

**EDITORIAL COMMENT**

**Ethnic Disparity in Intracranial Hemorrhage Among Anticoagulated Patients With Atrial Fibrillation**

An Answer in Search of a Question*

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Stroke due to intracranial hemorrhage (ICH) carries a higher morbidity and mortality than ischemic stroke, and it has been estimated that among persons 45 to 64 years of age, 8% to 12% of ischemic strokes and 37% to 38% of hemorrhagic strokes result in death within 30 days (1). The risk of ICH is increased among patients receiving heparin or warfarin, and the mortality of anticoagulant-associated ICH is approximately double that of spontaneous ICH (1–4). Atrial fibrillation (AF) is an independent risk factor for ischemic stroke. It increases stroke risk about 5-fold, and this risk is significantly reduced by warfarin.

In this issue of the *Journal of the American College of Cardiology*, Shen et al. (8) report on the prevalence of ICH among 18,867 patients, hospitalized for the first time with AF and followed for a median of approximately 3 years. The study was retrospective, and diagnosis was based on the International Classification of Diseases (ICD)-9 codes 430 to 432, which include both intracerebral and subarachnoid hemorrhage. During follow-up, 58.4% took warfarin for at least part of the time. One hundred seventy-five spontaneous ICHs occurred, the majority of them in patients who were taking warfarin when the bleed occurred. Although there was no difference in the prevalence of ICH among racial groups who were not receiving warfarin, nonwhite patients receiving warfarin had a significantly higher risk of ICH, with a hazard ratio, compared with whites, of 2.05 for blacks, 2.06 for Hispanics, and 4.1 for Asians. The findings of this study warrant careful examination, because they have the potential to modify practice and, if the results are incorrectly interpreted, any change in practice could be detrimental to patient care. To understand their significance, several questions need to be addressed. For example, are the findings related to overanticoagulation in minorities due to increased warfarin sensitivity or is the increased ICH rate with warfarin in minorities a function of their greater risk of ICH regardless of warfarin therapy? And, if minorities have a greater ICH risk with warfarin, might this reflect a higher prevalence of intracranial pathology or is it a feature of a greater prevalence of risk factors for ICH such as hypertension? Finally, should these results affect the prescribing of warfarin in minorities, particularly for Asians, who had the highest rate of this devastating condition?

Genetic variations play a role in determining the maintenance dose of warfarin and, among patients with mutations that result in a low warfarin maintenance dose, overanticoagulation during the initial phases of warfarin treatment is quite common (9). Rieder et al. (10) estimated that 21% to 25% of the maintenance dose of warfarin can be explained by variance in the gene-encoding vitamin K epoxide reductase complex 1. Five common haplotypes were identified, 2 of which resulted in the need for a lower warfarin dose. Haplotypes predictive of a low maintenance dose of warfarin were present in 35% of whites compared with 89% of Asians but only 14% of blacks; these findings have been subsequently confirmed in populations attending anticoagulation clinics in several different areas of the world (9,11–14). Warfarin sensitivity, partly mediated by genetic variation, is associated with an increased bleeding risk. This risk clusters in the early period of therapy, when excessively high international normalized ratio (INR) measurements might occur and greatly lessens during maintenance therapy once a therapeutic INR is achieved (9). Thus genetic differences in warfarin sensitivity would be expected to manifest themselves as differences in early bleeding rates.

In the current study, reference to the authors’ figure demonstrates that, rather than a cluster of bleeding risk early after...
warfarin therapy, excess bleeding risk among minorities persisted over several years. Data on anticoagulation intensity are presented and do not suggest that overanticoagulation accounted for excess ICH in minorities. Indeed, among blacks, there was a tendency toward underanticoagulation. Thus, although genetic variation might explain Asian sensitivity to warfarin, it would not account for excessive ICH rates in the Asian population and would certainly not explain the increased risk in blacks.

Hypertension is a major risk factor for ICH, and the risk of ICH is related to hypertension severity and consistency of blood pressure control (15–18). Blacks have a higher prevalence of hypertension than whites, and hypertension in this population might be more severe and more difficult to control. In the current study, 77.5% of the population had hypertension, but the black population had the highest prevalence. The nature of the study did not allow the severity of hypertension to be assessed, and hypertension was analyzed as a dichotomous variable, so it is conceivable that blacks had both a higher prevalence and more severe hypertension, potentially explaining some of their risk. However, there is inadequate information to be certain, and the precise role of poorly controlled hypertension remains intriguing but uncertain.

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of congophilic amyloid beta protein in cortical and leptomeningeal vessels (3,19,20) and is associated with lobar hemorrhage in elderly patients. Patients with CAA have a 4-fold increase in warfarin-associated intracranial bleeding, and several gene polymorphisms are associated with both the presence and severity of this condition (19). The authors do not indicate whether there was a predominance of lobar hemorrhage (which would suggest CAA), but other studies have addressed this issue. In a study in northern Manhattan, blacks and Hispanics were found to have an increased risk of all types of ICH, with nonlobar hemorrhage predominating (6), and in an autopsy series of Chinese patients, the prevalence of CAA was found to be much lower than expected in whites, despite a higher incidence of intracerebral hemorrhage in this population (21). Thus CAA is unlikely to explain the ethnic differences in the current study.

None of the aforementioned mechanisms give a satisfactory answer to the findings in this study. Therefore, rather than focus the question on why warfarin might have caused an increased ICH risk in minorities, it is worthwhile stepping back and asking whether ethnic variation in ICH occurs in the absence of warfarin. If so, then the results might well be explained by an increased overall ICH risk among warfarin-treated patients regardless of ethnicity. In the present study, minorities with AF did not have a statistically significant excess ICH risk unless they were using warfarin. This might suggest that the drug is the culprit rather than the existence of intrinsic interethic variations in ICH prevalence that are exaggerated by anticoagulation. However, extensive data in published reports suggest that this is not the case. Age standardized mortality rates in the U.S. between 1995 and 1998 for ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage were all higher among blacks than whites, and death rates from intracerebral hemorrhage but not ischemic stroke was higher among Asians and Pacific islanders than among whites (22). In a much larger study than the current one, also from Kaiser Permanente of California, black patients had a relative risk of intracerebral hemorrhage of 1.9 compared with whites, and Asians had a relative risk of 1.6 (23). Although information is not available about the rhythm in these patients or their anticoagulant use, this was a relatively young population, and it is unlikely that many were using anticoagulants. Finally, in a recently published study of a similar number of anticoagulant-associated ICH, almost one-half of whom had AF, Flaherty et al. (4) found no evidence of excess warfarin-related ICH risk in black patients compared with whites.

The risk of ischemic stroke is high among most patients with AF, and it would require overwhelmingly convincing data to result in a recommendation to withhold warfarin in minorities with AF. The present study does not offer such data, but the findings do underscore the importance of developing an approach to therapy that should include a consideration of ethnicity when choosing a dose of warfarin to initiate therapy. In addition, the data underscore the necessity for a vigorous approach to treating risk factors for ICH, particularly hypertension, which might be more common and more severe in minority populations.

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