Has genetic disposition implications for treatment decisions in atrial fibrillation?

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Genetic disposition largely facilitates the occurrence of atrial fibrillation (AF), stroke, or coronary artery disease. Particularly, genome-wide association studies (GWAS) identified hundreds of genetic variants that modulate the risk of these conditions.1,2,3 Two straightforward questions arise from these observations: first, do the same genetic variants predict recurrence of an event in individuals who have had a disease manifestation before, and second, do genetics interact with treatment responses?

For coronary artery disease, the answer to both questions is yes. Individuals with a high polygenic risk score (PRS) not only have an about two-fold increase for having a myocardial infarction, they have—within the group of coronary artery disease patients—also an about 30% increased risk for a second event.4 At the same time, intensive treatment with statins or protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors offers the largest treatment benefit for those who have a high polygenic risk.5

1. Genetic risk for re-occurrence of AF

In case of AF, the situation is less clear. A meta-analysis by Shoemaker et al.6 suggested that a high genetic risk for AF was associated with younger age and fewer other risk factors but not with AF recurrence after catheter ablation. Again: AF begets AF, so that here—once the carousel has started—genetics seem to play a minor role.

Kany et al.5 report data from the EAST-AFNET 4 trial on the effectiveness of early rhythm control (ERC) therapy in reducing cardiovascular events in patients with AF across different levels of genetic risk for AF or stroke. The EAST-AFNET 4 trial investigators already reported before that ERC is effective in reducing cardiovascular events in patients with early onset AF.6 Here, the authors report that a PRS for AF (PRS-AF) is associated with a small risk increase for recurrent AF, but genetics do not modulate the effectiveness of ERC in reducing cardiovascular events. Surprisingly, a PRS for stroke (PRS-Stroke) was associated with heart failure hospitalizations but not with stroke itself. The authors ascribe that to the high rate of anticoagulated patients (>90%) in the study cohort and underline the importance of treatment of concomitant cardiovascular conditions.5,6 This finding reiterates that the genetic roots of AF, stroke, and coronary artery disease can be traced across these conditions since one may affect the other—depending on the success of its treatment (Figure 1).7

Several factors, including differences in patient cohorts and ablation protocols, could explain the slight divergence of the results by Shoemaker et al. with the current study. The EAST-AFNET 4 trial enrolled patients with a shorter duration of AF diagnosis, where AF-related atrial remodelling might be less significant for AF recurrence compared to patients with longer AF durations.8

2. ERC and genetic risk

Previous observations and pathophysiological considerations suggest that patients with a higher genetic risk for AF might have a reduced response to rhythm control therapy or an increased risk of adverse events. However, this study found that ERC therapy was beneficial across the whole spectrum of PRS-AF, likely due to the good effectiveness and safety of modern rhythm control strategies used in the EAST-AFNET 4 trial.6 Although no interaction between polygenic risk and adverse events of rhythm control therapy was found, larger genetic studies are needed to detect possible interactions with rare adverse events in AF treatment. The authors’ findings may also underline the effectiveness of modern catheter ablation: Pulmonary vein isolation effectively eliminates the arrhythmo-genic substrate surrounding the antral pulmonary vein tissue. This results in a permanent inactivation of triggers, which would otherwise initiate AF in patients’ atria.9 Assuming that genetic risk for AF mainly determines the atrial susceptibility for AF and that ERC effectively eliminates initiating AF triggers could be a possible explanation for the finding that ERC therapy was effective across the whole spectrum of genetic AF risk.

3. Potential of PRSs

The information underlying PRS is largely derived from GWAS with a case-control design. Thus, their clinical use in predicting events matches best with primary prevention. The current data demonstrate that ERC therapy remains effective and safe across the spectrum of polygenic risk for AF or stroke. In addition, the authors suggest that treatment factors, including anticoagulation, can modify the genetic risk for stroke, highlighting the importance of a comprehensive approach in AF therapy.

4. Stroke and heart failure

In the EAST-AFNET 4 dataset, the PRS-Stroke was associated with an increased risk of heart failure hospitalization, but not with stroke itself.
These observations have to be taken with a note of caution. The numbers of events were low, e.g. 51 stroke events in 1567 EAST-AFNET patients vs. e.g. 110 182 stroke patients and 1 503 898 control individuals in the latest GIGASTROKE GWAS, which showed association of cardio-embolic stroke with loci for AF risk. The lack of association between PRS-Stroke and stroke in the EAST-AFNET 4 data set could also be due to a high rate of anticoagulated patients in the trial (>90%), since may stroke loci indeed affect the blood clotting. The association between PRS-Stroke and heart failure events might be mediated by AF, as suggested by shared genetic architecture.

5. Outlook

The current study provides valuable insights into the effectiveness of ERC therapy across the spectrum of genetic risk for AF and stroke. Further studies are needed to better understand the observed associations and interactions between genetic risk for AF, stroke, AF recurrence, cardiovascular events, and heart failure, as depicted in Figure 1. Recent studies emphasize that not only rhythm control but also the accompanying therapy of clinical conditions, such as diabetes, obesity, hypertension, and sleep apnoea, is mandatory in successful treatment of AF patients. The association of PRS-Stroke and heart failure in EAST-AFNET 4 patients now additionally points out to the importance of concomitant cardiovascular disease treatment. While PRSs offer risk information in addition to those clinical conditions, their utility in treatment strategies for patients requires further investigation. The study’s observations regarding heart failure hospitalization and stroke risk provide important step in this direction for future research.

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References


