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Chapter 57.4 **Personalized management of atrial fibrillation**

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Summary

- ◆ Clinical management of patients with atrial fibrillation (AF) today is merely guided by stroke risk, AF pattern, drug safety, and patient-reported symptoms.
- ◆ To facilitate more personalized treatment of patients with AF, clinical markers reflecting the major causes of AF in patients need to be validated and used in practice.
- ◆ More personalized and more integrated care will improve outcomes in patients with AF.

Introduction

Atrial fibrillation (AF) is a major cause of cardiovascular morbidity and mortality, despite excellent efforts to improve management

Figure 57.4.1 Different vicious circles driving and maintaining atrial fibrillation.

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of patients suffering from the condition.¹ While many strokes can be prevented by oral anticoagulants, heart failure and sudden death remain common, and unplanned hospitalizations contribute further to the burden of AF to affected patients and society.² It is well established that different mechanisms cause the arrhythmia in different models of AF,³ ranging from a genomic predisposition, altered calcium handling, and oxidative stress, to atrial infiltration with fat and fibrous tissue. A similar diversity of the drivers for AF can be found in patients,⁴ and several additional ‘vicious circles’ contribute to perpetuation of AF (Figure 57.4.1). Identification of the major drivers of AF in different patients has the potential to improve AF outcomes through personalized interventions, particularly recurrent AF, as exemplified by the therapeutic success of prevention of AF recurrence by intensive weight reduction in obese patients with AF.^{5, 6}

Current state of atrial fibrillation management

Clinical risk scores already guide treatment decisions in patients with AF, for example, the CHA₂DS₂VASc score that is used to

guide oral anticoagulation in AF patients.⁷ Other treatment areas are much less established, for example, the optimal type and intensity of ventricular rate control^{8–10} or the optimal rhythm control treatment.¹¹ Even less is currently known about the best methods to prevent the predicted rise in AF prevalence and incidence.¹² Understanding the major drivers causing AF in different patient populations, for example, those with AF and heart failure, those with AF due to a genetic predisposition, those with AF and hypertension, those with AF and chronic kidney disease, or those with AF and obesity or metabolic defects, is required to discern specific targets for personalized prevention and therapy of the arrhythmia.⁴

Recent advances underpinning personalized prevention and management of patients with atrial fibrillation

We have good knowledge of the vicious circles maintaining AF once it has been initiated (Figure 57.4.1). Our knowledge of the major drivers of AF, including drivers of AF that act prior to

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the first episode, has advanced in the last decades. To give a few examples:

- ◆ The first genome-wide association study of AF was published a decade ago in 2007,¹³ suggesting for the first time an important link between (left) atrial transcription factors such as PITX2 and AF. Further work inspired by this initial observation has

delineated a role for such transcription factors for atrial function and genesis of AF.^{14–16}

- ◆ In addition to the known effects of atrial dilatation and pressure overload on cellular calcium handling and metabolic homeostasis, recent work has identified relevant roles for subcellular domains for atrial function.¹⁷

Figure 57.4.2 (a) A road map for a new taxonomy of patients with atrial fibrillation (AF). (b) Interdisciplinary approaches to identify different types of patients with atrial fibrillation based on the major drivers causing the arrhythmia.

Panel (a) is reproduced with permission from Fabritz L, et al. Expert consensus document: Defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment. *Nat Rev Cardiol* 2016;13(4):230–7. doi:10.1038/nrcardio.2015.194. Copyright © 2017 Macmillan Publishers Limited, part of Springer Nature. Panel (b) with permission from Kirchhof P, et al. A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016;18(1):37–50. <https://doi.org/10.1093/europace/euv304>. Copyright © 2015 Oxford University Press.

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- ◆ Atrial fibroblasts,¹⁸ fat cells,¹⁹ and oxidative stress²⁰ have been shown to modulate atrial cardiomyocyte function to create an arrhythmogenic substrate.
- ◆ Yet other mechanisms cause AF in patients with inherited arrhythmogenic conditions and inherited cardiomyopathies.³

Thus, we have an approximate understanding of the potential drivers for AF in different patients, but we have yet to translate this into stratified approaches to the prevention of AF and management of individual patients with AF.

Development of personalized atrial fibrillation prevention and management

The pathophysiological heterogeneity driving AF and most likely its complications has led to a demand for a new disease taxonomy that better reflects disease mechanisms in AF.⁴ Genomic and biomedical differences could guide such a taxonomy as well as different social contexts and behavioural patterns (Figure 57.4.2a). It is necessary to describe and classify these drivers in patients, and define a valid taxonomy of different pathophysiological types of AF to underpin the development of stratified approaches to AF management. This requires flexible thinking and interdisciplinary interaction between scientists, clinicians, regulators, funders, and industry partners. Markers for such different types of AF could, for example, be derived from clinical parameters, careful analysis of the electrocardiogram, assessment of blood and urine, and others (Figure 57.4.2b). Importantly, the scientific method used to generate and validate knowledge, that is, identification of novel disease drivers and therapeutic targets, and experimental interventions to demonstrate their physiological relevance, through controlled, randomized clinical trials in patient subpopulations harbouring the identified disease drivers, needs to be upheld to allow robust development of such approaches.

Conclusion

Patients with AF are in need of personalized approaches to prevention and therapy. Interdisciplinary cooperation between scientists, clinicians and other healthcare providers, regulators, industry government agencies, and charities is required, to unleash the potential of personalized management of AF in the future, starting with the development of a new taxonomy of AF based on the major mechanisms causing the arrhythmia in different patients, allowing the identification of novel treatment targets and evaluation of personalized interventions reversing these drivers in clinical trials.

Online resources

➔ For full references and multimedia materials please visit the online version of the book (<http://www.oup.com/escardiomed>).

Further reading

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