Antihyperglycemic Agents Are Inversely Associated With Intracranial Aneurysm Rupture

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Background and Purpose—Previous studies have suggested a protective effect of diabetes mellitus on aneurysmal subarachnoid hemorrhage risk. However, reports are inconsistent, and objective measures of hyperglycemia in these studies are lacking. Our aim was to investigate the association between aneurysmal subarachnoid hemorrhage and antihyperglycemic agent use and glycated hemoglobin levels.

Methods—The medical records of 4701 patients with 6411 intracranial aneurysms, including 1201 prospective patients, diagnosed at the Massachusetts General Hospital and Brigham and Women's Hospital between 1990 and 2016 were reviewed and analyzed. Patients were separated into ruptured and nonruptured groups. Univariate and multivariate logistic regression analyses were performed to determine the association between aneurysmal subarachnoid hemorrhage and antihyperglycemic agents and glycated hemoglobin levels. Propensity score weighting was used to account for selection bias.

Results—In both unweighted and weighted multivariate analysis, antihyperglycemic agent use was inversely and significantly associated with ruptured aneurysms (unweighted odds ratio, 0.58; 95% confidence interval, 0.39–0.87; weighted odds ratio, 0.57; 95% confidence interval, 0.34–0.96). In contrast, glycated hemoglobin levels were not significantly associated with rupture status.

Conclusions—Antihyperglycemic agent use rather than hyperglycemia is associated with decreased risk of aneurysmal subarachnoid hemorrhage, suggesting a possible protective effect of glucose-lowering agents in the pathogenesis of aneurysm rupture. **(*Stroke*. 2018;49:34-39. DOI: 10.1161/STROKEAHA.117.019249.)**

Key Words: aneurysm ■ diabetes mellitus ■ humans ■ medical records ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) is a medical emergency associated with substantial mortality and morbidity, with an incidence between 8 and 11 per 100 000 per year.[1] Although advances in diagnosis and early surgical or endovascular intervention to occlude the aneurysm, as well as intensive care management and hemodynamic manipulations, have improved the number of survivors, mortality remains ≈50%, and half of the patients are <50 years of age.[2,3] Although the exact pathophysiology of intracranial aneurysm formation and rupture remains unknown, mainly because of the complex interaction between genetic and environmental factors, certain modifiable factors that may increase the risk of aSAH have been identified, including smoking and hypertension.[2] Interestingly, some studies and a recent review of the literature have suggested that diabetes mellitus could be a protective factor for rupture of intracranial aneurysms.[4–7] However, previous studies were inconsistent, were based on small sample sizes, did not always control for important confounders for aSAH, such as smoking and hypertension, and the biological basis for this inverse association remains unclear.[8–14] In addition, variability and lack of data on diagnostic tests used to diagnose diabetes mellitus (eg, fasting glucose levels and oral glucose tolerance tests) and lack of reliability of blood glucose level measurements as a measure of long-term glucose control in patients with ruptured intracranial aneurysms are important limitations. Because of its advantages over fasting blood glucose, such as low intraindividual variability and its reflection of long-term blood glucose control, glycated hemoglobin (HbA1c)—a parameter for average blood glucose levels for 12 weeks—has emerged as a reliable

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indicator of mean glucose control in patients with and without diabetes mellitus.[15–19] Therefore, to better understand the relationship between chronic hyperglycemia and risk of aSAH, we tested the hypothesis that regardless of the self-reported diagnosis of diabetes mellitus, higher HbA1c values increases the risk of rupture of intracranial aneurysms and that the use of antihyperglycemic agents is protective against rupture.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. With the use of machine learning algorithms and manual medical chart review, 4701 patients who were diagnosed with an intracranial aneurysm between 1990 and 2016 at the Brigham and Women's Hospital and Massachusetts General Hospital were included. This study was approved by our institutional review board and considered minimal risk. Patient consent was, therefore, waived by the board. Patients were identified both prospectively on clinical presentation (2007–2016) and retrospectively using natural language processing in conjunction with the Partners Healthcare Research Patients Data Registry, which includes 4.2 million patients who have received care from Brigham and Women's Hospital and Massachusetts General Hospital (1990–2013). With the use of *International Classification of Diseases, Ninth Revision* and Current Procedural Terminology (CPT) codes, an initial set of potential aneurysm patients from the Research Patients Data Registry was obtained, and natural language processing was then used to train a classification algorithm, which yielded 5589 patients.[20] Seven hundred twenty-seven of these patients were also seen on clinical presentation from 2007 to 2013 with prospectively collected data. In addition, 474 additional patients with prospectively collected data who were seen on clinical presentation from 2013 to 2016 were included, and the medical records and imaging studies of the 6063 patients were reviewed in detail (A.C. and R.D.) to ultimately identify 4701 patients with definite saccular aneurysms. The results of the imaging studies, including intracranial aneurysm site and size, were recorded, and patients with possible infundibula or nondefinitive diagnoses of aneurysms, feeding artery aneurysms associated with arteriovenous malformations, fusiform or dissecting aneurysms, and those lacking clinical notes or radiographic images were excluded. In addition, patients who received treatment of their aneurysm(s) before presentation were also excluded. Patients who presented with an aneurysmal SAH were categorized as harboring a ruptured aneurysm.

Information on patient characteristics, including age, sex and race, and comorbidities, including hypertension, myocardial infarction, and atrial fibrillation, were collected. The number and maximum size of intracranial aneurysms, family history of aneurysms or family history of SAH, and information on current tobacco and alcohol use was also collected. The diagnosis of aSAH was confirmed with a computed tomographic scan, cerebrospinal fluid analysis, or intraoperatively by a neurosurgeon. In addition, detailed data on the use of antihyperglycemic agents was collected. A risk factor was assumed to be absent if we found no documentation of its presence. HbA1c values were obtained within a year of diagnosis of ruptured and unruptured aneurysms. The HbA1c assays were performed with either high-performance liquid chromatography or turbidmetric inhibition immunoassay. We obtained clinical notes with antihyperglycemic agent details by using an expansive list of search terms as detailed in the online-only Data Supplement. These clinical notes were subsequently manually reviewed.

Differences in baseline characteristics between the ruptured and unruptured groups were evaluated using *t* tests for continuous variables and Pearson χ^2 test for categorical variables. Univariate and multivariate logistic regression models were implemented to test for effects because of antihyperglycemic agents and HbA1c values, with a backward elimination procedure to identify significant confounders. Cutoff *P* values of 0.1 were used to select the set of variables to be included in the initial multivariate model for backward elimination, with the exception of HbA1c values because this was one of the variables of interest. To control for differences in baseline characteristics between users and nonusers of antihyperglycemic agents, propensity score weighting with inverse probability weighting and the Huber–White sandwich estimator[21,22] for variance were applied. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated, and $P<0.05$ was considered significant. Missing values were accounted for by using multiple imputations with chained equations. Inferential statistics were obtained from 40 imputed datasets. Sensitivity analysis was performed using a subgroup consisting of complete cases only and a subgroup consisting of complete prospective patients only. All statistical analyses were performed using the Stata statistical software package (version 14; StataCorp, College Station, TX).

Results

Patient demographics and characteristics, including HbA1c values, stratified according to antihyperglycemic agent use and rupture status, are shown in Tables 1 and 2, respectively. A total of 4701 patients with 6411 aneurysms were included, of whom 1302 (27.7%) were ruptured. In general, patients on antihyperglycemic agents were significantly older, more frequently men, black or Hispanic, and less frequently white. In addition, patients on antihyperglycemic agents were significantly more frequently diagnosed with hypertension and myocardial infarction, whereas significantly less frequently current alcohol users. HbA1c values were significantly higher in patients on antihyperglycemic agents.

Table 3 shows the results of the unweighted and weighted multivariate analyses. In weighted multivariate analysis, black race (OR, 2.56; 95% confidence interval [CI], 1.73–3.77), Hispanic race (OR, 1.32; 95% CI, 1.42–3.79), Asian race (OR, 3.82; 95% CI, 1.37–10.65), other race (OR, 2.47; 95% CI, 1.34–4.58), current alcohol use (OR, 1.22; 95% CI, 1.05–1.40), and current tobacco use (OR, 2.12; 95% CI, 1.57–2.86) were significantly associated with aneurysmal SAH. In contrast, female sex (OR, 0.76; 95% CI, 0.58–0.92), age at diagnosis (OR, 0.99; 95% CI, 0.98–1.00), family history of aneurysms (OR, 0.51; 95% CI, 0.39–0.66), and antihyperglycemic agent use (OR, 0.57; 95% CI, 0.34–0.96) were significantly associated with a lower rupture risk. HbA1c values were not significantly associated with rupture. Table I in the online-only Data Supplement shows the unweighted and weighted analyses of complete cases only, with similar ORs for antihyperglycemic agent use (unweighted OR, 0.56; 95% CI, 0.39–0.81; weighted OR, 0.61; 95% CI, 0.41–0.90). In addition, a subgroup analysis using complete prospective cases only was performed. Although antihyperglycemic agent use is no longer statistically significant, the direction of effects is similar (Table I in the online-only Data Supplement).

Discussion

In the present study, we found that the use of antihyperglycemic agents was significantly inversely associated with ruptured intracranial aneurysms, even after controlling for important confounders, such as smoking and hypertension, and "treatment by indication" selection bias. In contrast, HbA1c values were not associated with the risk of aSAH. This is the largest case–control study to date to investigate the association between antihyperglycemic agents, hyperglycemia, and risk of aSAH. In addition, we are the first to use HbA1c values to investigate this association in this context, which is a more reliable and objective measure of hyperglycemia compared

Table 1. Patient Characteristics Stratified by Antihyperglycemic Agent Use

	All (n=4701)	Missing	Antihyperglycemic Agent Use (n=236)*	No Antihyperglycemic Agent Use (n=4465)	*P* Value
Women (%)	3666 (78.0)	0	168 (71.2)	3498 (78.3)	0.01
Race (%)					
White	3738 (79.5)	0	154 (65.3)	3584 (80.3)	<0.01
Black	291 (6.2)	0	29 (12.3)	262 (5.9)	<0.01
Hispanic	270 (5.7)	0	28 (11.9)	242 (5.4)	<0.01
Asian	107 (2.3)	0	4 (1.7)	103 (2.3)	0.55
Other	295 (6.3)	0	21 (8.9)	274 (6.1)	0.08
Age at diagnosis (SD), y	55.6 (13.7)	0	61.3 (12.1)	55.3 (13.7)	<0.01
Hypertension (%)	2152 (45.8)	0	174 (73.7)	1978 (44.3)	<0.01
Myocardial infarction (%)	193 (4.1)	0	25 (10.6)	168 (3.8)	<0.01
Atrial fibrillation (%)	142 (3.0)	0	7 (3.0)	135 (3.02)	0.96
Size of largest aneurysm (SD)	6.9 (4.8)	92	6.5 (4.6)	6.9 (4.8)	0.16
No. of aneurysms (SD)	1.4 (0.8)	0	1.3 (0.10)	1.4 (0.8)	0.68
Family history (%)					
Aneurysms	788 (16.8)	0	35 (14.8)	753 (16.9)	0.42
SAH	456 (9.7)	0	15 (6.4)	441 (9.9)	0.08
Current tobacco use (%)	1397 (30.4)	105	61 (26.1)	1336 (30.6)	0.14
Current alcohol use (%)	2033 (46.7)	347	62 (27.6)	1971 (47.7)	<0.01
HbA1c values within 1 y of diagnosis (SD)	6.11 (1.2)	4062	7.5 (1.9)	5.8 (0.8)	<0.01

DPP-4 indicates dipeptidyl-peptidase 4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; and SAH, subarachnoid hemorrhage.

*Insulin only (n=49), biguanides only (n=87), sulfonylureas only (n=38), thiazolidinediones only (n=7), biguanide combination therapy with insulin (n=11), sulfonylureas (n=27), or thiazolidinediones (n=5), or other combinations, including DPP-4 inhibitors, GLP-1 receptor agonists, and meglitinides (n=12).

with the use of fasting glucose levels, oral glucose tolerance tests, or the use of self-reported diagnosis of diabetes mellitus.

In a recent large Finnish case–control study, Lindgren et al compared the incidence of type 2 diabetes mellitus in 1058 ruptured versus 484 unruptured intracranial aneurysms and concluded that diabetes mellitus does not increase the risk of aSAH. However, the authors could not control this association for important confounders, such as smoking and alcohol intake, and based their conclusions on a national registry of prescribed medicine purchases.[4] According to a review of the literature in this same study, the pooled relative risk of diabetes mellitus on aSAH was 0.58 (95% CI, 0.48–0.70), suggesting that diabetes mellitus is protective of aSAH.[4] This inverse correlation was because of inclusion of 3 studies with significantly negative correlations between diabetes mellitus and aSAH risk. However, the diagnosis of diabetes mellitus was not standardized and based on self-reports,[5–7] the findings were not verified by multivariate analysis,[6] and the number of aSAH cases (ranging from 163–798 patients) was low, impairing statistical power.[5–7] Importantly, they were also unable to distinguish between the diagnosis of diabetes mellitus and antihyperglycemic medication use. Because of these inconsistencies and limitations, we think that the use of antihyperglycemic agents and HbA1c values are more reliable indicators and should be used as objective measures of diabetes mellitus and glucose control.

Hyperglycemia can lead to a variety of vascular complications, including micro- and macroangiopathy, vascular endothelial damage and dysfunction, and decrease in cerebral tight junction protein expression, of which the latter 2 have been implicated in intracranial aneurysm pathogenesis.[23–27] Nonenzymatic reactions between reducing sugars in diabetic blood vessels and amine residues on proteins, lipids, or nucleic acids form a complex group of compounds, called advanced glycation end products.[23] advanced glycation end-product receptors have been shown to induce MMP9 (matrix metalloproteinase 9) expression, which encodes zinc-dependent enzymes with proteolytic activity against connective tissue proteins (eg, collagens, elastin, and proteoglycans).[23,28,29] In addition, MMP9 has been shown to be involved in inflammation and plays an important role in tissue remodeling.[30] Increased levels of MMP9 were observed in the aneurysm wall of abdominal aortic and intracranial aneurysms.[29,31,32] Interestingly, doxycycline has recently been shown to inhibit expression of tissue MMP9 and consequently delay aneurysm rupture in a mouse model of Marfan syndrome.[33] In addition, TLR4 (toll-like receptor 4)—a proinflammatory factor, which upregulates MMP9 expression—was recently also found to be increased in rats with type 1 diabetes mellitus, providing a mechanistic link between hyperglycemic vascular changes and stimulation of proinflammatory mediators of intracranial aneurysm pathogenesis.[23] Finally, it has been shown that

treatment with antihyperglycemic agents, such as metformin,[34] insulin,[35] and glibenclamide,[36] results in MMP9 inhibition in mice, suggesting that antihyperglycemic agents use may affect the risk of aneurysm rupture directly rather than solely via reduction of blood glucose. Moreover, our data shows that modern antihyperglycemic agents were more frequently used by patients with unruptured aneurysms compared with patients with ruptured aneurysms (Table 2). Indeed, GLP-1 (glucagon-like peptide-1) and DPP-4 (dipeptidyl-peptidase 4) inhibitors have been shown to have several anti-inflammatory actions beyond the effects on glucose homeostasis.[37,38] These possible mechanistic links need to be further explored in future studies.

One of the major strengths of our study is the high-quality, standardized, single-institution database, the large sample size, the presence of a large control group with unruptured intracranial aneurysms, and the detailed collection of antihyperglycemic agent use and inclusion of HbA1c values as objective measures of hyperglycemia. The main limitations of our study include the partly retrospective design, the lack of information on the duration of antihyperglycemic medication use, and the lack of indicators of socioeconomic status, which may affect access to health care. In some cases of aSAH, history of tobacco and alcohol consumption was obtained from relatives of patients in poor clinical conditions, which could have led to information bias. Reporting bias in the setting of aSAH could have led to lower rates of antihyperglycemic medication use in the ruptured group. However, the nonsignificant difference in the reporting of antihypertensive medication use between the 2 groups makes this bias less likely. In addition, better access to medical care and subsequent earlier detection of unruptured aneurysms among antihyperglycemic agent users could have led to selection bias. However, propensity score weighting was used to mitigate this type of bias.

Summary

Despite earlier evidence that diabetes mellitus could have protective effects on aneurysm rupture, we are the first to report

Table 2. Patient Characteristics Stratified by Rupture Status

	All (n=4701)	Missing	Ruptured (n=1302)	Unruptured (n=3399)	*P* Value
Women (%)	3666 (78.0)	0	939 (72.1)	2727 (80.2)	<0.01
Race (%)					
White	3738 (79.5)	0	965 (74.1)	2773 (81.6)	<0.01
Black	291 (6.2)	0	117 (9.0)	174 (5.1)	<0.01
Hispanic	270 (5.7)	0	85 (6.5)	185 (5.4)	0.15
Asian	107 (2.3)	0	42 (3.2)	65 (1.9)	<0.01
Other	295 (6.3)	0	93 (7.1)	202 (5.9)	0.13
Age at diagnosis (SD), y	55.6 (13.7)	0	52.8 (13.8)	56.6 (13.4)	<0.01
Antihypertensive medication use (%)	2240 (47.6)	0	592 (45.5)	1648 (48.5)	0.06
Hypertension (%)	2152 (45.8)	0	621 (47.7)	1531 (45.0)	0.10
Myocardial infarction (%)	193 (4.1)	0	48 (3.7)	145 (4.3)	0.37
Atrial fibrillation (%)	142 (3.0)	0	40 (3.1)	102 (3.0)	0.90
Size of largest aneurysm (SD)	6.9 (4.8)	92	7.0 (4.2)	6.9 (5.0)	0.38
No. of aneurysms (SD)	1.4 (0.8)	0	1.4 (0.8)	1.4 (0.8)	0.61
Family history (%)					
Aneurysms	788 (16.8)	0	157 (12.1)	631 (18.6)	<0.01
SAH	456 (9.7)	0	88 (6.8)	368 (10.8)	<0.01
Current tobacco use (%)	1397 (30.4)	105	525 (41.7)	872 (26.1)	<0.01
Current alcohol use (%)	2033 (46.7)	347	619 (52.5)	1414 (44.5)	<0.01
HbA1c values within 1 y of diagnosis (SD)	6.11 (1.2)	4062	6.1 (1.1)	6.1 (1.3)	0.46
Antihyperglycemic agent use (all)	236 (5.0)	0	42 (3.2)	194 (5.7)	<0.01
Insulin only (%)	49 (1.0)	0	15 (1.2)	34 (1.0)	0.55
Biguanides only (%)	87 (1.9)	0	14 (1.1)	73 (2.1)	0.15
Sulfonylureas only (%)	38 (0.8)	0	5 (0.4)	33 (1.0)	0.04
Thiazolidinediones only (%)	7 (0.1)	0	2 (0.2)	5 (0.1)	0.39
Other (%)*	55 (1.2)	0	6 (0.5)	49 (1.4)	<0.01

DPP-4 indicates dipeptidyl-peptidase 4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; and SAH, subarachnoid hemorrhage.
*Including combination therapies and DPP-4 inhibitors, GLP-1 receptor agonists, and meglitinides.

Table 3. Unweighted and Weighted Multivariate Logistic Regression for Rupture Status in All Patients (n=4701)

	Unweighted Univariate		Unweighted Multivariate		Weighted Multivariate	
Characteristics	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Woman	0.64 (0.55–0.74)	<0.01	0.70 (0.60–0.81)	<0.01	0.76 (0.58–0.92)	<0.01
Race (vs white)						
Black	1.93 (1.51–2.47)	<0.01	2.09 (1.62–2.71)	<0.01	2.56 (1.73–3.77)	<0.01
Hispanic	1.32 (1.01–1.72)	0.04	1.45 (1.09–1.91)	0.01	1.32 (1.42–3.79)	<0.01
Asian	1.86 (1.25–2.76)	<0.01	2.05 (1.36–3.08)	<0.01	3.82 (1.37–10.65)	0.01
Other	1.32 (1.02–1.71)	0.03	1.49 (1.14–1.95)	<0.01	2.47 (1.34–4.58)	<0.01
Age at diagnosis, y	0.98 (0.97–0.98)	<0.01	0.99 (0.98–0.99)	<0.01	0.99 (0.98–1.00)	<0.01
Hypertension	1.11 (0.98–1.26)	0.10	…	…	…	…
Myocardial infarction	0.86 (0.62–1.20)	0.37	…	…	…	…
Atrial fibrillation	1.02 (0.71–1.49)	0.90	…	…	…	…
Size of largest aneurysm	1.01 (0.99–1.02)	0.41	…	…	…	…
No. of aneurysms	1.02 (0.94–1.11)	0.61	…	…	…	…
Family history						
Aneurysms	0.60 (0.50–0.73)	<0.01	0.54 (0.44–0.65)	<0.01	0.51 (0.39–0.66)	0.01
SAH	0.60 (0.47–0.76)	<0.01	…	…	…	…
Current tobacco use (vs not current)	2.01 (1.76–2.31)	<0.01	1.88 (1.63–2.17)	<0.01	2.12 (1.57–2.86)	<0.01
Current alcohol use (vs not current)	1.17 (1.10–1.26)	<0.01	1.13 (1.05–1.22)	<0.01	1.22 (1.05–1.40)	<0.01
Antihyperglycemic agents*	0.55 (0.39–0.77)	<0.01	0.58 (0.39–0.87)	<0.01	0.57 (0.34–0.96)	0.03
HbA1c levels within 1 y of diagnosis	0.94 (0.85–1.05)	0.29	0.97 (0.86–1.10)	0.67	1.05 (0.89–1.24)	0.54

Multiple imputation (40 imputations) with chained equations was used for missing data. CI indicates confidence interval; DPP-4, dipeptidyl-peptidase 4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; OR, odds ratio; and SAH, subarachnoid hemorrhage.

*Including DPP-4 inhibitors, GLP-1 receptor agonists, and meglitinides.

that increased HbA1c values are not associated with aneurysmal rupture, whereas the use of antihyperglycemic agents is associated with a lower risk of rupture. Our study suggests that it is the use of antihyperglycemic agents themselves rather than a diagnosis of diabetes mellitus that lowers the risk of aneurysmal rupture. Our results put previous studies in a different perspective, warrant further detailed evaluation of aSAH risk in patients with intracranial aneurysms and diabetes mellitus, and emphasize the use of objective measures of hyperglycemia (eg, HbA1c) and the use of antihyperglycemic agents instead of self-reported diagnosis of diabetes mellitus in future studies.

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Disclosures

None.

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Antihyperglycemic Agents Are Inversely Associated With Intracranial Aneurysm Rupture

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SUPPLEMENTAL MATERIAL

Search terms for antihyperglycemic agents

insulin, humulin, novolin, aspart, glulisine, apidra, lispro, humalog, isophane, novolin, degludec, tresiba, detemir, levemir, glargine, lantus, glargine, toujeo, novolog, humalog, humulin, novolin, ryzodeg, pramlintide, glucosidase, acarbose, miglitol, glyset, biguanide, metformin, glucophage, glumetza, riomet, fortamet, kazano, invokamet, xigduo, synjardy, glucovance, jentadueto, actoplus, prandimet, avandamet, kombiglyze, janumet, canagliflozin, dapagliflozin, glipizide, glyburide, linagliptin, pioglitazone, repaglinide, rosiglitazone, saxagliptin, sitagliptin, bromocriptine, parlodel, dpp-4, alogliptin, nesina, oseni, albiglutide, tanzeum, dulaglutide, trulicity, exenatide, byetta, bydureon, liraglutide, victoza, nateglinide, starlix, repaglinide, prandin, prandimet, SGLT, farxiga, xigduo, invokama, glyxambi, synjardy, sylfonylurease, amaryl, duetact, avandaryl, glucotrol, metaglip, diabeta, glynase, micronase, glucovance, diabinese, tolinase, orinase, gliclazide, glipizide, glyburide, chlorpropamide, tolazimide, tolbutamide, thiozolidinedione, rosiglitazone, avandia, glimepiride, avandaryl, actos, pioglitazone, oseni, duetact, actoplus, and pioglitazone.

Supplemental Table I: Univariate and multivariate logistic regression for rupture status in complete cases only (N= 4,335) and using complete prospective cases only (N= 841).

	Unweighted Multivariate		**Weighted Multivariate**		**Unweighted Multivariate****		**Weighted Multivariate****	
Characteristics	**OR (95% CI)**	**P-val.**	**OR (95% CI)**	**P-val.**	**OR (95% CI)**	**P-val.**	**OR (95% CI)**	**P-val.**
Female	0.71 (0.60-0.83)	<0.01	0.99 (0.71-1.38)	0.96	0.85 (0.60-1.21)	0.37	1.09 (0.60-2.01)	0.77
Black race (vs. white race)	2.13 (1.64-2.78)	<0.01	2.74 (1.49-5.03)	<0.01	2.05 (1.27-3.31)	<0.01	2.43 (1.02-5.76)	0.04
Hispanic race (vs. white race)	1.37 (1.02-1.84)	0.04	2.17 (1.23-3.82)	<0.01	0.76 (0.42-1.39)	0.38	0.43 (0.15-1.23)	0.12
Asian race (vs. white race)	2.11 (1.38-3.23)	<0.01	2.46 (0.89-6.81)	0.08	1.34 (0.53-3.40)	0.53	3.11 (0.66-14.7)	0.15
Other race (vs. white race)	1.53 (1.14-2.05)	<0.01	1.76 (0.91-3.40)	0.09	1.78 (0.84-3.74)	0.13	2.93 (0.78-11.0)	0.11
Age at diagnosis	0.99 (0.98-0.99)	<0.01	0.98 (0.97-0.99)	<0.01	1.00 (0.99-1.01)	0.69	0.99 (0.97-1.01)	0.31
Family history aneurysms	0.59 (0.48-0.72)	<0.01	0.55 (0.35-0.85)	<0.01	0.70 (0.51-0.96)	0.03	0.65 (0.38-1.10)	0.11
Current tobacco use (vs. not current)	1.95 (1.69-2.26)	<0.01	1.70 (1.24-2.33)	<0.01	1.59 (0.16-2.18)	<0.01	1.26 (0.71-2.24)	0.44
Current alcohol use (vs. not current)	1.16 (1.08-1.25)	<0.01	1.48 (1.26-1.73)	<0.01	1.00 (0.85-1.17)	0.99	0.99 (0.75-1.30)	0.94
Antihyperglycemic agents*	0.56 (0.39-0.81)	<0.01	0.61 (0.41-0.90)	0.01	0.71 (0.41-1.25)	0.24	0.73 (0.41-1.32)	0.30

* Including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, and meglitinides.

** Prospective cohort with complete cases only