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## Aims

The concept of “atrial cardiomyopathy” (AtCM) had been percolating through the literature since its first mention in 1972. Since then, publications using the term were sporadic until the decision was made to convene an expert working group with representation from four multinational arrhythmia organizations to prepare a consensus document on atrial cardiomyopathy in 2016 (EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication). Subsequently, publications on AtCM have increased progressively.

## Methods and results

The present consensus document elaborates the 2016 AtCM document further to implement a simple AtCM staging system (AtCM stages 1–3) by integrating biomarkers, atrial geometry, and electrophysiological changes. However, the proposed AtCM staging needs clinical validation. Importantly, it is clearly stated that the presence of AtCM might serve as a substrate for the development of atrial fibrillation (AF) and AF may accelerates AtCM substantially, but AtCM *per se* needs to be viewed as a separate entity.

## Conclusion

Thus, the present document serves as a clinical consensus statement of the European Heart Rhythm Association (EHRA) of the ESC, the Heart Rhythm Society (HRS), the Asian Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS) to contribute to the evolution of the AtCM concept.

## Keywords

Atrium • Cardiomyopathy • Atrial fibrillation • Pathophysiology • Fibrosis • Stroke • Mechanisms

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## 1. Background, definition and classification

The concept of ‘atrial cardiomyopathy’ (AtCM) had been percolating through the literature since its first mention in 1972.<sup>1</sup> Since then, publications using the term were sporadic until the decision was made to convene an expert working group with representation from four multinational arrhythmia organizations to prepare a consensus document on atrial cardiomyopathy (EHRA/HRS/APHS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication).<sup>2</sup> Subsequent to the publication of the working group report,<sup>2-4</sup> the number of publications on AtCM has increased progressively (Figure 1). In 2022, progress in the area motivated the decision to reconstitute the working group in order to take stock of a range of important developments. The present manuscript presents the results of that reflection.

In the first consensus document on AtCM, the working group recommended the following working definition of atrial cardiomyopathy: ‘Any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations’ (Table 1). This definition is of necessity broad, as AtCM is the basis for clinical manifestations of atrial arrhythmia (e.g. atrial fibrillation (AF) and atrial flutter), atrial thrombogenesis and clinically important functional–structural manifestations like atrial failure and atrio-ventricular valve dysfunction secondary to atrial dilation.

Accordingly, AtCM encompasses all functionally relevant complexes of atrial tissue changes, including those in contractility, electrophysiology and chamber architecture. Several systemic diseases or disease states can influence overall atrial function, causing pathophysiological changes and overt pathology. We also proposed a histological classification scheme for atrial cardiomyopathies in the consensus document, with the acronym EHRAS (for **E**HRA/**H**RS/**A**PHRS/**S**OLAECE), defining four classes: I (principally cardiomyocyte changes); II (principally fibrotic changes); III (combined cardiomyocyte-pathology/fibrosis); IV primarily non-collagen infiltration (with or without cardiomyocyte changes). This simple classification might help to convey the primary underlying atrial pathology in various clinical conditions; however, it has not, to date, been widely accepted.<sup>5-7</sup> A reason for this current situation might be that systematic analyses of atrial biopsies is not feasible *in vivo*, and therefore, histological validation of clinical findings/atrial imaging is rarely done.

Members of the working group considered that Table 2 might present a simple working system for staging AtCM by integrating biomarkers, atrial geometry, and electrophysiological changes to define different stages of AtCM. Importantly, AtCM has to be differentiated from AF, which might be a consequence of AtCM: AtCM commonly causes AF, however, AF may also accelerate AtCM. To concretize the suggested AtCM staging system, prospective trials are needed to validate the stages and cut-off values.

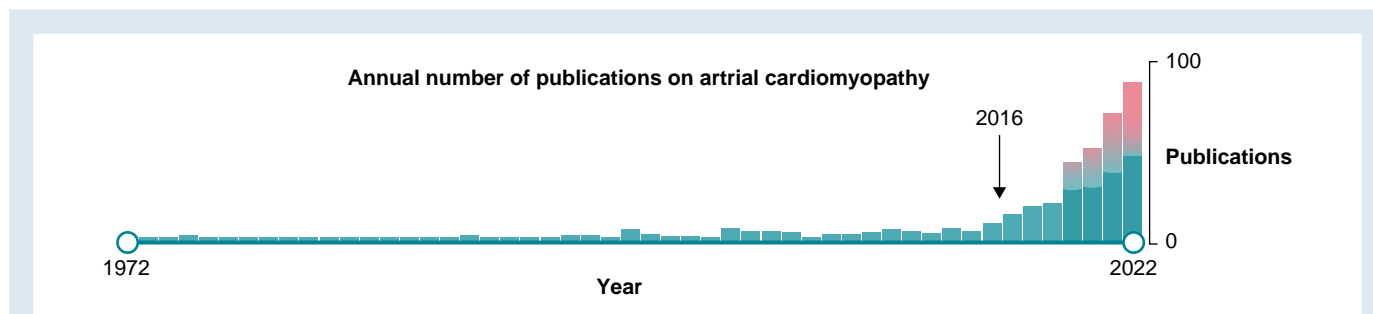
## 2. Important recent basic mechanistic insights

### 2.1. Early-onset atrial fibrillation due to underlying genetic cardiomyopathy and arrhythmia syndromes

Recent evidence indicates that AF developing in younger patients is often the initial manifestation of an atrial cardiomyopathy caused by rare variants in cardiomyopathy (CM) or arrhythmia syndrome genes.<sup>8</sup> In one study, patients with AF-onset at ages  $\leq 65$  years underwent whole-exome sequencing for 145 genes commonly included on commercial cardiomyopathy and arrhythmia syndrome panels including dilated cardiomyopathy, hypertrophic cardiomyopathy, Brugada syndromes and other inherited arrhythmia syndromes.<sup>9</sup> In a cohort of 1293 patients with a median age of 50 years, 10.1% had a disease-causing variant, with 62.8% carrying a variant of unknown significance (VUS), and 7.1% heterozygous for an autosomal recessive disease. Patients with AF-onset at  $< 30$  years of age are most likely to have a disease-associated variant (16.8%), with the most common genes being TTN, followed by MYH7, MYH6, LMNA, and KCNQ1. During a median follow-up of 9.9 years in the same cohort, the presence of a disease-causing variant was associated with a 50% increase in mortality that included 73 deaths related to cardiomyopathy, 40 sudden deaths, and 10 stroke-related deaths.<sup>10</sup> Thus, patients with early-onset AF have a significant risk of a disease-associated variant, primarily in cardiomyopathy genes, with increased mortality, supporting a potential role for genetic testing in these patients. However, while there are data pointing towards the potential value of genetic testing for AtCM, no major society guidelines presently recommend such testing, and it is not covered by most health insurers.<sup>11</sup> Further work in this promising area is certainly needed. A systematic multicenter registry of atrial-specific cardiomyopathies is a very-much needed first step.<sup>12</sup>

### 2.2. Atrial amyloidosis

Increasing evidence indicates that the prevalence of atrial amyloidosis is greater than previously suspected, particularly in the elderly.<sup>13-16</sup> The prevalence of heart failure with a preserved ejection fraction (HFpEF) increases with ageing, and senile amyloidosis due to wild-type transthyretin



**Figure 1** The colour shading is pretty but could be confusing, if readers think the red colour designates something different from the blue. Consider keeping simple monochrome (which avoids this potential confusion) or else adding a note to the figure legend indicating that each vertical bar represents the number of publications each year, with the colours simply being decorative.<sup>2-4</sup>

**Table 1** Definition of atrial cardiomyopathy (AtCM)

'Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations.'

(ATTRwt) accounts for up to 25% of HFpEF in patients >80 years of age, commonly with atrial involvement and AF.<sup>13,16</sup> In a recent study of HFpEF patients aged >60 years with LV hypertrophy,<sup>99m</sup>Tc-DPD scintigraphy was highly suggestive of ATTRwt in 13% of patients.<sup>14</sup> Isolated atrial amyloidosis (IAA) is a different entity mediated by atrial natriuretic peptide (ANP), and deposits containing both TTR and ANP have been detected in the same atria, indicating that both forms of senile atrial amyloidosis can co-exist.<sup>15</sup> Although some forms of amyloid were previously considered organ specific [e.g. amyloid  $\beta$  (A $\beta$ ) in Alzheimer's disease], cardiac involvement with A $\beta$  deposition and diastolic dysfunction has been identified in patients with Alzheimer's disease.<sup>17</sup> Mechanistically, there is increasing evidence for the cardiotoxicity of soluble pre-amyloid oligomers. Light-chain variable domain proteins from cardiac light-chain amyloidosis (AL) patients are highly toxic to atrial HL-1 cardiomyocytes,<sup>18</sup> while natriuretic peptide oligomers cause mitochondrial dysfunction, superoxide generation, and electrophysiological alterations in atrial cells.<sup>19</sup>

### 2.3. Inflammatory signalling

Recent findings showed that atrial NLRP3-inflammasome signalling creates AF-promoting AtCM in mouse models, and is increased in patients with common forms of AF including paroxysmal, persistent, and post-operative AF<sup>20,21</sup> as well as in conditions that promote AF (obesity,<sup>22</sup> diabetes,<sup>22</sup> gut dysbiosis,<sup>23</sup> sepsis,<sup>24</sup> and HFpEF<sup>25–27</sup>). Expression ('priming') and assembly ('triggering') of the NLRP3-inflammasome complex consisting of NLRP3, apoptosis-associated speck-like protein containing a C-terminal caspase activation and recruitment domain (ASC) and pro-caspase-1 accelerates auto-cleavage of pro-caspase-1 in atrial and immune cells. The resulting increase in active caspase-1 cleaves the inactive precursors of IL-1 $\beta$  and IL-18 to their active forms. In addition, caspase-1 degrades gasdermin-D, releasing the N-terminal fragment that forms plasma membrane pores, which allow IL-1 $\beta$  and IL-18 to leave the cells to exert autocrine and paracrine effects.<sup>25,26</sup> Mice with cardiomyocyte-restricted constitutive activation of the NLRP3 inflammasome show increased atrial ectopy associated with abnormal Ca<sup>2+</sup>-handling due to increased RyR2 expression, as well as reentry-promoting APD shortening (electrical remodelling), likely due to upregulation of atrial-selective ultra-rapid delayed-rectifier (I<sub>Kur</sub>) and acetylcholine-activated inward-rectifier (I<sub>KACH</sub>) K<sup>+</sup>-current, as well as structural remodelling involving hypertrophy and fibrosis.<sup>20</sup> The activation of the NLRP3 inflammasome is likely mediated by increased activity of CaMKII-related pathways<sup>21</sup> and impaired AMPK signalling.<sup>27</sup> Gut microbiota-derived lipopolysaccharide may constitute a biologically relevant upstream activator of the atrial NLRP3 inflammasome in AtCM, particularly during ageing.<sup>23</sup> Recent data have linked another inflammasome, the Absent-in-Melanoma 2 (AIM2) inflammasome, to AtCM, and AF susceptibility.<sup>28</sup> This study showed that high-protein diets create AF-promoting AtCM by activating the AIM2-inflammasome, which is associated with mitochondrial oxidative stress along with proarrhythmic sarcoplasmic reticulum Ca<sup>2+</sup>-release events.<sup>28</sup> These findings position the NLRP3 and AIM2 inflammasomes as potential novel drug targets for AF treatment.

Recent data point to an important role of recruited macrophages in the development of inflammatory signalling leading to AtCM and AF,<sup>29</sup> with macrophage targets being of potential interest as novel AF therapeutic compounds.<sup>30</sup> There is also evidence that genetic and epigenetic regulation of innate immunity may play a major role in conditioning AF susceptibility by controlling inflammatory responses.<sup>31</sup> Active resolution of inflammation is emerging as a theme in combatting inflammation and preventing

**Table 2** Classification of different stages of atrial cardiomyopathies

1. Mild (subclinical) atrial cardiomyopathy	Detected by electrophysiological measures or imaging technologies without overt arrhythmia or significant mechanical atrial dysfunction
2. Moderate (clinically manifest) atrial cardiomyopathy	Significant structural abnormalities or atrial mechanical dysfunction and elevated biomarkers (BNP, ANP, etc.) and /or manifestation of atrial fibrillation
3. Severe atrial cardiomyopathy:	Atrial systolic failure (severely reduced left atrial ejection fraction $\leq$ 35%) associated with substantially impaired atrial contractility (flow velocities: $\leq$ 20 cm/sec within LAA/tissue strain), and/or major degrees ( $\geq$ 35% of LA wall volume) of interstitial alterations (atrial fibrosis, fatty infiltrates, amyloid infiltration, inflammation), and/or severe atrial enlargement (LA diameter $\geq$ 5.0 cm, LA volume index $\geq$ 50 mL/m <sup>2</sup> ), and/or long-standing persistent/permanent atrial fibrillation

Functional measurements (LAEF etc.) in sinus rhythm; validation of suggested AtCM stages and cut-off values need to be done in prospective trials. LA, left atrium; LAA, left atrial appendage.

its chronicization.<sup>26</sup> Pro-resolution mediators like resolvin D1 have shown effectiveness in prevention of AF substrate development in animal models of both right<sup>32</sup> and left heart disease.<sup>32,33</sup> Nevertheless, specific differences between various types of inflammation, like sterile inflammatory processes or viral/bacterial infections, cannot be made at present.

### 2.4. Gut microbiome

The gut microbiota is a dynamic system containing microorganisms that produce bioactive metabolites, the type and quality of which depend on lifestyle-related factors (e.g. diet, exercise), among others. This microbiota contributes to the pathophysiology of many cardiovascular conditions like heart failure, hypertension, obesity, and coronary artery disease, and there is accumulating evidence for a role of gut microbiota in AtCM and related arrhythmogenesis.<sup>34</sup> Although many gut microbiota-derived metabolites could play a role in atrial arrhythmogenesis,<sup>34</sup> recent evidence suggests that gut dysbiosis may promote AtCM and AF partly through increased levels of circulating lipopolysaccharide and glucose, along with enhanced activity of the atrial NLRP3 inflammasome, which causes atrial fibrosis.<sup>23</sup> As a proof of causality, faecal microbiota transplantation (FMT) from young (2–3 months) to old (22–24 months) rats reduced atrial fibrosis and the age-related increase in AF susceptibility by attenuating atrial NLRP3-inflammasome activity. Selective inhibition of both lipopolysaccharide and the NLRP3 inflammasome also reduced AF susceptibility and atrial fibrosis, suggesting lipopolysaccharide as a key upstream driver of the atrial NLRP3 inflammasome and the associated arrhythmogenesis.<sup>25,26</sup> Although gut microbiota could create inflammatory AtCM, the precise cellular and molecular mechanisms, as well as the clinical contexts in which this system is active in AtCM, require further investigation.

## 2.5. Reactive lipid mediators of oxidative stress

During inflammation and oxidative stress, lipid peroxidation generates dicarbonyl compounds that adduct to proteins, DNA, and other lipids to promote molecular dysfunction and amyloid formation.<sup>35</sup> The most reactive dicarbonyls are isolevuglandins (IsoLGs),<sup>36</sup> and small molecule scavengers that selectively inactivate these and other lipid dicarbonyls are beneficial in multiple preclinical studies, indicating that IsoLGs are a major component of oxidative stress-related injury.<sup>37</sup> In a murine model of hypertension, IsoLG protein adducts and preamyloid oligomers (PAOs) developed in the atria prior to structural or histologic abnormalities coincident with AF susceptibility. These abnormalities and arrhythmia vulnerability were prevented by administration of a dicarbonyl scavenger 2-hydroxybenzylamine (2-HOBA), but not by an inactive analog 4-hydroxybenzylamine (4-HOBA). These findings support the concept of pre-emptively scavenging reactive downstream mediators, rather than targeting generation of reactive oxidative species *per se*, as a potential therapeutic approach to prevent AtCM. Preclinical and Phase I studies of 2-HOBA have demonstrated its safety and tolerability, and clinical trials in humans are in progress.<sup>38,39</sup>

## 2.6. Atrial adipose tissue and fibro-fatty infiltration

Altered metabolism and increased abundance of epicardial adipose tissue (EAT) in the atria is associated with a higher risk of AF.<sup>40–42</sup> EAT<sup>43–47</sup> could contribute to the formation of the AF substrate by several mechanisms. First, EAT continuously secrete fatty acids that fuel the myocardium, together with a variety of cytokines and peptides, as well as extracellular vesicles.<sup>48,49</sup> Some of these secreted molecules, like TGF $\alpha$ , KIL-1B, and FAPB4, can regulate myocardial electrophysiology, others like adiponectin regulate the oxidative stress of the atrial myocardium.<sup>50–52</sup> Furthermore, during AF, heart failure or in diabetic patients, EAT secretes profibrotic cytokines such as activin-A and metalloproteases that contribute to the spreading of fibrosis from the epicardial layer to the neighbouring subepicardial myocardium.<sup>53–55</sup> Clusters of mononuclear inflammatory cells including cytotoxic CD8+ T-lymphocytes are often observed at the junction between subepicardial fat and fibrotic tissue, resembling lymphocytic myocarditis of patients with AtCM.<sup>56,57</sup> Furthermore, the secretome of abnormal EAT contains several inflammatory chemokines. Therefore, EAT is an important potential contributor to atrial inflammation.<sup>58,59</sup>

The replacement of the EAT beneath the epicardial layer by fibrosis causes fibro-fatty infiltration of the subepicardial atrial layers in AF patients and in aged patients with heart failure or mitral regurgitation.<sup>55,58,60</sup> It is established that subepicardial fibro-fatty infiltration is a major arrhythmogenic substrate in both the ventricles and the atria, favouring epicardial–endocardial asynchrony with local conduction block, breakthroughs, and rotor formation.<sup>61–63</sup> Moreover, 3D computational modelling of human atria integrating MR images and histo-anatomical data suggests that there is a relationship between the slowing of electrical conduction and the degree of fibro-fatty infiltration.<sup>64</sup>

The precise mechanisms regulating the accumulation and shaping of the biological properties of EAT are poorly understood. EAT originates mainly from epicardial progenitor cells (EPC). EPC are normally quiescent in the adult heart, but can be reactivated to differentiate into various lineages, including adipocytes.<sup>65,66</sup> In human atrial myocardium, subsets of cells derived from EPC (EPDC) are confined to the sub-epicardium where they can differentiate into adipocytes or fibroblasts in response to local stimuli. For instance, the ANP secreted by stretched atrial cardiomyocytes induces, at low concentrations, the adipogenic differentiation of EPDC by activating cGMP-dependent signalling pathways.<sup>67</sup> Angiotensin-II produced by the atria can also induce the differentiation of EPDC into fibroblasts, primarily via activation of canonical SMAD2/3, and p38-MAPK signalling pathways.<sup>68</sup> Adipogenic differentiation of EPDC is related to lipid metabolism and

the capacity of EAT to store fat, for example when submitted to an excess dietary fatty acid load.<sup>69</sup> The multiple mechanisms causing the accumulation of EAT likely contribute to the formation of an arrhythmogenic AF substrate over time.

In conclusion, the formation of EAT is a complex interplay between metabolism, inflammation, and oxidative stress, promoting AtCM and AF by local and systemic mechanisms, and may offer new opportunities for management of AtCM/AF.

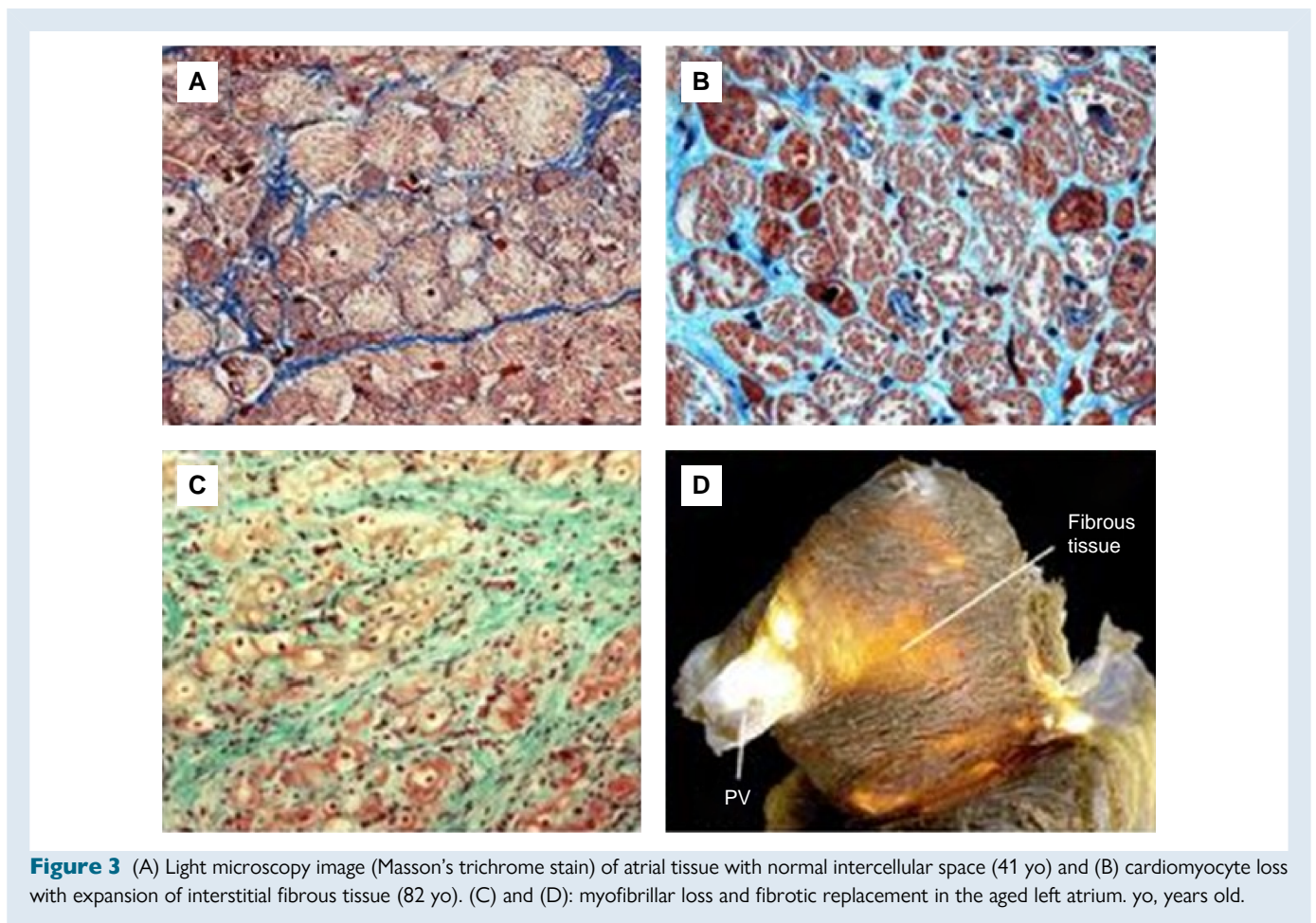
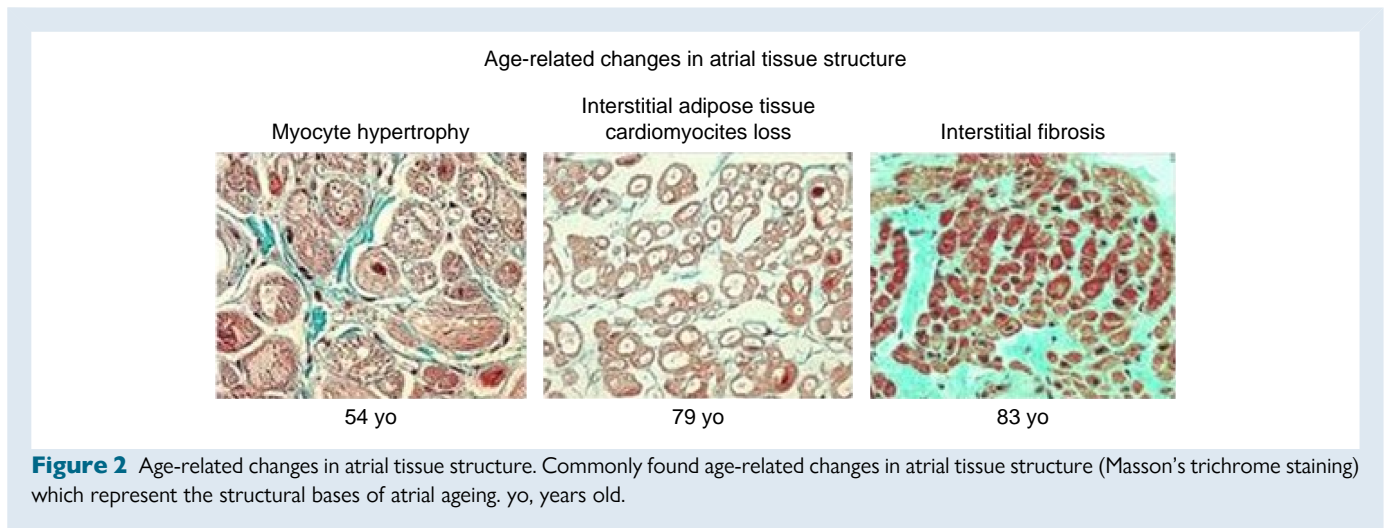
## 3. New findings in the pathophysiology of atrial cardiomyopathy

Many animal model and human studies have revealed a close interplay among AtCM, AF, and stroke, via various mechanisms such as ageing, inflammation, oxidative stress and stretch, which, in turn, lead to fibrosis, electrical, and autonomic remodelling and a pro-thrombotic state.<sup>70,71</sup> The complex interplay between the mechanisms creates a feedback loop of ever-worsening AtCM and higher risk of more sustained AF and strokes.<sup>70</sup> However, there is often a lack of a clear temporal relationship between the onset of AF and stroke. In fact, the current paradigm of selecting individuals at elevated risk of stroke and therefore warranting oral anticoagulation (OAC) therapy, endorsed by major international societies,<sup>71–73</sup> by CHA<sub>2</sub>DS<sub>2</sub>-VASc (including congestive heart failure, hypertension, age, diabetes mellitus, prior stroke/transient ischaemic attack/thromboembolism, vascular disease) or related scores, are all variables related to the risk of AtCM but not the properties of AF *per se* (frequency, duration, ventricular rates, etc.). This observation suggests that additional factors inherent in AtCM may be important contributors to stroke occurrence and that the presence of AF *per se* may not be necessary.<sup>74,75</sup> Of note, the recently published Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy (ARCADIA) trial failed to observe benefit from the oral anticoagulant apixaban in patients with cryptogenic stroke and biomarker evidence of AtCM.<sup>76</sup>

### 3.1. Ageing and atrial cardiomyopathy

One major factor leading to AtCM may be ageing, which leads to progressive decline in the structure and function of the heart and is a leading risk factor for cardiovascular diseases. There is strong epidemiological evidence for a close link between ageing, AF, and stroke. The prevalence of many AF and stroke risk factors, including diabetes, hypertension, and coronary/peripheral atherosclerotic vascular disease, steadily increases with age. All these risk factors contribute to the development of atrial cardiomyopathy, and there is mounting evidence supporting the concept that AtCM not only leads to stasis, but endothelial/endocardial dysfunction and a hypercoagulable state, three key factors in thrombogenesis, as originally described by Virchow.<sup>77</sup>

Tissue remodelling, characterized by myocyte loss, reactive cellular hypertrophy, fibrosis and autonomic nervous system dysregulation, is part of the pathophysiology of AtCM, and a possible common denominator of ageing, stroke, and other AF risk factors (Figures 2 and 3). On the other hand, recent evidence indicates that AF is a major accelerator of ageing of the atrial myocardium (Table 3). At the molecular level, the association between AtCM and ageing (Figure 4) appears to be mediated by oxidative stress,<sup>79</sup> calcium handling dysregulation,<sup>80</sup> electrophysiologic changes, and structural remodelling with apoptosis and fibrosis,<sup>70</sup> all of which contribute to the initiation and/or maintenance of AF, but the mechanisms have been inadequately explored.<sup>81</sup> In fact, it is unknown why some ageing individuals with AtCM develop AF while others do not. Chronic inflammation is associated with several age-related diseases such as atherosclerosis, Alzheimer's disease, sarcopenia, and arthritis.<sup>82</sup> The genesis of chronic inflammation with ageing (so-called 'inflammaging') is unclear but inflammation could be an underlying mechanism connecting



ageing to AtCM and AF.<sup>83</sup> Furthermore, several markers of cellular ageing, such as telomere length, SA- $\beta$ -gal, and p16a are associated with AF.<sup>81</sup> DNA damage, a mechanism underlying cell senescence, has been shown in tachypaced atrial myocytes and patients in persistent AF.<sup>84,85</sup> Clearly, a comprehensive understanding of the molecular mechanisms of intrinsic cardiac ageing, including atrial ageing, will be required to improve understanding of the relation between ageing, inflammation, AtCM, and AF.

Such new understanding should guide the development and future translation of novel therapies to clinical application.

### 3.2. Gender and atrial cardiomyopathy

Based on epidemiologic investigations, women seem less vulnerable to AF development than men,<sup>86</sup> with the prevalence-discrepancy between

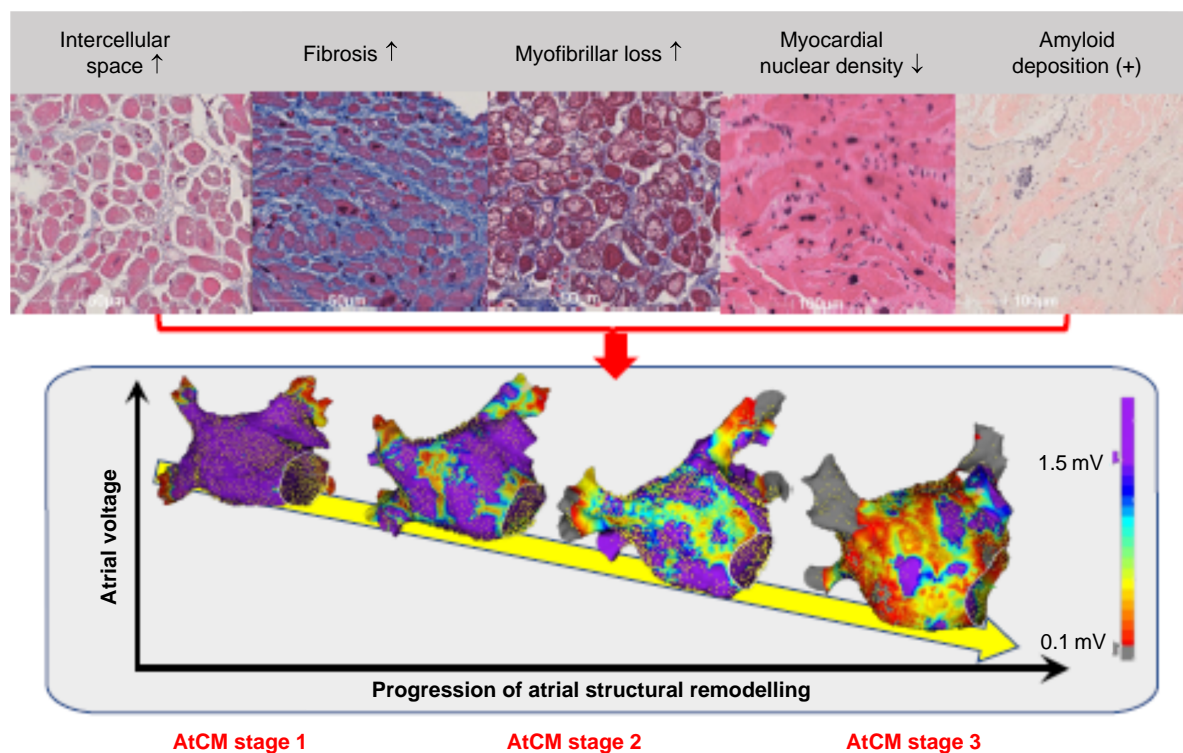
genders becoming less clear with advancing age, in part perhaps due to the higher life expectancy in women or increased amount of epicardial fat.<sup>86–88</sup> A substantial reason for the lower prevalence of AF in women vs. men appears to be their smaller size, since body size (and particularly lean body mass) is a major determinant of AF risk.<sup>89</sup> Furthermore, compared to men, women suffering from AF appear to be exposed to significantly greater risks of all-cause and cardiovascular death,<sup>90</sup> as well as reporting graver symptoms and a worse quality of life, all of which suggest more serious AF-related structural/functional impairment.<sup>91</sup>

Recent studies on AF ablation have also shown significant gender-based differences between males and females, with the latter showing

a higher risk of arrhythmia recurrence<sup>92,93</sup> and increased periprocedural complications and hospitalization rates.<sup>94</sup> In addition, a recent large systematic review and meta-analysis of post-ablation outcomes found that, independently of age, comorbidities, and hospital factors, women display higher rates of complications and readmissions following AF ablation.<sup>95</sup> In 2022, Wong et al. explored whether gender-based electrophysiological substrate differences might explain the aforementioned worse AF ablation outcomes in women. Intriguingly, they found that females are characterized by significantly more conduction velocity slowing, a greater proportion of complex fractionated signals, and at 22-month follow-up, notably poorer single-procedure and multi-procedure arrhythmia-free survival. These results strongly suggest more advanced atrial remodelling in women.<sup>96</sup> Clinical studies have suggested that oestrogen deficiency or oestrogen–progestin imbalance (as that in the luteal phase of the menstrual cycle, during oral contraceptive treatment, during pregnancy, and menopause) may be associated with an increased occurrence of cardiac arrhythmias. The RETAC-group, in a recent study involving 220 AF patients that underwent high-density voltage mapping in SR prior to their first PVI procedure, found that women had greater low-voltage LA voltage-mapping scores than men, with this propensity driven by older women (>60 years) with persistent AF while absent in younger women.<sup>97</sup> Moreover, it has already been demonstrated that administration of oestrogen, whose receptors are significantly expressed in cardiomyocytes, is linked with prolonged action potential duration, atrial and atrio-ventricular nodal

**Table 3** Age-related changes in atrial tissue structure

1. Age-dependent cardiomyocyte loss and myocyte hypertrophy
2. Interstitial changes and increase in intercellular space
3. Enhancement of the interstitial adipose and fibrosis tissue
3. Endocardial fibrosis
4. Inflammatory infiltrates
6. Vacuolar degeneration and Aschoff bodies
8. Iron depositions
9. Amyloidosis



**Figure 4** Histological factor associated with atrial structural remodelling characterized by electroanatomic mapping. The upper panel shows light microscopy images of atrial biopsy samples obtained from patients with non-valvular atrial fibrillation. The lower panel shows examples of high-density bipolar voltage map of the left atrium created during high right atrial pacing at 100 beats per minute. Not only fibrosis, but also increased intercellular space preceding fibrosis, myofibrillar loss, decrease in myocardial nuclear density, and amyloid deposition are associated with the progression of atrial structural remodelling.<sup>78</sup> The rightmost image in the upper panel shows Congo Red staining, the second from the right shows haematoxylin and eosin staining, and the others show Masson's trichrome staining. The colour gradation in the lower panel voltage maps indicates differences in voltage amplitude from purple at 1.5 mV to grey at 0.1 mV, as shown in the colour bar. AtCM, atrial cardiomyopathy (see Table 2 for explanation of AtCM stages).

conduction time, as well as atrial refractoriness, with these functional abnormalities likely due to increased calcium influx leading to weaker repolarizing currents or potassium channel downregulation.<sup>98,99</sup> Moreover, prior investigations had shown that, compared to men, and in individuals with or without AF, women possess greater amounts of atrial fibrosis both in histopathological and cardiac magnetic resonance (CMR) studies.<sup>100,101</sup>

### 3.3. Atrial failure: definitions, causes, and consequences

Over the past few years, various definitions of atrial failure have been proposed, which, in turn, have been based on functional, morphological, or morpho/functional approaches.<sup>102–104</sup> Generally, all of these are based on the concept of ‘atrial cardiomyopathy’ proposed by the original EHRA/HRS/APHRS/SOLAECE expert consensus document.<sup>2</sup> Based on the AtCM staging proposed in Table 2, atrial failure would primarily feature in stage 3 AtCM (Figure 3).

The causes of atrial failure are multiple: (i) Atrial rhythm disorders. Rapid atrial arrhythmias—such as AF—induce ineffective active muscle contraction, with both systolic and diastolic LV dysfunction. A similar LV impairment may also be a consequence of suboptimal electrical AV coupling [e.g. due to long PR interval, left bundle branch block, advanced interatrial block (IAB)]<sup>102</sup>; (ii) Atrial myocardial structural remodelling. Morphological changes at the histological and ultrastructural levels (cardiomyocyte and/or interstitial modifications), often as a consequence of associated cardiac or non-cardiac diseases, along with AF in a vicious cycle (‘AF begets AF’); (iii) Atrial ischaemia, myocarditis, and induced post-ablation stiff LA syndrome. These can lead to increased atrial stiffness, reduced contractility, and electromechanical dissociation.<sup>2,105–108</sup> As for the consequences of atrial failure, heart failure, increased thrombogenicity, and pulmonary hypertension may be caused by altered flow dynamics and suboptimal LV filling; AF may also result from atrial failure and contribute to the consequences.<sup>102,109</sup> Recent investigations have shown that both LA dysfunction and remodelling are independently associated with, or may even herald, the onset of HF in an asymptomatic healthy population, in which reduced atrial reserve during exercise can indicate the first evidence of a failing LA.<sup>110,111</sup> In addition to these pathogenetic mechanisms, atrial electrical dysfunction—and impaired LA–LV coupling—could play a key part in patients suffering from HFpEF.<sup>110,112</sup> By the same token, atrial failure may reveal previously latent LV dysfunction and precipitate a HF syndrome. According to the Frank–Starling law, in the initial stages of LV dysfunction, adaptive atrial chamber dilation develops to counteract higher preload, while an increase in active pump function contributes to preserving adequate LV filling. Further impairment in LA function does nothing to mitigate the above-mentioned disproportionate atrial volume/pressure, leading to higher LA and pulmonary-wedge pressures and manifest atrial failure syndrome, as well as perpetuating a harmful vicious cycle.<sup>102</sup>

Recent evidence suggests a relationship between atrial disease and the risk of stroke independent of AF.<sup>74,75</sup> The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) followed 2580 patients aged ≥65 years with a pacemaker and defibrillator and a history of hypertension but without a history of AF. The authors found that only 15% of patients with subclinical atrial fibrillation (SCAF)-associated embolic events had evidence of SCAF >6 min in duration during the month before their stroke or systemic embolism. In addition, most SCAF that had occurred before embolic events was far shorter than 48 h (the minimum duration which, in the past, was believed to be required for thrombus formation in the LAA before cardioversion).<sup>113,114</sup> Based on the results of this trial, it appears that some thromboembolic events may be secondary to stasis from an actual AF episode, some to persistent endothelial changes (e.g. due to previous AF episodes), and, lastly, some to mechanisms not directly related to AF, in which the supraventricular arrhythmia may simply

represent a risk marker or, if causal, related via complex indirect pathogenetic mechanisms within the context of AF-related AtCM.<sup>115</sup> Two additional clinical studies (TRENDS and IMPACT), have found similar results to those of the ASSERT study on the lack of temporal correlation between AF episodes and cerebrovascular events.<sup>74,75</sup> Interestingly, analysis of data from the Multi-Ethnic Study of Atherosclerosis (MESA) displayed an inverse association between LA reservoir function (as total LA emptying fractions), and the risk of cerebrovascular events, with this association being independent of acknowledged cerebrovascular risk factors and AF itself.<sup>102</sup> These findings suggest value of LA functional parameters in the stratification of individuals at risk for ischaemic cerebrovascular events, particularly in those with no clear evidence of AF.<sup>111</sup> In addition to the risk of thrombosis in AF, the amount of atrial fibrosis in patients with stroke of unknown aetiology seems to be greater than in patients with an identified cause and comparable to those suffering from AF.<sup>102,116–118</sup> Endothelial changes and regional/global wall motion abnormalities associated with increased fibrosis have been proposed as potential risk factors for atrial thrombosis and cerebrovascular events.<sup>102,116,119</sup> Müller-Edenborn et al., in a large cohort of AF patients undergoing TEE prior to electrical cardioversion for AF, found that in individuals with LAA thrombi, 97% of them had a p-wave-based diagnosis of AtCM, which was associated with reduced LAA-flow velocity at TEE. This study adds further evidence that AtCM is associated with both prolonged atrial conduction time and reduced contractile function with reduction in LAA-flow velocity, especially in those who develop LAA thrombi.<sup>120</sup> The observation of the ARCADIA trial of no benefit from apixaban in patients with cryptogenic stroke and biomarker evidence of AtCM argues against the idea that AtCM without clinical AF increases the risk of stroke appreciably, but further consideration of the results and design of the trial is needed before any definite conclusions can be made.<sup>76</sup>

The rhythm and contraction of the atria contribute to efficient coronary blood flow. Controlling for other known risk factors, patients with AF have a three-fold increased risk of myocardial infarction,<sup>121</sup> possibly because irregular, shortened diastole with altered flow reserve is a common cause of ventricular ischaemia and a contributor to type 2 myocardial infarction.<sup>122,123</sup> Additional mechanisms involved in the pathogenesis of atrial ischaemia/infarction in individuals with atrial myopathy/AF include increased inflammation/oxidative stress, altered platelet activation, and particularly atrial thromboembolism, which can occur even in the absence of AF.<sup>111,124</sup>

Atrial dysfunction secondary to supraventricular arrhythmias involves activation of neurohormonal pathways, (e.g. RAA system and vasoactive peptides) and can induce ventricular chamber dilation with altered systolic and diastolic cardiac function. In this scenario, the LV myocardium shows inflammation, cardiomyocyte histopathological changes, and loss of normal myocardial extracellular matrix (ECM) structure, composition, and function.<sup>125</sup>

### 3.4. Atrial functional valvular regurgitation

Atrial functional mitral and tricuspid regurgitation are clinicopathological conditions, which are closely related to atrial failure and atrial dilatation.<sup>126–129</sup> Secondary or functional mitral and tricuspid regurgitation (FMR; FTR) is defined as valvular regurgitation caused by abnormal left/right heart function as opposed to primary structural valve changes.<sup>130</sup> While FMR/FTR is most often the result of abnormalities in left/right ventricular remodelling, more recently recognized is the entity of atrial FMR (AFMR/AFTR). In this scenario, ventricular geometry and function are relatively preserved, the culprit being mitral/tricuspid annular enlargement associated with left/right atrial dilatation, which results in poor coaptation of the valve leaflets causing AFMR and AFTR. Compared to ventricular FMR, the entity of AFMR/AFTR, including its prevalence, pathophysiology, prognostic implication, and potential therapy, is less clear.<sup>126,127,129</sup> Variability in the literature as to the definition of AFMR is a contributing factor. Recently, an expert opinion paper has been communicated that

presents a unifying definition of AFMR.<sup>131</sup> The major criteria for AFMR include normal LV cavity size and systolic function (global and regional), and the presence of both mitral annular dilation and LA enlargement. The LV may dilate secondarily in later stages of significant AFMR. AFMR is primarily rooted in excessive LA and mitral annular dilation which pulls both leaflets apart and thereby causes leaflet tethering and malcoaptation.<sup>132,133</sup> Generally, two common clinical scenarios may lead to excessive LA and subsequent mitral annular dilation in the context of preserved LV function: AF and/or HFpEF.<sup>132</sup> Both syndromes are linked by LA remodelling and dysfunction. AF is known to be both cause and consequence of atrial remodelling.<sup>102</sup> In addition, chronically elevated filling pressures in HFpEF may induce adverse anatomical and functional LA remodelling. Furthermore, AF and HFpEF are strongly inter-related as they share common cardiovascular risk factors and potentiate each other. In patients with AF, restoration of sinus rhythm is associated with reduction in LA volumes, mitral annular size, and the degree of MR.<sup>134,135</sup> Although this observation suggests that rhythm rather than rate control in AF might mitigate AFMR, this idea has not been formally tested.

Recent data point to a high prevalence of occult HFpEF among patients with AF and dyspnoea, especially in those who remain symptomatic after sinus rhythm restoration.<sup>136,137</sup> This observation has led several groups to discern an AF-predominant HFpEF subtype with more advanced LA myopathy, disproportionate to the degree of LV dysfunction.<sup>137–139</sup> The occurrence of AFMR in HFpEF is another marker of this subtype of advanced AtCM, leading to worse haemodynamics and poorer exercise reserve.<sup>134</sup> A recent community study of moderate-to-severe isolated MR found that only 50% of patients with AFMR had a history of AF.<sup>135</sup> Even when mild-to-moderate, the presence of AFMR tended to be associated with worse outcomes, though this association faded after correcting for LA cardiomyopathy. While this latter finding may suggest that the degree of AtCM is of greater importance in prognostic significance compared to AFMR *per se*, it does not refute the concept that treating AFMR in HFpEF could be beneficial by improving AtCM and thereby outcomes. In addition, recent cross-sectional data cannot disentangle the sequence of causality between AFMR, LA cardiomyopathy, and HFpEF. Presumably, a bidirectional relationship exists between AFMR and AtCM.<sup>134</sup> Future prospective studies are needed to answer these questions.

### 3.5. Metabolic disorders and atrial cardiomyopathy

Metabolic disorders are the most common modifiable risk factors for AtCM and AF.<sup>43–47</sup> This relationship is well established for obesity, diabetes, and metabolic syndrome, whereas it is still debated for liver steatosis-associated diseases.<sup>140,141</sup> In the Framingham heart study, diabetes is associated with 40% increased risk of AF, and the risk increases with the duration of AF.<sup>142,143</sup> High BMI is also associated with a higher incidence of AF.<sup>144</sup>

Metabolic diseases can directly impact the progression of AF substrate and AtCM through several mechanisms and signalling pathways.<sup>43,45</sup> For instance, diabetes and glucose intolerance are characterized by inefficient energy production and metabolic inflexibility of the atrial myocardium with predominance of fatty acid beta-oxidation, mitochondrial dysfunction, and ROS production.<sup>145</sup> This metabolic remodelling has a marked impact on atrial excitability and contractile properties, for example, explaining the decreased peak longitudinal strain function and left atrial deformation reported in diabetes mellitus patients.<sup>111</sup> The excitation–contraction coupling process of cardiomyocytes is tightly controlled by cellular metabolism. Abnormal activity of several calcium and potassium channels of atrial cardiomyocytes have been reported in experimental models of diabetes.<sup>146</sup> K-ATP channels that are normally closed and preferentially coupled to glycolysis over beta-oxidation lipolysis, are open in atrial myocytes of dysmetabolic mice, contributing to action potential shortening.<sup>69</sup>

An excess of dietary fatty acids can induce an adaptive metabolic signature of the atrial myocardium characterized by impaired glycolysis and predominance of fatty acid oxidation.<sup>67</sup> Furthermore, when the uptake of lipid by atrial cardiomyocytes overwhelms their beta-oxidation capacity, a process of lipid storage ensues, activated through elongation of fatty acids, recruitment of adipogenic transcription factors, and adipogenic differentiation of progenitor cells.<sup>69</sup> Altogether, these phenomena result in accumulation of intramyocardial lipid and expansion of EAT,<sup>147</sup> whose role in the progression of AtCM and risk of AF is detailed elsewhere in this article. However, it must be noted here that metabolic disorders have specific impacts on EAT properties. For instance, in obese or diabetic patients, EAT secretes inflammatory cytokines which favour myocardial fibrosis and contribute to altered excitability.<sup>148</sup> By analogy with what is known for ventricle remodelling or atherosclerotic plaque, another potential interface between metabolic disorders and myocardial inflammation are macrophages.<sup>149,150</sup> Clinical studies are warranted to investigate the impact of improving metabolic status of patients on the risk of AF and AtCM.

### 3.6. Atrial cardiomyopathy and atrial ablation

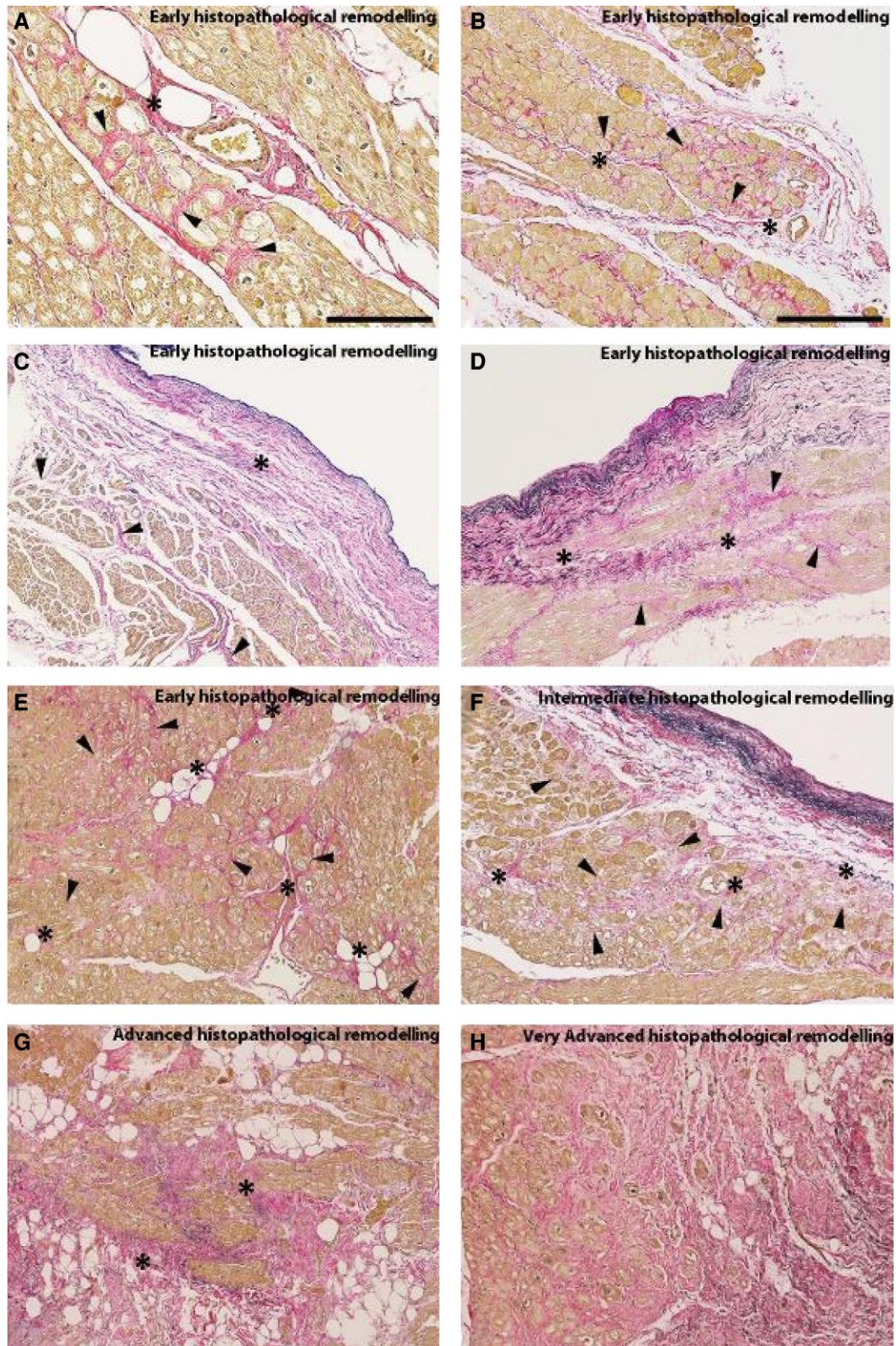
Structural remodelling, including histological and anatomical-structural changes, contributes to the trigger and maintenance mechanisms of AF<sup>151</sup> (Figure 4). Conversely, long-lasting AF itself also contributes to the progression of AF, leading to AtCM.<sup>152</sup> The most effective way to interrupt this vicious cycle between AF maintenance and AtCM is to restore sinus rhythm. AF ablation is the most effective rhythm control strategy; it significantly reduces AF burden and prevents the progression of AtCM.<sup>153,154</sup> Using bipolar voltage mapping and MRI, Sugumar et al.<sup>155</sup> reported that rhythm control by AF ablation induces recovery of atrial electrical and structural changes, suggesting that AF ablation may result in some reversal of AF-induced AtCM (see Section 7).

### 3.7. The development of atrial fibrosis

Fibrosis is a central, causally related pathophysiological component of AtCM.<sup>156,157</sup> It is now well established that the extent of LA interstitial fibrosis roughly parallels the biological/clinical history of AF; i.e. from early structural remodelling in most sinus rhythm patients, to paroxysmal, persistent, and, ultimately, long-standing lasting persistent AF.<sup>157,158</sup> Additionally, interstitial fibrosis is often a progressive multi-step event in anatomical/architectural terms, with, in most cases, the pulmonary vein outlet area being the predominant initial location, with subsequent progression extending the pathology to the rest of the LA.<sup>105,159,160</sup>

The above-mentioned pathogenic peculiarities have raised various interesting questions, such as (i) Why is the pulmonary vein area—and, in a broader sense, the left atrial posterior wall—the area most prone to fibrosis (and structural remodelling in general)? (ii) Assuming that interstitial collagen deposition occurs through autocrine/paracrine mechanisms, what are the key cellular sources and cell-networks involved? (iii) Is collagen deposition in the atria a ‘local affair’, i.e. are atrial mesenchymal cell-components the only players in this process? Do any extra-cardiac mesenchymal components cooperate in the development of interstitial structural remodelling?

There are several possible explanations for why fibrosis begins in the LA posterior wall: (i) According to Laplace’s law, the left atrial posterior wall is prone to greater stress than the left atrial appendage or other LA free walls. This is because the LA posterior wall is the thinnest part of the LA, blood pressure is similar throughout the LA and LA appendage, and the LA chamber volume is greater than that of the LA appendage; (ii) Anatomically, the LA posterior wall is close to the pulmonary vein orifices, a region subject to intense and continuous mechanical stretching; (iii) Embryologically, the LA appendage develops from the embryonic LA, whereas the LA proper originates from an outgrowth of the pulmonary vein.<sup>105,159</sup> It has also recently been suggested that, in AF



**Figure 5** Microphotographs captured from left atrial biopsies belonging to patients suffering from long-lasting atrial fibrillation associated with severe mitral-valve regurgitation. These histopathological sections have been stained with a combined Weigert/Van Gieson dye where cardiomyocytes are highlighted in yellow-brown, collagen fibres in red, and elastic fibres in black. (A) Medium-power view of a developing *Early-Stage histopathological remodelling* (ATCM stage 1) where multiple foci of interstitial fibrosis (arrowheads) stem from the adventitia of a penetrating coronary branch (asterisk). (continued)

patients, atrial fibrosis (assessed by magnetic resonance imaging (MRI) with late gadolinium enhancement) might be more extensive in the area adjacent to the descending thoracic aorta, with its extent inversely correlated with the distance between LA and the aorta.<sup>161,162</sup> A recent study explored fibrotic remodelling in LA biopsies from a series of patients with and without AF.<sup>158</sup> In the vast majority of cases, collagen fibre deposition begins unevenly throughout the atrial myocardium, with separate fronts of fibrosis progressing from both the adventitial/periadventitial tissues and the thickened sub endocardium into the inter-cardiomyocyte interstitium. This tendency might be explained by the fact that both the adventitia and sub endocardium are already richer in collagen-producing cells under normal conditions. Subsequently, fibrosis becomes increasingly widespread and more homogeneous by gradually filling in the preserved myocardial areas. On these grounds, fibrosis stages might be defined as follows: early, presence of sparse single myocardiosclerotic foci originating from the sub endocardium or the periadventitial tissues; intermediate, formation of multiple single myocardiosclerotic foci originating from the subendocardium or the periadventitial tissues; advanced, generation of confluent myocardiosclerotic foci; and very advanced, development of areas of diffuse fibrosis (Figure 5).<sup>163</sup> In agreement with this concept, elevated circulating fibrocytes have been proposed as a marker of left atrial fibrosis (in low-voltage regions) and AF recurrence.<sup>164,165</sup>

As mentioned above, the deposition of collagen in the extracellular space is an important hallmark of atrial fibrosis, and AtCM develops as a consequence of many pathophysiological processes, including inflammation, oxidative stress, ischaemia, and AF itself (Figure 5).<sup>2,43,45</sup> However, the process of fibrosis is broader than just the deposition of collagens and encompasses the proliferation of fibroblasts and other mesenchymal cells and their differentiation into  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) expressing myofibroblasts, and the deposition of significant amounts of a range of ECM proteins, including various molecular species of collagen as well as other matricellular proteins (Figure 5).<sup>166–168</sup> In a proteomic analysis of ECM proteins in left and right atria of patients with and without AF, the glycoprotein decorin was found to be most altered.<sup>169</sup> Decorin is implicated in collagen fibrillogenesis and the production of a variety of other ECM molecules involved in cellular signalling: cleaved decorin suppress myostatin activity and increases myocyte size. These effects are similar to observations in a goat model of pacing-induced AF.<sup>170</sup> Another analysis of the full proteome of atrial tissue of patients with and without AF identified neutrophil degranulation as the most upregulated process in AF, and the reactive oxygen donor myeloperoxidase as the most abundantly upregulated protein. Myeloperoxidase, in turn activates atrial fibroblasts and promotes ECM expansion.<sup>171,172</sup> A whole-genome RNA sequencing analysis of LA tissue of patients with no AF, paroxysmal or persistent AF suggested epithelial-to-mesenchymal transition as an important driver of fibrosis formation and AF progression. Interestingly, increased (or decreased) proteins in paroxysmal vs. non-AF tended to increase (or decrease) further in persistent vs. paroxysmal AF.<sup>173</sup> It has been shown in experimental models that early molecular and electrophysiological

abnormalities precede LA structural remodelling and the formation of fibrosis. Several kinases, including liver kinase B1 (LKB1) and atrial AMP-activated protein kinase (AMPK) regulate transcription factors involved in the expression of ion channels and fibrosis and contribute to AtCM.<sup>43,45,174</sup> These studies provide a link between inflammation and metabolic stress and the development of AtCM. The PREDICT AF trial demonstrated upregulation of various ECM proteins, including collagen1A1, collagen 3A1, collagen8A2, tenascin-C, thrombospondin-2, and biglycan in patients without a history of AF or AtCM who develop AF during the subsequent months or years.<sup>175</sup>

## 4. Imaging advances

The multimodality evaluation of atrial size and function using cardiac imaging is key to the diagnosis of AtCM and the characterization of the degree of atrial damage.<sup>176</sup>

### 4.1. Atrial imaging tools in the evaluation of atrial cardiomyopathy

AtCM can be evaluated with echocardiography, CMR imaging, and cardiac computed tomography (CCT). Echocardiography and CMR allow continuous recording of atrial volumes through the cardiac cycle. CCT evaluates accurately atrial volume at a single point in the cardiac cycle. Three-dimensional transthoracic echocardiography (TTE) avoids the problem of foreshortening of the atria that can occur with two-dimensional TTE.<sup>177</sup> Left and right atrial appendages are more specifically characterized by transoesophageal echocardiography (TEE) and CCT. CCT is also validated in the evaluation of EAT and has been recently implemented with deep learning algorithms.<sup>178</sup> The progression of LA roof shape, as determined by CT, is associated with the development of non-PV arrhythmic substrates in patients undergoing AF ablation.<sup>179,180</sup> Pre-AF ablation CCT-based regional wall deformations were better predictors of low-voltage area than other remodelling surrogates, suggesting potential clinical utility.<sup>181</sup>

CMR has been applied to evaluate atrial fibrosis with late gadolinium enhancement analysis and atrial velocity based on 4D flow imaging (see detailed discussion below).<sup>182,183</sup> The specific characteristics of each technique in atrial evaluation are summarized in Table 4.

### 4.2. Atrial size and function

The atria serve a variety of important functions, e.g. (i) as a reservoir for blood prior to ventricular filling, (ii) as a transport chamber for the conduit of blood during diastole, and (iii) as an active booster pump during atrial systole. Three main atrial volumes reflect these three main functional phases of the atria during the cardiac cycle: (i) maximum atrial volume, evaluated in end-systole during the reservoir phase, (ii) pre-atrial contraction volume evaluated in mid-diastole during the conduit phase and (iii) minimum atrial volume evaluated in late diastole during the booster-pump

#### Figure 5 Continued

(B) Low-power view of an incipient *Early-Stage histopathological remodelling* with multiple interstitial fibrosis foci (arrowheads) originating from a longitudinally oriented blood vessel (asterisks). (C) An initial *Early-Stage AtCM histopathological remodelling* with a fibroelastotic endocardial thickening (asterisk) from which newly deposited collagen fibres enlarge the adventitia of subendocardial blood vessels (arrowheads). (D) Incipient *Early-Stage histopathological remodelling* interstitial fibrosis (arrowheads) stemming from an endocardium thickened by fibroelastosis which had also enlarged local blood vessel adventitia (asterisk). (E) *Early-Stage histopathological remodelling* characterized by multiple foci of interstitial fibrosis (arrowheads) that had originated from sparse penetrating blood vessel adventitias (asterisks). (F) Another type of *Intermediate-Stage histopathological remodelling* (AtCM stage 2) compound interstitial fibrosis (arrowheads) which takes origin from two blood vessels and a thickened endocardium (asterisks). (G) *Advanced-Stage histopathological remodelling* characterized by confluent myocardiosclerotic foci (asterisks). H. Compact and diffuse areas of interstitial fibrosis (*Very Advanced-Stage histopathological remodelling*: AtCM stage 3). Staining. (A–G) Weigert/Van Gieson combined dye. Original magnifications. (A):  $\times 20$  (scale bar is  $150\mu\text{m}$ ); (B–G):  $\times 10$  (scale bar in (B) is  $300\mu\text{m}$ ).

**Table 4** Atrial imaging tools: utility of multimodality imaging

Atrial parameters	TTE	TEE	Cardiac MRI	Cardiac CT	Electroanatomic mapping <sup>a</sup>
Atrial Size	++ (more accurate in 3D TTE)	—	++	+++	+
Atrial Function	+++ (more accurate in 3D TTE)	—	+++	+	—
Atrial appendage size	—	+++	+	+++	—
Thrombus	+	+++	++	+++ (delayed acquisition) <sup>b</sup>	—
Epicardial adipose tissue	+	—	+	+++	—
Atrial fibrosis	—	—	+(LGE) <sup>b</sup>	—	+
Atrial velocity	—	++ (exclusively in atrial appendage)	+++ (4D flow imaging)	—	—
Atrial activation/ conduction time	—	—	—	—	+ p-wave duration

LGE, late gadolinium enhancement; 3D, Three-dimensional; TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; MRI, magnetic resonance imaging; CT, computed tomography.

<sup>a</sup>Electroanatomic mapping includes voltage mapping, activation sequence mapping, and evaluation of conduction velocity and fractionated electrograms.

<sup>b</sup>Contrast agents are necessary.



**Figure 6** Atrial size and function during the cardiac cycle: volume (A) and strain (B) curve analysis. Precise calculations: Total EF = [(maxAV – minAV)/maxAV]; Expansion Volume = [(maxAV – minAV)/minAV]; Passive EF = [(maxAV – preAV)/maxAV]; Active EF = [(preAV – minAV)/preAV]. Abbreviations: maxAV, Maximal Atrial Volume; minAV, Minimal Atrial Volume; preAV, Pre-atrial contraction Volume; EF, Emptying Fraction.

**Table 5** Multimodal assessment of cardiac chamber anatomy and function in AF: assessment of stroke risk prediction using LA strain study

Author, year, Reference	Population	Technique, methods of evaluating parameters	Results
<b>Stroke risk prediction with LA deformation studies</b>			
Shih, 2011 <sup>178</sup>	<ul style="list-style-type: none"> <li>66 patients</li> <li>Permanent AF</li> <li>two groups according to the presence of a history of stroke or not</li> </ul>	<ul style="list-style-type: none"> <li>2D TTE</li> <li>LA Strain</li> </ul>	<ul style="list-style-type: none"> <li>Compared to AF patients without stroke, AF + stroke patients have a lower atrial strain (all components)</li> <li>In multivariate analysis adjusted for age, indexed LA volume, and LVEF, active and reservoir phases of strain were independently associated with stroke risk, (association not present for conduit strain, E', and E/E')</li> </ul>
Azemi, 2012 <sup>182</sup>	<ul style="list-style-type: none"> <li>Retrospective study</li> <li>Patients with AF, stroke or TIA, and CHADS<sub>2</sub> scores ≤1 before their event were retrospectively identified and compared with age- and sex-matched controls</li> </ul>	<ul style="list-style-type: none"> <li>2D TTE</li> <li>LA Strain</li> </ul>	<p>Compared to controls, patients with AF, stroke or TIA and CHADS<sub>2</sub> scores ≤1 before their event had:</p> <ul style="list-style-type: none"> <li>Lower LVEF</li> <li>Larger LA size and LAV (32.3 ± 13.3 vs. 24.4 ± 11.9 mL/m<sup>2</sup>; P = 0.012)</li> <li>A lower peak of LA negative strain (−3.2 ± 1.2% vs. −6.9 ± 4.2%; P &lt; 0.001) and a lower peak of LA positive strain (14 ± 11% vs. 25 ± 12%; P &lt; 0.001)</li> <li>Peak negative of LA strain was significantly associated with stroke (OR 2.15; P &lt; 0.001)</li> </ul>
Obokata, 2014 <sup>183</sup>	<ul style="list-style-type: none"> <li>Prospective study</li> <li>Paroxysmal AF or persistent AF with an acute embolic event (82 patients) or without (204 controls)</li> </ul>	<ul style="list-style-type: none"> <li>2D TTE</li> <li>LA Strain</li> </ul>	<ul style="list-style-type: none"> <li>26 patients with acute embolism died during follow-up with a median follow-up time of 425 days</li> <li>The global LA strain was lower in patients with acute embolism compared to the control group (P &lt; 0.001)</li> <li>In multivariate analysis, global LA strain was independently associated with acute embolism (OR 0.74; 95% CI 0.67, 0.82; P &lt; 0.001) and had an incremental value in addition to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (P &lt; 0.0001)</li> <li>Global LA strain independently predicts mortality after embolism</li> </ul>
Leung, 2018 <sup>184</sup>	<ul style="list-style-type: none"> <li>1361 patients</li> <li>First diagnosis of AF</li> <li>7.9 years follow-up on stroke occurrence</li> </ul>	<ul style="list-style-type: none"> <li>2D TTE</li> <li>LAV, LA strain, LV GLS</li> <li>PA-TDI, reflects the total atrial conduction time</li> </ul>	<p>100 patients (7%) developed an ischemic stroke</p> <p>Despite the similarity of LV dimensions, LVEF, longitudinal global strain, LA volumes patients with AF and stroke have in comparison with patients without stroke have:</p> <ul style="list-style-type: none"> <li>Lower LA reservoir strain (14.5% vs. 18.9%; P = 0.005)</li> <li>Lower conducted strain (10.5% vs. 13.5%; P = 0.013)</li> <li>Longer PA-TDI (166 vs. 141 ms; P &lt; 0.001)</li> </ul>

2D, two-dimensional; 3D, three-dimensional; AF, atrial fibrillation, TTE, transthoracic echocardiography; LAV, LA volume; LA, left atrium; LVEF, left ventricular ejection fraction; CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LV, left ventricle; OR, odds ratio; PA-TDI, P-wave to A' duration on tissue Doppler imaging.

phase (Figure 6). Atrial function indices are calculated from the different atrial volumes. Atrial total emptying fraction and expansion index consider minimal and maximal atrial volumes, atrial passive emptying fraction considers maximal and pre-atrial contraction volumes, atrial active emptying fraction considers pre-atrial contraction and minimal volumes. Atrial strain is evaluated using TTE and cardiac CMR during the three phases of the atria: reservoir strain, conduit strain and contractile strain

(Figure 6; supplementary material online, Figure S1 and S1.1). Notably, CCT emerges as a valuable tool for comprehensively evaluating atrial function in AtCM. CCT provides unparalleled spatial resolution when compared to other imaging methods, allowing detailed assessment of atrial function and morphology.<sup>184</sup> Different studies define normal values of size and function for the left and right atria in the different phases of the cardiac cycle in TTE, CMR, and CCT (see Supplementary material online,

*Table S1*).<sup>185–192</sup> Recently, data in the literature suggest that LA reservoir strain <18% could be useful in heart failure to define high left ventricular filling pressures. However, to the best of our knowledge, there is no cut-off value defining irreversible atrial dysfunction in AtCM (*Table 2*; *Table 5*).

### 4.3. LA late gadolinium-enhanced cardiac magnetic resonance imaging

Late gadolinium-enhanced CMR (LGE-CMR) methods play a pivotal role for diagnostic and prognostic assessment of ventricular cardiomyopathies. LGE may be caused by conditions that significantly increase the interstitial space or that slow down gadolinium exit.<sup>193</sup> LGE is a marker of myocardial fibrosis in chronic myocardial infarction and various non-ischaemic cardiomyopathies. In addition, LGE may represent an increase in the interstitial space caused by interstitial oedema or by tissue infiltration of inflammatory cells, like acute myocarditis or cardiac sarcoidosis.<sup>193,194</sup> Interstitial overload of amyloid proteins is also a potential cause of LGE.<sup>193</sup> In recent years, LGE-CMR methods have been developed in an attempt to systematically image and quantify LA fibrosis.<sup>181</sup> However, LGE-CMR presents challenges for the detection of LA fibrosis, including lack of standardized acquisition protocols and processing techniques, and low image resolution related to the thin LA wall,<sup>2,195</sup> and is still available only in a limited number of research centers. Recent studies comparing the most common LGE-CMR methods revealed considerable discrepancies in global and regional LGE extent.<sup>196,197</sup> LGE-CMR cannot be used to visualize diffuse fibrosis because 'normal' myocardium with diffuse fibrosis is nulled to highlight focal scar, resulting in loss of information on any background interstitial expansion.<sup>198</sup> This limitation is potentially quite problematic in light of an autopsy study showed that atrial fibrosis is often a diffuse process.<sup>199</sup> LGE regions detected in the atria may represent relatively advanced fibrotic or non-fibrotic lesions. Studies using LGE-CMR to quantify LA fibrosis have provided interesting observations such as anchoring of LA rotors at the border between fibrotic and non-fibrotic zones,<sup>200</sup> a correlation between greater fibrosis and more AF recurrence post-AF ablation<sup>201</sup> and a relationship between the extent of LA fibrosis and stroke risk.<sup>202</sup> Two recent randomized controlled studies reported that targeting LA fibrosis detected on LGE-MRI in addition to PV isolation, compared to PV isolation alone, resulted in no significant improvement in atrial arrhythmia recurrence rates.<sup>203,204</sup>

### 4.4. Electroanatomic mapping

Electroanatomic mapping has been widely used during catheter ablation (CA) procedures to define AtCM. Electroanatomical mapping provides voltage mapping, activation sequence mapping, and evaluation of conduction velocity and fractionated electrograms.<sup>78,196,205,206</sup> A reduction in endocardial bipolar voltage amplitudes, represented as low-voltage areas on electroanatomic maps (LVA, commonly defined as an area with bipolar voltage <0.5 mV), has been widely used as a marker for AtCM. Diffuse voltage reductions are associated with increase in left atrial volume and other cardiovascular risk factors (*Figure 4*).<sup>205</sup> LVAs have been considered a surrogate of local fibrosis. An electroanatomical mapping study showed that atrial bipolar voltage reduction is a diffuse process; with LVAs being local reflections of diffuse voltage reduction associated with histological fibrosis.<sup>205</sup> However, a recent atrial biopsy study showed that not only fibrosis, but also other histological factors including increased extracellular space, myofibrillar loss, decreased myocardial nuclear density, and amyloid deposition are associated with atrial voltage reduction, reflecting associated complex pathological changes (*Figure 4*).<sup>78</sup>

### 4.5. Prediction of incident atrial fibrillation by cardiac imaging

At present, no specific AF treatment decision is based solely on cardiac imaging. In large cohort studies using TTE and CMR, increases in LA

volumes and decreases in LA function were associated with incident AF.<sup>207–211</sup> In a large multi-ethnic population, larger RA volume indices were also independently associated with incident AF after adjustment for cardiovascular risk factors and LA parameters.<sup>212</sup> CCT-determined EAT mass appears correlated with the risk of incident AF.<sup>213,214</sup> In addition, EAT volume is highly associated with paroxysmal and persistent AF independent of traditional cardiovascular risk factors.<sup>41</sup> Impaired LA function and LA enlargement were associated with the number of premature atrial contractions per hour on extended ambulatory electrocardiographic monitoring.<sup>215,216</sup>

### 4.6. Recurrent atrial fibrillation

The progression of LA roof shape, as determined by CT, is associated with the development of non-PV arrhythmic substrates in patients undergoing AF ablation.<sup>179,180</sup> Pre-AF ablation CCT-based regional wall deformations were better predictors of LVA presence than other remodelling surrogates, suggesting potential clinical utility.<sup>181</sup> LA fibrosis extent estimated by LGE-CMR is significantly and independently associated with recurrent arrhythmia post-AF ablation.<sup>201</sup> However, two recent randomized controlled studies reported that targeting LA fibrosis detected on LGE-MRI in addition to PV isolation, compared to PV isolation alone, resulted in no significant improvement in atrial arrhythmia recurrence rates.<sup>203,204</sup> The authors suggested that the lack of benefit from fibrosis-guided ablation is explained by limited overall fibrosis burden in the cohort<sup>204</sup> and technical challenges, including lack of standardized and established end-points for fibrosis ablation.<sup>203</sup> They also hypothesized that different types of fibrosis can occur in atrial tissue, including interstitial and reparative fibrosis, unequally contributing to AF development.<sup>203</sup>

### 4.7. Reverse atrial remodelling and atrial remodelling

Cardiac imaging could be useful to predict reverse cardiac remodelling following treatment of AF<sup>217</sup> and to evaluate anatomical and functional components of reverse remodelling, as well as improvement in functional atrio-ventricular valve regurgitation after restoration of sinus rhythm.<sup>218</sup> Using CCT, Huang et al.<sup>219</sup> observed that atrial remodelling begins with increased atrial (LA and RA) volumes after 6 min of atrial high-rate episodes (AHRE), and atrial contractile dysfunction (both LA and RA) manifests when the duration of AHRE exceeded 6 h.

### 4.8. Risk stratification

Using CCT, Tsao et al.<sup>220</sup> in their investigation of atrial remodelling in relation to AF-related stroke, found that increased age and reduced booster-pump function of the atria are independently associated with stroke occurrence, suggesting that substrate-based assessments might enhance stroke risk stratification in AF patients. LA strain analysis appeared to improve the risk stratification of thromboembolism in patients with AF<sup>183</sup> and to discriminate the presence of LA or LA appendage (LAA) thrombus on TEE.<sup>221,222</sup> LAA morphologies and volume are correlated with the history of ischaemic stroke and transient ischaemic attack.<sup>223,224</sup> AF resulted in overall impaired flow dynamics in both LA and LAA.<sup>225</sup> Regardless of history of AF, patients at moderate-to-high risk of stroke exhibit modified flow characteristics in the LA on CMR.<sup>225,226</sup> A greater atrial FDG uptake on PET-scanning was associated with a greater prevalence of stroke in AF patients.<sup>227</sup> The presence of LVA has been reported to be associated with history of stroke and subclinical cerebral ischaemia (SCI)<sup>228</sup> and concurrent heart failure with systolic dysfunction in patients with non-valvular AF.<sup>229</sup> In addition, a recent observational study enrolling 1488 patients undergoing AF ablation showed that LVA presence and its extent were both associated with poor long-term composite end-points of death, heart failure, and stroke, irrespective of AF recurrence or other confounders.<sup>230</sup> Cardiac imaging allows identification

of early atrial dysfunction and its systematic integration in the characterization of AtCM, and as a diagnostic and prognostic imaging tool merits active investigation.<sup>227</sup>

## 5. Biomarkers, omics, ECG parameters

### 5.1. Biomarkers

A whole range of biomarkers, whether urine, blood, imaging, or ECG-based, have been proposed as surrogates of an 'AtCM state' that may predict the occurrence and progression of AF. Blood-based biomarkers can be used in combination with ECG/electrophysiological or echocardiographic data, to define such a state. These biomarkers can be electrophysiological, structural, haemodynamic, serological, and genetic (Table 6). Importantly, these biomarkers of atrial cardiomyopathy have all been associated with the risk of stroke, even in the absence of overt AF. Hence, they have been used as inclusion criteria in some studies investigating AtCM in relation to stroke or cerebrovascular risk, as defining criteria for the condition. For example, in the ARCADIA trial,<sup>232</sup> which investigated patients with cryptogenic ischaemic stroke and atrial cardiomyopathy, the inclusion criteria included patients  $\geq 45$  years of age with embolic stroke of undetermined source (ESUS) and evidence of AtCM defined as  $\geq 1$  of the following markers:

**Table 6** Potential biomarkers associated with atrial cardiomyopathy and stroke risk

Biomarkers classified into categories	Specific examples
<b>Electrophysiological</b>	
Atrial fibrillation	Subclinical atrial fibrillation
P-wave features	P-wave terminal force in lead V1 Duration of amplified p-wave P-wave morphology
<b>Paroxysmal supraventricular tachycardia</b>	
Atrial ectopy	Excessive supraventricular ectopic activity
<b>Structural</b>	
Left atrial size	Left atrial enlargement, left atrial volume index
LAA morphology	Non-chicken wing type
Myocardial fibrosis	Regions of delayed gadolinium enhancement on cardiac MRI
<b>Haemodynamic</b>	
LAA-flow velocity	Low flow velocity
<b>Serological</b>	
NT-proBNP, BNP	
Hs-cTnT	
<b>Genetic</b>	
Polymorphisms	rs2200733, rs10033464 in chromosome 4q25

LAA, left atrial appendage; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; BNP, brain natriuretic peptide; Hs-cTnT, high-sensitivity cardiac troponin T.<sup>231</sup>

P-wave terminal force  $>5000 \mu\text{V} \times \text{ms}$  in ECG lead V<sub>1</sub>, serum NT-proBNP  $> 250 \text{ pg/mL}$ , and left atrial diameter index  $\geq 3 \text{ cm/m}^2$  on the echocardiogram. Of note, the ARCADIA trial did not confirm effectiveness of these biomarkers in selecting patients with cryptogenic stroke for OAC therapy.<sup>76</sup> The ARIC (Atherosclerosis Risk in Communities) study evaluated the association of echocardiographic left atrial function (reservoir, conduit, and contractile strain) and left atrial size (left atrial volume index) with ischaemic stroke.<sup>233</sup> A further analysis from ARIC found that the presence of AtCM (based on P-wave terminal, NT-proBNP, and LA volume index criteria) was significantly associated with an increased risk of dementia, with limited impact of the effect by AF or stroke.<sup>234</sup>

### 5.2. Blood-based biomarkers

While AF-related biomarkers have been studied extensively,<sup>235,236</sup> relatively few biomarkers reflecting AtCM *per se* (without AF) have been assessed.<sup>237,238</sup> Nonetheless, many biomarkers have been assessed in both scenarios, reflecting the non-specificity of many biomarkers (see later). Progression of AF from paroxysmal to persistent is sometimes taken to indicate underlying atrial substrate abnormalities, and some biomarkers have been tested in this scenario.

The natriuretic peptides closely associated with HF<sup>239</sup> are also associated with risk of incident AF and its complications.<sup>240,241</sup> Cardiac troponin (cTnT), a biomarker of myocardial damage used to diagnose myocardial ischaemic events, was associated cardioembolic stroke in the ARIC study.<sup>242</sup> Soluble suppressor of tumorigenicity-2 protein (sST2) and tissue inhibitor of matrix metalloproteinase (TIMP)-1 are associated with AF progression, independent of clinical characteristics and biomarkers.<sup>243</sup> Fibrosis biomarkers may predict AF recurrence after cardioversion.<sup>238</sup> Recently, elevated serum levels of bone morphogenetic protein 10 (BMP10), primarily expressed by atrial myocytes, was shown to be associated with recurrences of AF following CA.<sup>244</sup> Cohort studies in patients with AF demonstrated an association with ischaemic stroke,<sup>245</sup> all-cause mortality and major adverse cerebrovascular and cardiovascular events.<sup>246</sup>

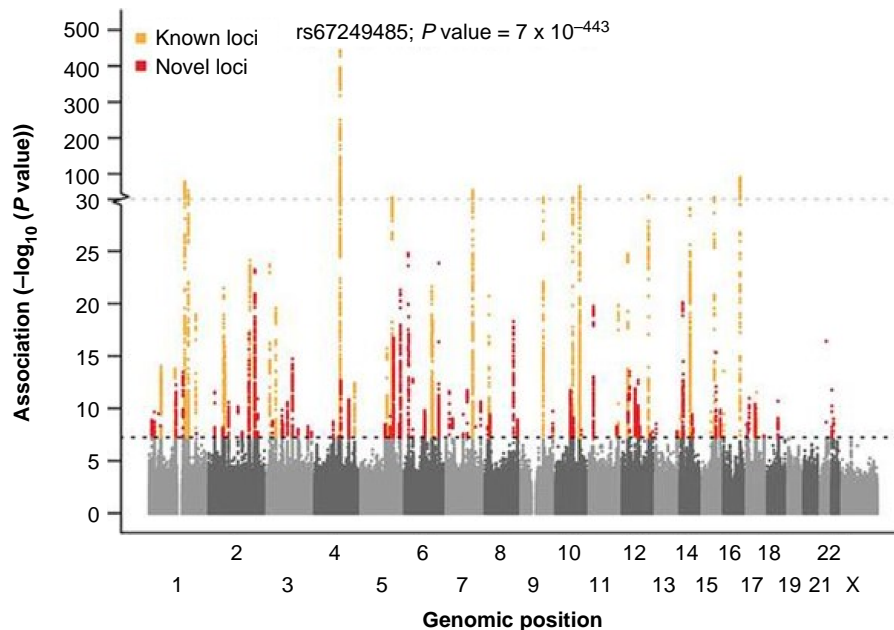
C-reactive protein (CRP) is associated with AF and AF burden in nonsurgical patients, suggesting that inflammatory processes contribute to atrial remodelling.<sup>247</sup> The association of van Willebrand factor and soluble P-selectin with stroke supports the role of hypercoagulability and endothelial damage to the risk for stroke in AF patients.<sup>248</sup>

### 5.3. Limitations of biomarkers

Some biomarkers are non-specific, perhaps reflecting a sick patient or a sick heart.<sup>249,250</sup> For example, Growth Differentiation Factor 15 (GDF-15) is a stress-responsive biomarker associated with several types of cardiovascular diseases, and has been proposed as a specific biomarker of bleeding risk in AF.<sup>251</sup> Nonetheless, GDF-15 is also associated with mortality and MACE in non-AF subjects.<sup>252</sup> Assay variability, diurnal variation of biomarker levels and costs may limit practical usability of both urine and blood biomarkers. A balance is needed between potentially useful information they can provide and simplicity/practical application in busy clinical settings.<sup>253</sup> Thus far, there are no biomarkers that are validated for clinical management guidance in AtCM.

### 5.4. Multi-omics and atrial cardiomyopathy

Primary atrial cardiomyopathy arises from atrial-specific gene variants, as well as genes that associate with extra-atrial features that are functional in the atrial myocardium.<sup>12,254</sup> One atrial-specific gene variant that gives rise to atrial electromechanical defects is the MYL4 gene, which encodes the highly atrial-selective essential myosin light chain.<sup>255,256</sup> Another example is the NPPA gene, which encodes ANP A: NPPA variants have been associated with extreme bi-atrial dilation, thromboembolic risk and atrial standstill.<sup>254,257</sup> Examples of gene variants that associate with



**Figure 7** Manhattan plot showing known loci and novel loci associated with atrial fibrillation. A total of 34 740 186 genetic variants (each represented by a dot) were tested, comparing 60 620 atrial fibrillation cases and 970 216 controls free of atrial fibrillation. The x axis represents the genome in physical order, and the y axis represents  $P$  values ( $-\log_{10}(P \text{ value})$ ) of association. The black horizontal dotted line represents a Bonferroni-corrected threshold of statistical significance corresponding to 1 000 000 independent tests ( $P < 5 \times 10^{-8}$ ). Reprinted by permission from Nielsen et al.<sup>264</sup>

ventricular and/or systemic disorders, but can also produce atrial dysfunction include HCN4, encoding the cardiac pacemaker channel,<sup>258</sup> SCN5A, encoding the main cardiac voltage-gated sodium channel,<sup>259</sup> SCN1B, which encodes the voltage-gated sodium channel  $\beta 1/\beta 1B$  subunits,<sup>260</sup> and LMNA, which encodes Lamin A/C.<sup>261</sup>

Most of our knowledge related to AtCM genomics, transcriptomics and epigenomics derives from studies on AF, which also leads to atrial dysfunction. Large-scale, genome-wide association studies (GWAS) have identified chromosomal loci harboring common variants that influence atrial ECG parameters, including heart rate, P-wave duration, and PR interval,<sup>262</sup> as well as variants associated with cardiac size, structure and contractile function.<sup>263</sup> Altogether, GWAS studies have revealed over 100 genetic loci associated with AF susceptibility (Figure 7).<sup>264,265</sup> It is unknown whether the expression of any of these variants also results in primary AtCM, but their association with AF may lead to secondary AtCM.

Transcriptional studies in human atrial samples using both microarrays and RNA-seq have identified genes responsible for atrial remodelling,<sup>266</sup> among them NPPA and NPPB,<sup>267</sup> GPR22 and RGS6, encoding G-protein signalling components; NTM, that encodes neurotrimin, a promising novel marker of HF,<sup>268</sup> or COLQ, which is found in both left and right atria, and encodes a variant collagen that anchors acetylcholinesterase to the basal lamina.<sup>269</sup> A recent mRNA sequencing study in atrial specimens from patients undergoing cardiac surgery identified 35 genes robustly associated with AF independently of the clinical diagnosis of heart failure.<sup>267</sup> Genes were involved in regulation of cardiomyocyte structure, conduction properties, fibrosis, inflammation, and endothelial dysfunction.<sup>270</sup> A large-animal model study on AF progression showed that significant differential transcriptomic and proteomic expression changes are established early during the transition from paroxysmal to persistent AF.<sup>271</sup>

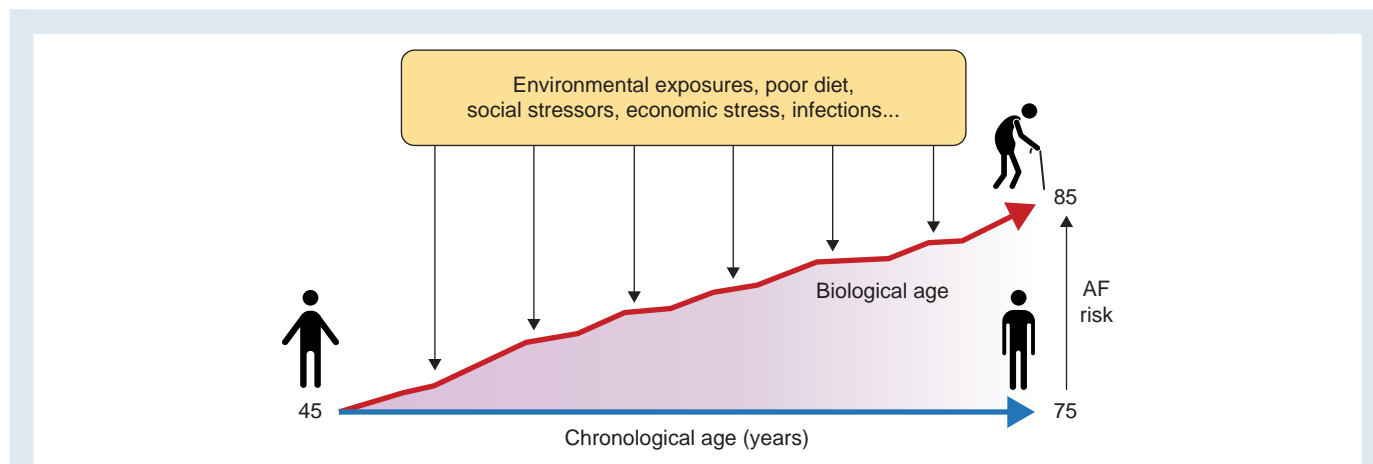
It is now clear that AF is a condition in which both environmental and genetic factors contribute to disease pathogenesis.<sup>265,272</sup> Most

AF-associated variants identified by GWAS lie within non-coding regions of the genome,<sup>273</sup> where they affect gene-expression by altering transcription factor activity and the epigenetic state of chromatin. Epigenetics refers to heritable alterations that are not due to changes in DNA. Methylation of cytosine-phosphate-guanine (CpG) islands by DNA methyltransferases (DNMTs) occurs in paroxysmal and permanent AF.<sup>274,275</sup> A recent article used 4 DNA methylation-based ageing biomarkers to provide an epigenetic basis for the known association between chronological age and incident AF (Figure 8).<sup>276,277</sup> Other studies demonstrated histone modifications associated with AF.<sup>278,279</sup> Specifically, histone deacetylases (HDAC) and histone transferases (HAT) appear to play an important role in AF.<sup>278</sup> Patients suffering from AF have increased expression of EZH2, encoding the histone methyltransferase responsible for the H3K27me3 signature, in both atrial cardiomyocytes and fibroblasts.<sup>279</sup> It is clear that progress in the understanding of the mechanisms of AtCM will require a new generation of multiomic studies in patients with AtCM independent of AF.

## 5.5. ECG parameters

In AtCM, structural, architectural, contractile, and electrophysiologic changes in the atria manifest as ECG abnormalities. Table 7 provides examples of studies supporting these associations, which have been reviewed in detail elsewhere.<sup>301–303</sup>

P-wave duration (IAB): a p-wave duration  $\geq 120$  ms indicates partial IAB.<sup>304</sup> Biphasic P-wave morphology in inferior leads (II, III, aVF) indicates complete block of Bachmann's bundle (advanced IAB).<sup>302,303</sup> IAB is strongly associated with LA enlargement.<sup>305</sup> Advanced IAB is associated with fibrotic atrial cardiomyopathy, an environment for re-entry, and premature atrial beats, which promote the development and progression of AF.<sup>306,307</sup> Patients with prolonged P-wave duration<sup>301</sup> or advanced IAB have a higher risk of recurrent AF after CA.<sup>308</sup> Paradoxically, abnormally short P-wave



**Figure 8** Although chronological age progresses at an immutable rate, biological ageing, measured by epigenetic age in this article, is modifiable by various exposures and life experiences. Thus, establishing a relationship between epigenetic age and atrial fibrillation (AF) risk gives a unique insight into modifiable ageing associated atrial fibrillation risks. Reprinted from Ward-Caviness et al.<sup>277</sup>

**Table 7** ECG parameters

	Associations	References
Amplified digital p-wave duration (APWD)	Atrial fibrosis/low voltage	280,281
	Atrial contractile dysfunction, LAA thrombogenesis	120,221
	Reduced LAA-velocity	120
	AF	282
PTFV1	AF recurrence after catheter ablation	280,281
	Low LA appendage ejection velocity	283
	Functional atrial remodelling	284
	AF	285
P-wave axis	AF	286
	AF recurrence after catheter ablation	287
P-wave voltage	AF	288
	AF recurrence after catheter ablation	289
P-wave area	LA enlargement	290
	AF in mitral stenosis	291
P-wave dispersion	Idiopathic paroxysmal AF	292,293
	AF recurrence after cardioversion	294
Fibrillatory wave (F-wave)	LA enlargement	295–297
	Low LA appendage flow	296
	Long-standing persistent AF	297,298
	Heart failure	297
	AF recurrence after catheter ablation	299,300

LA, left atrial; AF, atrial fibrillation.

duration is also a risk factor for incident<sup>309</sup> or recurrent AF.<sup>310</sup> Amplified (150–200 mm/sec, 80–100 mm/mV) digital P-wave duration can predict arrhythmia recurrences after PVI, detection of HF patients at risk for AF, and determine different AtCM-severity stages (discrete stage of AtCM: APWD 140–150 ms; moderate AtCM-stage: APWD 150–180 ms and advanced AtCM-stage: APWD > 180 ms or presence of pos-negative p-waves in two of three inferior leads) implicating LAA slow flow velocity and LAA thrombogenesis and major adverse event rates.<sup>120,280–282</sup>

Besides P-wave duration, P-wave terminal force in V1 (PTFV1) is a commonly used marker for AtCM. PTFV1 is calculated as the product of its duration component (PTDV1) and its absolute amplitude component (PTAV1). An absolute PTFV1 value >4 mV·ms is considered pathological.<sup>287</sup> Abnormal PTFV1 is associated with low LA appendage ejection velocity in TEE.<sup>283</sup> Originally, a pathological PTFV1 was suggested as a marker of LA enlargement and posterior displacement, but more recent studies suggest that it is caused by conduction abnormalities resulting in predominantly posterior terminal LA activation.<sup>284,311</sup> LA strain measured by speckle tracking echocardiography, an indicator of functional atrial remodelling, is reduced in the presence of PTFV1 abnormalities.<sup>284</sup> A recent meta-analysis showed that PTFV1 is associated with risk of AF and is a predictor of AF in patients with and without cardiovascular disease<sup>285</sup> and of AF recurrence after CA.<sup>286</sup> Recently, it was shown that amplified P-wave duration of digital 12-lead ECG is associated with left atrial low-voltage substrate and can identify patients with persistent AF who are at high risk for arrhythmia recurrence after CA<sup>312</sup> along with new-onset AF in patients with HFpEF.<sup>3,313</sup>

**P-wave axis:** a normal frontal plane p-wave axis is between 0 and +75.<sup>302</sup> A recent meta-analysis indicates that an abnormal P-wave axis is associated with future detection of AF.<sup>287</sup>

**P-wave voltage:** P-wave voltage  $\leq 0.1$  mV in lead I is considered abnormal.<sup>302</sup> A score incorporating abnormal p-wave voltage predicts new-onset AF.<sup>288</sup> Lead I P-wave amplitude  $\leq 0.1$  mV is associated with recurrence of AF after radiofrequency ablation.<sup>289</sup>

**P-wave area:** P-wave area is calculated in lead II using the following formula: P-wave area =  $\frac{1}{2}$  P-wave duration  $\times$  P-wave voltage.<sup>302</sup> Abnormal P-wave area is defined as  $\geq 4$  ms  $\times$  mV, and has been found to be associated with LA enlargement.<sup>290</sup> In patients with mitral stenosis, P-wave area in V3 predicts new-onset AF.<sup>291</sup> **P-wave dispersion:** P-wave dispersion is defined as the difference between P-wave maximum and P-wave minimum duration on the 12-lead ECG.<sup>302</sup> Greater P-wave dispersion was associated with incident AF and AF recurrence after cardioversion.<sup>292,294</sup> In patients

with cryptogenic stroke and an implantable loop recorder, P-wave dispersion >40 ms is a predictor of subsequent AF detection.<sup>293</sup>

Fibrillatory wave (f-wave): lower-amplitude f-waves are associated with larger LA size and lower LA appendage flow.<sup>295,296</sup> A low f-wave amplitude in lead II and high dominant rate in lead V1 independently discriminates long-standing persistent AF from other AF-types (paroxysmal/persistent).<sup>298</sup> In a community-based prospective survey, fine f-waves were more prevalent than coarse in patients with a larger LA diameter or with persistent AF, and was independently associated with a higher risk of HF.<sup>297</sup> Lower preprocedural f-wave amplitudes are associated with AF recurrence in patients undergoing AF ablation.<sup>299,300</sup>

Signal averaged P-wave analysis: technological advancement of ECG analysis is currently evolving rapidly and has the potential to further improve the prognostic value of ECG recordings in patients with atrial cardiomyopathy. Signal averaged P-wave analysis of ECG recording for several minutes gives more precise and reproducible information about atrial spread of activation. Prolonged signal averaged P-wave durations were found in patients with paroxysmal AF vs. controls without history of AF<sup>314</sup> and in patients with recurrences of AF after CA.<sup>315</sup> P-wave parameters from prolonged recordings better distinguish between patients with paroxysmal vs. persistent AF compared to standard 10-s ECGs.<sup>316</sup>

Premature atrial contractions: several studies have identified premature atrial contractions as marker for AtCM, AF and increased stroke risk.<sup>317,318</sup>

## 5.6. Artificial intelligence

Artificial intelligence (AI)-based P-wave wavelet analysis promises to provide significant advancements in the field.<sup>302</sup> Deep learning approaches have shown that patients at risk for AF can be identified by their ECG in sinus rhythm with very high accuracy,<sup>319</sup> suggesting that the commonly used arsenal of P-wave metrics for prediction of incident AF is most likely incomplete. In a pragmatic study to test the efficacy of an AI-ECG guided screening for AF,<sup>320</sup> the AF detection rate was five-fold higher in the high-risk AI-ECG group compared to the low-risk group, indicating that AI might increase the effectiveness of ECG-based AF screening. Other studies have successfully applied AI to quantify the substrate for AF and detect targets for AF ablation.<sup>321,322</sup>

## 5.7. Future directions

ECG analysis has the potential to identify patients at risk for AtCM, AF, AF recurrences and strokes, particularly if used in conjunction with imaging or circulating biomarkers. The potential clinical impact is significant. Patients at risk for AF or stroke might undergo intensified rhythm monitoring. Patients with high risk for AF recurrences might undergo more aggressive ablation strategies or the treating electrophysiologist might refrain from recommending AF ablation. However, successful implementation of these strategies will depend on finding solutions for structured collection of digital ECGs, standardization of analysis, identification of robust thresholds for risk assessment and ultimately the integration of ECG-derived parameters in prospective trials for clinical decision making.<sup>302</sup> Prospective randomized clinical trials will be needed to evaluate the prognostic value of pre-specified ECG parameters as inclusion criteria.

# 6. Stroke and cognitive decline

## 6.1. Empiric evidence that atrial cardiomyopathy leads to stroke

There is substantial and growing evidence that AtCM, even in the absence of AF, predicts (and presumably causes) stroke.<sup>117,118</sup> Multiple P-wave indices, as discussed above, have been associated with an increased stroke risk.<sup>323</sup> Frequent atrial ectopy predicts stroke even without interim

evidence of AF.<sup>324</sup> While inter-observer variability and changes over time may affect reliability,<sup>325</sup> P-wave terminal force in V1 appears to be especially predictive of embolic stroke, even in the absence of evident AF.<sup>326,327</sup> Echocardiographic measurements demonstrating a larger LA similarly predict increased risk of stroke, again even when no AF is present.<sup>328,329</sup> When P-wave terminal force in V1, left atrial diameter, and incident AF were included in the same multivariable model in a population-based longitudinal cohort, LA diameter did not emerge as an independent risk factor for stroke.<sup>330</sup> More recent investigations have focused on dynamic assessments of LA function, with evidence that, among community-dwelling individuals without AF, echocardiographically-ascertained reduced LA strain is associated with incident stroke and adds predictive value to the CHA2DS2-VASc score.<sup>233</sup>

## 6.2. Mechanisms underlying the relationship between atrial cardiomyopathy and stroke

Even in AtCM without AF, atrial-wall substrate changes may be evident in association with risk factors such as hypertension, coronary disease, diabetes mellitus, and HF.<sup>331–334</sup> Flow abnormalities associated with AtCM<sup>117,118</sup> may relate to the presence of diastolic dysfunction and (relative) atrial stasis, most evident as TEE-detected LAA spontaneous echo contrast, even in sinus rhythm,<sup>335</sup> or when a paroxysm of AF occurs. Global LA longitudinal strain assessed by speckle tracking TTE discriminates the presence of LA or LA appendage thrombus on TEE in patients with acute ischaemic stroke. Abnormal blood constituents include abnormalities of coagulation and platelets, which characterize the risk factors mentioned above.<sup>336,337</sup> Indeed, the concept of 'thrombogenic endocardial remodelling' suggests that a diseased atrial endocardium may facilitate the production of thrombi independent of the presence of AF.<sup>2</sup> In this circumstance, AF may be an epiphenomenon, with the true causal pathway between AtCM and stroke attributed more directly to pro-thrombotic properties of the atria itself.<sup>338–342</sup>

## 6.3. Does atrial cardiomyopathy lead to cognitive decline?

AF might induce cognitive decline through multiple mechanisms: hypoperfusion due to reduced cardiac output, silent brain infarction, inflammation, or platelet dysfunction.<sup>343–346</sup> Cerebral microbleeds associated with anticoagulation can also cause cognitive decline.<sup>347</sup> Finally, beat-to-beat variability seen in patients with AtCM and AF reduces cardiac output,<sup>343,348</sup> and brain hypoperfusion is associated with cognitive dysfunction, brain ageing, and low brain volume.<sup>343,348,349</sup> There are selected reports that have evaluated the potential association between abnormal atrial function and cognitive dysfunction, independent of AF or stroke occurrence. In an early consecutive series of 180 older individuals without AF, stroke, or a diagnosis of dementia, LA enlargement on echocardiography was significantly associated with cognitive impairment.<sup>350</sup> Greater LA volumes and reduced LA reservoir function are associated with subclinical cerebrovascular disease on brain MRI. The ARIC Study found that the association of LA enlargement with cognitive function was borderline,<sup>351</sup> and identified in cross-sectional analyses but not longitudinally.<sup>352</sup> Adverse LA electrical remodelling as measured by abnormal P-wave indices was associated with an increased risk of dementia after adjusting for incident AF and stroke.<sup>351</sup> In the most recent ARIC report focused on this question, LA enlargement was not associated with dementia risk,<sup>353</sup> but abnormal LA strain and emptying fraction were significantly associated with an increased risk of dementia independent of AF or stroke. It is also possible that AtCM and dementia commonly co-exist without a direct causal connection and without relationship to thromboembolism *per se*. For example, a propensity to amyloid deposits in both the atria and the brain may lead to a concomitant AtCM and Alzheimer's disease.<sup>15,354</sup> Left atrial

dysfunction as a predictor of cognitive decline may similarly suggest a general predilection to profibrotic remodelling that adversely affects both the heart and the brain.<sup>353</sup> In summary, based on existing data there is some evidence linking AtCM to risk of incident dementia, but no clear evidence of a strong independent association between AtCM and cognitive decline.

## 7. Therapeutic implications

### 7.1. Primary prevention of atrial cardiomyopathy

Pathological atrial remodelling may be prevented, or possibly even reversed, by addressing the initiating stimulus/disease (e.g. elevated pressure, volume, AF) or targeting the key underlying mechanisms.

Primary prevention refers to preventive therapies before the disease phenotype has emerged, for example preventing AF by preventing or reversing an AtCM.<sup>355</sup> Lifestyle modification including achieving/maintaining a healthy bodyweight, has been shown to reduce AF burden and prevent AtCM in patients with AF,<sup>356,357</sup> but there is limited evidence on primary prevention of AtCM (i.e. before AF presentation). Similarly, there are few data on the treatment of obstructive sleep apnoea for primary prevention of AtCM. Interventions in the renin-angiotensin-aldosterone system (RAAS) have yielded mixed results,<sup>358</sup> with particularly convincing data supporting mineralocorticoid receptor antagonists (MRA)<sup>359,360</sup> and RAAS inhibitors in general in primary prevention.<sup>352</sup> A meta-analysis of 14 studies (5 RCTs) showed an odds ratio of 0.52 for new-onset AF in patients treated with MRA.<sup>359</sup> An updated meta-analysis pooled data from 20 trials (21 791 participants, mean age: 65.2 years, 31.3% women) showed that MRA reduce AF events (risk ratio = 0.76; 95% CI: 0.67–0.87) in both patients with and without prior AF.<sup>361</sup> Our current inability to detect the early development of AtCM limits the options to provide effective preventive medicine.

### 7.2. Lifestyle interventions to reverse atrial cardiomyopathy

Lifestyle-related factors (obesity, smoking, alcohol excess, hypertension and obstructive sleep apnoea) are important contributors to adverse LA remodelling and AF risk.<sup>140,141,362–364</sup> The 2020 ESC guidelines list several risk factors and comorbidities, including cardiovascular and non-cardiovascular comorbidities and lifestyle factors, that increase the risk of AF and of AtCM.<sup>140</sup> Randomized controlled trials examining weight loss, cardiometabolic risk factor management,<sup>141</sup> and alcohol reduction<sup>365,366</sup> have demonstrated reduction in AF burden and recurrence rate. In the Framingham cohort, each 10-g/day increase in alcohol intake was associated with a 0.16-mm (95%CI: 0.10–0.21-mm) larger LA dimension<sup>367</sup> and among those with established AF, habitual drinkers had larger atria than lifelong non-drinkers (LAVi: 50 ± 13 mL/m<sup>2</sup> vs. 43 ± 12 mL/m<sup>2</sup>). A randomized trial on alcohol abstinence vs. continuation in alcohol users with AF demonstrated later and less frequent recurrence of AF in abstainers.<sup>366</sup> A meta-analysis of 10 prospective studies demonstrated a reduction in LA size upon obstructive sleep apnoea treatment with continuous positive airway pressure (CPAP).<sup>368</sup> A direct effect of CPAP on electrophysiological remodelling (LA voltage, conduction velocity and LVAs) was also demonstrated in a small randomized study.<sup>369</sup>

### 7.3. Pharmacological therapies to reduce progression of atrial cardiomyopathy

Inhibition of the renin-angiotensin aldosterone system has shown some efficacy in preventing new-onset AF, but mostly in those with a history of HF. In a meta-analysis of 14 randomized controlled trials (92 817 patients), angiotensin receptor blockers (RR: 0.78; 95% CI: 0.66–0.92),

and angiotensin-converting enzyme inhibitors (RR: 0.79; 95% CI: 0.65–1.00) both reduced the risk of incident AF.<sup>370</sup> Another meta-analysis showed that recurrent AF was less frequent (OR 0.37; 95%CI: 0.24–0.57  $P < 0.001$ ) in MRA treated patients.<sup>359</sup> MRA most prominently suppressed recurrent AF or AF in patients with reduced left ventricular function.<sup>371</sup> In a meta-analysis of 5 randomized trials involving HF patients, MRA were associated with modest reductions in LAVI (–1.12 mL/m<sup>2</sup>; 95%CI: –1.91–0.33 mL/m<sup>2</sup>).<sup>372</sup> Animal studies suggest that angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists can prevent LA enlargement, atrial fibrosis and markers (TGFβ), and atrial dysfunction.<sup>372–376</sup> There was no difference in AF burden, nor on AF burden in 425 patients with paroxysmal AF treated with the angiotensin receptor antagonist olmesartan, but this is perhaps not surprising given the lack of angiotensin-renin system activation and generally limited structural remodelling in paroxysmal AF patients.<sup>358</sup> SGLT-2 inhibitors are now often used as part of comprehensive therapy in systolic HF, with beneficial effects including improved cardiac energy metabolism, prevention of inflammation, oxidative stress, and adverse cardiac remodelling.<sup>377</sup> Treatment of diabetic rats for 8 weeks with empagliflozin prevented LA enlargement, fibrosis, atrial mitochondrial dysfunction, inflammation, and AF inducibility.<sup>378</sup> In type 2 diabetes, treatment with dapagliflozin was associated with a 19% reduction in AF events.<sup>379</sup>

### 7.4. Impact of rhythm control strategies on atrial cardiomyopathy

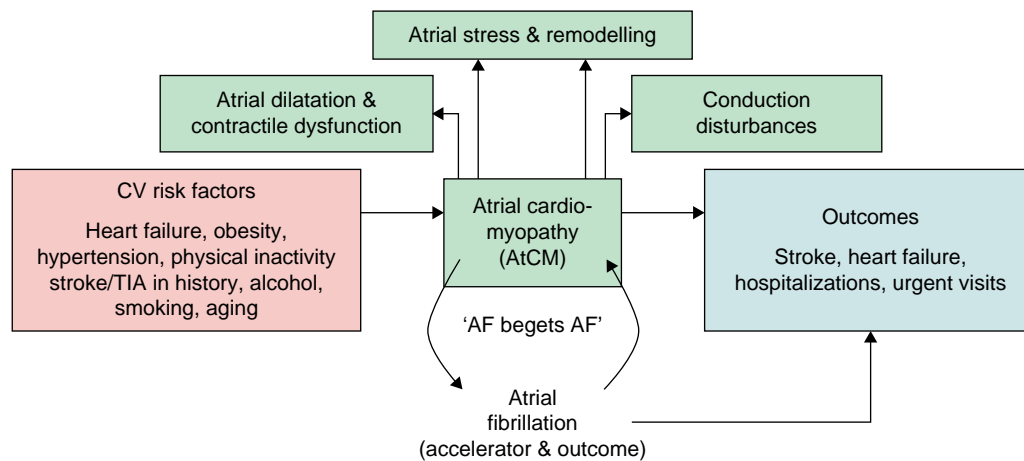
Although there is a large body of evidence linking atrial remodelling to the risk of AF and the lower success of medical rhythm control therapy or LA ablation, the opposite, i.e. studies linking reversal of atrial remodelling to improvement in AF-indices, is less well documented (Figure 9).

### 7.5. Rhythm control and atrial cardiomyopathy

The ATHENA trial demonstrated that dronedarone was associated with a reduction in the combined endpoint of first hospitalization or death.<sup>380</sup> The use of dronedarone was also associated with fewer cases of progression to permanent AF HR: 0.65; 95% CI: 0.56–0.75 ( $P < 0.001$ ).<sup>381</sup> The EAST-AFNET 4 trial demonstrated a reduction in adverse cardiovascular outcomes in patients with recently diagnosed AF treated with early (mostly medical) rhythm control, compared to standard of care (mostly rate control).<sup>382</sup> The effects were most pronounced in patients with cardiovascular comorbidities (CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥4).<sup>383</sup> Restoration of sinus rhythm in a selected population appeared to reduce cardiovascular complications, potentially through reduction or reversal of atrial remodelling/AtCM.

### 7.6. Reversal of atrial cardiomyopathy by rhythm control?

Catheter ablation by means of pulmonary vein isolation (PVI) is the most effective rhythm control strategy for AF and can partially reverse atrial structural (LA volume increases and mitral regurgitation).<sup>133,384</sup> and electrical remodelling. Patients with sinus rhythm after ablation showed a decrease in circulating C-reactive protein, whereas there was no change in patients with AF recurrence in the first 3 months after ablation.<sup>385</sup> Recent work suggests that effective rhythm control can prevent progression of AF to more persistent forms.<sup>153,386</sup> Potential mechanisms for post-ablation reduction in LA volume include the shrinkage of the left atrium through contraction of the ablation scar,<sup>387</sup> but also reduction of mitral regurgitation and reversal of AF-induced atrial remodelling/cardiomyopathy. In the absence of AF recurrence, there was a reduction in LAVI from 31 ± 4 to 28 ± 4 mL/m<sup>2</sup> and in atrial electromechanical conduction delay (19 ± 9–13 ± 5 msec), while no reversal of remodelling occurred in



**Figure 9** Interaction of risk factors, atrial cardiomyopathy, occurrence of atrial fibrillation and outcome. AtCM, atrial cardiomyopathy; AF, atrial fibrillation; CV, cardiovascular; TIA, transient ischaemic attack.

**Table 8** Knowledge gaps in AtCM

#### Knowledge Gaps in Atrial Cardiomyopathy (AtCM)

1. Optimal monitoring frequency and duration to measure development of AtCM
2. Threshold of AtCM that results in an increased risk of stroke, heart failure, dementia, and other AF-related outcomes
3. Prevalence of subclinical AtCM in broad community-based cohorts
4. Risk factors and determinants of AtCM in broad community-based cohorts
5. Temporal relationship between different types of AtCM
6. Precise correlation of various biomarkers (ECG, blood parameters etc.) with AtCM
7. Threshold of AtCM that indicates need for anticoagulation in patients without the presence of AF (e.g. CHA2DS2-VASc score  $\geq 4$ ?)
8. Reversibility of AtCM in response to different therapies, and time course
9. Diversity of structural alterations in atrial tissue in patients with AtCM
10. Association of AtCM (and its subtypes) with CV comorbidities.
11. Molecular mechanisms underlying the development and progression of AtCM
12. Histological findings associated with AtCM in patients without AF
13. Relationships between atrial function and histological findings in AtCM
14. Relationship between LGE-MRI and histology in the diagnosis of AtCM
15. Multiomic analysis to elucidate the mechanisms of development and progression of AtCM
16. Impact of incretins (GLP-1 analogues, GIP etc.) on AtCM development and regression

AtCM, atrial cardiomyopathy; AF, atrial fibrillation; CHA2DS2-VASc score, congestive heart failure, hypertension, age  $\geq 75$  (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female). CV, cardiovascular; ECG, electrocardiogram.

patients with AF recurrence after cryoballoon ablation.<sup>388</sup> In 106 patients with AF (43 paroxysmal and 63 persistent AF) undergoing PVI, a significant reduction in LAVi from  $43 \pm 13$  to  $33 \pm 12$  mL/m<sup>2</sup> was observed.<sup>389</sup> Although thoracoscopic AF ablation can be effective in patients with severe LA enlargement, it is uncertain whether reduced LA volume is due to restoration of sinus rhythm *per se*.<sup>133,387,390</sup> In a meta-analysis of 24 studies (2040 patients), maximum LA volume decreased by 6.5 mL (95%CI: 4.4–8.6 mL) after ablation, regardless of whether AF was paroxysmal or persistent.<sup>391</sup> Even in the presence of severe LA dilatation (LA volume >200 mL), a 10% reduction in LA size was observed in 52% and was a strong predictor of freedom from AF post-ablation.<sup>392</sup> In a sub-study of 15 patients with systolic dysfunction who underwent AF ablation

(the CAMERA-MRI [Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction-Magnetic Resonance Imaging] trial), RA and LA area decreased by 27% and 19%, respectively, after  $23 \pm 12$  months of follow-up, associated with improvements in LV systolic function and atrial electrical reverse remodelling.<sup>155</sup> In 86 patients undergoing ablation for persistent AF, those who maintained sinus rhythm at 12 months had a greater reduction in RA area, which correlated with reduced FTR.<sup>393</sup> CMR studies have shown that both LA and RA emptying fraction increased significantly by 30–40% after 6 months of follow-up after ablation for persistent AF in 20 consecutive patients.<sup>394</sup> LA functional reserve during exercise was lower in 61 patients with AF recurrence after ablation.<sup>395</sup> LA strain improved after CA ( $21.3\% \pm 1.7\%$  to  $28.6\%$

$\pm 1.7\%$ ), whereas it declined with medical management ( $26.3\% \pm 1.2\%$  to  $21.7\% \pm 1.2\%$ ), driven in part by AF burden.<sup>154</sup> Restoration of sinus rhythm was associated with greater reductions in LA volume, presence and extent of MR and annular size.<sup>133</sup> Electrical cardioversion of AF did result in return of atrial systolic function, but did not alter the elevated levels of plasma Von Willebrand factor, fibrinogen and soluble P-selectin concentrations.<sup>396</sup> Overall, the evidence strongly suggests that SR restoration and maintenance is effective in AtCM reversal.

## 7.7. Device therapy to reverse atrial cardiomyopathy

Cardiac resynchronization therapy (CRT) in patients with HFrEF can partially reverse atrial remodelling. In 107 patients (3 months post-CRT), LA volume was reduced, with improvements in emptying fraction; benefits were largely due to pressure and volume unloading effects from LV reverse remodelling.<sup>397</sup> Conduction system pacing is emerging as a more physiological alternative to RV apex pacing, but did not reduce left atrial size in AF patients with HFrEF or HFpEF.<sup>398,399</sup> Mitral-valve disease-induced LA enlargement and electrical remodelling can be partially reversed with valve surgery. In patients with severe mitral regurgitation, valve repair resulted in reductions in maximum LAVi ( $43 \pm 14$ – $25 \pm 8$  mL/m<sup>2</sup>).<sup>400</sup> In patients undergoing mitral commissurotomy, immediate reductions in LA pressure ( $23 \pm 7$  to  $10 \pm 4$  mm Hg) were accompanied by reductions in LA volume ( $75 \pm 20$  mL to  $52 \pm 18$  mL) with associated improvements in conduction.<sup>401</sup>

## 8. Conclusions and future directions

In this document, we have summarized the extensive progress in the area of AtCM since the first consensus document.<sup>2</sup> This substantial progress has provided new insights in many important areas, but important knowledge gaps remain, as summarized in *Table 8*. Additional experimental and clinical studies, registries and big data analyses are needed to fill these knowledge gaps in order to harness the full potential of the AtCM concept for improving the prevention and management of AF.<sup>402</sup> The proposed AtCM classification system (AtCM stages; *Table 2*) and the synopsis about the development/progression of AtCM (*Figure 9*) warrant further study (for stylistic symmetry), reflection and testing.

## Supplementary material

Supplementary material is available at *Europace* online.

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## Data availability

No new data were generated or analysed in support of this research.

## References

- Williams DO, Jones EL, Nagle RE, Smith BS. Familial atrial cardiomyopathy with heart block. *Q J Med* 1972;**41**:491–508.
- Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–90.
- Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm* 2017;**14**:e3–40.
- Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *J Arrhythm* 2016;**32**:247–78.
- Guichard JB, Nattel S. Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad? *J Am Coll Cardiol* 2017;**70**:756–65.
- Winters J, Isaacs A, Zeemering S, Kawczynski M, Maessen B, Maessen J et al. Heart failure, female sex, and atrial fibrillation are the main drivers of human atrial cardiomyopathy: results from the CATCH ME consortium. *J Am Heart Assoc* 2023;**12**:e031220.
- Chahine Y, Askari-Atapour B, Kwan KT, Anderson CA, Macheret F, Afroze T et al. Epicardial adipose tissue is associated with left atrial volume and fibrosis in patients with atrial fibrillation. *Front Cardiovasc Med* 2022;**9**:1045730.
- Abou Ziki MD, Bhat N, Neogi A, Driscoll TP, Ugwu N, Liu Y et al. Epistatic interaction of PDE4DIP and DES mutations in familial atrial fibrillation with slow conduction. *Hum Mutat* 2021;**42**:1279–93.
- Yoneda ZT, Anderson KC, Quintana JA, O'Neill MJ, Sims RA, Glazer AM et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol* 2021;**6**:1371–9.
- Yoneda ZT, Anderson KC, Ye F, Quintana JA, O'Neill MJ, Sims RA et al. Mortality among patients with early-onset atrial fibrillation and rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol* 2022;**7**:733–41.
- Roberts JD, Chalazan B, Andrade JG, Macle L, Nattel S, Tadros R. Clinical genetic testing for atrial fibrillation: are we there yet? *Can J Cardiol* 2024;**40**:540–53.
- Marcoux E, Sosnowski D, Ninni S, Mackasey M, Cadrin-Tourigny J, Roberts JD et al. Genetic atrial cardiomyopathies: common features, specific differences, and broader relevance to understanding atrial cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2023; **16**:675–98.
- Cornwell GG, 3rd, Murdoch WL, Kyle RA, Westermark P, Pitkanen P. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. *Am J Med* 1983;**75**:618–23.
- González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;**36**:2585–94.
- Röcken C, Peters B, Juenemann G, Saeger W, Klein HU, Huth C et al. Atrial amyloidosis: an arrhythmogenic substrate for persistent atrial fibrillation. *Circulation* 2002;**106**:2091–7.
- Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med* 2008;**40**:232–9.
- Troncone L, Luciani M, Coggins M, Wilker EH, Ho CY, Codispoti KE et al. Aβ amyloid pathology affects the hearts of patients with Alzheimer's disease: mind the heart. *J Am Coll Cardiol* 2016;**68**:2395–407.
- Sikkink LA, Ramirez-Alvarado M. Cytotoxicity of amyloidogenic immunoglobulin light chains in cell culture. *Cell Death Dis* 2010;**1**:e98.
- Yang Z, Subati T, Kim K, Murphy MB, Dougherty OP, Christopher IL et al. Natriuretic peptide oligomers cause proarrhythmic metabolic and electrophysiological effects in atrial myocytes. *Circ Arrhythm Electrophysiol* 2022;**15**:e010636.
- Yao C, Veleva T, Scott L, Jr., Cao S, Li L, Chen G et al. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. *Circulation* 2018;**138**:2227–42.
- Heijman J, Muna AP, Veleva T, Molina CE, Sutanto H, Tekook M et al. Atrial myocyte NLRP3/CaMKII nexus forms a substrate for postoperative atrial fibrillation. *Circ Res* 2020;**127**:1036–55.
- Scott L, Jr., Fender AC, Saljic A, Li L, Chen X, Wang X et al. NLRP3 inflammasome is a key driver of obesity-induced atrial arrhythmias. *Cardiovasc Res* 2021;**117**:1746–59.
- Zhang Y, Zhang S, Li B, Luo Y, Gong Y, Jin X et al. Gut microbiota dysbiosis promotes age-related atrial fibrillation by lipopolysaccharide and glucose-induced activation of NLRP3-inflammasome. *Cardiovasc Res* 2022;**118**:785–97.
- Bapat A, Schloss MJ, Yamazoe M, Grune J, Hulsmans M, Milan DJ et al. A mouse model of atrial fibrillation in sepsis. *Circulation* 2023;**147**:1047–9.
- Scott L, Jr., Li N, Dobrev D. Role of inflammatory signaling in atrial fibrillation. *Int J Cardiol* 2019;**287**:195–200.
- Dobrev D, Heijman J, Hiram R, Li N, Nattel S. Inflammatory signalling in atrial cardiomyocytes: a novel unifying principle in atrial fibrillation pathophysiology. *Nat Rev Cardiol* 2023;**20**:145–67.
- Tong D, Schiattarella GG, Jiang N, Daou D, Luo Y, Link MS et al. Impaired AMP-activated protein kinase signaling in heart failure with preserved ejection fraction-associated atrial fibrillation. *Circulation* 2022;**146**:73–6.
- Song J, Wu J, Robichaux DJ, Li T, Wang S, Arredondo Sancristobal MJ et al. A high-protein diet promotes atrial arrhythmogenesis via absent-in-melanoma 2 inflammasome. *Cells* 2024;**13**:108.
- Hulsmans M, Schloss MJ, Lee IH, Bapat A, Iwamoto Y, Vinegoni C et al. Recruited macrophages elicit atrial fibrillation. *Science* 2023;**381**:231–9.
- Huynh K. Novel macrophage targets for the treatment of atrial fibrillation. *Nat Rev Cardiol* 2023;**20**:648.

31. Ninni S, Dombrowicz D, de Winther M, Staels B, Montaigne D, Nattel S. Inherited and acquired genetic factors altering innate immune responses: an emerging actor in atrial fibrillation. *J Am Coll Cardiol* 2024;**83**:1163–76.
32. Hiram R, Xiong F, Naud P, Xiao J, Sirois M, Tanguay JF et al. The inflammation-resolution promoting molecule resolvin-D1 prevents atrial proarrhythmic remodelling in experimental right heart disease. *Cardiovasc Res* 2021;**117**:1776–89.
33. Hiram R, Xiong F, Naud P, Xiao J, Sosnowski DK, Saljic A et al. An inflammation resolution-promoting intervention prevents atrial fibrillation due to left-ventricular dysfunction. *Cardiovasc Res* 2024;**120**:345–59.
34. Gawalko M, Agbaedeng TA, Saljic A, Müller DN, Wilck N, Schnabel R et al. Gut microbiota, dysbiosis and atrial fibrillation. Arrhythmogenic mechanisms and potential clinical implications. *Cardiovasc Res* 2021;**118**:2415–27.
35. Boutaud O, Montine TJ, Chang L, Klein WL, Oates JA. PGH2-derived levuglandin adducts increase the neurotoxicity of amyloid beta1–42. *J Neurochem* 2006;**96**:917–23.
36. Davies SS, May-Zhang LS, Boutaud O, Amarnath V, Kirabo A, Harrison DG. Isolevuglandins as mediators of disease and the development of dicarbonyl scavengers as pharmaceutical interventions. *Pharmacol Ther* 2020;**205**:107418.
37. May-Zhang LS, Kirabo A, Huang J, Linton MF, Davies SS, Murray KT. Scavenging reactive lipids to prevent oxidative injury. *Annu Rev Pharmacol Toxicol* 2021;**61**:291–308.
38. Pitchford LM, Driver PM, Fuller JC, Jr., Akers WS, Abumrad NN, Amarnath V et al. Safety, tolerability, and pharmacokinetics of repeated oral doses of 2-hydroxybenzylamine acetate in healthy volunteers: a double-blind, randomized, placebo-controlled clinical trial. *BMC Pharmacol Toxicol* 2020;**21**:3.
39. Pitchford LM, Rathmacher JA, Fuller JC, Jr., Daniels JS, Morrison RD, Akers WS et al. First-in-human study assessing safety, tolerability, and pharmacokinetics of 2-hydroxybenzylamine acetate, a selective dicarbonyl electrophile scavenger, in healthy volunteers. *BMC Pharmacol Toxicol* 2019;**20**:1.
40. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol* 2011;**57**:1745–51.
41. Al Chekakie MO, Welles CC, Metoyer R, Ibrahim A, Shapira AR, Cytron J et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol* 2010;**56**:784–8.
42. Tsao HM, Hu WC, Wu MH, Tai CT, Lin YJ, Chang SL et al. Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left atrium in patients with atrial fibrillation and effect of recurrence after ablation. *Am J Cardiol* 2011;**107**:1498–503.
43. Su KN, Ma Y, Cacheux M, Ilkan Z, Raad N, Muller GK et al. Atrial AMP-activated protein kinase is critical for prevention of dysregulation of electrical excitability and atrial fibrillation. *JCI insight* 2022;**7**:e141213.
44. Hulsurkar MM, Lahiri SK, Moore O, Moreira LM, Abu-Taha I, Kamler M et al. Atrial-specific LKB1 knockdown represents a novel mouse model of atrial cardiomyopathy with spontaneous atrial fibrillation. *Circulation* 2021;**144**:909–12.
45. Kim GE, Ross JL, Xie C, Su KN, Zaha VG, Wu X et al. LKB1 deletion causes early changes in atrial channel expression and electrophysiology prior to atrial fibrillation. *Cardiovasc Res* 2015;**108**:197–208.
46. Perike S, Gonzalez-Gonzalez FJ, Abu-Taha I, Damen FW, Hanft LM, Lizama KS et al. PPP1R12C promotes atrial hypocontractility in atrial fibrillation. *Circ Res* 2023;**133**:758–71.
47. Rommel C, Rösner S, Lothar A, Barg M, Schwaderer M, Gilsbach R et al. The transcription factor ETV1 induces atrial remodeling and arrhythmia. *Circ Res* 2018;**123**:550–63.
48. Iacobellis G. Epicardial adipose tissue in contemporary cardiology. *Nat Rev Cardiol* 2022;**19**:593–606.
49. Gan L, Xie D, Liu J, Bond Lau W, Christopher TA, Lopez B et al. Small extracellular microvesicles mediated pathological communications between dysfunctional adipocytes and cardiomyocytes as a novel mechanism exacerbating ischemia/reperfusion injury in diabetic mice. *Circulation* 2020;**141**:968–83.
50. Gómez-Hurtado N, Domínguez-Rodríguez A, Mateo P, Fernández-Velasco M, Val-Blasco A, Aizpún R et al. Beneficial effects of leptin treatment in a setting of cardiac dysfunction induced by transverse aortic constriction in mouse. *J Physiol* 2017;**595**:4227–43.
51. Zhao Y, Sun Q, Zeng Z, Li Q, Zhou S, Zhou M et al. Regulation of SCN3B/scn3b by interleukin 2 (IL-2): IL-2 modulates SCN3B/scn3b transcript expression and increases sodium current in myocardial cells. *BMC Cardiovasc Disord* 2016;**16**:1.
52. Ernault AC, Meijborg VMF, Coronel R. Modulation of cardiac arrhythmogenesis by epicardial adipose tissue: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:1730–45.
53. Mazurek T, Zhang L, Zaleski A, Mannion JD, Diehl JT, Arafat H et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003;**108**:2460–6.
54. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cottillard A, Atassi F et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokinases. *Eur Heart J* 2015;**36**:795–805.
55. Wang Q, Yu Y, Zhang P, Chen Y, Li C, Chen J et al. The crucial role of activin A/ALK4 pathway in the pathogenesis of Ang-II-induced atrial fibrosis and vulnerability to atrial fibrillation. *Basic Res Cardiol* 2017;**112**:47.
56. Haemers P, Hamdi H, Guedj K, Suffee N, Farahmand P, Popovic N et al. Atrial fibrillation is associated with the fibrotic remodelling of adipose tissue in the subepicardium of human and sheep atria. *Eur Heart J* 2017;**38**:53–61.
57. Chaumont C, Suffee N, Gandjbakhch E, Balse E, Anselme F, Hatem SN. Epicardial origin of cardiac arrhythmias: clinical evidences and pathophysiology. *Cardiovasc Res* 2022;**118**:1693–702.
58. Tarsitano MG, Pandozzi C, Muscogiuri G, Sironi S, Pujja A, Lenzi A et al. Epicardial adipose tissue: a novel potential imaging marker of comorbidities caused by chronic inflammation. *Nutrients* 2022;**14**:2926.
59. Abe I, Teshima Y, Kondo H, Kaku H, Kira S, Ikebe Y et al. Association of fibrotic remodeling and cytokines/chemokines content in epicardial adipose tissue with atrial myocardial fibrosis in patients with atrial fibrillation. *Heart Rhythm* 2018;**15**:1717–27.
60. Ishii Y, Abe I, Kira S, Harada T, Takano M, Oniki T et al. Detection of fibrotic remodeling of epicardial adipose tissue in patients with atrial fibrillation: imaging approach based on histological observation. *Heart Rhythm O2* 2021;**2**:311–23.
61. Ravelli F, Masè M, Cristoforetti A, Avogaro L, D'Amato E, Tessarolo F et al. Quantitative assessment of transmural fibrosis profile in the human atrium: evidence for a three-dimensional arrhythmic substrate by slice-to-slice histology. *Europace* 2023;**25**:739–47.
62. Gharaviri A, Bidar E, Potse M, Zeemering S, Verheule S, Pezzuto S et al. Epicardial fibrosis explains increased endo-epicardial dissociation and epicardial breakthroughs in human atrial fibrillation. *Front Physiol* 2020;**11**:68.
63. Nalliah CJ, Bell JR, Raaijmakers AJA, Waddell HM, Wells SP, Bernasocchi GB et al. Epicardial adipose tissue accumulation confers atrial conduction abnormality. *J Am Coll Cardiol* 2020;**76**:1197–211.
64. De Coster T, Claus P, Kazbanov IV, Haemers P, Willems R, Sipido KR et al. Arrhythmogenicity of fibro-fatty infiltrations. *Sci Rep* 2018;**8**:2050.
65. Zhou B, Ma Q, Rajagopal S, Wu SM, Domian I, Rivera-Feliciano J et al. Epicardial progenitors contribute to the cardiomyocyte lineage in the developing heart. *Nature* 2008;**454**:109–13.
66. Yamaguchi Y, Cavallero S, Patterson M, Shen H, Xu J, Kumar SR et al. Adipogenesis and epicardial adipose tissue: a novel fate of the epicardium induced by mesenchymal transformation and PPAR $\gamma$  activation. *Proc Natl Acad Sci U S A* 2015;**112**:2070–5.
67. Suffee N, Moore-Morris T, Farahmand P, Rücker-Martin C, Dilanian G, Fradet M et al. Atrial natriuretic peptide regulates adipose tissue accumulation in adult atria. *Proc Natl Acad Sci U S A* 2017;**114**:E771–e80.
68. Suffee N, Moore-Morris T, Jagla B, Mougenot N, Dilanian G, Berthet M et al. Reactivation of the epicardium at the origin of myocardial fibro-fatty infiltration during the atrial cardiomyopathy. *Circ Res* 2020;**126**:1330–42.
69. Suffee N, Baptista E, Piquereau J, Ponnaiah M, Doisne N, Ichou F et al. Impacts of a high-fat diet on the metabolic profile and the phenotype of atrial myocardium in mice. *Cardiovasc Res* 2022;**118**:3126–39.
70. Shen MJ, Arora R, Jalife J. Atrial myopathy. *JACC Basic Transl Sci* 2019;**4**:640–54.
71. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr. et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:e199–267.
72. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–962.
73. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2020;**36**:1847–948.
74. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm* 2011;**8**:1416–23.
75. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Choucair WK, Lip GY et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J* 2015;**36**:1660–8.
76. Kamel H, Longstreth WT, Jr., Tirschwell DL, Kronmal RA, Marshall RS, Broderick JP et al. Apixaban to prevent recurrence after cryptogenic stroke in patients with atrial cardiopathy: the ARCADIA randomized clinical trial. *JAMA* 2024;**331**:573–81.
77. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009;**373**:155–66.
78. Takahashi Y, Yamaguchi T, Otsubo T, Nakashima K, Shinzato K, Osako R et al. Histological validation of atrial structural remodeling in patients with atrial fibrillation. *Eur Heart J* 2023;**44**:3339–53.
79. Kudryavtseva AV, Krasnov GS, Dmitriev AA, Alekseev BY, Kardyom OL, Sadritdinova AF et al. Mitochondrial dysfunction and oxidative stress in aging and cancer. *Oncotarget* 2016;**7**:44879–905.
80. Unni PA, Pillai GG, Sajithalulu S. Biological processes and key druggable targets involved in age-associated memory loss: a systematic review. *Life Sci* 2021;**270**:119079.
81. Mehdizadeh M, Aguilar M, Thorin E, Ferbeyre G, Nattel S. The role of cellular senescence in cardiac disease: basic biology and clinical relevance. *Nat Rev Cardiol* 2022;**19**:250–64.
82. Chung HY, Cesari M, Anton S, Marzetti E, Giovannini S, Seo AY et al. Molecular inflammation: underpinnings of aging and age-related diseases. *Ageing Res Rev* 2009;**8**:18–30.

83. Kalstad AA, Myhre PL, Laake K, Opstad TB, Tveit A, Solheim S *et al*. Biomarkers of ageing and cardiac remodeling are associated with atrial fibrillation. *Scand Cardiovasc J* 2021;**55**:213–9.
84. Ramos KS, Brundel B. DNA damage, an innocent bystander in atrial fibrillation and other cardiovascular diseases? *Front Cardiovasc Med* 2020;**7**:67.
85. Adili A, Zhu X, Cao H, Tang X, Wang Y, Wang J *et al*. Atrial fibrillation underlies cardiomyocyte senescence and contributes to deleterious atrial remodeling during disease progression. *Aging Dis* 2022;**13**:298–312.
86. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014;**11**:639–54.
87. Chen M, Li C, Liao P, Cui X, Tian W, Wang Q *et al*. Epidemiology, management, and outcomes of atrial fibrillation among 30 million citizens in Shanghai, China from 2015 to 2020: a medical insurance database study. *Lancet Reg Health West Pac* 2022;**23**:100470.
88. Westaby JD, Zullo E, Bicalho LM, Anderson RH, Sheppard MN. Effect of sex, age and body measurements on heart weight, atrial, ventricular, valvular and sub-epicardial fat measurements of the normal heart. *Cardiovasc Pathol* 2023;**63**:107508.
89. Fenger-Grøn M, Overvad K, Tjønneland A, Frost L. Lean body mass is the predominant anthropometric risk factor for atrial fibrillation. *J Am Coll Cardiol* 2017;**69**:2488–97.
90. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M *et al*. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *Bmj* 2016;**532**:h7013.
91. Volgman AS, Benjamin EJ, Curtis AB, Fang MC, Lindley KJ, Naccarelli GV *et al*. Women and atrial fibrillation. *J Cardiovasc Electrophysiol* 2021;**32**:2793–807.
92. Cheng X, Hu Q, Gao L, Liu J, Qin S, Zhang D. Sex-related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Europace* 2019;**21**:1509–18.
93. Kuck KH, Brugada J, Fürnkranz A, Chun KRJ, Metzner A, Ouyang F *et al*. Impact of female sex on clinical outcomes in the FIRE AND ICE trial of catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2018;**11**:e006204.
94. Cheung JW, Cheng EP, Wu X, Yeo I, Christos PJ, Kamel H *et al*. Sex-based differences in outcomes, 30-day readmissions, and costs following catheter ablation of atrial fibrillation: the United States Nationwide Readmissions Database 2010–14. *Eur Heart J* 2019;**40**:3035–43.
95. Wang L, Selzman KA, Shah RU. Peri-procedural complications in women: an alarming and consistent trend. *Eur Heart J* 2019;**40**:3044–5.
96. Wong GR, Nalliah CJ, Lee G, Voskoboinik A, Chieng D, Prabhu S *et al*. Sex-related differences in atrial remodeling in patients with atrial fibrillation: relationship to ablation outcomes. *Circ Arrhythm Electrophysiol* 2022;**15**:e009925.
97. Müller-Edenborn B, Moreno-Weidmann Z, Venier S, Defaye P, Park CI, Guerra J *et al*. Determinants of fibrotic atrial cardiomyopathy in atrial fibrillation. A multicenter observational study of the RETAC (reseau européen de traitement d'arythmies cardiaques)-group. *Clin Res Cardiol* 2022;**111**:1018–27.
98. Rosano GM, Leonardo F, Dicandia C, Sheiban I, Pagnotta P, Pappone C *et al*. Acute electrophysiologic effect of estradiol 17beta in menopausal women. *Am J Cardiol* 2000;**86**:1385–7. A5-6.
99. Tados R, Ton AT, Fiset C, Nattel S. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. *Can J Cardiol* 2014;**30**:783–92.
100. Li Z, Wang Z, Yin Z, Zhang Y, Xue X, Han J *et al*. Gender differences in fibrosis remodeling in patients with long-standing persistent atrial fibrillation. *Oncotarget* 2017;**8**:53714–29.
101. Cochet H, Mouries A, Nivet H, Sacher F, Derval N, Denis A *et al*. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. *J Cardiovasc Electrophysiol* 2015;**26**:484–92.
102. Bisbal F, Baranchuk A, Braunwald E, Bayés de Luna A, Bayés-Genís A. Atrial failure as a clinical entity: JACC review topic of the week. *J Am Coll Cardiol* 2020;**75**:222–32.
103. Thomas L, Abhayaratna WP. Left atrial reverse remodeling: mechanisms, evaluation, and clinical significance. *JACC Cardiovasc imaging* 2017;**10**:65–77.
104. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D *et al*. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;**113**:1807–16.
105. Corradi D, Callegari S, Maestri R, Benussi S, Alfieri O. Structural remodeling in atrial fibrillation. *Nat Clin Pract Cardiovasc Med* 2008;**5**:782–96.
106. Kühl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D *et al*. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with “idiopathic” left ventricular dysfunction. *Circulation* 2005;**111**:887–93.
107. Gibson DN, Di Biase L, Mohanty P, Patel JD, Bai R, Sanchez J *et al*. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. *Heart Rhythm* 2011;**8**:1364–71.
108. Enríquez-Vázquez D, Quintanilla JG, García-Escolano A, Couselo-Seijas M, Simón-Chica A, Lee P *et al*. Non-invasive electromechanical assessment during atrial fibrillation identifies underlying atrial myopathy alterations with early prognostic value. *Nat Commun* 2023;**14**:4613.
109. Pessoa-Amorim G, Mancio J, Vouga L, Ribeiro J, Gama V, Bettencourt N *et al*. Impaired left atrial strain as a predictor of new-onset atrial fibrillation after aortic valve replacement independently of left atrial size. *Rev Esp Cardiol (Engl Ed)* 2018;**71**:466–76.
110. Zakeri R, Moulay G, Chai Q, Ogut O, Hussain S, Takahama H *et al*. Left atrial remodeling and atrioventricular coupling in a canine model of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2016;**9**:e003238.
111. Habibi M, Zareian M, Ambale Venkatesh B, Samiei S, Imai M, Wu C *et al*. Left atrial mechanical function and incident ischemic cerebrovascular events independent of AF: insights from the MESA study. *JACC Cardiovasc imaging* 2019;**12**:2417–27.
112. Eicher JC, Laurent G, Mathé A, Barthez O, Bertaux G, Philip JL *et al*. Atrial dyssynchrony syndrome: an overlooked phenomenon and a potential cause of “diastolic” heart failure. *Eur J Heart Fail* 2012;**14**:248–58.
113. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC *et al*. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**:e531S–75S.
114. Weigner MJ, Caulfield TA, Danias PG, Silverman DI, Manning WJ. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. *Ann Intern Med* 1997;**126**:615–20.
115. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C *et al*. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094–9.
116. Fonseca AC, Alves P, Inácio N, Marto JP, Viana-Baptista M, Pinho EMT *et al*. Patients with undetermined stroke have increased atrial fibrosis: a cardiac magnetic resonance imaging study. *Stroke* 2018;**49**:734–7.
117. Tandon K, Tirschwell D, Longstreth WT, Jr., Smith B, Akoum N. Embolic stroke of undetermined source correlates to atrial fibrosis without atrial fibrillation. *Neurology* 2019;**93**:e381–7.
118. Kühnlein P, Mahnkopf C, Majersik JJ, Wilson BD, Mitlacher M, Tirschwell D *et al*. Atrial fibrosis in embolic stroke of undetermined source: a multicenter study. *Eur J Neurol* 2021;**28**:3634–9.
119. Nattel S. Atrial fibrosis, endocardial damage, and thrombosis in atrial fibrillation: association with underlying conditions or causal? *JACC Clin Electrophysiol* 2023;**9**:1169–71.
120. Müller-Edenborn B, Minners J, Keyl C, Eichenlaub M, Jander N, Abdelrazek S *et al*. Electrocardiographic diagnosis of atrial cardiomyopathy to predict atrial contractile dysfunction, thrombogenesis and adverse cardiovascular outcomes. *Sci Rep* 2022;**12**:576.
121. Lee HY, Yang PS, Kim TH, Uhm JS, Pak HN, Lee MH *et al*. Atrial fibrillation and the risk of myocardial infarction: a nation-wide propensity-matched study. *Sci Rep* 2017;**7**:12716.
122. Goette A, Borof K, Breithardt G, Camm AJ, Crijns H, Kuck KH *et al*. Presenting pattern of atrial fibrillation and outcomes of early rhythm control therapy. *J Am Coll Cardiol* 2022;**80**:283–95.
123. Goette A, Bukowska A, Dobrev D, Pfeiffenberger J, Morawietz H, Strugala D *et al*. Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles. *Eur Heart J* 2009;**30**:1411–20.
124. Shibata T, Kawakami S, Noguchi T, Tanaka T, Asaumi Y, Kanaya T *et al*. Prevalence, clinical features, and prognosis of acute myocardial infarction attributable to coronary artery embolism. *Circulation* 2015;**132**:241–50.
125. Mueller KAL, Heinzmann D, Klingel K, Fallier-Becker P, Kandolf R, Kilias A *et al*. Histopathological and immunological characteristics of tachycardia-induced cardiomyopathy. *J Am Coll Cardiol* 2017;**69**:2160–72.
126. Ortiz-Leon XA, Posada-Martinez EL, Trejo-Paredes MC, Ivey-Miranda JB, Pereira J, Crandall I *et al*. Understanding tricuspid valve remodeling in atrial fibrillation using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging* 2020;**21**:747–55.
127. Kwak S, Lim J, Yang S, Rhee TM, Choi YJ, Lee HJ *et al*. Atrial functional tricuspid regurgitation: importance of atrial fibrillation and right atrial remodeling and prognostic significance. *JACC Cardiovasc imaging* 2023;**16**:575–87.
128. Arndt M, Lendeckel U, Röcken C, Neppel K, Wolke C, Spiess A *et al*. Altered expression of ADAMs (a disintegrin and metalloproteinase) in fibrillating human atria. *Circulation* 2002;**105**:720–5.
129. Guta AC, Badano LP, Tomaselli M, Mihalcea D, Bartos D, Parati G *et al*. The pathological link between right atrial remodeling and functional tricuspid regurgitation in patients with atrial fibrillation: a three-dimensional echocardiography study. *J Am Soc Echocardiogr* 2021;**34**:585–94.e1.
130. Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. *Circulation* 2005;**112**:745–58.
131. Zoghbi WA, Levine RA, Flachskampf F, Grayburn P, Gillam L, Leipsic J *et al*. Atrial functional mitral regurgitation: a JACC: cardiovascular imaging expert panel viewpoint. *JACC Cardiovasc imaging* 2022;**15**:1870–82.
132. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD *et al*. Atrial functional mitral regurgitation: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:2465–76.

133. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski FE et al. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol* 2011;**58**:1474–81.
134. Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC et al. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:489–98.
135. Dziadzko V, Dziadzko M, Medina-Inojosa JR, Benfari G, Michelena HI, Crestanello JA et al. Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. *Eur Heart J* 2019;**40**:2194–202.
136. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. *Circulation* 2018;**137**:534–5.
137. Patel RB, Shah SJ. Therapeutic targeting of left atrial myopathy in atrial fibrillation and heart failure with preserved ejection fraction. *JAMA Cardiol* 2020;**5**:497–9.
138. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol* 2020;**76**:1051–64.
139. Packer M, Lam CSP, Lund LH, Redfield MM. Interdependence of atrial fibrillation and heart failure with a preserved ejection fraction reflects a common underlying atrial and ventricular myopathy. *Circulation* 2020;**141**:4–6.
140. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
141. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;**310**:2050–60.
142. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham heart study. *JAMA* 1994;**271**:840–4.
143. Dublin S, Glazer NL, Smith NL, Psaty BM, Lumley T, Wiggins KL et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. *J Gen Intern Med* 2010;**25**:853–8.
144. Fenger-Gron M, Vinter N, Frost L. Body mass and atrial fibrillation risk: status of the epidemiology concerning the influence of fat versus lean body mass. *Trends Cardiovasc Med* 2020;**30**:205–11.
145. Gong M, Yuan M, Meng L, Zhang Z, Tse G, Zhao Y et al. Wenxin Keli regulates mitochondrial oxidative stress and homeostasis and improves atrial remodeling in diabetic rats. *Oxid Med Cell Longev* 2020;**2020**:2468031.
146. Aromolaran AS, Colecraft HM, Boutjdir M. High-fat diet-dependent modulation of the delayed rectifier K(+) current in adult Guinea pig atrial myocytes. *Biochem Biophys Res Commun* 2016;**474**:554–9.
147. Goldberg IJ, Trent CM, Schulze PC. Lipid metabolism and toxicity in the heart. *Cell Metab* 2012;**15**:805–12.
148. Vyas V, Blythe H, Wood EG, Sandhar B, Sarker SJ, Balmforth D et al. Obesity and diabetes are major risk factors for epicardial adipose tissue inflammation. *JCI insight* 2021;**6**:e145495.
149. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012;**60**:2263–70.
150. Smorodinova N, Bláha M, Melenovský V, Rozsivalová K, Přidal J, Ďurišová M et al. Analysis of immune cell populations in atrial myocardium of patients with atrial fibrillation or sinus rhythm. *PLoS One* 2017;**12**:e0172691.
151. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol* 2014;**63**:2335–45.
152. Heijman J, Voigt N, Nattel S, Dobrev D. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. *Circ Res* 2014;**114**:1483–99.
153. Andrade JG, Deyell MW, Macle L, Wells GA, Bennett M, Essebag V et al. Progression of atrial fibrillation after cryoablation or drug therapy. *N Engl J Med* 2023;**388**:105–16.
154. Walters TE, Nisbet A, Morris GM, Tan G, Mearns M, Teo E et al. Progression of atrial remodeling in patients with high-burden atrial fibrillation: implications for early ablative intervention. *Heart Rhythm* 2016;**13**:331–9.
155. Sugumar H, Prabhu S, Voskoboinik A, Young S, Gutman SJ, Wong GR et al. Atrial remodeling following catheter ablation for atrial fibrillation-mediated cardiomyopathy: long-term follow-up of CAMERA-MRI study. *JACC Clin Electrophysiol* 2019;**5**:681–8.
156. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* 1999;**100**:87–95.
157. Nattel S. Molecular and cellular mechanisms of atrial fibrosis in atrial fibrillation. *JACC Clin Electrophysiol* 2017;**3**:425–35.
158. Corradi D. Atrial fibrillation from the pathologist's perspective. *Cardiovasc Pathol* 2014;**23**:71–84.
159. Corradi D, Callegari S, Benussi S, Nascimbene S, Pastori P, Calvi S et al. Regional left atrial interstitial remodeling in patients with chronic atrial fibrillation undergoing mitral-valve surgery. *Virchows Arch* 2004;**445**:498–505.
160. Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ et al. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. *J Cardiovasc Electrophysiol* 2012;**23**:232–8.
161. Caixal G, Althoff T, Garre P, Alarcón F, NuñezGarcía M, Benito EM et al. Proximity to the descending aorta predicts regional fibrosis in the adjacent left atrial wall: aetiological and prognostic implications. *Europace* 2021;**23**:1559–67.
162. Hopman L, Bhagiriath P, Mulder MJ, Eggink IN, van Rossum AC, Allaart CP et al. Quantification of left atrial fibrosis by 3D late gadolinium-enhanced cardiac magnetic resonance imaging in patients with atrial fibrillation: impact of different analysis methods. *Eur Heart J Cardiovasc Imaging* 2022;**23**:1182–90.
163. Callegari S, Macchi E, Monaco R, Magnani L, Tafuni A, Croci S et al. Clinicopathological bird's-eye view of left atrial myocardial fibrosis in 121 patients with persistent atrial fibrillation: developing architecture and main cellular players. *Circ Arrhythm Electrophysiol* 2020;**13**:e007588.
164. Liu Y, Niu XH, Yin X, Liu YJ, Han C, Yang J et al. Elevated circulating fibrocytes is a marker of left atrial fibrosis and recurrence of persistent atrial fibrillation. *J Am Heart Assoc* 2018;**7**:e008083.
165. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac fibrosis: the fibroblast awakens. *Circ Res* 2016;**118**:1021–40.
166. Frangogiannis NG. Cardiac fibrosis. *Cardiovasc Res* 2021;**117**:1450–88.
167. Yue L, Xie J, Nattel S. Molecular determinants of cardiac fibroblast electrical function and therapeutic implications for atrial fibrillation. *Cardiovasc Res* 2011;**89**:744–53.
168. Christensen G, Herum KM, Lunde IG. Sweet, yet underappreciated: proteoglycans and extracellular matrix remodeling in heart disease. *Matrix Biol* 2019;**75–76**:286–99.
169. Barallobre-Barreiro J, Gupta SK, Zoccarato A, Kitazume-Taneike R, Fava M, Yin X et al. Glycoproteomics reveals decorin peptides with anti-myostatin activity in human atrial fibrillation. *Circulation* 2016;**134**:817–32.
170. Ausma J, Wijffels M, Thoné F, Wouters L, Alessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. *Circulation* 1997;**96**:3157–63.
171. Kawasaki M, Meulendijks ER, van den Berg NWE, Nariswari FA, Neefs J, Wesselink R, et al. Neutrophil degranulation interconnects over-represented biological processes in atrial fibrillation. *Sci Rep*. 2021;**11**:2972.
172. Meulendijks ER, Al-Shama RFM, Kawasaki M, Fabrizio B, Neefs J, Wesselink R et al. Atrial epicardial adipose tissue abundantly secretes myeloperoxidase and activates atrial fibroblasts in patients with atrial fibrillation. *J Transl Med* 2023;**21**:366.
173. van den Berg NWE, Kawasaki M, Fabrizio B, Nariswari FA, Verduijn AC, Neefs J et al. Epicardial and endothelial cell activation concurs with extracellular matrix remodeling in atrial fibrillation. *Clin Transl Med* 2021;**11**:e558.
174. Harada M, Tadevosyan A, Qi X, Xiao J, Liu T, Voigt N et al. Atrial fibrillation activates AMP-dependent protein kinase and its regulation of cellular calcium handling: potential role in metabolic adaptation and prevention of progression. *J Am Coll Cardiol* 2015;**66**:47–58.
175. van den Berg NWE, Neefs J, Kawasaki M, Nariswari FA, Wesselink R, Fabrizio B et al. Extracellular matrix remodeling precedes atrial fibrillation: results of the PREDICT-AF trial. *Heart rhythm* 2021;**18**:2115–25.
176. Inoue K, Khan FH, Remme EW, Ohte N, García-Izquierdo E, Chetrit M et al. Determinants of left atrial reservoir and pump strain and use of atrial strain for evaluation of left ventricular filling pressure. *Eur Heart J Cardiovasc Imaging* 2021;**23**:61–70.
177. Smiseth OA, Morris DA, Cardim N, Cikes M, Delgado V, Donal E et al. Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2022;**23**:e34–61.
178. Shih JY, Tsai WC, Huang YY, Liu YW, Lin CC, Huang YS et al. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. *J Am Soc Echocardiogr* 2011;**24**:513–9.
179. Kurotobi T, Iwakura K, Inoue K, Kimura R, Toyoshima Y, Ito N et al. The significance of the shape of the left atrial roof as a novel index for determining the electrophysiological and structural characteristics in patients with atrial fibrillation. *Europace* 2011;**13**:803–8.
180. Mangiafico V, Saberwal B, Lavalle C, Rahaarja A, Ahmed Z, Papageorgiou N et al. The role of CT in detecting AF substrate. *Trends Cardiovasc Med* 2021;**31**:457–66.
181. Nediös S, Sanatkhan S, Oladosu M, Seewöster T, Richter S, Arya A et al. Association of low-voltage areas with the regional wall deformation and the left atrial shape in patients with atrial fibrillation: a proof of concept study. *Int J Cardiol Heart Vasc* 2021;**33**:100730.
182. Azemi T, Rabdiya VM, Ayirala SR, McCullough LD, Silverman DI. Left atrial strain is reduced in patients with atrial fibrillation, stroke or TIA, and low risk CHADS(2) scores. *J Am Soc Echocardiogr* 2012;**25**:1327–32.
183. Obokata M, Negishi K, Kurosawa K, Tateno R, Tange S, Arai M et al. Left atrial strain provides incremental value for embolism risk stratification over CHA<sub>2</sub>DS<sub>2</sub>-VASc score and indicates prognostic impact in patients with atrial fibrillation. *J Am Soc Echocardiogr* 2014;**27**:709–16.e4.
184. Leung M, van Rosendaal PJ, Abou R, Ajmone Marsan N, Leung DY, Delgado V et al. Left atrial function to identify patients with atrial fibrillation at high risk of stroke: new insights from a large registry. *Eur Heart J* 2018;**39**:1416–25.

185. Lang RM, Badano LP, Mor-Avi V, Afalalo J, Armstrong A, Ernande L et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1–39.e14.
186. Singh A, Carvalho Singulane C, Miyoshi T, Prado AD, Addetia K, Bellino M et al. Normal values of left atrial size and function and the impact of age: results of the World Alliance Societies of Echocardiography Study. *J Am Soc Echocardiogr* 2022;**35**:154–64.e3.
187. Kou S, Caballero L, Dulgheru R, Voilliot D, De Sousa C, Kacharava G et al. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. *Eur Heart J Cardiovasc Imaging* 2014;**15**:680–90.
188. Soulat-Dufour L, Addetia K, Miyoshi T, Citro R, Daimon M, Fajardo PG et al. Normal values of right atrial size and function according to age, sex, and ethnicity: results of the world alliance societies of echocardiography study. *J Am Soc Echocardiogr* 2021;**34**:286–300.
189. Krittanawong C, Maitra NS, Hassan Virk HU, Farrell A, Hamzeh I, Arya B et al. Normal ranges of right atrial strain: a systematic review and meta-analysis. *JACC Cardiovasc imaging* 2023;**16**:282–94.
190. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M et al. Reference ranges (“normal values”) for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. *J Cardiovasc Magn Reson* 2020;**22**:87.
191. Doria de Vasconcellos H, Win TT, Chamera E, Hong SY, Venkatesh BA, Young P et al. Reference values for left atrial volumes, emptying fractions, strains, and strain rates and their determinants by age, gender, and ethnicity: the multiethnic study of atherosclerosis (MESA). *Acad Radiol* 2021;**28**:356–63.
192. Stojanovska J, Cronin P, Patel S, Gross BH, Oral H, Chughtai K et al. Reference normal absolute and indexed values from ECG-gated MDCT: left atrial volume, function, and diameter. *AJR Am J Roentgenol* 2011;**197**:631–7.
193. Aquaro GD, De Gori C, Faggioni L, Parisella ML, Cioni D, Lencioni R et al. Diagnostic and prognostic role of late gadolinium enhancement in cardiomyopathies. *Eur Heart J Suppl* 2023;**25**:C130–6.
194. Okasha O, Kazmirczak F, Chen KA, Farzaneh-Far A, Shenoy C. Myocardial involvement in patients with histologically diagnosed cardiac sarcoidosis: a systematic review and meta-analysis of gross pathological images from autopsy or cardiac transplantation cases. *J Am Heart Assoc* 2019;**8**:e011253.
195. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M et al. EACVI/EHRA expert consensus document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2016;**17**:355–83.
196. Eichenlaub M, Mueller-Edenborn B, Minners J, Figueras IVRM, Forcada BR, Colomer AV et al. Comparison of various late gadolinium enhancement magnetic resonance imaging methods with high-definition voltage and activation mapping for detection of atrial cardiomyopathy. *Europace* 2022;**24**:1102–11.
197. Boyle PM, Sarairah S, Kwan KT, Scott GD, Mohamedali F, Anderson CA et al. Elevated fibrosis burden as assessed by MRI predicts cryoballoon ablation failure. *J Cardiovasc Electrophysiol* 2023;**34**:302–12.
198. Flett AS, Hayward MP, Ashworth MT, Hansen MS, Taylor AM, Elliott PM et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. *Circulation* 2010;**122**:138–44.
199. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. *J Am Coll Cardiol* 2011;**58**:2225–32.
200. Zahid S, Cochet H, Boyle PM, Schwarz EL, Whyte KN, Vigmond EJ et al. Patient-derived models link re-entrant driver localization in atrial fibrillation to fibrosis spatial pattern. *Cardiovasc Res* 2016;**110**:443–54.
201. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014;**311**:498–506.
202. King JB, Azadani PN, Suksaranjit P, Bress AP, Witt DM, Han FT et al. Left atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation. *J Am Coll Cardiol* 2017;**70**:1311–21.
203. Marrouche NF, Wazni O, McGann C, Greene T, Dean JM, Dagher L et al. Effect of MRI-guided fibrosis ablation vs conventional catheter ablation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation: the DECAAF II randomized clinical trial. *JAMA* 2022;**327**:2296–305.
204. Bisbal F, Benito E, Teis A, Alarcón F, Sarrias A, Caixal G et al. Magnetic resonance imaging-guided fibrosis ablation for the treatment of atrial fibrillation: the ALICIA trial. *Circ Arrhythm Electrophysiol* 2020;**13**:e008707.
205. Yamaguchi T, Otsubo T, Takahashi Y, Nakashima K, Fukui A, Hirota K et al. Atrial structural remodeling in patients with atrial fibrillation is a diffuse fibrotic process: evidence from high-density voltage mapping and atrial biopsy. *J Am Heart Assoc* 2022;**11**:e024521.
206. Chen J, Arentz T, Cochet H, Müller-Edenborn B, Kim S, Moreno-Weidmann Z et al. Extent and spatial distribution of left atrial arrhythmogenic sites, late gadolinium enhancement at magnetic resonance imaging, and low-voltage areas in patients with persistent atrial fibrillation: comparison of imaging vs. electrical parameters of fibrosis and arrhythmogenesis. *Europace* 2019;**21**:1484–93.
207. Hirose T, Kawasaki M, Tanaka R, Ono K, Watanabe T, Iwama M et al. Left atrial function assessed by speckle tracking echocardiography as a predictor of new-onset non-valvular atrial fibrillation: results from a prospective study in 580 adults. *Eur Heart J Cardiovasc Imaging* 2012;**13**:243–50.
208. Hauser R, Nielsen AB, Skaarup KG, Lassen MCH, Duus LS, Johansen ND et al. Left atrial strain predicts incident atrial fibrillation in the general population: the Copenhagen city heart study. *Eur Heart J Cardiovasc Imaging* 2021;**23**:52–60.
209. Nielsen AB, Skaarup KG, Hauser R, Johansen ND, Lassen MCH, Jensen GB et al. Normal values and reference ranges for left atrial strain by speckle-tracking echocardiography: the Copenhagen City Heart Study. *Eur Heart J Cardiovasc Imaging* 2021;**23**:42–51.
210. Habibi M, Samiei S, Ambale Venkatesh B, Opdahl A, Helle-Valle TM, Zareian M et al. Cardiac magnetic resonance-measured left atrial volume and function and incident atrial fibrillation: results from MESA (multi-ethnic study of atherosclerosis). *Circ Cardiovasc Imaging* 2016;**9**:51–56.
211. Lim DJ, Ambale-Venkatesh B, Ostovaneh MR, Zghaib T, Ashkaga H, Wu C et al. Change in left atrial function predicts incident atrial fibrillation: the multi-ethnic study of atherosclerosis. *Eur Heart J Cardiovasc Imaging* 2019;**20**:979–87.
212. Xie E, Yu R, Ambale-Venkatesh B, Bakhshi H, Heckbert SR, Soliman EZ et al. Association of right atrial structure with incident atrial fibrillation: a longitudinal cohort cardiovascular magnetic resonance study from the Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Magn Reson* 2020;**22**:36.
213. Chong B, Jayabakaran J, Ruban J, Goh R, Chin YH, Kong G et al. Epicardial adipose tissue assessed by computed tomography and echocardiography are associated with adverse cardiovascular outcomes: a systematic review and meta-analysis. *Circ Cardiovasc Imaging* 2023;**16**:e015159.
214. West HW, Siddique M, Williams MC, Volpe L, Desai R, Lyasheva M et al. Deep-learning for epicardial adipose tissue assessment with computed tomography: implications for cardiovascular risk prediction. *JACC Cardiovasc Imaging* 2023;**16**:800–16.
215. Heckbert SR, Jensen PN, Austin TR, Chen LY, Post WS, Ambale Venkatesh B et al. Associations of left atrial function and structure with supraventricular ectopy: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc* 2021;**10**:e018093.
216. Huber MP, Pandit JA, Jensen PN, Wiggins KL, Patel RB, Freed BH et al. Left atrial strain and the risk of atrial arrhythmias from extended ambulatory cardiac monitoring: MESA. *J Am Heart Assoc* 2022;**11**:e026875.
217. Tops LF, Delgado V, Bertini M, Marsan NA, Den Uijl DW, Trines SA et al. Left atrial strain predicts reverse remodeling after catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:324–31.
218. Soulat-Dufour L, Lang S, Addetia K, Ederhy S, Advane-Scheuble S, Chauvet-Droit M et al. Restoring sinus rhythm reverses cardiac remodeling and reduces valvular regurgitation in patients with atrial fibrillation. *J Am Coll Cardiol* 2022;**79**:951–61.
219. Huang SH, Tsao HM, Liao CF, Chen ZY, Chao TF, Chen SA. Multimodality imaging assessment of the Batrial remodeling of the burden of atrial high-rate episodes in patients with cardiac implanted electronic devices. *Int J Cardiol* 2023;**371**:175–83.
220. Tsao HM, Hu WC, Tsai PH, Lee CL, Wang HH, Chang SL et al. Functional remodeling of both atria is associated with occurrence of stroke in patients with paroxysmal and persistent atrial fibrillation. *Acta Cardiol Sin* 2017;**33**:50–7.
221. Huang T, Patrick S, Mayer LK, Müller-Edenborn B, Eichenlaub M, Allgeier M et al. Echocardiographic and electrocardiographic determinants of atrial cardiomyopathy identify patients with atrial fibrillation at risk for left atrial thrombogenesis. *J Clin Med* 2022;**11**:1332.
222. Kim D, Shim CY, Hong GR, Kim MH, Seo J, Cho JJ et al. Clinical implications and determinants of left atrial mechanical dysfunction in patients with stroke. *Stroke* 2016;**47**:1444–51.
223. Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol* 2012;**60**:531–8.
224. Burrell LD, Horne BD, Anderson JL, Muhlestein JB, Whisenant BK. Usefulness of left atrial appendage volume as a predictor of embolic stroke in patients with atrial fibrillation. *Am J Cardiol* 2013;**112**:1148–52.
225. Markl M, Lee DC, Furiassi N, Carr M, Foucar C, Ng J et al. Left atrial and left atrial appendage 4D blood flow dynamics in atrial fibrillation. *Circ Cardiovasc Imaging* 2016;**9**:e004984.
226. Spartera M, Stracquadanio A, Pessoa-Amorim G, Von Ende A, Fletcher A, Manley P et al. The impact of atrial fibrillation and stroke risk factors on left atrial blood flow characteristics. *Eur Heart J Cardiovasc Imaging* 2021;**23**:115–23.
227. Ayubcha C, Amanullah A, Patel KH, Teichner E, Gokhale S, Marquez-Valenzuela U et al. Stroke and molecular imaging: a focus on FDG-PET. *Am J Nucl Med Mol Imaging* 2023;**13**:51–63.
228. Müller P, Makimoto H, Dietrich JW, Fochler F, Nentwich K, Krug J et al. Association of left atrial low-voltage area and thromboembolic risk in patients with atrial fibrillation. *Europace* 2018;**20**:f359–f65.

229. Prabhu S, Voskoboinik A, McLellan AJA, Peck KY, Pathik B, Nalliah CJ et al. Batrial electrical and structural atrial changes in heart failure: electroanatomic mapping in persistent atrial fibrillation in humans. *JACC Heart Electrophysiol* 2018;**4**:87–96.
230. Masuda M, Matsuda Y, Uematsu H, Sugino A, Ooka H, Kudo S et al. Prognostic impact of atrial cardiomyopathy: long-term follow-up of patients with and without low-voltage areas following atrial fibrillation ablation. *Heart Rhythm* 2023;**21**:378–86.
231. Kato Y, Takahashi S. Atrial cardiopathy and cryptogenic stroke. *Front Neurol* 2022;**13**: 839398.
232. Kamel H, Longstreth WT, Jr., Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY et al. The Atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke* 2019;**14**:207–14.
233. Maheshwari A, Norby FL, Inciardi RM, Wang VV, Zhang MJ, Soliman EZ et al. Left atrial mechanical dysfunction and the risk for ischemic stroke in people without prevalent atrial fibrillation or stroke: a prospective cohort study. *Ann Intern Med* 2023;**176**: 39–48.
234. Johansen MC, Wang VV, Zhang M, Knopman DS, Ndumele C, Mosley TH et al. Risk of dementia associated with atrial cardiopathy: the ARIC study. *J Am Heart Assoc* 2022;**11**: e025646.
235. Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. *Heart* 2020;**106**:1463–8.
236. Khan AA, Lip GYH. The prothrombotic state in atrial fibrillation: pathophysiological and management implications. *Cardiovasc Res* 2019;**115**:31–45.
237. Goette A, Jentsch-Ullrich K, Lendeckel U, Röcken C, Agbaria M, Auricchio A et al. Effect of atrial fibrillation on hematopoietic progenitor cells: a novel pathophysiological role of the atrial natriuretic peptide? *Circulation* 2003;**108**:2446–9.
238. Mukherjee R, Akar JG, Wharton JM, Adams DK, McClure CD, Stroud RE et al. Plasma profiles of matrix metalloproteinases and tissue inhibitors of the metalloproteinases predict recurrence of atrial fibrillation following cardioversion. *J Cardiovasc Transl Res* 2013;**6**:528–35.
239. Lee KK, Doudesis D, Anwar M, Astengo F, Chenevier-Gobeaux C, Claessens YE et al. Development and validation of a decision support tool for the diagnosis of acute heart failure: systematic review, meta-analysis, and modelling study. *BMJ* 2022;**377**:e068424.
240. Nasab Mehrabi E, Toupch-Khosroshahi V, Athari SS. Relationship of atrial fibrillation and N terminal pro brain natriuretic peptide in heart failure patients. *ESC Heart Fail* 2023;**10**:3250–7.
241. Mu X, Qiu M, Li Y, Li Z, Qi B, Jing Z et al. N-terminal pro-B-type natriuretic peptide improves the predictive value of CHA(2) DS(2)-VASc risk score for long-term cardiovascular events in acute coronary syndrome patients with atrial fibrillation. *Clin Cardiol* 2023;**46**:810–7.
242. Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL et al. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. *Stroke* 2013;**44**:961–7.
243. Sun WP, Du X, Chen JJ. Biomarkers for predicting the occurrence and progression of atrial fibrillation: soluble suppression of tumorigenicity 2 protein and tissue inhibitor of matrix metalloproteinase-1. *Int J Clin Pract* 2022;**2022**:6926510.
244. Reyat JS, Chua W, Cardoso VR, Witten A, Kastner PM, Kabir SN et al. Reduced left atrial cardiomyocyte PITX2 and elevated circulating BMP10 predict atrial fibrillation after ablation. *JCI insight* 2020;**5**:e139179.
245. Hijazi Z, Benz AP, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW et al. Bone morphogenetic protein 10: a novel risk marker of ischaemic stroke in patients with atrial fibrillation. *Eur Heart J* 2023;**44**:208–18.
246. Hennings E, Blum S, Aeschbacher S, Coslovsky M, Knecht S, Eken C et al. Bone morphogenetic protein 10-A novel biomarker to predict adverse outcomes in patients with atrial fibrillation. *J Am Heart Assoc* 2023;**12**:e028255.
247. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;**104**:2886–91.
248. Conway DS, Pearce LA, Chin BS, Hart RG, Lip GY. Prognostic value of plasma von Willebrand factor and soluble P-selectin as indices of endothelial damage and platelet activation in 994 patients with nonvalvular atrial fibrillation. *Circulation* 2003;**107**: 3141–5.
249. Camelo-Castillo A, Rivera-Caravaca JM, Marín F, Vicente V, Lip GYH, Roldán V. Predicting adverse events beyond stroke and bleeding with the ABC-stroke and ABC-bleeding scores in patients with atrial fibrillation: the Murcia AF project. *Thromb Haemost* 2020;**120**:1200–7.
250. Esteve-Pastor MA, Roldán V, Rivera-Caravaca JM, Ramírez-Macias I, Lip GYH, Marín F. The use of biomarkers in clinical management guidelines: a critical appraisal. *Thromb Haemost* 2019;**119**:1901–19.
251. Gorog DA, Gue YX, Chao TF, Fauchier L, Ferreiro JL, Huber K et al. Assessment and mitigation of bleeding risk in atrial fibrillation and venous thromboembolism: executive summary of a European and Asia-Pacific expert consensus paper. *Thromb Haemost* 2022;**122**:1625–52.
252. Xie S, Li Q, Luk AOY, Lan HY, Chan PKS, Bayés-Genís A et al. Major adverse cardiovascular events and mortality prediction by circulating GDF-15 in patients with type 2 diabetes: a systematic review and meta-analysis. *Biomolecules* 2022;**12**:934.
253. Ding WY, McDowell G, Lip GYH. Utilizing biomarkers in atrial fibrillation: the pros and cons. *Cardiovasc Res* 2022;**118**:2035–6.
254. Fatkin D, Huttner IG, Johnson R. Genetics of atrial cardiomyopathy. *Curr Opin Cardiol* 2019;**34**:275–81.
255. Gudbjartsson DF, Arnar DO, Helgadóttir A, Gretarsdóttir S, Holm H, Sigurdsson A et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature* 2007;**448**:353–7.
256. Orr N, Arnaout R, Gula LJ, Spears DA, Leong-Sit P, Li Q et al. A mutation in the atrial-specific myosin light chain gene (MYL4) causes familial atrial fibrillation. *Nat Commun* 2016;**7**:11303.
257. Disertori M, Quintarelli S, Grasso M, Pilotto A, Narula N, Favalli V et al. Autosomal recessive atrial dilated cardiomyopathy with standstill evolution associated with mutation of Natriuretic Peptide Precursor A. *Circ Cardiovasc Genet* 2013;**6**:27–36.
258. Schulze-Bahr E, Neu A, Friederich P, Kaupp UB, Breithardt G, Pongs O et al. Pacemaker channel dysfunction in a patient with sinus node disease. *J Clin Invest* 2003;**111**:1537–45.
259. Tan RB, Gando I, Bu L, Cecchin F, Coetzee W. A homozygous SCN5A mutation associated with atrial standstill and sudden death. *Pacing Clin Electrophysiol* 2018;**41**: 1036–42.
260. Ramos-Mondragon R, Edokobi N, Hodges SL, Wang S, Bouza AA, Canugovi C et al. Neonatal Scn1b-null mice have sinoatrial node dysfunction, altered atrial structure, and atrial fibrillation. *JCI Insight* 2022;**7**:e152050.
261. Duparc A, Cintas P, Somody E, Bieth E, Richard P, Maury P et al. A cardio-neurological form of laminopathy: dilated cardiomyopathy with permanent partial atrial standstill and axonal neuropathy. *Pacing Clin Electrophysiol* 2009;**32**:410–5.
262. van Setten J, Brody JA, Jamshidi Y, Swenson BR, Butler AM, Campbell H et al. PR interval genome-wide association meta-analysis identifies 50 loci associated with atrial and atrioventricular electrical activity. *Nat Commun* 2018;**9**:2904.
263. Wild PS, Felix JF, Schillert A, Teumer A, Chen MH, Leening MJG et al. Large-scale genome-wide analysis identifies genetic variants associated with cardiac structure and function. *J Clin Invest* 2017;**127**:1798–812.
264. Nielsen JB, Thorolfsdóttir RB, Fritsche LG, Zhou W, Skov MW, Graham SE et al. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet* 2018;**50**:1234–9.
265. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM et al. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet* 2018;**50**:1225–33.
266. Steenman M. Insight into atrial fibrillation through analysis of the coding transcriptome in humans. *Biophys Rev* 2020;**12**:817–26.
267. Man JCK, van Duijvenboden K, Krijger PHL, Hooijkaas IB, van der Made I, de Gier-de Vries C et al. Genetic dissection of a super enhancer controlling the Nppa-Nppb cluster in the heart. *Circ Res* 2021;**128**:115–29.
268. Cao TH, Quinn PA, Sandhu JK, Voors AA, Lang CC, Parry HM et al. Identification of novel biomarkers in plasma for prediction of treatment response in patients with heart failure. *Lancet* 2015;**385**:S26.
269. Çubukçuoğlu Deniz G, Durdu S, Doğan Y, Erdemli E, Özdağ H, Akar AR. Molecular signatures of human chronic atrial fibrillation in primary mitral regurgitation. *Cardiovasc Ther* 2021;**2021**:5516185.
270. Zeemering S, Isaacs A, Winters J, Maesen B, Bidar E, Dimopoulou C et al. Atrial fibrillation in the presence and absence of heart failure enhances expression of genes involved in cardiomyocyte structure, conduction properties, fibrosis, inflammation, and endothelial dysfunction. *Heart Rhythm* 2022;**19**:2115–24.
271. Alvarez-Franco A, Rouco R, Ramirez RJ, Guerrero-Serna G, Tiana M, Cogliati S et al. Transcriptome and proteome mapping in the sheep atria reveal molecular features of atrial fibrillation progression. *Cardiovasc Res* 2021;**117**:1760–75.
272. Roselli C, Rienstra M, Ellinor PT. Genetics of atrial fibrillation in 2020: GWAS, genome sequencing, polygenic risk, and beyond. *Circ Res* 2020;**127**:21–33.
273. van Ouwkerk AF, Bosada FM, van Duijvenboden K, Hill MC, Montefiori LE, Scholman KT et al. Identification of atrial fibrillation associated genes and functional non-coding variants. *Nat Commun* 2019;**10**:4755.
274. Doñate Puertas R, Meugnier E, Romestaing C, Rey C, Morel E, Lachuer J et al. Atrial fibrillation is associated with hypermethylation in human left atrium, and treatment with decabazine reduces atrial tachyarrhythmias in spontaneously hypertensive rats. *Transl Res* 2017;**184**:57–67.e5.
275. Shen K, Tu T, Yuan Z, Yi J, Zhou Y, Liao X et al. DNA methylation dysregulations in valvular atrial fibrillation. *Clin Cardiol* 2017;**40**:686–91.
276. Roberts JD, Vittinghoff E, Lu AT, Alonso A, Wang B, Sitlani CM et al. Epigenetic age and the risk of incident atrial fibrillation. *Circulation* 2021;**144**:1899–911.
277. Ward-Caviness CK. Accelerated epigenetic aging and incident atrial fibrillation: new outlook on an immutable risk factor? *Circulation* 2021;**144**:1912–4.
278. Brunel B, Li J, Zhang D. Role of HDACs in cardiac electropathology: therapeutic implications for atrial fibrillation. *Biochim Biophys Acta Mol Cell Res* 2020;**1867**: 118459.
279. Song S, Zhang R, Mo B, Chen L, Liu L, Yu Y et al. EZH2 as a novel therapeutic target for atrial fibrosis and atrial fibrillation. *J Mol Cell Cardiol* 2019;**135**:119–33.

280. Müller-Edenborn B, Chen J, Algeier J, Didenko M, Moreno-Weidmann Z, Neumann FJ et al. Amplified sinus-P-wave reveals localization and extent of left atrial low-voltage substrate: implications for arrhythmia freedom following pulmonary vein isolation. *Europace* 2020;**22**:240–9.
281. Jaddi A, Müller-Edenborn B, Chen J, Keyl C, Weber R, Algeier J et al. The duration of the amplified sinus-P-wave identifies presence of left atrial low voltage substrate and predicts outcome after pulmonary vein isolation in patients with persistent atrial fibrillation. *JACC Clin Electrophysiol* 2018;**4**:531–43.
282. Huang T, Schurr P, Müller-Edenborn B, Pilla N, Mayer L, Eichenlaub M et al. Analysis of the amplified p-wave enables identification of patients with atrial fibrillation during sinus rhythm. *Front Cardiovasc Med* 2023;**10**:1095931.
283. McConkey N, Malamas P, Norby FL, Plamenac J, Park R, Weigel F et al. Abnormal P-wave terminal force in lead V1 is associated with low left atrial appendage ejection velocity. *J Electrocardiol* 2021;**67**:142–7.
284. Lebek S, Wester M, Pec J, Poschenrieder F, Tafelmeier M, Fisser C et al. Abnormal P-wave terminal force in lead V(1) is a marker for atrial electrical dysfunction but not structural remodelling. *ESC Heart Fail* 2021;**8**:4055–66.
285. Huang Z, Zheng Z, Wu B, Tang L, Xie X, Dong R et al. Predictive value of P wave terminal force in lead V1 for atrial fibrillation: a meta-analysis. *Ann Noninvasive Electrocardiol* 2020;**25**:e12739.
286. Li R, Yang X, Jia M, Wang D, Cui X, Bai L et al. Effectiveness of P-wave ECG index and left atrial appendage volume in predicting atrial fibrillation recurrence after first radiofrequency catheter ablation. *BMC Cardiovasc Disord* 2021;**21**:164.
287. German DM, Kabir MM, Dewland TA, Henrikson CA, Tereshchenko LG. Atrial fibrillation predictors: importance of the electrocardiogram. *Ann Noninvasive Electrocardiol* 2016;**21**:20–9.
288. Alexander B, Mildens J, Hazim B, Haseeb S, Bayes-Genis A, Elosua R et al. New electrocardiographic score for the prediction of atrial fibrillation: the MVP ECG risk score (morphology-voltage-P-wave duration). *Ann Noninvasive Electrocardiol* 2019;**24**:e12669.
289. Park JK, Park J, Uhm JS, Joung B, Lee MH, Pak HN. Low P-wave amplitude (<0.1 Mv) in lead I is associated with displaced inter-atrial conduction and clinical recurrence of paroxysmal atrial fibrillation after radiofrequency catheter ablation. *Europace*. 2016;**18**:384–91.
290. Zeng C, Wei T, Zhao R, Wang C, Chen L, Wang L. Electrocardiographic diagnosis of left atrial enlargement in patients with mitral stenosis: the value of the P-wave area. *Acta Cardiol* 2003;**58**:139–41.
291. Tse G, Lakhani I, Zhou J, Li KHC, Lee S, Liu Y et al. P-wave area predicts new onset atrial fibrillation in mitral stenosis: a machine learning approach. *Front Bioeng Biotechnol* 2020;**8**:479.
292. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. *Am Heart J* 1998;**135**:733–8.
293. Marks D, Ho R, Then R, Weinstock JL, Teklemariam E, Kakadia B et al. Real-world experience with implantable loop recorder monitoring to detect subclinical atrial fibrillation in patients with cryptogenic stroke: the value of p wave dispersion in predicting arrhythmia occurrence. *Int J Cardiol* 2021;**327**:86–92.
294. Dilaveris PE, Gialafos EJ, Andrikopoulos GK, Richter DJ, Papanikolaou V, Poralis K et al. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. *Pacing Clin Electrophysiol* 2000;**23**:352–8.
295. Aysha MH, Hassan AS. Diagnostic importance of fibrillatory wave amplitude: a clue to echocardiographic left atrial size and etiology of atrial fibrillation. *J Electrocardiol* 1988;**21**:247–51.
296. İcen YK, Koca H, Sümbül HE, Yıldırım A, Koca F, Yıldırım A et al. Relationship between coarse F waves and thromboembolic events in patients with permanent atrial fibrillation. *J Arrhythm* 2020;**36**:1025–31.
297. Kawaji T, Ogawa H, Hamatani Y, Kato M, Yokomatsu T, Miki S et al. Fine fibrillatory wave as a risk factor for heart failure events in patients with atrial fibrillation: the fushi-atrial fibrillation (AF) registry. *J Am Heart Assoc* 2022;**11**:e024341.
298. Park J, Lee C, Leshem E, Blau I, Kim S, Lee JM et al. Early differentiation of long-standing persistent atrial fibrillation using the characteristics of fibrillatory waves in surface ECG multi-leads. *Sci Rep* 2019;**9**:2746.
299. Lankveld T, Zeemering S, Scherr D, Kuklik P, Hoffmann BA, Willems S et al. Atrial fibrillation complexity parameters derived from surface ECGs predict procedural outcome and long-term follow-up of stepwise catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2016;**9**:e003354.
300. Zarzoso V, Latcu DG, Hidalgo-Muñoz AR, Meo M, Meste O, Popescu I et al. Non-invasive prediction of catheter ablation outcome in persistent atrial fibrillation by fibrillatory wave amplitude computation in multiple electrocardiogram leads. *Arch Cardiovasc Dis* 2016;**109**:679–88.
301. Intzes S, Zagoridis K, Symeonidou M, Spanoudakis E, Arya A, Dinov B et al. P-wave duration and atrial fibrillation recurrence after catheter ablation: a systematic review and meta-analysis. *Europace* 2023;**25**:450–9.
302. Chen LY, Ribeiro ALP, Platonov PG, Cygankiewicz I, Soliman EZ, Gorenek B et al. P wave parameters and indices: a critical appraisal of clinical utility, challenges, and future research—A consensus document endorsed by the International Society of Electrocardiology and the International Society for Holter and Noninvasive Electrocardiology. *Circ Arrhythm Electrophysiol* 2022;**15**:e010435.
303. Kreimer F, Gotzmann M. Left atrial cardiomyopathy—a challenging diagnosis. *Front Cardiovasc Med* 2022;**9**:942385.
304. Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol* 2012;**45**:445–51.
305. Tsao CW, Josephson ME, Hauser TH, O'Halloran TD, Agarwal A, Manning VJ et al. Accuracy of electrocardiographic criteria for atrial enlargement: validation with cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008;**10**:7.
306. Bayés de Luna A, Cladellas M, Oter R, Torner P, Guindo J, Martí V et al. Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. *Eur Heart J* 1988;**9**:1112–8.
307. Power DA, Lampert J, Camaj A, Bienstock SW, Kocovic N, Bayes-Genis A et al. Cardiovascular complications of interatrial conduction block: JACC state-of-the-art review. *J Am Coll Cardiol* 2022;**79**:1199–211.
308. Wu JT, Long DY, Dong JZ, Wang SL, Fan XW, Yang HT et al. Advanced interatrial block predicts clinical recurrence of atrial fibrillation after catheter ablation. *J Cardiol* 2016;**68**:352–6.
309. Nielsen JB, Kühl JT, Pietersen A, Graff C, Lind B, Struijck JJ et al. P-wave duration and the risk of atrial fibrillation: results from the Copenhagen ECG study. *Heart rhythm* 2015;**12**:1887–95.
310. Auricchio A, Özkartal T, Salghetti F, Neumann L, Pezzuto S, Gharaviri A et al. Short P-wave duration is a marker of higher rate of atrial fibrillation recurrences after pulmonary vein isolation: new insights into the pathophysiological mechanisms through computer simulations. *J Am Heart Assoc* 2021;**10**:e018572.
311. Truong QA, Charipar EM, Ptaszek LM, Taylor C, Fontes JD, Krieger M et al. Usefulness of electrocardiographic parameters as compared with computed tomography measures of left atrial volume enlargement: from the ROMICAT trial. *J Electrocardiol* 2011;**44**:257–64.
312. Leshem E, Zilberman I, Tschabrunn CM, Barkagan M, Contreras-Valdes FM, Govari A et al. High-power and short-duration ablation for pulmonary vein isolation: biophysical characterization. *JACC Clin Electrophysiol* 2018;**4**:467–79.
313. Müller-Edenborn B, Minners J, Kocher S, Chen J, Zeh W, Lehrmann H et al. Amplified P-wave duration predicts new-onset atrial fibrillation in patients with heart failure with preserved ejection fraction. *Clin Res Cardiol* 2020;**109**:978–87.
314. Dhala A, Underwood D, Leman R, Madu E, Baugh D, Ozawa Y et al. Signal-averaged P-wave analysis of normal controls and patients with paroxysmal atrial fibrillation: a study in gender differences, age dependence, and reproducibility. *Clin Cardiol* 2002;**25**:525–31.
315. Okumura Y, Watanabe I, Ohkubo K, Ashino S, Kofune M, Hashimoto K et al. Prediction of the efficacy of pulmonary vein isolation for the treatment of atrial fibrillation by the signal-averaged P-wave duration. *Pacing Clin Electrophysiol* 2007;**30**:304–13.
316. Zink MD, Laureanti R, Hermans BJM, Pison L, Verheule S, Philippens S et al. Extended ECG improves classification of paroxysmal and persistent atrial fibrillation based on P- and f-waves. *Front Physiol* 2022;**13**:779826.
317. Farinha JM, Gupta D, Lip GYH. Frequent premature atrial contractions as a signalling marker of atrial cardiomyopathy, incident atrial fibrillation, and stroke. *Cardiovasc Res* 2023;**119**:429–39.
318. Py A, Schaaf M, Duhamel S, Si-Mohamed S, Daher J, Altman M et al. Atrial premature activity detected after an ischaemic stroke unveils atrial myopathy. *Arch Cardiovasc Dis* 2020;**113**:227–36.
319. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* 2019;**394**:861–7.
320. Noseworthy PA, Attia ZI, Behnken EM, Giblon RE, Bews KA, Liu S et al. Artificial intelligence-guided screening for atrial fibrillation using electrocardiogram during sinus rhythm: a prospective non-randomised interventional trial. *Lancet* 2022;**400**:1206–12.
321. Liao S, Ragot D, Nayyar S, Suszko A, Zhang Z, Wang B et al. Deep learning classification of unipolar electrograms in human atrial fibrillation: application in focal source mapping. *Front Physiol* 2021;**12**:704122.
322. Lebert J, Ravi N, Fenton FH, Christoph J. Rotor localization and phase mapping of cardiac excitation waves using deep neural networks. *Front Physiol* 2021;**12**:782176.
323. He J, Tse G, Korantzopoulos P, Letsas KP, Ali-Hasan-Al-Saegh S, Kamel H et al. P-wave indices and risk of ischemic stroke: a systematic review and meta-analysis. *Stroke* 2017;**48**:2066–72.
324. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. *J Am Coll Cardiol* 2015;**66**:232–41.
325. Sajeev JK, Koshy AN, Dewey H, Kalman JM, Bhatia M, Roberts L et al. Poor reliability of P-wave terminal force V(1) in ischemic stroke. *J Electrocardiol* 2019;**52**:47–52.
326. Lattanzi S, Cagnetti C, Pulcini A, Morelli M, Maffei S, Provinciali L et al. The P-wave terminal force in embolic strokes of undetermined source. *J Neural Sci* 2017;**375**:175–8.

327. Stalikas N, Doundoulakis I, Karagiannis E, Kartas A, Gavrilaki M, Sofidis G et al. Prevalence of markers of atrial cardiomyopathy in embolic stroke of undetermined source: a systematic review. *Eur J Intern Med* 2022;**99**:38–44.
328. Li Z, Wang X, Liu Q, Li C, Gao J, Yang Y et al. Atrial cardiomyopathy markers predict ischemic cerebrovascular events independent of atrial fibrillation in patients with acute myocardial infarction. *Front Cardiovasc Med* 2022;**9**:1025842.
329. Froehlich L, Meyre P, Aeschbacher S, Blum S, Djokic D, Kuehn M et al. Left atrial dimension and cardiovascular outcomes in patients with and without atrial fibrillation: a systematic review and meta-analysis. *Heart* 2019;**105**:1884–91.
330. Kamel H, Bartz TM, Elkind MSV, Okin PM, Thacker EL, Patton KK et al. Atrial cardiomyopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study). *Stroke* 2018;**49**:980–6.
331. Tan S, Ho C, Teo YN, Teo YH, Chan MY, Lee CH et al. Prevalence and incidence of stroke, white matter hyperintensities, and silent brain infarcts in patients with chronic heart failure: a systematic review, meta-analysis, and meta-regression. *Front Cardiovasc Med* 2022;**9**:967197.
332. Mosenzon O, Cheng AY, Rabinstein AA, Sacco S. Diabetes and stroke: what are the connections? *J Stroke* 2023;**25**:26–38.
333. Jung H, Yang PS, Kim D, Jang E, Yu HT, Kim TH et al. Associations of hypertension burden on subsequent dementia: a population-based cohort study. *Sci Rep* 2021;**11**:12291.
334. Lee SR, Park CS, Choi EK, Ahn HJ, Han KD, Oh S et al. Hypertension burden and the risk of new-onset atrial fibrillation: a nationwide population-based study. *Hypertension* 2021;**77**:919–28.
335. Okamoto M, Fujii Y, Makita Y, Kajihara K, Yamasaki S, Iwamoto A et al. Left atrial appendage function in patients with systemic embolism in spite of in sinus rhythm. *J Am Soc Echocardiogr* 2006;**19**:211–4.
336. Lip GY. Hypertension and the prothrombotic state. *J Hum Hypertens* 2000;**14**:687–90.
337. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol* 1999;**33**:1424–6.
338. Ruf L, Bukowska A, Gardemann A, Goette A. Coagulation factor Xa has no effects on the expression of PAR1, PAR2, and PAR4 and no proinflammatory effects on HL-1 cells. *Cells* 2023;**12**:2849.
339. Goette A, Lendeckel U. Atrial cardiomyopathy: pathophysiology and clinical consequences. *Cells* 2021;**10**:2605.
340. Orlandi F, Jakil C, Damiani G, Lauricella S, Maggio A, D'Alcamo E et al. First trimester fetal blood sampling. *Acta Eur Fertil* 1988;**19**:23–4.
341. Goette A. Antithrombotic therapy after coronary artery stenting in atrial fibrillation: dual therapy encompassing NOAC plus P2Y12 inhibitor is ready for prime time!. *Ann Transl Med* 2019;**7**:S270.
342. Bukowska A, Hammwöhner M, Corradi D, Mahardhika W, Goette A. Atrial thrombogenesis in atrial fibrillation: results from atrial fibrillation models and AF-patients. *Herzschrittmacherther Elektrophysiol* 2018;**29**:76–83.
343. Farina E, Magni E, Ambrosini F, Manfredini R, Binda A, Sina C et al. Neuropsychological deficits in asymptomatic atrial fibrillation. *Acta Neurol Scand* 1997;**96**:310–6.
344. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;**62**:1990–7.
345. Lappegård KT, Pop-Purceleanu M, van Heerde W, Sexton J, Tendolkar I, Pop G. Improved neurocognitive functions correlate with reduced inflammatory burden in atrial fibrillation patients treated with intensive cholesterol lowering therapy. *J Neuroinflammation* 2013;**10**:78.
346. Barber M, Tait RC, Scott J, Rumley A, Lowe GD, Stott DJ. Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. *J Thromb Haemost* 2004;**2**:1873–8.
347. Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP et al. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam Scan Study. *Neurology* 2012;**78**:326–33.
348. Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. *Stroke* 1980;**11**:35–8.
349. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S et al. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation* 2010;**122**:690–7.
350. Karadag B, Ozyigit T, Ozben B, Kayaoglu S, Altuntas Y. Relationship between left atrial volume index and cognitive decline in elderly patients with sinus rhythm. *J Clin Neurosci* 2013;**20**:1074–8.
351. Gutierrez A, Norby FL, Maheshwari A, Rooney MR, Gottesman RF, Mosley TH et al. Association of abnormal P-wave indices with dementia and cognitive decline over 25 years: ARIC-NCS (the atherosclerosis risk in communities neurocognitive study). *J Am Heart Assoc* 2019;**8**:e014553.
352. Zhang MJ, Norby FL, Lutsey PL, Mosley TH, Cogswell RJ, Konety SH et al. Association of left atrial enlargement and atrial fibrillation with cognitive function and decline: the ARIC-NCS. *J Am Heart Assoc* 2019;**8**:e013197.
353. Wang W, Zhang MJ, Inciardi RM, Norby FL, Johansen MC, Parikh R et al. Association of echocardiographic measures of left atrial function and size with incident dementia. *JAMA* 2022;**327**:1138–48.
354. Goette A, Röcken C. Atrial amyloidosis and atrial fibrillation: a gender-dependent "arrhythmogenic substrate"? *Eur Heart J* 2004;**25**:1185–6.
355. Savelieva I, Kakkouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part I: primary prevention. *Eurpace* 2011;**13**:308–28.
356. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R et al. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol* 2015;**66**:985–96.
357. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;**65**:2159–69.
358. Goette A, Schön N, Kirchhof P, Breithardt G, Fetsch T, Häusler KG et al. Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial. *Circ Arrhythm Electrophysiol* 2012;**5**:43–51.
359. Neefs J, van den Berg NW, Limpens J, Berger WR, Boekholdt SM, Sanders P et al. Aldosterone pathway blockade to prevent atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2017;**231**:155–61.
360. 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.
361. Oraïi A, Healey JS, Kowalik K, Pandey AK, Benz AP, Wong JA et al. Mineralocorticoid receptor antagonists and atrial fibrillation: a meta-analysis of clinical trials. *Eur Heart J* 2024;**45**:756–74.
362. Goette A, Lendeckel U, Kuchenbecker A, Bukowska A, Peters B, Klein HU et al. Cigarette smoking induces atrial fibrosis in humans via nicotine. *Heart* 2007;**93**:1056–63.
363. Bukowska A, Nikonova Y, Wolke C, Lendeckel U, Kocksämper J, Goette A. Anti-inflammatory effects of endothelin receptor blockade in left atrial tissue of spontaneously hypertensive rats. *Int J Cardiol Heart Vasc* 2022;**42**:101088.
364. Goette A, Hammwöhner M, Bukowska A, Scalera F, Martens-Lobenhoffer J, Dobrev D et al. The impact of rapid atrial pacing on ADMA and endothelial NOS. *Int J Cardiol* 2012;**154**:41–6.
365. McManus DD, Yin X, Gladstone R, Vittinghoff E, Vasan RS, Larson MG et al. Alcohol consumption, left atrial diameter, and atrial fibrillation. *J Am Heart Assoc* 2016;**5**:e004060.
366. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S et al. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–8.
367. Deng F, Raza A, Guo J. Treating obstructive sleep apnea with continuous positive airway pressure reduces risk of recurrent atrial fibrillation after catheter ablation: a meta-analysis. *Sleep Med* 2018;**46**:5–11.
368. Khatib R, Joseph P, Briel M, Yusuf B, Healey J. Blockade of the renin-angiotensin-aldosterone system (RAAS) for primary prevention of non-valvular atrial fibrillation: a systematic review and meta analysis of randomized controlled trials. *Int J Cardiol* 2013;**165**:17–24.
369. Nalliah CJ, Wong GR, Lee G, Voskoboinik A, Kee K, Goldin J et al. Impact of CPAP on the atrial fibrillation substrate in obstructive sleep apnea: the SLEEP-AF study. *JACC Clin Electrophysiol* 2022;**8**:869–77.
370. Kapelios CJ, Murrow JR, Nührenberg TG, Montoro Lopez MN. Effect of mineralocorticoid receptor antagonists on cardiac function in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials. *Heart Fail Rev* 2019;**24**:367–77.
371. Sampaio Rodrigues T, Garcia Quarto LJ, Nogueira SC, Koshy AN, Mahajan R, Sanders P et al. Incidence and progression of atrial fibrillation in patients with and without heart failure using mineralocorticoid receptor antagonists: a meta-analysis. *Clin Res Cardiol* 2024;**113**:884–97.
372. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *J Am Coll Cardiol* 2003;**41**:2197–204.
373. Li Y, Li WM, Gong YT, Li BX, Liu W, Han W et al. The effects of cilazapril and valsartan on the mRNA and protein expressions of atrial calpains and atrial structural remodeling in atrial fibrillation dogs. *Basic Res Cardiol* 2007;**102**:245–56.
374. Takemoto Y, Ramirez RJ, Kaur K, Salvador-Montañés O, Ponce-Balbuena D, Ramos-Mondragón R et al. Eplerenone reduces atrial fibrillation burden without preventing atrial electrical remodeling. *J Am Coll Cardiol* 2017;**70**:2893–905.
375. Du L, Qin M, Yi Y, Chen X, Jiang W, Zhou L et al. Eplerenone prevents atrial fibrosis via the TGF- $\beta$  signaling pathway. *Cardiology* 2017;**138**:55–62.
376. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation* 2001;**104**:2608–14.
377. Mancini GBJ, O'Meara E, Zieroth S, Bernier M, Cheng AYY, Cherney DZI et al. 2022 Canadian Cardiovascular Society Guideline for use of GLP-1 receptor agonists and SGLT2 inhibitors for cardiorenal risk reduction in adults. *Can J Cardiol* 2022;**38**:1153–67.
378. Shao Q, Meng L, Lee S, Tse G, Gong M, Zhang Z et al. Empagliflozin, a sodium glucose co-transporter-2 inhibitor, alleviates atrial remodeling and improves mitochondrial

- function in high-fat diet/streptozotocin-induced diabetic rats. *Cardiovasc Diabetol* 2019; **18**:165.
379. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA *et al*. Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: insights from the DECLARE-TIMI 58 trial. *Circulation* 2020; **141**:1227–34.
380. Hohnloser SH, Crijns HJ, van Eckels 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.
381. Blomström-Lundqvist C, Naccarelli GV, McKindley DS, Bigot G, Wieloch M, Hohnloser SH. Effect of dronedarone vs. placebo on atrial fibrillation progression: a post hoc analysis from ATHENA trial. *Europace* 2023; **25**:845–54.
382. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A *et al*. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020; **383**:1305–16.
383. Rillig A, Borof K, Breithardt G, Camm AJ, Crijns H, Goette A *et al*. Early rhythm control in patients with atrial fibrillation and high comorbidity burden. *Circulation* 2022; **146**: 836–47.
384. Masuda M, Sekiya K, Asai M, Iida O, Okamoto S, Ishihara T *et al*. Influence of catheter ablation for atrial fibrillation on atrial and ventricular functional mitral regurgitation. *ESC Heart Fail* 2022; **9**:1901–13.
385. Rotter M, Jais P, Vergnes MC, Nurden P, Takahashi Y, Sanders P *et al*. Decline in C-reactive protein after successful ablation of long-lasting persistent atrial fibrillation. *J Am Coll Cardiol* 2006; **47**:1231–3.
386. Kuck KH, Lebedev DS, Mikhaylov EN, Romanov A, Gellér L, Kaléjs O *et al*. Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST). *Europace* 2021; **23**:362–9.
387. Hof IE, Velthuis BK, Chaldoupi SM, Wittkamp FH, van Driel VJ, van der Heijden JF *et al*. Pulmonary vein antrum isolation leads to a significant decrease of left atrial size. *Europace* 2011; **13**:371–5.
388. Canpolat U, Aytemir K, Özer N, Oto A. The impact of cryoballoon-based catheter ablation on left atrial structural and potential electrical remodeling in patients with paroxysmal atrial fibrillation. *J Interv Card Electrophysiol* 2015; **44**:131–9.
389. Yoshida K, Yui Y, Kimata A, Koda N, Kato J, Baba M *et al*. Troponin elevation after radiofrequency catheter ablation of atrial fibrillation: relevance to AF substrate, procedural outcomes, and reverse structural remodeling. *Heart rhythm* 2014; **11**:1336–42.
390. Neefs J, Wesselink R, van den Berg NWE, de Jong J, Piersma FR, van Boven WP *et al*. Thoracoscopic surgical atrial fibrillation ablation in patients with an extremely enlarged left atrium. *J Interv Card Electrophysiol* 2022; **64**:469–78.
391. Xiong B, Li D, Wang J, Gyawali L, Jing J, Su L. The effect of catheter ablation on left atrial size and function for patients with atrial fibrillation: an updated meta-analysis. *PLoS One* 2015; **10**:e0129274.
392. Pump A, Di Biase L, Price J, Mohanty P, Bai R, Santangeli P *et al*. Efficacy of catheter ablation in nonparoxysmal atrial fibrillation patients with severe enlarged left atrium and its impact on left atrial structural remodeling. *J Cardiovasc Electrophysiol* 2013; **24**:1224–31.
393. Bansilal S, Bloomgarden Z, Halperin JL, Hellkamp AS, Lokhnygina Y, Patel MR *et al*. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF trial). *Am Heart J* 2015; **170**:675–82.e8.
394. Muellerleile K, Groth M, Steven D, Hoffmann BA, Saring D, Radunski UK *et al*. Cardiovascular magnetic resonance demonstrates reversible atrial dysfunction after catheter ablation of persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2013; **24**:762–7.
395. Cho DH, Kim YG, Choi J, Kim HD, Kim MN, Shim J *et al*. Atrial cardiomyopathy with impaired functional reserve in patients with paroxysmal atrial fibrillation. *J Am Soc Echocardiogr* 2023; **36**:180–8.
396. Li-Saw-Hee FL, Blann AD, Gurney D, Lip GY. Plasma von Willebrand factor, fibrinogen and soluble P-selectin levels in paroxysmal, persistent and permanent atrial fibrillation. Effects of cardioversion and return of left atrial function. *Eur Heart J* 2001; **22**:1741–7.
397. Yu CM, Fang F, Zhang Q, Yip GW, Li CM, Chan JY *et al*. Improvement of atrial function and atrial reverse remodeling after cardiac resynchronization therapy for heart failure. *J Am Coll Cardiol* 2007; **50**:778–85.
398. Burri H, Jastrzebski M, Cano Ó, Čurila K, de Pootter J, Huang W *et al*. EHRA clinical consensus statement on conduction system pacing implantation: executive summary. Endorsed by the Asia-Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS) and Latin-American Heart Rhythm Society (LAHRS). *Europace* 2023; **25**:1237–48.
399. Su L, Cai M, Wu S, Wang S, Xu T, Vijayaraman P *et al*. Long-term performance and risk factors analysis after permanent his-bundle pacing and atrioventricular node ablation in patients with atrial fibrillation and heart failure. *Europace* 2020; **22**:ii19–26.
400. Marsan NA, Maffessanti F, Tamborini G, Gripari P, Caiani E, Fusini L *et al*. Left atrial reverse remodeling and functional improvement after mitral valve repair in degenerative mitral regurgitation: a real-time 3-dimensional echocardiography study. *Am Heart J* 2011; **161**:314–21.
401. John B, Stiles MK, Kuklik P, Brooks AG, Chandy ST, Kalman JM *et al*. Reverse remodeling of the atria after treatment of chronic stretch in humans: implications for the atrial fibrillation substrate. *J Am Coll Cardiol* 2010; **55**:1217–26.
402. Goette A, Auricchio A, Boriani G, Braunschweig F, Terradellas JB, Burri H *et al*. EHRA white paper: knowledge gaps in arrhythmia management-status 2019. *Europace* 2019; **21**:993–4.