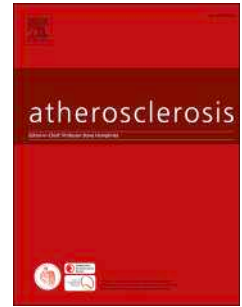


# Journal Pre-proof

Intracranial aneurysm is predicted by abdominal aortic calcification index: A retrospective case-control study

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PII: S0021-9150(21)01288-0

DOI: <https://doi.org/10.1016/j.atherosclerosis.2021.08.027>

Reference: ATH 16715

To appear in: *Atherosclerosis*

Received Date: 27 April 2021

Revised Date: 6 August 2021

Accepted Date: 12 August 2021

Please cite this article as: Rantasalo V, Gunn J, Kiviniemi T, Hirvonen J, Saarenpää I, Kivelev J, Rahi M, Lassila E, Rinne J, Laukka D, Intracranial aneurysm is predicted by abdominal aortic calcification index: A retrospective case-control study, *Atherosclerosis* (2021), doi: <https://doi.org/10.1016/j.atherosclerosis.2021.08.027>.

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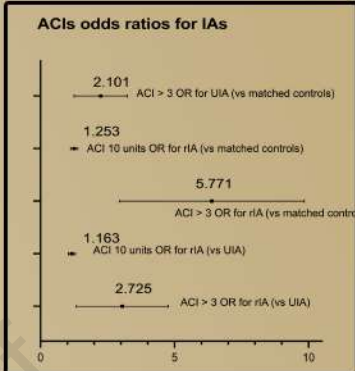
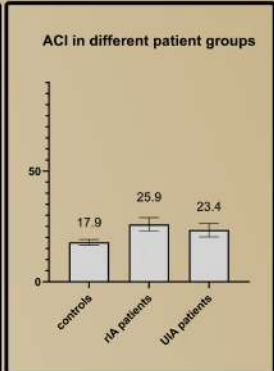
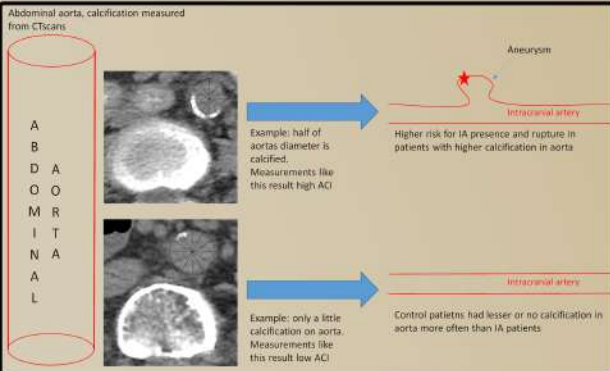
Journal Pre-proof

Intracranial aneurysm is predicted by abdominal aortic calcification index - a retrospective case-control study

Abdominal aortic calcification was measured from IA patients and matched controls  
Measurements were performed manually

IA patients were categorized as ruptured (rIA) or unruptured (UIA) patients  
Demographics were gathered manually from patient records

ACI was highest in rIA patients  
ACI increased risk for rIAs and UIAs  
rIA and UIA patients ACI was significantly higher than their respective matched controls



Journal Pre-proof

1 **Intracranial aneurysm is predicted by abdominal aortic calcification index: A**  
2 **retrospective case-control study**

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19 Key words: Intracranial aneurysm, calcification, atherosclerosis, subarachnoid hemorrhage

20

## 1 Abstract

2 **Background and aims:** Patients with intracranial aneurysms (IA) have excess mortality for  
3 cardiovascular diseases, but little is known on whether atherosclerotic manifestations and IA  
4 coexist. We investigated abdominal aortic calcification index's (ACI) association with  
5 unruptured and ruptured IAs.

6 **Methods:** This retrospective case-control study reviews all tertiary centers patients (n=24,660)  
7 who had undergone head computed tomography angiography (CTA), magnetic resonance  
8 angiography (MRA) or digital subtraction angiography (DSA) for any reason between January  
9 2003 and May 2018. Patients (n=2020) with unruptured or ruptured IAs were identified, and  
10 patients with available abdominal CT were included. IA patients were matched by sex and age  
11 to controls (available abdomen CT, no IAs) in ratio of 1:3. ACI was measured from abdomen  
12 CT scans and patient records were reviewed.

13 **Results:** 1720 patients (216 rIA, 246 UIA and 1258 control) were included. Mean age was  
14  $62.9 \pm 11.9$  years and 58.2% were female. ACI (OR 1.02 per increment, 95%CI 1.01–1.03) and  
15  $ACI > 3$  (OR 5.77, 95%CI 3.29–10.11) increased risk for rIA compared to matched controls. UIA  
16 patients' ACI was significantly higher but ACI did not increase odds for UIA compared to  
17 matched controls. History of coronary artery disease was less frequent in rIA patients. There  
18 was no calcification in aorta in 8.8% rIA and 13.6% UIA patients (matched controls 25.7% and  
19 22.6% respectively,  $p < 0.01$ )

20 **Conclusions:** Aortic calcification is greater in rIA and UIA patients than matched controls. ACI  
21 increases risk for rIAs.

22 Key words: Intracranial aneurysm, calcification, atherosclerosis, subarachnoid hemorrhage

23

## 24 1. Introduction

25 The prevalence of unruptured intracranial aneurysms (UIA) is around 3% in the general  
26 population[1] and only a small portion of UIAs rupture during lifetime, as the incidence of  
27 ruptured IAs (rIA), is around 10/100,000 per year. Smoking and hypertension are well-known  
28 modifiable risk factors for many cardiovascular diseases and also for UIAs and rIAs[2,3].  
29 Vessel wall inflammation is related to IA formation and IA rupture. Inflammation plays a critical  
30 role in peripheral and coronary artery atherosclerosis as well [4–8]. Intracranial aneurysm wall  
31 and atherosclerotic plaque have many common inflammation-mediating cytokines and  
32 leucocytes[6,9]. Hence, it is suggested a shared underlying pathophysiology between  
33 atherosclerosis and intracranial aneurysms[8,10].

1 Abdominal aortic calcification index (ACI) reflects general atherosclerotic burden and  
2 correlates with coronary artery calcium, which in turn predicts atherosclerotic cardiovascular  
3 diseases[11,12]. Atherosclerosis is considered to be a chronic systemic inflammatory disease  
4 with increased levels of circulating inflammatory cytokines. As a marker of atherosclerotic  
5 disease, ACI has been linked to coronary artery disease – and IAs could be linked to  
6 cerebrovascular atherosclerotic burden.[13–17]

7 Increasing amount of UIAs are found as incidental findings or as screening results. However,  
8 invasive treatment of intracranial aneurysms is not without risk, and IAs known risk factors are  
9 not yet sufficient for guiding preventive risk reduction. Therefore, there is a growing need to  
10 distinguish rupture-prone IAs more reliably from UIAs to select patients most likely to benefit  
11 from treatment.

12 In this study, we investigated if higher ACI index is related to UIAs and rIAs compared to  
13 controls without IAs. We hypothesized that higher ACI index could reflect more severe  
14 atherosclerotic burden and cardiovascular risk and could also be a risk factor for IAs.

## 15 **2. Materials and methods**

16 This is a retrospective study based on Turku University hospitals TuFIAS register data of  
17 patients with cerebrovascular imaging. Aneurysm and control patients are both selected from  
18 this register as shown in Figure 1A. Turku University Hospital is a tertiary center responsible  
19 for IAs in its geographical catchment areas population of 870,000 people. This study was  
20 approved by the Southwest Finland hospital district's ethical committee and institutional review  
21 board. Research number ID is T110/2018 and number for approval decision is T04/005/18.  
22 Patient consent was waived based on the retrospective registry design. TuFIAS register data  
23 consists of consecutive patients examined or treated in the department of neurosurgery  
24 between January 2003 and May 2018. Patients with IA were categorized as patients with  
25 incidental finding of an unruptured intracranial aneurysm (UIA) or as patients who had suffered  
26 a subarachnoidal hemorrhage due to a ruptured intracranial aneurysm (rIA). Control patients  
27 had no IA. Diagnostic imaging for IA was computed tomography (CT), computed tomography  
28 angiography (CTA), magnetic resonance angiography (MRA) or DSA (digital subtraction  
29 angiography).

### 30 **2.1 Aneurysm patients.**

31 Patient records and PACS (Picture archiving and communication system) were reviewed  
32 manually for radiological studies, comorbidities and cardiovascular risk factors. Patients  
33 with missing patient records or no adequate abdominal aorta imaging data were not  
34 included in this study. Patients with diagnosed connective tissue disorder (Marfan

1 syndrome, Ehlers-Danlos syndrome type IV and Loey-Dietz syndrome) were excluded.  
2 Included patient's records were reviewed for full medical history including relevant  
3 diagnoses and cardiovascular risk factors.

## 4 **2.2 Control patients.**

5 For control patients, similar demographic data (diagnosed diseases and common risk  
6 factors) was searched manually from patient records. They had undergone cranial and  
7 abdominal computed tomography imaging in emergency department showing abdominal  
8 aorta and had no evidence of an IA (Supplemental data 1). Each rIA and UIA patient was  
9 matched 1:3 to control patients based on age and gender. Age was noted as the patients'  
10 age at the time of abdominal aortic imaging. Study population demographics are described  
11 in Table 1.

## 12 **2.3 ACI-index.**

13 The abdominal aortic calcification index was measured from included cases and controls.  
14 Measurement of the ACI included the whole length of the abdominal aorta, from the level  
15 of the renal arteries to bifurcation. Computed tomography studies were viewed as  
16 multiplanar reformation (MPR) with slices 5 millimeters apart. Thus, every individual  
17 measurement included the number of slices 5 mm apart and the degree of calcification in  
18 each slice on a scale from 0 to 12. Index (ACI) was calculated using the following formula:

$$19 \quad ACI = \frac{\text{total sum of calcification in all slices}}{12*n} * 100$$

20 where  $n$  is the number of 5 mm slices in abdominal aorta. (Figure 1B.)

## 22 **2.4 Statistical analysis.**

23 Statistical analysis was carried out with IBM SPSS statistics 27 software for Windows (IBM,  
24 Armonk, NY). Between-group differences were evaluated with Chi-square test for  
25 proportions. Continuous variables are reported as mean and standard error, and between-  
26 group differences in variance were evaluated with independent samples t-test and one-  
27 way ANOVA test. Equality of variance was tested with Levene's test. Binary logistic  
28 regression analysis was performed with all demographic variables reported in Table 1 with  
29 backward selection (Wald).  $p$ -values  $<0.05$  were considered statistically significant.  
30 Classification and regression tree (CART) analysis was performed for the total population  
31 to identify cutoff values for variables independently associated with IAs. Validation was  
32 assessed by cross-validation through 10 folds. The minimum number of patients for a  
33 parent node was set at 100 and at 50 for child nodes and maximum tree depth was set at

5. Gini's method was used to measure impurity and minimum change in improvement was set at 0.0001. Receiver-operating characteristic (ROC) analyses were also performed. ROC curves area under curve (AUC) was used to measure the quality of test. ROC analysis curves are reported in Supplementary Materials. Multiple imputation was used for missing data. Interclass correlation (ICC) was used to assess the inter-rater reliability of imaging measurements. The subset of randomly selected subject's ACI measurements was repeated by a neuroradiologist. The following scale for ICC was used to determine the inter-rater reliability: poor ( $<0.5$ ), moderate ( $0.5-0.75$ ), good ( $0.75-0.9$ ) and excellent ( $\geq 0.9$ )[18].

The main variable of interest in this study was the abdominal aortic calcification index and its difference in distribution between rIA and UIA patients. Abdominal aortas calcification measurements produced ACI values on continuous scale and also on a categorical scale as study subjects were also categorized as patients with completely calcification-free aorta and patients with at least some calcification in the aorta (ACI = 0 meaning completely calcification free aorta, ACI > 0 meaning at least one plaque of calcification in abdominal aorta). Another derivative categorical variable used in the analysis was ACI over 3, meaning patients were categorized as patients with ACI > 3 and ACI < 3.

### 3. Results

From 2020 IA patients, 462 patients with abdominal CT were included. There were 216/462 (46.8%) rIA patients and 246/462 (53.2%) UIA patients. For the control group, a total of 1258 patients with abdominal imaging and sufficient patient records were selected from 22,640 patients without IAs. Baseline differences between groups are shown in Tables 1 and 2.

#### 3.1 rIA vs matched controls

Patients with rIA had higher mean ACI, 25.93 (SD 22.7 95% CI 18.6-21.8) than matched controls, 18.0 (SD 22.7, 95% CI 16.2-19.9,  $p < 0.001$ ). Fewer rIA patients had total calcification free aorta (8.8% vs. 25.7%,  $p < 0.001$ ) compared to matched controls. Hypertension was more common in the rIA group (73.2% vs. 62.7%). There was less hypercholesterolemia (27.8% vs. 37.7%) and alcohol abuse (15.5% vs 32.0%) in the rIA patient group. Markers of coronary artery disease, including previous percutaneous coronary interventions (PCI) and coronary artery bypass grafting surgery (CABG), were also less common among rIA patients than in matched control patients.

Results of multivariate logistic regression analyses are shown in Figure 2. Comparison of rIA patients and matched controls showed that hypercholesterolemia (OR 0.42, 95% CI 0.22-0.787), older age (OR 0.96 per year, 95% CI 0.93 – 0.99), prior PCI (OR 0.30 95% CI 0.10-

1 0.86) and alcohol abuse (OR 0.41, 95% CI 0.19 - 0.86) reduced the odds for rIA, and  
2 hypertension (OR 2.65, 95% CI 1.35-5.23), having calcification in the aorta (OR 3.35, 95% CI  
3 1.42-7.87) and ACI (OR 1.02, 95% CI 1.00 – 1.03 per increment) increased odds for rIA. ACI  
4 > 3 increased risk for rupture with OR 5.77, 95% CI 3.29 – 10.11.

### 5 3.2 UIAs vs. matched controls

6 Mean ACI for unruptured intracranial aneurysm (UIA) patients was 23.4 (SD 24.2, 95% CI  
7 20.3-26.4) and was significantly higher than for matched controls (mean ACI 17.8, 95% CI  
8 16.1-19.5). Compared to matched controls, UIA patients had more prior myocardial infarctions  
9 (15.6% vs. 10.3%), chronic-obstructive pulmonary disease (COPD) (20.3% vs. 12.9 and  
10 hypertension (75.8% vs. 63.1%). Matched controls had significantly more type I diabetes,  
11 history of alcohol abuse, asthma and dialysis treatment than UIA patients.

12 Comparison of UIA patients and matched controls showed that alcohol abuse (OR 0.56 95%  
13 CI 0.31-0.99) was a negative predictor of UIA, and total aortic calcification (OR 2.10 95% CI  
14 1.11-4.01), dialysis treatment (3.29 95% CI 1.46-7.45) and previous myocardial infarction (OR  
15 1.87 95% CI 1.01-3.48) showed increased odds for UIA. ACI was not associated with odds for  
16 UIA when compared to matched controls. ACI > 3 increased odds for UIA with OR 2.10, 95%  
17 CI 1.34 – 3.30.

### 18 3.3 rIA vs. UIA

19 There was no statistically significant difference in mean ACI between UIA and rIA patients  
20 although mean ACI was numerically higher for rIA patients (25.9 95% CI 22.9 – 29.0 vs. 23.4  
21 95% CI 20.3 – 26.4) Comparison of rIA patients and UIA patients showed that ACI (OR 1.02  
22 95% CI 1.00 -1.03 per increment) increased odds for rIA, and dialysis treatment (OR 0.26 95%  
23 CI 0.08 – 0.86), hypercholesterolemia (OR 0.47, 95% CI 0.28 – 0.78) and previous CABG (OR  
24 0.12, 95% CI 0.05 –0.77) reduced odds for rIA. ACI > 3 increased risk for rupture with OR 2.73  
25 95% CI 1.51 – 4.91. Patients with UIA and rIA patients were not matched to each others.

### 26 3.4 Decision-tree and ROC

27 CART-analysis on the entire study population revealed that ACI over 3.1 (range from 0 to  
28 134.0, mean 19.8) was associated with a two-fold risk of IA. Ruptured aneurysms were more  
29 prevalent in patients who had ACI over 3.1, diagnose of hypertension and age over 63. CART-  
30 analysis on only IA patients revealed that ACI over 3.3 was associated with rIAs. 49.6% of  
31 patients with ACI over 3.3 were rIA patients, whereas in patients with ACI under 3.3 only 34.6%  
32 had rIA. Decision tree is shown in figure 3.

1 ROC analysis of ACI in rIA, UIA and matched control patients as well as between rIA and UIA  
2 patients showed a biggest AUC (0.63 95% CI 0.59-0.67  $p < 0.0001$ ) in rIA patients compared  
3 to matched controls. Cut-off value of 3 in ACI showed sensitivity of 0.83 and 1-specificity was  
4 0.61. Comparison of rIA and UIA patients AUC was 0.62 (95% CI 0.58-0.67,  $p < 0.0001$ ) and a  
5 cut-off value of 3 yielded a sensitivity of 0.83 and 1-specificity was 0.62. UIA patients vs. their  
6 matched controls AUC was 0.58 (95% CI 0.54-0.62,  $p = 0.0002$ ). At the cut-off of 3, sensitivity  
7 was 0.73 and 1-specificity was 0.60.

### 8 3.5 Inter-rater reliability

9 ACI measurements inter-rater reliability was excellent when comparing ratings against board-  
10 certified neuroradiologist ratings (ICC value of 0.99, 95% CI 0.96 – 1.00).

## 11 **4. Discussion**

12 The main finding of this study was that higher abdominal aortic calcification was associated  
13 with a higher risk of intracranial aneurysms overall. Mean ACI was significantly higher in rIA  
14 (ruptured intracranial aneurysm) patients than matched controls and the risk for rIA increased  
15 with higher ACI when compared to matched controls. On the other hand, ACI did not increase  
16 odds for incidental intracranial aneurysms (UIA) when compared to matched controls even  
17 though mean ACI was significantly higher in UIA patients. CART-analysis confirmed that ACI  
18 is independently associated with IAs and especially with rIAs. Highest risk for IA was overall in  
19 patients with an ACI over 3.1 and who had hypertension and were older than 63 years. ACI  
20 over 3 was associated with increased risk of rIA and UIA when compared to matched controls,  
21 as well as with risk for rIA when rIA patients were compared to unmatched UIA patients.

22 Aortic calcification index is plausible, easily measurable and a relatively unbiased marker for  
23 systemic atherosclerosis: calcified plaques represent an arterial wall that is affected by  
24 atherosclerosis.[19] ACI reveals atherosclerosis regardless of recorded risk factors and it has  
25 been previously linked to increased carotid intima-media thickness, incidence and severity of  
26 coronary artery disease and cardiovascular events in patients with coronary artery  
27 disease[14,20–22]. Our results suggest that ACI indicates an increased risk for IAs, both rIAs  
28 and UIAs.

29 Pathophysiology of arterial calcification is multifactorial, including genetic and environmental  
30 risk factors[23], which could be also related to IA pathophysiology. Earlier studies suggest that  
31 inflammation has an important role in the pathophysiology of IA formation and rupture[9]. Also  
32 in atherosclerosis, the role of inflammation is well established[24]. Hence there could be  
33 several mechanisms explaining ACI association with intracranial aneurysms. Similarities in the  
34 inflammatory profile could be one of them, even though morphological devastation is different

1 in IAs, and atherosclerotic plaques and inflammatory cascade is initiated by different triggers:  
2 accumulated oxidized low-density lipoprotein in atherosclerosis and mechanical shear stress  
3 and hemodynamic disturbance in IAs, according to current understanding.

4 Endothelial dysfunction is a systemic disorder related to pathophysiology of atherosclerosis  
5 and IA formation, and endothelial dysfunction severity correlates with arterial calcifications  
6 [8,25]. Connection between these two clinical entities is under investigation. A recent study  
7 found out that atherosclerotic lesions and immunohistochemical signs of inflammation in  
8 intracranial aneurysms were associated with aneurysm wall enhancement in imaging [26].  
9 Intracranial aneurysms and atherosclerotic plaques harbor T-helper lymphocytes and  
10 macrophages, and the same types of cytokines (IL-1b, TNF-a) are found in both [7,9,11,24,27–  
11 29]. In IA, VSMCs phenotype is changed from contractile type to ECM-synthesizing type, and  
12 cells become pro-inflammatory, as in atherosclerotic plaques[30–32]. Markers of inflammation  
13 are more prominent in rupturing aneurysm: they harbor more pro-inflammatory cells,  
14 polarization of macrophage types is skewed towards type 1 pro-inflammatory macrophages  
15 and overall, rIAs harbor more inflammatory cells than UIAs [33–35].

16 Similarly to our results, lower prevalence of cardiovascular diseases in rIA patients was  
17 reported by Kang et al. earlier[36]. However, as Huhtakangas et al. revealed in their follow-up  
18 study[37], IA patients have excess mortality due to cardiovascular and cerebrovascular  
19 diseases at younger age than matched controls. They also found multiple IAs to be related to  
20 IA patients long-term mortality – perhaps describing more wide-spread inflammation of  
21 cerebral arteries. Even though markers of coronary artery disease were indeed fewest in rIA  
22 patients, within each IA patient group (rIA, UIA) and control patients, mean ACI was higher in  
23 those who had coronary artery disease or history of coronary interventions than those who had  
24 no coronary artery disease or intervention in history (see Supplementary Table). Thus our  
25 results give credence to the idea of IAs being related to atherosclerotic diseases - we used  
26 ACI to expose the subject's atherosclerotic status and found an association between IAs and  
27 atherosclerotic burden, even though other specific, heart-related atherosclerotic end-points  
28 were not present.

29 Our results did not show increased risk for IAs with hypercholesterolemia (OR 0.42, 95% CI  
30 0.27 – 0.91 for rIA) or alcohol abuse (OR 0.41, 95% CI 0.20 – 0.86 for rIA), which were  
31 previously associated with rIAs[38,39]. Also, in our study population smoking was not  
32 associated with increased risk for IAs, even though smoking is a well-established risk factor  
33 for IAs[40]. Several factors might explain these findings: first, these risk factors may be  
34 insufficiently reported in patient records, and thus such register-based data is susceptible to  
35 bias. Second, IA patient's risk profile might have improved (reduction of risk behavior, lipid

1 profile improvement) after diagnosis, but our data is not able to visualize this possible  
2 phenomenon. Third, in our data ex-smokers and current smokers are reported together.

3 It is noteworthy that smoking was not infrequent in our study population – 67.5% of all subjects  
4 were categorized as ex-smokers or current smokers. As our data on smoking relies on patient  
5 records, it is difficult to interpret findings with it. Our method does not allow us to classify  
6 smokers according to the smoking intensity. Reporting heavy smokers with those who barely  
7 are identifiable as smokers introduces perhaps a falsely increased number of smokers in our  
8 data. Still, separating smokers from ex-smokers could produce in the same way biased  
9 information on smoking. An earlier study reports that duration and intensity of smoking  
10 increase risk of aneurysm rupture but cessation and duration since cessation do not reduce  
11 the risk[40]. Thus we saw it most fit to report ex- and current smokers together. Retrospective  
12 setting does not allow us to reliably assess the intensity of smoking or duration since cessation.  
13 Most importantly, these inverse findings with recorded risk factors underline the relevance of  
14 ACI measurements. ACI is not dependent on reported vices but rather it summarizes  
15 individual's atherosclerotic vascular disease burden.

16 An inverse relation between rIA and cardiovascular diseases can be explained by rIA patients  
17 being asymptomatic until IA rupture and having not been diagnosed with cardiovascular  
18 diseases whereas patients with incidental aneurysms have been evaluated for intracranial  
19 aneurysms in part due to known risk factors and cardiovascular diseases. Coronary artery  
20 disease and other atherosclerotic diseases may not emerge as comorbidities in rIA patients  
21 because the aneurysmal rupture and subarachnoidal hemorrhage could be the first  
22 presentation of atherosclerotic disease. Also, in our study setting patients are categorized as  
23 rIA patients by having a diagnosed ruptured IA. This introduces a potential survivor bias, as  
24 some of the patients could have later developed further atherosclerotic burden, or they have  
25 not been evaluated for their cardiovascular comorbidities due to thus far being asymptomatic.

26 Other potential explanation is that patients with diagnosed coronary artery disease,  
27 cerebrovascular disease or peripheral vascular disease are more likely to have on-going  
28 pharmacotherapy with statins, antithrombotic medication (aspirin or clopidogrel) and  
29 antihypertensive medication for secondary prevention. Consequently, the lower prevalence of  
30 cardiovascular diseases in rIA patients is most likely a surrogate marker for lacking optimal  
31 preventive pharmacotherapy. Some UIA patients may be future rIA patients, and some UIA  
32 patient's aneurysms are treated electively before rupture. Thus, some patients with  
33 atherosclerotic burden and inflammation possibly leading to aneurysm rupture are categorized  
34 as UIA patients due to an early diagnosis rather than being diagnosed with a different disease

1 entity. This is plausible as it is already established that inflammation extinguishing medication  
2 such as aspirin and statins reduces IA rupture risk and growth[39,41,42].

3 There are few limitations to this study. Some demographic variables (smoking, alcohol abuse,  
4 cardiovascular diseases) revealed controversial findings as discussed above. In addition, our  
5 method and retrospective approach is susceptible to selection bias: IA and control patients are  
6 hospitalized patients, admittedly in part due their risk profile. However, IA patients abdominal  
7 imaging is not performed due to IAs, and control patients are selected from emergency  
8 departments patients who had undergone abdominal imaging at their emergency visit.  
9 Selection bias therefore is presumably present, but we claim it has minor effect on our  
10 hypothesis, because abdominal imaging rarely has much to do with atherosclerotic and/or IA  
11 events. Even further, abdominal imaging is not performed with the intention to find out the  
12 atherosclerotic status of an individual. The inflammatory mechanism of atherosclerosis is  
13 based on earlier research, and we did not have results on subjects pro-inflammatory markers.  
14 We think that it is not needed in this study, mainly because ACI index is cumulative in nature,  
15 i.e. it summarizes the results of an individual atherosclerotic process regardless of other kind  
16 of measurements.

17 Abdominal aortic calcification is more common in patients with IAs compared to matched  
18 controls. In addition, higher abdominal aortic calcification could be associated with ruptured  
19 IAs. Our results suggest that IA and especially rIA could be a marker and a result of increased  
20 atherosclerotic burden, and careful consideration for primary prevention in IA patients would  
21 be reasonable.

## 22 **Declaration of competing interests**

23 The authors declare that they have no known competing financial interests or personal  
24 relationships that could have appeared to influence the work reported in this paper.

## 25 **Author contributions**

26 Study design: Dan Laukka, Jarmo Gunn

27 Materials & manuscript preparation: Ville Rantasalo, Dan Laukka

28 Manuscript editing & statistical analysis: Ville Rantasalo, Dan Laukka, Jarmo Gunn, Tuomas  
29 Kiviniemi, Ilkka Saarenpää, Juri Kivelev, Melissa Rahi, Elli Lassila, Jaakko Rinne

30 Inter-rater reliability: Jussi Hirvonen

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2 **References:**

- 3 1. Vlak MHM, Algra A, Brandenburg R, Rinkel GJE. Prevalence of unruptured intracranial  
4 aneurysms, with emphasis on sex, age, comorbidity, country, and time period: A  
5 systematic review and meta-analysis. *Lancet Neurol.* 2011;10(7):626-636.  
6 doi:10.1016/S1474-4422(11)70109-0
- 7 2. Kent KC, Zwolak RM, Egorova NN, Riles TS, Manganaro A, Moskowitz AJ, Gelijns AC,  
8 Greco G. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than  
9 3 million individuals. *J Vasc Surg.* 2010;52(3):539-548. doi:10.1016/j.jvs.2010.05.090
- 10 3. Thompson BG, Brown RD, Amin-hanjani S, Broderick JP, Cockroft KM, Connolly ES,  
11 Duckwiler GR, Harris CC, Howard VJ, Johnston SCC, et al. *AHA / ASA Guideline*  
12 *Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms.;*  
13 2015. doi:10.1161/STR.0000000000000070
- 14 4. Kaptoge S, Seshasai SRK, Gao P, Freitag DF, Butterworth AS, Borglykke A, Di  
15 Angelantonio E, Gudnason V, Rumley A, Lowe GDO, et al. Inflammatory cytokines and  
16 risk of coronary heart disease: New prospective study and updated meta-analysis. *Eur*  
17 *Heart J.* 2014;35(9):578-589. doi:10.1093/eurheartj/eh367
- 18 5. Etminan N, Rinkel GJ. Unruptured intracranial aneurysms: Development, rupture and  
19 preventive management. *Nat Rev Neurol.* 2016;12(12):699-713.  
20 doi:10.1038/nrneurol.2016.150
- 21 6. Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. *Circ Res.*  
22 2019;124(2):315-327. doi:10.1161/CIRCRESAHA.118.313591
- 23 7. Hasan D, Chalouhi N, Jabbour P, Dumont AS, Kung DK, Magnotta VA, Young WL,  
24 Hashimoto T, Winn HR, Heistad D. Early Change in Ferumoxytol-Enhanced Magnetic  
25 Resonance Imaging Signal Suggests Unstable Human Cerebral Aneurysm. *Stroke.*  
26 2012;43:3258-3265. doi:10.1161/STROKEAHA.112.673400
- 27 8. Tulamo R, Frösen J, Hernesniemi J, Niemelä M. Inflammatory changes in the aneurysm  
28 wall: a review. *J Neurointerv Surg.* 2018;10:i58-i67. doi:10.1136/neurintsurg-2018-  
29 014090
- 30 9. Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, Koch  
31 WJ, Dumont AS. Biology of intracranial aneurysms : role of inflammation. *J Cereb Blood*  
32 *Flow & Metab.* 2012;32(9):1659-1676. doi:10.1038/jcbfm.2012.84

- 1 10. Cho BH, Kim JH, Suh SH, Baik SJ, Lee HS, Kim J, Lee KY. Characteristics of  
2 Intracranial Aneurysms According to Levels of Coronary Artery Calcium. *Stroke*.  
3 2019;50(6):1403-1408. doi:10.1161/STROKEAHA.119.024726
- 4 11. Moriya J. Critical roles of inflammation in atherosclerosis. *J Cardiol*. 2019;73(1):22-27.  
5 doi:10.1016/j.jjcc.2018.05.010
- 6 12. Philip Greenland, MDa, Michael J. Blaha, MD, MPHb, Matthew J. Budoff, MDc, Raimund  
7 Erbel, MDd, and Karol E. Watson, MD PhD, ADepartments. Coronary Calcium Score  
8 and Cardiovascular Risk. *J Am Coll Cardiol*. 2018;72(4):434-447.  
9 doi:10.1016/j.jacc.2018.05.027. Coronary
- 10 13. Kushiya F, Wada H, Sakakura M, Mori Y, Gabazza EC, Nishikawa M, Nobori T, Noguchi  
11 M, Izumi K, Nakasaki T, et al. Prognostic impact of aortic calcification index and ankle-  
12 arm blood pressure index in patients under hemodialysis. *Clin Appl Thromb*.  
13 2005;11(2):161-169. doi:10.1177/107602960501100205
- 14 14. Tsushima M, Terayama Y, Momose A, Funyu T, Ohyama C, Hada R. Carotid intima  
15 media thickness and aortic calcification index closely relate to cerebro- and  
16 cardiovascular disorders in hemodialysis patients. *Int J Urol*. 2008;15(1):48-51.  
17 doi:10.1111/j.1442-2042.2007.01925.x
- 18 15. Feng X, Qi P, Wang L, Lu J, Wang HF, Wang J, Hu S, Wang D. Relationship between  
19 cerebrovascular atherosclerotic stenosis and rupture risk of unruptured intracranial  
20 aneurysm: A single-center retrospective study. *Clin Neurol Neurosurg*.  
21 2019;186(1):105543. doi:10.1016/j.clineuro.2019.105543
- 22 16. Yamamoto D, Suzuki S, Ishii H, Hirayama K, Harada K, Aoki T, Shibata Y, Negishi Y,  
23 Tatami Y, Sumi T, et al. Predictors of abdominal aortic calcification progression in  
24 patients with chronic kidney disease without hemodialysis. *Atherosclerosis*.  
25 2016;253:15-21. doi:10.1016/j.atherosclerosis.2016.08.004
- 26 17. Roh JW, Kwon BJ, Ihm SH, Lim S, Park CS, Chang K, Chung WS, Kim D Bin, Kim SR,  
27 Kim HY. Predictors of Significant Coronary Artery Disease in Patients with Cerebral  
28 Artery Atherosclerosis. *Cerebrovasc Dis*. 2019;48:226-235. doi:10.1159/000504927
- 29 18. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation  
30 Coefficients for Reliability Research. *J Chiropr Med*. 2016;15(2):155-163.  
31 doi:10.1016/j.jcm.2016.02.012
- 32 19. New SEP, Aikawa E. Cardiovascular calcification-an inflammatory disease. *Circ J*.  
33 2011;75(6):1305-1313. doi:10.1253/circj.CJ-11-0395

- 1 20. Takayama Y, Yasuda Y, Suzuki S, Shibata Y, Tatami Y, Shibata K, Niwa M, Sawai A,  
2 Morimoto R, Kato S, et al. Relationship between abdominal aortic and coronary artery  
3 calcification as detected by computed tomography in chronic kidney disease patients.  
4 *Heart Vessels*. 2016;31(7):1030-1037. doi:10.1007/s00380-015-0712-y
- 5 21. An C, Lee HJ, Lee HS, Ahn SS, Choi BW, Kim MJ, Chung YE. CT-based abdominal  
6 aortic calcification score as a surrogate marker for predicting the presence of  
7 asymptomatic coronary artery disease. *Eur Radiol*. 2014;24(10):2491-2498.  
8 doi:10.1007/s00330-014-3298-3
- 9 22. Tatami Y, Yasuda Y, Suzuki S, Ishii H, Sawai A, Shibata Y, Ota T, Shibata K, Niwa M,  
10 Morimoto R, et al. Impact of abdominal aortic calcification on long-term cardiovascular  
11 outcomes in patients with chronic kidney disease. *Atherosclerosis*. 2015;243(2):349-  
12 355. doi:10.1016/j.atherosclerosis.2015.10.016
- 13 23. Rutsch F, Nitschke Y, Terkeltaub R, Calcification A. Genetics in Arterial Calcification  
14 Pieces of a Puzzle and Cogs in a Wheel. Published online 2011:1381-1391.  
15 doi:10.1161/CIRCRESAHA.111.247965
- 16 24. Raggi P, Genest J, Giles JT, Rayner KJ, Dwivedi G, Beanlands RS, Gupta M. Role of  
17 inflammation in the pathogenesis of atherosclerosis and therapeutic interventions.  
18 *Atherosclerosis*. 2018;276:98-108. doi:10.1016/j.atherosclerosis.2018.07.014
- 19 25. Engstr G, Frantz S, Tornngren K, Rylance R, Bj J, Malmqvist U, Erlinge D. Association  
20 of coronary calcium score with endothelial dysfunction and arterial stiffness.  
21 2020;313(September):70-75. doi:10.1016/j.atherosclerosis.2020.09.022
- 22 26. Zhong W, Su W, Li T, Tan X, Chen C, Wang Q, Wang D, Su W, Wang Y. Aneurysm  
23 wall enhancement in unruptured intracranial aneurysms: A histopathological evaluation.  
24 *J Am Heart Assoc*. 2021;10(2):1-10. doi:10.1161/JAHA.120.018633
- 25 27. Kataoka K, Taneda M, Asai T, Kinoshita A, Ito M, Kuroda R. Structural Fragility and  
26 Inflammatory Response of Ruptured Cerebral Aneurysms A Comparative Study  
27 Between Ruptured and Unruptured Cerebral Aneurysms. *Stroke*. 1999;30:1396-1401.  
28 doi:10.1161/01.STR.30.7.139
- 29 28. Hasan D, Chalouhi N, Jabbour P, Dumont AS, Kung DK, Magnotta VA, Young WL,  
30 Hashimoto T, Winn HR, Heistad D. Early change in ferumoxytol-enhanced magnetic  
31 resonance imaging signal suggests unstable human cerebral aneurysm: A pilot study.  
32 *Stroke*. 2012;43(12):3258-3265. doi:10.1161/STROKEAHA.112.673400
- 33 29. Caird J, Napoli C, Taggart C, Farrell M, Bouchier-Hayes D. Matrix metalloproteinases 2

- 1 and 9 in human atherosclerotic and non-atherosclerotic cerebral aneurysms. *Eur J*  
2 *Neurol.* 2006;13(10):1098-1105. doi:10.1111/j.1468-1331.2006.01469.x
- 3 30. Nakajima N, Nagahiro S, Sano T, Satomi J, Satoh K. Phenotypic modulation of smooth  
4 muscle cells in human cerebral aneurysmal walls. *Acta Neuropathol.* 2000;100(5):475-  
5 480. doi:10.1007/s004010000220
- 6 31. Bennett MR, Sinha S, Owens GK. Vascular Smooth Muscle Cells in Atherosclerosis.  
7 *Circ Res.* 2016;118(4):692-702. doi:10.1161/CIRCRESAHA.115.306361
- 8 32. Starke RM, Chalouhi N, Ding D, Raper DMS, Mckisic MS, Owens GK, Hasan DM, Medel  
9 R, Dumont AS. Vascular Smooth Muscle Cells in Cerebral Aneurysm Pathogenesis.  
10 *Transl Stroke Res.* 2014;5(3):338-346. doi:10.1007/s12975-013-0290-1
- 11 33. Frösen J, Piippo A, Paetau A, Kangasniemi M, Niemelä M, Hernesniemi J, Jääskeläinen  
12 J. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture:  
13 Histological analysis of 24 unruptured and 42 ruptured cases. *Stroke.*  
14 2004;35(10):2287-2293. doi:10.1161/01.STR.0000140636.30204.da
- 15 34. Cebra J, Ollikainen E, Chung BJ, Mut F, Sippola V, Jahromi BR, Tulamo R,  
16 Hernesniemi J, Niemelä M, Robertson A, et al. Flow conditions in the intracranial  
17 aneurysm lumen are associated with inflammation and degenerative changes of the  
18 aneurysm wall. *Am J Neuroradiol.* 2017;38(1):119-126. doi:10.3174/ajnr.A4951
- 19 35. Rodemerk J, Junker A, Chen B, Pierscianek D, Dammann P, Darkwah Oppong M,  
20 Radbruch A, Forsting M, Maderwald S, Quick HH, et al. Pathophysiology of Intracranial  
21 Aneurysms: COX-2 Expression, Iron Deposition in Aneurysm Wall, and Correlation with  
22 Magnetic Resonance Imaging. *Stroke.* 2020;51(8):2505-2513.  
23 doi:10.1161/STROKEAHA.120.030590
- 24 36. Kang HG, Kim BJ, Lee J, Kim MJ, Kang DW, Kim JS, Kwon SU. Risk Factors Associated  
25 with the Presence of Unruptured Intracranial Aneurysms. *Stroke.* 2015;46(11):3093-  
26 3098. doi:10.1161/STROKEAHA.115.011351
- 27 37. Huhtakangas J, Lehto H, Seppä K, Kivisaari R, Niemelä M, Hernesniemi J, Lehecka M.  
28 Long-Term Excess Mortality after Aneurysmal Subarachnoid Hemorrhage: Patients with  
29 Multiple Aneurysms at Risk. *Stroke.* 2015;46(7):1813-1818.  
30 doi:10.1161/STROKEAHA.115.009288
- 31 38. Feigin VL, Rinkel GJE, Lawes CMM, Algra A, Bennett DA, Van Gijn J, Anderson CS.  
32 Risk factors for subarachnoid hemorrhage: An updated systematic review of  
33 epidemiological studies. *Stroke.* 2005;36(12):2773-2780.

- 1 doi:10.1161/01.STR.0000190838.02954.e8
- 2 39. Can A, Castro VM, Dligach D, Finan S, Yu S, Gainer V, Shadick NA, Savova G, Murphy  
3 S, Cai T, et al. Lipid-Lowering Agents and High HDL (High-Density Lipoprotein) Are  
4 Inversely Associated With Intracranial Aneurysm Rupture. *Stroke*. 2018;49(5):1148-  
5 1154. doi:10.1161/STROKEAHA.117.019972
- 6 40. Can A, Castro VM, Ozdemir YH, Dagen S, Yu S, Dligach D, Finan S, Gainer V, Shadick  
7 NA, Murphy S, et al. Association of intracranial aneurysm rupture with smoking duration,  
8 intensity, and cessation. *Neurology*. 2017;89(13):1408-1415.  
9 doi:10.1212/WNL.0000000000004419
- 10 41. Hasan DM, Mahaney KB, Brown RD, Meissner I, Piepgras DG, Huston J, Capuano AW,  
11 Torner JC. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm  
12 rupture. *Stroke*. 2011;42(11):3156-3162. doi:10.1161/STROKEAHA.111.619411
- 13 42. Cheng W, Jia X, Li J, Cheng W, Liu Z, Lin Z, Yang C. Relationships of Statin Therapy  
14 and Hyperlipidemia with the Incidence, Rupture, Postrepair Mortality, and All-Cause  
15 Mortality of Abdominal Aortic Aneurysm and Cerebral Aneurysm: A Meta-analysis and  
16 Systematic Review. *J Cardiovasc Pharmacol*. 2019;73(4):232-240.  
17 doi:10.1097/FJC.0000000000000653

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20 Table 1. Study population demographics

	All controls	rIA	UIA	p-value
Age	63.0 (±12.0)	62.9 (± 12.3)	62.5 (± 11.0)	0.683
Abdominal aortic calcification index	17.9 (± 22.7 95%CI 16.6 - 19.1)	25.9 (± 22.7 95%CI 22.9 29.0)	23.4 (± 24.2 95%CI 20.3 26.4)	<0.001*
Smoking	746 (67.0%)	120 (67, 0%)	161 (70.3%)	0.626
Prior percutaneous coronary intervention	125 (9.9%)	8 (3.8%)	22 (9.0%)	0.019
Female	722 (57.4 %)	128 (60.7%)	145 (59.7%)	0.578
Male	536 (42.6%)	83 (39.3%)	98 (40.3%)	0.578
Coronary artery disease	279 (22.2%)	28 (13.4%)	53 (21.7%)	0.015*

Prior myocardial infarction		139 (11.0%)	14 (6.7%)	38 (15.6%)	0.011*
Treatment for Hypertension		791 (62.9%)	153 (73.2%)	185 (75.8%)	$p < 0.001^*$
Treatment for dyslipidemia		460 (36.6%)	58 (27.8%)	102 (41.8%)	0.007*
Type 2 diabetes		317 (25.2%)	45 (10.9%)	49 (11.9%)	0.158
Type 1 diabetes		60 (4.8%)	2 (3.1%)	3 (1.2%)	0.003*
Dialysis		34 (2.7%)	5 (2.3%)	17 (6.9%)	0.003*
Chronic-obstructive pulmonary disease		170 (13.5%)	30 (17.6%)	43 (20.3%)	0.02*
Calcified aorta		954 (74.0%)	196 (91.2%)	210 (86.4%)	$p < 0.001^*$
Calcification free aorta		302 (24.0%)	19 (8.8%)	33 (13.6%)	$p < 0.001^*$
Prior coronary bypass		60 (4.8%)	4 (1.9%)	12 (4.9%)	0.169
Asthma		317 (25.2%)	33 (19.5%)	37 (17.5%)	0.02*
Peripheral artery disease		92 (7.3%)	15 (7.2%)	16 (6.6%)	0.918
Alcohol abuse		399 (31.7%)	32 (15.5%)	55 (22.5%)	$p < 0.001^*$

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1 Table 2. (A) rIA patients and matched controls. (B) UIA patients and matched controls. (C).  
 2 UIA and rIA patients.

3 (A)

	Matched controls	rIA	<i>p</i> -value
Alcohol abuse	179 (32.0%)	32 (15.5%)	<i>p</i> <0.001*
Calcification free aorta	144 (25.7%)	19 (8.8%)	<i>p</i> <0.001*
Prior percutaneous coronary intervention	68 (12.1%)	8 (3.8%)	<i>p</i> <0.001*
Type 1 diabetes	30 (5.4%)	2 (1.0%)	0.007*
Coronary artery disease	122 (21.8%)	28 (13.4%)	0.01*
Dyslipidemia	211 (37.7%)	58 (27.8%)	0.011*
Prior coronary bypass	30 (5.4%)	4 (1.9%)	0.04*
Prior myocardial infarction	68 (12.1%)	14 (6.7%)	0.035*
Abdominal calcification index	18.0 (22.7 95% CI 16.2-19.9)	25.9 (22.7 95%CI 18.6-21.8)	0.001*
Calcified aorta	416 (74.3%)	196 (91.2%)	0.001*
Hypertension	351 (62.7%)	153 (73.2%)	0.006*
Age	63.6 (11.7, 62.6-64.5)	63.9 (12.3, 61.2-64.6)	0.448
Asthma	139 (24.8%)	33 (19.5%)	0.155
Type 2 diabetes	150 (26.8%)	45 (21.6%)	0.158
Male	236 (42.1%)	83 (39.3%)	0.578
Female	324 (57.9%)	128 (60.7%)	0.578
Dilaysis	18 (3.2%)	5 (2.3%)	0.64
Peripheral artery disease	47 (8.4%)	15 (7.2%)	0.657
Chronic obstructive pulmonary disease	80 (14.3%)	30 (17.6%)	0.283
Smoking	321 (66.0%)	120 (67.0%)	0.853

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1 (B)

	Matched controls	UIA	<i>p</i> -value
Hypertension	435 (63.1%)	185 (75.8%)	<i>p</i> <0.001*
Abdominal calcification index	17.8 (22.7, 95%CI 16.1-19.5)	23.4 (24.2 95%CI 20.3-26.4)	<i>p</i> <0.001*
Dialysis	16 (2.3%)	17 (6.9%)	<i>p</i> <0.001*
Calcified aorta	533 (77.4%)	210 (86.4%)	0.003*
Calcification free aorta	156 (22.6%)	33 (13.6%)	0.003*
Alcohol abuse	218 (31.6%)	55 (22.5%)	0.009*
Chronic obstructive pulmonary disease	89 (12.9%)	43 (20.3%)	0.01*
Type 1 diabetes	30 (4.4%)	3 (1.2%)	0.013*
Asthma	176 (25.5%)	37 (17.5%)	0.016*
Prior myocardial infarction	71 (10.3%)	38 (15.6%)	0.036*
Dyslipidemia	248 (36.0%)	102 (41.8%)	0.124
Type 2 diabetes	166 (24.1%)	49 (20.1%)	0.216
Prior coronary bypass	30 (4.4,%)	12 (4.9%)	0.412
Female	392 (56.9%)	145 (59.7% <sup>9</sup> )	0.497
Male	297 (43.1%)	98 (24.8%)	0.497
Smoking	421 (67.9%)	161 (70.3%)	0.507
Prior percutaneous coronary intervention	57 (8.3%)	22 (9.0%)	0.789
Coronary artery disease	157 (22.8%)	53 (21.7%)	0.789
Age	62.6 (12.1)	62.5 (11.0)	0.841
peripheral artery disease	43 (6.2%)	16 (6.6%)	0.879

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1 (C)

	rIA	IUA	<i>p</i> -value
Dyslipidemia	58 (27.8%)	102 (41.8%)	0.002*
Prior myocardial infarct	14 (6.7%)	38 (15.6%)	0.003*
Dialysis	5 (2.3%)	17 (6.9%)	0.021*
Coronary artery disease	28 (13.4%)	53 (21.7%)	0.021*
Prior percutaneous coronary intervention	8 (3.8%)	22 (9.0%)	0.028*
Alcohol abuse	32 (15.5%)	55 (22.5%)	0.058
Prior coronary bypass	4 (1.9%)	12 (4.9%)	0.084
Calcification free aorta	19 (8.8%)	33 (13.6%)	0.11
Calcified aorta	196 (91.2%)	210 (86.4%)	0.11
Abdominal calcification index	25.9 (22.9-29.0)	23.4 (24.2, 20.3-26.4)	0.242
Smoking*	120 (67.0%)	161 (70.3%)	0.479
chronic obstructive pulmonary disease	30 (17.6%)	43 (20.3%)	0.515
Hypertension	153 (73.2%)	185 (75.8%)	0.524
Asthma	33 (19.5%)	37 (17.5%)	0.604
Age	62.9 (12.3, 61.3-64.6)	62.5 (11.0, 61.1-63.9)	0.658
Type 2 diabetes	45 (21.6%)	49 (20.1%)	0.685
peripheral artery disease	15 (7.2%)	16 (6.6%)	0.784
Type 1 diabetes	2 (1.0%)	3 (1.2%)	0.786
Male	85 (39.4%)	99 (40.2%)	0.845
Female	131 (60.6%)	147 (59.8%)	0.845

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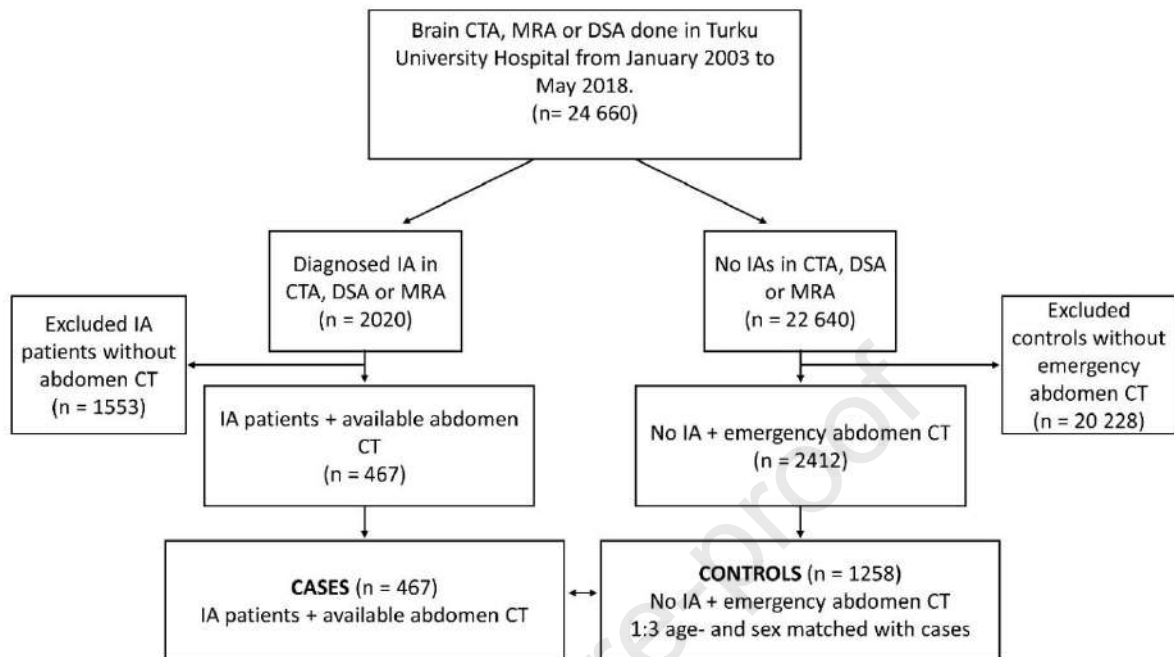
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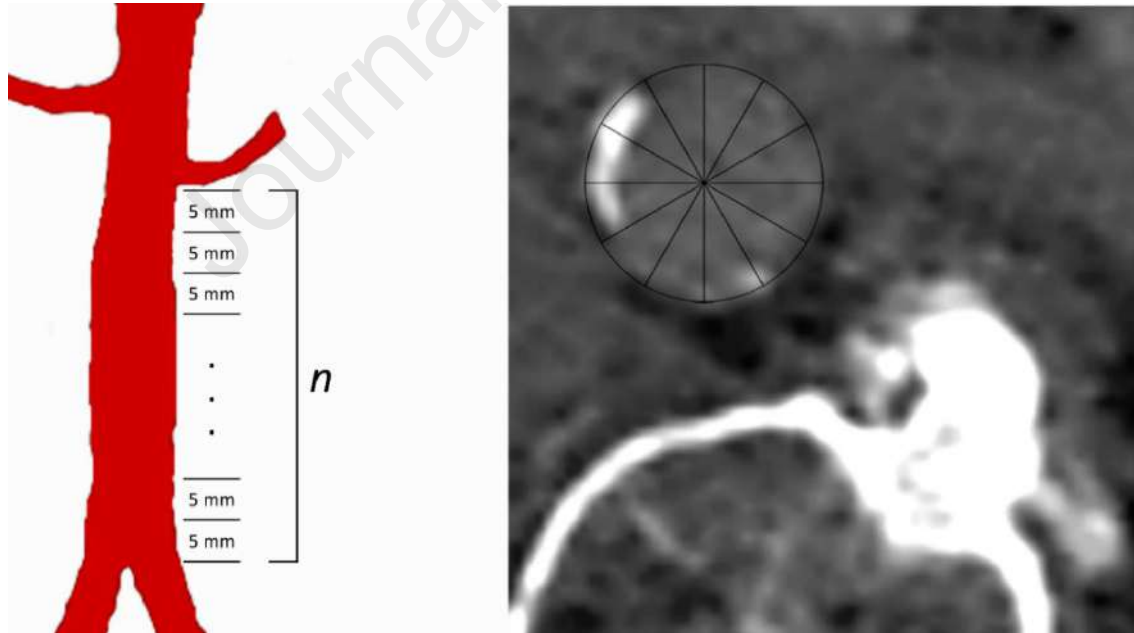
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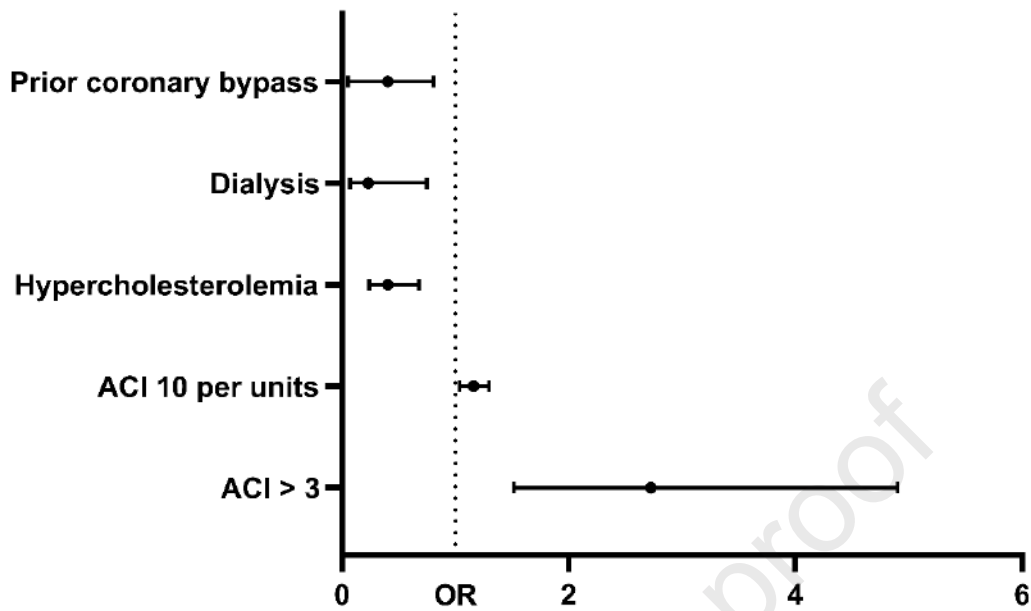
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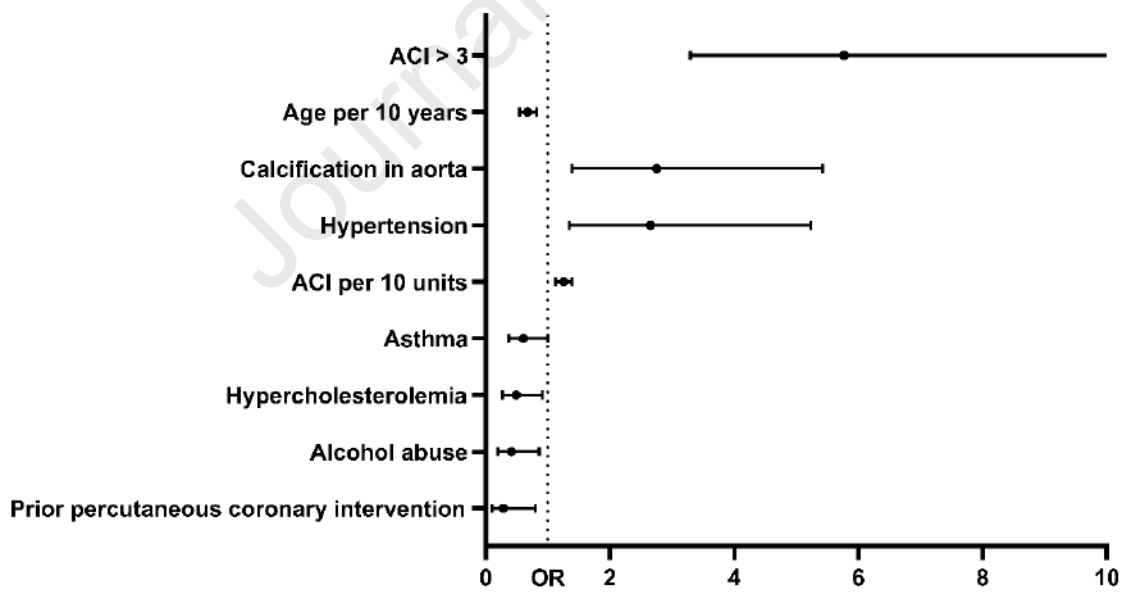
5 Figure 1(A) Flow-chart presenting TuFIAS registers aneurysm- and control patients selection  
 6 and exclusion together with ACI measurements. (B) Aortic calcification index measurement  
 7 method. Left panel = number of slices 5mm apart (=n), right panel = individual CT slice, 12-  
 8 part pie-chart represents template which is used to estimate degree of calcification.

### Odds ratio for rIA when compared to UIA



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### OR for rIA when compared to matched controls



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OR for UIA when compared to matched controls

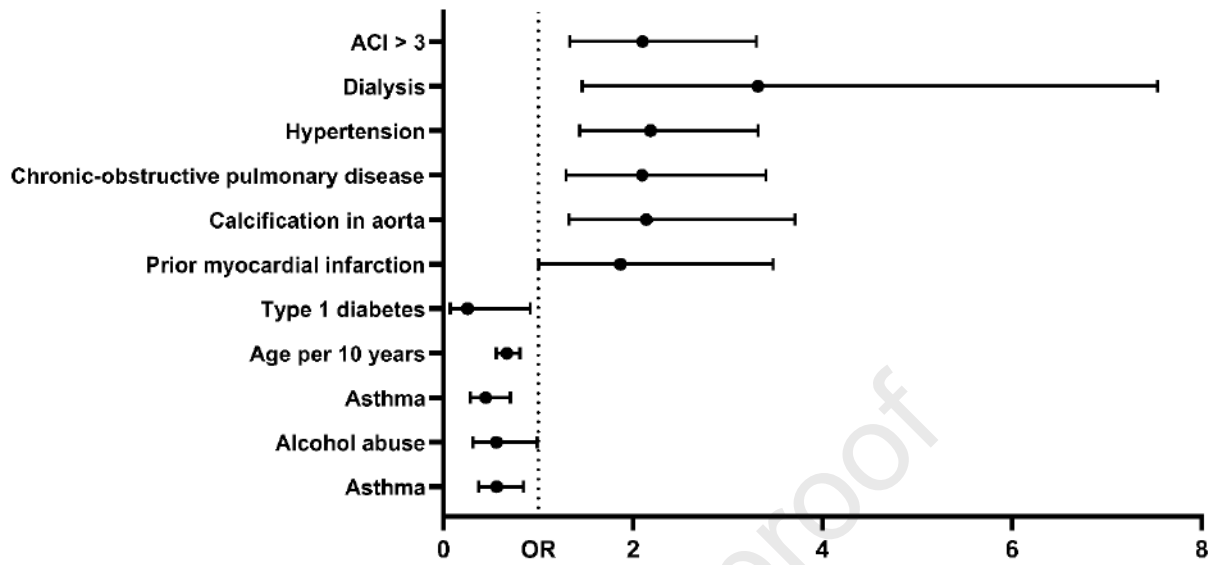
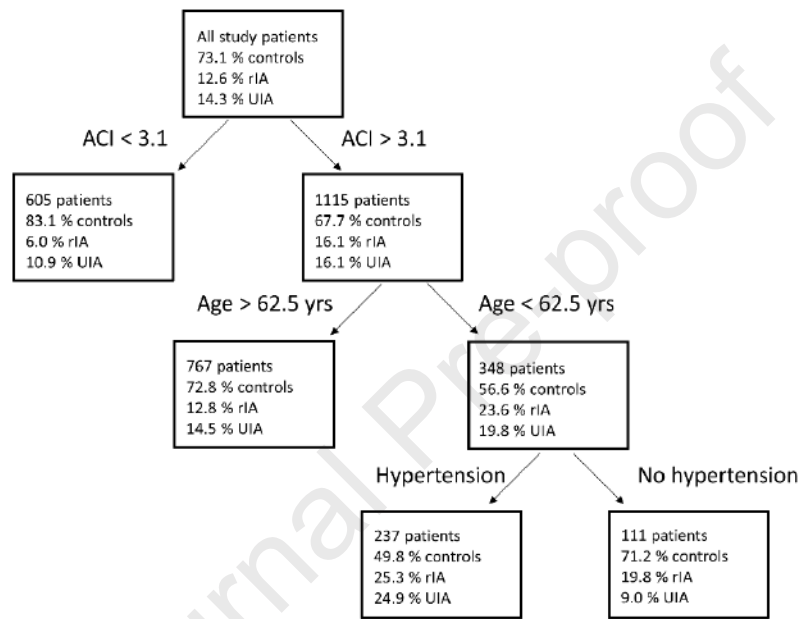


Figure 2. Diseases, risk factors and ACI: odds ratios for rIA and UIA.

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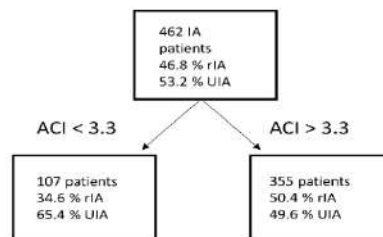
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Figure 3A



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Figure 3B



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1 Figure 3. CART-analysis decision tree.

2 (A) All study patients, including rIA, UIA and control patients. (B) CART-analysis of only rIA  
3 and UIA patients.

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Journal Pre-proof

**Highlights**

- ACI were measured from abdomen CT in patients with ruptured or unruptured IAs and matched (age/sex) controls without IA.
- Higher ACI is associated with intracranial aneurysms and especially ruptured IAs
- Higher ACI increases risk for IAs, both rIAs and UIAs
- Abdominal aortic calcification index (ACI) reflects systemic atherosclerotic burden
- Atherosclerosis is a systemic disease characterized by chronic inflammation. Inflammation plays a key role in the formation and rupture of the intracranial aneurysms.
- Association between systemic atherosclerosis and intracranial aneurysms (IA) is yet poorly studied.

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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