Published in final edited form as:
J Am Coll Cardiol. 2012 August 7; 60(6): 546–547. doi:10.1016/j.jacc.2012.02.060.

Polymorphisms and Response to Antiarrhythmic Drugs in Atrial Fibrillation: Mechanism or Association?

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Ready or not, routine use of genetic information is imminent in everyday cardiology practice. This reality stems partly from the declining cost of whole genome sequencing now approaching the $1,000 barrier. We surely could use such insight in managing atrial fibrillation (AF) an extremely common and costly condition. However, analyzing and applying the vast amount of data housed in the human genome will undoubtedly present huge challenges. With this backdrop, Parvez *et al.*, report in this issue of the *Journal* that response to certain antiarrhythmic drugs (AADs) may be genotype-dependent.

Using a single institution registry, the authors examined success of AAD therapy in 676 Caucasian patients with AF. Patients were included in the study if they had a documented history of AF with concurrent use of at least 1 conventional AAD (Vaughan Williams Class I or Class III agents). About two-thirds had typical AF—i.e., AF in conjunction with hypertension, coronary artery disease, congestive heart failure, or diabetes—with the remainder having lone AF. Response to therapy was analyzed with a questionnaire(1) that yielded a symptomatic AF burden score by quantifying AF symptom frequency, duration, and severity. A patient was deemed a responder if s/he remained on the same AAD therapy for a minimum of 6 months and had a >75% reduction in their AF burden score. The investigators examined the association between AAD responder status and the presence of four single nucleotide polymorphisms (SNPs) that had previously been linked with AF in genome wide association (GWA) studies.

Motivation for this study built from the recent recognition that family history is a risk factor for non-valvular AF on top of traditional risk factors, such as age, hypertension, congestive heart failure, compromised respiratory function, and hyperthyroidism. Like many complex polygenic disorders, AF is inherited only rarely in Mendelian fashion, yet having at least one parent with AF doubles the risk of AF.(2) For lone AF family history confers an even greater risk.(3) Several GWA studies (4) have recently identified specific genetic variants with AF, including 2 common single nucleotide polymorphisms (SNPs) on chromosome

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4q25 (rs2200733 and rs10033464) near the transcription factor PITX2. (5) Subsequent studies have found a strong association for rs2200733 than for rs10033464.(6) (7) (8) Two additional SNPs on chromosomes 1q21 and 16q22 with modest effects have also been identified. (9) (10)

With the rationale that the multiple genetic variants associated with AF might indicate variable mechanisms contributing to AF susceptibility, or variable sub-types of AF, Parvez *et al.* (11) hypothesized that response to AAD therapy might also be genotype-dependent. Testing first in a discovery cohort of 478 patients, the authors identified an association between a response to AAD therapy and the rs10033464 SNP, but not with the other SNPs tested. The association with rs10033464 was predominantly if not exclusively seen in patients with typical AF as opposed to the patients with lone AF. Using multivariate regression, the association of AAD response with rs10033464 persisted after controlling for clinical variables such as age, gender, hypertension, coronary artery disease, heart failure, and diabetes. Interestingly, the investigators further found that the response rate to Class I AADs was higher in patients with one or more minor alleles at rs10033464. On the other hand, the response rate to Class III AADs was higher in patients with only wild type alleles. In a validation cohort of 178 Caucasian patients from Vanderbilt the association of rs10033464 with response to ADDs was also significant in the combined group patients; analysis for typical *versus* lone AF was not performed because of sample size.

While this innovative study associating the SNP rs10033464 with AAD response breaks new ground, it should be considered hypothesis generating, until confirmed by a randomized, double-blinded trial. We share the authors' optimism that the genomic revolution will yield opportunities to inform and tailor treatment, but this study raises several questions. First, the response rate of 72-83% to AAD was much higher than we are accustomed to seeing, even if amiodarone use was high (data not provided), and reflects relatively non-rigorous criteria for AAD success. Although freedom from any AF may be too stringent and miss useful clinical benefit of AAD (or ablation), success rates for AAD in a recent randomized trial was only 16%. (12) Even with a more lenient endpoint in the AFFIRM antiarrhythmic substudy, the 1-year success was only 23% for Class I AADs and only 38% for sotalol.(13) Since AADs alone or in combination with rate control agents may render AF less symptomatic or even asymptomatic, the 75% reduction in AF symptoms used to determine success in this study may underestimate actual AF prevalence. The relatively subjectivity of the endpoint reduces confidence in the differences observed for the rs10033464 SNP and for different AADs. Concerning the secondary endpoint, AF recurrence, the intensity of monitoring was less than that advocated by the HRS/EHRA/ECAS Expert Consensus Statement on AF Ablation, namely a 24-hour Holter every 3 to 6-months for 1 to 2-years.(14)

A second weakness of the study is that the AAD selection was not random, and the decision to continue it relatively subjective, depending upon the patient and physician's preferences and the AF burden score. The patient-completed AF symptom questionnaire may be dependent upon patient and physician bias, and may not equate with actual AF burden.

Third, the specific associations in this study are somewhat at odds with findings from the large studies that first identified these AF-related SNPs. The SNP highlighted in this study, rs10033464, has been the polymorphism less strongly associated with AF in GWA studies than its neighbor on 4q25 (rs2200733). Since both SNPs are thought to involve PITX2, the biological plausibility of the association is strained somewhat. Also, it is curious that rs10033464 was more clearly associated with AAD response in typical AF patients in this study, while SNPs at 4q25 had previously been more strongly associated with lone AF. (6)

Fourth, moving from statistical associations between rs10033464 SNP status and AAD response to using the SNP information to guide therapy is problematic. For example, the positive predictive value of minor allele carrier status for predicting non-response to AAD is only 23%; i.e., 25 of 109 total MAC patients in the discovery cohort were non-responders per Table 2. (11) Similarly, the differential response to AADs is interesting and hypothesis generating, but difficult to act on with the degree of differences found. Lastly, as with any initial report, one needs to consider the possibility that the associations arose by chance; such positive associations may be more likely to be reported than negative ones. (15)

In summary, Parvez et al (11) are to be commended for extending the epidemiologic associations between several SNPs and AF to an exploration of potential therapeutic ramifications. Lacking patient-specific predictors for efficacy, current AF drug selection considers only comorbidities seeking to minimize proarrhythmia(16). Pharmacogenetic insights could theoretically help predict efficacy and toxicity. Although we are closer to the beginning than to the point of clinical usage, Parvez et al, (11) have started us on an exciting journey.

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