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Review

Left atrial cardiomyopathy: Pathophysiological insights, assessment methods and clinical implications[☆]

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ABSTRACT

Atrial cardiomyopathy is defined as any complex of structural, architectural, contractile or electrophysiological changes affecting atria, with the potential to produce clinically relevant manifestations. Most of our knowledge about the mechanistic aspects of atrial cardiomyopathy is derived from studies investigating animal models of atrial fibrillation and atrial tissue samples obtained from individuals who have a history of atrial fibrillation. Several noninvasive tools have been reported to characterize atrial cardiomyopathy in patients, which may be relevant for predicting the risk of incident atrial fibrillation and its related outcomes, such as stroke. Here, we provide an overview of the pathophysiological mechanisms involved in atrial cardiomyopathy, and discuss the complex interplay of these mechanisms, including aging, left atrial pressure overload, metabolic disorders and genetic factors. We discuss clinical tools currently available to characterize atrial cardiomyopathy, including electrocardiograms, cardiac imaging and serum biomarkers. Finally, we discuss the clinical impact of atrial cardiomyopathy, and its potential role for predicting atrial fibrillation, stroke, heart failure and dementia. Overall, this review aims to highlight the critical need for a clinically relevant definition of atrial cardiomyopathy to improve treatment strategies.

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1. Abbreviations

ACM	atrial cardiomyopathy
AF	atrial fibrillation
AI	artificial intelligence
APD	action potential duration
ARIC	Atherosclerosis Risk in Communities
Ca ²⁺	calcium
CI	confidence interval
CMR	cardiac magnetic resonance

EAT	epicardial adipose tissue
HFpEF	heart failure with preserved ejection fraction
IAB	interatrial block
I _{CaL}	L-type calcium current
K ⁺	potassium
LA	left atrium/atrial
LGE	late gadolinium enhancement
MAFLD	metabolic-associated fatty liver disease
PTFV1	P-wave terminal force in lead V1

2. Introduction

Atria play an important role in cardiac function, including haemodynamic regulation and endocrine function, and host an important part of the conduction system (i.e. pacemaker cells and atrioventricular node). The term “atrial fibrotic cardiomyopathy” was introduced by Kottkamp in 2012 as a common denominator of all forms of atrial fibrillation (AF) [1]. This concept was further developed in a specific consensus paper published in 2016 by the European Heart Rhythm Association, the Heart Rhythm Society, the

[☆] Tweet: Atrial cardiomyopathy (ACM) challenges the conventional approach focused solely on managing atrial fibrillation. Ninni et al. explore ground-breaking research that elucidates the current understanding of ACM's pathogenesis, the tools available for clinical evaluation, and the related outcomes.

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Table 1
Classification of atrial cardiomyopathy.

EHRA class	Histological characterization
I	Morphological or molecular changes affecting “primarily” the cardiomyocytes, in terms of cell hypertrophy and myocytolysis; no significant pathological tissue fibrosis or other interstitial changes
II	Predominantly fibrotic changes; cardiomyocytes show normal appearance
III	Combination of cardiomyocyte changes (e.g. cell hypertrophy, myocytolysis) and fibrotic changes
IV	Alteration of interstitial matrix without prominent collagen fibre accumulation
IVa	Accumulation of amyloid
IVf	Fatty infiltration
IVi	Inflammatory cells
IVo	Other interstitial alterations

EHRA: European Heart Rhythm Association.

Asia Pacific Heart Rhythm Society and the *Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiología*, in collaboration with the American College of Cardiology and the American Heart Association [2].

In this consensus paper, the term “atrial cardiomyopathy” (ACM) is defined as “any complex of structural, architectural, contractile or electrophysiological changes affecting atria, with the potential to produce clinically relevant manifestations” (Table 1). Although these changes were first associated with AF occurrence, accumulating evidence suggests a link between ACM and major adverse cardiovascular events, independent of AF. Therefore, the clinical relevance of patient management based on atrial phenotype, rather than AF, is an emerging question. In this review, the mechanisms, assessment and clinical impact of ACM will be discussed.

3. Conditions leading to ACM

Several clinical conditions are associated with ACM (Fig. 1 and Table 2).

3.1. Aging

Among the factors associated with ACM, aging and senescence processes have been reported as cornerstones. The senescence process is characterized by several changes involving a stable cell-cycle arrest associated with specific physiological, cellular and molecular alterations. Electrophysiological studies performed in elderly patients revealed increased effective refractory periods, as well as low voltage areas associated with slow conduction [14]. Moreover, electrophysiological remodelling, suggesting acquired calcium (Ca^{2+}) handling impairments, was also found in isolated human cardiomyocytes, with a decrease in the sarcoplasmic reticulum Ca^{2+} content, a reduction in L-type Ca^{2+} current (I_{CaL}) amplitude and a decrease in the Ca^{2+} transient amplitude [21]. Importantly, the senescent phenotype resulting from alterations in the p16 and p53–p21 related pathways is characterized by senescent cell-secreted products known as the “senescence-associated secretory phenotype” [66]. The senescence-associated secretory phenotype encompasses proinflammatory cytokines (e.g. interleukin-6, tumour necrosis factor) and chemokines (e.g. C-X-C motif chemokine ligands 1 and 2), but also growth factors (e.g. vascular endothelial growth factor), matrix remodelling proteases (e.g. matrix metalloproteinases 1 and 3) and lipids, produced by cardiomyocyte and non-cardiomyocyte cells (e.g. fibroblasts and endothelial cells) [66,67]. Components of senescence-associated secretory phenotype have been shown to be involved in atrial remodelling, especially as a result of a shift toward a cardiac fibroblast profibrotic phenotype [68].

Previous studies have reported metabolic atrial remodelling associated with ageing, such as impaired fatty acid oxidation, depressed respiratory performances and increased susceptibility to mitochondrial permeability transition pore opening [69]. Advanced age is also accompanied by extracardiac processes, such as an increase in arterial stiffness, leading to increased left atrial (LA) pressure [70]. Thus, in elderly patients, atrial remodelling is believed to be a multifactorial process, involving cardiac senescence as well as age-related clinical conditions.

3.2. Metabolic disorders

Metabolic disorders have been closely linked to changes in the structure and function of the atria. Most research has focused on the impact of obesity and diabetes on atrial remodelling. In humans, obesity is associated with electrophysiological, structural and haemodynamic impairment of the LA [71]. In obese patients, electrophysiological remodelling is suggested by shorter effective refractory periods and regional slow conductions related to low voltage areas in the LA [25]. This electrophysiological remodelling has been further characterized in animal models, demonstrating several alterations, such as depressed action potential duration (APD) involving increased K^{+} current, such as adenosine triphosphate-activated K^{+} current (I_{KATP}) [24], but also alterations to connexin 43 expression [31]. Structural changes are a prominent characteristic of atrial remodelling in the context of obesity. Consequently, individuals with obesity exhibit a significant increase in LA volume, and histopathological investigations have unveiled concurrent fibrosis and apoptosis processes [26,29,32]. Metabolic remodelling was also observed in the context of obesity, with depressed mitochondrial respiration despite increased fatty acid β -oxidation, thereby leading to myocardial lipidosis [72].

Whereas diabetes and obesity are often intertwined, several observations have hinted at a distinct influence of diabetes on the atria [73]. In humans, this association is proposed based on electrophysiological studies that revealed intra-atrial conduction delays and reduced voltages [74]. Animal studies conducted on streptozotocin-induced diabetic rat models confirmed these findings. These studies showed alterations in connexin 43 expression, prolonged APD, impaired Ca^{2+} handling, and heightened atrial vulnerability, as evidenced by the prolonged duration of atrial tachyarrhythmia induced by rapid atrial stimulation [33,75]. Additionally, a recent study has shed light on the impact of impaired mitochondria-mediated Ca^{2+} handling. More specifically, this study highlighted dysfunction in the mitochondrial Ca^{2+} uniporter complex in the context of metabolic syndrome, an insulin-resistant condition that precedes diabetes [76].

The mechanisms underlying the association between atrial remodelling and metabolic disorders are poorly understood, but potential mediators have been identified. More specifically, inflammatory processes involving immune cell recruitment, nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 inflammasome activation and epicardial adipose tissue (EAT) have been suggested [77].

EAT is a metabolically active tissue located around the heart, directly interacting with cardiomyocytes. Increasing evidence points to EAT playing a crucial role in connecting metabolic disorders with ACM. For instance, in obese individuals, EAT mediators have been linked to the release of factors associated with monocyte recruitment, a subset of innate immune cells shown to be involved in AF pathogenesis [78]. Moreover, diabetes-induced changes in the EAT secretory profile have been connected to altered sarcomere shortening and impaired cytosolic Ca^{2+} fluxes [79]. The EAT secretome is also implicated in atrial fibrogenesis, primarily through the secretion of activin A [80]. The radiodensity of EAT has been correlated with low voltage areas in the LA in patients

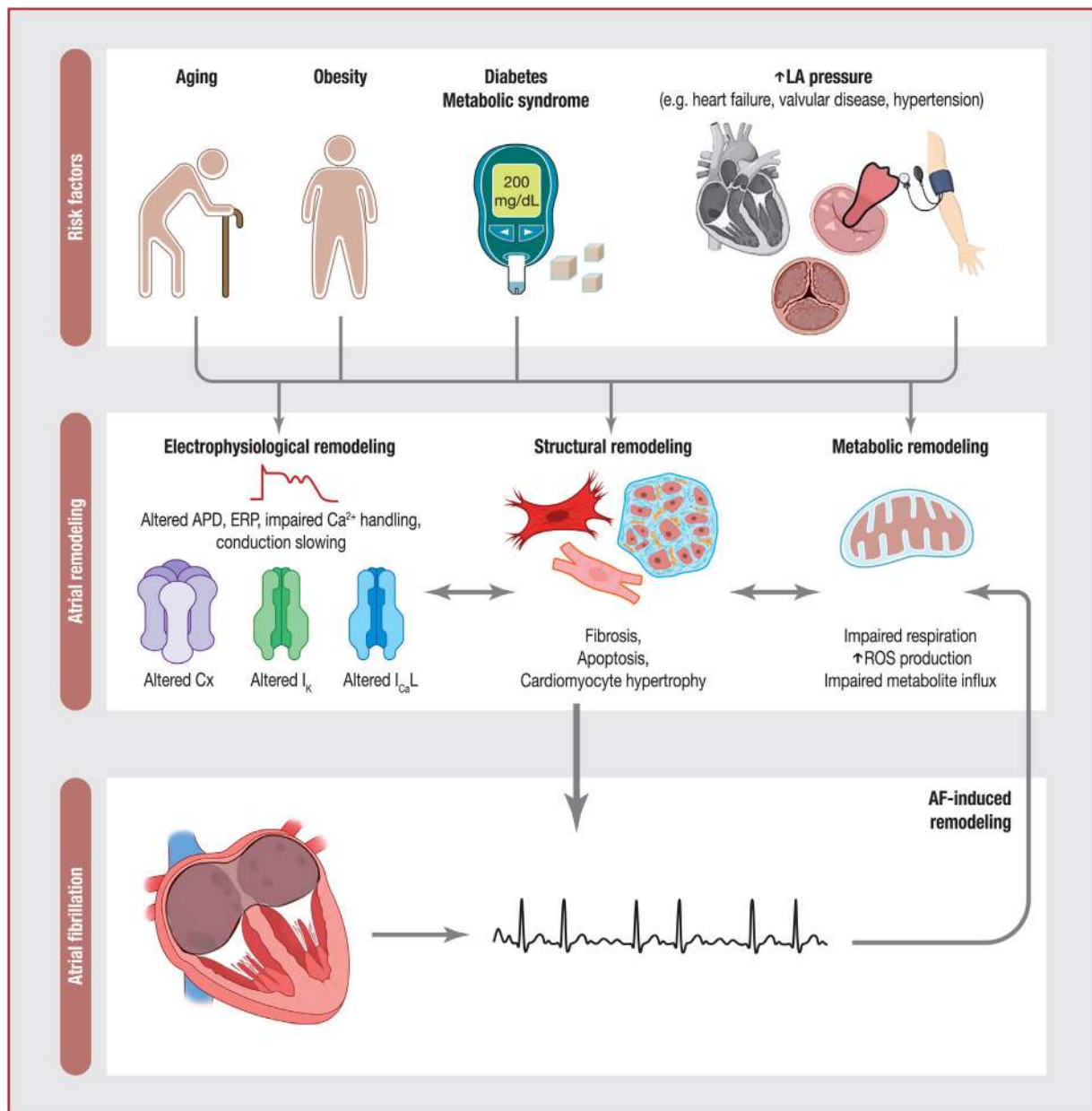


Fig. 1. Clinical conditions leading to atrial cardiomyopathy. AF: atrial fibrillation; APD: action potential duration; Ca^{2+} : calcium; Cx: connexin; ERP: effective refractory period; I_{CaL} : L-type calcium current; I_{K} : potassium current; LA: left atrial; ROS: reactive oxygen species.

undergoing AF ablation [81]. Associations have also been reported between EAT volume or thickness and atrial conduction delays, such as prolonged P-wave duration, interatrial conduction block and longer P-R interval [82]. Interestingly, atrial natriuretic factor secreted by atrial myocytes in response to mechanical stress has adipogenic properties that can contribute to atrial EAT development [83]. Importantly, the epicardium undergoes reactivation during the development of ACM, and contributes to fibro-fatty infiltration of the subepicardium [84].

Previous studies have suggested that metabolic disorders may trigger atrial remodelling through a liver-mediated process. Obesity and diabetes are often associated with liver steatosis, leading to metabolic-associated fatty liver disease (MAFLD), which is represented by a wide spectrum of liver alterations, including steatosis, inflammation and, ultimately, fibrosis. In a recent study, patients with MAFLD carrying advanced liver fibrosis presented several hallmarks of advanced atrial remodelling, such as increased LA volume, altered LA strain and increased low voltage areas [46]. However,

Table 2
Main clinical conditions leading to atrial cardiomyopathy.

Clinical condition	Atrial remodelling			
	Electrophysiological	Structural	Metabolic	Haemodynamic
Aging	APD↑/↓ [3–6] ^a	LA volume↑/= [7–9] ^a	Global respiration↓ [10] ^a	Atrial compliance↓ [11–13] ^a
	ERP↑ [14] ^a	Cardiomyocyte hypertrophy [15] ^a	Impaired FFA and ketone flux [16] ^a	
	Regional conduction slowing [14,17] ^a	Fibrosis [4,15] ^a	Fatty acid oxidation↓ [16,18] ^a	
	Cx 43 expression↓ [19] ^a		Susceptibility to MPTP opening↑ [20]	
Obesity	SR Ca ²⁺ content↓ [21] ^a			
	L-type Ca ²⁺ current↓ [4,21] ^a			
	Low voltage areas [22]			
	AF burden↑ [23]			
Diabetes	APD↓ [24] ^a	LA volume↑ [25–28] ^a	Global respiration↓ [29] ^a	Atrial compliance↓ [25,30]
	ERP↓ [25] ^a	Fibrosis [27,28,31] ^a	β-oxidation activation [24] ^a	LA pressure↑ [31] ^a
	Regional conduction slowing [27,28,32] ^a	Apoptosis [29] ^a	Myocardial lipidosis [24,27] ^a	
	Cx 43 expression↓ [31] ^a			
MAFLD	K _{ATP} current↑ [24] ^a			
	Low voltage areas [32]			
	AF burden↑ [28,31]			
	APD↑ [33] ^a	LA volume↑ [26] ^a	Global respiration↓ [34] ^a	Atrial compliance↓ [35–37] ^a
LA pressure/volume overload ^b	Regional conduction slowing [33,38,39] ^a	Fibrosis [33,39,40] ^a	Myocardial lipidosis [41] ^a	
	Lower bipolar voltage [38]		Glutamate and fatty acid-supported respiration↓ [41] ^a	
	Cx 43 phosphorylation↓ [42] ^a		ROS production↑ [41] ^a	
	Cx 40 expression↓ [33] ^a		Susceptibility to MPTP opening↑ [43] ^a	
AF-induced remodelling	Impaired Ca ²⁺ handling [44,45] ^a			
	AF burden↑ [33]			
	Low voltage areas [46]	Fibrosis [46] ^a		Atrial compliance↓ [46]
	APD↑ [47,48] ^a	LA volume↑ [49,50] ^a		LA pressure↑ [49] ^a
	ERP↑/↓ [50–52] ^a	Cardiomyocyte hypertrophy [51,52] ^a		LA systolic function↓ [53] ^a
	Regional conduction slowing [51,52] ^a	Fibrosis [49–52,54,55] ^a		
	L-type Ca ²⁺ current↓ [56] ^a			
	Impaired Ca ²⁺ handling [57] ^a			
	AF burden↑ [49–52,56]			
	APD↓ [58]	LA volume↑ [8]	Global respiration↓ [59–61]	Atrial compliance↓ [8]
	L-type Ca ²⁺ current↓ [58]	Fibrosis [62]	ROS production↑ [59]	
	I _{K1} ↑ [63]			
	I _{KACH} dysregulation [64]			
	Impaired Cx 40–43 expression/localization [65]			

AF: atrial fibrillation; APD: action potential duration; Ca²⁺: calcium; Cx: connexin; ERP: effective refractory period; FFA: free fatty acids; I_{K1}: inward rectifier potassium current; K_{ATP}: adenosine triphosphate-sensitive potassium channel; LA: left atrium; MPTP: mitochondrial permeability transition pore; ROS: reactive oxygen species; SR: sarcoplasmic reticulum.

^a Studies providing association independent of AF.

^b Including hypertension, heart failure and valvular diseases.

conflicting findings arose from epidemiological studies [85,86]. This inconsistency may be attributed to differences in screening methods and diagnostic criteria used to identify MAFLD, liver fibrosis and AF. Consequently, further research is needed to thoroughly explore and establish the relationship between MAFLD and AF.

Hence, the process of atrial remodelling induced by metabolic disorders appears to be intricate, encompassing both cardiac and extracardiac mechanisms. Further research is warranted to enhance our understanding of this area.

3.3. LA pressure and volume overload

Various clinical and physiological factors can increase LA pressure. Pathologically, hypertension, heart failure, shunts and valvular diseases are common chronic contributors. Physiological factors, such as exercise and pregnancy, also elevate LA pressure. Importantly, the impact on electrophysiological and structural remodelling varies depending on the underlying clinical context.

Hypertension, heart failure and valvular diseases lead to similar hallmarks of atrial remodelling. More specifically, electrophysiological remodelling is a prominent hallmark of pathological LA pressure overload, resulting in APD increase, impaired Ca^{2+} handling and regional conduction slowing [87]. Structural remodelling involving cardiomyocyte hypertrophy and fibrosis is frequently associated [49–52,54,55], typically caused by the release of mediators, such as angiotensin II, endothelin 1, transforming growth factor beta and inflammatory cytokines [88].

Of note, LA pressure alterations can result from conditions primarily inducing LA volume overload, such as exercise and mitral regurgitation.

The impact of increased LA pressure during exercise depends critically on the intensity of the exercise [89]. Exercise promotes cardiac remodelling, leading to proportional symmetrical enlargement of all four cardiac chambers [90]. In healthy individuals, there is a linear increase in LA pressures (measured using pulmonary capillary wedge pressure) during exercise [91]. Consequently, athletes experience a significant increase in atrial pressure during exercise, which can be similar to that observed in disease settings. These pressure changes are expected to manifest as increased atrial volumes during exercise, a phenomenon demonstrated through exercise cardiac magnetic resonance (CMR) and, to varying degrees, in some echocardiography studies [92]. Notably, fibrosis has been observed in rodent models in response to extreme endurance exercise [93], but not during regular exercise [94]. In a rat model of treadmill running for 16 weeks, biatrial fibrosis was detected, and this was associated with an increased susceptibility to AF [93]. In mice subjected to 6 weeks of intense exercise, inflammation-induced atrial fibrosis was noted [95]. In a recent study, highly trained endurance athletes were found to have greater atrial fibrosis (as assessed by late gadolinium enhancement [LGE] CMR) compared with control subjects [96].

Mitral regurgitation leads to an excess LA volume load. Additionally, LA dilation, serving as an indicator of LA remodelling, is associated with higher cardiovascular morbidity and mortality, irrespective of LV function, in patients with mitral regurgitation [97]. In cases of acute mitral regurgitation in animal models, there is an initial adaptive response in the LA, characterized by increased reservoir and contractile function. However, this adaptive state progresses towards decompensation at 4 weeks, marked by evolving changes in LA structure and function as a result of a combination of progressive eccentric remodelling and fibrosis [98]. The long-term atrial remodelling observed in mitral regurgitation is probably a result of atrial myocardial overstretching and elevated myocyte oxidative stress, leading to programmed myocyte death, independent of AF [99,100]. Although fibrosis is a common occurrence in various cardiac pressure and/or volume overload scenarios, the evidence regarding direct activation of cardiac fibroblasts by mechanical forces remains controversial. Key responses, such as fibroblast proliferation, collagen production and differentiation into myofibroblasts, exhibit divergent and sometimes opposing changes in different studies in response to stretch [101]. Resolving these discrepancies could be crucial to the development of innovative and more efficient therapies to prevent the onset and progression of atrial remodelling, subsequently mitigating adverse clinical outcomes.

Heart failure with preserved ejection fraction (HFpEF) exhibits significant specificity for in-depth investigations into LA remodelling. HFpEF is a complex clinical syndrome marked by both cardiac and extracardiac features; it is now recognized as a systemic disease linked to a broad spectrum of clinical risk factors and co-morbidities, such as aging, female sex, hypertension, pulmonary congestion, metabolic syndrome, obesity, type 2 diabetes mellitus, hyperlipidaemia and renal disease [102]. These risk factors

and co-morbidities contribute to intertwined disease mechanisms in the pathophysiology of HFpEF and the associated atrial remodelling. Given the diverse potential underlying causes of HFpEF, such as structural myocardial abnormalities or abnormal loading conditions (e.g. hypertension, valvular diseases, volume overload, or rhythm disorders), developing preclinical HFpEF models that accurately capture the complexity of the human condition is challenging. Animal models employed in research typically rely on combinations of aging, metabolic disorders, hypertension and endothelial dysfunction to induce left ventricular hypertrophy, diastolic dysfunction, LA enlargement, fibrosis and natriuretic peptide release [103]. Clinical studies emphasize the importance of LA remodelling in patients with HFpEF, demonstrating reduced emptying fractions and contractile reserve compared with control subjects and patients with hypertension [104]. Moreover, LA compliance and mechanics deteriorate progressively, with an increasing AF burden in HFpEF, elevating the risk of new-onset AF and progressive AF. These changes contribute to the development of a distinctive HFpEF phenotype, characterized by heightened ventricular interaction, right heart failure and worsening pulmonary vascular disease [105]. Whereas these observations establish a robust foundation for acknowledging the role of ACM in patients with HFpEF, further research is necessary to understand the predominant pathophysiological mechanisms involved in HFpEF-related atrial remodelling, and to tailor strategies to improve patient outcomes.

3.4. Genetic factors

Most of the evidence associating genetic factors with ACM is based on AF studies. The genetic contribution to AF has been reported extensively across various methodological approaches, based on family linkage studies, identification of rare genetic variants in AF population or genome-wide association studies. Furthermore, a variety of genes affected by mutations have been associated with AF, including genes encoding ion channels, gap junctions, structural proteins, endocrine factors and transcription factors [106]. Furthermore, the prevalence of rare variants contributing to AF has been reported as being high as 10–16% in patients presenting early-onset AF [107]. In addition, the presence of rare variants in patients presenting early-onset AF has been associated with a higher mortality rate.

However, fewer data have correlated genetic factors with other features of ACM. Two recent studies based on the genome-wide association study approach reported an association between genetic loci and ACM features, including LA volume and P-wave duration [108,109]. In a small cohort of patients presenting atrial fibrotic cardiomyopathy without AF, several rare variants were reported based on whole exome sequencing [110]. Animal studies have provided additional insights linking rare variants to advanced atrial remodelling. More specifically, a rare variant affecting the atrial-specific sarcomere protein myosin light-chain 4 has been associated with major atrial dilatation, the fibrotic process and severe atrial conduction defects [111]. Most of the variants found in ACM overlap, in some instances, with heart failure, and may be associated with a higher risk of heart failure over time. Finally, some variants found in ACM (e.g. variants affecting the *natriuretic peptide A* gene) have been associated with a higher risk of stroke [112]. Taken together, these data suggest a relatively high prevalence of genetic factors in ACM, especially in young patients, with various consequences for the atrial remodelling process. Accumulating evidence supports the role of variants in genes encoding sarcomeric proteins. However, the genetic landscape of ACM critically needs further investigation to establish its relevance in routine clinical practice.

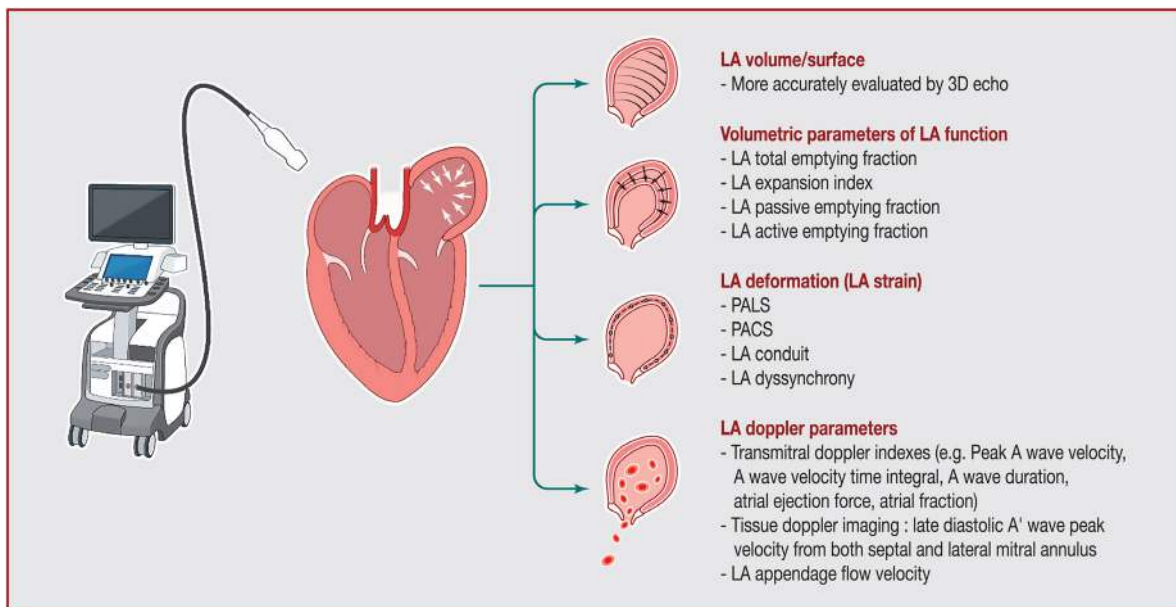


Fig. 2. Evaluation of left atrial cardiomyopathy using echocardiography. 3D: three-dimensional; LA: left atrium; PALS: peak atrial longitudinal strain; PACS: peak atrial contraction strain.

3.5. AF-induced atrial remodelling

It is now well established that electrical and structural remodelling of the atrial myocardium contributes to the progression of AF. Studies from animal models and biopsies from patients have shown that, at the cellular level, a shortening of the APD results from a decrease in inward I_{CaL} and enhanced background outward K^+ currents. In particular, the inward rectifier K^+ current (I_{K1}) is increased and the acetylcholine-activated K^+ current (I_{KACh}) is constitutively active. In contrast, voltage K^+ channel expression is reduced. Reductions in the ultra-rapidly activating delayed rectifier K^+ current (I_{Kur}) and the transient outward K^+ current (I_{to}) participate in the triangulation of action potential [113]. Ca^{2+} cycling alterations participate in cardiac arrhythmogenesis [114]. Triggered activity can result from early or delayed after-depolarization. Increased sarcoplasmic reticulum Ca^{2+} leaks, resulting from ryanodine receptor dysfunction, can produce focal ectopic firing [115]. Calmodulin-dependent protein kinase II has also been involved, and may provide a novel therapy for AF [116]. Recent studies have highlighted that Ca^{2+} cycling differences across different regions of LA are involved in the proarrhythmic activity [117,118]. At the tissue level, a reduction in the effective refractory period is observed. Alteration in conduction velocity is associated with connexin alteration (e.g. lateralization [119]). Structural remodelling, including fibrosis and hypertrophy, affects wavefront propagation and participates in re-entry. Over the last decade, metabolic remodelling has been investigated extensively. In contrast to electrical remodelling, which is fast (a few days) and structural remodelling (several weeks later), metabolic remodelling is likely to occur during the period in between [120].

4. Noninvasive assessment of LA cardiomyopathy

Based on ACM expert consensus, the classification of ACM relies on histopathological findings and the presence of fibrosis and/or non-collagen deposits [2]. Although the use of this classification is routinely limited for clinicians, several tools have been developed to assess LA remodelling and function. These tools aim to establish

clinically meaningful variables for ACM. Consequently, the clinical instruments currently at hand enable the assessment of various aspects of the LA. Because of its widespread and routine application, echocardiography emerges as the primary approach for evaluating ACM and LA anatomy. Fig. 2 illustrates the measurable variables acquired through this method.

Atrial fibrosis predominantly contributes to structural remodelling, and is linked to significant alterations in the geometry of the LA. The LA size is the most widely studied variable using different imaging tools, including two-dimensional and three-dimensional echocardiography, computed tomography and CMR. LA dilatation has been widely investigated and correlated to several clinical outcomes. More specifically, LA enlargement has been extensively explored in the context of pressure and volume overload. The relationship between increased LA size and increased filling pressures has been validated against invasive measures [121,122]. LA enlargement as a result of pressure overload is usually secondary to an increase in LA afterload, in the setting of mitral valve disease or LV dysfunction. However, some studies have suggested that LA enlargement might result from the fibrotic process, resulting in impaired LA compliance and leading to an increase in LA pressure [123]. In line with other studies, LA enlargement has been associated with adverse clinical outcomes, independent of AF, such as stroke and heart failure [124].

More recently, LA strain has been proposed as an attractive tool to assess LA function. Basically, LA strain evaluates atrial wall deformation during the cardiac cycle. More specifically, LA deformation during atrial diastole is considered as a surrogate for LA reservoir function, whereas LA deformation during atrial systole is considered as an indicator of pump function. A study has demonstrated a direct correlation between atrial strain measurements obtained through two-dimensional speckle-tracking echocardiography and histologically confirmed fibrosis of the LA [125]. Watanabe et al. found a correlation between electroanatomical mapping and three-dimensional speckle-tracking echocardiography methods in patients with paroxysmal AF during sinus rhythm, even in those with less advanced anatomical remodelling [126]. Furthermore, this group showed that LA dyssynchrony is latent in patients with

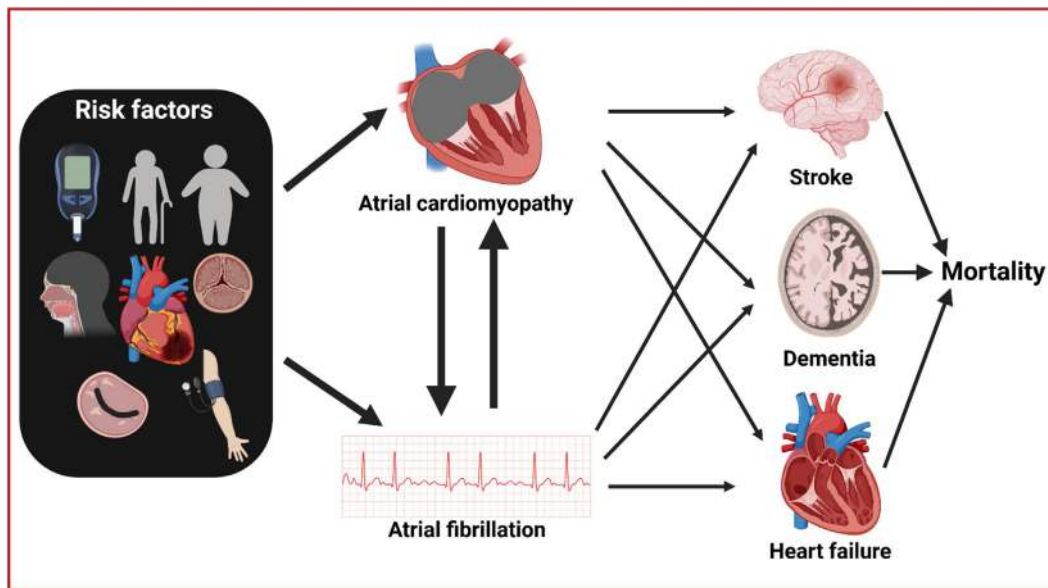


Fig. 3. Clinical impact of atrial cardiomyopathy.

AF in the early remodelling phase, and that the early remodelling changes can be detected using three-dimensional speckle-tracking echocardiography. Furthermore, LA strain has been associated with various clinical outcomes, such as AF [127], stroke [128,129] and heart failure [130–132].

CMR imaging has become a gold standard for assessing the volume of cardiac chambers [133], but additional methods for evaluating atrial function and fibrosis using CMR have emerged as valuable tools for ACM characterization. LGE is a well-validated method for detecting fibrosis in the myocardium. Moreover, LGE of the LA was assessed comprehensively by a group in Utah that refined the technique and developed a staging system where the degree of fibrosis is divided into stages I–IV. LGE has been investigated extensively in the field of AF ablation, and has been correlated with electroanatomical mapping and AF recurrence following ablation [134]. However, fewer works have correlated LGE of the LA with other clinical outcomes, such as sinus node dysfunction [135], LA thrombus formation [136] or stroke [137]. Beyond LGE assessment, CMR allows atrial function assessment using tissue tracking with deformation indexes similar to those applied on echocardiography speckle-tracking echocardiography.

Recently, CMR-based techniques have been improved to include four-dimensional flow that encodes velocity in all three spatial directions (three-dimensional) as well as time. This technique provides robust flow quantification in clinical practice [138], and has been used in the context of AF burden to show that LA peak velocity and vorticity are the reproducible and temporally stable novel LA four-dimensional flow biomarkers [139]. However, data acquisition using four-dimensional flow is time consuming. Therefore, efforts were undertaken recently to develop a five-dimensional flow CMR framework to reduce scan times [140]. This approach has been validated in the context of AF, and allows resolution of three-dimensional haemodynamics in less than 10 minutes [141].

Several electrocardiogram-based indexes have been developed to assess ACM. The P-wave represents the atrial depolarization of first the right atrium and then the LA, and is therefore of

particular interest with regard to atrial electrical remodelling. Interatrial excitation conduction disturbances via the Bachmann bundle can also be detected on the electrocardiogram. P-wave variables comprise P-wave duration, P-wave dispersion, P-wave axis, P-wave voltage, P-wave area, interatrial block (IAB) and P-wave terminal force in lead V1 (PTFV1). These electrocardiogram markers have been associated with histological remodelling of atria, such as terminal crest fibrosis or extensive fibrosis associated with fatty tissue infiltration [142]. More recently, artificial intelligence (AI)-based electrocardiogram analysis has emerged as an attractive means of investigating ACM and ACM-related outcomes. Furthermore, AI-based electrocardiogram analysis has revealed a correlation between AI probability of AF and larger LA volumes and lower LA reservoir function [143]. Furthermore, a recent study based on saliency mapping and median waveform analysis highlighted that the electrocardiogram-AI probability of predicting AF is critically influenced by the period of atrial depolarization and repolarization (i.e. P-wave and surrounding period) [144].

Finally, several circulating biomarkers have been proposed to estimate atrial remodelling and ACM [145,146]; they include markers of inflammation (e.g. interleukin-6, matrix metalloproteinase 9, transforming growth factor beta), markers of fibrosis (e.g. galectin-3) and atrial peptides (N-terminal prohormone of B-type natriuretic peptide, natriuretic peptide A). For more details see [147].

5. Clinical impact of ACM

ACM is associated with several clinical outcomes (Fig. 3) that are reviewed below.

5.1. AF incidence and ACM

Although the clinical impact of AF screening in the general population remains controversial, the potential interest in AF screening in patients presenting hallmarks of ACM is increasing.

A recent study conducted in a large retrospective cohort of more than 30,000 patients demonstrated a strong association between LA enlargement and incident AF, independent of age, sex, hypertension, diabetes, heart failure, history of myocardial infarction, stroke and left ventricular hypertrophy [148]. In line with this, other studies have highlighted the predictive value of other LA function variables, such as LA emptying fraction [149,150]. Alexander et al. [151] proposed an AF risk score that considers P-wave characteristics and durations. The scoring system assigns points based on criteria, including P-wave morphology in the inferior leads, voltage in lead I and P-wave duration. Patients with the highest scores and those with mid-range scores had a 2-fold increased risk of developing AF compared with those with lowest scores. Furthermore, the group exhibiting highest scores took a significantly shorter average time to develop AF compared with the group presenting mid-range scores and the group with the lowest scores. Whereas other studies have corroborated these findings, there remains variability in how these P-wave variables contribute to the overall prediction of AF risk [152]. AI-based electrocardiogram analysis obtained during sinus rhythm is also emerging as a useful tool to predict incident AF, based on large-scale studies [153,154].

Previous large-scale studies have failed to demonstrate a substantial clinical benefit for AF screening in the general population [155]. In light of the limited outcomes data, the United States Preventive Services Task Force concluded that there is insufficient evidence to recommend screening for AF, and that the balance of benefits and harms of screening cannot be determined. Further studies are needed to establish the clinical impact of ACM-related variables and their relevance for the selection of elective patients for AF screening.

5.2. Risk of stroke and/or systemic embolism

AF is a major risk factor for ischaemic stroke, and one fifth of ischaemic strokes are believed to result from AF [156]. Several clinical risk factors have been identified, and have been shown to modulate the stroke risk in patients with AF. Among them, age, hypertension, diabetes mellitus, history of stroke and/or transient ischaemic attack, history of vascular disease, history of heart failure and female sex (all pooled in the CHA₂DS₂-VASC score) are the widest used in daily practice. The incremental value of ACM markers for stroke prediction is established in patients presenting AF. Previous studies have demonstrated that the CHA₂DS₂-VASC score predictive value can be improved by ACM-related variables. Maheshwari et al. enhanced the CHA₂DS₂-VASC scoring system by introducing the P-wave axis component to create the P2-CHA₂DS₂-VASC score [157]. Utilizing data from both the Atherosclerosis Risk in Communities (ARIC) and Multi-Ethnic Study of Atherosclerosis (MESA) cohorts, the authors observed that, when compared with the CHA₂DS₂-VASC score, the P2-CHA₂DS₂-VASC score demonstrated an improvement in the C-statistic, as well as net reclassification improvement and integrated discrimination improvement. In a retrospective cohort study, King et al. assessed LA fibrosis, using magnetic resonance imaging LGE in 1200 patients who underwent AF ablation, and its association with incident strokes [158]. A total of 62 strokes or transient ischaemic attacks occurred, and advanced LGE was associated with a 4-fold increased risk of stroke after adjustment.

Several studies have emphasized the possible significance of markers associated with ACM in evaluating the risk of stroke in patients who do not have documented AF. This link was first

suggested by studies assessing the temporality between AF episodes and stroke [159]. In a substudy of Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), the temporal association between monitored AF and ischaemic stroke was evaluated. Interestingly, in patients presenting stroke during follow-up, only 8% presented AF within the 30 days preceding the event. Furthermore, 16% of patients presented AF after stroke. A similar observation was found in the IMPACT study (The IMPACT of Biotronik Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy With Defibrillator Devices), where 29% of thromboembolic events followed atrial tachyarrhythmia. In line with this, several studies have established associations between LA variables and ischaemic stroke in patients without a history of AF [160]. A study conducted by Benjamin et al. was the first to link atrial enlargement to stroke [161]. In this study, including over 3400 patients from the Framingham Heart Study, a strong association was found between LA size and stroke risk, even in patients free from AF. A few studies have highlighted similar associations between various LA imaging modalities, such as CMR LGE or LA strain, and stroke risk. Similarly, electrocardiographic hallmarks of ACM have been associated with stroke, such as the PTFV1.

Since the association between ACM-related variables and stroke risk was raised, the potential value of anticoagulation in patients without AF has been suggested. The Atrial Cardiomyopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) trial has recently assessed such a strategy in patients who presented a recent cryptogenic stroke [162]. In this study, ACM was assessed using a composite criterion (including PTFV1, N-terminal prohormone of B-type natriuretic peptide and LA diameter index), and led to 1:1 randomization to aspirin or apixaban. The results of this study were recently presented at the 9th European Stroke Organisation Conference, and showed that the rate of recurrent stroke during follow-up was 4.4% both in patients treated with apixaban and in those treated with aspirin (hazard ratio: 1.00, 95% confidence interval [95% CI]: 0.64–1.55), and that lack of difference was consistent across stroke types. This result raises several questions regarding the relevant definition of ACM for stroke risk, and the need for extensive research in this field.

5.3. Heart failure

AF is a major risk factor for heart failure. In the CARDIONOR registry, in 4973 outpatients with AF, incident heart failure during follow-up (10.5% at 3 years) was five times more frequent than bleeding and three times more frequent than stroke, and these results were confirmed when the analysis was restricted to patients without a history of AF at inclusion [163]. In the Framingham Heart Study, the incidence of heart failure was 33 per 100,000 patient-years [164].

Data investigating the predictive value of ACM-related variables for new-onset heart failure are sparse. In a large general population study ($n=1951$ without prevalent AF or heart failure), participants underwent a health examination with echocardiography. LA volumes and emptying fractions were correlated with incident heart failure [165]. After multivariable adjustment for clinical and echocardiographic variables, only minimum LA indexed volume remained an independent predictor of incident heart failure. Other studies have suggested that ACM-related variables have prognostic value in patients with heart failure. For example, in the Multicenter

Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT CRT) trial, patients with normal PTFV1 were associated with a lower risk of heart failure or death than those with abnormal PTFV1 [166]. In another study of patients with heart failure who received cardiac resynchronization therapy, the presence of IAB was associated with a 1.9-fold higher risk of AF, death or heart transplant [167].

5.4. Dementia

AF has been linked to the emergence of cognitive decline, and this association holds true even when considering cases without clinical symptomatic stroke. Evidence from a meta-analysis involving over 80,000 participants with AF indicates that AF, even in the absence of documented stroke, may independently contribute to cognitive impairment [168,169]. As ACM is associated with a higher risk of stroke, and both stroke and AF are linked to an elevated risk of dementia, a potential connection between ACM and dementia has been proposed.

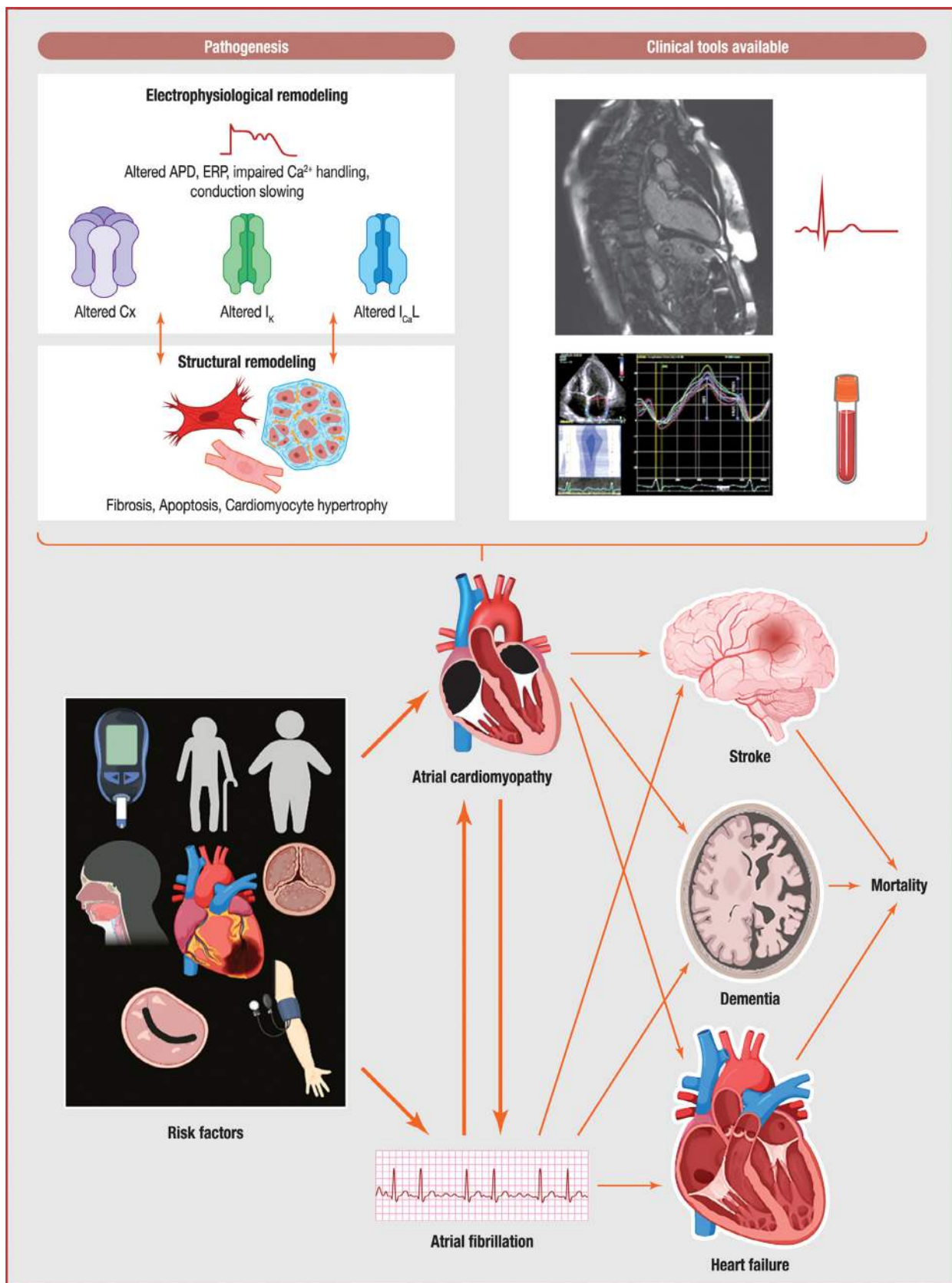
Drawing from the ARIC study, Gutierrez et al. recently revealed that the presence of abnormal P-wave variables is linked to more pronounced cognitive decline and an elevated risk of dementia [170]. Their investigation involved 13,714 middle-aged participants, with an average age of 57 years, 56% of whom were women. These individuals were tracked for dementia occurrence and changes in cognitive function over an average follow-up period of 18 years. Abnormal PTFV1, abnormal P-wave axis, prolonged P-wave duration and advanced IAB were identified through electrocardiograms conducted during the study. All abnormal P-wave variables, except advanced IAB, were associated with a heightened dementia risk, even after accounting for the occurrence of AF and stroke. Specifically, the multivariable hazard ratio for abnormal PTFV1 was 1.60 (95% CI: 1.41–2.83), for abnormal P-wave axis was 1.36 (95% CI: 1.17–2.57) and for prolonged P-wave duration

was 1.60 (95% CI: 1.42–1.80). Furthermore, the presence of abnormal PTFV1 was also linked to a more pronounced decline in overall cognitive function.

In this context, Martinez-Selles et al. conducted an assessment of the relationship between partial and advanced IAB and cognitive impairment in the BAYES registry, which consisted of 332 participants [171]. Their analysis revealed that, at baseline, the prevalence of cognitive impairment was 2.7% among individuals with a normal P-wave, 5.1% among those with partial IAB and 10.3% among those with advanced IAB, showing a statistically significant difference. Furthermore, advanced IAB was found to be independently associated with baseline cognitive impairment, with an odds ratio of 4.9 (95% CI: 1.4–16.5). Additionally, both partial IAB and advanced IAB were independently associated with cognitive impairment at follow-up. In a recent study including 4096 participants in the ARIC study, several echocardiographic measures of lower LA function were significantly associated with an increased risk of incident dementia. These findings were robust to sensitivity analyses that excluded participants with incident AF or stroke [172].

6. Conclusions

ACM is characterized by atrial structural and electrophysiological remodelling that facilitates the development of clinically relevant events. Despite the clinical tools available, including imaging, electrocardiography and biomarkers (Central Illustration), there are still no clear noninvasive diagnostic criteria for ACM. Various animal models of ACM have improved our understanding of pathophysiological mechanisms. Additional basic research is needed to investigate the complex relationship between ACM and strokes. Numerous clinical tools used to characterize ACM have shown their capacity to forecast adverse clinical events. Nevertheless, additional research is necessary to pinpoint individuals who necessitate therapeutic intervention.



Central Illustration. Atrial cardiomyopathy: pathophysiology, clinical tools, risk factors and relationship between atrial fibrillation, stroke, heart failure and dementia. APD: action potential duration; Ca^{2+} : calcium; Cx: connexin; ERP: effective refractory period; I_{CaL} : L-type calcium current; I_K : potassium current.

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The authors declare that they have no competing interest.

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