

University of Groningen

The road goes ever on

Heijman, Jordi; Vernooy, Kevin; C van Gelder, Isabelle

Published in:
Europace

DOI:
[10.1093/europace/euab061](https://doi.org/10.1093/europace/euab061)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Heijman, J., Vernooy, K., & C van Gelder, I. (2021). The road goes ever on: innovations and paradigm shifts in atrial fibrillation management. *Europace*, 23(2), 1-3. <https://doi.org/10.1093/europace/euab061>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

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

Jordi Heijman ^{1*}, Kevin Vernooij ^{1,2}, and Isabelle C. van Gelder ³

¹Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Faculty of Health, Medicine, and Life Sciences, Maastricht University and Maastricht University Medical Center+, PO Box 616, 6200 MD Maastricht, The Netherlands; ²Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands; and ³Department of Cardiology, Thoraxcentre, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

Received 18 February 2021; editorial decision 19 February 2021; accepted after revision 25 February 2021

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

* Corresponding author. Tel: +31 43 38 76046. E-mail address: jordi.heijman@maastrichtuniversity.nl

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2021. For permissions, please email: journals.permissions@oup.com.

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.

References

- McMichael J. History of atrial fibrillation 1628-1819 Harvey - de Senac - Laennec. *Br Heart J* 1982;**48**:193-7.
- Fazekas T, Liszakai G, Bielik H, Luderitz B. [History of atrial fibrillation]. *Z Kardiol* 2003;**92**:122-7.
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021; **42**:373-498.
- Burdett P, Lip GYH. Atrial fibrillation in the United Kingdom: predicting costs of an emerging epidemic recognising and forecasting the cost drivers of atrial fibrillation-related costs. *Eur Heart J Qual Care Clin Outcomes* 2020;doi: 10.1093/ehjqcco/qcaa093.
- Tieleman RG, De Langen C, Van Gelder IC, de Kam PJ, Grandjean J, Bel KJ et al. Verapamil reduces tachycardia-induced electrical remodeling of the atria. *Circulation* 1997;**95**:1945-53.
- Tieleman RG, Blaauw Y, Van Gelder IC, De Langen CD, de Kam PJ, Grandjean JG et al. Digoxin delays recovery from tachycardia-induced electrical remodeling of the atria. *Circulation* 1999;**100**:1836-42.
- Brundel BJ, van Gelder IC, Henning RH, Tuinenburg AE, Deelman LE, Tieleman RG et al. Gene expression of proteins influencing the calcium homeostasis in patients with persistent and paroxysmal atrial fibrillation. *Cardiovasc Res* 1999;**42**: 443-54.
- Rienstra M, Siland JE, Ellinor PT. Role of genetics in atrial fibrillation management. *Europace* 2021;**23**(Suppl 2):ii4-ii8.
- Schotten U, Lee S, Zeemering S, Waldo AL. Paradigm shifts in electrophysiological mechanisms of atrial fibrillation. *Europace* 2021;**23**(Suppl 2):ii9-ii13.
- Crijns H, Van Gelder IC. Paradigm shifts in pathophysiology and management of atrial fibrillation—a tale of the RACE trials in the Netherlands. *Neth Heart J* 2020;**28**:3-12.
- Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T et al.; Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**: 1834-40.
- Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB et al.; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825-33.
- Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668-78.
- Pison L, La Meir M, Crijns HJ. Hybrid therapy for atrial fibrillation—optimizing treatment strategies. *J Atr Fibrillation* 2013;**6**:857.
- Heijman J, Hohnloser SH, Camm AJ. Antiarrhythmic drugs for atrial fibrillation: lessons from the past and opportunities for the future. *Europace* 2021;**23** (Suppl 2):ii14-ii22.
- Mulder BA, Luermans JGLM, Hindricks G, Blaauw Y. Innovations and paradigm shifts in atrial fibrillation ablation. *Europace* 2021;**23**(Suppl 2):ii23-ii27.
- Maesen B, Luermans JGLM, Bidar E, Chaldoupi S-M, Gelsomino S, Maessen JG et al. A hybrid approach to complex arrhythmias. *Europace* 2021;**23**(Suppl 2): ii28-ii33.
- Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A et al.; EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305-16.
- Reissmann B, Breithardt G, Camm AJ, Van Gelder IC, Metzner A, Kirchhof P. The RACE to the EAST. In pursuit of rhythm control therapy for atrial fibrillation. *Europace* 2021;**23**(Suppl 2):ii34-ii39.
- Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J et al.; for the RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**:2987-96.
- Fabritz L, Crijns H, Guasch E, Goette A, Hausler KG, Kotecha D et al. Dynamic risk assessment to improve quality of care in patients with atrial fibrillation: the 7th AFNET/EHRA Consensus Conference. *Europace* 2021;doi: 10.1093/europace/ueaa279.

22. Linz D, Hermans A, Tieleman RG. Early atrial fibrillation detection and the transition to comprehensive management. *Europace* 2021;**23**(Suppl 2):ii46–ii51.
23. Hendriks JM, Gallagher C, Middeldorp ME, Lau DH, Sanders P. Risk factor management and atrial fibrillation. *Europace* 2021;**23**(Suppl 2):ii52–ii60.
24. Verhaert DVM, Brunner-La Rocca H-P, Van Veldhuisen DJ, Vernoooy K. The bidirectional interaction between atrial fibrillation and heart failure: consequences for the management of both diseases. *Europace* 2021;**23**(Suppl 2):ii40–ii45.
25. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**: 154–62.
26. Goette A, Auricchio A, Boriani G, Braunschweig F, Terradellas JB, Burri H et al.; ESC Scientific Document Group. EHRA White Paper: knowledge gaps in arrhythmia management-status 2019. *Europace* 2019;**21**:993–4.