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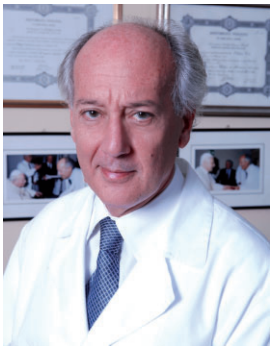
Management of arrhythmias: the increasing role of artificial intelligence, genetics and cardiac resynchronization



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Despite the fact that the electrocardiogram (ECG) has been in use for >100 years and is a central tool in clinical medicine, we are only now beginning to unleash its full potential with the application of artificial intelligence (AI).[1–5] This Focus Issue on arrhythmias contains the State of the Art Review '**Application of artificial intelligence to the electrocardiogram**' by Zachi Attia from the Mayo Clinic, Rochester, MN, USA, and colleagues.[6] The authors note that AI has given the ECG and clinicians reading it superhuman diagnostic abilities. Trained without hard-coded rules by finding often subclinical patterns in huge datasets, AI transforms the ECG, a ubiquitous, non-invasive cardiac test that is integrated into practice workflows, into a screening tool and predictor of cardiac and non-cardiac diseases, often in asymptomatic individuals. This review describes the mathematical background behind supervised AI algorithms and discusses selected AI ECG cardiac screening algorithms including those for the detection of left ventricular dysfunction, episodic atrial fibrillation from a tracing recorded during normal sinus rhythm, and other structural and valvular diseases. The ability to learn from big datasets, without the need to understand the biological mechanism, has created opportunities for detecting non-cardiac diseases such as coronavirus disease 2019 (COVID-19) and introduced challenges with regards to data privacy. Like all medical tests, the AI ECG must be carefully vetted and validated in real-world clinical environments. Finally, with mobile form factors that allow acquisition of medical-grade ECGs from smartphones and wearables, the use of AI may enable massive scalability to democratize healthcare.

Patients with permanent atrial fibrillation (AF) and heart failure (HF) are often treated with pharmacological rate control. However, the optimal rate control in patients with AF and HF is unknown.[7] Not only rapid heart rate but also its irregularity may contribute to symptoms and possibly to impaired prognosis. In patients with AF and HF, strict and regular rate control with atrioventricular junction ablation and biventricular pacemaker has been shown to be superior to pharmacological rate control in reducing HF hospitalizations. In a Fast Track clinical research article entitled '**AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial**', Michele Brignole from the IRCCS Istituto Auxologico Italiano in Milano, Italy, and colleagues point out that whether or not ablation and cardiac resynchronization therapy (CRT) also improve survival is unknown.[8] In this international, open-label, blinded outcome trial, the authors randomly assigned patients with severely symptomatic permanent AF >6 months, narrow QRS (≤110 ms), and at least one HF hospitalization in the previous year to Ablation + CRT or to pharmacological rate control. A total of 133 patients were randomized. The mean age was 73 years, and 47% were females. The trial was stopped for efficacy at interim analysis after a median of 29 months of follow-up per patient. The primary endpoint occurred in 7 patients (11%) in the Ablation + CRT arm and in 20 patients (29%) in the control arm [hazard ratio (HR) 0.26; $P = 0.004$]. The estimated death rates at 2 years were 5% and 21%, respectively; at 4 years, these were 14% and 41%. The benefit of Ablation + CRT on all-cause mortality was similar in patients with ejection fraction (EF) ≤35% and in those with EF >35%. The secondary endpoint combining all-cause mortality or HF hospitalization was significantly lower in the Ablation + CRT arm (HR 0.40; $P = 0.002$) (*Figure 1*).

The authors conclude that Ablation + CRT is superior to pharmacological therapy in reducing mortality in patients with permanent AF and narrow QRS who were hospitalized for HF, irrespective of their baseline EF. The contribution is linked to a thought-provoking **Editorial** by Cecilia Linde from the Karolinska Institutet in Stockholm, Sweden.[9] Linde concludes that the results of APAF-CRT are indeed impressive. With this addition to the APAF-CRT

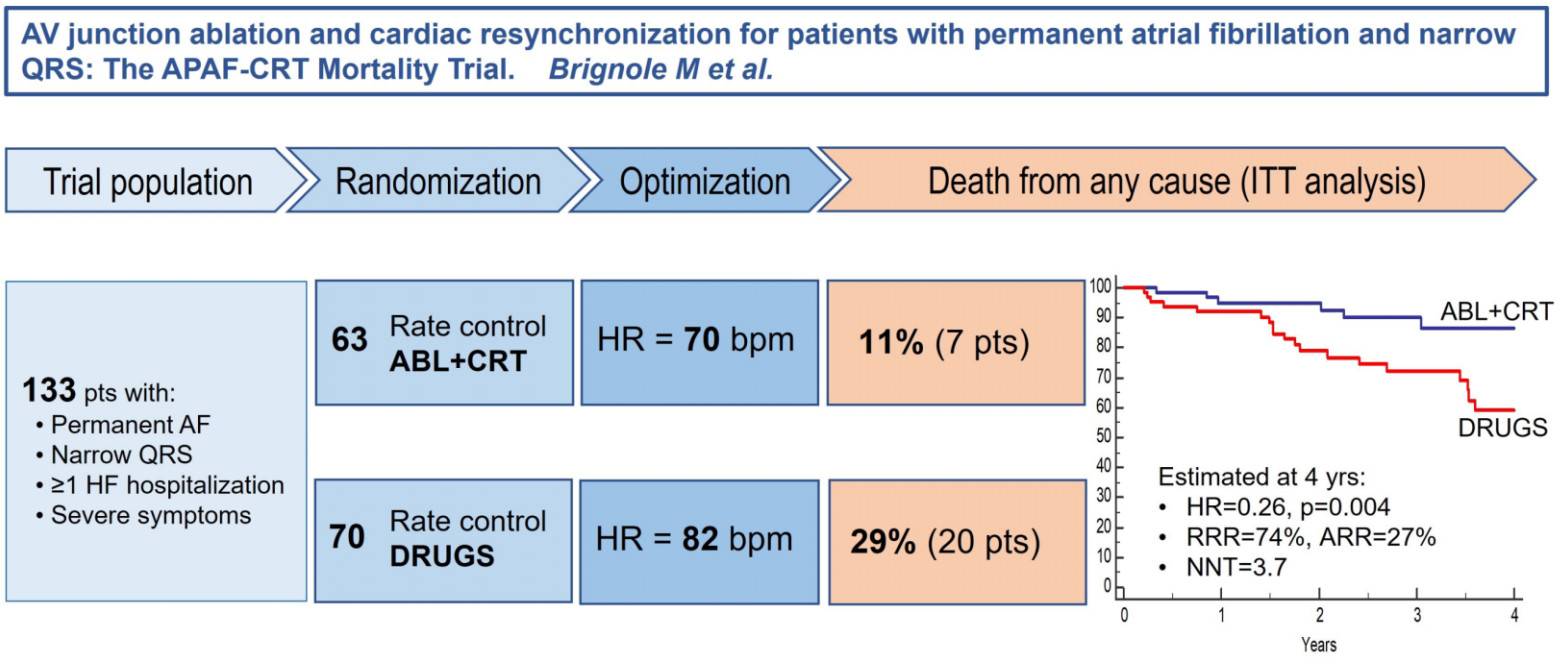

Figure 1 Graphical Abstract (from Brignole M, Pentimalli F, Palmisano P, Landolina M, Quartieri F, Occhetta E, Calo' L, Mascia G, Mont L, Vernooy K, van Dijk V, Allaart C, Fauchier L, Gasparini M, Parati G, Soranna D, Rienstra M, Van Gelder IC; for the APAF-CRT Trial Investigators. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. See pages 4731–4739).

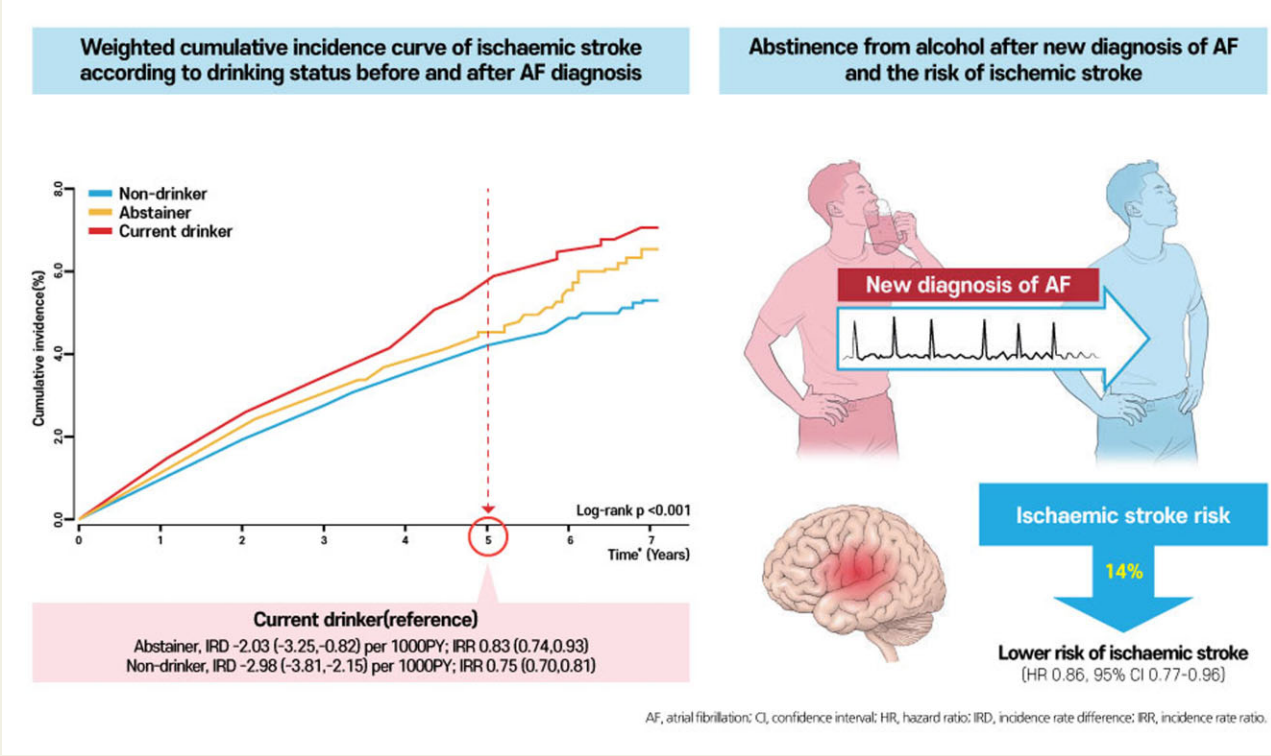

Figure 2 Alcohol abstinence after atrial fibrillation diagnosis could reduce the risk of ischaemic stroke. Lifestyle intervention, including attention to alcohol consumption, should be encouraged as part of a comprehensive approach to atrial fibrillation management to improve clinical outcomes (from Lee SR, Choi EK, Jung JH, Han KD, Oh S, Lip GYH. Lower risk of stroke after alcohol abstinence in patients with incident atrial fibrillation: a nationwide population-based cohort study. See pages 4759–4768).

morbidity trial, we now know that AV junction ablation combined with CRT improves mortality and HF morbidity, and thus is a superior strategy for rate control in elderly HF patients with permanent AF.

In a second Fast Track Clinical Research article entitled '**Mutation location and IKs regulation in the arrhythmic risk of long QT syndrome type 1: the importance of the *KCNQ1* S6 region**', Peter J. Schwartz from the IRCCS in Milan, Italy, and colleagues assessed whether mutations neighbouring p.A341V in the S6 channel segment could increase arrhythmic risk.[10] Clinical and genetic data were obtained from 1316 long QT syndrome type 1 (LQT1) patients (450 families, including 277 patients p.A341V-positive subjects, 139 patients with p.A341-neighbouring mutations, and 900 other LQT1 subjects). A first cardiac event represented the primary endpoint. S6 segment missense variant characteristics, particularly cAMP stimulation responses, were analysed by cellular electrophysiology. p.A341-neighbouring mutation carriers had a QTc shorter than p.A341V carriers (477 ± 33 ms vs. 490 ± 44 ms) but longer than the remaining LQT1 patient population (467 ± 41 ms) ($P < 0.05$ for both). Similarly, the frequency of symptomatic subjects in the p.A341-neighbouring subgroup was intermediate between that of the other two groups (43% vs. 73% vs. 20%; $P < 0.001$). p.A341 and p.A341-neighbouring mutations were associated with a more deleterious arrhythmia phenotype and a poorer cumulative survival than mutations from any other region. The differences in clinical severity can be explained, for p.A341V vs. p.A341-neighbouring mutations by the p.A341V-specific impairment of IKs regulation. The differences between the p.A341-neighbouring subgroup and the rest of LQT1 mutations may be explained by the functional importance of the S6 segment for channel activation.

The authors conclude that while the p.A341V mutation stands out in severity, as previously reported, largely due to its loss of PKA-dependent IKs regulation, all other p.A341-neighbouring mutations tested show an almost normal IKs enhancement. Nonetheless, they do correlate with a more severe phenotype compared to all other LQT1 mutations (although not due to PKA insensitivity). This manuscript is accompanied by an **Editorial** by Andrew Tinker from the Queen Mary University of London in the UK.[11] Tinker concludes that the study by Schwartz and colleagues identifies a series of mutations at and around A341 that lead to worse outcomes than those in other regions of the channel. These mutant complexes do not show impaired PKA regulation, and the exact molecular mechanism will need further experimentation. In addition, as polygenic risk scores are developed for several cardiovascular traits including ventricular arrhythmia, it will be interesting to see whether these can also contribute to additional risk stratification in long QT syndrome and other hereditary arrhythmic syndromes.

Alcohol consumption is associated with an increased risk of incident atrial AF. Not only heavy drinking but also a 'low spectrum of alcohol consumption' could be a risk factor for incident AF. In a Clinical Research article entitled '**Lower risk of stroke after alcohol abstinence in patients with incident atrial fibrillation: a nationwide population-based cohort study**', So-Ryoung Lee from the

Seoul National University Hospital in Korea, and colleagues evaluated the association between alcohol consumption status (and its changes) after newly diagnosed AF and the risk of ischaemic stroke.[12] Using the Korean nationwide claims and health examination database, the authors included subjects who were newly diagnosed with AF between 2010 and 2016. Patients were categorized into three groups according to the status of alcohol consumption before and after AF diagnosis: non-drinkers; abstainers from alcohol after AF diagnosis; and current drinkers. The primary outcome was incident ischaemic stroke during follow-up. Non-drinkers, abstainers, and current drinkers were compared using incidence rate differences after inverse probability of treatment weighting (IPTW). Among a total of >97 000 newly diagnosed AF patients, 51% were non-drinkers, 13% were abstainers, and 36% were current drinkers. During follow-up, 3120 patients were diagnosed with incident ischaemic stroke (10 per 1000 person-years). At 5-year follow-up, non-drinkers and abstainers were associated with a significantly lower risk for stroke than current drinkers (incidence rate ratios after IPTW, 0.75 and 0.83, respectively) (*Figure* 2).

The authors conclude that current alcohol consumption is associated with an increased risk of ischaemic stroke in patients with newly diagnosed AF, while alcohol abstinence after AF diagnosis could reduce the risk of ischaemic stroke. Lifestyle intervention, including attention to alcohol consumption, should be encouraged as part of a comprehensive approach to AF management to improve clinical outcomes. The contribution is linked to an interesting **Editorial** by Andrea Russo from the Cooper University Hospital Camden, NJ, USA.[13] Russo highlights that the authors should be commended on further highlighting the importance of modifiable risk factors, including alcohol intake, in an integrated approach to healthcare delivery for the treatment of AF. In addition to rate control, rhythm control and anticoagulation, risk factor management is now considered the "fourth pillar" of AF care. While more research is needed to identify mechanisms by which alcohol cessation may result in improved outcomes and stroke reduction, an integrated and comprehensive approach to care is essential for patients with AF.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**Prediction of sudden arrhythmic death in patients with heart failure: towards validation in a worldwide broader range of patients**',[14] Ryomo Fukuoka from the School of Medicine, Chiba, Japan, and colleagues comment on the recent publication '**Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score**': by Arwa Younis from the University of Rochester Medical Center in New York, USA, and colleagues.[15] Younis et al. respond in a separate comment.[16]

The editors hope that readers of this issue of the European Heart Journal will find it interesting.

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