ORIGINAL RESEARCH

Association of Aortic Aneurysms and Dissections With Subarachnoid Hemorrhage

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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

Aneurysms of the intracranial circulation and the aorta can rupture, with life-threatening consequences. Although the pathophysiological characteristics underlying aortic and intracranial aneurysm formation are poorly understood, both diseases share similar risk factors for aneurysm formation, such as hypertension, smoking, and the presence of certain connective tissue diseases.[1–3] Case series have found a high prevalence of unruptured intracranial aneurysms in patients with aortic aneurysms and dissections.[4–8] However, without comparable control groups, the existing evidence leaves it unclear whether patients with aortic aneurysms face a higher risk of cerebral aneurysms and subarachnoid hemorrhage (SAH). Therefore, we sought to evaluate whether aortic aneurysms are associated with SAH in a population-based cohort.

Methods

Design

We performed a retrospective cohort study using inpatient and outpatient claims data from a 5% sample of Medicare beneficiaries between 2008 and 2015. The US federal government's Centers for Medicare and Medicaid Services provides health insurance to a large majority of US residents, aged ≥65 years. The Centers for Medicare and Medicaid Services provides limited deidentified data sets to researchers that include data on claims submitted by providers and hospitals in the course of Medicare beneficiaries' clinical care. Each beneficiary is given a unique anonymous identifier to allow longitudinal analyses to be performed. Investigators can obtain access to these data by application to the Centers for Medicare and Medicaid Services.[9] Analytical methods can be made available to researchers through an e-mail request to the corresponding author. This study was approved by the Weill Cornell Medical College institutional review board.

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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 factors[13]: 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 χ^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 α=0.05.

Results

Among 1 781 917 beneficiaries, we identified 32 551 patients with aortic aneurysm/dissection. These patients were more

Table 1. Baseline Characteristics of US Medicare Beneficiaries, Stratified by Aortic Rupture or Dissection, 5% National Sample

Characteristic	Aortic Dissection/ Rupture (N=32 551)	No Aortic Dissection/ Rupture (N=1 749 366)
Age, mean (SD), y	78.6 (7.5)	73.4 (7.7)
Women	11 717 (36.0)	1 004 320 (57.4)
Race		
White	29 625 (91.01)	1 504 027 (86.0)
Black	1794 (5.5)	138 927 (7.9)
Other	1132 (3.5)	106 412 (6.1)
Hypertension	27 859 (85.6)	423 596 (24.2)
Coronary heart disease	18 676 (57.4)	108 908 (6.2)
Congestive heart failure	9552 (29.3)	33 310 (1.9)
Atrial fibrillation	9767 (30.0)	49 238 (2.8)
Diabetes mellitus	10 424 (30.0)	171 953 (9.8)
Valvular heart disease	8262 (25.3)	27 318 (1.6)
Chronic obstructive pulmonary disease	13 498 (41.5)	69 299 (4.0)
Chronic kidney disease	8317 (25.6)	24 642 (1.4)
Peripheral vascular disease	35 511 (96.8)	35 486 (2.0)
Tobacco use	6942 (21.3)	6779 (0.4)
Alcohol abuse	6001 (18.4)	17 329 (1.0)

Data are represented as number (percentage), unless otherwise specified.

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.

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

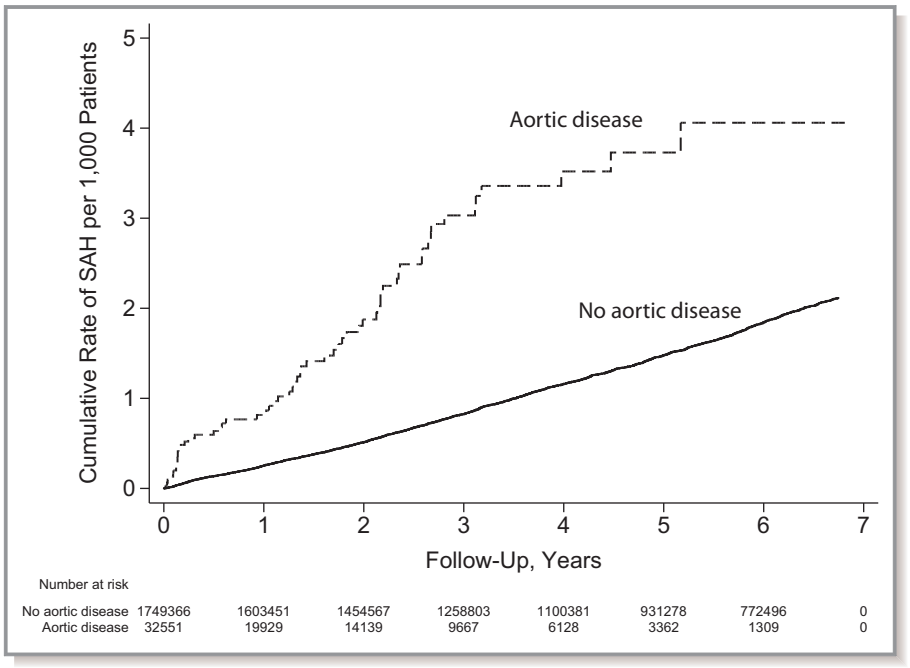

Figure 1. Cumulative rate of subarachnoid hemorrhage (SAH) in Medicare beneficiaries with and without aortic aneurysm/dissection.

Table 3. Hazard Ratios for the Association Between Aortic Aneurysm/Dissection and SAH in Medicare Beneficiaries, 5% National Sample

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.
‖P=0.04.

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.[4,15] 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.[12,16] 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.[4,6,8,17–19] 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.

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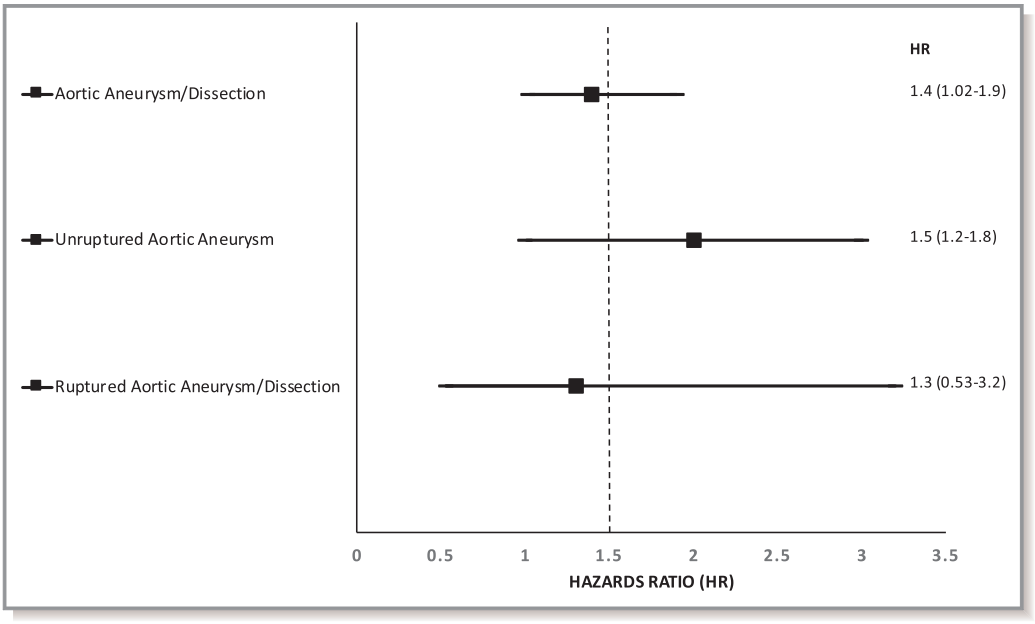

Figure 2. Forest plot of subarachnoid hemorrhage association with aortic aneurysms/dissections collectively, unruptured aortic aneurysms, and ruptured aortic aneurysms/dissections. HR indicates hazard ratio.

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Disclosures

None.

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