Association of Aortic Aneurysms and Dissections With Subarachnoid Hemorrhage
Mais Al-Kawaz, MD; Hooman Kamel, MD; Santosh B. Murthy, MD, MPH; Alexander E. Merkler, MD

Background—It is uncertain whether aortic diseases, such as aneurysm and dissection, are associated with intracranial aneurysm formation and aneurysmal subarachnoid hemorrhage (SAH).

Methods and Results—We used data on claims between 2008 and 2015 from a nationally representative 5% sample of Medicare beneficiaries. Our exposure variable was hospitalization with an unruptured or ruptured aortic aneurysm or aortic dissection. The outcome was nontraumatic SAH. Variables were ascertained by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis codes. Survival statistics were used to calculate incidence rates. Cox proportional hazards analysis was used to examine the association between aortic aneurysm/dissection and SAH while adjusting for demographics, vascular risk factors, and Charlson comorbidities. Among 1 781 917 beneficiaries, 32 551 (1.8%) had a documented aortic aneurysm or dissection. During 4.6±2.2 years of follow-up, 2538 patients (0.14%) developed a nontraumatic SAH. The incidence of SAH was 9 (95% CI, 7–11) per 10 000 patients per year in those with aortic aneurysm/dissection compared with 3 (95% CI, 3–3) per 10 000 patients per year in those without aortic aneurysm/dissection. After adjustment for demographics, stroke risk factors, and Charlson comorbidities, patients with aortic aneurysm/dissection faced an increased risk of SAH (hazard ratio, 1.4; 95% CI, 1.02–1.9; P=0.04).

Conclusions—In a nationally representative sample of Medicare beneficiaries, aortic aneurysm/dissection was associated with an increased risk of nontraumatic SAH. (J Am Heart Assoc. 2019;8:e013456. DOI: 10.1161/JAHA.119.013456.)

Key Words: aneurysm • aorta • aortic dissection • subarachnoid hemorrhage
Aortic Aneurysms and Subarachnoid Hemorrhage  Al-Kawaz et al

Clinical Perspective

What Is New?

- Patients with aortic aneurysms and dissections are at increased risk of nontraumatic subarachnoid hemorrhage, although the overall risk is very small (9 per 10,000 patient-year).

What Are the Clinical Implications?

- Aortic aneurysm and dissections may share risk factors with nontraumatic subarachnoid hemorrhages. Identifying subpopulations of patients with aortic aneurysms and dissections that may benefit from screening for intracranial aneurysms should be further investigated.

Patient Population

Our cohort comprised beneficiaries ≥65 years of age with continuous coverage in traditional fee-for-service Medicare (both Parts A and B) for at least 1 year, or until death if applicable.

Measurements

Our exposure variable was aortic aneurysm (ruptured or unruptured) or aortic dissection documented in any hospital discharge diagnosis position using the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), codes: 441.4, 441.3, 441.2, 441.1, or 441.03.10,11 Our outcome was hospitalization with nontraumatic SAH, defined using a previously validated ICD-9-CM diagnosis code algorithm: 430 without concomitant codes for rehabilitation (V57) or trauma (800–804 or 850–854). This algorithm has a sensitivity of 90%, a specificity of 97%, and a positive predictive value of 94%.12

We used ICD-9-CM codes from outpatient and inpatient visits to define the following demographic variables and vascular risk factors13: age, sex, race, hypertension, diabetes mellitus, peripheral vascular disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, valvular disease, alcohol abuse, tobacco use, and the Charlson comorbidity index.14

Statistical Analysis

Patients’ baseline characteristics were compared using the $\chi^2$ test and the $t$ test, as appropriate. Survival statistics were used to calculate annual incidence rates. Patients were censored at the time of SAH, death, or loss of Medicare coverage, or on September 30, 2015. The cumulative risks of SAH in patients with and without aortic aneurysms/dissections were calculated using Kaplan-Meier statistics and compared using the log-rank test. Cox proportional hazards models were used to evaluate the association between aortic aneurysms/dissections and SAH while adjusting for demographics and vascular risk factors. We checked the proportional hazard assumption by visually inspecting to log-log plots. Models were built stepwise. Model 1 was unadjusted. Model 2 was adjusted for age, sex, and race. Model 3 was additionally adjusted for hypertension, diabetes mellitus, peripheral vascular disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, valvular disease, alcohol abuse, and tobacco use. Model 4 was additionally adjusted for the Charlson comorbidity index. In a sensitivity analysis, we assessed only unruptured aortic aneurysms. In addition, we examined the association between aortic disease and SAH in subgroups defined by sex and race (white versus nonwhite). All statistical analyses were performed using Stata/MP, version 13 (StataCorp, College Station, TX). The threshold of statistical significance was set at $\alpha=0.05$.

Results

Among 1,781,917 beneficiaries, we identified 32,551 patients with aortic aneurysm/dissection. These patients were more...
often men and had a substantially higher burden of vascular risk factors (Table 1). During 4.6±2.2 years of follow-up, 2538 patients developed SAH. Sixty patients (0.18%) with aortic aneurysm/dissection developed an SAH compared with 2478 patients (0.14%) without aortic aneurysm/dissection. Patients with SAH were older and also had a higher burden of vascular risk factors (Table 2).

The incidence of SAH was 9 (95% CI, 7–11) per 10 000 patients per year in those with aortic aneurysms/dissections versus 3 (95% CI, 3–3) per 10 000 patients per year among the remaining beneficiaries, equating to a substantial association between aortic aneurysm/dissection and the subsequent risk of SAH (hazard ratio, 3.1; 95% CI, 2.4–4.0) (Figure 1). This association attenuated with increasing adjustment for demographics, vascular risk factors, and the Charlson comorbidity index (Table 3), but remained significant even in the most adjusted model (hazard ratio, 1.4; 95% CI, 1.02–1.9; P=0.04). We found no effect modification by sex (P=0.25 for interaction) or race (P=0.32 for interaction). Our findings were similar in a sensitivity analysis limited to patients with unruptured aortic aneurysms (Figure 2).

**Discussion**

In a large sample of elderly patients, we found an association between aortic aneurysm/dissection and nontraumatic SAH. This association substantially attenuated with increasing adjustment for shared risk factors, such as age, hypertension, smoking, and other vascular risk factors, indicating that much of the co-occurrence of cerebral and aortic aneurysms hypothesized by earlier case series is likely driven by shared upstream factors.4–8 However, even in our most adjusted

---

**Table 2.** Baseline Characteristics of US Medicare Beneficiaries, Stratified by SAH, 5% National Sample

| Characteristic                        | SAH (N=2538) | No SAH (N=1 779 379) |
|---------------------------------------|--------------|----------------------|
| Age, mean (SD), y                     | 75.5 (7.5)   | 73.5 (7.8)           |
| Women                                 | 1519 (59.9)  | 1 014 518 (57.0)     |
| Race                                  |              |                      |
| White                                 | 2112 (83.2)  | 1 531 540 (87.1)     |
| Black                                 | 235 (9.3)    | 140 486 (7.9)        |
| Other                                 | 191 (7.5)    | 107 353 (6.0)        |
| Hypertension                          | 769 (30.3)   | 450 686 (25.3)       |
| Coronary heart disease                | 248 (9.8)    | 127 336 (7.2)        |
| Congestive heart failure              | 80 (3.2)     | 42 782 (2.4)         |
| Atrial fibrillation                   | 134 (5.3)    | 58 871 (3.3)         |
| Diabetes mellitus                     | 285 (11.2)   | 182 092 (10.2)       |
| Valvular heart disease                | 79 (3.1)     | 35 501 (2.0)         |
| Chronic obstructive pulmonary disease | 154 (6.1)    | 82 643 (4.6)         |
| Chronic kidney disease                | 59 (2.3)     | 32 900 (1.9)         |
| Peripheral vascular disease           | 153 (6.0)    | 66 844 (3.8)         |
| Tobacco use                           | 29 (1.1)     | 13 692 (0.8)         |
| Alcohol abuse                         | 50 (2.0)     | 23 280 (1.3)         |

Data are represented as number (percentage), unless otherwise specified. SAH indicates subarachnoid hemorrhage.
model, there remained an independent association between aortic aneurysm/dissection and SAH. Prior studies found that ≈10% of patients with aortic aneurysms also have cerebral aneurysms. Our study builds on these case series by comparing the incidence of SAH, the most feared outcome of cerebral aneurysms, in patients with aortic aneurysms/dissections with a comparable population without documented aortic disease. Our findings support the hypothesis that patients with a known aortic aneurysm/dissection are at a higher risk of cerebral aneurysms and aneurysmal SAH.

Our study has several limitations. First, our use of administrative claims data may have led to misclassification of both the exposure and outcome variables. To minimize such misclassification, we used previously used and validated ICD-9-CM codes. Second, we lacked clinical details that may help to further adjust for confounders, such as the number of pack-years of cigarette use. Therefore, even in our most adjusted model, there may be potential for residual confounding. Third, because our cohort was limited to individuals who were ≥65 years of age, our findings may not be generalizable to younger patients.

Conclusions

In a large sample of elderly Americans, aortic aneurysm/dissection appeared to be associated with the development of nontraumatic SAH. These findings may help inform the debate about whether to screen patients with aortic disease for cerebral aneurysms. In addition, our findings suggest that further investigation into any overlapping factors in the pathogenesis of aortic and cerebral aneurysms may elucidate new targets for prevention.

Sources of Funding

Dr Kamel is supported by National Institutes of Health/National Institute of Neurological Disorders and Stroke grants K23NS082367, R01NS097443, and U01NS095869; and the Michael Goldberg Research Fund. Dr Merkler is supported by

| Model          | Hazard Ratio (95% CI) |
|---------------|-----------------------|
| Model 1*      | 3.1 (2.4–4.0)         |
| Model 2†      | 2.7 (2.1–3.5)         |
| Model 3‡      | 1.5 (1.1–2.0)         |
| Model 4§      | 1.4 (1.02–1.9)        |

SAH indicates subarachnoid hemorrhage.

*Unadjusted Cox proportional hazards model.
†Adjusted for age, sex, and race.
‡Adjusted for age, sex, race, hypertension, diabetes mellitus, peripheral vascular disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, valvular disease, alcohol abuse, and tobacco use.
§Adjusted for age, sex, race, hypertension, diabetes mellitus, peripheral vascular disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, valvular disease, alcohol abuse, tobacco use, and the Charlson comorbidity index.

Figure 2. Forest plot of subarachnoid hemorrhage association with aortic aneurysms/dissections collectively, unruptured aortic aneurysms, and ruptured aortic aneurysms/dissections. HR indicates hazard ratio.
American Heart Association grant 18CDA34110419 and the Leon Levy Fellowship in Neuroscience.

Disclosures

None.

References

1. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. *Stroke*. 1986;17:831–835.

2. Forsdahl SH, Singh K, Solberg S, Jacobsen BK. Risk factors for abdominal aortic aneurysms: a 7-year prospective study: the Tromso Study, 1994–2001. *Circulation*. 2009;119:2202–2208.

3. Hansen PA, Richards JM, Tambyraja AL, Khan LR, Chalmers RT. Natural history of thoraco-abdominal aneurysm in high-risk patients. *Eur J Vasc Endovasc Surg*. 2010;39:266–270.

4. Kuzmik GA, Feldman M, Tranquilli M, Rizzo JA, Johnson M, Elefteriades JA. Concurrent intracranial and thoracic aortic aneurysms. *Am J Cardiol*. 2010;105:417–420.

5. Rouchaud A, Brandt MD, Rydberg AM, Kadinell MP, Hedblad B, Newton-Cheh C, Melander O, Smith JG. Risk profiles for aortic dissection and ruptured or surgically treated aneurysms: a prospective cohort study. *J Am Heart Assoc*. 2015;4:e001513. DOI: 10.1161/JAHA.114.001513.

6. Sundboll J, Adelborg K, Munch T, Frohlich T, Sorensen HT, Botker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832.

7. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. *Stroke*. 2002;33:2465–2470.

8. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P, American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–1737.

9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.

10. Jung WS, Kim JH, Ahn SJ, Song SW, Kim BM, Seo KD, Suh SH. Prevalence of intracranial aneurysms in patients with aortic dissection. *AJNR Am J Neuroradiol*. 2017;38:2089–2093.

11. Gialdini G, Parikh NS, Chatterjee A, Lerario MP, Kamel H, Schneider DB, Navi BB, Murthy SB, Iadecola C, Merkler AE. Rates of spinal cord infarction after repair of aortic aneurysm or dissection. *Stroke*. 2017;48:2073–2077.

12. Cook SC, Hickey J, Maul TM, Zumberge N, Krieger EV, Valente AM, Zaidi AN, Daniels CJ. Assessment of the cerebral circulation in adults with coarctation of the aorta. *Congenit Heart Dis*. 2013;8:295–298.

13. Schievink WI, Raissi SS, Maya MM, Velebir A. Screening for intracranial aneurysms in patients with bicuspid aortic valve. *Neurology*. 2010;74:1430–1433.