

MANAGING ATRIAL FIBRILLATION: FROM SCREENING TO TREATMENT SELECTION

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Keywords: atrial fibrillation; pulmonary vein isolation; rhythm control; screening

The year 2018 was a year where many events related to atrial fibrillation occurred. Results from major trials in the field of atrial fibrillation were published this year in different areas of research: screening for atrial fibrillation (DIGITAL-AF), rhythm control therapy (RACE 3), and pulmonary vein isolation for atrial fibrillation (CASTLE-AF and CABANA). The results of these trials were presented at this year's ESC congress, Heart Rhythm Society Scientific Sessions, or published after being presented last year at a major congress.

SCREENING FOR ATRIAL FIBRILLATION

An important aspect of atrial fibrillation is screening. In the guidelines, opportunistic screening has a class I recommendation, but what is the best screening method? This year, the results of DIGITAL-AF were presented at the ESC congress in Munich! DIGITAL-AF examined the feasibility and effectiveness of screening with a smartphone-based app. In a local newspaper, the app was advertised with a free token for downloading. In total, 12328 individuals had already downloaded the app in the first 48 hours. By means of photoplethysmography (putting the left index finger in front of the smartphone camera), an analysis of the cardiac arrhythmia was made. In total, 9889 (80%) participants had a regular rhythm, 136 (1.1%) had atrial fibrillation, 2111 (17%) had other irregular rhythms, and 191 (2%) had measurements of insufficient quality to be analyzed. Not all patients were known to have atrial fibrillation; in total, around 40 patients were newly diagnosed. Since smartphone use is widespread today (also among the elderly) and smartphone watches are becoming more advanced with ECG monitoring capacities, health care providers will likely see more digital referrals in the near future.

NEWS ON ANTICOAGULATION

Also at this year's ESC congress, data from the GARFIELD-AF registry was presented. GARFIELD-AF is a registry used to prospectively track daily anticoagulation practice globally and to study the uptake of non-vitamin K antagonist therapy in atrial fibrillation. It was shown that non-vitamin K antagonists are superior

to vitamin K antagonists in reducing 2-year mortality in higher risk patients ($\text{CHA}_2\text{DS}_2\text{-VASC}$ score ≥ 2)^{2,3}; there was a 19% relative risk reduction. However, the most interesting fact was that patients who concomitantly started anticoagulation and antiplatelet therapy (as compared with anticoagulation alone) at the time of diagnosis had a nonsignificantly higher risk of bleeding (HR, 1.45; 95% CI, 0.94-2.23; $P=\text{ns}$), but importantly, an increase in mortality (HR, 1.31; 95% CI, 1.05-1.62) with an increased risk for stroke (HR, 1.60; 95% CI, 1.08-2.35). Moreover, there appeared to be an ever-worse prognosis for those not having an indication for the use of antiplatelets (no peripheral artery disease); in these patients, the HR was 1.48 vs 1.31 (for having an indication) for mortality, stroke, and major bleeding.^{2,3} So, it is very important to evaluate anticoagulation and antiplatelet therapy at the time of atrial fibrillation diagnosis and to make the right choices in terms of therapy.

Other news on anticoagulation is that, in 2018, andexanet alfa (a recombinant modified FXa protein with no enzymatic activity), which was designed to bind and sequester factor Xa and thus reverse anticoagulation for apixaban and rivaroxaban, was approved by the U.S. Food and Drug administration in patients who need it in case of life-threatening or uncontrolled bleeding.⁴

NEWS ON RHYTHM CONTROL STRATEGIES

Presented last year at the annual meeting of the ESC and published this year in the *European Heart Journal* was the RACE 3 trial.⁵ RACE 3, tested whether the addition of upstream or targeted therapy (mineralocorticoid receptor antagonist, statins, and ACE inhibitors or ARBs, cardiac rehabilitation with focus on exercising, dietary restrictions, and counseling) could improve sinus rhythm maintenance in 240 patients treated with rhythm control for persistent atrial fibrillation. At follow-up, the patients who were randomized to the upstream therapy group had lower blood lipid levels, lower brain natriuretic peptide levels, and lower blood pressure than did the control group. After 1-year of follow-up, more patients were in sinus rhythm (during a 7-day Holter follow-up) in the upstream or targeted therapy group compared with only guideline-recommended rhythm control. In addition, quality of life was improved in the upstream therapy arm, even in patients who were in atrial fibrillation at 1 year. RACE 3 taught us that a careful consideration of associated cardiovascular conditions and lifestyle modifications improves sinus rhythm maintenance. Where RACE 3 patients were predominantly treated with medical rhythm control (7 patients underwent pulmonary vein isolation), CASTLE-AF and CABANA were completely focused on ablation.

PULMONARY VEIN ISOLATION: THE IDEAL RHYTHM CONTROL STRATEGY?

Two major trials have seen daylight in 2018: CASTLE-AF and CABANA.^{6,7} CASTLE-AF randomized patients with symptomatic paroxysmal or persistent atrial fibrilla-

tion who had failed antiarrhythmic drug therapy (or had side effects) and were in New York Heart Association class II-IV with a left ventricular ejection fraction equal or below 35% (and importantly had an implanted cardioverter defibrillator) to either undergo catheter ablation (n=179) or pharmacological therapy (which could be either rate or rhythm control, n=184).⁶ The primary end point was a composite of death from any cause or heart failure hospital admission. The catheter ablation group had a relative risk reduction in the primary outcome of 38%; mortality rates were 28.5% vs 44.6% after a median 38-month follow-up. Furthermore, catheter ablation also reduced cardiovascular death by 51% and the cardiovascular mortality rate by 11.2% vs 22.3%. Furthermore, the burden of atrial fibrillation (as measured by the device) at all follow-up visits was significantly lower in the catheter ablation group than in the medical group. Overall, the conclusion of this (nonblinded) trial was that atrial fibrillation in the presence of heart failure confers a worse prognosis and the reduction in atrial fibrillation by catheter ablation improves overall survival. There are some important concerns about the generalizability of the findings of this trial: only patients with heart failure who could tolerate all heart failure medications were included, the number of patients with ischemic etiology was low compared with other heart failure trials, and the total inclusion period was over 8 years with only 363 patients included.

Another ablation trial, CABANA, was presented at this year's Heart Rhythm Society Scientific Sessions.⁷ In CABANA, 2204 patients were included at 126 sites worldwide (during a 7-year period); all patients were considered candidates for catheter ablation. Patients were randomized to either drug therapy, which could be rate or rhythm control (with use of antiarrhythmic drugs), or to catheter ablation and then at least all pulmonary veins were isolated (some got additional lines ablated). The primary outcome was a composite of clinical events, including death, stroke, serious bleeding, or cardiac arrest. There were also some secondary end points: including quality of life. The primary outcome was seen in 89 patients (8%) randomized to the ablation arm and 101 patients (9.2%) randomized to drug therapy. Catheter ablation did not produce a significant reduction in the primary end point and in all-cause mortality (HR, 0.86; 95% CI, 0.65-1.15; $P=0.3$). None of the components of the primary end point differed significantly. In addition, this trial has some major limitations: 102 patients (9.2%) did not undergo catheter ablation. In the drug therapy group, 301 patients (27.5%) crossed over and did undergo an ablation. Interestingly (and controversially), in a per-protocol analysis, ablation did reduce the rate of the primary end point by 27% (HR, 0.73; 95% CI, 0.54-0.99; $P=0.046$), but this remains very speculative as the trial was not powered to do this analysis. Therefore, we should wait for more data; for example, the results of the EAST trial are expected in the upcoming years. In the meantime, a major change in our current atrial fibrillation ablation practice is not expected.

CONCLUSIONS

In different areas of atrial fibrillation management, important results were published in 2018. Screening for atrial fibrillation is becoming more advanced with smartphone-based apps and watches. Starting anticoagulation is essential in atrial fibrillation and should be carefully performed. Targeted therapies of underlying conditions and lifestyle modifications are important for maintaining long-term rhythm control. Catheter ablation can be safely performed in selected patients with heart failure and atrial fibrillation. Whereas the superiority of catheter ablation was difficult to assess due to high crossover rates and as a reduction in mortality (by rhythm control) has not been proven, atrial fibrillation treatment should remain focused on symptoms and patient preferences. ■

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