispanic + hyperglycemicgroup$dapt +
hyperglycemicgroup$htn + hyperglycemicgroup$chf + hyperglycemicgroup$af + hyperglycemicgroup$cad +
hyperglycemicgroup$valvedisease + hyperglycemicgroup$carotiddisease + hyperglycemicgroup$smoking +
hyperglycemicgroup$diabetes, method="breslow")
summary(coxph)
#In normoglycemic group
time <- normoglycemicgroup$itt_outcome_type1_days
event <- normoglycemicgroup$itt_outcome_type1
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ normoglycemicgroup$minorstroke + normoglycemicgroup$age +
normoglycemicgroup$female + normoglycemicgroup$black + normoglycemicgroup$hispanic +
normoglycemicgroup$dapt + normoglycemicgroup$htn + normoglycemicgroup$chf + normoglycemicgroup$af +
```

```
normoglycemicgroup$cad + normoglycemicgroup$valvedisease + normoglycemicgroup$carotiddisease +
normoglycemicgroup$smoking + normoglycemicgroup$diabetes, method="breslow")
summary(coxph)


#10. Subgroup analyses
#Variables used:
#---data$diabetes - Diabetes mellitus (1=Yes, 0=No)
#---data$F20Q01 - Adjudicated final etiology (2=minor stroke, 1=TIA)
#10-1 - TIA
#10-2 - minorstroke
#10-5 - Hypergylcemia only (for DAPT)
#10-6 - Normoglycemia only (for DAPT)

#SA 10-1 - Minor stroke only
#1. Create group
#2. Get number of events by creating table
#3. Do survival analysis
#4. Create two groups within (exposed/not exposed) to obtain KM estimates + 95% CI
#5. Plot K-M curves
#6. Add Log Rank test
#7. Make figure (NB include box(lwd=2))
#8. Cox model
#1. Create group
#Patients with minor stroke
minorstrokeonly <- data[data$minorstroke == 1,]
#2. Get number of events by creating table
table(minorstrokeonly$stroke, minorstrokeonly$hyperglycemia)
#3. Survival analysis
time <- minorstrokeonly$days
event <- minorstrokeonly$stroke
group <- minorstrokeonly$hyperglycemia
summary(time)
summary(event)
summary(group)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
kmsurvival <- survfit(Surv(time,event) ~ minorstrokeonly$hyperglycemia)
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
#4. Create two subgroups
#Subgroup 1 - Hyperglycemia in minorstrokeonly
minorstrokeonlyhyperglycemia <- minorstrokeonly[minorstrokeonly$hyperglycemia ==1,]
time <- minorstrokeonlyhyperglycemia$days
event <- minorstrokeonlyhyperglycemia$stroke
event <- as.numeric(event)
```

```
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.885
#Upper CI
1-0.85
#Lower CI
1-0.921
#Subgroup 2 - Normoglycemia in minorstrokeonly
minorstrokeonlynormoglycemia <- minorstrokeonly[minorstrokeonly$hyperglycemia ==0,]
time <- minorstrokeonlynormoglycemia$days
event <- minorstrokeonlynormoglycemia$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.923
#Upper CI
1-0.911
#Lower CI
1-0.935
#5. Create Kaplan-Meier curves
time <- minorstrokeonly$days
event <- minorstrokeonly$stroke
group <- minorstrokeonly$hyperglycemia
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
#6. Add Log Rank test
event <- as.numeric(event)
survdiff(Surv(time,event) ~ group, data=minorstrokeonly)
#7. Make figure (NB include box(lwd=2))
#LARGE GRAPH
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,1))
box(lwd=2)
axis(side=1, at = c(0,10,20,30,40,50,60,70,80,90), lwd=2)
axis(side=2, at = c(0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9,1), lwd=2)
#dlegend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#INSERT
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,0.15), axes = FALSE, lty=1)
box(lwd=2)
axis(side=1, at = c(0, 30, 60, 90), lwd=2)
axis(side=2, at = c(0,0.01,0.02,0.03,0.04,0.05,0.06,0.07,0.08,0.09,0.1,0.11,0.12,0.13,0.14,0.15), lwd=2)
```

```
#legend("bottomright", c("SAPT", "DAPT"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#8. Cox model
#A. Unadjusted Cox model
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ minorstrokeonly$hyperglycemia, method="breslow")
summary(coxph)
#B. Adjusted Cox model (NB minorstroke not included as a covariate but DM included)
coxph <- coxph(Surv(time,event) ~ minorstrokeonly$hyperglycemia + minorstrokeonly$age + minorstrokeonly$female +
minorstrokeonly$black + minorstrokeonly$hispanic + minorstrokeonly$dapt + minorstrokeonly$htn +
minorstrokeonly$chf + minorstrokeonly$af + minorstrokeonly$cad + minorstrokeonly$valvedisease +
minorstrokeonly$carotiddisease + minorstrokeonly$smoking + minorstrokeonly$diabetes, method="breslow")
summary(coxph)

######################
#CLEAR ENVIRONMENT AND RESTART DATASET USING ONLY 2,330 PATIENTS WITH TIA THEN EXCLUDE 3 WITH MISSING
GLUCOSE DATA
#SA 10-2 - TIA only
# [X]
#1. Create group
#2. Get number of events by creating table
#3. Do survival analysis
#4. Create two groups within (exposed/not exposed) to obtain KM estimates + 95% CI
#5. Plot K-M curves
#6. Add Log Rank test
#7. Make figure (NB include box(lwd=2))
#8. Cox model
#1. Create group
#Have to re set up dataset and use data$F20Q01[data$F20Q01==1] for the 2,327 patients with TIA
#Patients with TIA
tiaonly <- data[data$F20Q01 == 1,]
tiaonly[is.na(tiaonly$F00Q28),]
nrow(tiaonly)
tiaonly <- tiaonly[!(is.na(tiaonly$F00Q28)),]
nrow(tiaonly) #3 subjects have been excluded from this analysis
#2. Get number of events by creating table
table(tiaonly$stroke, tiaonly$hyperglycemia)
#3. Survival analysis
time <- tiaonly$days
event <- tiaonly$stroke
group <- tiaonly$hyperglycemia
summary(time)
summary(event)
summary(group)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
kmsurvival <- survfit(Surv(time,event) ~ tiaonly$hyperglycemia)
```

```
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
#4. Create two subgroups
#Subgroup 1 - Hyperglycemia in tiaonly
tiaonlyhyperglycemia <- tiaonly[tiaonly$hyperglycemia ==1,]
time <- tiaonlyhyperglycemia$days
event <- tiaonlyhyperglycemia$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.935
#Upper CI
1-0.902
#Lower CI
1-0.97
#Subgroup 2 - Normoglycemia in tiaonly
tiaonlynormoglycemia <- tiaonly[tiaonly$hyperglycemia ==0,]
time <- tiaonlynormoglycemia$days
event <- tiaonlynormoglycemia$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.974
#Upper CI
1-0.967
#Lower CI
1-0.981
#5. Create Kaplan-Meier curves
time <- tiaonly$days
event <- tiaonly$stroke
group <- tiaonly$hyperglycemia
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
#6. Add Log Rank test
event <- as.numeric(event)
survdiff(Surv(time,event) ~ group, data=tiaonly)
#7. Make figure (NB include box(lwd=2))
#LARGE GRAPH
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,1))
box(lwd=2)
```

```
axis(side=1, at = c(0,10,20,30,40,50,60,70,80,90), lwd=2)
axis(side=2, at = c(0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9,1), lwd=2)
#dlegend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#INSERT
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,0.15), axes = FALSE, lty=1)
box(lwd=2)
axis(side=1, at = c(0, 30, 60, 90), lwd=2)
axis(side=2, at = c(0,0.01,0.02,0.03,0.04,0.05,0.06,0.07,0.08,0.09,0.1,0.11,0.12,0.13,0.14,0.15), lwd=2)
#legend("bottomright", c("SAPT", "DAPT"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#8. Cox model
#A. Unadjusted Cox model
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ tiaonly$hyperglycemia, method="breslow")
summary(coxph)
#B. Adjusted Cox model (NB minorstroke not included as a covariate but DM included)
#WITH DIABETES
coxph <- coxph(Surv(time,event) ~ tiaonly$hyperglycemia + tiaonly$age + tiaonly$female + tiaonly$black +
tiaonly$hispanic + tiaonly$dapt + tiaonly$htn + tiaonly$chf + tiaonly$af + tiaonly$cad + tiaonly$valvedisease +
tiaonly$carotiddisease + tiaonly$smoking + tiaonly$diabetes, method="breslow")
summary(coxph)

############################################################
############################################################
### RE SET-UP DATASET FROM BEGINNING SKIPPING OVER PREVIOUS SECTION


#SA 10-3 - DAPT EFFECT in hyperglycemia
#1. Create group
#2. Get number of events by creating table
#3. Do survival analysis
#4. Create two groups within (exposed/not exposed) to obtain KM estimates + 95% CI
#5. Plot K-M curves
#6. Add Log Rank test
#7. Make figure (NB include box(lwd=2))
#8. Cox model

#For analysis of DAPT effects in those with/without hyperglycemia
#1. Create group
hyperglycemicgroup <- data[data$hyperglycemia ==1,]
#2. Get number of events by creating table (first term is on x axis, second term is on y axis)
table(hyperglycemicgroup$stroke, hyperglycemicgroup$dapt)
#3. Do survival analysis
time <- hyperglycemicgroup$days
event <- hyperglycemicgroup$stroke
group <- hyperglycemicgroup$dapt
summary(time)
summary(event)
```

```
summary(group)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
#4. Create two groups within (exposed/not exposed) to obtain KM estimates + 95% CI
#4A. DAPT + Hyperglycemia group
dapthyperglycemia <- hyperglycemicgroup[hyperglycemicgroup$dapt ==1,]
time <- dapthyperglycemia$days
event <- dapthyperglycemia$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.895
#Upper CI
1-0.861
#Lower CI
1-0.932
#4B. SAPT + Hyperglycemia group
sapthyperglycemia <- hyperglycemicgroup[hyperglycemicgroup$dapt ==0,]
time <- sapthyperglycemia$days
event <- sapthyperglycemia$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.911
#Upper CI
1-0.877
#Lower CI
1-0.946
#5. Plot Kaplan-Meier Curves:
time <- hyperglycemicgroup$days
event <- hyperglycemicgroup$stroke
group <- hyperglycemicgroup$dapt
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
plot(kmsurvival, fun="event")
```

```
#LARGE GRAPH
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,1))
box(lwd=2)
axis(side=1, at = c(0,10,20,30,40,50,60,70,80,90), lwd=2)
axis(side=2, at = c(0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9,1), lwd=2)
dlegend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#INSERT
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,0.15), axes = FALSE, lty=1)
box(lwd=2)
axis(side=1, at = c(0, 30, 60, 90), lwd=2)
axis(side=2, at = c(0,0.01,0.02,0.03,0.04,0.05,0.06,0.07,0.08,0.09,0.1,0.11,0.12,0.13,0.14,0.15), lwd=2)
legend("bottomright", c("SAPT", "DAPT"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#6. Log Rank Test to compare curve and add as annotation to figure - NB event has to be numeric and not a factor
event <- as.numeric(event)
survdiff(Surv(time,event) ~ group, data=hyperglycemicgroup)
#7. Optimize in powerpoint
#8. Proportional Hazards Regression Modelling
#A. Unadjusted Cox model
time <- hyperglycemicgroup$days
event <- hyperglycemicgroup$stroke
group <- hyperglycemicgroup$dapt
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ group, method="breslow")
summary(coxph)
#B. Adjusted Cox model
#Maybe don't do for DAPT vs. SAPT comparisons
coxph <- coxph(Surv(time,event) ~ hyperglycemicgroup$dapt + hyperglycemicgroup$age + hyperglycemicgroup$female
+ hyperglycemicgroup$black + hyperglycemicgroup$minorstroke + hyperglycemicgroup$hispanic +
hyperglycemicgroup$htn + hyperglycemicgroup$chf + hyperglycemicgroup$af + hyperglycemicgroup$cad +
hyperglycemicgroup$valvedisease + hyperglycemicgroup$carotiddisease + hyperglycemicgroup$smoking +
hyperglycemicgroup$diabetes, method="breslow")
summary(coxph)

#SA 10-4 - DAPT EFFECT in normoglycemia
#1. Create group
#2. Get number of events by creating table
#3. Do survival analysis
#4. Create two groups within (exposed/not exposed) to obtain KM estimates + 95% CI
#5. Plot K-M curves
#6. Add Log Rank test
#7. Make figure (NB include box(lwd=2))
#8. Cox model
#1. Create group:
normoglycemicgroup <- data[data$hyperglycemia == 0,]
#2. Get number of events by creating table (first term is on x axis, second term is on y axis)
table(normoglycemicgroup$stroke, normoglycemicgroup$dapt)
#3. Do survival analysis
```

```
time <- normoglycemicgroup$days
event <- normoglycemicgroup$stroke
group <- normoglycemicgroup$dapt
summary(time)
summary(event)
summary(group)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
plot(kmsurvival)
plot(kmsurvival, fun="event")
#4. Create two groups within (exposed/not exposed) to obtain KM estimates + 95% CI
#4A. DAPT + Normoglycemia group
daptnormoglycemia <- normoglycemicgroup[normoglycemicgroup$dapt ==1,]
time <- daptnormoglycemia$days
event <- daptnormoglycemia$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.96
#Upper CI
1-0.951
#Lower CI
1-0.968
#4B. SAPT + Normoglycemia group
saptnormoglycemia <- normoglycemicgroup[normoglycemicgroup$dapt ==0,]
time <- saptnormoglycemia$days
event <- saptnormoglycemia$stroke
event <- as.numeric(event)
kmsurvival <- survfit(Surv(time,event) ~ 1)
summary (kmsurvival)
plot(kmsurvival)
kmsurvivalestimate <- survfit(Surv(time,event) ~ 1)
summary (kmsurvivalestimate, times=90)
#Estimate
1-0.937
#Upper CI
1-0.927
#Lower CI
1-0.948
#5. Plot K-M curves
time <- normoglycemicgroup$days
```

```
event <- normoglycemicgroup$stroke
group <- normoglycemicgroup$dapt
kmsurvival <- survfit(Surv(time,event) ~ group)
summary (kmsurvival)
plot(kmsurvival, fun="event")
#6. Add Log Rank test
event <- as.numeric(event)
survdiff(Surv(time,event) ~ group, data=normoglycemicgroup)
#7. Make figure (NB include box(lwd=2))
#LARGE GRAPH
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,1))
box(lwd=2)
axis(side=1, at = c(0,10,20,30,40,50,60,70,80,90), lwd=2)
axis(side=2, at = c(0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9,1), lwd=2)
legend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#INSERT
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,0.15), axes = FALSE, lty=1)
box(lwd=2)
axis(side=1, at = c(0, 30, 60, 90), lwd=2)
axis(side=2, at = c(0,0.01,0.02,0.03,0.04,0.05,0.06,0.07,0.08,0.09,0.1,0.11,0.12,0.13,0.14,0.15), lwd=2)
legend("bottomright", c("SAPT", "DAPT"), col=c("red", "blue"), lty=1)
#---EXPORT TO POWERPOINT
#8. Cox model
#B. Unadjusted Cox model
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ group, method="breslow")
summary(coxph)
#Adjusted Cox model
#Will not do it for this one as it is for DAPT/SAPT
#coxph <- coxph(Surv(time,event) ~ normoglycemicgroup$dapt + normoglycemicgroup$age +
normoglycemicgroup$female + normoglycemicgroup$black + normoglycemicgroup$hispanic +
normoglycemicgroup$minorstroke + normoglycemicgroup$htn + normoglycemicgroup$chf + normoglycemicgroup$af +
normoglycemicgroup$cad + normoglycemicgroup$valvedisease + normoglycemicgroup$carotiddisease +
normoglycemicgroup$smoking + normoglycemicgroup$diabetes, method="breslow")
#summary(coxph)

#11. Sensitivity analyses
#11.1 Glucose as continuous variable
#Base model assuming linear relationship between glucose and the hazard of subsequent stroke
#UNADJUSTED
time <- data$days
event <- data$stroke
event <- as.numeric(event)
survival <- Surv(time,event)
coxph <- coxph(survival ~ data$glucose, method="breslow")
summary(coxph)
#ADJUSTED
```

```
coxph <- coxph(survival ~ data$glucose + data$age + data$female + data$black + data$hispanic + data$dapt +
data$minorstroke + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking + data$diabetes, method="breslow")
summary(coxph)
rsq(coxph)
#Checking proportional hazards assumption
fit.coxph_zph <- cox.zph(coxph)
fit.coxph_zph
plot(fit.coxph_zph,var="data$glucose")
# Transform glucose as restrcited cubic spline  (5 knots between 0-1)
rcs_glucose <- rcs(data$glucose, quantile(data$glucose, c(0, .05, .275, .5, .725, .95, 1)))
rcscoxph <- coxph(survival ~ rcs_glucose + data$age + data$female + data$black + data$hispanic + data$dapt +
data$minorstroke + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking + data$diabetes, method="breslow")
summary(rcscoxph)
# likelihood ratio test for linearity
anova(coxph,rcscoxph, test="Chisq" )
#Figure 2 - plot of hazard of ischemic stroke vs serum blood glucose
glucose <- data$glucose
age <- data$age
sex <- data$female
black <- data$black
hispanic <- data$hispanic
dapt <- data$dapt
minorstroke <- data$minorstroke
htn <- data$htn
chf <- data$chf
af <- data$af
cad <- data$cad
valvedisease <- data$valvedisease
carotiddisease <- data$carotiddisease
smoking <- data$smoking
diabetes <- data$diabetes
dd <- datadist(glucose, age, sex, black, hispanic, dapt, minorstroke, htn, chf, af, cad, valvedisease, carotiddisease,
smoking, diabetes)
options(datadist="dd")
amod <- cph(survival ~ rcs(glucose,5) + age + sex + black + hispanic + dapt + minorstroke + htn + chf + af + cad +
valvedisease + carotiddisease + smoking + diabetes, x=TRUE, y=TRUE)
summary(amod5)
y <- Predict(amod,fun=exp, glucose)
theme_set(theme_bw())
ggplot(y, colfill="violetred3")+
  labs(x="Glucose (mg/dl)", y="Relative Hazard")+
  xlim(c(50,350))+
  theme(axis.title = element_text(size = 15, color = "black"), axis.text = element_text(size = 15))+
  theme(axis.line = element_line(size = 1))+
  geom_line(color = "firebrick", size=1.3)+
  geom_hline(yintercept = c(1), size=0.5, linetype="dashed")+
  theme(panel.grid.major = element_blank(), panel.grid.minor = element_blank(),
```

```
      panel.background = element_blank(), axis.line = element_line(colour = "black"),
      panel.border = element_blank())+
  theme(axis.ticks.length=unit(0.25, "cm"))

#11.2. Propensity score matched analysis
data$hyperglycemia <- as.numeric(data$hyperglycemia)
psmodel <- glm(data$hyperglycemia ~ data$age + data$female + data$black + data$hispanic + data$dapt +
data$minorstroke + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking + data$diabetes, family=binomial, data=data)
summary(psmodel)
pscore <- psmodel$fitted.values
#Comparing characteristics before and after matching/PSM diagnostics
m.out <- matchit(data$hyperglycemia ~ data$age + data$female + data$black + data$hispanic + data$dapt +
data$minorstroke + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking + data$diabetes, family=binomial, data=data, caliper = 0.05, method = "nearest")
summary(m.out)
plot(m.out,type="hist")
plot(summary(m.out), xlim=c(0,2))

#Creating new object containing two matched groups
match1 <- match.data(m.out)

#Kaplan-Meier curves comparing propensity score-matched groups
time <- match1$days
event <- match1$stroke
group <- match1$hyperglycemia
summary(time)
summary(event)
summary(group)
kmsurvival <- survfit(Surv(time,event) ~ group)
summary(kmsurvival)
plot(kmsurvival)
#LARGE GRAPH
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,1))
axis(side=1, at = c(0,10,20,30,40,50,60,70,80,90))
axis(side=2, at = c(0,0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9,1))
legend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#INSERT
plot(kmsurvival, fun="event", col=c("red","blue"), ylim = c(0,0.15), axes = TRUE)
axis(side=1, at = c(0,10, 20, 30, 40, 50, 60, 70, 80, 90))
axis(side=2, at = c(0,0.01,0.02,0.03,0.04,0.05,0.06,0.07,0.08,0.09,0.1,0.11,0.12,0.13,0.14,0.15))
legend("bottomright", c("Normoglycemia (<180mg/dl)", "Hyperglycemia (>180mg/dl)"), col=c("red", "blue"), lty=1)
#Add in proportional hazards regression modelling
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ group, method="breslow")
summary(coxph)

#12.Final Sensitivity Analysis - Replacing final adjudicated etiology with infarct on imaging
#Infarct on imaging attributable to index event
```

```
data$F20Q04
str(data$F20Q04)
sum(is.na(data$F20Q04)==FALSE)
sum(is.na(data$F20Q04)==TRUE)
#5 subjects missing data on imaging attributable to index event
time <- data$days
event <- data$stroke
event <- as.numeric(event)
coxph <- coxph(Surv(time,event) ~ data$hyperglycemia + data$age + data$female + data$black + data$hispanic +
data$dapt + data$F20Q04 + data$htn + data$chf + data$af + data$cad + data$valvedisease + data$carotiddisease +
data$smoking + data$diabetes, method="breslow")
summary(coxph)
```

Table S1. Proportional hazards regression models performed separately in patients with and without hyperglycemia. The interaction term is derived from a model including all patients in the study sample including the term (hyperglycemia*final adjudicated etiology). Hazard ratios are for the association between minor stroke and the endpoint within the <180mg/dl and ≥180mg/dl strata.

Outcome	Minor stroke (n=2,304)	TIA/Other (n=2,574)	HR (95% CI)	P-value	P-value for interaction
Ischemic Stroke					
<180mg/dl	147/1,967	66/2,317	2.83 (2.11-3.80)[a]	<0.001	0.17
≥180mg/dl	37/337	17/257	1.84 (1.01-3.33)[a]	0.04	
Major Hemorrhage					
<180mg/dl	15/1,967	16/2,317	1.18 (0.58-2.39)[b]	0.65	-
≥180mg/dl	0/337	2/257	-	-	
Primary Endpoint[c]					
<180mg/dl	152/1,967	71/2,317	2.71 (2.04-3.60)[a]	<0.001	0.23
≥180mg/dl	40/337	18/257	1.90 (1.07-3.38)[a]	0.03	

a. Adjusted for age, sex, race, ethnicity, treatment assignment, hypertension, congestive cardiac failure, atrial fibrillation, coronary artery disease, valve disease, carotid disease, smoking and diabetes.
b. Adjusted for age, sex, race, ethnicity, treatment assignment and hypertension.
c. Subsequent ischemic stroke, myocardial infarction, ischemic vascular death.

Figure S1. Propensity-scores across hyperglycemic and normoglycemic subgroups before (LEFT PANELS) and after (RIGHT PANELS) the matching procedure.