Risk factor management matters more than pharmaceutical cyclooxygenase-2 inhibition in the prevention of de novo intracranial aneurysms

Sari Räisänen MD[a,b], Jukka Huttunen MD PhD[a], Terhi J. Huuskonen MD PhD[a], Mikael von und zu Fraunberg, MD PhD[a,c], Timo Koivisto MD PhD[a], Juha E. Jääskeläinen MD PhD[a], Antti Lindgren* MD PhD[a,b,f,g] , Juhana Frösen* MD PhD[b,d,e]
*=shared last authorship

[a] Neurosurgery of NeuroCenter, Kuopio University Hospital, and
Neurosurgery, Institute of Clinical Medicine, University of Eastern Finland,
Kuopio, Finland

[b] Hemorrhagic Brain pathology Research Group, NeuroCenter, Kuopio University Hospital

[c] University of Oulu and Oulu University Hospital, Neurosurgery at Neurocenter.

[d] Department of Neurosurgery, Tampere University Hospital

[e] Faculty of Medicine and Medical Technology, Tampere University, Tampere, Finland

[f] Department of Clinical Radiology, Kuopio University Hospital, Kuopio, Finland

[g] Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

Address of all authors
Neurosurgery of NeuroCenter,
Kuopio University Hospital,
P.O. Box 1777, 70211 Kuopio, Finland

Correspondence to:
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Sari Räisänen
Neurosurgery of NeuroCenter,
Kuopio University Hospital,
P.O. Box 1777, 70211 Kuopio, Finland,
sari.raisanen@kuh.fi
tel: +358 44 717 9430
fax: (+358) 17 172 628

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Abstract

Background

Pathophysiological studies of saccular intracranial aneurysm (sIA) disease have shown that inflammation plays a crucial role in a sIA development. Pharmaceutical inhibition of COX-2 –PGE2 – NFkB signaling has been shown in animal models to inhibit sIA formation and progression suggesting that use of medication inhibiting COX-2 could reduce IA formation also in patients.

Methods

We studied the impact of COX-2 inhibition on de novo sIA formation in two cohorts: in a previously described angiographically followed cohort of 1419 sIA patients and in a cohort of 117 sIA patients treated with stenting or stent assisted embolization. Patients were identified from our population-based Kuopio Intracranial Aneurysm Database. Data of the use of anti-inflammatory medications and hospital diagnoses were obtained from national registries. Risk factors were identified by univariate and multivariate analyses.

Results

De novo sIA patients were younger and more often smokers. Use of COX-2 selective inhibitors or NSAIDs did not significantly reduce de novo sIA formation, but the percentage of patients with de novo sIA formation was smaller in patients with prescribed regular ASA medication (1.1% vs 3.6%). In the multivariate analysis, however, neither ASA use nor other type of pharmaceutical inhibition of COX-2 reduced the formation of de novo sIAs. The risk was mostly affected by age, smoking history, and irregular usage of antihypertensive medication regardless of used COX-2 inhibition level.

Conclusion

For the prevention of de novo sIA formation, risk factor management with focus on cessation of smoking and treating hypertension adequately seems more important than pharmaceutical COX-2 inhibition.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a form of stroke caused by rupture of saccular intracranial aneurysm (sIA). Approximately 3% of people develop sIAs (1) and approximately 30 % of sIAs rupture during lifetime (2). Consequences of aSAH are dreadful with high mortality and morbidity (3) (4). To prevent aSAH, we need to prevent sIAs from rupture. Optimally this would be achieved by preventing the development of sIAs since the current treatment options of unruptured sIAs (UIAs) are invasive with risks for morbidity and mortality (5).

While risk factors for aSAH have been extensively studied, epidemiological studies looking at risk factors for sIA formation in humans are scarce. Study of risk factors for sIA formation in humans would require repeated angiographies to confirm the time of sIA formation. New, so-called "de novo" sIAs that form during follow-up to patients previously diagnosed with sIA disease offer a way to investigate sIA formation.

Studies of pathophysiology of sIA disease have shown that inflammation plays a crucial role in a sIA development. Several studies in animal models induced sIA formation have demonstrated crucial role of macrophages infiltrating the artery wall in the initiation of IA formation (6) (7) (8). Cyclooxygenase- 2 (COX-2) is an inducible enzyme that mediates and potentiates the macrophage recruitment and inflammatory vessel remodeling during IA formation and progression through prostaglandin E2 (PGE2) mediated activation of the transcription factor nuclear factor kappa b (NFkB) (7) (9). Pharmaceutical inhibition of COX-2 –PGE2 – NFkB signaling has been shown in animal models to inhibit sIA formation and progression (7) (9) suggesting that use of medication inhibiting COX-2 could reduce IA formation also in patients. Recently a few studies have also showed promising results of aspirin reducing growth of aneurysms also in humans (10) (11).

We investigated whether pharmaceutical inhibition of COX-2 reduces the risk of de novo aneurysm formation in a previously described cohort of 1419 sIA patients that were angiographically followed for at least 5 years or longer (12) and in a cohort of 117 patients treated with daily acetylsalicylic acid (ASA) after stenting or stent assisted embolization of sIA.

Materials and Methods

Kuopio Intracranial Aneurysm Patient and Family Database (http://kuopioneurosurgery.fi)

Kuopio Intracranial Aneurysm Database includes all intracranial aneurysm patients admitted to Kuopio University Hospital (KUH) from its catchment area in Eastern Finland during the study period (supplementary Table s1).

From every patient the existence of sIA has been confirmed by four-vessel DSA, magnetic resonance angiography (MRA) or computed tomography angiography (CTA). Patients suffering from aSAH were diagnosed by CT or spinal tap and all of them were acutely admitted to KUH. All the patients with UIA(s) have also had neurosurgical consultation in KUH for elective treatment of sIAs.

De novo sIA was defined as a new aneurysm identified during follow-up by vascular imaging (CTA, MRA or DSA). Most index sIAs in this series have been treated microsurgically. In these cases, all sIAs seen in the operative field were clipped if technically possible. In rare cases, tiny aneurysms were found in the operative field, not seen in the preoperative angiography. These were not considered de novo sIAs but were added to our database (12).

Study cohorts

The first study cohort consisted of 1419 sIA patients from KUH sIA Database fulfilling the following criteria (supplementary Figures s1 and s2) (12):

1. a citizen of Finland and resident of the KUH catchment area at the first diagnosis of sIA disease between January 1, 1975, and December 31, 2014
2. angiographically verified de novo aneurysm during the follow up, available for re-review OR
3. at least 5 years of de novo negative angiographic (CTA, MRA or DSA) follow up after the first sIA diagnosis.

A second study cohort was collected to study further and validate the finding, that use of ASA might reduce the incidence rate of de novo aneurysm formation. This second cohort consisted of 117

patients with sIA treated with stenting or stent assisted embolization and follow-up since our institution's first case in 29.7.1992 until 16.2.2017. 26 of these patients were included already in the cohort of 1419 sIA patients. In our institution, all patients treated with intracranial stents are prescribed with permanent ASA medication (100mg once per day).

Medication use in the first study cohort

The Social Insurance Institution of Finland maintains a nationwide registry of prescribed drug purchases encompassing all Finnish pharmacies. The registry includes all the medications that are available in Finland by prescription identified by their Anatomic Therapeutic Chemical (ATC) codes. Information of prescription drug purchases of the 1419 sIA patients in our first study cohort, including date of first purchase, date of last purchase and total number of purchases were obtained from the registry from January 1, 1995, to December 31, 2014, and combined to database (Data supplement).

Patient was regarded to use nonsteroidal anti-inflammatory medication if there was at least one purchase by prescription. ASA, ibuprofen, and naproxen are also available without prescription in Finland.

Because ASA is cheaper when bought without prescription in Finland, we could not accurately identify ASA users from the registry of prescribed drugs, so we looked for indications for ASA use. To do that we combined our Database with Register for Health Care (HILMO) which is a registry that includes all hospital diagnoses (ICD-10) covering all secondary and tertiary referral hospitals in Finland. This registry is managed by the Finnish Institution for Health and Welfare. By combining Register of Health Care and register of prescribed drugs with our Database, we gathered patients who were regarded to use ASA if the following criteria were fulfilled (supplementary Figure s2):

1) Diagnosis of
    a. ischemic cardiac event
    b. ischemic stroke
    c. transient ischemic attack
    d. occlusion / stenosis of precerebral / cerebral arteries or
    e. atherosclerosis of extremities

2) Diagnoses listed in 1) made before de novo sIA diagnosis
3) No use of other antiplatelet or anticoagulant medications only sold by prescription in Finland

Use of antihypertensive medications was analysed from the National registry of prescribed drugs. Antihypertensive medications are available in Finland only by prescription. Patient was considered as a regular user of antihypertensive medication if the following criteria were fulfilled:

1) At least 12 months of antihypertensive medication use
2) Patients purchased at least 80% of packages required for regular 12 months usage
3) Antihypertensive medication was started at least 6 months before the angiographic diagnosis of de novo sIA

If patient had antihypertensive medication, but did not full fill above criteria, he/she was considered to use antihypertensive medication irregularly.

Smoking history

Patient was considered to have positive smoking history if he or she had been categorised as active smoker even once by our research nurse based either on personal interview at that time, or markings on the medical records of any medical speciality. This was done to ensure that intermittent smokers are correctly classified as smokers in our analysis, and that those classified in our analysis as non-smokers, would not have any kind of known smoking history.

Statistical Analysis

The variables are present in Tables 1, 2 and 3. To compare the groups we used Chi-square test, Fisher exact test or independent samples t-test when appropriate. Cox regression analysis was used to analyse the risk of developing de novo aneurysm in patients who used ASA, selective COX-2 inhibitors or NSAIDs and non-users, respectively.

Ethical aspects

The study was approved by the Ethics Committee of the Kuopio University Hospital and Finnish Institute for Health and Welfare approved data fusion from the national registries.

Results

Effect of COX-2 inhibitor use on formation of de novo aneurysms

The percentage of de novo patients did not differ between patients who used selective COX-2 inhibitors and those who did not (3% vs. 3 %) (Table 1, Fig. 1) and the incidence rate of de novo sIAs was in fact higher in a group that used COX-2 inhibitors than in a group that did not, 0.58 % per patient-year (8 de novo patients during 1364 person-years with COX-2 inhibitor use) vs. 0.24 % per patient-year (34 de novo patients during 14429 person-years of follow up after initial sIA diagnosis).

De novo patients were younger at primary presentation of sIA disease than other sIA patients in a group of patients that used selective COX-2 inhibitors (p=0.000) as well as in a group that did not use selective COX-2 inhibitors (p = 0.000) (Table 1). De novo patients were also more often smokers, but smoking was significantly more common only among patients who did not use COX-2 inhibitors (p= 0.000) (Table 1).

In Cox regression -multivariate analysis, age at primary diagnosis of sIA (HR 0.95, 95% Cl 0.92-0.97), smoking history (HR 4.98, 95% Cl 2.49-9.95) and irregular use of antihypertensive medication (HR 3.86, 95% Cl 1.61-9.30) were significant risk factors for de novo sIA formation. Use of selective COX-2 inhibition did not have an effect on de novo sIA formation (HR 0.63, 95% Cl 0.29-1.39) (Table 2, Fig. 2).

Effect of NSAID use on formation of de novo aneurysm

Percentage of de novo patients (3% vs 2%) (Table 1, Fig. 1) as well as incidence ratio per patient-year 0.34% (34 de novo patients during 9934 patient-years with use of NSAIDs) vs. 0.19% (8 de novo patients during 4314 patient-years of follow-up after initial diagnosis of sIA disease) were slightly higher among the patients who used NSAIDs than those who did not.

De novo patients were younger at primary presentation of sIA disease among NSAID users (p=0.000) as well as non-users (p=0.000) (Table 1). De novo patients were also more often smokers among NSAID users (p=0.001) (Table 1).

In Cox regression -multivariate analysis, age at primary diagnosis of sIA (HR 0.95, 95% Cl 0.92-0.97), smoking history (HR 4.87, 95% Cl 2.44-9.69) and irregular use of antihypertensive medication (HR 3.88, 95% Cl 1.60-9.42) were significant risk factors for de novo sIA formation. Whereas use of NSAIDs seemed to have no effect on de novo sIA formation (HR 1.11, 95% Cl 0.50-2.45) (Table 2, Fig. 2).

Effect of ASA use on formation of de novo aneurysm

Percentage of de novo patients was clearly smaller in the group who had ASA prescribed or recommended because of concomitant diagnosis, when compared with patients who did not (1.1 % vs 3.6 %) (Table 1) as well as the incidence ratio 0.10% per patient-year (3 de novo patients during 2919 patient-years after diagnosis of concomitant disease or first purchase of ASA by prescription) vs 0.28% per patient-years (39 de novo patients during 13862 patient-years of follow-up after initial diagnosis), respectively.

In Cox regression -multivariate analysis, age at primary diagnosis of sIA (HR 0.95, 95 % Cl 0.92–0.98), smoking history (HR 4.77, 95 % Cl 2.40-9.47) and irregular use of antihypertensive medication (HR 3.69, 95 % Cl 1.53-8.93) were significant risk factors for de novo sIA formation, while use of ASA did not have significant effect (HR 0.49, 95 % Cl 0.15–1.66). However, use of ASA seemed to have a trend of reducing the risk for aneurysm formation even when comparing smokers and non-smokers. (Table 2, Fig. 2)

117 sIA patients treated with stenting or stent assisted embolization

A cohort of 117 sIA patients treated with stenting or stent assisted embolization (Table 3) included 4 de novo sIA patients, of whom only one patient (0.9%) was diagnosed with de novo sIA after stenting and starting of regular ASA use. These patients were followed all in all for 287 patient-years, and mean follow-up time was 2.5 years (range 0-12 years). The incidence rate of de novo patients in this cohort was 0.35 %. Multivariate analysis was not possible due to lack of statistical power.

Those patients who had de novo sIA diagnosis before stenting had median follow-up time of 2.3 years (range 0.45 -10.7 years) without new aneurysm formation.

Discussion

We investigated the effect of medical inhibition of COX-2 on de novo aneurysm formation in a previously described cohort of 1419 sIA patients, who were selected based on angiographic follow-up from 4414 sIA patients treated at our institute during the study period (12) and in a validation cohort of 117 sIA patients whose aneurysm had been treated with stenting.

We concluded that selective COX-2 inhibition does not significantly reduce the rate of aneurysm formation. Much more significant factors affecting de novo aneurysm formation are smoking, effective treatment of hypertension and patient characteristics that suggest propensity to form aneurysms such as aneurysm multiplicity and young age at first sIA diagnosis.

Because of their ability to inhibit inflammatory pathways, also non-selective COX inhibitors have been considered as a potential pharmacological treatment for sIA (13). We investigated the effect of these non-selective COX inhibitors on sIA formation. We discovered that use of other NSAIDs did not have any clear effect on sIA formation, but low dose ASA (100mg / day) seemed to somewhat reduce the rate of aneurysm formation. Since ASA is most often purchased in Finland as an over-the-counter drug, even when prescribed by a physician to a specific medical indication reimbursable by the national health insurance, we took in our initial study cohort the approach of looking at ASA indications. Since this approach is prone to multiple sources of bias, we also gathered a second study cohort to specifically investigate the effect of ASA on the formation of de novo sIAs. Since also in our validation cohort the rate of de novo aneurysm formation was significantly lower in patients taking ASA regularly after stent placement, we conclude that regular use of ASA might reduce the formation of intracranial aneurysms in patients. However, it is also worth to notice that cardioprotective low dose ASA (100mg / day) has mainly an antithrombotic effect and therefore might not have a significant effect on COX-2 signaling. On the other hand, the study of Hasan et al. (14) showed that also low dose ASA (81 mg/ day) might attenuate inflammatory process in the sIA walls.

Our findings suggest that use of ASA should be investigated in a specified clinical trial also as a prevention for aneurysm formation and not only as an inhibitor of aneurysm growth. Although previous studies have reported COX-2 inhibition to have a favorable effect on sIA growth and rupture (15) (16) it doesn't necessarily mean that this effect is directly applicable to sIA formation.

We are planning to investigate the impact of anti-inflammatory medication to sIA growth in a separate study.

In favor for ASA in comparison to other NSAIDs as a pharmaceutical treatment for sIA is also the fact that it has not been shown to raise blood pressure on patients using antihypertensive medications (17) nor being a risk factor for acute myocardial infarction like other NSAIDs (18). Patients identified already at a young age with high risk of sIA formation are the patient population that especially would benefit and need pharmaceutical therapy to prevent sIA formation, and thus we find our analysis of COX-2 inhibitor use in a patient population with a prior sIA diagnosis and sIA risk factors is highly relevant.

For the future, animal models have shown that there are other potential inflammation related signaling pathways that can be targeted, for example TNF-alpha-TNFR1 (19) thus offering another possible pharmaceutical treatment strategy for sIA to be studied.

Limitations of the study

Because of the low incidence of de novo aneurysms (1-4 %), our study cohort might be limited in statistical power despite of our large sample.

Although we can be certain that we have picked all users of selective COX-2 inhibitors, we cannot be sure how regularly patients have used these medications (20). Finns consume NSAIDs clearly more than other Scandinavians (21), and because some NSAIDs can be bought without prescription in Finland, it is likely that some of the patients who were considered as non-users were actually using NSAIDs without prescription. However, we had data on the number of purchased prescribed NSAID packages per patient. Therefore, we conclude that if use of NSAIDs other than ASA had any dose response, it would have shown in the analysis at least as a trend.

Another possible source of bias is use of COX-2 inhibitory drugs due to underlying diseases that might in turn predispose to aneurysm formation. This could lead to situation where the underlying disease that is the indication of COX-2 inhibitor use promotes IA formation thus nullifying the potential protective effect of COX- 2 inhibition.

In Finland ASA is cheaper when bought without prescription and consequently the usage of ASA is

not reliably represented in the National registry for prescribed drugs. To compensate for this limitation, we identified the diagnoses that should trigger ASA use if properly treated. However, also this method is subject to bias. Therefore, we also investigated a second cohort of patients whose aneurysm had been treated with stenting and used ASA since. However, it is also worth noting that the follow-up times for the cohort using coxib or NSAID medication and the multiple cohorts using ASA were not equal. Also, the median follow-up time in the validation cohort was shorter (2.3 yrs) than median de novo diagnosis time (11.7 yrs) in our study cohort (12).

Conclusions

For the prevention of de novo sIA formation, risk factor management with focus on cessation of smoking and treating hypertension adequately seem more important than pharmaceutical COX-2 inhibition. Continuous long-term COX-2 inhibition with drugs like ASA may, however, merit further clinical studies as drugs reducing sIA formation.

Author contributions

S.R. Study concept and design, acquisition of data, analysis and interpretation of data, literature search and writing
J.H. and T.H. Critical revision of the manuscript for intellectual content
T.K, M.F. and J.E.J. Acquisition of data, critical revision of the manuscript for intellectual content
J.F. and A.L. Acquisition of data, study concept and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content, study supervision.

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Disclosures

None.

Conflicts of interest

The author/s declare no conflict/s of interest.

Data availability

Deidentified data of the study can be accessed from the authors upon reasonable request.

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Figure Legends

Figure 1. Figure showing usage time of selective COX-2 inhibitors and NSAIDs, respectively and follow-up time after initial diagnosis of sIA disease among de novo patients and the control patients.

Figure 2. Cox hazard ratio curves showing the association of medical inhibition of COX-2 and formation of de novo sIA among smokers and non-smokers.

Figure S1. Flowchart of patients using selective COX-2 inhibitors and NSAID

Figure S2. Flowchart showing selection of patients considered to use aspirin according to hospital diagnoses and prescription purchases

Tables

Table 1. Characteristics of the first study cohort of 1419 sIA patients

	Use of selective COX-2 inhibition			
	Yes n=319		No n= 1100	
	De novo patient		De novo patient	
	Yes n = 8 (3 %)	No n = 311 (97 %)	Yes n = 34 (3 %)	No n = 1066 (97 %)
Median age at primary presentation	38 (14-49) **	51 (15-82)	41 (17-73) **	52 (5-83)
Median age at de novo diagnosis	43 (31-68)		53 (26-81)	
Median time to de novo diagnosis (years)	14.3 (3.1-26.3)		11.1 (0.74-30)	
Positive family history for IA	3 (38%)	71 (23%)	10 (29%)	169 (16%)
Positive smoking history	5 (63%)	99 (32%)	20 (59%) **	272 (26%)
Positive family and smoking history				
Yes	3 (38%)	30 (10%)	5 (15%)	62 (6%)
Neither	3 (38%)	170 (55%)	9 (27%)	687 (64%)
Presenting with multiple sIAs	4 (50%)	96 (31%)	13 (38%)	307 (29%)
Antihypertensive medication				
Regular	3 (38%)	204 (66%)	17 (50%)	617 (58%)
Irregular	0	40 (13%)	12 (35%)	73 (7%)
	Use of NSAIDs			
	Yes n= 1079		No n=340	

	De novo patient		De novo patient	
	Yes n = 34 (3 %)	No n = 1045 (97 %)	Yes n = 8 (2 %)	No n= 332 (98 %)
Median age at primary presentation	42 (14-59) **	50 (11–83)	28 (22-73) **	54 (5-80)
Median age at de novo diagnosis	55 (26-81)		44 (32-75)	
Median time to de novo diagnosis (years)	12.02 (0.74-29.6)		10.3 (1.6-28.1)	
Positive family history for IA	10 (29%)	194 (19 %)	3 (38%)	46 (14%)
Positive smoking history	21 (62%) **	326 (31 %)	4 (50%) *	45 (14%)
Positive family and smoking history				
Yes	7 (21%)	80 (8%)	1 (12.5%)	12 (4%)
Neither	10 (29%)	604 (58%)	2 (25%)	253 (76%)
Presenting with multiple sIAs	13 (38%)	307 (29 %)	4 (50%)	96 (29%)
Antihypertensive medication				
Regular	18 (53%)	701 (67%)	2 (25%)	120 (36%)
Irregular	6 (18%)	100 (10%)	6 (75%)	13 (4%)
	Use of ASA			
	Yes n = 325		No n=1094	
	De novo patient		De novo patient	
	Yes n = 3 (1 %)	No n = 322 (99 %)	Yes n = 39 (4 %)	No n=1055 (96 %)
Median age at	45 (44-49)	56 (23-80)	38 (14-73) **	50 (5-83)

primary presentation				
Median age at de novo diagnosis	68 (50-73)		51 (26-81)	
Median time to de novo diagnosis (years)	18.6 (5.4-29.6)		11.5 (0.74-29.0)	
Positive family history for IA	2 (67%) *	35 (11%)	11 (28%)	205 (19%)
Positive smoking history	2 (67%)	55 (17%)	23 (59%) *	316 (30%)
Positive family and smoking history				
Yes	2 (67%)	10 (3%)	6 (15%)	82 (8%)
Neither	1 (33%)	242 (75%)	11 (28%)	615 (58%)
Presenting with multiple sIAs	1 (33%)	93 (29%)	16 (41%)	310 (29%)
Antihypertensive medication				
Regular	2 (67%)	206 (64%)	18 (46%)	615 (58%)
Irregular	1 (33%)	11 (3 %)	11 (28%)	102 (10%)

Table 2. Multivariate analysis of risk factors for de novo sIA formation showing that the risk is mostly affected by age, smoking history and irregular usage of antihypertensive medication regardless of used COX2 - inhibition level

	Multivariate Analysis	
	HR (95%Cl)	**p-value**
Model 1		
Female sex	1.52 (0.79-2.90)	0.208
Age at primary presentation	0.95 (0.92-0.97)	0.000*
Positive family history for IA	1.37 (0.69-2.72)	0.368
Presenting with multiple sIAs	1.82 (0.96-3.42)	0.066
Positive smoking history	4.98 (2.49-9.95)	0.000*
Irregular antihypertensive medication	3.86 (1.61-9.30)	0.003*
Use of selective COX-2 inhibitors	0.63 (0.29-1.39)	0.249
Model 2		
Female sex	1.40 (0.74-2.68)	0.304
Age at primary presentation	0.95 (0.92-0.97)	0.000*
Positive family history for IA	1.34 (0.67-2.65)	0.406
Presenting with multiple sIAs	1.87 (0.99-3.54)	0.053
Positive smoking history	4.87 (2.44-9.69)	0.000*
Irregular antihypertensive medication	3.88 (1.60-9.42)	0.003*
Use of NSAIDs	1.11 (0.50-2.45)	0.805

Model 3		
Female sex	1.44 (0.76-2.72)	0.266
Age at primary presentation	0.95 (0.92-0.98)	0.000*
Positive family history for IA	1.13 (0.65-2.56)	0.468
Presenting with multiple sIAs	1.85 (0.98-3.49)	0.058
Positive smoking history	4.77 (2.40-9.47)	0.000*
Irregular antihypertensive medication	3.69 (1.53-8.93)	0.004*
Use of ASA	0.49 (0.15-1.66)	0.251

Table 3. Characteristics of 117 sIA patients treated with stenting or stent assisted embolization

	117 sIA patients treated with stenting or stent assisted embolization	
	De novo sIA patient after stenting	
	Yes n =1	No n=116
Median age at primary presentation	39	53 (22-75)
Median age at de novo diagnosis	50	
Time to de novo or end of follow-up (yrs, median and range)	11.54	3.04 (0-23.8)
Females	1 (100%)	76 (66%)
Positive family history for IA	1 (100%)	18 (16%)
Positive smoking history	1 (100%)	66 (57%)
Antihypertensive medication		
Regular	1 (100%)	72 (62%)
Irregular		10 (9%)