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The road goes ever on: innovations and paradigm shifts in atrial fibrillation management

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Symptoms suggestive of atrial fibrillation (AF) have been described for centuries, and William Harvey already noted an undulating palpitation of the right auricle in animals in 1628.¹ However, it was not until 1906 that the Dutch physician and physiologist Willem Einthoven published the first electrocardiogram showing AF in a patient and it took several more years before AF was recognized as a clinical entity.² Today, in 2021, AF remains a major clinical challenge, negatively affecting the morbidity and mortality of millions of individuals worldwide³ and consuming a significant share of the healthcare budget in the Western world.⁴ Since the initial reports of 'rebellious palpitations',² our understanding of the underlying mechanisms, debilitating consequences and therapeutic management of AF have advanced tremendously. The progress has been particularly rapid during the last 40 years: in 1980, there were 221 papers published on AF according to PubMed, but by 2020 this number had increased to 7849 papers in 1 year. Together, this research has led to a number of important innovations and paradigm shifts in AF management.

The work of Prof. Harry J.G.M. Crijns, first at the University of Groningen and thereafter at Maastricht University, where he was appointed as the chairman of the department of cardiology in 2001, has contributed significantly to these innovations and paradigm shifts. This *Europace* supplement, bringing together a number of reviews that highlight some of these innovations and paradigm shifts in AF management, was established on the occasion of his retirement in December 2020.

Although Harry Crijns' most notable contributions are in clinical AF management, he has also been extensively involved in translational studies assessing the fundamental mechanisms of AF. For example, in collaboration with Prof. Maurits Allesie, he employed the famous goat model of AF to demonstrate that verapamil reduces AF-related remodelling, whereas digoxin worsens remodelling.^{5,6} He was also among the first to demonstrate differences in the expression

of various genes and proteins in atrial tissue between patients with paroxysmal and persistent AF and patients in sinus rhythm,⁷ providing insight into primary (causal) and secondary components of atrial remodelling. Translational studies such as these have revealed a plethora of potential AF mechanisms promoted by a complex interplay between genetic susceptibility and atrial remodelling resulting from advancing age, concomitant cardiovascular and non-cardiovascular diseases, as well as by AF itself. In this issue, Rienstra *et al.*⁸ summarize the most important paradigm shifts in the field of AF genetics and describe the future role of genetics in personalized AF management. Furthermore, Schotten *et al.*⁹ describe the importance and challenges involved in the interpretation of electrograms in AF mapping for understanding AF mechanisms, as well as providing the 'Maastricht' and 'Cleveland' perspectives on AF mechanisms.

Conceptually, a better understanding of AF mechanisms would be expected to facilitate the development of safer, more effective treatment options. Evaluating AF therapy in order to improve outcome and quality of life for his AF patients has been a central theme in Harry Crijns' career. Among other things, he conceived and co-coordinated the 'RATE Control vs. Electrical cardioversion for persistent atrial fibrillation' (RACE) studies.¹⁰ The first of the RACE trials established, together with the AFFIRM study from North-America that was published in the same issue of the *New England Journal of Medicine*, that a rate-control strategy was non-inferior to a rhythm-control strategy.^{11,12} Despite this initial setback for rhythm control, Harry Crijns remained actively involved in improving rhythm-control therapy. He contributed significantly to innovations in antiarrhythmic drug therapy, notably the clinical development and evaluation of dronedarone,¹³ as well as AF ablation, e.g. pioneering the collaboration between cardiologists and cardiothoracic surgeons to enable hybrid AF ablation.¹⁴ In this issue, Heijman *et al.*¹⁵ summarize important milestones in

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antiarrhythmic drug research that have shaped their current role in AF management, including awareness about the proarrhythmic potential and pleiotropic effects of antiarrhythmic drugs. Mulder *et al.*¹⁶ give an overview of the evolution of catheter ablation, highlighting the latest technologies, future developments, as well as the importance of patient selection. Maesen *et al.*¹⁷ review the history of the different surgical approaches for treating AF and discuss the benefits of hybrid AF ablation. These advances in antiarrhythmic drugs and ablation, together with a better understanding of the negative impact of AF progression on therapeutic success, have recently prompted a reappraisal of (early) rhythm-control therapy. The EAST-AFNET-4 trial, in which Harry Crijns was one of the co-ordinating investigators, showed that early rhythm-control therapy in patients with recently diagnosed AF was indeed associated with a lower risk of adverse cardiovascular outcomes than usual care.¹⁸ In this issue, Reissmann *et al.*¹⁹ describe the 'RACE to EAST'; explaining the insights and advances obtained since the first RACE trial that provided the rationale for the EAST-AFNET-4 trial.

Finally, Harry Crijns has increasingly focused on comprehensive AF management, e.g. arguing that AF is a vascular disease.¹⁰ In agreement, the RACE 3 trial showed that targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent AF.²⁰ Thus, identification of the dynamic drivers of AF-related complications holds promise for stratified therapy.²¹ In this issue, Linz *et al.*²² summarize strategies and mHealth approaches for early AF detection and the subsequent transition to early comprehensive AF management. Furthermore, Hendriks *et al.*²³ review the evidence for the role of risk-factor management as an essential pillar in the treatment of patients with AF and evaluate how this can be best integrated into routine clinical practice. Harry Crijns has similarly emphasized the importance of the interplay between AF and heart failure, stating that 'the greatest challenge is to bridge the disconnect between the world of arrhythmologists and heart failure cardiologists'.¹⁰ This topic is addressed by Verhaert *et al.*,²⁴ who review the bidirectional interaction between AF and heart failure, as well as the consequences for the management of both diseases.

Together, the review articles in this supplement highlight the progress that has been made in the management of AF during the last few decades. The resultant paradigm shifts have contributed to the favourable trends in outcomes for patients with AF that have been observed in long-term registries.²⁵ Indeed, Harry Crijns himself recently presented a comparison of outcomes between the RACE and RACE II trials, revealing a significant decrease in stroke and cardiovascular mortality in the decade between these two trials.¹⁰ Nonetheless, it is clear that numerous challenges remain.²⁶ As such, like in the novels by J.R.R. Tolkien, 'the road goes ever on' for AF research. Harry Crijns has demonstrated that by addressing knowledge gaps through effective (inter)national collaborations and by implementing recent innovations and discoveries into routine clinical practice, AF management can be improved, with tangible benefits for patients. We believe that his work will provide a foundation for many more future innovations and improvements in AF management and wish him all the best for his post-retirement career.

Conflict of interest: none declared.

Data availability

This editorial does not contain original data.

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