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EDITORIAL

Is the Benefit of Antithrombotics and Statins Worth the Risk of Intracerebral Hemorrhage?

It Depends

Jose Gutierrez, MD, MPH

Antithrombotics (such as antiplatelets and anticoagulants) and statins are often prescribed for primary or secondary vascular prevention. From a clinical perspective, practitioners often weigh the risk of bleeding, which is traditionally associated with antithrombotics, against their potential benefit. Such benefit/risk considerations have been the driver of randomized clinical trials investigating the role of aspirin in primary or secondary vascular prevention among specific populations at risk.[1–3] Intracerebral hemorrhage (ICH) is perhaps one of the most feared side effects of antithrombotic use because of its high risk of mortality and morbidity.[4] Although the initial publication of results from the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial[5] suggested that the risk of ICH associated with statins among patients with noncardioembolic stroke was a concern, subsequent analyses from the SPARCL trial[6] and other population-based and hospital studies[7–9] reassuringly showed that statins do not increase the risk of ICH.

See Article by Sharma et al.

In this context, in this issue of *The Journal of the American Heart Association* (*JAHA*), Sharma et al[10] leveraged medication-use data collected longitudinally in the ARIC (Atherosclerosis Risk in Communities) study to investigate whether the use of antiplatelets, antithrombotics, or statins was associated with a higher risk of ICH or higher odds of clinically covert, magnetic resonance imaging-based cerebral microbleeds (CMB). To this end, the investigators used telephone or in-person interview data to code exposure to each medication class along 3 categorical variables: any exposure, any exposure temporally close to an ICH event, and remote exposure. To account for indication bias, the author created a propensity score measuring the likelihood of being prescribed any of the 3 medication classes. The author then performed sensitivity analyses using self-reported levothyroxine and antihypertensives use to explore compliance bias and the plausibility of the models, respectively. The authors found no evidence of increased risk of ICH among users of antiplatelets or statins. On the contrary, the risk of ICH was lower among ARIC participants who used either antiplatelet or statins. Participants who used anticoagulation had a lower proportion of ICH compared to nonusers, but adjusted, time-varying models were not built because of the low number of events. Similarly, the odds of CMB were lower among antiplatelet or statin users. Participants with anticoagulation use had higher odds of CMB, but the association was attenuated by adjusting for the confound of brain small vessel disease. Based on the reported methods, it is uncertain if an ischemic stroke with secondary hemorrhagic transformation was considered an ICH.

Key Words: Editorials ■ antithrombotic ■ intracerebral hemorrhage

Correspondence to: Jose Gutierrez, MD, MPH, Columbia University Irving Medical Center, 710 W 168th Street, 6th floor, Suite 639, New York, NY 10032. E-mail: jg3233@cumc.columbia.edu

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The results presented here are unexpected, particularly those related to antithrombotics, and should be contextualized within the study's strengths and limitations. The strengths of this study include its population-based design, the relatively large and biracial sample, the longitudinal follow-up for ICH outcomes, and the availability of brain magnetic resonance imaging to replicate the clinical observations. Furthermore, the investigator should be commended for the robustness of the analytic methods, which seek to identify possible bias inherent to nonrandomized observational design, such as recall bias, indication bias, left-truncation bias, etc. Despite these efforts, there remain important confounders. For example, it is uncertain if the results of lower odds of ICH may be confounded by access to or adequacy of health care. It is possible that those who received statins or antithrombotics also regularly visited their primary care doctor and, therefore, had better controlled risk factors and consequently healthier brain arteries. In this same vein, it is uncertain if the degree of risk factor control may play an effect modification role in the reported findings. It is plausible that among people with uncontrolled hypertension or diabetes mellitus, exposure to antithrombotics may increase the risk of ICH. The results presented in this work suggest a role for the use of antihypertensive medication as protection against ICH, and although use of antihypertensives partially accounts for access to care, it would have been ideal to look at systolic and diastolic blood pressure or hemoglobin A1C longitudinally. It is worth noting that the same population with uncontrolled risk factors is the one most likely to obtain the benefit of ischemic event reduction. The results presented here do not provide information about the subpopulations who received antithrombotics, their indications (eg, coronary artery disease, atrial fibrillation, prior stroke, primary prevention, etc) or whether high-risk subpopulations may indeed have a higher risk of bleeding upon exposure to antiplatelets or anticoagulants.

Other clinically relevant questions may have included subgroup analysis for use of dual antiplatelets or anticoagulation plus an antiplatelet, effect mediation of low-density lipoprotein levels on statin exposure and ICH risk, racial/ethnic disparities in ICH risk, or model using continuous measure of exposures in years or months as opposed to discrete categories of exposure. Finally, compliance bias may still be a problem. It is possible that levothyroxine compliance is higher than antithrombotic compliance given that stopping levothyroxine would result in symptoms after discontinuation as opposed to no symptoms after not taking antithrombotics.

In spite of these shortcomings, it is reassuring that exposure to these commonly used medication classes was not associated with a higher risk of ICH or CMB in the ARIC population. The generalizability of the ARIC population to the population of the United States or other populations is limited by the geographic disparities in care and vascular health within the United States and across other countries as well as the exclusion of other racial and ethnic groups. Furthermore, the clinical impact of these findings is unclear. Practitioners would most likely continue to use randomized clinical trial data to prescribe antiplatelets, anticoagulation medication, or statins if indicated. Even if the results shown here had demonstrated a higher risk of ICH with any of these medications, the lack of the relative benefit of these medications would make the result hard to apply or interpret. Therefore, if there remain questions regarding the risk of ICH associated with any of these medication classes, future research, preferably using randomized clinical trials, should focus on targeted or focused populations of clinical relevance. Until then, these data offer partial reassurance that if indicated, these 3 classes of medications do not significantly increase the risk of ICH or CMB within the studied population.

ARTICLE INFORMATION

Affiliation

From the Department of Neurology, Columbia University Irving Medical Center, New York, NY.

Disclosures

None.

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