


# openheart Multimorbidity in patients with atrial fibrillation

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## ABSTRACT

There is an escalating trend in both the incidence and prevalence of atrial fibrillation (AF). AF is linked to numerous other comorbidities, contributing to the emergence of multimorbidity. The sustained rise in multimorbidity and AF prevalences exerts a significant strain on healthcare systems globally. The understanding of the relation between multimorbidity and AF is essential to determine effective healthcare strategies, improve patient outcomes to adequately address the burden of AF. It not only begins with the accurate identification of comorbidities in the setting of AF. There is also the need to understand the pathophysiology of the different comorbidities and their common interactions, and how multimorbidity influences AF perpetuation. To manage the challenges that rise from the increasing incidence and prevalence of both multimorbidity and AF, such as adverse events and hospitalisations, the treatment of comorbidities in AF has already gained importance and will need to be a primary focus in the forthcoming years. There are numerous challenges to overcome in the treatment of multimorbidity in AF, whereby the identification of comorbidities is essential. Integrated care strategies focused on a comprehensive multimorbidity management with an individual-centred approach need to be determined to improve healthcare strategies and reduce the AF-related risk of frailty, cardiovascular diseases and improve patient outcomes.

## INTRODUCTION

As the population ages and the prevalence of chronic diseases rises, the coexistence of atrial fibrillation (AF) with multiple other comorbidities, known as multimorbidity, has gained importance. The coexistence of multimorbidity and AF poses challenges to the current methods of diagnosis, treatment and patient-centred care. Therefore, it is important to understand the relationship between multimorbidity and AF to develop more effective healthcare strategies to improve patient outcomes.

In the management of AF, the treatment of comorbidities already is highlighted in the European Society of Cardiology 2020 AF guidelines.<sup>1</sup> However, in clinical practice, the treatment of comorbidities is still far from optimal and largely focused on individual comorbidities. Additionally, before

a comorbidity can be treated it needs to be identified, and this often remains under-attended. The opportunity to improve the identification of comorbidities is now being addressed within the EHRA-PATHS project to further define multimorbidity in patients with AF.<sup>2</sup> Due to previous literature focusing mostly on individual comorbidities,<sup>3 4</sup> in the present review, we aim to address the challenges regarding multimorbidity and its relationship with (the management of) patients with AF.

## DEFINITION OF MULTIMORBIDITY

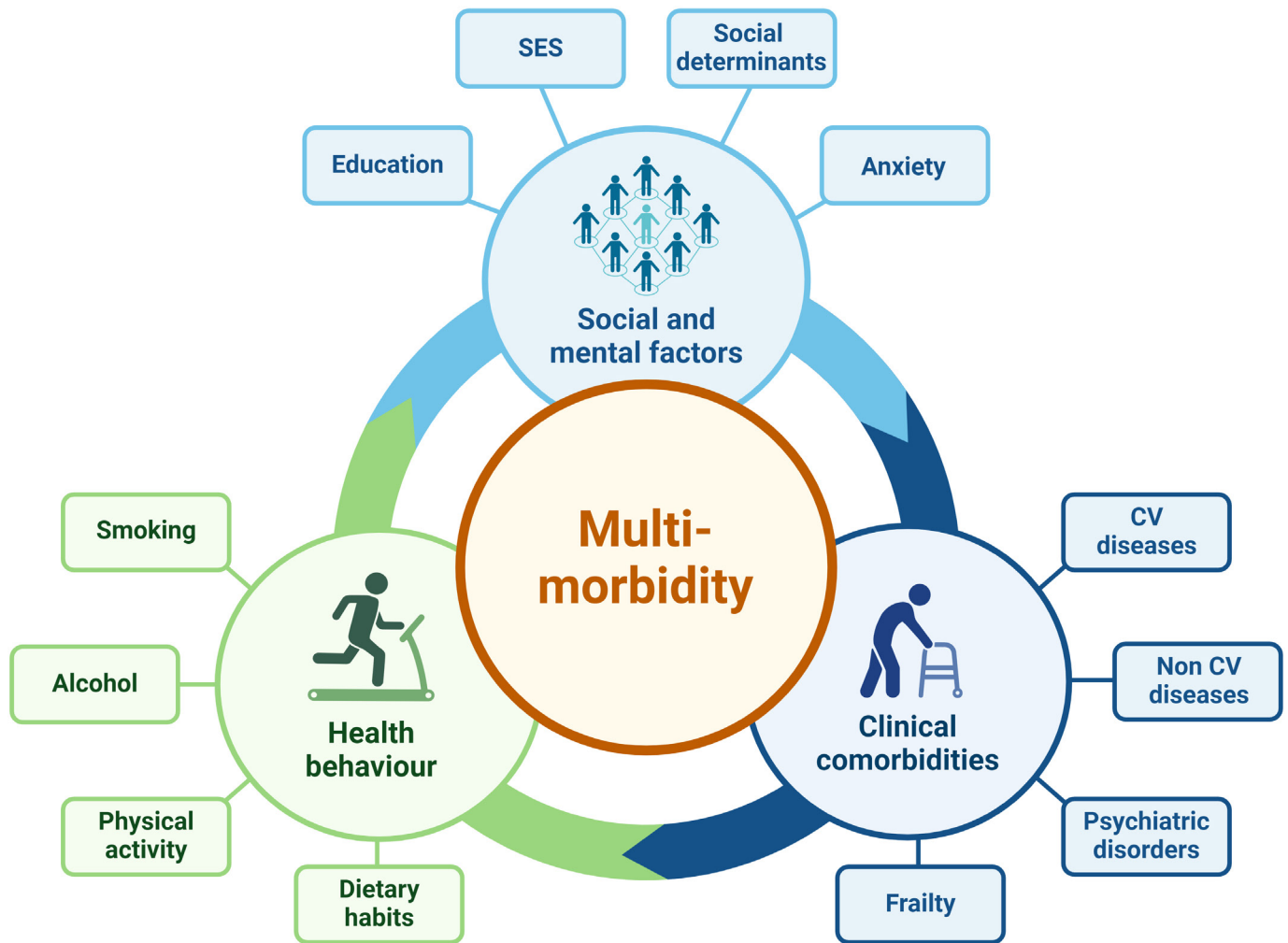
Multimorbidity, typically defined as the coexistence of two or more chronic health conditions, is commonly observed in elderly patients with AF. While the definition of 'multimorbidity' may seem straightforward, numerous variations in the definition exist to date. There is a substantial diversity in the specific comorbidities included in the definition of multimorbidity.<sup>5</sup> The definition of multimorbidity includes acute and chronic (non-) cardiovascular diseases as well as mental, social and lifestyle conditions. Although that in patients with AF we generally focus on cardiovascular comorbidities, many non-cardiovascular comorbidities may have an impact on the lives of patients with AF. Additionally, not only which comorbidities to consider is open for debate, but also the definition of the individual comorbidities themselves sometimes lacks clarity.<sup>6</sup> This becomes increasingly important since the prevalence of both individual comorbidities and multimorbidity is expanding rapidly. The comorbidities associated with AF can range from common conditions such as hypertension and diabetes mellitus to more complex conditions such as obesity, renal impairment and heart failure.<sup>7</sup> Multimorbidity is often subdivided into cardiovascular and non-cardiovascular comorbidities, or clustering of comorbidities that are inherently interconnected, such as obesity and physical inactivity.<sup>4 6</sup> Moreover, mental comorbidities (eg,



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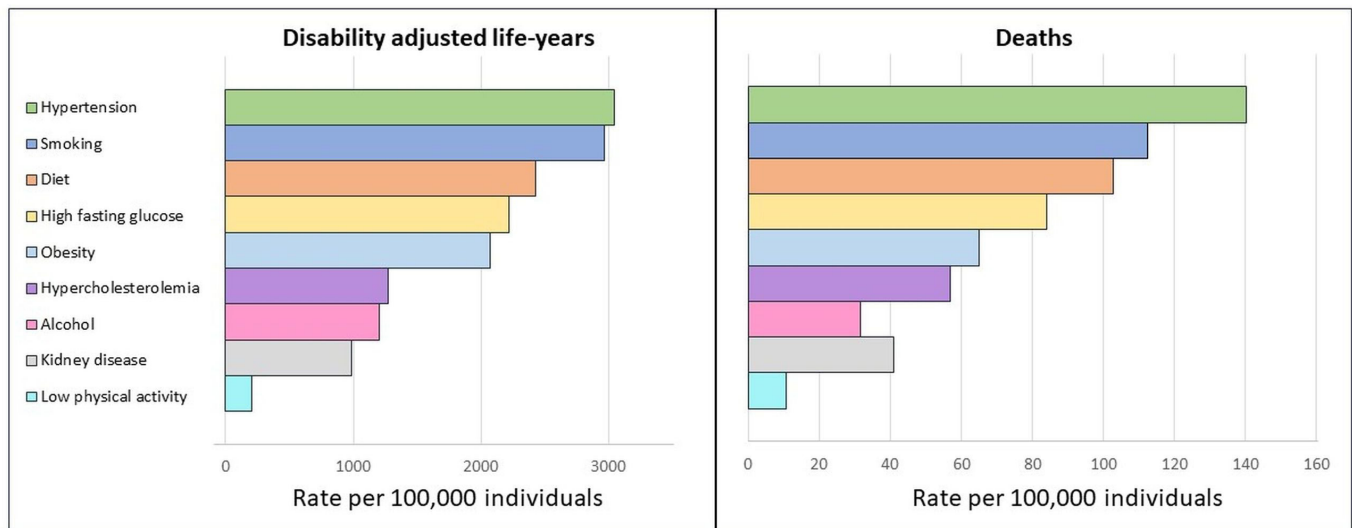
**Figure 1** Different aspects of multimorbidity in patients with atrial fibrillation. Multimorbidity in patients with AF can be subdivided in clinical comorbidities (such as cardiovascular (CV) and non-CV diseases), social and mental factors (such as socioeconomic status (SES), race and ethnicity, financial resources, social support, access to healthcare, rurality and residential environment, local language proficiency and health literacy), and health behaviour (such as dietary habits and physical activity).

depression and anxiety and social determinants, eg, socioeconomic status, race and ethnicity, financial resources, social support, access to healthcare, rurality and residential environment, local language proficiency and health literacy),<sup>8</sup> have emerged as potential contributors to the occurrence of AF.<sup>9 10</sup> However, the causal relation between mental comorbidities, social determinants and AF remains unclear and understudied. To date, mental comorbidities and social determinants are often not considered in patients with AF. Equally of importance is the presence of frailty. Frailty identifies a syndrome characterised by high biological vulnerability, decreased physiological reserve and reduced capacity to resist stressors, due to multiple impairments in inter-related systems, leading to reduced homeostatic reserve.<sup>11 12</sup> The number of patients with frailty increases sharply when patients reach 70 years of age.<sup>13</sup> Figure 1 shows an overview of comorbidities involved in multimorbidity related to AF. To define optimal treatment strategies for our patients, there still remains an opportunity to improve the

identification of comorbidities, awareness and definition of multimorbidity.

## EPIDEMIOLOGY

Epidemiological investigations have consistently depicted an escalating trend in both the incidence and prevalence of multimorbidity and AF across the globe. Recent findings from the Global Burden of Disease study indicate that the global prevalence of AF currently stands at approximately 59.7 million individuals. Furthermore, these data suggest that the future prevalence of AF may surge by over 60% of individuals by the year 2050.<sup>14 15</sup> Similarly, there is an expanding incidence and prevalence of cardiovascular and non-cardiovascular comorbidities such as hypertension, obesity, diabetes mellitus and renal impairment, data demonstrate that multimorbidity is rising rapidly with more than half the adult population worldwide >60 years suffering multimorbidity.<sup>16</sup> The escalation in both multimorbidity and AF can be attributed



**Figure 2** Disability-adjusted life-years and death per 100 000 individuals of modifiable comorbidities in patients with atrial fibrillation in 2019. Data are derived from the Global Burden of Disease 2019 Study.

to multiple factors, including the advancing age of the population as well as the refinement of diagnostics to detect comorbidities, and heightened awareness among healthcare practitioners. The sustained rise in both multimorbidity and AF prevalences exerts a notable strain on healthcare systems and contributes substantially measured in disability-adjusted life-years (DALYs). Multimorbidity and AF also impose a profound effect on overall quality of life and symptoms, including dyspnoea, fatigue and impaired exercise intolerance. The most prominent attributable comorbidities to DALYs associated with AF are demonstrated in figure 2.<sup>17</sup> It is imperative to recognise the intricate interplay among these comorbidities. Lifestyle behaviours such as smoking, alcohol consumption, physical activity and dietary habits often coexist with social and mental factors such as socioeconomic status, education and social determinants.<sup>18</sup> Lifestyle behaviours also coexist with cardiovascular comorbidities such as hypertension, obesity, diabetes mellitus and others, and with many non-cardiovascular diseases. Each of these inter-related comorbidities and lifestyle behaviours has been consistently linked to the promotion and exacerbation of AF.<sup>19</sup>

Numerous population-based investigations have explored the association between multimorbidity and AF.<sup>3</sup> Findings from Swedish data have underscored that individuals who have 3–4 comorbidities are exposed to a notable 28%–50% increased risk of incident AF.<sup>20</sup> In addition, results from the EPIC-NORFOLK study revealed an even more substantial AF risk increase, with the presence of 3–4 comorbidities correlating with an elevated incidence AF risk ranging from 83% to 282%.<sup>21</sup> Not every comorbidity appears to have an equal influence on the risk of AF, as pointed out in the Atherosclerosis risk in communities (ARIC) study.<sup>22</sup> Consequently, optimising individuals' comorbidities may have a substantial impact on the reduction of AF risk, attributable to the interplay

among comorbidities. It has been suggested that there is great potential for treatment of comorbidities and multimorbidity whereby an optimal comorbidity profile can result in a noteworthy risk reduction of 21%–67% in developing incident AF.<sup>23–27</sup>

Multimorbidity itself is associated with increased mortality.<sup>28</sup> Patients with AF who have  $\geq 4$  comorbidities had a 6-fold higher risk of mortality compared with patients without comorbid conditions.<sup>29</sup> It is important to consider the interplay between comorbidities to adequately address the increasing incidence and prevalence of AF and multimorbidity.

### **PATHOPHYSIOLOGICAL MECHANISMS OF MULTIMORBIDITY**

Studying the pathophysiological mechanisms of multimorbidity in patients with AF is complicated by the heterogeneity in comorbidities present in each patient.<sup>5</sup> The different comorbidities may have a shared pathophysiology or management approach but also can incorporate comorbidities with unrelated pathophysiology and different treatments. The comorbidities with a shared pathophysiology may exert reciprocal influences on one another. The extent to which this occurs and the implications for the prevalence and incidence of the reciprocal influences are currently uncertain and partly understood. Various pathophysiological mechanisms have been described to manifest in individual comorbidities and cross-link the same pathophysiological mechanisms in different comorbidities.<sup>30</sup> Well-known pathophysiological mechanisms that underlie multiple different comorbidities are oxidative stress and inflammation.<sup>31 32</sup> The pathophysiological mechanisms of oxidative stress and inflammation are interconnected and exhibit overlapping characteristics, such as an accumulation of cellular damage, including mitochondrial dysfunction, deregulated neurohormonal signalling and upregulated

inflammatory pathways.<sup>33</sup> The concurrent occurrence of multiple comorbidities with shared pathophysiological mechanisms is likely to reinforce each other, thereby exacerbating these mechanisms or increasing the occurrence of additional comorbidities. The extent to which this occurs with the various pathophysiological mechanisms within multimorbidity remains unclear.

Conditions such as obesity, heart failure, diabetes mellitus, smoking, alcohol consumption and sleep apnoea are known for their influences directly or indirectly on myocardial cells which initiate or sustain AF.<sup>33 34</sup> The concept that AF is a consequence of remodelling of atrial tissue, often referred to as atrial cardiomyopathy, has gained prominence. In the presence of atrial cardiomyopathy, the atria undergo changes in electrical, mechanical and structural characteristics.<sup>35 36</sup> Various mediators have been identified as drivers in promoting changes in atrial tissue including pressure and volume overload, atrial stretch, inflammation and oxidative stress.<sup>37</sup> These recognised mediators commonly contribute to the occurrence or persistence of AF and various comorbidities.

Considerable research has been conducted into the underlying mechanisms of various comorbidities. We use obesity as an example to provide some more details into the underlying mechanisms and demonstrating also the complexity of studying the interacting comorbidities accompanying obesity in patients with AF. Obesity is associated with many comorbidities including diabetes mellitus, hypertension, sleep apnoea and many more.<sup>38</sup> With regard to obesity, a growing attention is directed towards ectopic fat depots, such as visceral adipose tissue, which gives a better reflection of general adiposity. Adipose tissue is known to have an endocrine function releasing hormones (eg, leptin), peptides (eg, angiotensinogen) and inflammatory cytokines (eg, interleukin-6, tumour necrosis factor  $\alpha$ ).<sup>39</sup> However, it is visceral adiposity that is seen as an important player in the pathways responsible for causing the metabolic syndrome.<sup>40</sup> The metabolic syndrome forms a cluster of metabolic dysregulation including insulin resistance, central obesity and hypertension.<sup>39</sup> The pathophysiology of metabolic syndrome is not fully elucidated but likely encompasses chronic inflammation and neurohormonal activation, all pathways related with AF, but non-specific for AF and also related to many other cardiovascular diseases.<sup>39</sup> Given the role of endocrine function in adipose tissue, a growing interest has emerged in the presence of epicardial adipose tissue that is directly connected with myocardial tissue. This physical proximity allows epicardial adipose tissue to directly interfere with the underlying myocardial tissue and potentially induce pathophysiological processes leading to AF. The exact mechanisms responsible for these interactions remain poorly understood.<sup>41</sup> The role of epicardial adipose tissue in the pathophysiology of AF still needs to be clarified, as well as its significance role in treatment- and prevention strategies. Additional research is essential to elucidate the comorbidities existing within multimorbidity and AF.

## TREATMENT CHALLENGES OF MULTIMORBIDITY

Since most studies focus on an individual comorbidity and the accumulation of comorbidities instead of focusing on multimorbidity, it is unclear how the treatment of comorbidities influence, or even support each other. Hendriks *et al* demonstrated in a single-centre randomised controlled trial a dedicated clinic which used a nurse-led care approach which focused on guideline adherence resulted in a 35% relative risk reduction in a composite endpoint of cardiovascular hospitalisation and death compared with standard care. When this was extrapolated out to a multicentre study, however, the results were less encouraging.<sup>42</sup> The RACE 4 study built on this through addressing multimorbidity through nurse-led care compared with standard of care failed to show a reduction in the primary endpoint of cardiovascular death and hospitalisation. Interestingly, however, on further analysis, the investigators were able to demonstrate that this was driven by the experience of the centre delivering the care. Those who were experienced in managing multimorbidity saw a significant reduction in cardiovascular death and hospitalisation while those who were less experienced did not see a difference.<sup>43</sup> In many trials, multimorbid patients are frequently excluded, making it difficult to extrapolate study results to clinical practice.<sup>44</sup> The evidence used in the guidelines often prescribes strict therapeutic goals and combinations of multiple medications for better control of for individual comorbidities. Applying the AF guidelines with recommendations for individual comorbidities to AF patients with multimorbidity, results in a multitude of lifestyle advices and medication prescriptions. Although that established treatments for individual comorbidities result in better prognosis of patients with AF, it also drives polypharmacy, medication interactions, counteracting effects of medication on one comorbidity to another and negatively impacts patient empowerment and treatment adherence. Polypharmacy is usually considered the use of five or more medications.<sup>45</sup> The risk of polypharmacy has been demonstrated in various studies, revealing the association of polypharmacy and adverse drug events. As the number of medications increasing alongside the number of comorbidities, the potential harm of medication markedly increases due to an increase of side effects or medication errors. The benefit of the combination of therapies might decrease due to poor medication adherence, other comorbidities, frailty and limited life expectancy.<sup>13</sup>

An important additional challenge in patients with AF, multimorbidity and frailty are the appropriate use of anticoagulants. Existing literature demonstrated that frail patients are more frequently prescribed non-recommended, often lower dose of anticoagulants, primarily due to concerns about potential bleeding risks.<sup>46</sup> However, undertreating a patient with AF could increase the prothrombotic status, and treatment with anticoagulation improves patient outcomes across all degrees of frailty.<sup>47</sup> Additionally, there are limited data

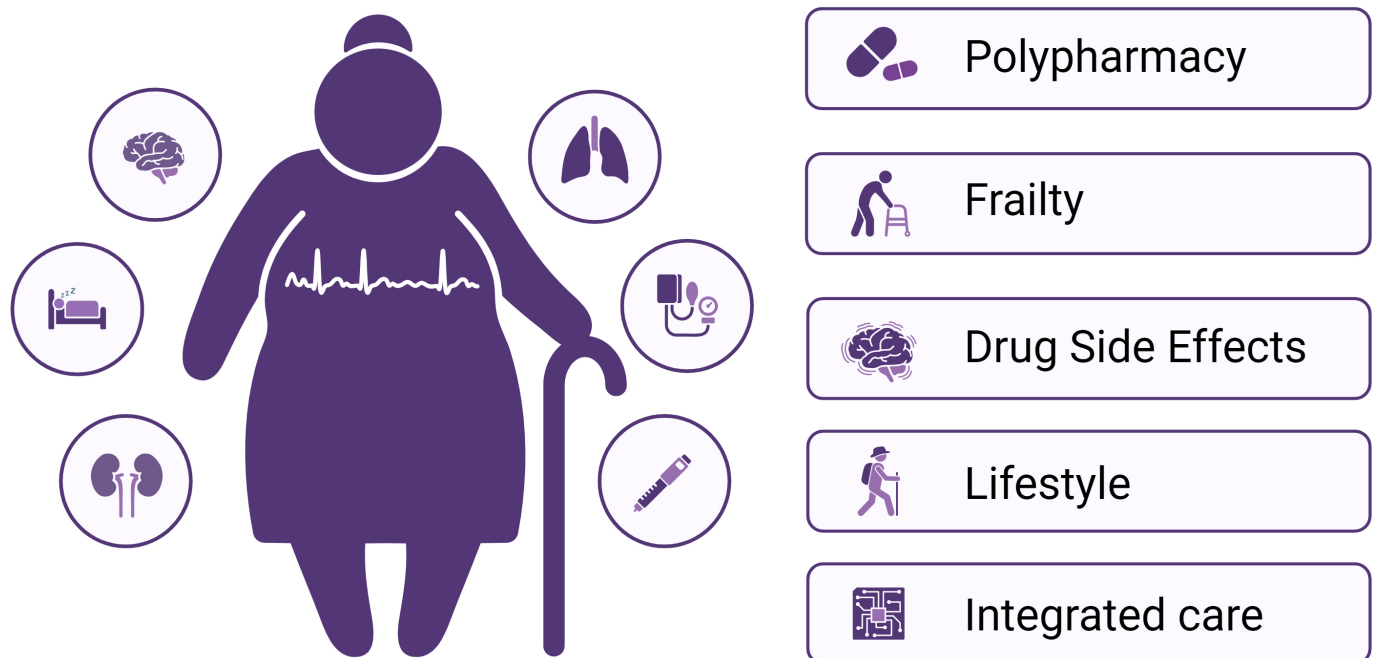
on how to best manage or alter existing drugs in patients with AF and frailty. The recent FRAIL-AF trial showed that switching vitamin K antagonists in non-vitamin-K antagonist oral anticoagulants in frail older patients with AF was associated with more bleeding complications compared with continuing treatment with vitamin-K Antagonist, without an associated reduction in thromboembolic complications.<sup>48</sup> The presence of multimorbidity and polypharmacy in a patient asks for an integrated care strategy with individual-centred approach where no clear prioritisation of comorbidities has been predefined.<sup>49</sup>

It is not clear how to improve identification of comorbidities and prioritise recommendations on treatment of multimorbidity and AF on an individual base.<sup>50</sup> To address the challenges posed by the increasing prevalence of multimorbidity and AF, a greater emphasis is needed to stop the further increase of comorbidities. Implementing a single-disease approach for patients with multimorbidity without considering the cumulative impact can lead to impractical or even potentially harmful treatment strategies, for example, the prescription of contraindicated medication with another disease.<sup>5</sup> However, determining the best individual treatment strategy remains difficult because of the heterogeneity in comorbidities between different patients. The decision-making about treatment strategies in AF patients with multimorbidity, especially in patients with frailty, requires consideration of patient-centred outcome measures such as quality of life versus burden of treatment.<sup>12</sup>

It is important to target the most (individual-) prominent comorbidities that contribute to multimorbidity to reduce the risk of frailty, AF and improve patient outcomes.<sup>12</sup> However, integrating these aspects effectively

may be challenging. Various specialties with different expertise may be needed to integrate their knowledge, in a system where currently, the patient visits each medical specialty separately. It is important to recognise the treatment of one comorbidity can significantly impact another comorbidity. For example, the treatment of chronic pulmonary obstructive disease with salbutamol can significantly influence the heart rate and thus the treatment AF. It will be crucial to assess the comorbidities on an individual patient basis, addressing them comprehensively, as many comorbidities exert reciprocal influences. Although the complexity associated with the treatment of multimorbidity, there are specific opportunities that we may currently seize. Figure 3 provides an overview of treatment challenges in patients with multimorbidity and AF.

In multimorbid patients with AF, there is potential for considerable improvement of treatment of all comorbidities such as hypertension, diabetes mellitus and physical inactivity. Significant value appears to be derived from the treatment of obesity. Obesity not only influences the occurrence of multimorbidity but also complicates the treatment of various other comorbidities.<sup>51</sup> For example, in the context of AF, rhythm control interventions, such as electrical cardioversion, are less successful in patients with a higher BMI, most likely due to an increased interelectrode distance and transthoracic impedance in these individuals.<sup>52</sup> Moreover, obesity is associated with persistent AF at first diagnosis, a higher risk of postablation AF<sup>53 54</sup> and with progression of AF.<sup>55 56</sup> The greatest clinical benefit can be achieved through weight reduction. Furthermore, weight loss has many additional positive effects on other inter-related comorbidities,



**Figure 3** Treatment challenges in patients with multimorbidity and atrial fibrillation (AF). Polypharmacy, frailty, drug sides effects, lifestyle and the lack of integrated care all contributes to the complexity surrounding the management of patients with multimorbidity and AF.

including a reduction in blood pressure and improved lipid levels.<sup>57</sup> The combined effects of weight loss have the potential to reduce signs and symptoms of multiple diseases, enhancing a patient's quality of life, achieving a better balance in treatment, potentially reducing polypharmacy and lowering the risk of developing other (cardiovascular) conditions. Research has demonstrated that weight loss together with management of other comorbidities, significantly reduces AF duration, symptom burden and cardiac remodelling in patients with AF.<sup>58</sup> However, achieving significant and sustained weight loss continues to be a challenge. Bariatric surgery has proven effective in achieving sustained weight reduction.<sup>59</sup> Patients who underwent bariatric surgery had reduced AF recurrence after ablation compared with the control group.<sup>60</sup> Additionally, the recent emergence of GLP-1 receptor agonists gives potential medical therapies to reach significant weight loss.<sup>61 62</sup> These medications may influence multimorbidity with their weight-loss effect together with improvement in blood pressure, diabetes control, improved mental health and other cardiovascular conditions, also in patients with AF.

## CONCLUSION

In patients with multimorbidity and AF, it is important to concentrate on multimorbidity rather than solely on individual comorbidities. The various comorbidities and their treatments are often interconnected and can mutually influence each other. It is crucial to determine effective healthcare strategies to overcome the challenges regarding multimorbidity and subsequently improve patient outcomes. Integrated care strategies focused on multimorbidity with an individual-centred comprehensive approach may have the potential to improve the lives of patients with AF but warrant more research.

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