

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: A case-control study

In their retrospective case-control study of nearly 5,000 patients with saccular aneurysms, Can et al. found a protective effect of aspirin use with regard to aneurysm rupture. Furthermore, there appeared to be a dose-response relationship, which added to the biologic plausibility of their findings. The investigators postulated that the anti-inflammatory effect of aspirin may attenuate rupture risk in these patients. Vilanilam et al. mention that the data of Can et al. corroborate at least 2 prior investigations. Dr. Juvela, of the University of Helsinki, contends that the protective effect in this study may be confounded by selection bias—in which sicker, older patients were more likely to have taken aspirin prior to aneurysm identification or be on antihypertensive medications. At the request of Dr. Juvela, Can et al. also evaluate statin use and prior stroke as potential confounders, and find no significant association with aneurysm rupture. While aspirin may attenuate the risk of the index rupture event, the investigators found that aspirin use was associated with a significant, 8-fold higher odds of rerupture prior to definitive aneurysm treatment, although event rates were small. Vilanilam et al. question the relationship between aspirin dose and risk of rerupture; however, only 4 of 17 patients who reruptured were on aspirin prior to the index event, limiting a formal dose-response assessment.

James E. Siegler III, MD, and Steven Galetta, MD
Neurology® 2019;92:1024. doi:10.1212/WNL.0000000000007547

Reader response: Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: A case-control study

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This retrospective study consisted of 4,701 patients with 6,411 aneurysms, of which 1,302 (27.7%) were ruptured.¹ A total of 517 (11%) patients were on aspirin only; of them, 99 had subarachnoid hemorrhage (SAH). Aspirin users were less likely to have SAH or be smokers, but they were significantly older, and more likely to have hypertension, coronary artery disease, myocardial infarction, atrial fibrillation, and to use antihypertensive medication. The authors forgot previous stroke and hypercholesterolemia, common indications for aspirin use.² These should have also been tested, because unruptured aneurysm cases now are a selected subpopulation of elderly sick patients with common aspirin use for which results are difficult to generalize to unruptured aneurysms of the general population (Berkson bias). In a previous prospective study with use of urine salicylate measurement, use of aspirin both before and after aneurysm rupture increased rebleeding risk.³

1. Can A, Rudy RF, Castro VM, et al. Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: a case-control study. *Neurology* 2018;91:e1175–e1181.

- Hostettler IC, Alg VS, Shahi N, et al. Characteristics of unruptured compared to ruptured intracranial aneurysms: a multicenter case-control study. *Neurosurgery* 2018;83:43–52.
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Reader response: Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: A case-control study

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We read with interest the study by Can et al.¹ The result that the association between aspirin use and rerupture of saccular aneurysms before treatment was intriguing.

The effect of aspirin in preventing acute subarachnoid hemorrhage from intracranial aneurysm rupture is well-studied.^{2,3} However, with the advent of endovascular and neurosurgical procedures, the data on aspirin use and rerupture are definitively unknown. It might be beneficial to know what the average dose of aspirin was in the 17 patients with rerupture before initial treatment.¹ In the event of a ruptured intracranial aneurysm, can a certain threshold of aspirin be tolerated in both prior aspirin users and aspirin-naïve patients until definitive treatment? This clinical scenario serves best in rural and resource-limited settings where aspirin is ubiquitous and neurointerventional procedures are not.

In addition, does aspirin have a causative effect in rerupture or merely an association?¹ Animal studies suggested that aspirin inhibits cyclooxygenase-2 in the wall of aneurysms, more so in ruptured.⁴ We hypothesize that, while an anti-inflammatory state decreases the risk of intracranial aneurysmal rupture, aspirin also attempts to inhibit the effects of the upregulated cyclooxygenase-2 after rupture, hindering the inflammatory healing efforts of the ruptured vessel.

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Author response: Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: A case-control study

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Dr. Juvela brought up some good points in the comment on our article.¹ We reexamined our data and included statin use in all patients. With that, our results remain essentially unchanged,

with similar results for aspirin. We also examined history of strokes in a random set of 100 patients and found no association between stroke history and rupture of aneurysms. As such, the lack of inclusion of statin use and stroke history should not affect our results.

Dr. Juvela's study² examined patients who already had ruptured aneurysms. The urine salicylate levels were measured after the patients presented with a subarachnoid hemorrhage. The authors did find increased rebleeding, which is consistent with our findings. They did not study the effects of aspirin on unruptured aneurysms, however.

I thank Vilanilam et al. for the comment on our article.¹ Of the 4 patients on aspirin who reruptured, 2 were on 81 mg of aspirin and the other 2 had unknown doses. The numbers are too small to reach a conclusion regarding aspirin dose; however, it does not appear that a low dose of aspirin leads to decreased risk. At our institution, we typically administer platelets to patients who present with an intracranial hemorrhage who were taking aspirin.

While our study does not prove causality, the differential effects of aspirin on cyclooxygenase-2 in unruptured vs ruptured aneurysms is an interesting concept and merits further investigation. Indeed, consistent with what Vilanilam et al. hypothesized, some studies have shown that inflammation is involved in the healing of aneurysms.³

1. Can A, Rudy RF, Castro VM, et al. Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: a case-control study. *Neurology* 2018;91:e1175–e1181.
2. Juvela S. Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 1995;82:945–952.
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CORRECTION

Financial relationships between neurologists and Industry: The 2015 Open Payments database

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The Contemporary Issues paper, “Financial Relationships between Neurologists and Industry: The 2015 Open Payments database,” by Drs. Ahlawat and Narayanaswami,¹ is republished in this issue.² While working on a follow-up analysis, the authors noted that 2011 data, rather than the 2015 data, collected during the program were inadvertently used for the analysis. The error presumably occurred during an automatic sort from a large database and pertains only to the non-research payments. The authors reanalyzed the 2015 data and revised the paper; reanalysis shows increases in the numbers and amounts of the payments. There are no substantial changes to the discussion or conclusions. A version of the originally published paper with the updated data highlighted is included with the republication. Figures were similarly updated. The authors thank Nathaniel M. Robbins, MD, Assistant Professor of Neurology, Geisel School of Medicine, Dartmouth, for his help in correcting the data. The authors apologize for the errors.

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Financial relationships between neurologists and Industry: The 2015 Open Payments database

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