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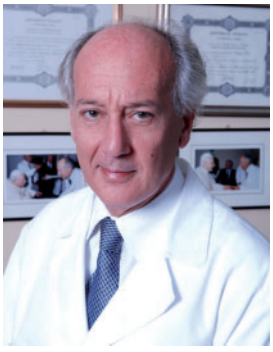
The growing role of artificial intelligence and of wearable devices in the management of arrhythmias



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Artificial intelligence (AI) is being applied in various fields of cardiology. The primary advantage of AI is its ability to discover features of certain data that cannot be discovered from a human perspective.[1,2] This Focus Issue on Arrhythmias contains the State of the Art Review article '**Artificial intelligence in the diagnosis and management of arrhythmias**' by Venkat Nagarajan from the Royal Brompton and Harefield NHS Foundation Trust, UK, and colleagues.[3] The authors note that the field of cardiac electrophysiology (EP) has adopted simple AI methodologies for decades. Recent renewed interest in deep learning techniques has opened up new frontiers in electrocardiography analysis including signature identification of diseased states. Advances in AI, coupled with simultaneous rapid growth in computational power, sensor technology, and availability of web-based platforms, have seen the rapid growth of AI-aided applications and big data research. Changing lifestyles with an expansion of telecommunication technology have opened doors to population-based detection of atrial fibrillation (AF) in ways which were previously unimaginable. AI-aided advances in 3D cardiac imaging heralded the concept of virtual hearts and the simulation of cardiac arrhythmias. Robotics, completely non-invasive ablation therapy, and the concept of extended realities show promise to revolutionize the future of EP. In this review, the authors discuss the impact of AI and recent technological advances in all aspects of arrhythmia care.

With the explosion of anticancer drugs which have substantially improved the outcomes of cancer patients, an emerging concern is the risk for cancer and drug-associated cardiovascular diseases.[4–7] In a clinical research article entitled '**Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study**', Joe-Elie Salem from the UNICO-GRECO Cardio-Oncology Program in Paris, France, and colleagues used the international pharmacovigilance database VigiBase (>18 000 000 reports) to compare drug-induced long QT (diLQT) and ventricular arrhythmias (VAs) reporting for 663 anticancer drugs vs. all other drugs.[8] The analysis used the 95% lower end credibility interval of the information component (IC025), an indicator for disproportionate Bayesian reporting, which is significant when IC025 is >0. There were 2301 reports (14% fatal) for 40 anticancer drugs significantly associated with diLQT, with 27 also associated with VAs or sudden cardiac death (SCD) and 9 drugs associated with VAs without diLQT. Most (41%) were kinase inhibitors, 8% were hormonal therapies, 6% were immunotherapies, 24% were cytotoxics, and 21% were miscellaneous. In VigiBase, reports of diLQT, torsade de pointe, or VAs increased from 580 in the period 1967–1983 to >15 000 in 2014–2018, with the proportion related to anticancer drugs increasing from 0.9% to 14.0% ($P < 0.0001$). Twenty-three drugs represented new signals (*Figure 1*).

Thus, the authors propose a three-level SCD risk stratification relying on isolated long QT (low risk), associated with VA without SCD (moderate risk), and VA with SCD (high risk). The contribution is accompanied by an **Editorial** by Michael G. Fradley and Lohit Garg from the Perelman School of Medicine at the University of Pennsylvania, USA.[9] The authors conclude that the results of this study significantly enhance our understanding of the potential for QT prolongation and VAs associated with anticancer drugs which parallels the rapid expansion of novel cancer treatments over the last decade. While we must remain vigilant in monitoring our patients, it is also essential that we standardize our approach to QT monitoring and continue to develop and refine risk prediction models to minimize arrhythmic complications without unnecessary cessation of potentially life-saving cancer therapy.

Patients with hypertrophic cardiomyopathy (HCM) have a higher risk of sudden death.[10–12] Risk stratification algorithms for SCD in HCM and regional differences in clinical practice have evolved over time. In a clinical article entitled '**Worldwide differences in primary prevention implantable cardioverter defibrillator**

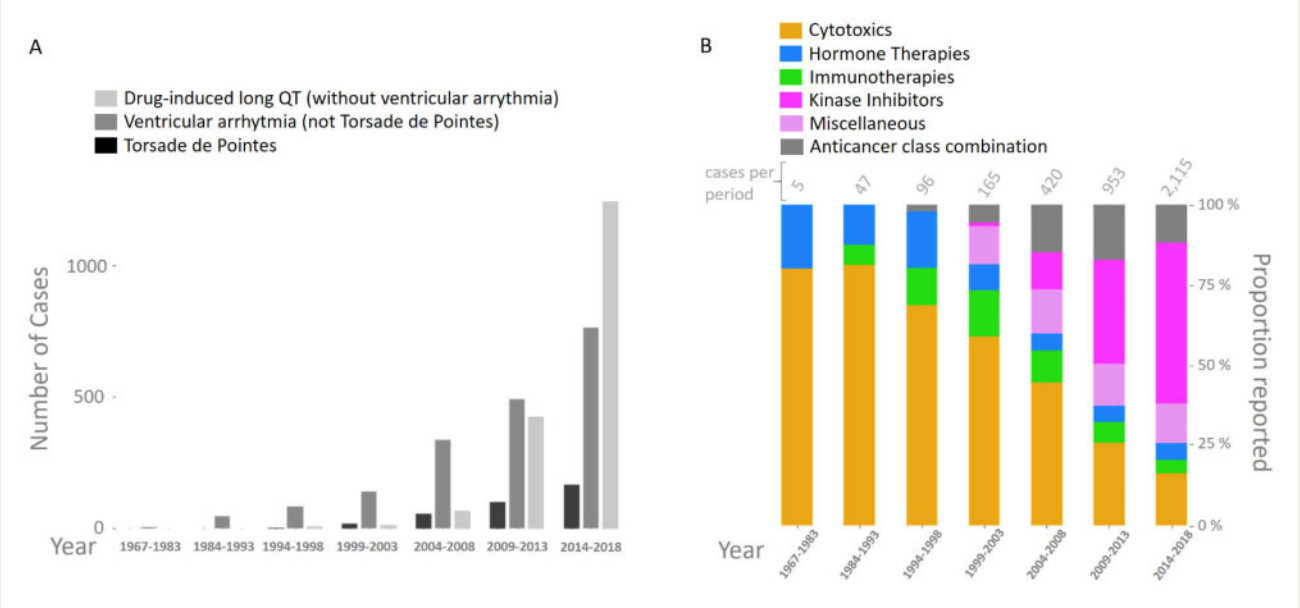

Figure 1 Graphical Abstract (from Salem JE, Nguyen LS, Moslehi JJ, Ederhy S, Lebrun-Vignes B, Roden DM, Funck-Brentano C, Gougis P. Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study. See pages 3915–3928).

utilization and outcomes in hypertrophic cardiomyopathy', Carolyn Ho from Brigham and Women's Hospital in Boston, Massachusetts, USA, and colleagues sought to compare primary prevention implantable cardioverter defibrillator (ICD) implantation rates and associated clinical outcomes in US vs. non-US tertiary HCM centres within the international Sarcomeric Human Cardiomyopathy Registry (SHaRe).[13] The authors included patients with HCM enrolled from eight US (n = 2650) and five non-US (n = 2660) sites, and used multivariable Cox proportional hazards models to compare outcomes between sites. Primary prevention ICD implantation rates in US sites were two-fold higher than in non-US sites [hazard ratio (HR) 2.27], including in individuals deemed at high 5-year SCD risk (≥6%) based on the HCM Risk-SCD score (HR 3.27). US ICD recipients also had fewer traditional SCD risk factors. Among ICD recipients, rates of appropriate ICD therapy were significantly lower in US than in non-US sites (HR 0.52). No significant difference was identified in the incidence of SCD/resuscitated cardiac arrest among non-recipients of ICDs in US vs. non-US sites (HR 1.21)

The authors conclude that primary prevention ICDs are implanted more frequently in patients with HCM in US vs. non-US sites across the spectrum of SCD risk. There was a lower rate of appropriate ICD therapy in US sites, consistent with a lower risk population, and no significant difference in SCD in US vs. non-US patients who did not receive an ICD. This manuscript is accompanied by an **Editorial** by Perry Elliott from UCL in London, UK.[14] Professor Elliott concludes that the quest to find new risk predictors in HCM will continue, but low event rates and disease heterogeneity will make prospective validation of prognostic biomarkers extremely challenging. In the short to medium term, the best we can expect is a recalibration of existing models with routinely collected data including left ventricular function and genotype, while recognizing that overtreatment with ICDs will be the norm. This puts a huge onus on industry to redouble the effort to mitigate the downsides of ICD therapy. More optimistically, a plethora of emerging disease-modifying strategies including small molecules and gene therapies create new horizons in patient care that—in the same way that drug therapies reduce arrhythmic and heart failure deaths in patients with left ventricular systolic dysfunction—offer new opportunities for the improvement of survival and quality of life of patients with HCM.

Congenital long-QT syndromes (cLQTSs) or drug-induced long-QT syndromes (diLQTSs) can cause torsade de pointes (TdP), a life-threatening ventricular arrhythmia.[15–17] The current strategy for the identification of drugs at high risk of causing TdP relies on measuring the QT interval corrected for heart rate (QTc) on the electrocardiogram (ECG). However, QTc has a low positive predictive value. In a clinical research article entitled '**Deep learning analysis of electrocardiogram for risk prediction of drug-induced arrhythmias and diagnosis of long QT syndrome**', Edi Prifti from INSERM in Paris, France, and colleagues used convolutional neural network (CNN) models to quantify ECG alterations induced by sotalol, an IKr blocker associated with TdP, aiming to provide new tools (CNN models) to enhance the prediction of drug-induced TdP (diTdP) and diagnosis of cLQTS.[18] Tested CNN models used single or multiple 10 s recordings/patient using eight leads or single leads in various cohorts: 1029 healthy subjects before and after sotalol intake; 487 cLQTS patients; and 48 patients with diTdP. CNN models outperformed models using QTc to identify exposure to sotalol [area under the receiver operating characteristic curve (ROC-AUC) = 0.98 vs. 0.72, $P \leq 0.001$]. CNN models had a higher ROC-AUC using multiple vs. a single 10 s ECG ($P \leq 0.001$). Performances were comparable for eight-lead vs. single-lead models. CNN models predicting sotalol exposure also accurately detected the presence and type of cLQTS vs. healthy controls, particularly for cLQT2 (AUC-ROC =

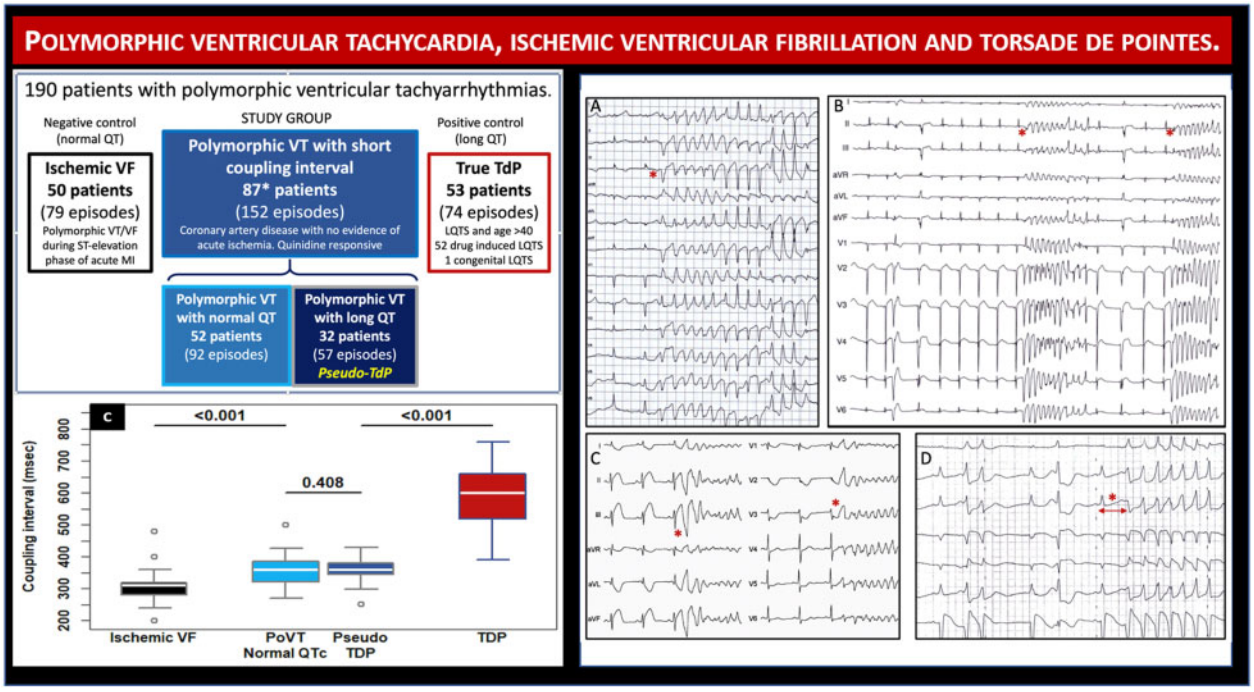

Figure 2 Graphical Abstract (from Rosso R, Hochstadt A, Viskin D, Chorin E, Schwartz AL, Tovia-Brodie O, Laish-Farkash A, Havakuk O, Gepstein L, Banai S, Viskin S. Polymorphic ventricular tachycardia, ischaemic ventricular fibrillation, and torsade de pointes: importance of the QT and the coupling interval in the differential diagnosis. See pages 3965–3975).

0.9), and were greatest shortly after a diTdP event and declined over time ($P \leq 0.001$), after controlling for QTc and intake of culprit drugs.

The authors conclude that CNN models applied to ECGs outperform QTc measurements to identify exposure to drugs altering the QT interval and cLQTS, and are greatest shortly after a diTdP episode. The contribution is accompanied by an **Editorial** by Peter Schwartz from the Istituto Auxologico Italiano Istituto di Ricovero e Cura a Carattere Scientifico in Milan, Italy and Hanno Tan from the University of Amsterdam, the Netherlands.[19] The authors conclude that the study by Prifti *et al.* has the potential of being groundbreaking conceptually and in its translational impact. Indeed, the possibility that the risk of life-threatening arrhythmia might be reduced by involving patients in monitoring their own risk with an easy-to-use wearable device that uses AI to detect tell-tale ECG changes well in time for them to call on their physician and for the physician to take appropriate life-saving actions may no longer belong to science fiction.

Distinctive types of polymorphic ventricular tachycardia (VT) respond differently to different forms of therapy.[20] In a clinical research article entitled '**Polymorphic ventricular tachycardia, ischaemic ventricular fibrillation, and torsade de pointes: importance of the QT and the coupling interval in the differential diagnosis**', Raphael Rosso from Tel Aviv University in Israel, and colleagues performed the present study to define the ECG characteristics of different forms of polymorphic VT.[21] The authors studied 190 patients for whom the onset of 305 polymorphic VT events was available. The study group included 87 patients with coronary artery disease who had spontaneous polymorphic VT triggered by short-coupled extrasystoles in the absence of myocardial ischaemia. This group included 32 patients who had a long QT interval but nevertheless had their polymorphic VT triggered by ectopic beats with a short coupling interval—a subcategory termed 'pseudo-torsade-de-pointes'. For comparison, Rosso and colleagues included 50 patients who had ventricular fibrillation (VF) during acute myocardial infarction ('ischaemic-VF' group) and 53 patients with drug-induced TdP ('true-TdP' group). The QT of patients with pseudo-TdP was (by definition) longer than that of patients with polymorphic VT and normal QT (QTc 491 ms vs. 447 ms, $P < 0.001$). However, their QT was significantly shorter than that of patients with true-TdP (QTc 565 ms, $P < 0.001$). Importantly, the coupling interval of the ectopic beat triggering the arrhythmia was just as short during pseudo-TdP as during polymorphic VT with normal QT (359 ms vs. 357 ms, $P = 0.467$) but was much shorter than during true-TdP (581 ms, $P < 0.001$) (*Figure 2*).

Rosso *et al.* conclude that the coupling interval helps discriminate between polymorphic VT that occurs despite a long QT interval (pseudo-TdP) and polymorphic arrhythmias striking because of a long QT (true-TdP). The manuscript is accompanied by an **Editorial** by Christian van der Werf from the Amsterdam Universitair Medische Centra in the Netherlands and Pier Lambiase from the University College London in the UK.[22] van der Werf and Lambiase congratulate the authors on providing new and clinically relevant

insights even after decades of publications on ventricular tachyarrhythmias. They indicate that these new insights into polymorphic VTs have been made possible simply by going back to the carefully curated series of ECGs that they have collected over the years, hence re-establishing an approach using a historical simple investigation in the modern era.

The relationships between physical activity and AF are complex.[23,24] In a clinical research article entitled '**Day-to-day measurement of physical activity and risk of atrial fibrillation**', Mathias Pinto Bonnesen from the Copenhagen University Hospital in Denmark, and colleagues investigated the association between within-individual changes in physical activity and onset of AF.[25] A total of 1410 participants from the general population with risk factors but with no prior AF diagnosis underwent continuous monitoring for AF episodes along with daily accelerometric assessment of physical activity using an implantable loop recorder during ~3.5 years. The combined duration of monitoring was ~1.6 million days, where 10 851 AF episodes lasting ≥60 min were detected in 361 participants (26%). The median daily physical activity was 112 min/day. A dynamic parameter describing within-individual changes in daily physical activity, i.e. average daily activity in the last week compared with the previous 100 days, was computed and used to model the onset of AF. A 1 hour decrease in average daily physical activity was significantly associated with AF onset the next day (odds ratio 1.24). This effect was modified by overall level of activity ($P < 0.001$ for interaction), and the signal was strongest in the tertile of participants with lowest activity overall.

The authors conclude that within-individual changes in physical activity are associated with the onset of AF episodes as detected by continuous monitoring in a high-risk population. The manuscript is accompanied by an **Editorial** by Dominik K. Linz from the University of Adelaide in Australia, and colleagues.[26] Linz *et al.* conclude that despite several limitations, the current study is encouraging in that (i) it makes a valuable contribution to our understanding of how we can draw upon the vast quantity of data being recorded with implantable devices, and (ii) it enhances our understanding about how risk factors and lifestyle behaviours vary on a day-to-day basis, which may determine the daily AF risk and thereby the daily AF pattern. This enables us to take a glimpse into the future, in which the rapid growth of wearables may enable real-time monitoring of risk factors prior to the onset of AF. A key question is then whether we can use this longitudinal risk factor and lifestyle monitoring to guide interventions to keep AF away. Clearly there are several significant steps that need to be taken before this occurs, but the efficacy of risk factor management in this population, coupled with the growth of wearable devices that permit the detection of AF and longitudinal monitoring of lifestyle components simultaneously, makes this a very real possibility.

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

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