The Interplay between Stroke Severity, Antiplatelet Use, and Aspirin Resistance in Ischemic Stroke

Nergiz Agayeva, MD, Mehmet Akif Topcuoglu, MD, and Ethem Murat Arsava, MD

Background: The issue of whether prior antiplatelet use favorably affects stroke severity is currently unresolved. In this study, we evaluated the effect of antiplatelet use on clinical stroke severity and ischemic lesion volume, and assessed the confounding effect of laboratory-defined aspirin resistance on this relationship. *Methods:* Admission National Institutes of Health Stroke Scale (NIHSS) score, ischemic lesion volumes on diffusion-weighted imaging (DWI), and in vitro aspirin resistance, in addition to other pertinent stroke features, were determined in a series of ischemic stroke patients. Univariate and multivariate analyses were performed to compare clinical and imaging markers of stroke severity among patients with and without prior antiplatelet use, taking into consideration the presence or absence of aspirin resistance. *Results:* Antiplatelet users experienced more severe strokes, per NIHSS score, in comparison to antiplatelet-naive patients ($P = .007$). No significant difference was observed with respect to admission DWI lesion volume. When analyses were repeated after adjustment for stroke subtype and other confounders, no association was observed between antiplatelet use and stroke severity. On the other hand, NIHSS scores were significantly higher in aspirin-unresponsive patients than in both aspirin responders ($P = .049$) and aspirin nonusers ($P = .005$). *Conclusion:* We were unable to demonstrate a substantial positive influence of prestroke antiplatelet usage on stroke severity. Although the presence of more severe strokes among patients with laboratory resistance suggests a protective influence of aspirin sensitivity on stroke severity, the hypothesis could not be validated as no difference was observed among aspirin-naive and aspirin-sensitive patients with respect to admission NIHSS score or DWI lesion volume. **Key Words:** Ischemic stroke—aspirin resistance—antiplatelet—lesion volume—DWI.

In addition to their established efficacy in ischemic stroke prevention, various agents like warfarin, aspirin, and statin have been evaluated for their potential on influencing stroke severity, if being used prior to stroke.[1-5] The most striking relationship in this regard has been demonstrated for warfarin, wherein the presence of therapeutic international normalized ratio levels at the time of stroke onset was associated with lower admission stroke severities, smaller lesion volumes, and better long-term functional outcomes.[1,5] Similarly, patients on statin and angiotensin-converting enzyme inhibitors (ACEIs) were more likely to have more favorable outcomes when compared with their counterparts who were not using any of these medications prior to stroke.[2-4]

The relationship between antiplatelet therapy and stroke severity is a little bit more complicated. Some studies, including observations from the Trial of Org 10172 in Acute Stroke Treatment, have suggested a favorable clinical profile

From the Department of Neurology, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

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Address correspondence to Ethem Murat Arsava, MD, Department of Neurology, Faculty of Medicine, Hacettepe University, 06100 Sihhiye, Ankara, Turkey. E-mail: arsavaem@hotmail.com.

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in aspirin users.[6-12] On the other hand, several studies, among which the large-scale International Stroke Trial can be included, have shown no beneficial effect of aspirin or other antiplatelets in terms of lessening stroke severity.[13-24] More importantly, analyses from the International Stroke Trial dataset have shown higher odds of death or dependency among aspirin users, a relationship that diminished following adjustment for baseline clinical characteristics.[20] The issue gets more intricate by hints of smaller acute ischemic lesion volumes—a surrogate marker of stroke severity—among antiplatelet users, and by literature suggesting less severe strokes among patients who are demonstrated to be responsive to aspirin by laboratory tests assessing in vitro platelet reactivity.[25] In the present study, our aim was to analyze the interplay between antiplatelet therapy and stroke severity in a large sample of patients by primarily focusing on admission lesion volume and also to assess the confounding effect of laboratory-defined aspirin resistance on this relationship.

Methods

The study included a consecutive series of patients admitted with a diagnosis of ischemic stroke to our center between the period of 2011 and 2013. Patients using anticoagulant agents at the time of the incident event or not undergoing a magnetic resonance imaging study within 24 hours of symptom onset were excluded from analyses. The study was approved by the local institutional review board.

Demographic and clinical data were collected prospectively for all patients. These included age, gender, stroke risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, atrial fibrillation, active smoking, prior history of stroke), and admission National Institutes of Health Stroke Scale (NIHSS) score. Concomitant use of statins or ACEIs/angiotensin receptor blockers (ARBs) was also noted. Stroke subtype was determined according to the Causative Classification System for Ischemic Stroke.[26] Diffusion-weighted imaging (DWIs) was performed 1.5 T scanners (Magnetom TIM, Siemens, Erlangen, Germany; and Intera, Achieva, Philips, The Netherlands) according to the following protocol: single-shot echo planar, three *b* values applied with a maximum of 1000 seconds/mm^2, TR/TE of 4800/120 milliseconds, matrix of 96-256, slice thickness of 5 mm with 10% interslice distance and field of view of 220-240 mm. DWI lesion volume was calculated by manual outlining and thresholding of ischemic lesions on a slice-by-slice basis using the MRIcro software (University of Nottingham, Nottingham, United Kingdom). Volume calculations were performed while being blinded to clinical information of the patient, including the presence or absence of aspirin use prior to stroke. For the secondary analyses regarding the influence of level of laboratory-defined platelet inhibition on stroke severity, we assessed in vitro aspirin resistance using the VerifyNow Aspirin Assay (Accumetrics, San Diego, CA) in aspirin users. Laboratory evidence of aspirin resistance was considered to be present when the aspirin response unit value was 550 or higher, per the reference values suggested by the manufacturer.

Categorical variables are expressed as n (%) and continuous variables as median (interquartile range [IQR]). Groupwise categorical and continuous variables were compared by chi-square test and the Mann–Whitney *U*-test, respectively. Linear regression models (with dependent variables being either admission NIHSS score or DWI lesion volume) were used to determine independent predictors of stroke severity. A *P* value less than .05 was considered significant. All statistical analyses were performed by SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 343 patients were admitted with a diagnosis of ischemic stroke within 24 hours of symptom onset during the study period. Seventy-nine did not receive an MRI within the same day (28 with contraindications to MRI and 51 with MRI obtained >24 hours), and 29 were further excluded from the study due to concurrent use of anticoagulant agents. Therefore the final study population was composed of 235 patients.

Table 1 summarizes the baseline clinical features of the study population, stratified according to prestroke use of antiplatelet agents. The majority of patients using antiplatelets (n = 79) were on aspirin monotherapy (n = 52); the remaining patients were either using clopidogrel or combined aspirin–clopidogrel therapy. Antiplatelet users were older, more likely to harbor hypertension, coronary artery disease, atrial fibrillation, and prior history of stroke, and were more likely to use statins or ACEI/ARBs. More importantly, stroke subtype significantly differed among both groups, with cardioaortic embolism being more commonly encountered in patients on antiplatelet therapy. The median (IQR) admission NIHSS score was 6 (2-13) in antiplatelet users and was significantly higher than those in antiplatelet-naive patients 3 (1-9) ($P = .007$). On the other hand, the median (IQR) admission DWI lesion volume did not significantly differ between both groups.

As patients with and without prior antiplatelet use significantly differed with respect to stroke subtype, a factor critically related to stroke severity, the relationship between stroke severity and antiplatelet use was assessed after the patients were stratified according to the presence or absence of cardioembolic stroke subtype. In these analyses, antiplatelet use was not related to stroke severity as determined by either clinical or imaging measures (Fig 1). Additionally, in the linear regression models, which assessed the effect of all clinical confounders that might be related to stroke severity, antiplatelet use was not related in any way to admission NIHSS score or DWI lesion volume (Table 2).