JACC: ASIA VOL. 2, NO. 1, 2022

EDITORIAL COMMENT

Risk of Incident Atrial Fibrillation in ALDH2-Deficient Variant Carriers

Genetic Predisposition or Habitual Lifestyle?*

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Atrial fibrillation (AF) is the most common type of symptomatic arrhythmias worldwide, which has been propelled to an "emerging epidemic disease" owing to the combination of an aging population and lifestyle factors.[1] Genetic, nongenetic, and/or environmental risk factors contribute to AF development. As a reversible risk factor, habitual alcohol consumption increases AF risk with a dose-effect relationship.[2] The impact on alcohol metabolism of targeting aldehyde dehydrogenase 2 (ALDH2) is critical. However, compared with other races, East Asian populations have a higher risk for ALDH2-deficient variants.[3] Given the negative association between the dysfunctional ALDH2 allele and AF, the limited metabolic activity postponed the conversion process from alcohol to acetaldehyde and then increased the risk of AF occurrence.[4]

Also known as "holiday heart syndrome," habitual alcohol consumption and binge drinking increase AF susceptibility through various mechanisms, including heart function deterioration, dilated cardiomyopathy, electromechanical delay, autonomic regulation, oxidative stress, hypertension, and sleep apnea syndrome.[2,5,6] Based on the number of standard drinks per week, alcohol consumption is classified into light, moderate, or heavy levels; however, the existing results in the observational and nonrandomized studies did not support a margin for safety on daily alcohol intake in AF development.[6] Due to the potential biases and reverse causation in the previous research, randomized controlled trials or Mendelian randomization approaches can be implemented to assess the causal effects of alcohol consumption on AF risk. Current evidence suggests that genetically predicted alcohol intake was not causally associated with AF.[7] Hence, the activity of alcohol metabolism via ALDH2 genotypes is a brand-new direction of the research on the prevalence of AF.

In this issue of *JACC: Asia*, Yamashita et al.[8] evaluated the association between ALDH2-deficient variant carriers and AF in habitual drinkers. This single-center retrospective study enrolled 656 patients, including 385 patients with catheter ablation for AF, 196 patients with catheter ablation for other arrhythmias, 49 patients with aortic disease, and 26 patients with coronary angiography. Mean age was 64 years and percentage of males was 61.4%. According to ALDH2 genotype and the allele ratio, the distributions of the genotypes were divided into 430 carriers with ALDH2 homozygous wild-type (*1/*1), 199 carriers with ALDH2 heterozygous-deficient allele (*1/*2), and 27 carriers with ALDH2 homozygous-deficient allele (*2/*2). ALDH2*1/*2 carrier was not associated with AF, but ALDH2*2/*2 was negatively correlated with AF risk. The proportions of habitual alcohol consumption were 53.7% for ALDH2 wild-type, 25.6% for ALDH2*1/*2 carriers, and 0% for ALDH2*2/*2 carriers. Interestingly, ALDH2*1/*2 allele carriers with habitual alcohol consumption had higher incidence of AF due to slowly metabolic activity of ALDH2. These main findings provide insights into how to identify an individual with an ALDH2*1/*2 allele carrier and whether abstinence from alcohol might help the prevention of AF occurrence. However, the conclusions in this study need to be interpreted with the following concerns.

*Editorials published in *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2021.11.005

First, the authors aimed to estimate the association between ALDH2 genotypes and AF prevalence. From the genetic perspective, ALDH2-deficient variant was defined as inherited exposure, and incident AF was considered as disease outcome. A randomized controlled trial or Mendelian randomization approach should be performed to explore the causal effects of ALDH2 genotypes on the risk of AF, rather than this retrospective study.

Second, the ALDH2 heterozygous-deficient allele (*1/*2) itself had no significant correlation with AF. ALDH2*1/*2 carriers with habitual alcohol consumption had higher incidence of AF, suggesting that the positive relationship between the 2 was driven by habitual alcohol consumption. It is well-known that alcohol use was affected greatly by other related conditions (eg, the socioeconomically disadvantaged, regional disparity, education, occupation, and incomes).[9,10] The investigators should gather the above baseline characteristics to avoid potential biases and enroll the measurable confounders to multiple logistic regression analyses.

Third, the frequency of the ALDH2 mutation allele was applied to expound the richness of GenBank in the entire group, not a single individual. Given that large samples are necessary for the genetic variation analysis of a population, 3 types of ALDH2 allele carriers in 656 patients were insufficient to compare the relevance, especially in 27 ALDH2*2 allele carriers. Accordingly, the sample size should be calculated using Power Analysis and Sample Size (PASS) software to achieve a sufficient statistical power of AF signature.

Fourth, the follow-up period of new AF onset was restricted to 10 months in this study. Ageing was considered an independent risk factor of AF, and longer time follow-up is essential to assess the effect of ALDH2-deficient variant on the occurrence and persistence of AF.

Fifth, ALDH 2*2/*2 was negatively associated with the risk of AF because of inappreciable activity of ALDH2, in which the patients failed to have regular alcohol intake. This biological behavior induces the lower incidence of AF. Abstinence from alcohol improves the maintenance of sinus rhythm in drinkers with AF.[11] Thus, alcohol abstinence can help prevent the occurrence and recurrence of AF in every ALDH2-deficient variant carrier, not just in patients with ALDH2*1/*2 carrier.

In conclusion, this research has found clinical evidence of a significant association between ALDH2 genotypes and AF prevalence. ALDH2-deficient variants with habitual alcohol consumption could play a major role in the pathological mechanism of AF from this retrospective study at a single center. Reducing or abstaining from alcohol contributes to prevention of the pathogenesis of AF etiologically in patients with ALDH2-deficient variants. Further randomized controlled trial or Mendelian randomization study, adjusted multiple logistic regression analysis, adequate sample size and statistical power, and long-term follow-up would greatly reinforce the reliability and efficacy of these findings.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS alcohol, aldehyde dehydrogenase, atrial fibrillation, East Asians