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The year in cardiovascular medicine 2022: the top 10 papers in arrhythmias

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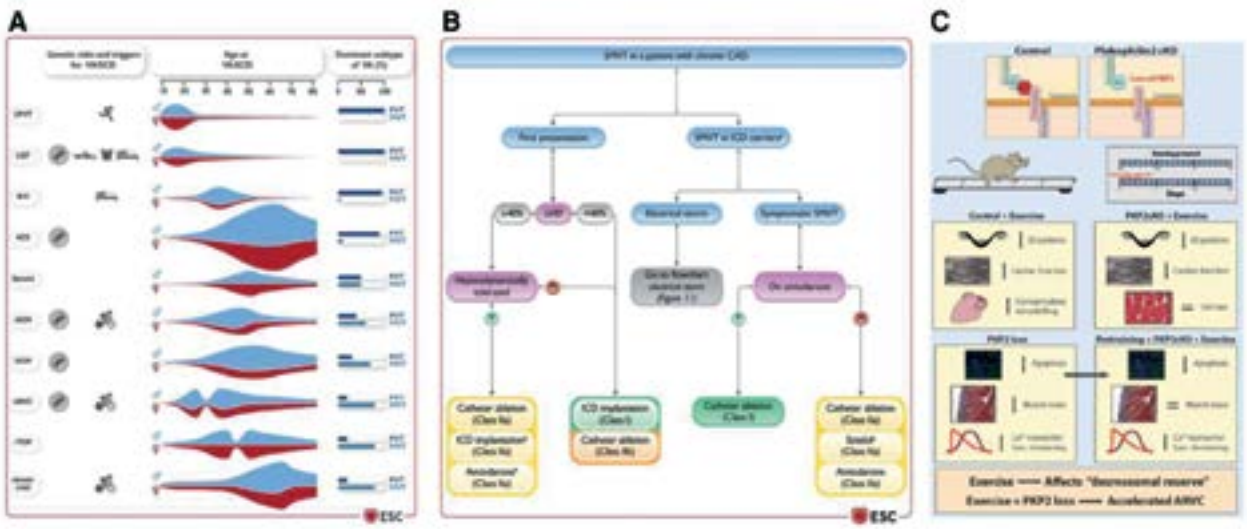

GRAPHICAL ABSTRACT (A) Comprehensive clinical, electrocardiographic, and genetic overview of the various diseases associated with VA or SCD as reported in the 2022 ESC Guidelines for VA and SCD (1). The VA/SCD Guidelines provide many updated recommendations for the management of patients with congenital heart disease, idiopathic VF, acquired Long QT, Brugada and early repolarization syndrome, as well as catecholaminergic polymorphic VT, and short QT syn- drome (B). From the same Guidelines, an algorithm for the management of sustained monomorphic ventricular tachycardia in patients with chronic coronary artery disease (1). The algorithm also holds—in part—for non-ischaemic pathologies. Note, the new VA/SCD Guidelines promote VT ablation significantly. It may e.g. be performed to ameliorate or avoid ICD therapy, or to enhance resynchronization therapy by ablation of frequent mono- morphic PVCs (extrasystolopathy). The trials PARTITA, PAUSE-SCD, and SURVIVE-VT, discussed in the present paper, all strengthen the recommen- dations for application of catheter ablation (5–7) (C). Exercise causes downregulation of genes coding intercalated disk proteins, as well as scaffolding and ion channel proteins, both in normal mice and PKP2 conditional knockouts. Consistent with PKP2-dependent muscle mass deficit, cardiac dimensions in human athletes carrying PKP2 mutations were reduced (data not shown), compared with matched controls. Exercise challenges a cardiomyocyte 'desmosomal reserve' which, if impaired genetically (e.g. Plakophilin2 loss), can cause accelerated progression of the cardiomyopathy (3). Reprinted with permission.

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Top arrhythmia papers – the 2022 ventricular arrhythmia guidelines

Among the top 10 arrhythmia papers are the 2022 ESC guidelines for the management of patients with ventricular arrhythmias (VAs) and the prevention of sudden cardiac death (SCD) (1). The Guidelines summarizing figure provides a comprehensive clinical, electrocardiographic, and genetic overview of the various diseases associated with VA or SCD *(Graphical Abstract, A)*. They promote public access to defibrillation supported by mobile health and a much larger role in catheter ablation *(Graphical Abstract, B)*. Also, multiple recommendations are provided on the use of CMR and genetic testing to improve diagnosis and steer therapy for several cardiomyopathies in particular if specific risk features are present. To enhance efficient ICD therapy in cardiomyopathies, novel risk factor-based recommendations are provided (1).

Crossing borders – imaging and arrhythmias

The increasing role of CMR in VAs contrasts with the negative rando mized DECAAF trial in persistent atrial fibrillation (AF) indicating that CMR-steered ablation targeting gadolinium late-enhanced potentially arrhythmogenic atrial areas does not impact recurrences compared with standard pulmonary vein isolation, and the extended approach may even be associated with stroke (2). At present, atrial CMR is not robust enough in identifying relevant ablation targets. Studies linking CMR findings with electro-anatomic and functional arrhythmogenesis are clearly needed including studies into electrophysiologic and pathological effects of ablation in socalled fibrotic tissue.

Translational papers – arrhythmogenic right ventricular cardiomyopathy

How exercise aggravates arrhythmogenic right ventricular cardiomyopathy (ARVC) is not well known. In their translational study, *Cerrone et al* (3) speculate that exercise challenges a cardiomyocyte's desmosomal reserve which, if impaired genetically [e.g. plakophilin (PKP2) loss], accelerates the progression of cardiomyopathy *(Graphical Abstract, C)*. Desmosomes not only regulate cell–cell mechanical coupling but also play a significant role in cell signaling regulating cell proliferation, apoptosis, electrolyte signaling, and mitochondrial and metabolic functioning. When desmosomal reserve is reduced, myocytes are not well protected by their desmosomes against the effects of exercise leading to cell death and arrhythmias (3).

One clinical study in ARVC highlighted for the first time that desmosomal mutation status plays a key role in the risk of VA events, whilst previous risk models have focused on ventricular function, PVC burden, and ECG biomarkers (4). Patients with a definite diagnosis of ARVC and no history of sustained VAs were followed for a mean of 6 years. Classical risk estimates for VA using the 2019 ARVC risk model showed reasonable discriminative ability but overestimated VA risk. Four gene groups were studied: plakophilin-2 (PKP2), desmoplakin (DSP), other desmosomal, and geneelusive patients. PKP2 had the highest discrimination and calibration of risk while these were lowest in geneelusive patients. Interestingly, clinical markers performed differently in the specific gene groups e.g. right ventricular dimensions and systolic function are significant risk markers in PKP2 but not in DSP patients and the opposite was true for left ventricular systolic function. Overall, the 2019 ARVC risk model performed reasonably well in genepositive ARVC (particularly for PKP2) but is more limited in geneelusive patients. This study highlights that gene status should be included in future risk models for ARVC. Furthermore, there still needs to be independent cohort comparisons of risk models in ARVC, a major challenge for all rare diseases.

Novel, read all about it! – randomized VT ablation studies

In the field of VT ablation, three randomized controlled trials were published this year focusing on the timing of VT ablation, either first-line pre-emptive ablation at the time of ICD implantation5 or after the first ICD therapy (6, 7) *(Graphical Abstract, B)*. PARTITA randomized 56 patients with ischaemic and non-ischaemic cardiomyopathy to ablation vs. medical therapy after their first appropriate ICD shock. Interestingly, amiodarone was not allowed (6). No deaths occurred in the ablation group vs. eight deaths (33%) in the control group (P = 0.004); there were one (4%) and four (17%) worsening heart failure hospitalizations, respectively; P = 0.159. ICD shocks were less frequent in the ablation group (9%) than in the control group (42%; P = 0.039). The ablation strategy employed an extensive substrate-modification approach with multiple inductions of VT to ensure non-inducibility which almost certainly contributed to the positive outcome in highly experienced centres of excellence for VT ablation. The fact that mor tality was reduced by early VT ablation is a key observation but not proven in previous randomized trials. In SURVIVE-VT, 144 patients with ischaemic cardiomyopathy who suffered ICD shock, had syncopal VT or monomorphic VT needing ICD, were randomized to complete endocardial substrate-based catheter ablation or antiarrhythmic therapy (amiodarone, sotalol, beta-blockers). The primary outcome was a composite of cardiovascular death, appropriate ICD shock, unplanned hospitali-

zation for worsening heart failure, or severe treatment-related complications. After 24 months, the primary outcome occurred in 28.2% of patients in the ablation group and 46.6% of those in the AAD group (7). This difference was driven by a significant reduction in severe antiarrhythmic treatment-related complications, in particular slow or incessant VT. In the PAUSE-SCD trial, 121 patients comprising 35% ischaemic, 30% non-ischaemic, and 35% ARVC, were randomly assigned (1:1) to ablation vs. conventional medical therapy at the time of ICD implantation (5). The primary outcome was a composite endpoint of VT recurrence, cardiovascular hospitalization, or death. At 31 months, the primary outcome occurred in 49.3% of the ablation group and 65.5% in the control group (P = 0.04). The observed difference was driven by a reduction in VT recurrence in the ablation arm (P = 0.02). Similar results were seen in a non-ICD registry arm receiving ablation. No differences in cardiovascular hospitalization or mortality occurred and 8.3% of patients had ablation-related complications (5). Although all these studies were relatively small (5–7) and had very long inclusion periods (6, 7) their findings promote early ablation of VT in ICD carriers at risk of recurrences, with PARTITA and PAUSE-SCD helping to expand early VT ablation to structural heart disease other than ischaemic cardiomyopathy (5, 6). The fact there was a significant complication burden needs to be minimized especially if first-line ablation is to develop traction more widely. Since AAD complications drove the outcomes in SURVIVE-VT, this indicates that these drugs especially amiodarone are not an optimal alternative in a high proportion of patients. The challenge is to achieve successful ablation with minimal complications in these often fragile patients as it is clear that ablation is certainly effective in reducing VA events. However, newer heart failure medications including SGLT2 inhibitors and sacubitril-valsartan mean the background risk is changing.

And more news – stroke prevention in atrial fibrillation

In 2022, three innovative and guideline-relevant arrhythmia papers dealt with stroke prevention in AF. Patients with inherited factor XI deficiency do not suffer from spontaneous bleeding and may have lower rates of cardiovascular events, including cardioembolic stroke. This seeming paradox may relate to FXIa contributing to clot progression but not to clot consolidation. In the dose-finding PACIFIC-AF trial, 20 and 50 mg of asundexian reliably suppressed activated coagulation factor XI (FXIa) with once-daily dosing and resulted in significantly lower rates of bleeding compared with apixaban (8). Therefore, FXIa may represent a novel therapeutic target for clot prevention across a variety of thromboembolic diseases significantly avoiding the bleeding side effect which remains to be seen in larger clinical outcome studies. The randomized non-inferiority INVICTUS trial fills an evidence gap in the application of non-vitamin K oral anticoagulants (NOACs) in AF and is very relevant to countries with a high prevalence of rheumatic heart disease-related AF (9). Patients with AF and echocardiographically documented rheumatic heart disease (including moderate to severe mitral stenosis in over 80%) were randomized to vitamin K antagonist (VKA) therapy or 20 mg rivaroxaban daily. Vitamin K antagonist led to a lower rate of the composite of cardiovascular events or death (in particular sudden death and mechanical or pump failure death) than rivaroxaban, without a higher rate of bleeding. Vitamin K antagonist patients were regularly monitored for INR and for that reason may have received better care overall; whilst randomized therapy (and any anticoagulation) was stopped more often in the NOAC arm.
Nevertheless, trial results indicate that VKAs should be the preferred oral anticoagulants over NOACs (9). The third study in this area was RAFAS, an open-label randomized clinical trial comparing early rhythm con-

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trol with usual AF care in 273 patients with newly documented AF in the setting of an acute ischaemic stroke (10). Re-stroke rate at 12 months after index stroke was lower in the early rhythm control group [3 (1.7%) vs. 6 patients (6.3%)] whilst overall mortality, any hospitalization, and arrhythmia-related events did not differ. Sustained AF at 12 months was less frequent under early rhythm control (34%) compared with usual care (63%). Although small-scale and open-label, the study addressed an important clinical problem since the re-stroke rate is high in acute ischaemic stroke particularly when it is complicated by new-onset AF. In these patients, rhythm control is generally not considered whilst RAFAS suggests early ablation may be beneficial (10). Larger well-controlled clinical trials on catheter ablation in patients with AF detected early after acute ischaemic stroke are definitely needed to settle the issue.

Conclusion

In conclusion, in 2022 several important trials and translational studies have been published in the top cardiovascular journals to push knowledge in the arrhythmia field promisingly forward. They will not only contribute to future cardiovascular guidelines but will also form stepping stones for novel translational research stimulating advances in our field.

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