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Editorial

Atrial Fibrillation – How Does Race/Ethnicity Matter?

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Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinic practice and its incidence and prevalence have steadily increased worldwide [1]. Estimates from 2010 placed the number of affected individuals at 33.5 million worldwide with about 5 million new cases each year. Prevalence varies, with the highest rate in North America (700 to 775 per 100,000 in 2010) and the lowest in Asian countries such as Japan and South Korea (250 to 325 per 100,000). Prevalence of AF is around 475-550 per 100,000 in African countries where data are available.

In the United States, significant differences are found between ethnic groups. Whites have a significantly higher risk of atrial fibrillation than do Blacks, Asians, or Hispanics [2], despite the higher burden of traditional risk factors for atrial fibrillation in nonwhite groups [3]. After adjusting for established AF risk factors, the hazard ratio for developing AF is 0.84 for Blacks, 0.78 for Hispanics, and 0.78 for Asians when compared with Whites [2].

Genetic variability may help explain the differences in AF susceptibility. In African Americans, a 10% increase in European ancestry has been associated with a corresponding 13% rise in incident AF risk [4]. However, the genetic variants accounting for these differences remain unclear, particularly because large genome-wide association studies (GWAS) that have facilitated discovery of genetic loci associated with AF primarily involve individuals of European ancestry.

One of the most important complications of AF is ischemic stroke. AF increases the risk of stroke approximately 5-fold, even after adjusting for major stroke risk factors [5]. Anticoagulant therapy is recommended for most AF patients for the prevention of stroke [6].

Randomized clinical trials showed that warfarin use imparts a relative risk reduction of68% for stroke in atrial fibrillation (absolute risk reduction of 3.1%). However, warfarin therapy is associated with an absolute 0.3% increase in the annual risk of intracranial hemorrhage [7,8]. When deciding whether to initiate anticoagulant therapy, the risk of bleeding, particularly intracranial hemorrhage must be weighed against the benefit of stroke reduction. This risk-benefit ratio differs among patients from different ethnic groups, in part due to important differences in the incidence and distribution of stroke types.

The total incidence of stroke in Black and Hispanic populations is greater than that in Whites [9-12]. However, important differences in the type of stroke exist. For example, compared to other ethnic groups, Asians have a much higher incidence of hemorrhagic stroke [13]. While hemorrhagic stroke usually comprises 20% of strokes in White patients, hemorrhagic stroke accounts for >30% of all strokes in Asian patients [14,15]. In black patients with stroke, lacunar infarcts and intracranial hemorrhage are more common than cardioembolic strokes [16]. Among patients with ischemic strokes, the proportion of strokes assessed as being cardioembolic is lower among Black and Hispanic patients than among White patients [17]. One study that specifically studied ethnic differences in stroke risk factors showed that in White patients, AF was associated with a higher odds ratio for ischemic stroke than in Black and Hispanic patients, with an odds ratio (OR) of 4.4 for AF in White, 3.0 in Hispanic, and 1.7 in Black patients [18].

The difference in stroke type is important because warfarin is not effective for the treatment of non-cardioembolic strokes [19] and would exacerbate hemorrhagic strokes. As a result, Black, Hispanic, and Asian patients may not derive as much clinical benefit from warfarin, since their increased risk of intracranial hemorrhage may potentially offset any gain in cardioembolic stroke reduction.

The randomized trial evidence supporting the use of warfarin in reducing stroke risk is based on populations with very little ethnic heterogeneity. Among the main trials upon which the current guideline recommendations are based, 95% of the patients included were White patients [7].

In an observational study evaluating Medicare patients hospitalized for AF, warfarin use was associated with a 39% relative risk reduction of ischemic stroke compared with no antithrombotic therapy, but a significant protective association was not observed in Black or Hispanic patients. Moreover, there was a 44% higher relative risk of major bleeding in Black patients compared to White patients [20].

Another observational study that evaluated a multi-ethnic cohort of patients in California showed that the crude rate ratio of intracranial hemorrhage with warfarin therapy compared to those not taking warfarin was 2.3 for White patients, 4.8 for Hispanic patients, 5.0 for Black patients, and 14.9 for Asian patients [21]. Even after adjusting for stroke risk factors and warfarin use, the hazard ratio for intracranial hemorrhage in Asian patients was 4 times higher than in White patients, while Black and Hispanic patients had twice the risk of intracranial hemorrhage compared to White patients. Because of the higher risk of bleeding, some physicians in Asia keep the target INR dose in a lower range (e.g. INR 1.5-2.5 as opposed to INR 2-3) despite limited evidence to justify the practice [22].

The observed time in therapeutic range (TTR), a key determinant of warfarin efficacy, was shown in one study to be lower in Black patients than in White patients, whereas TTR was similar in Asian and Hispanic patients when compared to White patients [23]. The pharmacokinetics of warfarin also differs between ethnic groups.

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Compared to White patients, Black patients require higher doses of warfarin, whereas Asian patients require lower warfarin doses to achieve the same INR level [24]. This is partly due to variations in the metabolism of warfarin. Warfarin is metabolized by the cytochrome P450 enzyme CYP2C9, and there are population-differences in the frequencies of variant CYP2C9 alleles that confer different metabolic activities [25]. There is also a population variation in the warfarin target gene which encodes vitamin K epoxide reductase complex 1 (VKORC1). Different VKORC1 haplotypes are associated with different warfarin dosing requirements to achieve the same INR. Asian populations have a higher proportion of patients with the VKORC1 haplotypes that require low dose warfarin, and Black patients more frequently carry the VKORC1 haplotypes that require high-dose warfarin. These differences may affect the optimal dose of warfarin and patient's response to warfarin [26].

New oral anticoagulants (NOACs) have been developed as alternative agents for thromboembolic prevention in patients with non-valvular AF. These include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban. Randomized trials and early experience showed many promising aspects with their use. Compared to warfarin, the therapeutic effect of the NOACs is more predictable without the need for routine monitoring and with fewer food and drug interactions. The plasma half-life is shorter, and there appears to be an improved efficacy to safety ratio [27-29]. Randomized clinical trials showed that compared to warfarin, the newer anticoagulants led to a significant reduction of stroke or systemic embolism [30], a trend towards reduced major bleeding, and a significant reduction in hemorrhagic stroke [31]. There is, however, an increase in gastrointestinal bleeding with these agents.

How the newer anticoagulants perform in ethnic minorities is not well understood because the majority of the patients enrolled in the randomized clinical trials were White patients. For example, in the RE-LY trial which compared dabigatran to warfarin, 87.7% of the study participants were White, 10.3% were Asian, and only 1.9% were Black [27]. Similarly, more than 80% of enrollees in the ROCKET-AF trial were white [28].

Reassuringly, the pharmacokinetic profile of dabigatran appears to be consistent across a broad range of different patient populations and appears to be unaffected by patient's ethnic origin [32]. Also, early analysis of the Asian subgroup in RE-LY suggests that these new oral anticoagulants may be just as effective as if not superior to warfarin. Subgroup analysis in RE-LY showed that the effects of dabigatran against stroke and systemic embolism are similar in Asians and non-Asian patients. More important, while Asian patients on warfarin had more total bleeding and hemorrhagic strokes, excess of bleeding was not found in Asian patients when dabigatran was used [33]. These data suggest that the new anticoagulants may provide a safe and effective alternative to warfarin, and may even be preferentially indicated in certain subgroups such as Asian patients [22]. A recent analysis of the ROCKET-AF trial showed that being black or Asians was associated with 2-3 times the risk of ICH compared with whites. However, rivaroxaban was associated with a substantially lower risk of ICH compared with warfarin regardless of race and ethnicity [34].

In summary, there are important ethnic differences in the risk/benefit ratio of anticoagulation therapy for stroke prevention in patients with AF. While warfarin has been shown to be highly effective in preventing ischemic strokes in White patients with AF with a small increase risk of intracranial hemorrhage, patients from other ethnic groups appear to derive a smaller benefit in ischemic stroke reduction and assume a high risk of intracranial hemorrhage. The newer anticoagulants, with their lower associated risk of intracranial hemorrhage, have been proven mostly in white patients. Further research studying the use of the newer anticoagulants in different ethnic minorities will be important.

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