Original Contribution

Prevalence of Intracranial Aneurysms in Patients With Systemic Vessel Aneurysms

A Nationwide Cohort Study

Jihye Song, MD; Yong Cheol Lim, MD; Inseok Ko, MS; Jong-Yeup Kim, MD, PhD*; Dong-Kyu Kim, MD, PhD*

Background and Purpose—Most aneurysms are a focal manifestation of a systemic condition. Some reports have suggested genetic and environmental factors may play a role in pathogenesis. The aim of the present study was to evaluate the prevalence of intracranial aneurysms (IA) in a large cohort of patients with other systemic vessel aneurysms and dissections (OVAD) and identify potential risk factors for IA in this population.

Methods—We defined OVAD as systemic vessel aneurysms, excluding aortic dissections and aneurysms. A cohort of 1.1 million patients was extracted from the population-based cohort from the Korea National Health Insurance Service, which holds almost all medical data including diagnostic codes, procedures, and personal information. Using χ^2 or Fisher exact test, the prevalence of the IA concerning OVAD status was analyzed.

Results—In OVAD individuals, 25.7% (261/1017) of patients had been concurrently diagnosed with IA. The odds ratios for having concurrent IA in patients with OVAD were 56.31 (95% CI, 48.821–64.949; *P*=0.000). OVAD patients with dyslipidemia were >7× likely to be affected by IA (adjusted odds ratio, 7.7 [95% CI, 6.59–9.01]; *P*=0.000). Hypertension, diabetes mellitus, old age (>60 years), and male sex had increased odds for having concurrent IA by 5.89, 3.48, 1.83, and 1.35, respectively. Subgroup analysis with socioeconomic or disability revealed that the prevalence of IA was significantly higher in all groups. Uncertainty regarding the temporal sequence of onset and lack of detail on disease severity and subtype prevented more conclusive results.

Conclusions—Patients with OVAD have a higher prevalence of IA than control groups. Therefore, we may approach aneurysms as systemic disease, and further investigations about their pathophysiology must follow. **(*Stroke*. 2020;51:00-00. DOI: 10.1161/STROKEAHA.119.027285.)**

Key Words: diabetes mellitus ■ intracranial aneurysms ■ patients ■ prevalence ■ risk factors

Most aneurysms are a focal manifestation of a systemic condition. The pathological processes of most degenerative aneurysms include upregulation of proteolytic pathways, inflammation, and degradation of the arterial wall matrix. During its development, genetic, environmental, and hemodynamic factors are involved. Some reports showed the coexistence of these aneurysms or their coexistence with the rarer aneurysms in other locations. In an autopsy study, 40% of men and 25% of women with a thoracic aneurysm had coexisting abdominal aortic, iliac, or femoral aneurysms.[1,2] Approximately 30% of patients with popliteal artery aneurysms have an abdominal aortic aneurysm.[2]

Intracranial aneurysms (IA) are found in ≈0.4% to 3% of the general population, and subarachnoid hemorrhage secondary to IA rupture is a life-threatening event with substantial morbidity and mortality.[3–7] The guidelines for unruptured IAs have suggested that there is an increased risk of aneurysm formation in some aortic pathologies, such as bicuspid aortic valve and coarctation of the aorta.[8] Some reports demonstrated the higher prevalence of IA in patients with aortic dissection or aneurysms and suggest the associations in their genetic or pathological process.[9–11] However, studies on the associations between IA and other vessel aneurysms are scarce. Because aneurysms in most other arteries are either rare (eg, splenic or pulmonary arteries) or exceedingly rare (eg, upper limb arteries), little is known about their prevalence. Therefore, we aimed to evaluate the prevalence of IA in a large cohort of patients with systemic vessel aneurysms

Received August 7, 2019; final revision received October 3, 2019; accepted October 10, 2019.

From the Department of Neurosurgery, Ajou College of Medicine, Ajou University Hospital, Suwon, Republic of Korea (J.S., Y.C.L.); Department of Biomedical Informatics (I.K., J.-Y.K.) and Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Konyang University, Daejeon, Republic of Korea (J.-Y.K.); and Department of Otorhinolaryngology-Head and Neck Surgery, Chuncheon Sacred Heart Hospital (D.-K.K.) and Institutes of New Frontier Research (D.-K.K.), Hallym University College of Medicine, Chuncheon, Republic of Korea.

Drs J.-Y. Kim and D.-K. Kim contributed equally.

Correspondence to Jong-Yeup Kim, MD, PhD, Department of Otorhinolaryngology, College of Medicine, Konyang University Hospital, Konyang University Myunggok Medical Research Institute, 58, Gwanjeodong-ro, Seo-gu, Daejeon, Republic of Korea, 35365, Email k@kyuh.ac.kr or Dong-Kyu Kim, MD, PhD, Department of Otorhinolaryngology-Head and Neck Surgery, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine (200-704), 77, Sakju-ro, Chuncheon-si, Gangwon-do, Republic of Korea. Email doctordk@naver.com

and dissections (OVAD) and identify potential risk factors for IA in this population.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Database

All studies conducted adhered to the tenants of the Declaration of Helsinki. This study used Korean National Health Insurance Service (KNHIS) data (National Health Insurance Service-2018-2-142), made by National Health Insurance Service, and was approved by the Institutional Review Board of Hallym Medical University Chuncheon Sacred Hospital (Institutional Review Board No. 2019-05-015-002). The need for written informed consent was waived because the KNHIS–National Sample Cohort data set consisted of deidentified secondary data for research purposes. South Korea has maintained a nationwide health insurance system since 1963 under the KNHIS and controls all medical costs among beneficiaries, medical facilities, and the government. The KNHIS database holds a vast amount of inpatient and outpatient data, including diagnostic codes, length of inpatient admission, type of treatment, and prescription records. In the KNHIS, the *Korean Classification of Diseases* (*KCD*), which is a system similar to the *International Classification of Diseases*, is used as a system of diagnostic practice codes. The National Health Insurance Service is a compulsory healthcare plan for all Korean nationals; eligible citizens are covered either through community- or employee-based plans. No patient's health care records are duplicated or omitted because all South Korean residents receive a unique identification number at birth. The health care utilization database, one of the main databases run by the service, was used in the present study.

Study Cohort and Predictors

The criteria we used for extracting OVAD cohort from the database were subjects who had been diagnosed at least once with *KCD* diagnosis code I72.x, including aneurysm and dissection involving carotid artery (I72.0), artery of upper extremity (I72.1), renal artery (I72.2), iliac artery (I72.3), artery of lower extremity (I72.4), other precerebral artery (I72.5), splanchnic artery (I72.8), or unspecified site artery (I72.9). Likewise, the IA cohort was included both unruptured and ruptured IA. Unruptured IA was defined as those who had been diagnosed at least once with *KCD* diagnosis code I67.1. Ruptured IA individuals were defined as those who had been diagnosed at least once with KCD diagnosis code I60.x. Details of patients' age, sex, household income, disabilities, and comorbidities (hypertension and diabetes mellitus) were obtained from the database. For subgroup analysis, the cohort was regrouped into younger and senile sides. The cohort was divided into 10 income brackets (deciles) and then regrouped as lower (brackets 1 to 4), middle (brackets 5 to 7), or upper (brackets 8 to 10)

Table 1. Sites of Other Systemic Vessel Aneurysms According to Their Code

Code	Sites	n (%)
Total		4113 (100%)
I72	Aneurysm and dissection	421 (10.2%)
I720	Aneurysm and dissection of carotid artery	683 (16.6%)
I721	Aneurysm and dissection of artery of upper extremity	45 (1.1%)
I722	Aneurysm and dissection of renal artery	134 (3.3%)
I723	Aneurysm and dissection of iliac artery	351 (8.5%)
I724	Aneurysm and dissection of artery of lower extremity	249 (6.1%)
I725	Aneurysm and dissection of other precerebral arteries	64 (1.6%)
I728	Aneurysm and dissection of splanchnic artery	657 (16.0%)
I729	Aneurysm and dissection of unspecified site	1509 (36.7%)

Table 2. Baseline Characteristics

Variables	Numbers (%)
Total	1 113 656 (100.0%)
Sex	
Female	555 470 (49.9%)
Male	558 186 (50.1%)
Age	
<60 y	994 001 (89.3%)
≥60 y	119 655 (10.7%)
Hypertension	
No	1 047 836 (94.1%)
Yes	65 820 (5.9%)
Diabetes mellitus	
No	1 073 321 (96.4%)
Yes	40 335 (3.6%)
Dyslipidemia	
No	1 080 761 (97.0%)
Yes	32 895 (3.0%)
Household income	
Low income (0–4)	326 695 (29.3%)
Middle income (5–7)	356 214 (32.0%)
High income (8–10)	430 747 (38.7%)
Disability grade	
Normal (grade 0)	1 086 953 (97.6%)
Moderate (grade 1 and 2)	9038 (0.8%)
Severe (grade 3 to 6)	17 665 (1.6%)
Other vessel aneurysms and dissections	
No	1 112 639 (99.9%)
Yes	1017 (0.1%)
IA	
No	1 106 615 (99.4%)
Yes	7041 (0.6%)
Unruptured intracranial aneurysms	
No	1 109 710 (99.6%)
Yes	3946 (0.4%)
Ruptured intracranial aneurysms	
No	1 109 883 (99.7%)
Yes	3773 (0.3%)

IA indicates intracranial aneurysm.

income tiers. The study cohort was also divided from the grade of 0 to 6 according to the extent of their disability, and regrouped as normal (grade 0), moderate (grade 1–2), and severe (grade 3–6), if present. We analyzed comorbidities, including hypertension (*KCD* code I10), diabetes mellitus (*KCD* code E10-E14), and dyslipidemia (*KCD* code E78), which are known risk factors for OVAD and IA. We defined the presence of comorbidities as any diagnoses of these codes up to the OVAD diagnosis date and enrollment year, respectively.

Statistical Analysis

A summary of demographic and baseline characteristics was constructed using descriptive analysis; the frequency and percentage (%) for qualitative variables. The prevalence of IA with respect to the status of OVAD was analyzed using χ^2 test. All statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS software package for Windows (version 22.0, Chicago, IL). All tests were 2-sided and *P* values <0.05 were deemed statistically significant.

Results

Baseline Characteristics

The detailed numbers for OVAD are described in Table 1. The baseline prevalence of the aneurysms and dissections of the carotid artery and splanchnic artery is 0.06% (683/1 113 656) and 0.058% (657/1 113 656), respectively. Aneurysms and dissection of the carotid artery consist of 16.6% (683/4113) of total OVAD. The entire cohort consisted of 1 113 656 individuals, with nearly equal sex distribution (male: female=50.1:49.9). For the entire cohort, the baseline prevalence of OVAD and IA was computed at 0.1% and 0.6%, respectively (Table 2). Patients with dyslipidemia, hypertension, and diabetes mellitus were at increased odds of having OVAD by 8.10, 6.93, and 3.47, respectively (Table 3).

Prevalence of All IA in Relation to OVAD Status and Risk Factors

Of 1017 OVAD individuals, 261 (25.7%) had concurrently been diagnosed with IA (Table 4). In contrast, the prevalence of all IA in non-OVAD individuals (1 112 639 in total) was 0.6% (6780).The crude odds ratio was 56.31 (95% CI, 48.821–64.949; *P*=0.000). OVAD patients with dyslipidemia were roughly 7× more likely to be affected by IA (adjusted odds ratio, 7.7 [95% CI, 6.59–9.01]; *P*=0.000). Also, OVAD individuals with hypertension were roughly 5× more likely to be affected by IA (adjusted odds ratio, 5.89 [95% CI, 4.96–6.98]; *P*=0.000). OVAD individuals with diabetes mellitus, old age (>60 years), and male sex were also at increased odds of having concurrent IA by 3.48, 1.83, and 1.35, respectively. The adjusted odds ratio for IA in patients with OVAD and controls in the entire study sample stratified by age, sex, hypertension, diabetes mellitus, and dyslipidemia is presented in Table 5.

Subgroup Analysis

χ^2 test revealed that the pattern of the OVAD-IA relationship was valid in all household income groups and disability groups (*P*=0.000 in all household income and disability groups, Table 6).

Discussions

Aneurysms are localized pathological dilations of any vessel.[12] Although aneurysms are by definition focal, they may be multiple and associated with generalized arteriomegaly in some individuals. This highlights the importance of both systemic and focal factors in their pathogenesis. The natural history of most aneurysm consists of 3 phases: initiation,

Table 3. Risk Factors for Other Vessel Aneurysms and Dissections

	Other Vessel Aneurysms and Dissections					
	Univariable			Multivariable		
Variables	Crude OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
Sex						
Female	1			1		
Male	0.94	0.83–1.06	0.290	1.20	1.05–1.36	0.010
Age groups						
<60 y	1			1		
≥60 y	9.89	8.74–11.19	0.000	1.91	1.66–2.20	0.000
Hypertension						
No	1			1		
Yes	36.01	35.52–41.13	0.000	6.93	5.84–8.23	0.000
Diabetes mellitus						
No	1			1		
Yes	30.19	26.69–34.16	0.000	3.47	2.99–4.02	0.000
Dyslipidemia						
No	1			1		
Yes	48.76	42.98–55.25	0.000	8.10	6.94–9.47	0.000

Adjusted by sex, age, hypertension, diabetes mellitus, and dyslipidemia. OR indicates odds ratio.

Table 4. Prevalence of Intracranial Aneurysms in Relation to the Status of Other Vessel Aneurysms and Dissections

Variables	Total (n=1 112 639)	Other Vessel Aneurysms and Dissections (n=1017)	*P* Value
Sex			0.301
Female	554 946 (49.9%)	524 (51.5%)	
Male	557 693 (50.1%)	493 (48.5%)	
Age groups			0.000
<60 y	993 846 (89.3%)	466 (45.8%)	
≥60 y	118 793 (10.7%)	551 (54.2%)	
Hypertension			0.000
No	1 048 075 (94.2%)	316 (31.1%)	
Yes	64 564 (5.8%)	701 (68.9%)	
Diabetes mellitus			0.000
No	1 073 338 (96.5%)	483 (47.5%)	
Yes	39 301 (3.5%)	534 (52.5%)	
Dyslipidemia			0.000
No	1 080 347 (97.1%)	414 (40.7%)	
Yes	32 292 (2.9%)	603 (59.3%)	
IA			0.000
No	1 105 859 (99.4%)	756 (74.3%)	
Yes	6780 (0.6%)	261 (25.7%)	
Unruptured intracranial aneurysms			0.000
No	1 108 907 (99.7%)	803 (79.0%)	
Yes	3732 (0.3%)	214 (21.0%)	
Ruptured intracranial aneurysms			0.000
No	1 108 949 (99.7%)	934 (91.8%)	
Yes	3690 (0.3%)	83 (8.2%)	

IA indicates intracranial aneurysms.

growth, and rupture or, in some cases (particularly popliteal aneurysms), thrombosis, distal embolization, or both. Environmental and genetic factors may play a role during its development. A large number of studies have been published on analyzing the associations between a range of genetic variants and aneurysms in different locations. They have focused mostly on genes for the structural components of the vessel wall (collagens, proteoglycans, elastin, fibrillin, etc), genes for enzymes responsible to degrade the structural molecules (matrix metalloproteinases, tissue inhibitors of metalloproteinases, etc), and genes for proteins involved in the immune response.[13] For IAs, disruption of the extracellular matrix is likely to be a factor in the pathophysiology and showed high prevalence in patients with heritable connective tissue disease, such as Marfan syndrome, Ehlers-Danlos syndrome, neurofibromatosis type 1, and Loeys-Dietz syndrome.[14] IA also showed higher prevalence in polycystic kidney disease which are associated with mutations in *PKD1* and *PKD2* genes that encode proteins regulating smooth muscle cell contractility through calcium-regulatory mechanisms.[15,16] It is important to note that genetic sequence changes are not usually the cause of the disease but rather contribute to the susceptibility for developing aneurysms. Additional factors, genetic and environmental, are needed to manifest the disease.[13]

Only minorities of aneurysms have specific pathological causes, whereas the underlying mechanisms of most aneurysms are unknown and debated. The role of atherosclerosis in the causation of aneurysms is argued. Some pathologists insist that aortic and cerebral aneurysms have histological changes of atherosclerosis and that thinning and fragility of the media are prominent in atherosclerosis.[17] Other epidemiologists showed distinct differences in risk factors for aneurysmal versus atherosclerotic disease.[18] In some locations, such as a superficial femoral artery, aneurysms prone to atherosclerosis are very rare.

There is some evidence that the entire vascular tree is abnormal in patients with aneurysmal disease. For example, abdominal aortic aneurysm has been reported to be associated with generalized arteriomegaly.[19] Alterations in matrix composition seen in the walls of abdominal aortic aneurysms have been detected in both nonaneurysmal aortic segments and the inferior mesenteric vein.[20,21] And varicose veins are common in patients with coronary artery ectasia.[22] Previous reports also showed the coexistence of aneurysms in other locations. About 2% of IA patients concurrently have extracranial carotid artery aneurysms.[23] Approximately 7% of patients with abdominal aortic aneurysms and 5% with thoracic aortic aneurysms have a cerebral aneurysm.[1,24] Aneurysms of most other arteries are rare, and little is known about the prevalence or pathophysiology. And there are currently no specific recommendations for screening of IA in patient with systemic vessel aneurysms and dissections. This nationwide, population-based cross-sectional study shows a 25.7% prevalence of IA in patients with OVAD, which is roughly 56× higher prevalence than in the general population. No studies systematically investigated the prevalence of IA and OVAD.

There are several limitations. First, the cross-sectional nature of the study meant that these new findings were built on the premise of the IA preceding OVAD in onset. The validity of this assumption is difficult to ascertain since the exact prevalence and onset of OVAD tends to fluctuate from one report to another. Second, lack of information regarding disease severity and subtype impeded more detailed analysis, which would have allowed the authors to propose a more elaborate disease mechanism. Although this study was based on a 1-million strong, population-based cohort in which statistical power is hardly an issue and selection bias less of a concern (ie, in comparison to hospital records), it might not have been completely free from the clutches of accessibility bias). Third, this study lacks the data on the subtype analysis of other genetic collagen vascular disease (ie, Marfan syndrome, Ehlers-Danlos syndrome, neurofibromatosis type 1, Loyes-Dietz syndrome, fibromuscular dysplasia, and others). A detailed analysis may allow understanding the pathophysiology of the aneurysms and may lead to new therapeutic interventions to help prevent the development, growth, or rupture of IAs. Fourth, the diagnosis of IA and OVAD was only based

Table 5. Relationship Between Intracranial Aneurysm and Other Vessel Aneurysms and Dissections

	Other Vessel Aneurysms and Dissections						Other Vessel Aneurysms and Dissections						Other Vessel Aneurysms and Dissections					
	Crude			Adjusted			Crude			Adjusted			Crude			Adjusted		
Variables	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
IA							Unruptured Intracranial Aneurysm						Ruptured Intracranial Aneurysm					
No	1			1			1			1			1			1		
Yes	56.31	48.821–64.949	0.000	19.86	16.89–23.35	0.000	79.19	67.873–92.386	0.000	28.86	22.40–32.21	0.000	26.71	21.287–33.506	0.000	9.66	7.51–12.41	0.000
Sex																		
Female				1						1						1		
Male				1.35	1.19–1.54	0.000				1.37	1.20–1.56	0.000				1.22	1.08–1.39	0.000
Age groups																		
<60 y				1						1						1		
≥60 y				1.83	1.58–2.11	0.000				1.84	1.59–2.13	0.000				1.89	1.64–2.18	0.000
Hypertension																		
No				1						1						1		
Yes				5.89	4.96–6.98	0.000				6.16	5.19–7.31	0.000				6.54	5.50–7.76	0.000
DM																		
No				1						1						1		
Yes				3.48	2.99–4.04	0.000				3.46	2.98–4.03	0.000				3.49	3.01–4.05	0.000
Dyslipidemia																		
No				1						1						1		
Yes				7.7	6.59–9.01	0.000				7.60	6.50–8.90	0.000				8.08	6.91–9.43	0.000

Adjusted by sex, age, hypertension, DM, and dyslipidemia. DM indicates diabetes mellitus; IA, intracranial aneurysm; and OR, odds ratio.

on *KCD* code. The accuracy of diagnosis might be affected because KNHIS database had been established for medical service claims and reimbursement, not for research purpose. For disease other than OVAD or IA, which did not prescribe drugs, investigating prescription records can improve diagnostic accuracy.

Conclusions

This is the first prevalence study of IA in patients with OVAD. This nationwide, population-based study suggests a prevalence of 25.7% for IA in patients with OVAD. However, sparse knowledge on optimal work-up of IA is suggested in patients with OVAD. We may approach aneurysms as systemic

Table 6. Subgroups Analysis by Socioeconomic Status and Disability Grade

		Other Vessel Aneurysms and Dissections		
Household Income	IA	No	Yes	*P* Value
Low (0–4)	No	324 278 (99.4%)	240 (76.9%)	0.000
	Yes	2090 (0.6%)	72 (23.1%)	
Middle (5–7)	No	354 070 (99.5%)	192 (75.6%)	0.000
	Yes	1901 (0.5%)	62 (24.4%)	
High (8–10)	No	427 511 (99.4%)	324 (71.8%)	0.000
	Yes	2789 (0.6%)	127 (28.2%)	
Disabilities	IA			
Normal (grade 0)	No	1 079 901 (99.4%)	630 (74.4%)	0.000
	Yes	6391 (0.6%)	217 (25.6%)	
Moderate (grade 1–2)	No	8769 (98.4%)	43 (71.7%)	0.000
	Yes	146 (1.6%)	17 (28.3%)	
Severe (grade 3–6)	No	17 189 (98.6%)	83 (75.5%)	0.000
	Yes	243 (1.4%)	27 (24.5%)	

IA indicates intracranial aneurysm.

disease, and further investigations, using more sophisticated databases, would enable us to build upon this ground and yield more refined conclusions.

Acknowledgments

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C2412 to J.-Y. Kim).

Sources of Funding

This research was also supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT; NRF-2017M3A9E8033231 to D.-K. Kim).

Disclosures

None.

References

1. Svensjö S, Bengtsson H, Bergqvist D. Thoracic and thoracoabdominal aortic aneurysm and dissection: an investigation based on autopsy. *Br J Surg*. 1996;83:68–71. doi: 10.1002/bjs.1800830122
2. Oshin OA, Scurr JR, Fisher RK. Nationwide study of the outcome of popliteal artery aneurysms treated surgically (Br J Surg 2007; 94: 970-977). *Br J Surg*. 2007;94:1437; author reply 1437–1437; author reply 1438. doi: 10.1002/bjs.6063
3. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10:626–636. doi: 10.1016/S1474-4422(11)70109-0
4. Schievink WI, Parisi JE, Piepgras DG, Michels VV. Intracranial aneurysms in Marfan's syndrome: an autopsy study. *Neurosurgery*. 1997;41:866–70; discussion 871. doi: 10.1097/00006123-199710000-00019
5. Schievink WI. Intracranial aneurysms. *N Engl J Med*. 1997;336:28–40. doi: 10.1056/NEJM199701023360106
6. Brisman JL, Song JK, Newell DW. Cerebral aneurysms. *N Engl J Med*. 2006;355:928–939. doi: 10.1056/NEJMra052760
7. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet*. 2007;369:306–318. doi: 10.1016/S0140-6736(07)60153-6
8. Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention; American Heart Association; American Stroke Association. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2368–2400. doi: 10.1161/STR.0000000000000070
9. Lee D, Ahn SJ, Cho ES, Kim YB, Song SW, Jung WS, et al. High prevalence of intracranial aneurysms in patients with aortic dissection or aneurysm: feasibility of extended aorta CT angiography with involvement of intracranial arteries. *J Neurointerv Surg*. 2017;9:1017–1021. doi: 10.1136/neurintsurg-2016-012619
10. Jung WS, Kim JH, Ahn SJ, Song SW, Kim BM, Seo KD, et al. Prevalence of intracranial aneurysms in patients with aortic dissection. *AJNR Am J Neuroradiol*. 2017;38:2089–2093. doi: 10.3174/ajnr.A5359
11. Rouchaud A, Brandt MD, Rydberg AM, Kadirvel R, Flemming K, Kallmes DF, et al. Prevalence of intracranial aneurysms in patients with aortic aneurysms. *AJNR Am J Neuroradiol*. 2016;37:1664–1668. doi: 10.3174/ajnr.A4827
12. Norman PE, Powell JT. Site specificity of neurismal disease. *Circulation*. 2010;121:560–568. doi: 10.1161/CIRCULATIONAHA.109.880724
13. Kuivaniemi H, Platsoucas CD, Tilson MD 3rd. Aortic aneurysms: an immune disease with a strong genetic component. *Circulation*. 2008;117:242–252. doi: 10.1161/CIRCULATIONAHA.107.690982
14. Schievink WI, Michels VV, Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders. A review. *Stroke*. 1994;25:889–903. doi: 10.1161/01.str.25.4.889
15. Chapman AB, Rubinstein D, Hughes R, Stears JC, Earnest MP, Johnson AM, et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. *N Engl J Med*. 1992;327:916–920. doi: 10.1056/NEJM199209243271303
16. Ruigrok YM, Rinkel GJ, Wijmenga C. Genetics of intracranial aneurysms. *Lancet Neurol*. 2005;4:179–189. doi: 10.1016/S1474-4422(05)01015-X
17. Stehbens WE. Evaluation of aneurysm models, particularly of the aorta and cerebral arteries. *Exp Mol Pathol*. 1999;67:1–14. doi: 10.1006/exmp.1999.2271
18. Norman PE, Davis TM, Le MT, Golledge J. Matrix biology of abdominal aortic aneurysms in diabetes: mechanisms underlying the negative association. *Connect Tissue Res*. 2007;48:125–131. doi: 10.1080/03008200701331524
19. Johnsen SH, Joakimsen O, Singh K, Stensland E, Forsdahl SH, Jacobsen BK. Relation of common carotid artery lumen diameter to general arterial dilating diathesis and abdominal aortic aneurysms: the Tromsø Study. *Am J Epidemiol*. 2009;169:330–338. doi: 10.1093/aje/kwn346
20. Baxter BT, Davis VA, Minion DJ, Wang YP, Lynch TG, McManus BM. Abdominal aortic aneurysms are associated with altered matrix proteins of the nonaneurysmal aortic segments. *J Vasc Surg*. 1994;19:797–802; discussion 803. doi: 10.1016/s0741-5214(94)70004-4
21. Goodall S, Crowther M, Hemingway DM, Bell PR, Thompson MM. Ubiquitous elevation of matrix metalloproteinase-2 expression in the vasculature of patients with abdominal aneurysms. *Circulation*. 2001;104:304–309. doi: 10.1161/01.cir.104.3.304
22. Androulakis AE, Katsaros AA, Kartalis AN, Stougiannos PN, Andrikopoulos GK, Triantafyllidi EI, et al. Varicose veins are common in patients with coronary artery ectasia. Just a coincidence or a systemic deficit of the vascular wall? *Eur J Vasc Endovasc Surg*. 2004;27:519–524. doi: 10.1016/j.ejvs.2004.02.023
23. Pourier VEC, van Laarhoven CJHCM, Vergouwen MDI, Rinkel GJE, de Borst GJ. Prevalence of extracranial carotid artery aneurysms in patients with an intracranial aneurysm. *PloS One*. 2017;12:e0187479. doi: 10.1371/journal.pone.0187479
24. Miyazawa N, Akiyama I, Yamagata Z. Risk factors for the association of intracranial and aortic aneurysms. *Acta Neurochir (Wien)*. 2007;149:221–9; discussion 229. doi: 10.1007/s00701-006-1077-x