ESC HEART FAILURE
ESC Heart Failure (2022)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14089

REVIEW

Atrial cardiomyopathy: from cell to bedside

Mengmeng Li[1], Yuye Ning[1,2], Gary Tse[3,4], Ardan M. Saguner[5], Meng Wei[1], John D. Day[6], Guogang Luo[1]* and Guoliang Li[7]*

[1]*Stroke Centre and Department of Neurology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China;* [2]*Department of Neurology, Shaanxi People's Hospital, Xi'an, China;* [3]*Kent and Medway Medical School, Canterbury, UK;* [4]*Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China;* [5]*Arrhythmia Division, Department of Cardiology, University Heart Centre, University Hospital Zurich, Zurich, Switzerland;* [6]*Department of Cardiology, St. Mark's Hospital, Salt Lake City, UT, USA; and* [7]*Department of Cardiovascular Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China*

Abstract

Atrial cardiomyopathy refers to structural and electrical remodelling of the atria, which can lead to impaired mechanical function. While historical studies have implicated atrial fibrillation as the leading cause of cardioembolic stroke, atrial cardiomyopathy may be an important, underestimated contributor. To date, the relationship between atrial cardiomyopathy, atrial fibrillation, and cardioembolic stroke remains obscure. This review summarizes the pathogenesis of atrial cardiomyopathy, with a special focus on neurohormonal and inflammatory mechanisms, as well as the role of adipose tissue, especially epicardial fat in atrial remodelling. It reviews the current evidence implicating atrial cardiomyopathy as a cause of embolic stroke, with atrial fibrillation as a lagging marker of an increased thrombogenic atrial substrate. Finally, it discusses the potential of antithrombotic therapy in embolic stroke with undetermined source and appraises the available diagnostic techniques for atrial cardiomyopathy, including imaging techniques such as echocardiography, computed tomography, and magnetic resonance imaging as well as electroanatomic mapping, electrocardiogram, biomarkers, and genetic testing. More prospective studies are needed to define the relationship between atrial cardiomyopathy, atrial fibrillation, and embolic stroke and to establish a prompt diagnosis and specific treatment strategies in these patients with atrial cardiomyopathy for the secondary and even primary prevention of embolic stroke.

Keywords Atrial cardiomyopathy; Atrial fibrillation; Embolic stroke; Pathogenesis; Diagnosis

Received: 1 April 2022; Revised: 9 June 2022; Accepted: 10 July 2022
**Correspondence to: Guogang Luo, Stroke Centre and Department of Neurology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. Email: lguogang@163.com*
Guoliang Li, Department of Cardiovascular Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. Email: liguoliang_med@163.com
Mengmeng Li and Yuye Ning are co-first authors.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, affecting ~60 million adults worldwide.[1] AF is thought to be the main driver of left atrial (LA) thrombogenesis and the resultant cardioembolic stroke (CS). However, this classical theory has been questioned by more recent studies.[2–4] If AF is the major cause of CS, then embolic risk should be reduced after reversing and maintaining sinus rhythm, yet some studies have failed to demonstrate this observation.[5–7] Moreover, the temporal dissociation between AF and stroke had been examined by several recent clinical studies. For instance, only 27.5% and 8% of the patients in the TRENDS and ASSERT trial, respectively, were detected to have an atrial tachycardia/AF episode within 30 days prior to stroke.[3,8] In the LOOP study, continuous electrocardiographic monitoring increased the rate of AF detection [31.8% vs. 12.2%, hazard ratio (HR): 3.17] and anticoagulation initiation (29.7% vs. 13.1%, HR: 2.72) compared with the usual care group, but the risk of stroke or systemic arterial embolism was not significantly reduced (4.5% vs. 5.6%, P = 0.11).[4] The STROKESTOP study, which included 27 975 older participants, found that screening for AF significantly reduced the overall incidence of stroke, systemic embolism, hospitalization for major bleeding, and all-cause mortality compared with the control group (31.9% vs. 33.0%, P = 0.045). However, there was no significant difference in the incidence of ischaemic stroke (5.5% vs. 5.9%, P = 0.084) or systemic embolism (0.43% vs. 0.38%, P = 0.60) between the two groups.[9] The aforementioned results indicate that AF may not always be directly associated

with stroke or systemic embolism.[4,9] Meanwhile, patients with a CHA2DS2-VASc score of 0 are unlikely to have a stroke even with persistent AF.[2] As a result, a more complex relationship between AF and CS exists.

While AF may worsen underlying atrial structural and functional abnormalities, impaired mechanical function of LA is associated with increased risks of CS independent of AF.[10] In addition, some studies have reported that atrial cardiomyopathy (ACM) was a potential source of embolic stroke of undetermined source (ESUS) in ~45% of ESUS patients.[11] These studies suggest that ACM may be the primary cause of LA thrombogenesis and resultant CS.[12] Therefore, identifying the value of ACM may help to better understand the risk of CS in patients without AF.

Definition of atrial cardiomyopathy

The atria are a critical, and often overlooked, component of normal cardiac function. For example, the atria serve as a reservoir, a conduit, and a booster pump to regulate ventricular filling. In addition, the atria are responsible for cardiac conduction and the secretion of natriuretic peptides. While the concept of ACM was initially proposed a decade ago, it was not widely accepted at that time.[13] According to EHRA/HRS/APHRS/SOLAECE expert consensus, ACM refers to 'structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations'.[14] This concept is impractical for the clinical diagnosis of ACM. While there is no unified diagnostic standard for ACM at present, previous studies have used criteria such as LA enlargement, increased P-wave terminal force in lead V1 (PTFV1) of the electrocardiogram (ECG), and elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) for the diagnosis of ACM.[15–18]

Aetiologies of atrial cardiomyopathy

There are various aetiologies of ACM, including genetic factors, aging, congestive heart failure (CHF), AF, myocarditis, valvular heart disease, hypertension, obstructive sleep apnoea,[14] chronic systemic inflammatory, often autoimmune, diseases (e.g. rheumatoid arthritis, psoriasis, and systemic sclerosis), metabolic disorders characterized by adipose tissue inflammation (e.g. obesity, diabetes mellitus, and non-alcoholic liver disease), and hormonal diseases promoting adipogenesis and adipose tissue dysfunction (e.g. hypothyroidism and primary hyperaldosteronism).[19] In addition, mental disorders can increase the risk of cardiovascular disease and worsen its prognosis.[20] A recent study showed that anxiety was also independently associated with ACM.[21]

In this review, we focused on the effect of heart failure (HF) on atrial pathologies. The prevalence of atrial enlargement in patients with chronic HF ranged from 19% to 66% with great differences between studies, likely attributable to the heterogeneous aetiologies and stages of HF.[22] A recent study investigated the progression of atrial fibrosis in 42 non-AF patients and showed that patients with CHF had significantly more atrial fibrosis progression than those without HF after 25.5 ± 18 months (mean Δfibrosis 8.80 ± 8.88% vs. 3.50 ± 5.81%, $P = 0.0338$).[23] In addition, atrial electrophysiological remodelling is common in patients with HF. AF is a typical representative of electrophysiological remodelling. A study from Swedish Heart Failure Registry observed that the prevalence of AF was 65%, 60%, and 53% in HF with ejection fraction (EF) $\geq$ 50%, 40–49%, and $\leq$39%, respectively.[24] In patients with HF, both pressure and volume overload of the left ventricle can increase LA wall stress and myocyte stretching, thereby triggering adrenergic activation and atrial remodelling. Risk factors of HF may synergistically aggravate atrial remodelling.[22] In a rat model of HF with preserved ejection fraction (HFpEF), mediated by metabolic syndrome, atrial myocytes exhibited enhanced mitochondrial fission, increased production of reactive oxygen species (ROS), abnormal Ca^{2+} handling, and interleukin (IL)-10 can attenuate the dysfunction of Ca^{2+} handling.[25] Dual inhibition of sodium-glucose linked transporter type (SGLT)-1 and SGLT-2 also ameliorated LA remodelling in metabolic HFpEF.[26] Therefore, HF mediated by differing aetiologies may participate in atrial remodelling through different mechanisms. Furthermore, HF may promote atrial thrombosis. A substudy of the ENSURE-AF trial analysed determinants of LA thrombus detected by transoesophageal echocardiography in patients with AF scheduled for electrical cardioversion. The results of this ENSURE-AF trial substudy showed that LA thrombus was reported in 91 of 1183 subjects (8.2%) and that only age $\geq$ 75 years [odds ratio (OR): 2.13, $P = 0.0202$] and HF (OR: 1.97, $P = 0.0064$) were independent risk factors of LA thrombus.[27] A meta-analysis including 20 516 AF patients also showed that HF is associated with LA thrombus presence [OR: 3.67, 95% confidence interval (CI): 2.40–5.60].[28]

Pathogenesis of atrial cardiomyopathy

Atrial cardiomyopathy is caused by atrial structural and electrophysiological remodelling stimulated by various aetiologies. Structural remodelling manifests as cardiomyocyte abnormalities (the absence of sarcomeres, accumulation of glycogen, dedifferentiation of mature cells, expression of a foetal gene pattern, and display of homogeneous chromatin), atrial fibrosis (fibroblast proliferation and excessive accumulation of extracellular matrix),[29] changes of atrial endothelial cells (irregularly hypertrophied, disorganization, the forma-

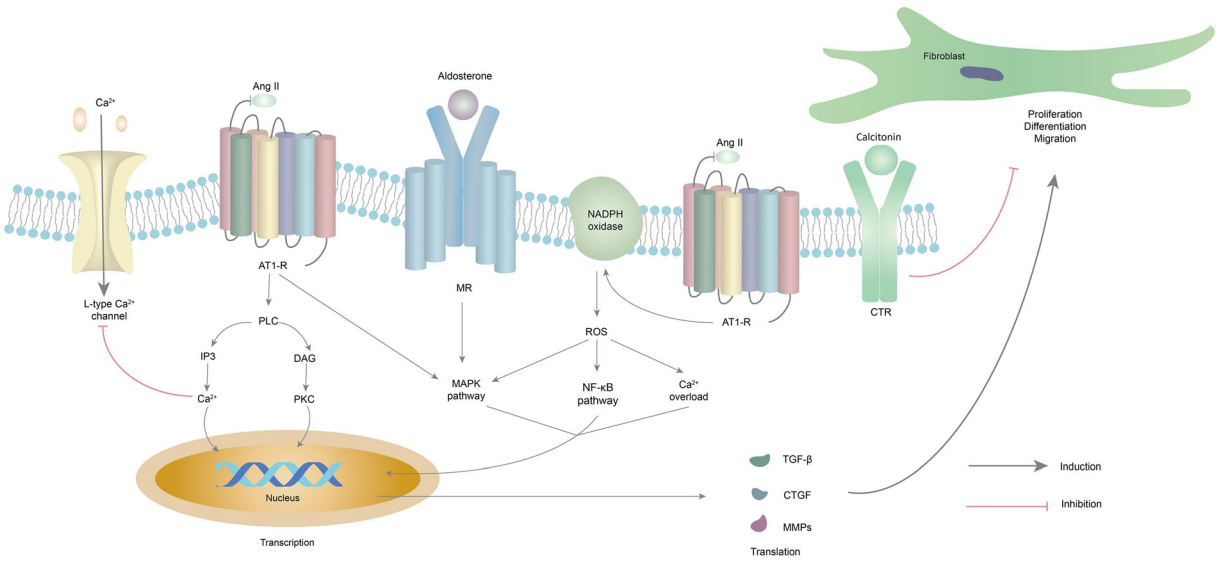
tion of different-sized gaps along the border of cells, and the enhanced expression of monocyte chemoattractant protein-1 and adhesion molecules),[30] the infiltration of adipose tissue and inflammatory cells,[31] glycosphingolipids and amyloid deposition, and granuloma formation.[14] Electrophysiological remodelling involves the alterations of excitation–contraction coupling, ion channels, gap junctions, and autonomic nerve distribution.[29] To date, the pathogenesis of ACM has not been completely clarified.

Neurohormonal mechanisms

Normally, the renin-angiotensin-aldosterone system (RAAS) is essential for regulating haemodynamic stability. However, increased angiotensin II (Ang II) plays a key role in promoting atrial remodelling by binding to angiotensin receptor 1 (AT1-R). Firstly, the combination of Ang II and AT1-R activates the mitogen-activated protein kinase (MAPK) pathway and thus regulates the expression of pro-fibrotic molecules, such as transforming growth factor β (TGF-β), connective tissue growth factor (CTGF), and matrix metalloproteinases (MMPs).[32] Secondly, AT1-R is a G-protein-coupled receptor, and its activation hydrolyses phospholipase C (PLC) to generate inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG). Abnormally increased IP3 can lead to intracellular Ca^{2+} overload that promotes the proliferation and differentiation of fibroblasts and down-regulates the L-type Ca^{2+} current.[33] Thirdly, Ang II stimulates ROS excessive release by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which induces intracellular Ca^{2+} overload and activates MAPK, nuclear factor-κB, and cytokines to participate in myocardial fibrosis.[34,35] Sacubitril/valsartan can prevent Ang II from binding AT1-R. Li *et al*.[36] observed that sacubitril/valsartan reduced the extent of atrial fibrosis and alleviated susceptibility to AF in rats stimulated by Ang II. This result may be conducive to therapies targeting both ACM and AF (*Figure 1*).[36] While angiotensin-converting enzyme (ACE) is a key enzyme for Ang II production, ACE2 can convert Ang II to Ang 1–7, largely counteracting Ang II effects.[37] There seems to be a gender difference in allele types of *ACE1* encoding ACE as the *I* allele is more commonly seen in females and the *D* allele (associated with high expression of ACE) is more frequently observed in males.[38] An accumulating body of evidences suggest that the balance between ACE/Ang II/AT1-R pathways and ACE2/Ang(1–7)/Mas receptor and angiotensin receptor 2 pathways was affected by gender as oestrogen may contribute to this difference given that the prevalence of cardiovascular disease in premenopausal women is lower than in aged-matched men.[39] Bukowska *et al*. showed that oestrogen in atrial tissue significantly down-regulated the ratio of ACE/ACE2 and inhibited the atrial expression of nuclear factor-κB target genes that had pro-inflammatory or pro-oxidative effects. However, whether oestrogen or selective oestrogen receptor modulators can be used to delay the progression of atrial remodelling should be further studied.[37]

Aldosterone can activate MAPK pathway in atrial myocytes to promote fibrosis by binding the mineralocorticoid receptor

Figure 1 The neurohormonal mechanisms involved in atrial remodelling. Ang II, angiotensin II; AT1-R, angiotensin receptor 1; CTGF, connective tissue growth factor; CTR, calcitonin receptor; DAG, diacylglycerol; IP3, inositol-1,4,5-triphosphate; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; MR, mineralocorticoid receptor; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; PKC, protein kinase C; PLC, phospholipase C; ROS, reactive oxygen species; TGF-β, transforming growth factor β.



(MR) (*Figure 1*). Eplerenone, an MR antagonist, attenuates the effect on atrial fibrosis of animals through an unclear mechanism.[32] Yi *et al*. explored the influence of osteoblast MR on atrial fibrosis, finding that the osteoblast MR deficiency alleviated atrial fibrosis by reducing the expression of osteocalcin. Osteocalcin promoted the proliferation and migration of atrial fibroblasts and thus may be a potential target for atrial fibrosis.[40]

Transforming growth factor β is one of the most effective stimulators of cardiac fibrosis. It correlates with phosphorylation of the Smads family to form complexes that translocate into the nucleus of myofibroblasts to up-regulate the generation of fibrin.[35] It should be noted that Ang II cannot cause cardiac hypertrophy and fibrosis in the absence of TGF-β. TGF-β can also induce cardiomyocyte apoptosis and stimulate the expression of AT1-R.[32,41] Similarly, platelet-derived growth factor (PDGF), fibroblast growth factor, CTGF, and MMPs are also significant participators in atrial remodelling.[32]

Calcitonin, a hormone involved in bone metabolism, is mainly secreted from the thyroid parafollicular cells. Recently, it has been demonstrated that the atrial myocardial cell is also an active source of calcitonin. Moreira *et al*.[42] found that the mRNA level of calcitonin in human atrial myocardial cells is half that in human medullary thyroid carcinoma TT cells. Interestingly, calcium-induced calcitonin secretion in atrial myocardial cells was 16 times higher than that in TT cells. Calcitonin from atrial myocytes acts on adjacent atrial fibroblasts to inhibit their proliferation and migration as well as collagen 1 production (*Figure 1*). In addition, this study revealed that the calcitonin content was markedly reduced and subcellular localization of calcitonin receptors was transformed from cell surfaces to intracellular spaces in patients with persistent AF. In the final analysis, the calcitonin gene knockout and overexpression mouse model further verified the importance of calcitonin–calcitonin receptor signalling in atrial remodelling.[42] Hence, restoring damaged calcitonin–calcitonin receptor signalling of the myocardium may provide a new strategy for inhibiting atrial fibrosis.

Inflammatory mechanisms

Cardiac inflammation (myocarditis, pericarditis, infective endocarditis, etc.), noncardiac inflammation (pneumonia, intestinal inflammatory disease, etc.), and systemic subclinical inflammatory conditions (obesity, hypertension, ischaemic heart disease, etc.) are prone to promote the initiation and maintenance of AF.[32] C-reactive protein (CRP) was shown to be a strong predictor of new onset or recurrence of post-operative atrial fibrillation (POAF).[43] Inflammation can activate the RAAS and oxidative stress, thereby bringing about atrial remodelling. A variety of inflammatory cytokines are involved in atrial structural and electrophysiological remodelling, such as tumour necrosis factor (TNF), PDGF, and IL-6.[44] In the sterile pericarditis rat model, intraperitoneal injection of anti-rat-IL-6 antibody not only ameliorated atrial fibrosis but also reversed the abnormalities of Ca^{2+} handling, particularly ryanodine receptor 2 (RyR2) dysfunction. Moreover, vascular leakage and consequent cardiac oedema caused by inflammation can induce intercalated disk remodelling and slow atrial conduction.[45]

Inflammasomes, macromolecular protein complexes contained in the cytoplasm, are of significance in reaction to cellular stress. The best known inflammasome is NOD-like receptor protein 3 (NLRP3) composed of NACHT, LRR, and PYD domain containing protein 3. The NLRP3 inflammasome activates caspase-1, regulates the maturation and release of IL-1β and IL-18, and possibly induces pyroptosis.[46] Yao *et al*.[47] have confirmed that NLRP3 inflammasome is activated in atrial cardiomyocytes from AF patients. They also found that the cardiomyocyte-specific knockin (CM-KI) mouse model expressing constitutively active NLRP3 manifested abnormal Ca^{2+} release of atrial myocardial sarcoplasmic reticulum (SR), shortened atrial effective refractory period, and a hypertrophic and fibrotic atrium. At the molecular level, the mRNA level encoding RyR2, acetylcholine-activated K^+ channel, ultrafast delayed rectifier K^+ channel, and fibrosis markers (collagen 1a and galectin 3) were increased in the CM-KI mouse model. In contrast, the cardiomyocyte-specific knockdown of NLRP3 reduced susceptibility to AF.[47] These results revealed the pathophysiological role of NLRP3 inflammasome in atrial remodelling. The detailed upstream factors activating NLRP3 are not entirely clear. A recent study indicated that gut microbiota dysbiosis induced the up-regulation of atrial NLRP3 level by increasing lipopolysaccharide and glucose and thus promoted atrial fibrosis.[48] Suppressing the NLRP3 inflammasome signalling of atrial cardiomyocytes established a new potential target for the treatment of ACM or AF.

Role of adipose tissue in atrial cardiomyopathy

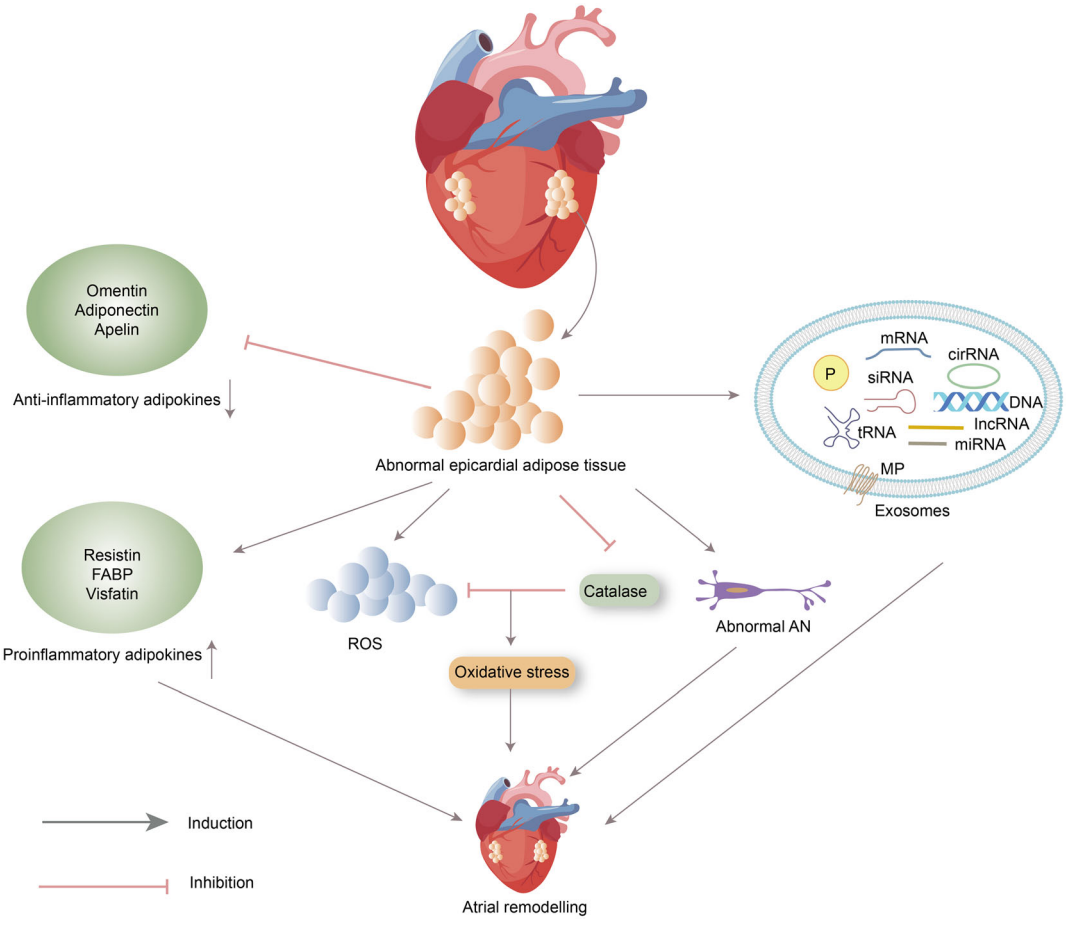
Being overweight and clinical obesity have presented a significant threat to the global public health system. It is estimated that there are currently 2 billion adults and 43 million children under the age of 5 who are overweight or obese in the world.[49] Obesity is a known risk factor for ACM and AF. The incidence of pacing-induced AF in obese mice (100%) is dramatically higher than that in lean controls (25%). In addition, diet-induced obese mice exhibited the remodelling of ion channels and corresponding atrial fibrosis.[50] Another study demonstrated that a chronic high-fat diet also altered the expression and distribution of atrial connexin that is an essential component of gap junction.[51]

Epicardial adipose tissue (EAT) is a beige fat located between the visceral pericardium and myocardium, accounting

for ~20% of heart weight and covering nearly 80% of the cardiac surface. The volume of EAT may be affected by various factors such as age, gender, weight, and race. EAT consists of a variety of different cell types including adipocytes, preadipocytes, adipose-derived stem cells, monocytes, fibrocytes, immunocytes, ganglion, and stromal vascular cells.[52] Normally, the function of EAT are to provide energy, protect myocardium from hypothermic injury, serve as a mechanical buffer to avoid distortion of coronary arteries, and secrete cytokines to regulate coronary circulation and myocardial structure. In the pathologic state, EAT participated in the development of atrial fibrosis and atrial arrhythmia.[53]

The LA appendage specimens from AF patients were analysed histologically and biochemically with results showing that the extent of infiltration and fibrotic remodelling of EAT affected LA myocardial fibrosis and that the collagen content of the LA myocardium was positively related to the expression level of pro-inflammatory and pro-fibrotic cytokines/chemokines in EAT.[54] EAT can secrete multiple adipokines to regulate fibroblasts, myocytes, and leukocytes in the myocardium. This imbalance between anti-inflammatory (omentin, apelin, adiponectin, etc.) and pro-inflammatory adipokines (resistin, fatty acid binding protein, visfatin, etc.) contributes to the atrial remodelling. Activin A and angiopoietin-like protein 2 in EAT have been confirmed to play a key role in the atrial fibrosis process.[55,56] In addition, extracellular vesicles from EAT are also a significant participator in atrial remodelling. Shaihov-Teper *et al*.[57] collected and cultured EAT of AF patients and then extracted exosomes from culture medium. The proteomic analysis, *in vivo* and *in vitro* experiments, all showed that the exosomes from EAT of AF patients have a distinctive pro-inflammatory, pro-fibrotic, and pro-arrhythmic properties. In patients with cardiovascular diseases, EAT has more ROS, less catalase, and different post-translational modifications of oxidative stress-related proteins compared with subcutaneous

Figure 2 The possible mechanisms of epicardial adipose tissue promoting atrial remodelling under pathological conditions. AN, autonomic nerve; cirRNA, circular RNA; FABP, fatty acid binding protein; lncRNA, long non-coding RNA; miRNA, microRNA; MP, membrane protein; mRNA, messenger RNA; P, proteins; ROS, reactive oxygen species; siRNA, small interfering RNA; tRNA, transfer RNA.



adipose tissue (SAT). These differences make the level of oxidative stress in EAT higher, thereby resulting in atrial remodelling (*Figure 2*).[58]

Moreover, EAT has potential arrhythmogenic properties. Jhuo *et al*. analysed the association between EAT volume and various ECG findings, showing that the PR interval, P-wave duration, and inter-atrial conduction block were correlated with EAT volume.[59] Epicardial adipocytes-incubated LA myocytes exhibited different electrophysiological characteristics and ionic currents from the control.[60] Adipokines and exosomes secreted from EAT promote atrial arrhythmias through paracrine signalling. Abundant autonomic nerves are distributed in epicardial fat pads. Abnormalities of autonomic nerves can also lead to atrial electrophysiological remodelling (*Figure 2*). Stimulating autonomic nerves of EAT can shorten the duration of the action potential, increase Ca^{2+} release from SR, reduce atrial conduction velocity, and raise the heterogeneity of conduction.[61] Botulinum toxin (BTX) may block parasympathetic nerves to release acetylcholine. Recently, it was found that BTX injections into epicardial fat pads significantly reduced the incidence of atrial arrhythmias and the burden of AF in patients with AF during a 3 year follow-up.[62] However, the study from Waldron *et al*. showed that BTX injections into epicardial fat pads did not reduce the incidence of POAF during hospitalization.[63] In this study, patients without AF accounted for the majority of patients and the atrial diameter of patients without AF was smaller than that of the former study. These differences indicate that BTX injections into epicardial fat pads may represent a potential POAF prevention strategy more suitable for AF patients with severe atrial remodelling. In addition, whether epicardial BTX injection is more effective than antiarrhythmic drugs in the prevention of POAF deserves attention.

Atrial cardiomyopathy contributes to embolic stroke

Atrial cardiomyopathy, atrial fibrillation, and embolic stroke

Cryptogenic ischaemic stroke accounts for 25% of all ischaemic strokes. Compelling evidence exists suggesting that most cryptogenic strokes arise from an inapparent thromboembolic event. Thus, the term ESUS, introduced in 2014, is defined as a non-lacunar cerebral infarction without any large arterial stenoses $\geq$ 50% or identifiable cardioembolic causes.[64] ESUS comprises 17% of all ischaemic strokes with an annual stroke recurrence rate of 4–5%.[65] Initially, silent paroxysmal AF was implicated as the most cause of ESUS. However, further studies have challenged this opinion as described previously in this manuscript. Although the EAST-AFNET 4 trial showed that early rhythm control compared with no rhythm control for patients with AF was associated with lower incidence of adverse cardiovascular events including stroke, it should be noted that most patients in this trial received anticoagulation therapy, rate control, and management of cardiovascular conditions[66]; such comprehensive management is actually a treatment of atrial substrate and not only rhythm control. Previous studies demonstrated that rhythm control compared with rate control failed to reduce the incidence of cardiovascular adverse events.[5,6] Hence, the lower risk of adverse cardiovascular outcomes in early rhythm control group may be attributed to better treatment of atrial substrate for AF patients in the EAST-AFNET 4 trial. Kottkamp[67] contributed one of the first reports on the relationship between ACM, AF, and CS. Kottkamp correctly observed that the fibrotic ACM supplied the substrate necessary for both AF and thromboembolic complications.

Emerging evidence suggests ACM as an important contributor to ESUS. A prospective multicentre study of 800 ESUS patients showed that 45% of patients carried ACM that was defined as mild or severe LA enlargement or frequent supraventricular extrasystoles.[11] A recent study defining ACM as PTFV1 $>$ 5000 μV*ms or severe LA enlargement found that the incidence of ACM in ESUS patients was higher than that in the large artery atherosclerosis or small vessel disease group (26.6% vs. 12.1% vs. 16.9%, respectively).[18] There is a significant difference in the proportion of ACM in ESUS between the aforementioned two studies, which may be partly due to the different diagnostic criteria of ACM and the different populations studied.

Atrial fibrillation tends to occur in the cases experiencing atrial abnormalities, such as endothelial damage, fibrosis, decreased myocardial contractility, and atrial enlargement. These atrial abnormalities are related to stroke independently of AF.[68] Thus, AF may be a lagging marker of a thrombogenic atrial substrate. With sustained AF, ACM is exacerbated by AF promoting atrial remodelling. Atrial high-rate episodes, short asymptomatic episodes of AF that are detected by a pacemaker or implantable cardioverter-defibrillator but often not recognized clinically by ECG and Holter monitors, may also induce chronic atrial changes.[69] Atrial functional mitral regurgitation (AFMR) refers to functional mitral regurgitation caused by persistent AF or HFpEF. The prevalence of AFMR was 28% in persistent AF with duration $>$ 10 years. This proportion rose to 37–44% in patients with persistent AF and HFpEF.[70] Atrial remodelling in AF is one of the significant mechanisms of AFMR. Conversely, AFMR will accelerate the development of atrial abnormalities.[71] Rapid depolarization of the atrium during AF results in intracellular Ca^{2+} overload that causes adaptive or inflammatory changes promoting atrial fibrosis and systolic dysfunction.[72] AF can induce platelet activation. Activated platelets promote atrial fibrosis by releasing significant amounts of TGF-β into the plasma or regional atrial tissue and interacting with fibroblasts.[73] Recent animal experimen-

tation has shown that the hypercoagulable state during AF can also promote atrial remodelling by enhancing the expression of pro-fibrotic and pro-inflammatory molecules of fibroblasts.[74]

Atrial remodelling and thrombosis

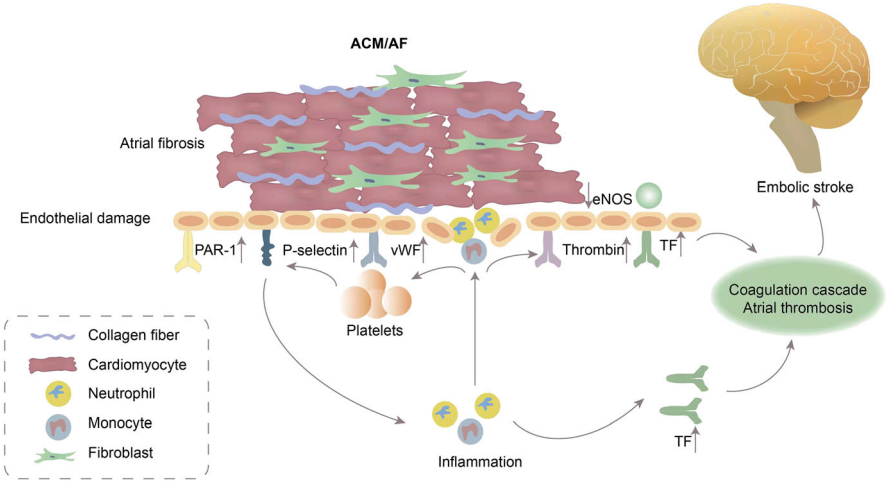
Blood stasis, endothelial injury, and hypercoagulability are the three elements of thrombosis. The mechanism underlying thrombosis in AF patients meets all three criteria[75] and is specifically reflected as atrial enlargement, decreased myocardial contractility, endothelial dysfunction, fibrosis, and the release of pro-thrombotic factors such as IL-6 and von Willebrand factor.[76] According to this description, the pro-thrombotic conditions of AF are the result of atrial remodelling rather than just a rhythm disturbance alone. Therefore, ACM may be the real cause of atrial thrombosis.

Inflammation is one of the important mechanisms of atrial remodelling. It may also play a key role in atrial thrombosis. Prospective clinical studies showed that CRP or IL-6 was an independent predictor of stroke in AF patients.[77,78] The infiltration of inflammatory factors and immune cells induces endothelial injury and dysfunction, decreasing the expression of endothelial nitric oxide synthase, but increasing the amount of von Willebrand factor, thrombin, tissue factor, and protease-activated receptor 1 in the atrial endocardium.[44] The von Willebrand factor interacts with GPIb-IX and GPIIb/IIIa proteins to mediate the adhesion and aggregation of platelets in the endocardium. This platelet aggregation-induced P-selectin expression may then recruit additional neutrophils and monocytes to the endocardial surface. Inflammatory cells and damaged endothelial cells express tissue factors, initiating the coagulation cascade and promoting atrial thrombosis (*Figure 3*).[79]

Atrial cardiomyopathy and antithrombotic therapy

The selection of antithrombotic drugs is crucial for stroke prevention.[80] At present, guidelines recommend that patients with ESUS should receive antiplatelet drugs for secondary prevention of stroke.[81] The multicentre, randomized, double-blind clinical studies, NAVIGATE ESUS and the RE-SPECT ESUS, concluded that rivaroxaban or dabigatran was not better than aspirin in the prevention of stroke recurrence after ESUS, and the incidence of bleeding events caused by these two anticoagulants was higher than aspirin. The failure to classify potential embolic sources, or the overlap of embolic sources, may be one of the reasons for these results.[82,83] Based on the secondary analysis of NAVIGATE ESUS, rivaroxaban showed significant benefits in preventing ischaemic stroke over aspirin for 361 ESUS patients with an LA diameter $>$ 4.6 cm (HR: 0.26, 95% CI: 0.07–0.94).[84] The WARSS trial revealed that the incidence of recurrent ischaemic stroke or death within 2 years in the warfarin group was significantly lower than that in the aspirin group for patients with NT-proBNP $>$ 750 pg/mL but without known AF.[85] The ongoing ARCADIA will further investigate whether apixaban is better than aspirin in the prevention of stroke recurrence to patients with cryptogenic ischaemic stroke and ACM.[15] If the primary hypothesis of this trial is successfully verified, it will be of great clinical significance for the transformation of antithrombotic therapy for patients with cryptogenic ischaemic stroke and ACM. Studies evaluating the relationship between ACM and thromboembolism will help

Figure 3 The relationship between inflammation and atrial thrombosis in patients with ACM or AF. ACM, atrial cardiomyopathy; AF, atrial fibrillation; eNOS, endothelial nitric oxide synthase; PAR-1, protease-activated receptor 1; TF, tissue factor; vWF, von Willebrand factor.



promote a conceptual reorientation that LA thrombosis is related to not only blood stasis during AF but also LA abnormalities of different aetiologies. This conceptual transformation will enable more accurate and individualized strategies for stroke prevention. In addition, it will help to develop new therapeutic targets for stroke prevention that can complement anticoagulant therapy, such as the improvement of endothelial function, interventions to halt or delay atrial fibrosis, enhancement of atrial contractility, and the comprehensive management of many risk factors of ACM.[15] Moreover, as ablation is the first-line treatment for AF, it has been reported that AF recurrence after ablation is associated with pre-existing atrial fibrosis. Therefore, it is worth studying whether the identification of ACM could better differentiate which patients can benefit most from AF ablation.[86]

Diagnosis of atrial cardiomyopathy

Imaging technique

Echocardiography is the first choice for screening and tracking atrial morphological or functional abnormalities due to its low cost and ease of use. Because of the three-dimensional structural characteristics of the atria and the heterogeneity of atrial remodelling, measurement of atrial volume is more accurate for evaluating the true atrial state. Compared with two-dimensional echocardiography that underestimates LA volume, the accuracy of three-dimensional echocardiography in evaluating LA volume is close to cardiac computed tomography (CCT) or cardiac magnetic resonance imaging (CMR).[14] Traditionally, maximal LA volume is used to evaluate LA size. Nevertheless, emerging data support the important role of minimal LA volume in assessing atrial disease.[87,88] Two-dimensional speckle-tracking echocardiography is a very sensitive technology to identify functional abnormalities before anatomical changes develop in the atria.[89] The Copenhagen City Heart Study including 1641 healthy subjects recently revealed the normal reference range for peak atrial longitudinal strain of 39.4% (23.0–67.6%), peak atrial contraction strain of 15.5% (6.4–28.0%), and LA strain during the conduit phase of 23.7% (8.8–44.8%).[90] Decreased peak atrial longitudinal strain is an excellent marker for assessing the fibrosis of LA.[91] LA strain parameters can also predict incident AF and ischaemic stroke.[92]

Multidetector CCT with great spatial resolution has advantages in evaluating LA volume and wall thickness, the anatomy of pulmonary veins, and the location and morphology of LA appendage.[93] CCT with a delayed imaging is a reliable tool with a 0.98 sensitivity and a 1.00 specificity in detecting LA appendage thrombus compared with transesophageal echocardiography.[94] CCT is also the preferred method for identifying and quantifying EAT that is involved in the process of atrial remodelling.[93]

Cardiac magnetic resonance imaging is considered the gold standard for assessing cardiac structural and functional states. Contrast-enhanced CMR with gadolinium shows good performance in evaluating atrial fibrosis.[95] A study assessing the local image intensity ratio (IIR) of the LA by late-gadolinium-enhanced CMR (LGE-CMR) in 10 healthy young persons and 30 patients with AF concluded that IIR was $\leq$1.20 in healthy young individuals and $>$1.32 in dense scar with IIR values ranging between 1.2 and 1.32 for interstitial fibrosis.[96] Atrial fibrosis identified by LGE-CMR may help to select patients suitable for AF ablation and predict the evolution of sinoatrial node dysfunction, progression of AF, and stroke risk for AF patients.[14,91] However, Althoff *et al*.[97] found that the ability of LGE-CMR to detect ablation-induced fibrosis decreased over time. Thus, it is recommended to perform LGE-MRI at 3 months post-ablation. A multicentre study demonstrated that patients with ESUS had comparable atrial fibrosis detected by LGE-CMR with AF patients, and atrial fibrosis $\geq$ 12% in ESUS patients was related to a higher incidence of recurrent stroke, incident AF, or both (25.0% vs. 4.8%, P = 0.039).[98] The result hinted that atrial fibrosis in ESUS patients may be a good indicator of anticoagulation therapy for secondary prevention. Some studies revealed that increased LA volume or deteriorated LA function measured by CMR could also increase the risk of AF and ischaemic stroke.[10,99,100] The application of CMR in ablation procedures has received attention in recent years. Quinto *et al*.[101] found that localizing veno-atrial gaps using delayed enhancement CMR in repeat pulmonary vein isolation (PVI) procedures could shorten the duration of ablation (161 ± 52 vs. 195 ± 72 min) and decreased the rate of recurrent AF, atrial tachycardia, or flutter (30% vs. 61%) compared with the conventional group during a 2 year follow-up. Recently, the ALICIA trial showed that CMR-guided fibrosis ablation plus PVI did not improve the primary outcome nor did it reduce the risk of adverse events compared with PVI alone. This result may be partly attributed to the fact that the atrial fibrosis burden of participants was relatively mild (mean: 12%; only ~50% of patients had small-size fibrosis areas outside the pulmonary veins).[102] Whether CMR-guided fibrosis ablation could improve the outcomes in patients with advanced atrial remodelling and persistent AF is under study (unique identifier: NCT02529319). Advanced four-dimensional flow CMR can directly display and quantify the blood stasis of the LA and LA appendage with full volumetric coverage.[95] Unfortunately, although CMR has developed rapidly, it has not been widely used in clinical evaluation of atrial structure and function due to its high price and technical challenges, especially in developing regions. Thin atrial wall (2–4 mm), arrhythmias, and irregular breathing patterns are major challenges of atrial imaging using CMR.[103]

Electroanatomic mapping system is an invasive method to assess ACM, which can be used for anatomical replication of atria and assessing atrial substrate.[14] It has been regarded as the gold standard in determining atrial abnormality. Low-voltage areas detected by electroanatomic mapping systems are a powerful predictor of atrial remodelling and poor prognosis post-ablation.[104,105] But as an invasive procedure, electroanatomic mapping cannot be used for preprocedural and prognostic evaluation. A recent study revealed that there existed large discrepancies in identifying both extent and regional distribution of ACM between the most common LGE-CMR methods and endocardial mapping. Thus, optimizing the ACM-detection methods of LGE-CMR is required.[105]

Electrocardiogram

Various ECG markers have been associated with ACM, such as P-wave dispersion, PTFV1, and the burden of premature atrial contractions.[106,107] Among these markers, PTFV1 is one of the most frequently used indices for the diagnosis of ACM. Specifically, PTFV1 is defined as the negative area of the P-wave in lead V1 of the 12-lead ECG and it is calculated by the product of duration and amplitude.[108] These P-wave parameters have been shown to predict not only new-onset AF but also stroke independently of AF.[109–111]

A study conducted among 91 AF-free patients with structural heart disease showed that PTFV1 was related to increased LA volumes, decreased LA emptying fraction, and decreased LA reservoir function.[112] In contrast, there was no correlation between PTFV1 and LA size in 504 healthy athletes.[113] A recent study concluded that abnormal PTFV1 ($\geq$4000 ms*μV) can predict functional and electrical but not structural remodelling of the LA.[108] Surprisingly, this study also observed that the area of atrial fibrosis for patients with an abnormal PTFV1 was smaller than that for patients with normal PTFV1 (12.32 ± 1.63% vs. 20.50 ± 2.09%). In addition, a negative correlation between the degree of atrial fibrosis and the value of PTFV1 was observed. One possible explanation for this result is that only key cardiomyocytes, but not fibrotic tissue, have normal electroactivity. A decrease of cardiomyocytes with an accompanying progressive fibrosis will reduce P-wave terminal amplitude. But a degree of atrial fibrosis may not be enough to prolong P-wave terminal duration due to the high atrial conduction reserve.[108] However, the relationship between PTFV1 and atrial structural remodelling requires further study.

Non-invasive body surface electrocardiographic imaging (ECGI) is an emerging diagnostic tool for ACM.[114] In a study exploring the value of ECGI relative to high-density LA voltage and biatrial activation maps in diagnosing ACM before PVI ablation for AF, a total atrial conduction time (TACT) $\geq$ 148 ms in ECGI is an effective index for the diagnosis of ACM with $>$90% sensitivity and specificity.[114] Nevertheless, the high cost and limited clinical application make ECGI not widely used. In addition, sinus rhythm is essential in TACT measurement, so ECGI is not applicable to patients with persistent AF. Reducing electrode numbers, developing automatic analysis system, and investigating alternative imaging modalities of CT to reduce radiation damage would save cost and increase the usage of ECGI.[114]

Serum biomarkers

A variety of serum biomarkers have been associated with atrial abnormalities. For example, brain natriuretic peptide (BNP) and NT-proBNP are primarily secreted in response to myocyte stretch arising from volume or pressure overload.[115] Elevated NT-proBNP is a predictor of LA fibrosis and has been used as one of the diagnostic criteria of ACM in some studies.[15–17,116] However, a recent study defining ACM as LA enlargement (diameter $\geq$ 47 mm) or NT-proBNP $>$ 250 pg/mL indicated a significant difference in the proportion of severe LA enlargement (5.3% vs. 1.4%) rather than elevated NT-proBNP (32.7% vs. 32.3%) between ESUS patients and non-cardioembolic patients,[16] which may be attributed to the fact that NT-proBNP was elevated in the acute stage of ischaemic stroke and thus cannot truly represent ACM.[117] The atrial natriuretic peptide (ANP) is secreted predominantly by the atria, which could more accurately identify ACM than BNP and NT-proBNP in theory. Mid-regional pro-atrial natriuretic peptide (MR-proANP) shows greater stability than ANP, making it widely used in clinical practice. A study including 346 patients without HF showed that both MR-proANP and NT-proBNP were both positively correlated with LA volume.[118] Similarly, MR-proANP was found to be a more powerful marker than NT-proBNP for atrial volume overload and LA volume index in patients with HFpEF.[119] In addition, amyloid deposition in the atria is a special type of pathological change of ACM. ANP, the precursor molecule of ANP, BNP, and NT-proBNP are all the main components of amyloid.[120–122] However, it is noteworthy to remember that the secretion of natriuretic peptides is affected by many factors besides ACM, such as body mass index and acute stage of ischaemic stroke.[117,123] Therefore, whether natriuretic peptides are reliable markers of ACM need individualized analysis and dynamic observation.

A disintegrin and metalloproteinases (ADAMs) are a kind of membrane-bound glycoproteins with the function of proteolysis, signal transduction, adhesion, and fusion. They play an important role in maintaining normal cardiac structure and myocardial tissue by regulating cell–cell and cell–matrix interactions.[124] Arndt *et al.*[124] found that the expression of ADAM10 and ADAM15 was significantly increased in the atrial tissue of AF patients. Importantly, the ADAM15/integrin β1 ratio was significantly associated with the LA diameter. Animal studies indicated that ADAM12 and ADAM19 may also

be related to myocardial hypertrophy or cardiac morphogenesis.[125,126] A study from Patel *et al*. showed that ADAM17 mediated the cleavage and shedding of myocardial ACE2 induced by Ang II, which established a positive feedback of RAAS.[127] Animal experiments revealed that ADAM17 could promote cardiac hypertrophy and fibrosis.[128] However, recent clinical research indicated that post-operative AF patients had lower plasma levels of ADAM17 compared with patients free from AF, suggesting a possible beneficial effect of ADAM17 against post-operative AF occurrence.[129] This seemingly contradictory result may be partly caused by other clinical factors. Whether the role of ADAM17 in atrial remodelling is protective or harmful should be further clarified.

Vascular cell adhesion molecule 1 (VCAM-1), a cell surface protein, belongs to immunoglobulin superfamily. It plays an important role in the adhesion and trafficking of leukocytes.[130] Normal endocardial surfaces express low levels of VCAM-1. Atrial VCAM-1 expression has been observed to increase during rapid atrial pacing both *in vivo* and *in vitro* models.[131] Local up-regulated VCAM-1 contributes to the leukocytes infiltration and inflammation that gives rise to subsequent atrial remodelling. A cohort study with a 20 year follow-up was conducted in 909 participants and revealed the association between the levels of 13 inflammation markers and incident AF, showing that only the level of soluble VCAM-1, rather than other 12 inflammation markers (including monocyte chemoattractant protein-1, P-selectin, and high-sensitivity CRP), was correlated with new-onset AF.[132] A recent study from Contreras-Briceño *et al*.[133] demonstrated that circulating VCAM-1 has direct correlation with LA remodelling in male long-distance runners. In addition, the up-regulation of soluble VCAM-1 was reported to be linked with AF-associated cardiovascular events, which may be partly attributed to the 'endocardial remodelling' caused by VCAM-1.[130,132,134] The circulating levels of some molecules related to fibrosis (e.g. collagen I and III synthesis and turnover products, and galectin-3) can also reflect the ACM and predict the occurrence and maintenance of AF.[35,135] However, other interference factors should be comprehensively considered when serum biomarkers are used to identify ACM.

Genetic testing

Atrial cardiomyopathy can be caused by variants of genes that are important to maintain the normal atrial structure, function, and metabolism. The natriuretic peptide precursor A (*NPPA*) gene encodes for ANP and it is essential to prevent atrial remodelling. Investigators conducting a 37 year follow-up of 13 patients with atrial dilation and standstill from 6 families found that all affected patients were characterized by onset in adulthood, severe biatrial enlargement, atrial standstill, thromboembolic events, decreased ANP, and normal left ventricular function. Further genetic analysis revealed that all eight living affected patients from the aforementioned six families carried a homozygous mutation of the *NPPA* gene (p.Arg150Gln).[136] The myosin light-chain 4 (*MYL4*) gene encoding for myosin light chain is atrial specific and its expression is almost disappeared in the ventricles by

Table 1 Genetic variations of atrial cardiomyopathy

Gene	Encoded protein	Mutation	Phenotype
NPPA[136]	ANP	c.G449A (p.Arg150Gln)	Severe biatrial enlargement, atrial standstill, thromboembolic events, decreased ANP, and normal left ventricular function
MYL4[137]	Myosin light chain	c.234delC	Early-onset AF or other types of arrhythmias, impaired left atrial function, ischaemic stroke, or sudden death
LMNA[139]	Lamin A/C	c.1003C > T (p.R335W)	Familial heart-hand syndrome characterized by prominent atrial lesions and brachydactyly
SCN5A[140]	The alpha subunits of cardiac voltage-gated sodium channel (Nav1.5)	Multiple	Brugada syndrome with atrial conduction abnormalities, atrial fibrosis, or atrial standstill
SYNPO2L[141]	Cytoskeletal heart-enriched actin-associated protein	rs766868752	Cardiac fibrosis, atrial cardiomyopathy, and AF
PITX2[142]	The homeobox transcription factor Pitx2	Multiple	Congenital heart diseases and AF
SIX5[88]	Sine oculis homeobox homologue 5 protein	Expansion of CTG repeats	It is related to myotonic dystrophy type 1 with atrial conduction abnormalities
DMPK[143]	Dystrophia myotonica protein kinase	Expansion of CTG repeats	Myotonic dystrophy type 1 with atrial conduction abnormalities
MYO18B[145]	Myosin 18B	Multiple	Compromised sarcomere assembly and atrial enlargement
CILP[146]	Cartilage intermediate layer protein 1	Multiple	Cardiac fibrosis
TTN[147]	A giant sarcome protein (titin)	Multiple	Dilated or hypertrophic cardiomyopathy, and early-onset AF
CASQ2[148]	Calsequestrin-2	Multiple	AF and catecholaminergic polymorphic ventricular tachycardia

AF, atrial fibrillation; ANP, atrial natriuretic peptide.

birth in normal hearts. The expression of *MYL4* is necessary for the normal contractile characteristics of cardiomyocytes.[137] Patients with the *MYL4* gene mutation presented with early-onset AF or other types of arrhythmias, impaired LA function, ischaemic stroke, or sudden death.[115,137] Mutations in Lamin A/C gene (*LMNA*) are associated with a series of cardiac phenotypes including dilated cardiomyopathy, arrhythmia, and conduction disorders. Cardiomyopathy caused by *LMNA* mutations is characterized by ventricular dilation or non-compaction according to previous literatures.[138] However, a recent study revealed the *LMNA* p.R335W mutation in a heart-hand syndrome pedigree manifesting as atrial abnormality and brachydactyly. Then researchers confirmed the pathogenicity of *LMNA* p.R335W mutation in the atrial lesions.[139] In addition, genetic changes in other diseases, such as Brugada syndrome caused by *SCN5A* gene mutations,[140] hereditary AF syndromes resulting from *PITX2* gene or *SYNPO2L* gene mutations, and hereditary muscular dystrophies caused by *DMPK* gene mutations, can also induce abnormalities of atrial structure or function.[76,141–143] Ahlberg *et al*. used the UK Biobank to conduct genome-wide association study on LA volume and function derived from CMR. They identified 18 novel loci and provided evidence for seven plausible casual mutants related to LA function in the genes including *DSP*, *SIX5*, *MYO18B*, *CILP*, *TTN*, and *CASQ2*, and these genes are associated with cardiomyopathy or muscular dystrophy or AF (*Table 1*).[88,143–148] In a recent study of whole genome sequencing in 1293 patients with AF, the overall positive rate of disease-related gene mutation was 10.1%, and the positive proportion was highest (16.8%) in patients diagnosed as AF before 30 years of age, while lowest (7.1%) after 60 years of age. In addition, this study also suggested that the genetic overlap rate between AF and hereditary cardiomyopathy syndromes was higher than that between AF and other hereditary arrhythmia syndromes.[149] However, the positive rate of gene variation in patients with ACM has not been identified. Generally, genetic testing is necessary for patients with early-onset or familial atrial abnormalities, usually $<$60 years of age, which may be vital for the treatment and risk factor management of ACM.

Conclusions and directions

Atrial cardiomyopathy is the common pathway of atrial structural and electrical remodelling caused by various factors. The pathogenesis of ACM is complex, including classic neurohormonal and inflammatory mechanisms. The role of EAT in atrial remodelling has also been important in recent years. Although many potential targets for controlling atrial remodelling have been found, there is still a lack of effective strategies for intervening in the pathogenesis of ACM. The complexity of the mechanism determines that the intervention measures of atrial remodelling should be comprehensive. Future studies should explore the effect of intervening simultaneously on multiple pathways thereby targeting atrial remodelling.

Atrial cardiomyopathy is associated with embolic stroke independent of AF. ESUS patients are mainly treated with antiplatelet therapy according to established guidelines. The ongoing ARCADIA trial aims to explore whether apixaban is better than aspirin in preventing stroke recurrence of ESUS patients with ACM. The results of this trial will guide the secondary and even primary prevention strategies of stroke in the future.

Despite the rapid progression of various ACM diagnostic means, including imaging technology, ECG, serum, and genetic markers, there are no clear diagnostic criteria of ACM, which may limit the interpretability of ongoing and future studies. The diagnostic value of serum biomarkers in ACM, such as NT-proBNP, needs individualized analysis and dynamic observation. What is more, previous work regarding the relationship between ACM and the occurrence of embolic stroke is mainly confined to cross-sectional studies, which cannot prove whether there is a causal relationship between them. Hopefully, more prospective studies could further clarify this relationship, which will help to expand the strategies for the secondary and even primary prevention of embolic strokes, such as anti-inflammatory therapy, anti-oxidative stress therapy, or anti-fibrosis therapy.

Conflict of interest

A.M.S. received educational grants through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, BMS/Pfizer, and Medtronic and speaker fees/proctoring fees from Bayer Healthcare, Daiichi-Sankyo, and Medtronic. The other authors report no conflicts of interest.

Funding

This work was supported by grants from the Clinical Research Center of the First Affiliated Hospital of Xi'an Jiaotong University (grants XJTU1AF-CRF-2018-015 and XJTU1AFCRF-2016-013) and the Natural Science Foundation of Shaanxi Province (2020JM-373).

References

1. Essien UR, Kornej J, Johnson AE, Schulson LB, Benjamin EJ, Magnani JW. Social determinants of atrial fibrillation. *Nat Rev Cardiol*. 2021; **18**: 763–773.
2. Sajeev JK, Kalman JM, Dewey H, Cooke JC, Teh AW. The atrium and embolic stroke: myopathy not atrial fibrillation as the requisite determinant? *JACC Clin Electrophysiol*. 2020; **6**: 251–261.
3. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, Lau CP, van Gelder I, Hohnloser SH, Carlson M, Fain E, Nakamya J, Mairesse GH, Halytska M, Deng WQ, Israel CW, Healey JS, ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014; **129**: 2094–2099.
4. Svendsen JH, Diederichsen SZ, Højberg S, Krieger DW, Graff C, Kronborg C, Olesen MS, Nielsen JB, Holst AG, Brandes A, Haugan KJ, Køber L. Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP study): a randomised controlled trial. *Lancet*. 2021; **398**: 1507–1516.
5. van Gelder I, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002; **347**: 1834–1840.
6. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002; **347**: 1825–1833.
7. Proietti M, Vitolo M, Harrison SL, Lane DA, Fauchier L, Marin F, Nabauer M, Potpara TS, Dan GA, Boriani G, Lip G. Real-world applicability and impact of early rhythm control for European patients with atrial fibrillation: a report from the ESC-EHRA EORP-AF long-term general registry. *Clin Res Cardiol*. 2022; **111**: 70–84.
8. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, Ziegler PD, TRENDS Investigators. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm*. 2011; **8**: 1416–1423.
9. Svennberg E, Friberg L, Frykman V, al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet*. 2021; **398**: 1498–1506.
10. Habibi M, Zareian M, Ambale Venkatesh B, Samiei S, Imai M, Wu C, Launer LJ, Shea S, Gottesman RF, Heckbert SR, Bluemke DA, Lima JAC. Left atrial mechanical function and incident ischemic cerebrovascular events independent of AF: insights from the MESA study. *JACC Cardiovasc Imaging*. 2019; **12**: 2417–2427.
11. Ntaios G, Perlepe K, Lambrou D, Sirimarco G, Strambo D, Eskandari A, Karagkiozi E, Vemmou A, Koroboki E, Manios E, Makaritsis K, Vemmos K, Michel P. Prevalence and overlap of potential embolic sources in patients with embolic stroke of undetermined source. *J Am Heart Assoc*. 2019; **8**: e012858.
12. Ning Y, Tse G, Luo G, Li G. Atrial cardiomyopathy: an emerging cause of the embolic stroke of undetermined source. *Front Cardiovasc Med*. 2021; **8**: 674612.
13. Dong M, Liu T, Li G. Atrial cardiomyopathy—a not yet classified cardiomyopathy? *Int J Cardiol*. 2011; **151**: 394–396.
14. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, van Wagoner D, Nattel S, Document Reviewers. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace*. 2016; **18**: 1455–1490.
15. Kamel H, Longstreth WJ, Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, Meinzer C, Dillon C, Ewing I, Spilker JA, di Tullio MR, Hod EA, Soliman EZ, Chaturvedi S, Moy CS, Janis S, Elkind MSV. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke*. 2019; **14**: 207–214.
16. Chen J, Gao F, Liu W. Atrial cardiopathy in embolic stroke of undetermined source. *Brain Behav*. 2021; **11**: e02160.
17. Yaghi S, Boehme AK, Hazan R, Hod EA, Canaan A, Andrews HF, Kamel H, Marshall RS, Elkind MSV. Atrial cardiopathy and cryptogenic stroke: a cross-sectional pilot study. *J Stroke Cerebrovasc Dis*. 2016; **25**: 110–114.
18. Jalini S, Rajalingam R, Nisenbaum R, Javier AD, Woo A, Pikula A. Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. *Neurology*. 2019; **92**: e288–e294.
19. Packer M. Characterization, pathogenesis, and clinical implications of inflammation-related atrial myopathy as an important cause of atrial fibrillation. *J Am Heart Assoc*. 2020; **9**: e015343.
20. Michal M, Beutel M. Mental disorders and cardiovascular disease: what should we be looking out for? *Heart*. 2021; **107**: 1756–1761.
21. Wang Z, Qin H, Chen G, Dai Y, Cai Y, Cheng X, Qian Y, Chu M, Lu X. Anxiety is associated with increased risk for atrial cardiopathy. *Acta Neurol Belg*. 2020; **120**: 1383–1388.
22. Hohendanner F, Messroghli D, Bode D, Blaschke F, Parwani A, Boldt LH, Heinzel FR. Atrial remodelling in heart failure: recent developments and relevance for heart failure with preserved ejection fraction. *ESC Heart Fail*. 2018; **5**: 211–221.
23. Dagher L, Shi H, Zhao Y, Mitlacher M, Schnupp S, Ajmi I, Forkmann M, Marrouche N, Mahnkopf C. Atrial fibrosis progression in patients with no history of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2021; **32**: 2140–2147.
24. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail*. 2017; **5**: 565–574.
25. Bode D, Wen Y, Hegemann N, Primessnig U, Parwani A, Boldt LH, M. Pieske B, R. Heinzel F, Hohendanner F. Oxidative stress and inflammatory modulation of Ca^{2+} handling in metabolic HFpEF-related left atrial cardiomyopathy. *Antioxidants (Basel)*. 2020; **9**: 860.
26. Bode D, Semmler L, Wakula P, Hegemann N, Primessnig U, Beindorff N, Powell D, Dahmen R, Ruetten H, Oeing C, Alogna A, Messroghli D, Pieske BM, Heinzel FR, Hohendanner F. Dual SGLT-1 and SGLT-2 inhibition improves left atrial dysfunction in HFpEF. *Cardiovasc Diabetol*. 2021; **20**: 7.
27. Merino JL, Lip G, Heidbuchel H, Cohen AA, de Caterina R, De Groot JR, Ezekowitz MD, le Heuzey JY, Themistoclakis S, Jin J, Melino M, Winters SM, Merkely B, Goette A. Determinants of left atrium thrombi in scheduled cardioversion: an ENSURE-AF study analysis. *Europace*. 2019; **21**: 1633–1638.
28. di Minno MN, Ambrosino P, dello Russo A, Casella M, Tremoli E, Tondo C. Prevalence of left atrial thrombus in patients with non-valvular atrial fibrillation. A systematic review and meta-analysis of the literature. *Thromb Haemost*. 2016; **115**: 663–677.

29. Shen MJ, Arora R, Jalife J. Atrial myopathy. *JACC Basic Transl Sci*. 2019; **4**: 640–654.
30. Kume O, Teshima Y, Abe I, Ikebe Y, Oniki T, Kondo H, Saito S, Fukui A, Yufu K, Miura M, Shimada T, Takahashi N. Role of atrial endothelial cells in the development of atrial fibrosis and fibrillation in response to pressure overload. *Cardiovasc Pathol*. 2017; **27**: 18–25.
31. Li G, Fontaine GH, Fan S, Yan Y, Bode PK, Duru F, Frank R, Saguner AM. Right atrial pathology in arrhythmogenic right ventricular dysplasia. *Cardiol J*. 2019; **26**: 736–743.
32. Sygitowicz G, Maciejak-Jastrzebska A, Sitkiewicz D. A review of the molecular mechanisms underlying cardiac fibrosis and atrial fibrillation. *J Clin Med*. 2021; **10**: 4430.
33. Li CY, Zhang JR, Hu WN, Li S. Atrial fibrosis underlying atrial fibrillation (review). *Int J Mol Med*. 2021; **47**:9.
34. Harada M, van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. *Circ J*. 2015; **79**: 495–502.
35. Xintarakou A, Tzeis S, Psarras S, Asvestas D, Vardas P. Atrial fibrosis as a dominant factor for the development of atrial fibrillation: facts and gaps. *Europace*. 2020; **22**: 342–351.
36. Li SN, Zhang JR, Zhou L, Xi H, Li CY, Zhao L. Sacubitril/valsartan decreases atrial fibrillation susceptibility by inhibiting angiotensin II-induced atrial fibrosis through p-Smad2/3, p-JNK, and p-p38 signaling pathways. *J Cardiovasc Transl Res*. 2022: 131–142.
37. Bukowska A, Spiller L, Wolke C, Lendeckel U, Weinert S, Hoffmann J, Bornfleth P, Kutschka I, Gardemann A, Isermann B, Goette A. Protective regulation of the ACE2/ACE gene expression by estrogen in human atrial tissue from elderly men. *Exp Biol Med (Maywood)*. 2017; **242**: 1412–1423.
38. Gemmati D, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V. COVID-19 and individual genetic susceptibility/receptivity: role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-chromosome in females be protective against SARS-CoV-2 compared to the single X-chromosome in males? *Int J Mol Sci*. 2020; **21**: 3474.
39. Hilliard LM, Sampson AK, Brown RD, Denton KM. The "his and hers" of the renin-angiotensin system. *Curr Hypertens Rep*. 2013; **15**: 71–79.
40. Yi Y, du L, Qin M, Chen XQ, Sun XN, Li C, du LJ, Liu Y, Liu Y, Sun JY, Tang Z, Xu M, Fang B, Liu X, Duan SZ. Regulation of atrial fibrosis by the bone. *Hypertension*. 2019; **73**: 379–389.
41. Heger J, Warga B, Meyering B, Abdallah Y, Schlüter KD, Piper HM, Euler G. TGFβ receptor activation enhances cardiac apoptosis via SMAD activation and concomitant NO release. *J Cell Physiol*. 2011; **226**: 2683–2690.
42. Moreira LM, Takawale A, Hulsurkar M, Menassa DA, Antanaviciute A, Lahiri SK, Mehta N, Evans N, Psarros C, Robinson P, Sparrow AJ, Gillis MA, Ashley N, Naud P, Barallobre-Barreiro J, Theofilatos K, Lee A, Norris M, Clarke MV, Russell PK, Casadei B, Bhattacharya S, Zajac JD, Davey RA, Sirois M, Mead A, Simmons A, Mayr M, Sayeed R, Krasopoulos G, Redwood C, Channon KM, Tardif JC, Wehrens XHT, Nattel S, Reilly S. Paracrine signalling by cardiac calcitonin controls atrial fibrogenesis and arrhythmia. *Nature*. 2020; **587**: 460–465.
43. Li T, Sun ZL, Xie QY. Meta-analysis identifies serum C-reactive protein as an indicator of atrial fibrillation risk after coronary artery bypass graft. *Am J Ther*. 2016; **23**: e1586–e1596.
44. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol*. 2015; **12**: 230–243.
45. Mezache L, Struckman HL, Greer-Short A, Baine S, Györke S, Radwański PB, Hund TJ, Veeraraghavan R. Vascular endothelial growth factor promotes atrial arrhythmias by inducing acute intercalated disk remodeling. *Sci Rep*. 2020; **10**: 20463.
46. Chen G, Chelu MG, Dobrev D, Li N. Cardiomyocyte inflammasome signaling in cardiomyopathies and atrial fibrillation: mechanisms and potential therapeutic implications. *Front Physiol*. 2018; **9**: 1115.
47. Yao C, Veleva T, Scott LJ, Cao S, Li L, Chen G, Jeyabal P, Pan X, Alsina KM, Abu-Taha I Dr, Ghezelbash S, Reynolds CL, Shen YH, LeMaire SA, Schmitz W, Müller FU, el-Armouche A, Tony Eissa N, Beeton C, Nattel S, Wehrens XHT, Dobrev D, Li N. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. *Circulation*. 2018; **138**: 2227–2242.
48. Zhang Y, Zhang S, Li B, Luo Y, Gong Y, Jin X, Zhang J, Zhou Y, Zhuo X, Wang Z, Zhao X, Han X, Gao Y, Yu H, Liang D, Zhao S, Sun D, Wang D, Xu W, Qu G, Bo W, Li D, Wu Y, Li Y. Gut microbiota dysbiosis promotes age-related atrial fibrillation by lipopolysaccharide and glucose-induced activation of NLRP3-inflammasome. *Cardiovasc Res*. 2022; **118**: 785–797.
49. Henning RJ. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. *Am J Cardiovasc Dis*. 2021; **11**: 504–529.
50. McCauley MD, Hong L, Sridhar A, Menon A, Perike S, Zhang M, Da Silva IB, Yan JJ, Bonini MG, Ai X, Rehman J, Darbar D. Ion channel and structural remodeling in obesity-mediated atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2020; **13**: e008296.
51. Meng T, Cheng G, Wei Y, Ma S, Jiang Y, Wu J, Zhou X, Sun C. Exposure to a chronic high-fat diet promotes atrial structure and gap junction remodeling in rats. *Int J Mol Med*. 2017; **40**: 217–225.
52. Berg G, Miksztowicz V, Morales C, Barchuk M. Epicardial adipose tissue in cardiovascular disease. *Adv Exp Med Biol*. 2019; **1127**: 131–143.
53. Gaborit B, Sengenes C, Ancel P, Jacquier A, Dutour A. Role of epicardial adipose tissue in health and disease: a matter of fat? *Compr Physiol*. 2017; **7**: 1051–1082.
54. Abe I, Teshima Y, Kondo H, Kaku H, Kira S, Ikebe Y, Saito S, Fukui A, Shinohara T, Yufu K, Nakagawa M, Hijiya N, Moriyama M, Shimada T, Miyamoto S, Takahashi N. 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**: 1717–1727.
55. Kira S, Abe I, Ishii Y, Miyoshi M, Oniki T, Arakane M, Daa T, Teshima Y, Yufu K, Shimada T, Takahashi N. Role of angiopoietin-like protein 2 in atrial fibrosis induced by human epicardial adipose tissue: analysis using an organo-culture system. *Heart Rhythm*. 2020; **17**: 1591–1601.
56. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F, Amour J, Leprince P, Dutour A, Clément K, Hatem SN. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. *Eur Heart J*. 2015; **36**: 795–805a.
57. Shaihov-Teper O, Ram E, Ballan N, Brzezinski RY, Naftali-Shani N, Masoud R, Ziv T, Lewis N, Schary Y, Levin-Kotler LP, Volvovitch D, Zuroff EM, Amunts S, Regev-Rudzki N, Sternik L, Raanani E, Gepstein L, Leor J. Extracellular vesicles from epicardial fat facilitate atrial fibrillation. *Circulation*. 2021; **143**: 2475–2493.
58. Pabon MA, Manocha K, Cheung JW, Lo JC. Linking arrhythmias and adipocytes: insights, mechanisms, and future directions. *Front Physiol*. 2018; **9**: 1752.
59. Jhuo SJ, Hsieh TJ, Tang WH, Tsai WC, Lee KT, Yen HW, Lai WT. The association of the amounts of epicardial fat, P wave duration, and PR interval in electrocardiogram. *J Electrocardiol*. 2018; **51**: 645–651.
60. Lin YK, Chen YC, Chen JH, Chen SA, Chen YJ. Adipocytes modulate the electrophysiology of atrial myocytes: implications in obesity-induced atrial fibrillation. *Basic Res Cardiol*. 2012; **107**: 293.
61. de Groot JR. Botulinum toxin injection in the autonomic ganglion plexi to prevent postoperative atrial fibrillation: more than a cosmetic treatment. *Heart Rhythm*. 2019; **16**: 185–186.

62. Romanov A, Pokushalov E, Ponomarev D, Bayramova S, Shabanov V, Losik D, Stenin I, Elesin D, Mikheenko I, Strelnikov A, Sergeevichev D, Kozlov B, Po SS, Steinberg JS. Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: three-year follow-up of a randomized study. *Heart Rhythm*. 2019; **16**: 172–177.
63. Waldron NH, Cooter M, Haney JC, Schroder JN, Gaca JG, Lin SS, Sigurdsson MI, Fudim M, Podgoreanu MV, Stafford-Smith M, Milano CA, Piccini JP, Mathew JP. Temporary autonomic modulation with botulinum toxin type a to reduce atrial fibrillation after cardiac surgery. *Heart Rhythm*. 2019; **16**: 178–184.
64. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ, Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014; **13**: 429–438.
65. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. *Stroke*. 2017; **48**: 867–872.
66. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbüchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns HJGM, Breithardt G. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020; **383**: 1305–1316.
67. Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. *J Cardiovasc Electrophysiol*. 2012; **23**: 797–799.
68. Kamel H, Healey JS. Cardioembolic stroke. *Circ Res*. 2017; **120**: 514–526.
69. Camm AJ, Simantirakis E, Goette A, Lip GYH, Vardas P, Calvert M, Chlouverakis G, Diener HC, Kirchhof P. Atrial high-rate episodes and stroke prevention. *Europace*. 2017; **19**: 169–179.
70. Abe Y, Takahashi Y, Shibata T. A new disease entity: atrial functional mitral regurgitation. *J Cardiol*. 2021; **77**: 565–569.
71. Silbiger JJ. Mechanistic insights into atrial functional mitral regurgitation: far more complicated than just left atrial remodeling. *Echocardiography*. 2019; **36**: 164–169.
72. Schotten U, Neuberger HR, Allessie MA. The role of atrial dilatation in the domestication of atrial fibrillation. *Prog Biophys Mol Biol*. 2003; **82**: 151–162.
73. Liu Y, Lv H, Tan R, An X, Niu XH, Liu YJ, Yang X, Yin X, Xia YL. Platelets promote Ang II (angiotensin II)-induced atrial fibrillation by releasing TGF-β1 (transforming growth factor-β1) and interacting with fibroblasts. *Hypertension*. 2020; **76**: 1856–1867.
74. Spronk HM, de Jong AM, Verheule S, de Boer HC, Maass AH, Lau DH, Rienstra M, van Hunnik A, Kuiper M, Lumeij S, Zeemering S, Linz D, Kamphuisen PW, Ten Cate H, Crijns HJ, van Gelder IC, van Zonneveld AJ, Schotten U. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. *Eur Heart J*. 2017; **38**: 38–50.
75. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009; **373**: 155–166.
76. Darlington A, McCauley MD. Atrial cardiomyopathy: an unexplored limb of Virchow's triad for AF stroke prophylaxis. *Front Cardiovasc Med*. 2020; **7**: 11.
77. Lip GY, Patel JV, Hughes E, Hart RG. High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis. *Stroke*. 2007; **38**: 1229–1237.
78. Roldán V, Marín F, Díaz J, Gallego P, Jover E, Romera M, Manzano-Fernández S, Casas T, Valdés M, Vicente V, Lip GYH. High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. *J Thromb Haemost*. 2012; **10**: 1500–1507.
79. Harada M, Nattel S. Implications of inflammation and fibrosis in atrial fibrillation pathophysiology. *Card Electrophysiol Clin*. 2021; **13**: 25–35.
80. Li K, Jesuthasan A, Kui C, Davies R, Tse G, Lip GYH. Acute ischemic stroke management: concepts and controversies. A narrative review. *Exp Rev Neurother (Wyd polskie)*. 2021; **21**: 65–79.
81. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC(C), Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson DJ, Schwamm LH, Wilson JA. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014; **45**: 2160–2236.
82. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, de Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ, NAVIGATE ESUS Investigators. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med*. 2018; **378**: 2191–2201.
83. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmünzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K, RE-SPECT ESUS Steering Committee and Investigators. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med*. 2019; **380**: 1906–1917.
84. Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE, Haeusler KG, Mikulik R, Kasner SE, Toni D, Arauz A, Ntaios G, Hankey GJ, Perera K, Pagola J, Shuaib A, Lutsep H, Yang X, Uchiyama S, Endres M, Coutts SB, Karlinski M, Czlonkowska A, Molina CA, Santo G, Berkowitz SD, Hart RG, Connolly SJ. Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the NAVIGATE ESUS randomized clinical trial. *JAMA Neurol*. 2019; **76**: 764–773.
85. Longstreth WJ, Kronmal RA, Thompson JL, Christenson RH, Levine SR, Gross R, Brey RL, Buchsbaum R, Elkind MSV, Tirschwell DL, Seliger SL, Mohr JP, deFilippi CR. Amino terminal pro-B-type natriuretic peptide, secondary stroke prevention, and choice of antithrombotic therapy. *Stroke*. 2013; **44**: 714–719.
86. Guichard JB, Nattel S. Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad? *J Am Coll Cardiol*. 2017; **70**: 756–765.
87. Thomas L, Muraru D, Popescu BA, Sitges M, Rosca M, Pedrizzetti G, Henein MY, Donal E, Badano LP. Evaluation of left atrial size and function: relevance for clinical practice. *J Am Soc Echocardiogr*. 2020; **33**: 934–952.
88. Ahlberg G, Andreasen L, Ghouse J, Bertelsen L, Bundgaard H, Haunsø S, Svendsen JH, Olesen MS. Genome-wide association study identifies 18 novel loci associated with left atrial volume and function. *Eur Heart J*. 2021; **42**: 4523–4534.
89. Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, Marino E,

Galderisi M. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. *Cardiovasc Ultrasound*. 2009; **7**: 6.
90. Nielsen AB, Skaarup KG, Hauser R, Johansen ND, Lassen MH, Jensen GB, Schnohr P, Mogelvang R, Biering-Sørensen T. Normal values and reference ranges for left atrial strain by speckle-tracking echocardiography: the Copenhagen City Heart Study. *Eur Heart J Cardiovasc Imaging*. 2021; **144**.
91. Mandoli GE, D'Ascenzi F, Vinco G, Benfari G, Ricci F, Focardi M, Cavigli L, Pastore MC, Sisti N, De Vivo O, Santoro C, Mondillo S, Cameli M. Novel approaches in cardiac imaging for non-invasive assessment of left heart myocardial fibrosis. *Front Cardiovasc Med*. 2021; **8**: 614235.
92. Alhakak AS, Biering-Sørensen SR, Møgelvang R, Modin D, Jensen GB, Schnohr P, Iversen AZ, Svendsen JH, Jespersen T, Gislason G, Biering-Sørensen T. Usefulness of left atrial strain for predicting incident atrial fibrillation and ischaemic stroke in the general population. *Eur Heart J Cardiovasc Imaging*. 2020; **23**: 363–371.
93. de Sensi F, Penela D, Soto-Iglesias D, Berruezo A, Limbruno U. Imaging techniques for the study of fibrosis in atrial fibrillation ablation: from molecular mechanisms to therapeutical perspectives. *J Clin Med*. 2021; **10**.
94. Yu S, Zhang H, Li H. Cardiac computed tomography versus transesophageal echocardiography for the detection of left atrial appendage thrombus: a systemic review and meta-analysis. *J Am Heart Assoc*. 2021; **10**: e022505.
95. Paddock S, Tsampasian V, Assadi H, Mota BC, Swift AJ, Chowdhary A, Swoboda P, Levelt E, Sammut E, Dastidar A, Broncano Cabrero J, Del Val JR, Malcolm P, Sun J, Ryding A, Sawh C, Greenwood R, Hewson D, Vassiliou V, Garg P. Clinical translation of three-dimensional scar, diffusion tensor imaging, four-dimensional flow, and quantitative perfusion in cardiac MRI: a comprehensive review. *Front Cardiovasc Med*. 2021; **8**: 682027.
96. Benito EM, Carlosena-Remirez A, Guasch E, Prat-González S, Perea RJ, Figueras R, Borràs R, Andreu D, Arbelo E, Tolosana JM, Bisbal F, Brugada J, Berruezo A, Mont L. Left atrial fibrosis quantification by late gadolinium-enhanced magnetic resonance: a new method to standardize the thresholds for reproducibility. *Europace*. 2017; **19**: 1272–1279.
97. Althoff TF, Garre P, Caixal G, Perea R, Prat S, Tolosana JM, Guasch E, Roca-Luque I, Arbelo E, Sitges M, Brugada J, Mont L. Late gadolinium enhancement-MRI determines definite lesion formation most accurately at 3 months post ablation compared to later time points. *Pacing Clin Electrophysiol*. 2022; **45**: 72–82.
98. Kühnlein P, Mahnkopf C, Majersik JJ, Wilson BD, Mitlacher M, Tirschwell D, Longstreth WT Jr, Akoum N. Atrial fibrosis in embolic stroke of undetermined source: a multicenter study. *Eur J Neurol*. 2021; **28**: 3634–3639.
99. Bertelsen L, Diederichsen SZ, Haugan KJ, Brandes A, Graff C, Krieger D, Kronborg C, Køber L, Højberg S, Vejlstrup N, Svendsen JH. Left atrial volume and function assessed by cardiac magnetic resonance imaging are markers of subclinical atrial fibrillation as detected by continuous monitoring. *Europace*. 2020; **22**: 724–731.
100. Habibi M, Samiei S, Ambale Venkatesh B, Opdahl A, Helle-Valle TM, Zareian M, Almeida ALC, Choi EY, Wu C, Alonso A, Heckbert SR, Bluemke DA, Lima JAC. 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**.
101. Quinto L, Cozzari J, Benito E, Alarcón F, Bisbal F, Trotta O, Caixal G, San Antonio R, Garre P, Prat-Gonzalez S, Perea RJ, Tolosana JM, Berruezo A, Arbelo E, Roca-Luque I, Sitges M, Brugada J, Guasch E, Mont L. Magnetic resonance-guided re-ablation for atrial fibrillation is associated with a lower recurrence rate: a case-control study. *Europace*. 2020; **22**: 1805–1811.
102. Bisbal F, Benito E, Teis A, Alarcón F, Sarrias A, Caixal G, Villuendas R, Garre P, Soto N, Cozzari J, Guasch E, Juncà G, Prat-Gonzalez S, Perea RJ, Bazán V, Tolosana JM, Arbelo E, Bayés-Genís A, Mont L. Magnetic resonance imaging-guided fibrosis ablation for the treatment of atrial fibrillation: the ALICIA trial. *Circ Arrhythm Electrophysiol*. 2020; **13**: e008707.
103. Siebermair J, Kholmovski EG, Marrouche N. Assessment of left atrial fibrosis by late gadolinium enhancement magnetic resonance imaging: methodology and clinical implications. *JACC Clin Electrophysiol*. 2017; **3**: 791–802.
104. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, Schweikert RA, Saliba W, Cummings J, Burkhardt JD, Bhargava M, Belden WA, Abdul-Karim A, Natale A. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *J Am Coll Cardiol*. 2005; **45**: 285–292.
105. Eichenlaub M, Mueller-Edenborn B, Minners J, Figueras i Ventura RM, Forcada BR, Colomer AV, Hein M, Ruile P, Lehrmann H, Schoechlin S, Allgeier J, Bohnen M, Trenk D, Neumann FJ, Arentz T, Jadidi A. 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**: 1102–1111.
106. Acampa M, Lazzerini PE, Martini G. Atrial cardiopathy and sympatho-vagal imbalance in cryptogenic stroke: pathogenic mechanisms and effects on electrocardiographic markers. *Front Neurol*. 2018; **9**: 469.
107. Alexander B, Tse G, Martinez-Selles M, Baranchuk A. Atrial conduction disorders. *Curr Cardiol Rev*. 2021; **17**: 68–73.
108. Lebek S, Wester M, Pec J, Poschenrieder F, Tafelmeier M, Fisser C, Provaznik Z, Schopka S, Debl K, Schmid C, Buchner S, Maier LS, Arzt M, Wagner S. Abnormal P-wave terminal force in lead V1 is a marker for atrial electrical dysfunction but not structural remodelling. *ESC Heart Fail*. 2021; **8**: 4055–4066.
109. Tse G, Wong CW, Gong M, Wong WT, Bazoukis G, Wong SH, Li G, Wu WKK, Tse LA, Lampropoulos K, Xia Y, Liu T, Baranchuk A. Predictive value of inter-atrial block for new onset or recurrent atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2018; **250**: 152–156.
110. He J, Tse G, Korantzopoulos P, Letsas KP, Ali-Hasan-al-Saegh S, Kamel H, Li G, Lip GYH, Liu T. P-wave indices and risk of ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2017; **48**: 2066–2072.
111. Alexander B, Haseeb S, van Rooy H, Tse G, Hopman W, Martinez-Selles M, de Luna AB, Çinier G, Baranchuk A. Reduced P-wave voltage in Lead I is associated with development of atrial fibrillation in patients with coronary artery disease. *J Atr Fibrillation*. 2017; **10**: 1657.
112. Tiffany Win T, Ambale Venkatesh B, Volpe GJ, Mewton N, Rizzi P, Sharma RK, Strauss DG, Lima JA, Tereshchenko LG. Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: the PRIMERI study. *Heart Rhythm*. 2015; **12**: 155–162.
113. Petersson R, Berge HM, Gjerdalen GF, Carlson J, Holmqvist F, Steine K, Platonov PG. P-wave morphology is unaffected by atrial size: a study in healthy athletes. *Ann Noninvasive Electrocardiol*. 2014; **19**: 366–373.
114. Eichenlaub M, Mueller-Edenborn B, Lehrmann H, Minners J, Nairn D, Loewe A, Allgeier J, Jander N, Allgeier M, Ruile P, Hein M, Rees F, Trenk D, Weber R, Neumann FJ, Arentz T, Jadidi A. Non-invasive body surface electrocardiographic imaging for diagnosis of atrial cardiomyopathy. *Europace*. 2021; **23**: 2010–2019.
115. Fonseca AC, Coelho P. Update on biomarkers associated to cardioembolic

stroke: a narrative review. *Life (Basel)*. 2021; **11**.
116. Rossi VA, Krizanovic-Grgic I, Steffel J, Hofer D, Wolber T, Brunckhorst CB, Ruschitzka F, Duru F, Breitenstein A, Saguner AM. Predictors of left atrial fibrosis in patients with atrial fibrillation referred for catheter ablation. *Cardiol J*. 2022; **29**: 413–422.
117. Mäkikallio AM, Mäkikallio TH, Korpelainen JT, Vuolteenaho O, Tapanainen JM, Ylitalo K, Sotaniemi KA, Huikuri HV, Myllylä VV. Natriuretic peptides and mortality after stroke. *Stroke*. 2005; **36**: 1016–1020.
118. Truong QA, Siegel E, Karakas M, Januzzi JL Jr, Bamberg F, Mahabadi AA, Dasdemir S, Brady TJ, Bergmann A, Kunde J, Nagurney JT, Hoffmann U, Koenig W. Relation of natriuretic peptides and midregional proadrenomedullin to cardiac chamber volumes by computed tomography in patients without heart failure: from the ROMICAT trial. *Clin Chem*. 2010; **56**: 651–660.
119. Cui K, Huang W, Fan J, Lei H. Midregional pro-atrial natriuretic peptide is a superior biomarker to N-terminal pro-B-type natriuretic peptide in the diagnosis of heart failure patients with preserved ejection fraction. *Medicine (Baltimore)*. 2018; **97**: e12277.
120. Louros NN, Iconomidou VA, Tsiolaki PL, Chrysina ED, Baltatzis GE, Patsouris ES, Hamodrakas SJ. An N-terminal pro-atrial natriuretic peptide (NT-proANP) 'aggregation-prone' segment involved in isolated atrial amyloidosis. *FEBS Lett*. 2014; **588**: 52–57.
121. Iconomidou VA, Pheida D, Hamodraka ES, Antony C, Hoenger A, Hamodrakas SJ. An amyloidogenic determinant in N-terminal pro-brain natriuretic peptide (NT-proBNP): implications for cardiac amyloidoses. *Biopolymers*. 2012; **98**: 67–75.
122. Röcken C, Peters B, Juenemann G, Saeger W, Klein HU, Huth C, Roessner A, Goette A. Atrial amyloidosis: an arrhythmogenic substrate for persistent atrial fibrillation. *Circulation*. 2002; **106**: 2091–2097.
123. Asferg CL, Andersen UB, Linneberg A, Goetze JP, Jeppesen JL. Obese hypertensive men have lower circulating proatrial natriuretic peptide concentrations despite greater left atrial size. *Am J Hypertens*. 2018; **31**: 645–650.
124. Arndt M, Lendeckel U, Röcken C, Nepple K, Wolke C, Spiess A, Huth C, Ansorge S, Klein HU, Goette A. Altered expression of ADAMs (a disintegrin and metalloproteinase) in fibrillating human atria. *Circulation*. 2002; **105**: 720–725.
125. Duffy MJ, McKiernan E, O'Donovan N, McGowan PM. The role of ADAMs in disease pathophysiology. *Clin Chim Acta*. 2009; **403**: 31–36.
126. Nakamura Y, Kita S, Tanaka Y, Fukuda S, Obata Y, Okita T, Kawachi Y, Tsugawa-Shimizu Y, Fujishima Y, Nishizawa H, Miyagawa S, Sawa Y, Sehara-Fujisawa A, Maeda N, Shimomura I. A disintegrin and metalloproteinase 12 prevents heart failure by regulating cardiac hypertrophy and fibrosis. *Am J Physiol Heart Circ Physiol*. 2020; **318**: H238–H251.
127. Patel VB, Clarke N, Wang Z, Fan D, Parajuli N, Basu R, Putko B, Kassiri Z, Turner AJ, Oudit GY. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. *J Mol Cell Cardiol*. 2014; **66**: 167–176.
128. Gooz M. ADAM-17: the enzyme that does it all. *Crit Rev Biochem Mol Biol*. 2010; **45**: 146–169.
129. Racca V, Torri A, Grati P, Panzarino C, Marventano I, Saresella M, Castiglioni P. Inflammatory cytokines during cardiac rehabilitation after heart surgery and their association to postoperative atrial fibrillation. *Sci Rep*. 2020; **10**: 8618.
130. Troncoso MF, Ortiz-Quintero J, Garrido-Moreno V, Sanhueza-Olivares F, Guerrero-Moncayo A, Chiong M, Castro PF, García L, Gabrielli L, Corbalán R, Garrido-Olivares L, Lavandero S. VCAM-1 as a predictor biomarker in cardiovascular disease. *Biochim Biophys Acta Mol Basis Dis*. 2021; **1867**: 166170.
131. Goette A, Bukowska A, Lendeckel U, Erxleben M, Hammwöhner M, Strugala D, Pfeiffenberger J, Röhl FW, Huth C, Ebert MPA, Klein HU, Röcken C. Angiotensin II receptor blockade reduces tachycardia-induced atrial adhesion molecule expression. *Circulation*. 2008; **117**: 732–742.
132. Willeit K, Pechlaner R, Willeit P, Skroblin P, Paulweber B, Schernthaner C, Toell T, Egger G, Weger S, Oberhollenzer M, Kedenko L, Iglseder B, Bonora E, Schett G, Mayr M, Willeit J, Kiechl S. Association between vascular cell adhesion molecule 1 and atrial fibrillation. *JAMA Cardiol*. 2017; **2**: 516–523.
133. Contreras-Briceño F, Herrera S, Vega-Adauy J, Salinas M, Ocaranza MP, Jalil JE, Mandiola J, García L, Chiong M, Castro PF, Lavandero S, Gabrielli L. Circulating vascular cell adhesion molecule-1 (sVCAM-1) is associated with left atrial remodeling in long-distance runners. *Front Cardiovasc Med*. 2021; **8**: 737285.
134. Ehrlich JR, Kaluzny M, Baumann S, Lehmann R, Hohnloser SH. Biomarkers of structural remodelling and endothelial dysfunction for prediction of cardiovascular events or death in patients with atrial fibrillation. *Clin Res Cardiol*. 2011; **100**: 1029–1036.
135. Gong M, Cheung A, Wang QS, Li G, Goudis CA, Bazoukis G, Lip GYH, Baranchuk A, Korantzopoulos P, Letsas KP, Tse G, Liu T. Galectin-3 and risk of atrial fibrillation: a systematic review and meta-analysis. *J Clin Lab Anal*. 2020; **34**: e23104.
136. Disertori M, Quintarelli S, Grasso M, Pilotto A, Narula N, Favalli V, Canclini C, Diegoli M, Mazzola S, Marini M, del Greco M, Bonmassari R, Masè M, Ravelli F, Specchia C, Arbustini E. Autosomal recessive atrial dilated cardiomyopathy with standstill evolution associated with mutation of *Natriuretic Peptide Precursor A*. *Circ Cardiovasc Genet*. 2013; **6**: 27–36.
137. Gudbjartsson DF, Holm H, Sulem P, Masson G, Oddsson A, Magnusson OT, Saemundsdottir J, Helgadottir HT, Helgason H, Johannsdottir H, Gretarsdottir S, Gudjonsson SA, Njølstad I, Løchen ML, Baum L, Ma RCW, Sigfusson G, Kong A, Thorgeirsson G, Sverrisson JT, Thorsteinsdottir U, Stefansson K, Arnar DO. A frameshift deletion in the sarcomere gene MYL4 causes early-onset familial atrial fibrillation. *Eur Heart J*. 2017; **38**: 27–34.
138. Crasto S, My I, Di Pasquale E. The broad spectrum of LMNA cardiac diseases: from molecular mechanisms to clinical phenotype. *Front Physiol*. 2020; **11**: 761.
139. Zhang Y, Lin Y, Zhang Y, Wang Y, Li Z, Zhu Y, Liu H, Ju W, Cui C, Chen M. Familial atrial myopathy in a large multigenerational heart-hand syndrome pedigree carrying LMNA missense variant in rod 2B domain (p.R335W). *Heart Rhythm*. 2022; **19**: 466–475.
140. Tse G, Reddy S, Chopra J, Lee S, Liu T, Bazoukis G, Haseeb S, Lee APW, Letsas KP, Li KHC. Electrocardiographic evidence of abnormal atrial phenotype in Brugada syndrome. *J Electrocardiol*. 2019; **55**: 102–106.
141. Clausen AG, Vad OB, Andersen JH, Olesen MS. Loss-of-function variants in the SYNPO2L gene are associated with atrial fibrillation. *Front Cardiovasc Med*. 2021; **8**: 650667.
142. Franco D, Sedmera D, Lozano-Velasco E. Multiple roles of Pitx2 in cardiac development and disease. *J Cardiovasc Dev Dis*. 2017; **4**.
143. Thornton CA. Myotonic dystrophy. *Neurol Clin*. 2014; **32**: 705–719.
144. Norman M, Simpson M, Mogensen J, Shaw A, Hughes Ŝ, Syrris P, Sen-Chowdhry S, Rowland E, Crosby A, McKenna WJ. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. *Circulation*. 2005; **112**: 636–642.
145. Gurung R, Ono Y, Baxendale S, Lee SLC, Moore S, Calvert M, Ingham PW. A zebrafish model for a human myopathy associated with mutation of the unconventional myosin MYO18B. *Genetics*. 2017; **205**: 725–735.
146. van Nieuwenhoven FA, Munts C, op't Veld RC, González A, Díez J, Heymans S, Schroen B, Van Bilsen M. Cartilage intermediate layer protein 1 (CILP1):

a novel mediator of cardiac extracellular matrix remodelling. *Sci Rep*. 2017; **7**: 16042.

147. Choi SH, Weng LC, Roselli C, Lin H, Haggerty CM, Shoemaker MB, Barnard J, Arking DE, Chasman DI, Albert CM, Chaffin M, Tucker NR, Smith JD, Gupta N, Gabriel S, Margolin L, Shea MA, Shaffer CM, Yoneda ZT, Boerwinkle E, Smith NL, Silverman EK, Redline S, Vasan RS, Burchard EG, Gogarten SM, Laurie C, Blackwell TW, Abecasis G, Carey DJ, Fornwalt BK, Smelser DT, Baras A, Dewey FE, Jaquish CE, Papanicolaou GJ, Sotoodehnia N, Van Wagoner DR, Psaty BM, Kathiresan S, Darbar D, Alonso A, Heckbert SR, Chung MK, Roden DM, Benjamin EJ, Murray MF, Lunetta KL, Lubitz SA, Ellinor PT, For the DiscovEHR study and the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Association between titin loss-of-function variants and early-onset atrial fibrillation. *JAMA*. 2018; **320**: 2354–2364.
148. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP, Potts JE, Maginot KR, Salerno JC, Cohen MI, Hamilton RM, Pflaumer A, Mohammed S, Kimlicka L, Kanter RJ, LaPage MJ, Collins KK, Gebauer RA, Temple JD, Batra AS, Erickson C, Miszczak-Knecht M, Kubuš P, Bar-Cohen Y, Kantoch M, Thomas VC, Hessling G, Anderson C, Young ML, Choi SHJ, Cabrera Ortega M, Lau YR, Johnsrude CL, Fournier A, Van Petegem F, Sanatani S. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. *Europace*. 2018; **20**: 541–547.
149. Yoneda ZT, Anderson KC, Quintana JA, O'Neill MJ, Sims RA, Glazer AM, Shaffer CM, Crawford DM, Stricker T, Ye F, Wells Q, Stevenson LW, Michaud GF, Darbar D, Lubitz SA, Ellinor PT, Roden DM, Shoemaker MB. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol*. 2021; **6**: 1371–1379.