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Review Article

Atrial cardiomyopathy: An entity of emerging interest in the clinical setting

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ABSTRACT

Since 1995, the concept of atrial cardiomyopathy (ACM) has been associated with myocardial fibrosis. Despite a consensus document in 2016, ACM's definition primarily relies on histopathological findings. The focus on diagnostic criteria for ACM is driven by the potential link to thromboembolic events even independently on atrial fibrillation (AF). The complexity of the mutual relationships between ACM and AF makes difficult any assessment of the thromboembolic risk associated to ACM per se. ACM's thrombogenicity is a multifaceted clinical phenomenon involving electrical, functional, and structural modifications. Factors such as cardiovascular risk factors (e.g., hypertension), common cardiac comorbidities (e.g., heart failure), and extracardiac conditions (e.g., neuromuscular disorders) can promote atrial derangement, triggering atrial fibrillation (AF) and increasing the risk of thromboembolic events. Several diagnostic methods are available to detect the key features of ACM, including electrical changes assessed by surface and intracavitary ECG, and structural and functional alterations evaluated through echocardiography and cardiac magnetic resonance (CMR). These methods can be complemented by electro-anatomical mapping (EAM) to enhance the accuracy of myocardial tissue characterization and assessment of atrial fibrosis. Although certain clinical conditions (e.g., atrial high-rate episodes, AHREs; embolic stroke of undetermined source, ESUS) often exhibit atrial alterations in their thromboembolic presentations, recent randomized trials have failed to demonstrate the benefits of oral anticoagulation in patients with ACM without AF. However, ACM constitutes the substrate for the development of AF, as proposed in the AF European guidelines under the 4S-AF scheme. This review emphasizes the lack of a diagnostic gold standard and the need for clinical criteria for ACM, aiming to better understand the potential therapeutic implications of atrial structural and functional derangements, even in the absence of clinical evidence of AF.

1. Introduction

The term "atrial electrical remodeling" encompasses the changes observed within the atrial myocardium, whether or not they are linked to atrial fibrillation (AF). This term was initially introduced in 1995 by Allessie's group in the context of experimental studies that demonstrated the concept of 'AF begets AF'. This phenomenon arises as a consequence of the shortening of the atrial action potential and other electrical alterations in the atria [1]. Since 2016, the term atrial cardiomyopathy (ACM) was introduced by Goette et al. as "any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations" [2]. In the same consensus document, the authors first reported a new EHRAS (for European Heart Rhythm Association; EHRA/Heart Rhythm Society; HRS/Asian Pacific Heart Rhythm Association; APHRS/Latin American Society of Electrophysiology and Cardiac Stimulation; SOLAECE) classification for ACM taking into account four classes of ACM: (I) principal cardiomyocyte changes; (II) principally fibrotic changes; (III) combined cardiomyocyte-pathology/fibrosis; and (IV) primarily non-collagen infiltration (with or without cardiomyocyte changes). However, it must be considered that ACM is an entity that should be approached with different diagnostic methods, while the EHRAS classification is based only on histopathologic findings, thus making it of complex application in the daily clinical practice (PMID: 37169,634) [3]. Within this evolving scenario, characterized by an increasing interest on ACM, in recent years the number of publications on PubMed with the term "atrial cardiomyopathy" steeply increased (Fig. 1).

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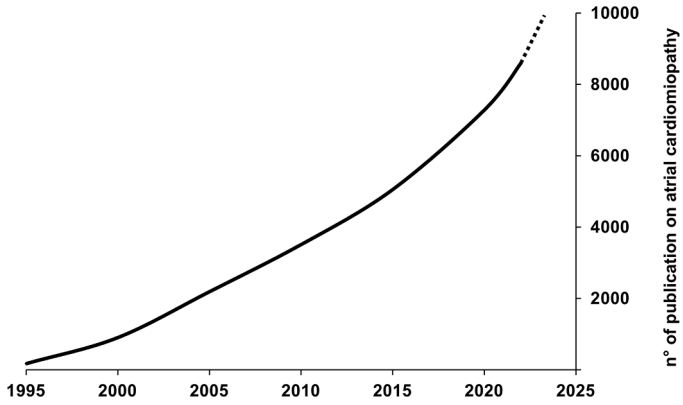

Fig. 1. Number of publications per year since 1995 about atrial cardiomyopathy (ACM).

1.2. Atrial cardiomyopathy: characterization and associated clinical conditions

One of the primary healthcare concerns associated with atrial cardiomyopathy (ACM) is the potential increase in thromboembolic risk, which may occur due to atrial contractile dysfunction and fibrosis, regardless of the presence of atrial fibrillation (AF) [4]. Among thromboembolic events linked to AF, ischemic stroke stands out as a significant concern. Globally, ischemic stroke remains the third leading cause of death, as per WHO [5], and within the European Union (EU), its annual incidence varies from 95 to 290 cases per 100,000 people, resulting in approximately 440,000 deaths per year [6,7]. The estimated direct and indirect costs range from 25 to 45 billion euros, posing a growing social challenge due to the aging population and its consequences [8]. According to literature, AF is a significant contributor to the risk of stroke, especially cardioembolic stroke, and the beneficial effects of anticoagulation are well-established. [9,10] However, thrombogenicity at the atrial level is a complex phenomenon involving electrical and structural changes in addition to external factors [11,12]. Atrial fibrillation without concomitant conditions, previously defined as "lone" AF, is associated with a lower risk of stroke (1–2 % cumulative 15-year risk) compared to AF patients with multiple comorbidities [13–15]. Numerous cardiovascular risk factors and complex clinical conditions contribute to the risk of thromboembolic events, prompting the question of ACM's contribution to thromboembolic risk, regardless of the clinical detection of atrial fibrillation. Notably, patients with heart failure (HF) often exhibit a degree of atrial cardiomyopathy, leading to an increased risk of stroke due to elevated filling pressure and blood stasis in the left atrium (LA), irrespective of ejection fraction [16,17]. Addressing atrial remodeling in HF through tailored AF ablation and novel therapeutic strategies, such as SGLT2 inhibitors, appears crucial in reducing adverse clinical outcomes associated with ACM [18–20]. Atrial function impairment is also observed in valvular HF, particularly in mitral stenosis and mitral regurgitation due to LA dilation accompanied by interstitial fibrosis, chronic inflammation, and cellular glycogen accumulation [21]. Furthermore, primary cardiomyopathies like hypertrophic cardiomyopathy are associated with an increased risk of thrombus formation, primarily due to ventricular diastolic dysfunction [22].

While ACM may result from ventricular dysfunction, substantial evidence indicates that ACM can occur as a primary myocardial disorder, as is the case with amyloidosis. LA remodeling is particularly pronounced in wild-type transthyretin amyloidosis (ATTRwt), leading to an enhanced risk of stroke, likely linked to a longer onset of symptoms compared to AL amyloidosis [23]. Neuromuscular disorders, such as Emery–Dreifuss disease, are linked to dilated cardiomyopathy and atrial involvement with extensive fibrosis, increasing the risk of thromboembolic events [24,25]. Moreover, common cardiovascular risk factors like diabetes mellitus, hypertension, and obesity trigger atrial derangements [26–28], as does population aging [29], elevating the risk of thromboembolism and necessitating comprehensive patient care. Similarly, the presence of coronary artery disease (CAD), even in the context of acute coronary syndromes, [30] and peripheral artery disease (PAD) [31], is often associated with LA enlargement, suggesting ongoing atrial remodeling and underlying ACM in patients with a high atherosclerotic burden, ultimately leading to the development of AF and stroke [32]. Additional coexisting conditions linked to AF and impaired atrial function encompass chronic kidney disease, malignancies, and the medications used in cancer treatment [33–35]. Lastly, inflammation plays a crucial role in triggering atrial dysfunction, acting as the common pathway across various conditions, ranging from infective conditions to invasive therapeutic strategies such as cardiac and non-cardiac surgeries [36–38]. Given this heterogeneous panorama of cardiovascular and non-cardiovascular conditions related to atrial dysfunction, AF could be considered an expression of the ACM spectrum and a specific marker of atrial thrombogenicity progression, rather than a direct causative factor for cerebrovascular events [39].

The ACM is essentially the result of a complex interplay of factors that substantially influence structural and functional changes in the atrium (Fig. 2)., and there are complex inter-relationships with a wide spectrum of atrial arrhythmias, including frequent atrial premature ectopias (APCs), AHREs, and of course AF. These pathogenetic factors intricately intertwine, giving rise to a unique clinical picture. The intricate interactions between various pathogenetic mechanisms and the structural, functional, and electrical manifestations of atrial cardiomyopathy are pivotal to its understanding. However, once appropriately identified and comprehended during its natural history, these interactions can be partially modulated through pharmacological interventions (eg., antiarrhythmic drugs, AAD) and invasive procedures (e.g., ablation procedures). Therefore, it is essential to underscore that atrial dysfunction is closely associated with progressive left ventricular cardiac dysfunction. This may entail an increase in mitral valve regurgitation entity, a reduction in ventricular performance, and consequently, an elevation in adverse cardiac events and all cause death, including acute thromboembolic events (stroke/TIA) and a worsening of the quality of life through a cognitive decline [40]. Within this vicious cycle, early diagnosis of ACM assumes a paramount role. A feasible and reliable diagnosis in routine clinical practice could allow for effective interventions in mitigating adverse outcomes, through the implementation of beneficial therapies. This approach can significantly enhance the quality of life for patients with ACM and reduce the risk of severe complications. The complexity of the mutual relationships between ACM and AF makes difficult any assessment of the thromboembolic risk associated to ACM per se. Indeed, it is essential to emphasize that at present, ACM itself, in the absence of AF, is not an indication for long-term oral anticoagulation to prevent thromboembolic events and stroke.

2.1. ECG and intracavitary ECG

The standard 12-lead ECG is a fundamental diagnostic tool in cardiology. Primary evaluation of the P wave across leads can typically be carried out in D2 and V1. Any alterations in the P wave may be linked to an underlying ACM, as shown in various studies [30,41,42]. Many studies have sought to assess early P wave changes associated with stroke and AF incidence before structural manifestations of this subclinical electrical disturbance become evident. For example, Kohsaka et al. demonstrated that a P-wave duration >120 ms or P-terminal force in precordial lead V1 (PTFV1) ≤ -4000 μV × ms could increase the risk of systemic thromboembolism [43]. Similarly, the Multi-Ethnic Study of Atherosclerosis found that P-wave terminal force in lead V1 was more associated with incident stroke than AF development [44]. In the Northern Manhattan Study, ECG-LA abnormalities were linked to cryptogenic/cardioembolic stroke even without AF [45]. This suggests

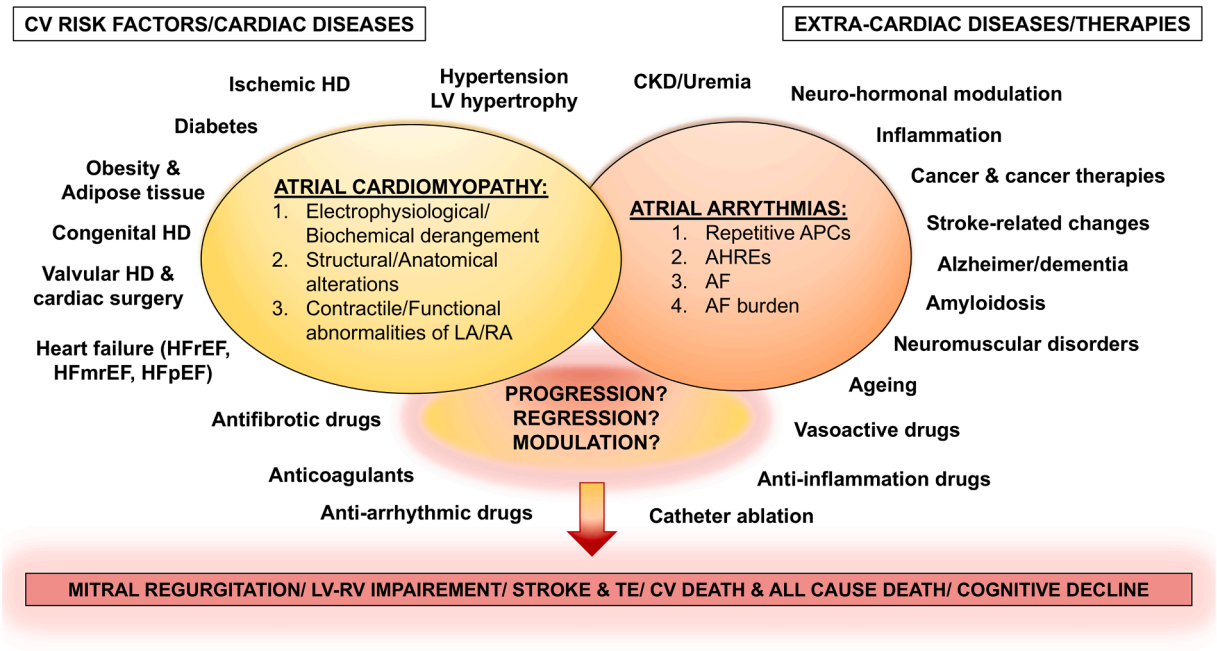

Fig. 2. Pathogenesis, clinical features and natural evolution of atrial cardiomyopathy. AAD: antiarrhythmic drugs; AF: atrial fibrillation; AHREs: atrial high rate episodes; APCs: atrial premature complexes; CKD: chronic kidney disease; CV: cardiovascular; HD: heart diseases; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; TE: thromboembolism.

that electrical instability, potentially due to atrial fibrosis, plays a role as a pre-AF substrate, as supported by studies showing an increased incidence of AF in patients with excessive APCs [46,47]. Recently, amplified P-wave analysis (APWA) has shown promise in detecting low-voltage areas in atrial cardiomyopathy patients, enabling early diagnosis and improved patient management [48,49]. In this context, 12-lead ECG, while a simple tool, could offer essential insights for patient management through machine learning [50].

Furthermore, continuous monitoring via cardiac implantable electronic devices can provide valuable information for detecting ACM. Atrial High-Rate Episodes (AHREs), detected with an atrial lead as an intracavitary electrogram (EGM), have been associated with an increased risk of clinical AF and systemic thromboembolism [51,52]. A higher burden of AHREs strongly correlates with the development of clinical AF and ACM progression [53,54]. An AHREs duration exceeding 24 h justifies oral anticoagulation (OAC) in patients with a high/very high estimated individual risk of stroke [55]. While AHREs detection may indicate atrial electrophysiological derangement, further research is required to establish the correlation between AHREs burden and the extent of structural ACM.

2.2. Electroanatomic mapping (EAM)

Invasive electroanatomic mapping systems (EAM) enable the assessment of the substrate in atrial cardiomyopathy and atrial fibrillation [56–58]. These systems provide a detailed anatomical description of the structures, even in complex cases such as variations in PV anatomy, coupled with their electrical activity. Additional imaging modalities like pre-acquired anatomic images (3D-Echocardiography or cMRI) or real-time contrast angiography can enhance accuracy [59]. EAM software generates a 3D-colored model where each color scale corresponds to a local bipolar voltage value [60]. Despite being an invasive technique, EAM may enable the detection of electrophysiological alterations in the LA, potentially occurring in the early stages of ACM development. Findings such as increased effective refractory period, conduction time, bi-atrial activation time, decreased conduction velocity, corrected sinus node recovery time, and lower voltage areas are typical in AF patients undergoing AF ablation for paroxysmal AF and may serve as electrophysiological indicators of ACM even in patients with sinus rhythm [61].

Low-voltage areas (LVAs) detected with endocardial mapping correspond to regions in the atria with local fibrosis [62]. An association between increased LVAs and diffuse voltage reduction in the LA has been demonstrated. Additionally, LA voltage is significantly lower in patients with high CHA_2DS_2VASc scores, suggesting a link between electroanatomic LA remodeling and stroke risk in AF patients [63]. Notably, when performing extensive voltage mapping of the LA before AF ablation, larger LA fibrosis areas correlated significantly with increased LA size and inflammatory markers, which are distinctive features of ACM [64]. However, there is currently no consensus on cutoff values for fibrosis, and the extent of low voltage area does not strongly correlate with the clinical history in AF patients [65–70], despite multimodal investigations with EAM and imaging techniques potentially improving substrate detection for atrial arrhythmias [71]. The possibility of non-invasively atria mapping to detect ACM presence and its extent is an intriguing area currently under investigation [72].

2.3. Echocardiography

Echocardiography is the leading non-invasive imaging technique used in cardiology, and it is the most widespread imaging technique used to diagnose ACM and assess left atrial function. The left atrium (LA) plays a crucial role in the cardiac cycle by modulating the diastolic filling of the left ventricle. Both anatomical and functional derangement of the LA characterize ACM [50]. LA enlargement, measured as LA size (LA diameter and area) [73] or LA volume, [74] has an undoubtedly prognostic value for its association with cerebrovascular and cardiovascular events and mortality, [75] with LA volume being a more robust predictor of cardiovascular events [74]. As known, the asymmetric LA dilatation raises questions about measuring the deformation of the LA. 2D Echocardiography represents the most widely used technique, and left atrial volume (limit of normality of 34 ml/m2) is commonly

measured with the biplane method by disk summation or area–length method [76]. Although maximum LAVi is reported in many studies as the primary marker of ACM, also minimum LAV has been described as a good surrogate of LV filling pressure with more excellent prognostic value than maximum LAVi [77,78]. 2-dimensional Echocardiography (2DE) often underestimates LAVi when compared to 3-dimensional Echocardiography (3DE) or cardiac magnetic resonance, and this is due to geometric assumptions about LA shape, but also foreshortening of the LA cavity in the apical views [79,80]. Indeed, the long axis of the left ventricle does not correspond to the long axis of the LA [76]. Therefore, new reference values must be applied with 3DE [79]. Left atrial enlargement depicts only one of many aspects of ACM-related left atrial dysfunction. Moreover, left atrial enlargement may be preceded by left atrial dysfunction [81]. LA phasic functions represent the different roles of the LA during the cardiac cycle. Specifically, the LA acts as a reservoir, conduit, and booster pump during systole, early diastole, and late diastole, respectively [82]. 2D-Speckle-tracking technology measures tissue deformation via myocardial speckles and evaluates the different phases of left atrial function. Strain and strain rate correspond to the extent and the rate of myocardial deformation [83], allowing us to evaluate the contractility of the LA in the clinical setting. In a recent metanalysis, the average normality value of reservoir strain was 39 % (95% CI: 38–41 %). [84] Speckle-tracking Echocardiography has improved the ACM characterization. Eichenlaub et al. found that an LA longitudinal strain rate <23.5 % predicted ACM, defined by endocardial mapping [85]. Moreover, in patients with sinus rhythm, reduced peak atrial longitudinal strain is strongly associated with low amplitude voltage areas in the LA [86]. Lastly, in a study a reservoir LA strain value <26 % was associated to ESUS [87], suggesting that more LA dysfunction leads to more thromboembolic events. Finally, 3DE analysis using fully automated software allow a more accurate measure of the volume and a direct measurement of the LA ejection fraction (EFLA) in a single acquisition. Recently, Figliozzi et al. [88] reported 55.94 % (95 % CI: 51.92 %, 59.96 %) as the average value for EFLA and Russo et al. [89]. demonstrated that EFLA assessed by 3DE is a robust independent predictor of adverse cardiovascular outcomes.

2.4. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) stands as the gold standard for measuring left atrium (LA) size and assessing volumetric changes. Typically, CMR provides higher normal reference volumes for the LA when compared to 2D echocardiography. Moreover, only 3-Tesla CMR has the capability to evaluate atrial fibrosis, enabling the characterization of atrial wall tissue [90]. However, there are limitations associated with assessing atrial fibrosis using CMR, including the need for specialized technical capabilities, associated costs, limited availability of 3-Tesla CMR machines, and the non-specific nature of atrial fibrosis, which is a common feature in various myocardial diseases [91]. Myocardial fibrosis is detected through late gadolinium enhancement (LGE) extension and T1 relaxation time images. According to Marrouche et al. [92], the estimation of atrial tissue fibrosis using CMR 3-T mapping could prove valuable in predicting atrial fibrillation recurrences and play a pivotal role in achieving more robust long-term results in ablation procedures. This study introduced the UTAH score, categorizing atrial fibrosis into stages 1 (<10 % of the atrial wall), 2 (≥10 %-<20 %), 3 (≥20 %-<30 %), and 4 (≥30 %) [93]. In patients with atrial fibrillation, the integration of the CMR fibrosis detection and scoring system with electroanatomic mapping (EAM) has proven to be beneficial and practical in improving outcomes in ablation procedures over an extended follow-up period [94]. CMR findings can also be utilized in invasive mapping (EAM) to enhance the detection of areas of fibrosis and tissue remodeling. However, this method presents challenges related to standardization and achieving proper image resolution in the thin-walled atrium [95]. A recent review by Gal et al. emphasized the valuable synergy between CMR and EAM [92]. CMR with LGE can identify LA scarring associated with post-ablation atrial fibrillation recurrences, potentially aiding in guiding the AF ablation procedure. These findings shift the focus from the arrhythmia itself to the substrate where AF originates [96].

3. Current and future perspectives

The diagnosis of ACM in clinical practice is complex, and the therapeutic implications following such a diagnosis need to be clarified, especially since the current diagnostic criteria primarily focus on histopathological elements. Over time, the characterization of ACM has evolved. Initially, it was mainly associated with atrial fibrillation (AF), encompassing electrical, contractile, and structural derangements, often referred to as "remodeling," which could be observed in association with AF, particularly in longstanding cases [97]. However, it later became evident that ACM might not only be associated with AF but could also precede AF, as seen in neuromuscular diseases [25]. Furthermore, it can be detected even in the absence of AF, especially in individuals at an increased risk of left atrial thrombus formation [98]. Indeed, ACM should be considered a spectrum of alterations linked to increased thrombogenesis that occurs over time in the atria [99]. Atrial fibrillation typically arises in a deranged atrium, contributing to atrial remodeling in a vicious cycle. This remodeling increases the risk of thromboembolism, necessitating integrated therapeutic care [29,100]. The emerging paradigm shift suggests shifting the focus from merely analyzing the relationship between stroke and AF, which represents the “tip of the iceberg,” to a more comprehensive assessment of the substrate from which AF emerges [10]. This approach is supported by the 4S-AF scheme endorsed by the latest ESC guidelines, which suggests characterizing AF within the context of the patient’s clinical background [101,102]. It underscores the importance of assessing the severity of the substrate for optimal patient management rather than addressing only the arrhythmia itself [103]. This review aimed to highlight promising diagnostic tools and imaging techniques that can aid clinicians and standardize the intricate diagnosis of ACM and its management (Fig. 3).

Given the difficulty of obtaining histological characterization of the LA in the clinical setting, novel imaging techniques such as tissue characterization with CMR may help stratify the risk associated with ACM more effectively. Advanced echocardiography techniques, including atrial longitudinal strain and 3D LA ejection fraction analysis, can provide insights into LA performance throughout the cardiac cycle. Additionally, surface electrocardiography and electro-anatomical invasive mapping can detect electrical derangements resulting from atrial fibrosis, a characteristic feature of ACM associated with AF recurrences after ablation. Another paradigm shift involves considering the existence of a thrombogenic syndrome associated with ACM and systemic factors, and in this perspective AF may have the role of a marker of very high risk. In patients with numerous risk factors for thromboembolic events, clinicians should be mindful of the importance of using advanced imaging and electrophysiological techniques to detect ACM in its early stages, as well as monitoring serum biomarkers associated with cardiovascular adverse events (e.g., troponins, NT-pro BNP) [15,104]. It is essential to note that, according to current evidence from randomized trials, a diagnosis of ACM in the absence of overt AF does not change the therapeutic management of patients and, specifically, long-term anticoagulation is currently not indicated. However, in patients with ACM who have a high probability of developing AF, more intensive clinical and instrumental monitoring should be applied to promptly detect the occurrence of clinical AF. In such cases, closer ambulatory follow-up and the use of mobile health devices for early AF detection could be beneficial [105,106]. Furthermore, in a population with multiple cardiovascular risk factors and signs of ACM, AF screening could be a valuable approach for preventing thromboembolic events. In the CRYSTAL-AF trial, which enrolled patients with previous cryptogenic stroke, AF was detected in 12 % of patients at 1-year follow-up (with up to 30 % AF detection after the total follow-up period). This suggests that AF could

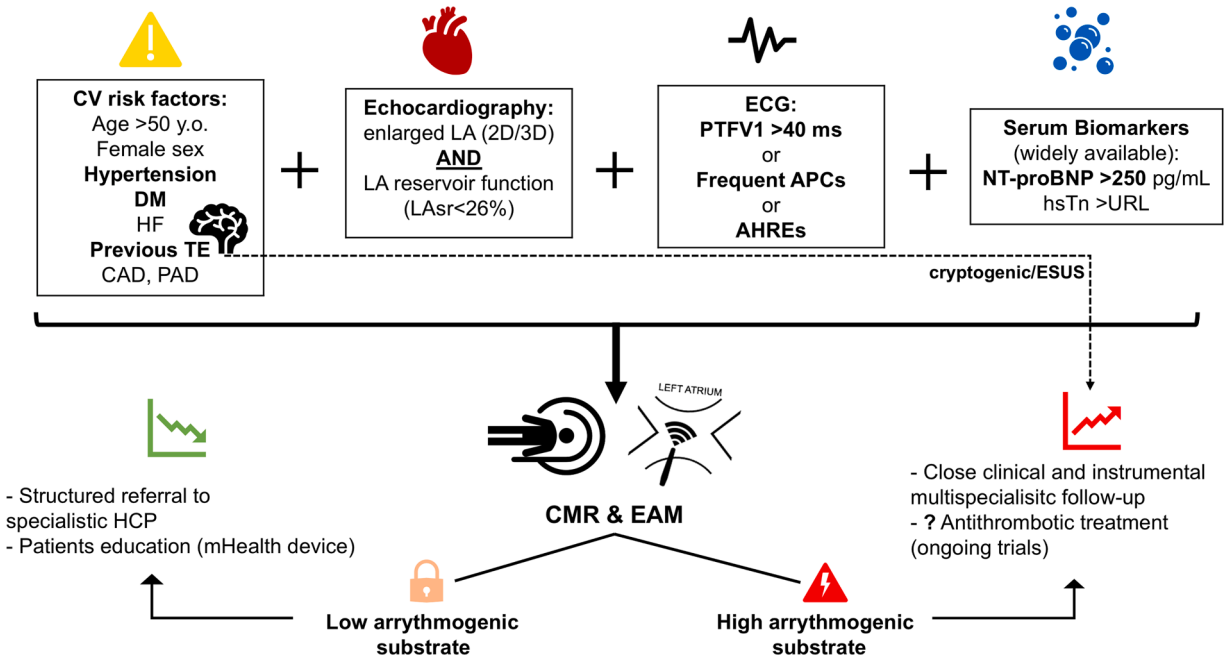

Fig. 3. Diagnostics and proposed clinical management for atrial cardiomyopathy patients. AHREs: atrial high-rate episodes; APCs: atrial premature complexes; CAD: coronary artery disease; CMR: cardiac magnetic resonance; CV: cardiovascular; DM: diabetes mellitus; EAM: electroanatomical mapping; ESUS: embolic stroke of undetermined source; HCP: healthcare professionals; HF: heart failure; LA: left atrium; LAsr: left atrium strain; PAD: peripheral artery disease; PTFV1: P-terminal force in precordial lead V1; TE: thromboembolism.

be an expression of a pre-existing thromboembolic condition [107]. Continuous cardiac implantable electronic devices (CIED) can assist in the detection of atrial high-rate episodes (AHREs) and AF, which are possible markers of ACM and significantly increase the risk of thromboembolic events, especially in high-risk populations [52,108,109]. However, recent results from the NOAH-AFNET 6 trial did not show a reduction in embolic stroke with Edoxaban in AHREs [110]. The results from the ARTESiA trial on anticoagulation in AHREs patients may provide further insights into the benefit of oral anticoagulation therapy in these patients [111].

A complex issue is the possibility of prescribing antithrombotic therapy even without evidence of clinical AF. While this concept is intriguing, evidence from randomized trials, including secondary analyses of the WARCEF and WARSS trials, focused on high-risk ACM patients identified by atrial enlargement and elevated NT-pro BNP, has failed to demonstrate the efficacy of anticoagulation therapy on stroke outcomes in the absence of prior AF diagnosis [112,113]. Specifically, the NAVIGATE-ESUS and RE-SPECT ESUS trials, which enrolled patients with embolic stroke of an undetermined source (ESUS), did not show a benefit of DOACs over aspirin regarding stroke recurrence [114,115]. Additionally, as demonstrated in the ARCADIA trial, anticoagulation therapy did not show superiority to aspirin in preventing recurrent strokes among patients with ESUS and signs of ACM [116]. To date, the results from randomized clinical trials indicate that detection of ACM does not alter the therapeutic management of patients in the absence of a prior clinical AF diagnosis. Future studies should aim to assess the potential role of oral anticoagulants in high-risk ACM patients. However, at present, documented AF remains a prerequisite for initiating oral anticoagulant therapy in patients at risk of stroke/systemic embolism.

4. Conclusions

Atrial cardiomyopathy (ACM) has been associated with an increased risk of thromboembolic events. However, it remains challenging to validate the independent role of factors such as atrial diameter/volumes or other elements directly related to ACM in enhancing risk stratification for atrial fibrillation (AF). Currently, risk stratification systems, standard diagnostic pathways, and targeted therapies to slow the progression of ACM are still subjects of ongoing research and cannot yet be applied in everyday clinical practice. The most appropriate approach for gathering data and potentially leading to more tailored treatment strategies for patients with AF based on the severity of ACM is to investigate clinical and imaging characteristics through a multiparametric diagnostic pathway. Atrial imaging exams, preferably using echocardiography, should form the foundation for quantifying ACM in terms of volumes and contractile derangements. However, essential information like the extent of atrial fibrosis is not routinely assessed in clinical practice, despite some studies using MRI in specific patient subsets. Simultaneously, the detection of ACM through CMR and EAM may increase the likelihood of identifying an arrhythmic cardiac origin of embolic strokes in cases of unknown or cryptogenic strokes. Currently, anticoagulants are recommended only for patients with documented AF, with clinical characteristics suggestive of a risk of stroke not quantifiable as a “low risk”. Ongoing trials may improve our therapeutic decision-making, particularly for AF patients who appear to be at low risk of stroke but have underlying ACM. Therefore, it is crucial to anticipate the standardization of diagnostic criteria for ACM, with the goal of early identification of high-risk patients, as the basis for an evidence-based assessment of the potential benefit of strategies to reduce thromboembolic events. This could ultimately lead to a reduction in the significant public health impact and the direct and indirect costs associated with stroke-related sequelae.

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References

[1] Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92(7):1954–68. https://doi.org/10.1161/01.cir.92.7.1954.

[2] Goette A, Kalman JM, Aguinaga L, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace 2016;18(10):1455–90. https://doi.org/10.1093/europace/euw161.

[3] Boriani G, Venturelli A, Imberti JF, Bonini N, Mei DA, Vitolo M. Comparative analysis of level of evidence and class of recommendation for 50 clinical practice guidelines released by the European society of cardiology from 2011 to 2022. Eur J Intern Med 2023. https://doi.org/10.1016/j.ejim.2023.04.020.

[4] Yaghi S, Kamel H. Stratifying stroke risk in atrial fibrillation: beyond clinical risk scores. Stroke 2017;48(10):2665–70. https://doi.org/10.1161/STROKEAHA.117.017084.

[5] Estimates WHO. The top 10 causes of death, https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

[6] Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. Presse Med 2016;45(12 Pt 2):e391–8. https://doi.org/10.1016/j.lpm.2016.10.003.

[7] Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of stroke in Europe: thirty-year projections of incidence, prevalence, deaths, and disability-adjusted life years. Stroke 2020;51(8):2418–27. https://doi.org/10.1161/STROKEAHA.120.029606.

[8] Timmis A, Townsend N, Gale CP, et al. European society of cardiology: cardiovascular disease statistics 2019. Eur Heart J 2020;41(1):12–85. https://doi.org/10.1093/eurheartj/ehz859.

[9] Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest 2018;154(5): 1121–201. https://doi.org/10.1016/j.chest.2018.07.040.

[10] Boriani G, Vitolo M, Lane DA, Potpara TS, Lip GY. Beyond the 2020 guidelines on atrial fibrillation of the European society of cardiology. Eur J Intern Med 2021;86: 1–11. https://doi.org/10.1016/j.ejim.2021.01.006.

[11] Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol 2015;65(20):2239–51. https://doi.org/10.1016/j.jacc.2015.03.557.

[12] Delgado V, Di Biase L, Leung M, et al. Structure and function of the left atrium and left atrial appendage: AF and stroke implications. J Am Coll Cardiol 2017;70 (25):3157–72. https://doi.org/10.1016/j.jacc.2017.10.063.

[13] Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation 2011;123(10):e269–367. https://doi.org/10.1161/CIR.0b013e318214876d.

[14] Romiti GF, Proietti M, Bonini N, et al. Clinical complexity domains, anticoagulation, and outcomes in patients with atrial fibrillation: a report from the GLORIA-AF registry phase II and III. Thromb Haemost 2022;122(12): 2030–41. https://doi.org/10.1055/s-0042-1756355.

[15] Vitolo M, Malavasi VL, Proietti M, et al. Cardiac troponins and adverse outcomes in European patients with atrial fibrillation: a report from the ESC-EHRA EORP atrial fibrillation general long-term registry. Eur J Intern Med 2022;99:45–56. https://doi.org/10.1016/j.ejim.2022.01.025.

[16] Boriani G, Imberti JF, Vitolo M. The burden of atrial fibrillation in patients with preserved or mildly reduced heart failure: a call to action for detecting atrial fibrillation and improving outcome. Eur J Heart Fail 2022;25(1):74–6. https://doi.org/10.1002/ejhf.2755.

[17] Boriani G, Bonini N, Vitolo M, et al. Asymptomatic vs. symptomatic atrial fibrillation: clinical outcomes in heart failure patients. Eur J Intern Med 2023. https://doi.org/10.1016/j.ejim.2023.09.009.

[18] Boriani G, Mei DA, Imberti JF. Atrial Fibrillation ablation in patients recently hospitalized for worsening heart failure: need for individualized decision-making. JACC Clin Electrophysiol 2023;9(9):1960–3. https://doi.org/10.1016/j.jacep.2023.06.012.

[19] Boriani G, Vitolo M, Imberti JF. Effectiveness of atrial fibrillation ablation in heart failure across the entire spectrum of left ventricular ejection fraction. Eur J Heart Fail 2022;24(9):1647–51. https://doi.org/10.1002/ejhf.2642.

[20] Boriani G, Mei DA, Imberti JF. Therapeutic effects of sodium-glucose cotransporter 2 inhibitors in patients with heart failure with preserved ejection fraction: from outcome improvement to potentially favourable influences on atrial fibrillation burden, atrial fibrillation progression and atrial cardiomyopathy. Eur J Heart Fail 2023;25(7):978–80. https://doi.org/10.1002/ejhf.2891.

[21] Verheule S, Wilson E, Everett T, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation 2003;107(20):2615–22. https://doi.org/10.1161/01.CIR.0000066915.15187.51.

[22] Patten M, Pecha S, Aydin A. Atrial fibrillation in hypertrophic cardiomyopathy: diagnosis and considerations for management. J Atr Fibrillation 2018;10(5): 1556. https://doi.org/10.4022/jafib.1556.

[23] Nochioka K, Quarta CC, Claggett B, et al. Left atrial structure and function in cardiac amyloidosis. Eur Heart J Cardiovasc Imaging 2017;18(10):1128–37. https://doi.org/10.1093/ehjci/jex097.

[24] Boriani G, Gallina M, Merlini L, et al. Clinical relevance of atrial fibrillation/flutter, stroke, pacemaker implant, and heart failure in Emery-Dreifuss muscular dystrophy: a long-term longitudinal study. Stroke 2003;34(4):901–8. https://doi.org/10.1161/01.STR.0000064322.47667.49.

[25] Valenti AC, Albini A, Imberti JF, et al. Clinical profile, arrhythmias, and adverse cardiac outcomes in Emery-Dreifuss muscular dystrophies: a systematic review of the literature. Biology (Basel) 2022;11(4). https://doi.org/10.3390/biology11040530.

[26] Boriani G, Proietti M. Atrial fibrillation prevention: an appraisal of current evidence. Heart 2018;104(11):882–7. https://doi.org/10.1136/heartjnl-2017-311546.

[27] Vitolo M, Imberti JF, Proietti M, Lip GYH, Boriani G. Atrial high rate episodes as a marker of atrial cardiomyopathy: in the quest of the Holy Grail. Author's reply. Eur J Intern Med 2022;98:115–6. https://doi.org/10.1016/j.ejim.2022.01.032.

[28] Guo Y, Corica B, Romiti GF, et al. Mobile health technology integrated care in atrial fibrillation patients with diabetes mellitus in China: a subgroup analysis of the mAFA-II cluster randomized clinical trial. Eur J Clin Investig 2023;53(9): e14031. https://doi.org/10.1111/eci.14031.

[29] Guo Y, Romiti GF, Proietti M, et al. Mobile health technology integrated care in older atrial fibrillation patients: a subgroup analysis of the mAFA-II randomised clinical trial. Age Ageing 2022;51(11). https://doi.org/10.1093/ageing/afac245.

[30] Li Z, Liu Q, Liu F, et al. Atrial cardiomyopathy markers and new-onset atrial fibrillation risk in patients with acute myocardial infarction. Eur J Intern Med 2022;102:72–9. https://doi.org/10.1016/j.ejim.2022.04.019.

[31] Boriani G, Vitolo M, Diemberger I, et al. Optimizing indices of atrial fibrillation susceptibility and burden to evaluate atrial fibrillation severity, risk and outcomes. Cardiovasc Res 2021;117(7):1–21. https://doi.org/10.1093/cvr/cvab147.

[32] Proietti M, Raparelli V, Laroche C, et al. Adverse outcomes in patients with atrial fibrillation and peripheral arterial disease: a report from the EURObservational research programme pilot survey on atrial fibrillation. Europace 2017;19(9): 1439–48. https://doi.org/10.1093/europace/euw169.

[33] Ding WY, Potpara TS, Blomström-Lundqvist C, et al. Impact of renal impairment on atrial fibrillation: ESC-EHRA EORP-AF long-term general registry. Eur J Clin Investig 2022;52(6):e13745. https://doi.org/10.1111/eci.13745.

[34] Malavasi VL, Vitolo M, Proietti M, et al. Impact of malignancy on outcomes in European patients with atrial fibrillation: a report from the ESC-EHRA EURObservational research programme in atrial fibrillation general long-term registry. Eur J Clin Investig 2022;52(7):e13773. https://doi.org/10.1111/eci.13773.

[35] Vitolo M, Proietti M, Malavasi VL, et al. Adherence to the "Atrial fibrillation Better Care" (ABC) pathway in patients with atrial fibrillation and cancer: a report from the ESC-EHRA EUR observational research programme in atrial fibrillation (EORP-AF) general long-term registry. Eur J Intern Med 2022;105:54–62. https://doi.org/10.1016/j.ejim.2022.08.004.

[36] Boriani G, Vitolo M, Imberti JF. Atrial fibrillation post-coronary or cardiac surgery: a transient inflammation-related event or the expression of a pre-existing arrhythmogenic atrial substrate? Kardiol Pol 2022;80(9):877–9. https://doi.org/10.33963/KP.a2022.0212.

[37] Malavasi VL, Muto F, Ceresoli PACM, et al. Atrial fibrillation in vascular surgery: a systematic review and meta-analysis on prevalence, incidence and outcome implications. J Cardiovasc Med (Hagerstown) 2023;24(9):612–24. https://doi.org/10.2459/JCM.0000000000001533.

[38] Vitolo M, Bonini N, Imberti JF, Boriani G. Atrial fibrillation in pneumonia: what clinical implications at long-term? Intern Emerg Med 2023;18(2):347–50. https://doi.org/10.1007/s11739-022-03181-9.

[39] Guichard JB, Nattel S. Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad? J Am Coll Cardiol 2017;70(6):756–65. https://doi.org/10.1016/j.jacc.2017.06.033.

[40] Malavasi VL, Zoccali C, Brandi MC, et al. Cognitive impairment in patients with atrial fibrillation: implications for outcome in a cohort study. Int J Cardiol 2021; 323:83–9. https://doi.org/10.1016/j.ijcard.2020.08.028.

[41] Stalikas N, Doundoulakis I, Karagiannidis E, et al. Prevalence of markers of atrial cardiomyopathy in embolic stroke of undetermined source: a systematic review. Eur J Intern Med 2022;99:38–44. https://doi.org/10.1016/j.ejim.2022.01.024.

[42] Baturova MA, Svensson A, Aneq M, et al. Evolution of P-wave indices during long-term follow-up as markers of atrial substrate progression in arrhythmogenic right ventricular cardiomyopathy. Europace 2021;23(23 Suppl 1):i29–37. https://doi.org/10.1093/europace/euaa388.

[43] Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Electrocardiographic left atrial abnormalities and risk of ischemic stroke. Stroke 2005;36(11):2481–3. https://doi.org/10.1161/01.STR.0000185682.09981.26.

[44] Kamel H, Soliman EZ, Heckbert SR, et al. P-wave morphology and the risk of incident ischemic stroke in the multi-ethnic study of atherosclerosis. Stroke 2014; 45(9):2786–8. https://doi.org/10.1161/STROKEAHA.114.006364.

[45] Kamel H, Hunter M, Moon YP, et al. Electrocardiographic left atrial abnormality and risk of stroke: northern Manhattan study. Stroke 2015;46(11):3208–12. https://doi.org/10.1161/STROKEAHA.115.009989.

[46] Binici Z, Intzilakis T, Nielsen OW, Køber L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation 2010;121(17):1904–11. https://doi.org/10.1161/CIRCULATIONAHA.109.874982.

[47] Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. J Am Coll Cardiol 2015;66(3):232–41. https://doi.org/10.1016/j.jacc.2015.05.018.
[48] Jadidi A, Müller-Edenborn B, Chen J, et al. The duration of the amplified sinus-P-wave identifies presence of left atrial low voltage substrate and predicts outcome after pulmonary vein isolation in patients with persistent atrial fibrillation. JACC Clin Electrophysiol 2018;4(4):531–43. https://doi.org/10.1016/j.jacep.2017.12.001.
[49] Müller-Edenborn B, Minners J, Keyl C, et al. Electrocardiographic diagnosis of atrial cardiomyopathy to predict atrial contractile dysfunction, thrombogenesis and adverse cardiovascular outcomes. Sci Rep 2022;12(1):576. https://doi.org/10.1038/s41598-021-04535-7.
[50] Boriani G, Imberti JF, Vitolo M. The challenge to improve knowledge on the interplay between subclinical atrial fibrillation, atrial cardiomyopathy, and atrial remodeling. J Cardiovasc Electrophysiol 2021;32(5):1364–6. https://doi.org/10.1111/jce.14992.
[51] Khan AA, Boriani G, Lip GYH. Are atrial high rate episodes (AHREs) a precursor to atrial fibrillation? Clin Res Cardiol 2020;109(4):409–16. https://doi.org/10.1007/s00392-019-01545-4.
[52] Vitolo M, Imberti JF, Maisano A, et al. Device-detected atrial high rate episodes and the risk of stroke/thrombo-embolism and atrial fibrillation incidence: a systematic review and meta-analysis. Eur J Intern Med 2021;92:100–6. https://doi.org/10.1016/j.ejim.2021.05.038.
[53] Imberti JF, Bonini N, Tosetti A, et al. Atrial high-rate episodes detected by cardiac implantable electronic devices: dynamic changes in episodes and predictors of incident atrial fibrillation. Biology (Basel) 2022;11(3):443. https://doi.org/10.3390/biology11030443.
[54] Sagris D, Georgiopoulos G, Pateras K, et al. Atrial high-rate episode duration thresholds and thromboembolic risk: a systematic review and meta-analysis. J Am Heart Assoc 2021;10(22):e022487. https://doi.org/10.1161/JAHA.121.022487.
[55] Boriani G, Vitolo M, Imberti JF, Potpara TS, Lip GYH. What do we do about atrial high rate episodes? Eur Heart J Suppl 2020;22(Suppl O):O42–52. https://doi.org/10.1093/eurheartj/suaa179.
[56] Donal E, Lip GY, Galderisi M, et al. EACVI/EHRA expert consensus document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging 2016;17(4):355–83. https://doi.org/10.1093/ehjci/jev354.
[57] Guglielmo M, Baggiano A, Muscogiuri G, et al. Multimodality imaging of left atrium in patients with atrial fibrillation. J Cardiovasc Comput Tomogr 2019;13(6):340–6. https://doi.org/10.1016/j.jcct.2019.03.005.
[58] Maesen B, Verheule S, Zeemering S, et al. Endomysial fibrosis, rather than overall connective tissue content, is the main determinant of conduction disturbances in human atrial fibrillation. Europace 2022;24(6):1015–24. https://doi.org/10.1093/europace/euac026.
[59] Roney CH, Sillett C, Whitaker J, et al. Applications of multimodality imaging for left atrial catheter ablation. Eur Heart J Cardiovasc Imaging 2021;23(1):31–41. https://doi.org/10.1093/ehjci/jeab205.
[60] Del Carpio Munoz F, Buescher TL, Asirvatham SJ. Three-dimensional mapping of cardiac arrhythmias: what do the colors really mean? Circ Arrhythm Electrophysiol 2010;3(6):e6–11. https://doi.org/10.1161/CIRCEP.110.960161.
[61] Stiles MK, John B, Wong CX, et al. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the "second factor". J Am Coll Cardiol 2009;53(14):1182–91. https://doi.org/10.1016/j.jacc.2008.11.054.
[62] Yamaguchi T, Otsubo T, Takahashi Y, et al. Atrial structural remodeling in patients with atrial fibrillation is a diffuse fibrotic process: evidence from high-density voltage mapping and atrial biopsy. J Am Heart Assoc 2022;11(6):e024521. https://doi.org/10.1161/JAHA.121.024521.
[63] Park JH, Joung B, Son NH, et al. The electroanatomical remodelling of the left atrium is related to CHADS2/CHA2DS2VASc score and events of stroke in patients with atrial fibrillation. Europace 2011;13(11):1541–9. https://doi.org/10.1093/europace/eur135.
[64] Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol 2005;45(2):285–92. https://doi.org/10.1016/j.jacc.2004.10.035.
[65] Jadidi AS, Cochet H, Shah AJ, et al. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping. J Am Coll Cardiol 2013;62(9):802–12. https://doi.org/10.1016/j.jacc.2013.03.081.
[66] Spragg DD, Khurram I, Zimmerman SL, et al. Initial experience with magnetic resonance imaging of atrial scar and co-registration with electroanatomic voltage mapping during atrial fibrillation: success and limitations. Heart Rhythm 2012;9(12):2003–9. https://doi.org/10.1016/j.hrthm.2012.08.039.
[67] Vlachos K, Letsas KP, Korantzopoulos P, et al. Prediction of atrial fibrillation development and progression: current perspectives. World J Cardiol 2016;8(3):267–76. https://doi.org/10.4330/wjc.v8.i3.267.
[68] Kapa S, Desjardins B, Callans DJ, Marchlinski FE, Dixit S. Contact electroanatomic mapping derived voltage criteria for characterizing left atrial scar in patients undergoing ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2014;25(10):1044–52. https://doi.org/10.1111/jce.12452.
[69] Kottkamp H, Bender R, Berg J. Catheter ablation of atrial fibrillation: how to modify the substrate? J Am Coll Cardiol 2015;65(2):196–206. https://doi.org/10.1016/j.jacc.2014.10.034.
[70] 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(3):342–51. https://doi.org/10.1093/europace/euaa009.
[71] Zghaib T, Keramati A, Chrispin J, et al. Multimodal examination of atrial fibrillation substrate: correlation of left atrial bipolar voltage using multi-electrode fast automated mapping, point-by-point mapping, and magnetic resonance image intensity ratio. JACC Clin Electrophysiol 2018;4(1):59–68. https://doi.org/10.1016/j.jacep.2017.10.010.
[72] Eichenlaub M, Mueller-Edenborn B, Lehrmann H, et al. Non-invasive body surface electrocardiographic imaging for diagnosis of atrial cardiomyopathy. Europace 2021;23(12):2010–9. https://doi.org/10.1093/europace/euab140.
[73] Rossi A, Temporelli PL, Quintana M, et al. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MeRGE Heart Failure). Eur J Heart Fail 2009;11(10):929–36. https://doi.org/10.1093/eurjhf/hfp112.
[74] Tsang TS, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006;47(5):1018–23. https://doi.org/10.1016/j.jacc.2005.08.077.
[75] Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham heart study. Circulation 1995;92(4):835–41. https://doi.org/10.1161/01.cir.92.4.835.
[76] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2015;28(1):1–39. https://doi.org/10.1016/j.echo.2014.10.003. e14.
[77] Fatema K, Barnes ME, Bailey KR, et al. Minimum vs. maximum left atrial volume for prediction of first atrial fibrillation or flutter in an elderly cohort: a prospective study. Eur J Echocardiogr 2009;10(2):282–6. https://doi.org/10.1093/ejechocard/jen235.
[78] Wu VC, Takeuchi M, Kuwaki H, et al. Prognostic value of LA volumes assessed by transthoracic 3D echocardiography: comparison with 2D echocardiography. JACC Cardiovasc Imaging 2013;6(10):1025–35. https://doi.org/10.1016/j.jcmg.2013.08.002.
[79] Badano LP, Miglioranza MH, Mihăilă S, et al. Left atrial volumes and function by three-dimensional echocardiography: reference values, accuracy, reproducibility, and comparison with two-dimensional echocardiographic measurements. Circ Cardiovasc Imaging 2016;9(7):e004229.. https://doi.org/10.1161/CIRCIMAGING.115.004229.
[80] Barbieri A, Albini A, Maisano A, et al. Clinical value of complex echocardiographic left ventricular hypertrophy classification based on concentricity, mass, and volume quantification. Front Cardiovasc Med 2021;8:667984. https://doi.org/10.3389/fcvm.2021.667984.
[81] Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. J Am Coll Cardiol 2019;73(15):1961–77. https://doi.org/10.1016/j.jacc.2019.01.059.
[82] Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014;63(6):493–505. https://doi.org/10.1016/j.jacc.2013.10.055.
[83] Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese society of echocardiography. Eur J Echocardiogr 2011;12(3):167–205. https://doi.org/10.1093/ejechocard/jer021.
[84] Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. J Am Soc Echocardiogr 2017;30(1):59–70. https://doi.org/10.1016/j.echo.2016.09.007. e8.
[85] Eichenlaub M, Mueller-Edenborn B, Minners J, et al. Echocardiographic diagnosis of atrial cardiomyopathy allows outcome prediction following pulmonary vein isolation. Clin Res Cardiol 2021;110(11):1770–80. https://doi.org/10.1007/s00392-021-01850-x.
[86] Pilichowska-Paszkiet E, Baran J, Sygitowicz G, et al. Noninvasive assessment of left atrial fibrosis. Correlation between echocardiography, biomarkers, and electroanatomical mapping. Echocardiography 2018;35(9):1326–34. https://doi.org/10.1111/echo.14043.
[87] Sade LE, Keskin S, Can U, et al. Left atrial mechanics for secondary prevention from embolic stroke of undetermined source. Eur Heart J Cardiovasc Imaging 2022;23(3):381–91. https://doi.org/10.1093/ehjci/jeaa311.
[88] Figliozzi S, Georgiopoulos G, Pateras K, et al. Normal ranges of left atrial volumes and ejection fraction by 3D echocardiography in adults: a systematic review and meta-analysis. Int J Cardiovasc Imaging 2022;38:1329–40. https://doi.org/10.1007/s10554-021-02520-9.
[89] Russo C, Jin Z, Homma S, et al. LA phasic volumes and reservoir function in the elderly by real-time 3D echocardiography: normal values, prognostic significance, and clinical correlates. JACC Cardiovasc Imaging 2017;10(9):976–85. https://doi.org/10.1016/j.jcmg.2016.07.015.
[90] Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, et al. Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. J Cardiovasc Magn Reson 2020;22(1):87. https://doi.org/10.1186/s12968-020-00683-3.
[91] Kuchynka P, Podzimkova J, Masek M, et al. The role of magnetic resonance imaging and cardiac computed tomography in the assessment of left atrial anatomy, size, and function. Biomed Res Int 2015;2015:247865. https://doi.org/10.1155/2015/247865.

[92] Gal P, Marrouche NF. Magnetic resonance imaging of atrial fibrosis: redefining atrial fibrillation to a syndrome. Eur Heart J 2017;38(1):14–9. https://doi.org/10.1093/eurheartj/ehv514.
[93] Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA 2014;311(5):498–506. https://doi.org/10.1001/jama.2014.3.
[94] Bisbal F, Benito E, Teis A, et al. Magnetic resonance imaging-guided fibrosis ablation for the treatment of atrial fibrillation: the ALICIA trial. Circ Arrhythm Electrophysiol 2020;13(11):e008707. https://doi.org/10.1161/CIRCEP.120.008707.
[95] Harrison JL, Sohns C, Linton NW, et al. Repeat left atrial catheter ablation: cardiac magnetic resonance prediction of endocardial voltage and gaps in ablation lesion sets. Circ Arrhythm Electrophysiol 2015;8(2):270–8. https://doi.org/10.1161/CIRCEP.114.002066.
[96] Caixal G, Alarcón F, Althoff TF, et al. Accuracy of left atrial fibrosis detection with cardiac magnetic resonance: correlation of late gadolinium enhancement with endocardial voltage and conduction velocity. Europace 2021;23(3):380–8. https://doi.org/10.1093/europace/euaa313.
[97] Boriani G, Vitolo M, Imberti JF. Atrial cardiomyopathy: a derangement in atrial volumes, geometry, function, and pathology with important clinical implications. J Cardiovasc Med (Hagerstown) 2022;23(6):359–62. https://doi.org/10.2459/JCM.0000000000001316.
[98] Tufano A, Lancellotti P. Atrial cardiomyopathy: pathophysiology and clinical implications. Eur J Intern Med 2022;101:29–31. https://doi.org/10.1016/j.ejim.2022.03.007.
[99] Shen MJ, Arora R, Jalife J. Atrial myopathy. JACC Basic Transl Sci 2019;4(5):640–54. https://doi.org/10.1016/j.jacbts.2019.05.005.
[100] Ding WY, Proietti M, Romiti GF, et al. Impact of ABC (atrial fibrillation better care) pathway adherence in high-risk subgroups with atrial fibrillation: a report from the ESC-EHRA EORP-AF long-term general registry. Eur J Intern Med 2022;107:60–5. https://doi.org/10.1016/j.ejim.2022.11.004.
[101] Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. Eur Heart J 2021;42(5):373–498. https://doi.org/10.1093/eurheartj/ehaa612.
[102] Guo Y, Imberti JF, Kotalczyk A, Wang Y, Lip GYH, Investigators CR.. 4S-AF scheme and ABC pathway guided management improves outcomes in atrial fibrillation patients. Eur J Clin Investig 2022;52(6):e13751. https://doi.org/10.1111/eci.13751.
[103] Malavasi VL, Vitolo M, Colella J, et al. Rhythm- or rate-control strategies according to 4S-AF characterization scheme and long-term outcomes in atrial fibrillation patients: the FAMo (Fibrillazione Atriale in Modena) cohort. Intern Emerg Med 2021. https://doi.org/10.1007/s11739-021-02890-x.
[104] Aulin J, Hijazi Z, Lindbäck J, et al. Biomarkers and heart failure events in patients with atrial fibrillation in the ARISTOTLE trial evaluated by a multi-state model. Am Heart J 2022;251:13–24. https://doi.org/10.1016/j.ahj.2022.03.009.
[105] Bonini N, Vitolo M, Imberti JF, et al. Mobile health technology in atrial fibrillation. Expert Rev Med Devices 2022;19(4):327–40. https://doi.org/10.1080/17434440.2022.2070005.
[106] Boriani G, Palmisano P, Malavasi VL, et al. Clinical factors associated with atrial fibrillation detection on single-time point screening using a hand-held single-lead ECG device. J Clin Med 2021;10(4). https://doi.org/10.3390/jcm10040729.
[107] Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370(26):2478–86. https://doi.org/10.1056/NEJMoa1313600.
[108] Boriani G, Bertini M, Manzo M, et al. Performance of a multi-sensor implantable defibrillator algorithm for heart failure monitoring in the presence of atrial fibrillation. Europace 2023;25(9). https://doi.org/10.1093/europace/euad261.
[109] Boriani G, Imberti JF, Bonini N, et al. Remote multiparametric monitoring and management of heart failure patients through cardiac implantable electronic devices. Eur J Intern Med 2023;115:1–9. https://doi.org/10.1016/j.ejim.2023.04.011.
[110] Kirchhof P, Toennis T, Goette A, et al. Anticoagulation with Edoxaban in patients with atrial high-rate episodes. N Engl J Med 2023;389(13):1167–79. https://doi.org/10.1056/NEJMoa2303062.
[111] Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial. Am Heart J 2017;189:137–45. https://doi.org/10.1016/j.ahj.2017.04.008.
[112] Di Tullio MR, Qian M, Thompson JLP, et al. Left atrial volume and cardiovascular outcomes in systolic heart failure: effect of antithrombotic treatment. ESC Heart Fail 2018;5(5):800–8. https://doi.org/10.1002/ehf2.12331.
[113] Longstreth WT, Kronmal RA, Thompson JL, et al. Amino terminal pro-B-type natriuretic peptide, secondary stroke prevention, and choice of antithrombotic therapy. Stroke 2013;44(3):714–9. https://doi.org/10.1161/STROKEAHA.112.675942.
[114] Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378(23):2191–201. https://doi.org/10.1056/NEJMoa1802686.
[115] Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380(20):1906–17. https://doi.org/10.1056/NEJMoa1813959.
[116] Kamel H. et al. Primary results of the atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke (ARCADIA) randomized trial. https://eso-stroke.org/esoc-2023-session-report-official-welcome-and-large-clinical-trials/.