Atrial fibrillation and heart failure temporality

Van Deutekom, Colinda; Van Gelder, Isabelle C.; Rienstra, Michiel

Published in:
Europace

DOI:
10.1093/europace/euac255

Publication date:
2023

ESC European Society of Cardiology

Europace (2023) **25**, 247–248
https://doi.org/10.1093/europace/euac255

EDITORIAL

Atrial fibrillation and heart failure temporality: does it matter?

Colinda Van Deutekom, Isabelle C. Van Gelder, and Michiel Rienstra *

Department of Cardiology, University of Groningen, University Medical Centre Groningen, PO Box 30.001, Hanzeplein 1, 9700 RB Groningen, The Netherlands

Online publish-ahead-of-print 28 December 2022

This editorial refers to 'Atrial fibrillation onset before heart failure or vice versa: what is worst? a nationwide register study' by J. Pallisgaard *et al.*, https://doi.org/10.1093/europace/euac186.

Atrial fibrillation (AF) and heart failure (HF) are highly prevalent diseases that can trigger each other and sustain each other.[1] The worldwide prevalence was estimated to be around 38 million AF patients and 64 million HF patients in 2017. Between 30% and 60% of both AF and HF patients will develop the other disease at some point during their life.[2] The co-occurrence of these diseases can be explained by (i) shared risk factors and comorbidities; (ii) AF leading to the development of HF; and (iii) HF leading to the development of AF. First, commonly shared risk factors and comorbidities associated with AF and HF are, among others, advancing age, hypertension, obesity, and coronary heart disease. With shared risk factors and comorbidities, it is likely that there are shared pathophysiological mechanisms for AF and HF as well, which may predispose to the development of both diseases simultaneously—AF due to diseased atria and HF due to diseased ventricles. Second, AF could lead to the development of HF through the high and irregular heart rate and loss of atrial contraction, even setting the stage for tachycardiomyopathy to occur in selected patients. Third, HF could lead to the development of AF through various mechanisms including loading of the atria, which may result in structural and functional atrial remodelling, predisposing to AF.[3] With different underlying pathophysiological mechanisms, the timing of when these diseases present themselves in patients can be different: AF first before HF, HF first before AF, or AF and HF starting at the same time. While both diseases alone impair prognosis, it is known that they have an even worse prognosis when they occur together.[4] The sequence in which AF and HF occur may have a differential effect on prognosis, yet the literature on this topic is sparse.[5]

In this issue of *Europace*, Pallisgaard *et al.*[6] aimed to determine the differential prognosis and absolute rates of mortality and stroke in patients with coexisting AF and HF according to the sequence in which AF and HF occurred. Multiple nationwide Danish registers were cross-linked to obtain a comprehensive overview of the patients. For this analysis, 49 042 patients with both AF and HF and information about the sequence of both events were included. The authors observed that HF occurring before AF was associated with a higher rate of death compared to AF occurring first and AF and HF diagnosed concurrently (10-year mortality rates 81.8% compared with 76.8% and 69.6%, respectively). There was, however, no significant difference between the groups with regard to the incidence of stroke (5.8% in HF first, 6.0% in AF first, and 5.7% in AF and HF starting simultaneously). In addition, they found several mainly treatment-related covariates associated with a lower risk of stroke and death, namely antihypertensive treatment [hazard ratio (HR): 0.89, 95% confidence interval (CI): (0.85–0.93)], oral anticoagulant use [HR: 0.63, 95% CI: (0.61–0.64)], amiodarone use [HR: 0.93, 95% CI: (0.89–0.97)], statin use [HR: 0.80, 95% CI: (0.78–0.82)], and AF ablation [HR: 0.37, 95% CI: (0.23–0.58)].

The authors should be congratulated for their contribution to the knowledge on the prognostic impact of the temporality of AF and HF occurrence. Strong aspects of this observational study include a large number of patients and the comprehensiveness of the data. The results from the present study are in line with previous smaller cohort studies. One observational study included 182 patients hospitalized for HF and compared patients who had developed AF before or consecutively with HF with patients who developed AF after HF.[5] The study showed that the primary outcome, cardiovascular hospitalizations, occurred more often in those with HF first. Another observational community-based study reported similar findings with higher mortality rates in patients with HF first.[2]

Why do patients with HF occurring before AF seem to have a worse prognosis? First, there may be differences in underlying risk factors and comorbidities between those with HF first and those with AF first. In the registry of Pallisgaard *et al.*,[6] ischaemic heart disease was, for example, more prevalent in patients with HF first. Ischaemic HF is associated with increased mortality compared with non-ischaemic HF.[7] Second, the degree of reversibility of the conditions after optimal therapy may also be different depending on which condition, AF or HF, develops first. When HF occurs first and AF starts later during disease progression, this may be less likely to be reversible than with reversed temporality. When it all starts with AF leading to HF, mechanisms like tachycardia and irregulopathy setting the stage for tachycardiomyopathy could be reversible when ventricular rates are well controlled or sinus rhythm is restored.[3]

Unfortunately, the authors did not provide data on the subtypes of HF. There exist differences between HF with reduced ejection fraction, mildly reduced ejection fraction, and with preserved ejection fraction in circulating biomarkers emphasizing distinct underlying pathophysiological mechanisms of AF in these HF subtypes.[8] Future studies

* Corresponding author. Tel: +31 50 3611327; fax: +31 50 3614391. *E-mail address:* m.rienstra@umcg.nl

exploring the temporality of AF and the different LVEF-based subtypes of HF and its prognostic impact are to be awaited.

Interestingly, Pallisgaard *et al.* observed several treatment-related covariates associated with a lower risk of stroke and death. This suggests that to some extent the prognostic impact of the co-occurrence of AF and HF is modifiable. This notion is further supported by the previous literature showing beneficial effects of treatment of underlying comorbidities and sinus rhythm maintenance on the outcome.[9] If so, then the temporality of AF and HF can also inform treatment decision-making. In the GENETIC-AF trial, including patients with both AF and HF, no overall benefit of a genetically informed treatment with bucindolol was observed.[10] However, a subgroup analysis suggested that both the interval of time from the initial diagnosis of AF and HF to treatment initiation and HF before AF diagnosis, was associated with the attenuation of a bucindolol treatment response. This indicates that the temporality of AF and HF matters for treatment decision-making. Although patients with AF and HF should be treated with all recommended therapies as established by the AF and HF guidelines, the condition that presents first may need to have the first treatment priority.

As with all observational studies, the present study has limitations as also acknowledged by the authors. The presence of AF, HF, and cardiovascular hospitalizations was based on ICD-10 codes. Information on the prevalence of comorbidities was limited. No differentiation could be made between the LVEF-based subtypes of HF, nor between the different subtypes of AF (paroxysmal, persistent, permanent, or post-operative). This withholds the generalizability of findings to other populations and direct implementation into clinical practice.

Nevertheless, this study emphasizes that the temporality of AF and HF occurrence matters. Patients with HF first seem to have a worse prognosis. Future studies are needed since this temporality may have implications for the management of patients with AF and HF.

Funding

C.V.D., I.C.V.G., and M.R. are supported by a grant from the European Union's Horizon 2020 research and innovation programme (grant agreement No 945260).

Conflict of interest: None declared.

References

1. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. *Int J Stroke* 2021;**16**:217–21.
2. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA *et al.* Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016; **133**:484–92.
3. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A *et al.* Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol* 2017;**70**:1949–61.
4. Ziff OJ, Carter PR, McGowan J, Uppal H, Chandran S, Russell S *et al.* The interplay between atrial fibrillation and heart failure on long-term mortality and length of stay: insights from the United Kingdom ACALM registry. *Int J Cardiol* 2018;**252**:117–21.
5. Smit MD, Moes ML, Maass AH, Achekar ID, Van Geel PP, Hillege HL *et al.* The importance of whether atrial fibrillation or heart failure develops first. *Eur J Heart Fail* 2012;**14**:1030–40.
6. Pallisgaard J, Greve A, Lock-Hansen M, Thune J, Loldrup Fosboel E, Devereux R *et al.* Atrial fibrillation onset before heart failure or vice versa—what is worst? A nationwide register study. *Europace* 2023;**25**:283–90.
7. Silverdal J, Sjöland H, Bollano E, Pivodic A, Dahlström U, Fu M. Prognostic impact over time of ischaemic heart disease vs. Non-ischaemic heart disease in heart failure. *ESC Heart Fail* 2020;**7**:264–73.
8. Santema BT, Kloosterman M, Van Gelder IC, Mordi I, Lang CC, Lam CSP *et al.* Comparing biomarker profiles of patients with heart failure: atrial fibrillation vs. sinus rhythm and reduced vs. Preserved ejection fraction. *Eur Heart J* 2018;**39**:3867–75.
9. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brügemann J *et al.* 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.
10. Piccini JP, Abraham WT, Dufton C, Carroll IA, Healey JS, van Veldhuisen DJ *et al.* Bucindolol for the maintenance of sinus rhythm in a genotype-defined HF population: the GENETIC-AF trial. *JACC Heart Fail* 2019;**7**:586–98.