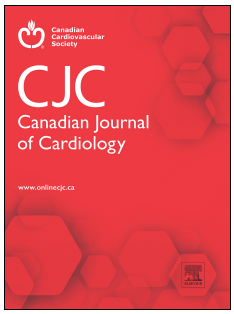
Journal Pre-proof



From atrial fibrillation management to atrial myopathy assessment: the evolving concept of left atrium disease in hypertrophic cardiomyopathy

Carlo Fumagalli, MD, Chiara Zocchi, MD, Michele Ciabatti, MD, Alessandra Milazzo, MD, Francesco Cappelli, MD, PhD, Stefano Fumagalli, MD, PhD, Maurizio Pieroni, MD, PhD, Iacopo Olivotto, MD

PII: S0828-282X(24)00074-6

DOI: https://doi.org/10.1016/j.cjca.2024.01.026

Reference: CJCA 4971

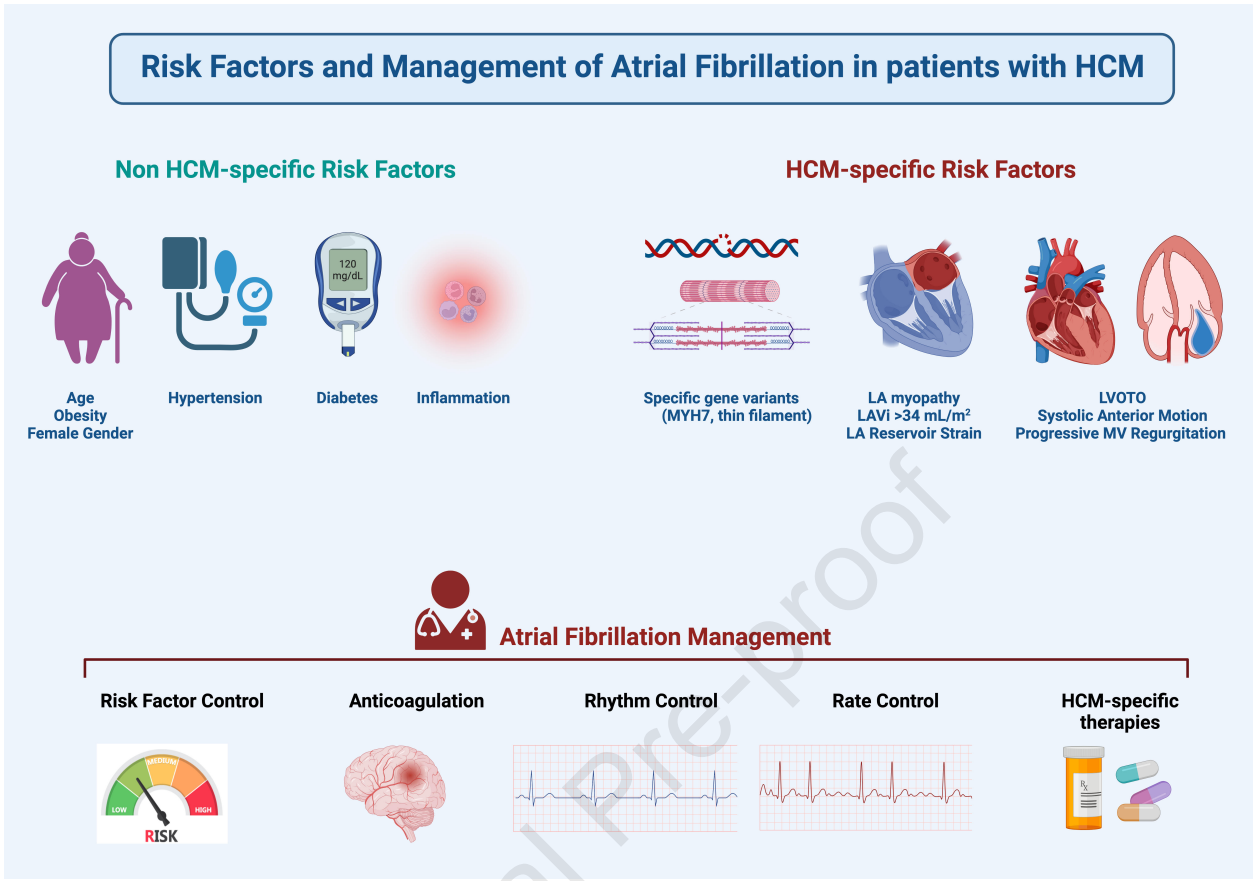
To appear in: *Canadian Journal of Cardiology*

Received Date: 10 December 2023

Revised Date: 21 January 2024

Accepted Date: 23 January 2024

Please cite this article as: Fumagalli C, Zocchi C, Ciabatti M, Milazzo A, Cappelli F, Fumagalli S, Pieroni M, Olivotto I, From atrial fibrillation management to atrial myopathy assessment: the evolving concept of left atrium disease in hypertrophic cardiomyopathy, *Canadian Journal of Cardiology* (2024), doi: https://doi.org/10.1016/j.cjca.2024.01.026.



From atrial fibrillation management to atrial myopathy assessment: the evolving concept of left atrium disease in hypertrophic cardiomyopathy

Short Title: AF and LA myopathy in HCM

Carlo Fumagalli, MD[1,2], Chiara Zocchi, MD[1,3], Michele Ciabatti, MD[3], Alessandra Milazzo, MD[1], Francesco Cappelli, MD, PhD[1], Stefano Fumagalli, MD, PhD[4], Maurizio Pieroni, MD, PhD[3], Iacopo Olivotto, MD[1,5]

Author Affiliations

1. Cardiomyopathy Unit, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
2. Department of Advanced Medical and Surgical Sciences, University of Campania, "Luigi Vanvitelli", Naples, Italy
3. Cardiovascular Department, San Donato Hospital, Arezzo, Italy
4. Geriatric Intensive Care Unit and Geriatric Arrhythmia Unit, Department of Experimental and Clinical Medicine, University of Florence and AOU Careggi, Florence, Italy
5. Meyer Children's Hospital, IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico), Florence, Italy

Word Count: 3505 words

Keywords: atrial myopathy, hypertrophic cardiomyopathy, atrial fibrillation, atrial strain, stroke.

Address for correspondence
Carlo Fumagalli, MD
Cardiomyopathy Unit,
Careggi University Hospital
Department of Experimental and Clinical Medicine,
University of Florence
Largo Brambilla 3, 50134 – Florence, Italy
Tel: +39 055 7945138
e-mail: carlo.fumagalli@unifi.it

Disclosures: Prof. Dr. Iacopo Olivotto is supported by grants for "Respect", "StratifyHF" and "SmashHCM" and has received grants from Bayer, MyoKardia, Inc, which is a wholly owned subsidiary of Bristol Myers Squibb, Sanofi Genzyme, and Shire, which is now part of Takeda; personal fees from Bayer, Sanofi Genzyme, and Shire/Takeda; and payments as a consultant from MyoKardia, Inc.
Funding: No funding was granted for the present article.
Acknowledgements: We also acknowledge Mr. Andrea Tatini for graphical Support.
Patients Consent: The authors confirm that patient consent is not applicable to this article.

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most prevalent genetically inherited cardiovascular disorder in adults and a significant cause of heart failure and sudden cardiac death. Historically, atrial fibrillation (AF) has been considered a critical aspect in HCM patients as it is considered a marker of disease progression, escalates the frequency of heart failure hospitalizations, increases the risk of thromboembolic events and worsens quality of life and outcome. Increasing evidence suggests that AF is the result of a subtle, long-standing process which starts early in the history of HCM. The process of left atrial dilatation accompanied by morpho/functional remodeling, is the quintessential prerequisite for the onset of AF. This review aims to describe the current understanding of AF pathophysiology in HCM, emphasizing the role of left atrial myopathy in its development. Additionally, we discuss risk factors and management strategies specific to AF in the context of HCM, providing insights into the complexities and challenges of treating such specific patient population.

1. Pathophysiology and clinical impact of atrial myopathy and atrial fibrillation in hypertrophic cardiomyopathy

Atrial fibrillation (AF) is the most prevalent sustained supraventricular arrhythmia in patients diagnosed with hypertrophic cardiomyopathy (HCM), with a clinical incidence of 2-4% per year and a prevalence exceeding 20% in several cohorts, far surpassing rates in the general population of similar age[1], [2]. In addition, up to 25% of HCM patients with implantable cardioverter defibrillators (ICD) or cardiac monitors (ICM) exhibit clinically silent, paroxysmal AF episodes[3]–[5]. Nowadays, paralleling an increased awareness of this condition, HCM is often diagnosed at an earlier stage, often before AF develops[6]. This suggests that prolonged exposure to left ventricular (LV) remodeling, diastolic dysfunction, mitral regurgitation, left ventricular outflow tract obstruction (LVOTO) play a significant role in the hemodynamic changes leading to AF [7]–[13] (Fig. 1): accordingly, the prevalence of AF in HCM increases with worsening disease stage, from subclinical to end-stage phenotypes, with a final cumulative incidence >40% among patients with severe LV dysfunction[10].

A precise timeline of the pathophysiology of the left atrium (LA) leading to AF in HCM remains elusive. At a cellular level, myocardial hypertrophy, myocyte disarray, fibrosis, and microvascular dysfunction are known to increase myocardial wall stress in HCM. These factors, together with LVOTO, systolic anterior motion (SAM), mitral regurgitation, and elevated filling pressures may contribute to an increase in LA afterload, leading to adverse remodeling [9], LA enlargement and functional impairment[14](**Figure 1**): in turn, myofibrillar disarray and atrial fibrosis impair interatrial conduction, facilitating ectopic triggers for AF onset[15].

While the exact timeline of LA disease is yet to be determined, the clinical consequences and burden of LA myopathy and AF at long-term have been described. Impaired atrial function, reduction or loss of atrial systole and overt AF significantly impact morbidity and risk of heart failure (HF) and embolic stroke[10]. Patients with HCM and AF experience HF symptoms four to six times more frequently than the general population, leading to increased hospitalization rates, and overall impaired quality of life[10]: recently, AF was shown to be the leading cause of cardiovascular elective and/or acute hospitalizations, accounting for 42% of admissions[16]. Although HCM-specific risk factors for AF and LA myopathy bear important prognostic

relevance, lifestyle and non-modifiable factors should also be acknowledged given their additive effect on the incidence of AF. Among these, obesity and diabetes mellitus have been associated with higher prevalence and incidence of AF[17], [18]. Furthermore, while the prevalence of hypertension in AF patients varies, with some studies showing similar rates among those in sinus rhythm and those with AF[19]–[21], others indicate an increased AF risk in hypertensive individuals[12]. Finally, similar to the general population, age, female gender and HF symptoms are associated with higher incidence of AF at long-term[12]. A novel element is post-operative AF (POAF, typically post myectomy): recent evidence suggests that POAF may be a risk factor for AF at long-term, but not for stroke[22], [23]. In the present document we aim to summarize the determinants of AF in HCM including the potential framework of changes in LA function and structure (i.e. LA myopathy), discussing how these impact clinical management.

2. Risk factors for AF– emerging role of LA myopathy

Female gender, hypertension, aging, increasing LA size and function and a worsening NYHA class are strong predictors of new onset of AF[1], [12]. The time-honored predictor of AF is an increase in LA size (LA antero-posterior diameter or volume), which is also a sensitive and specific marker of disease progression in HCM[24]: reduced values of indexed LA volume (LAVi), especially when <34 ml/m^2 have been associated with an early and mild HCM disease stage and with a low risk of incident AF[25]. Conversely, a LAVi >34 ml/m^2 has been correlated to both AF (with high sensitivity and specificity[26]) and hospitalizations[16]. For this reason, strategies aimed at identifying early markers of worsening LA (and impaired LV coupling) have become an area of active research. In general, the LA and LV are directly connected during ventricular diastole, and, in absence of mitral valve stenosis, their function and filling pressures are coupled. An increase in LA volume relative to that of the LV at end-diastole directly reflects the impairment of LV compliance. Following this concept, the left atrioventricular coupling index (defined as LA end-diastolic volume divided by LV end-diastolic volume) was shown to be independently associated with incident AF after adjustment of common LA dimension parameters, suggesting that early change in LV hemodynamics, compliance and pressure could track early – pre-clinical – functional worsening of LA physiology before overt enlargement[27]. LA function (both expressed as fractional shortening and ejection fraction) predict AF independently of LA size[28], [29].

Consistently, recent evidence suggests that a reduced LA strain (<23.4%) with a normal LA diameter is a relevant predictor of new-onset AF and, broadly, of adverse outcome[15], [30]. Last, in a cohort of 208 patients, the total atrial conduction time (a parameter which has been associated with structural and electrical remodeling), estimated by tissue Doppler imaging, was found to be independently associated with new-onset AF in patients with HCM irrespective of LAVi[31]. For this reason, multiparametric systematic assessment of LA dimension and function should become part of a standardized evaluation to predict arrhythmia onset, even in the absence of other AF risk factors.

Studies focused on cardiac magnetic resonance (CMR) tissue characterization did not find any other powerful structural factor predictors of AF better than LA enlargement or dysfunction[32], [33]. However, it is interesting that the quantitative analysis of LGE in LA correlates with the recurrence of AF after transcatheter ablation[34]. Beyond loading and structural conditions, non-classical factors such as genetic HCM-causing variants and disease modifiers may play a pivotal role in increasing AF incidence. A study from our group did not identify any reliable relation between HCM genotype and likelihood of AF, which seemed rather driver by hemodynamic determinants[35]. However, recent evidence demonstrated that the incidence of AF in HCM with sarcomeric mutation was as high as 19% and that the presence of a pathogenic variant in MYH7 increased the risk of early AF development, regardless of echocardiographic and clinical parameters[36]. Furthermore, in adult HCM patients, thin-filament mutations are associated with increased likelihood of advanced LV dysfunction and heart failure compared with thick-filament disease: triphasic LV filling is particularly common in thin-filament HCM, reflecting profound diastolic dysfunction potentially predisposing to LA remodeling and incident AF[37]. Finally, Orenes-Pinero et al. showed that non-sarcomeric gene mutations involved in the renin-angiotensin-aldosterone pathway are independent predictors of AF development and should be regarded as potential HCM phenotype modifiers[38].

Considering the importance and clinical relevance of an early diagnosis of AF, the European Guidelines indicate a close ambulatory ECG monitoring in HCM patients with LA diameter >45 mm[39]. Several attempts to develop a clinical risk stratification algorithm to predict AF occurrence in this population have been proposed. Recently, a clinical predictive model for stratifying AF risk at 5 years (the HCM-AF Risk score) has been validated in a large cohort of

HCM patients. Starting from factors associated with AF in the general population (CHARGE-AF, C_2HEST and CHA_2DS_2-VASc), a list of variables was selected and later validated (LA diameter, age, age at HCM diagnosis, HF symptoms) with an overall better predictive performance when compared to CHA_2DS_2-VASc. Within this algorithm, patients are categorized in three risk groups (low, intermediate and high) to develop AF within the proceeding 5 years[40]. Ultimately, when patients are considered at high risk of AF, a multistep strategy involving rhythm monitoring (regular 48h ECG Holter recordings, implantable cardiac monitors, wearable monitors [e.g. Kardia, Apple Watch etc.]) and active engagement educating on the signs and symptoms of AF, is warranted.

Additional electroanatomical substrates of AF are plausible in HCM, but poorly known. For example, HCM patients with AF exhibit a shorter refractory period and increased repolarization dispersion [41]. Clinically, a P-wave duration exceeding 140ms is a likely indicator of AF development [42]. Electroanatomical mapping has revealed that HCM patients with AF tend to have more extensive low voltage areas in the LA compared to the general AF population. Specifically, a low voltage area exceeding 14.1% of the total LA section significantly predicts AF recurrence with high sensitivity and specificity[43].

3. The evolving concept of LA myopathy in HCM patients: implications for a fine-tuned multimodal evaluation

Timely detection of LA remodeling remains a goal of HCM management to reduce AF burden, improve HF symptoms, and prevent embolic stroke[39], [44].

Adverse LA remodeling, defined as LA enlargement coupled with systolic dysfunction, is the strongest echocardiographic predictor of AF and adverse outcome. It can be attributed to both genetic and epigenetic factors, irrespective of pre-existing loading conditions[14]. Furthermore, there is growing evidence suggesting that an increased inflammatory status can trigger AF onset in the general population and is likely to occur also in HCM[45], [46]. These changes in atrial structure and function result in blood stasis, endothelial and endocardial dysfunction, triggering Virchow's triad, even in the presence of stable sinus rhythm (SR)[47]–[49]. Thus, several studies

emphasize the importance of analyzing LA function in detail, irrespective of the underlying rhythm[12], [14], [25].

Echocardiographic parameters such as LA antero-posterior dimension, fractional shortening, biplane maximal LA volume, and LA end-diastolic volume are effective in evaluating LA enlargement and predicting new AF onset [12], [14], [25]. Speckle-tracking analysis (ST) is a valuable tool for early identification of patients at higher risk of AF and early sign of LA dysfunction, even when LA size is preserved. Both a decrease in LA global wall deformation and impairment in the three functional phases of the LA emptying (reservoir, conduit and booster function– **Figure 2**) are strong predictors of new AF onset and its recurrence post-ablation[50], [51]. Contrary to expectations, the most critical phase affecting HCM patients at risk of new AF is a reduction in reservoir ST strain during left ventricular systole[50], [52]. HCM patients with a global LA strain <23.4% and/or a reservoir strain below 20% are particularly susceptible to developing AF, regardless of LA dimension [25], [52]. In a recent report of 241 patients in stable sinus rhythm referred to cardiopulmonary exercise testing, LA myopathy was associated with worse exercise capacity and reduced ventilatory efficiency: in particular, LA reservoir strain was the only common predictor of %peakVO2 and VE/VCO2 slope[53].

Cardiac magnetic resonance (CMR) evaluates LA function by measuring wall deformation using feature tracking and is considered highly accurate and reproducible[54]. A large meta-analysis found that an increase in LA fibrosis is a significant predictor of AF and its recurrence after catheter ablation[34], [55]. Furthermore, a novel non-invasive CMR technique, 4-dimensional (4D) flow, was superior to transesophageal echocardiography in detecting atrial blood velocity dynamics, offering insights into LA stasis and thrombus formation [43].

Fostering the concept of a latent and intrinsic LA myopathy in HCM is the lack of a strong association of LAVI with LA pressure measured during cardiac catheterization (R<0.25)[56]: while a normal LAVI is suggestive of normal ventricular filling pressures in HCM, increased volumes may reflect only in part diastolic dysfunction and LV pressure.

LA dysfunction may be detectable in preclinical HCM mutation carriers by CMR despite normal LV wall thickness and LA volume[57]: although LA volumes were similar between preclinical, controls and overt HCM cohorts, LA function was impaired – with decreased LA total emptying function – in both preclinical and overt HCM, compared with controls, with overt HCM patients with LV fibrosis showing the worst performance[57].

Finally, LA myopathy and arrhythmogenesis may be a primary process occurring irrespective of LV hypertrophy: as a case in point, 47% of those with the β–cardiac myosin heavy chain missense mutation Arg663His developed AF during 7 years of follow up – a significantly higher incidence than any other HCM cohorts. Furthermore, a missense sequence variant in the gene encoding the α-actinin 2 protein (ACTN2) was associated with familial mid-apical HCM and juvenile onset of AF[58]. Notably onset of arrhythmia and atrial enlargement preceded any evidence of diastolic dysfunction, indicating an arrhythmic atrial process may not always be secondary to abnormal hemodynamics. Overall, this body of evidence suggest that LA myopathy is a decisive element contributing to HCM progression, generally mediated by AF. Whether, and to what extent, early identification of this component and disease-modifying therapy initiation may help improve the natural history of the LA and reduce risk of embolic events is currently unresolved (**Figure 3**).

4. Management of AF in patients with HCM

Anticoagulation

Management of AF in patients with HCM should follow recommendations from the ABC pathway proposed by the European Society of Cardiology Guidelines on AF and the recent guidelines for cardiomyopathies[59], [60]. Given the high thromboembolic risk linked to AF, patients should be referred to anticoagulation irrespective of age or CHA_2DS_2-VASc [61] (Class I B). Although vitamin K antagonists or direct oral anticoagulants are equally effective for thromboprophylaxis, the latter maintain a better safety profile and increased tolerability and are thus the preferred option – unless contraindicated[62], [63]. The role of LA appendage closure is unknown in HCM.

Recent research highlighted that incidence of ischemic stroke in patients with HCM and LA dilatation >48mm might be similar among patients both in sinus rhythm and with AF[4], which raises the compelling doubt whether patients with extreme LA remodeling and dysfunction should receive prophylactic anticoagulation even when in sinus rhythm.

This phenomenon of electro-mechanical dissociation in the LA has been observed in various clinical scenarios and is a characteristic shared by other cardiomyopathies exhibiting hypertrophic features, such as Fabry disease and cardiac amyloidosis[48], [64]. In cases of cardiac amyloidosis, there is a well-documented occurrence of atrial thrombi even in patients maintaining sinus rhythm. This is believed to result from the combined impact of changed atrial hemodynamics and the

disruption of the endomyocardium by amyloid deposits. Advanced strain imaging techniques could potentially offer a more nuanced assessment of left atrial morphology and functionality, aiding in the stratification of embolic risk associated with left atrial remodeling prior to the onset of atrial fibrillation. Additionally, certain morphologies of the left atrial appendage are known to correlate with an increased likelihood of thromboembolic events. However, the frequency of these morphologies as a potential manifestation of the HCM phenotype remains unexplored. [65].

Rhythm control

Anti-arrhythmic drug therapy

Contribution of atrial systole during LV filling is usually increased in patients with HCM compared to controls, both in obstructive and non-obstructive forms[66]. Therefore, acute AF onset can determine severe symptoms and hemodynamic deterioration, especially in the presence of high ventricular rates. Multiple studies have shown that AF is associated with severe outcomes in terms of HF and thromboembolic events in HCM patients and may accelerate disease progression[9], [67]–[69]. Due to these peculiar hemodynamic characteristics, sinus rhythm maintenance represents an important therapeutic goal. However, current antiarrhythmic therapy presents significant limitations in terms of efficacy and safety.

Adequate rhythm control can be obtained only in a minority of subjects undergoing antiarrhythmic treatment (42% at 3 years of follow-up)[70]. Amiodarone is generally safe in the HCM population, and may reduce arrhythmic burden[70], [71]. Pathological prolongation of the QT interval is rare and pro-arrhythmogenicity is very limited[70]. However, long-term treatment can determine liver, thyroid and pulmonary toxicity leading to worse prognosis and drug discontinuation [70]. These elements are particularly important in this clinical setting since most patients affected by HCM present long-life expectancies.

Disopyramide is an old class IA antiarrhythmic drug, commonly used for left ventricular outflow tract obstruction (LVOTO) reduction in HCM patients[71]. Disopyramide represent a reasonable fist line choice for rhythm control, although its overall efficacy is modest (35% after 3 years) and tachyphylaxis could further reduce its anti-arrhythmic long-term power [70]. Data from clinical and translational research demonstrated that disopyramide determines only a slight increase in QT interval in patients with baseline QT elevation due its combined effects on sodium, calcium, and potassium currents[72]. These properties could potentially explain the low risk of drug-induced

VT in HCM. However, a significant proportion of patients undergoing this treatment necessitate discontinuing the drug due its anticholinergic effects.

Type 1C antiarrhythmic molecules (such as flecainide and propafenone) are widely used in the general population for treating AF. A small observational study showed a good safety profile in obstructive HCM patients undergoing flecainide therapy with moderate improvement of obstruction and symptomatic status[73]. The authors did not report any data regarding efficacy in suppressing atrial or ventricular arrhythmias and the limited sample size did not permit drawing any definite conclusion from this cohort. At present, however, treatment with these drugs is generally confined to HCM patients who have an ICD.

Sotalol, a beta-blocker with class III antiarrhythmic properties, can be used for rhythm control but efficacy is low (effective rhythm control in 50% of cases after 3 years) [70]. QT interval should be routinely checked to prevent polymorphic ventricular tachycardia (VT) or torsade de pointes onset and excessive bradycardia could potentially limit its use and titration.

Finally, data regarding the use of dofetilide in patients with HCM is limited[70], [74]. Some authors reported increased QT interval in 12% of HCM patients treated with this drug[74], but high-quality evidence on safety and efficacy is currently lacking.

Invasive rhythm control strategies

Transcatheter ablation is a more effective rhythm control strategy than antiarrhythmic therapy in the general population[75]. However, HCM presents many peculiar features portending an increased risk of AF recurrences due to the presence of mitral regurgitation, LVOTO, diastolic dysfunction and atrial myopathy[28], [32], [60], [76]. Freedom from AF recurrences after single catheter ablation is approximately 40% at 3-5 years [43], [77]–[85]. In case of multiple procedures, higher success rates (52%) can be achieved[84], [85]. It is to note that the ablation success rate vary critically depending on the timing and modality of follow-up (Holter ECG, external or implantable loop recorder). However, even in patients with AF recurrences, ablation is often associated with significant symptomatic improvement[85].

Catheter ablation is more effective in subjects who are younger, less symptomatic, with lesser degrees of atrial remodeling and in those presenting with paroxysmal rather than persistent AF[84]. However, antiarrhythmic therapy continuation is commonly required after ablation to reduce AF recurrences. Notably, studies performed over the last 15 years present wide heterogeneity in terms

of patient selection, concomitant drug therapy and procedural techniques. Creta et al reported comparable efficacy between cryoablation and radiofrequency techniques[82]. Some groups performed different ablation procedures based upon AF subtype and substrate characteristics[78], [79], [83]. Usually, standard pulmonary vein isolation (PVI)-only is performed in patients with paroxysmal AF. Non-PV triggers are typically targeted in case of persistent AF or extensive pathological atrial substrate. Linear ablations in the posterior wall, the roof and the mitral isthmus line can be performed to improve the success rate of the procedure. Moreover, homogenization of complex fractionated atrial electrocardiogram can be pursued, but it could increase the complexity of the ablation[79]. Targeting the cavotricuspid isthmus is common practice in case of concomitant atrial flutter. In general, LA size, increased QT intervals, presence of fragmented QRS complexes (**Figure 4**), diastolic dysfunction, extension of pathological mapping substrate, presence of apical aneurysms and persistent AF have been associated with AF recurrences[43], [81]–[83], [86]. Pericardial effusions, pulmonary vein stenosis, atrial tachycardias and vascular access-related complications can occur after the procedure. For these reasons, catheter ablation and invasive strategies should be tailored to the patients to maximize efficacy, increase benefits, and reduce the onset of potential unnecessary complications.

Surgical ablation is a feasible option in HCM patients undergoing septal myectomy[87], [88]. Surgeons can perform classical PVI and additional lesions addressing the left atrial appendage, the mitral isthmus and the roof and floor segments. Biatrial Maze procedure (Maze IV) can be safely done in the presence of right atrial dilation or significant tricuspid regurgitation[87]. After surgery, 75-80% of patients have been shown to be free from AF recurrences at follow-up [87], [88]. However, it might be difficult to discern the additional impact of Maze procedure over LVOTO reduction alone, due to its important impact on the atrial substrate. Of note, advanced atrioventricular blocks requiring pacemaker implantation occur in 3-4% of cases [87], [88] similar to historical data reported when performing myectomy alone[89].

Rate control

Beta-blockers and nondihydropyridine calcium antagonists are widely used in HCM patients, especially for treating LVOTO, and can represent effective rate-control treatments[60], [71]. Calcium channel blockers should be generally avoided in case of overt LV dysfunction (left

ventricular ejection fraction, LVEF<50%)[71]. Digoxin could potentially increase LVOTO and its use should be limited to selected cases refractory to conventional therapies.

An ablate-and-pace strategy represents an attractive option in patients presenting high-rate AF unresponsive to rate-control treatments or suffering multiple ICD inappropriate shocks [90]. Butcher et al. described a significant symptomatic improvement with this strategy in patients with HCM and AF refractory to conventional therapy [90]. Notably, they did not report any significant difference in LVEF at follow-up between subjects undergoing conventional therapy or cardiac resynchronization. The complication rate was 3.4%, mainly related to the implanted device (lead fracture and device infection). However, the impact of device-related complications in the long term should be cautiously evaluated, especially in case of young subjects with long life expectancy.

Potential role of cardiac myosin inhibitors

The development of disease-modifying therapies, such as myosin inhibitors (mavacamten and aficamten), represent a very promising option for HCM patients [60], [91], [92] showing substantial hemodynamic and clinical improvement in both obstructive and non-obstructive HCM [93]–[95]. Although a 30-day analysis on a small patient cohort on mavacamten showed a reduction in left atrial function suggesting or potential facilitating effect of AF development [96], a CMR substudy of the EXPLORER-HCM trial showed a significant reduction of LV mass and left atrial volume indexes in patients undergoing mavacamten treatment at long-term [97]. Similar results were obtained via ultrasound studies[98]. Therefore, it is reasonable to postulate that long-term treatment with myosin inhibitors might prevent severe LA remodeling and ultimately reduce AF burden in the long term. Further studies based on real-world experience will hopefully resolve this issue.

5. Conclusions

AF is the predominant arrhythmia observed in patients with HCM. The development of AF in these patients is often a consequence of left atrial myopathy, which encompasses structural and functional impairments of the LA. This myopathy, alongside factors such as increased left ventricular filling pressures, the occurrence of mitral regurgitation and systolic anterior motion (SAM), as well as genetic predisposition, contributes to left atrial dilatation and fibrosis. These

changes compromise both the mechanical and electrical integrity of the left atrium, predisposing patients to AF. Given the elevated risk of stroke in this patient group, irrespectively to CHA_2DS_2-VASc score, lifelong anticoagulation becomes a necessity, with DOAC being the preferred choice. While catheter ablation or the surgical maze procedure present effective alternatives to antiarrhythmic drug treatment in managing AF, the most favorable outcomes are often achieved through a combination of therapeutic strategies. This integrated approach is particularly significant in the context of managing the complex interplay of left atrial myopathy and arrhythmia in HCM. Future research will help determine whether myosin modulators will be able to reduce the degree of LA myopathy and incidence of AF at long term.

Figure Legends

Figure 1. Spectrum of left atrial myopathy in patients with hypertrophic cardiomyopathy. **AF**: Atrial Fibrillation; **HCM**: Hypertrophic Cardiomyopathy; **LA**: left atrium; **LACI**: left atrioventricular coupling index; **LV**: left ventricle. The HCM diagram was adapted from BioRender.com.

Figure 2. A 4-chamber echocardiographic image of LA strain through the three different phases (reservoir, conduit and booster) in a 45-year old male patient affected by HCM (measurements by EchoPAC, GE healthcare). Despite a slight enlargement of LAVi (36 ml/mq), LA reservoir phase is significantly reduced (13,8%) in this subject, giving an insights into LA myopathy.

Figure 3. Relationship between atrial fibrillation, left atrial myopathy and stroke.

Figure 4. Electrocardiogram with QRS fragmentation of a man diagnosed with HCM in his late 40s, with a previous diagnosis paroxysmal atrial fibrillation who experienced recurrent episodes of arrhythmia.

References

[1] O. P. Guttmann, M. S. Rahman, C. O'Mahony, A. Anastasakis, and P. M. Elliott, 'Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review', *Heart*, vol. 100, no. 6, pp. 465–472, Mar. 2014, doi: 10.1136/heartjnl-2013-304276.

[2] C. Y. Ho *et al.*, 'Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy', *Circulation*, vol. 138, no. 14, pp. 1387–1398, Oct. 2018, doi: 10.1161/CIRCULATIONAHA.117.033200.

[3] E. J. Rowin *et al.*, 'Occurrence and Natural History of Clinically Silent Episodes of Atrial Fibrillation in Hypertrophic Cardiomyopathy', *Am J Cardiol*, vol. 119, no. 11, pp. 1862–1865, Jun. 2017, doi: 10.1016/j.amjcard.2017.02.040.

[4] C. Fumagalli *et al.*, 'Incidence of stroke in patients with hypertrophic cardiomyopathy in stable sinus rhythm during long-term monitoring', *Int J Cardiol*, vol. 381, pp. 70–75, Jun. 2023, doi: 10.1016/j.ijcard.2023.04.008.

[5] H. G. van Velzen, D. A. M. J. Theuns, S. C. Yap, M. Michels, and A. F. L. Schinkel, 'Incidence of Device-Detected Atrial Fibrillation and Long-Term Outcomes in Patients With Hypertrophic Cardiomyopathy', *Am J Cardiol*, vol. 119, no. 1, pp. 100–105, Jan. 2017, doi: 10.1016/J.AMJCARD.2016.08.092.

[6] M. Canepa *et al.*, 'Temporal Trend of Age at Diagnosis in Hypertrophic Cardiomyopathy: An Analysis of the International Sarcomeric Human Cardiomyopathy Registry', *Circ Heart Fail*, vol. 13, no. 9, pp. 376–381, 2020, doi: 10.1161/CIRCHEARTFAILURE.120.007230.

[7] C. R. Vissing *et al.*, 'Cardiac Remodeling in Subclinical Hypertrophic Cardiomyopathy', *JAMA Cardiol*, vol. 8, no. 11, p. 1083, Nov. 2023, doi: 10.1001/jamacardio.2023.2808.

[8] I. Olivotto, F. Cecchi, C. Poggesi, and M. H. Yacoub, 'Patterns of Disease Progression in Hypertrophic Cardiomyopathy', *Circ Heart Fail*, vol. 5, no. 4, pp. 535–546, Jul. 2012, doi: 10.1161/CIRCHEARTFAILURE.112.967026.

[9] I. Olivotto, F. Cecchi, S. A. Casey, A. Dolara, J. H. Traverse, and B. J. Maron, 'Impact of Atrial Fibrillation on the Clinical Course of Hypertrophic Cardiomyopathy', *Circulation*, vol. 104, no. 21, pp. 2517–2524, Nov. 2001, doi: 10.1161/hc4601.097997.

[10] E. J. Rowin *et al.*, 'Clinical Profile and Consequences of Atrial Fibrillation in Hypertrophic Cardiomyopathy', *Circulation*, vol. 136, no. 25, pp. 2420–2436, 2017, doi: 10.1161/CIRCULATIONAHA.117.029267.

[11] P. Marstrand *et al.*, 'Hypertrophic Cardiomyopathy With Left Ventricular Systolic Dysfunction', *Circulation*, vol. 141, no. 17, pp. 1371–1383, Apr. 2020, doi: 10.1161/CIRCULATIONAHA.119.044366.

[12] O. P. Guttmann *et al.*, 'Predictors of atrial fibrillation in hypertrophic cardiomyopathy', *Heart*, vol. 103, no. 9, pp. 672–678, May 2017, doi: 10.1136/heartjnl-2016-309672.

[13] L. Cavigli *et al.*, 'Timing of invasive septal reduction therapies and outcome of patients with obstructive hypertrophic cardiomyopathy', *Int J Cardiol*, vol. 273, pp. 155–161, Dec. 2018, doi: 10.1016/j.ijcard.2018.09.004.

[14] M. J. Shen, R. Arora, and J. Jalife, 'Atrial Myopathy', *JACC Basic Transl Sci*, vol. 4, no. 5, pp. 640–654, Sep. 2019, doi: 10.1016/j.jacbts.2019.05.005.

[15] Z. Starek *et al.*, 'Baseline left atrial low-voltage area predicts recurrence after pulmonary vein isolation: WAVE-MAP AF results', *Europace*, vol. 25, no. 9, Aug. 2023, doi: 10.1093/europace/euad194.
[16] M. Ciabatti *et al.*, 'Prevalence, causes and predictors of cardiovascular hospitalization in patients with hypertrophic cardiomyopathy', *Int J Cardiol*, vol. 318, pp. 94–100, Nov. 2020, doi: 10.1016/j.ijcard.2020.07.036.
[17] C. Fumagalli *et al.*, 'Association of Obesity With Adverse Long-term Outcomes in Hypertrophic Cardiomyopathy', *JAMA Cardiol*, p. 1, Nov. 2019, doi: 10.1001/jamacardio.2019.4268.
[18] Y. Wasserstrum *et al.*, 'The impact of diabetes mellitus on the clinical phenotype of hypertrophic cardiomyopathy', *Eur Heart J*, vol. 40, no. 21, pp. 1671–1677, Jun. 2019, doi: 10.1093/eurheartj/ehy625.
[19] R. T. Carrick *et al.*, 'Development and Validation of a Clinical Predictive Model for Identifying Hypertrophic Cardiomyopathy Patients at Risk for Atrial Fibrillation: The HCM-AF Score', *Circ Arrhythm Electrophysiol*, vol. 14, no. 6, Jun. 2021, doi: 10.1161/CIRCEP.120.009796.
[20] F. Aslam, A. Haque, J. Foody, and J. Shirani, 'The Frequency and Functional Impact of Overlapping Hypertension on Hypertrophic Cardiomyopathy: A Single-Center Experience', *The Journal of Clinical Hypertension*, vol. 12, no. 4, pp. 240–245, Apr. 2010, doi: 10.1111/j.1751-7176.2009.00251.x.
[21] Q. Luo, J. Chen, T. Zhang, X. Tang, and B. Yu, 'Retrospective analysis of clinical phenotype and prognosis of hypertrophic cardiomyopathy complicated with hypertension', *Sci Rep*, vol. 10, no. 1, p. 349, Jan. 2020, doi: 10.1038/s41598-019-57230-z.
[22] R. Bataiosu *et al.*, 'Clinical Significance of Postoperative Atrial Fibrillation in Hypertrophic Cardiomyopathy Patients Undergoing Septal Myectomy', *Canadian Journal of Cardiology*, vol. 39, no. 12, pp. 1931–1937, Dec. 2023, doi: 10.1016/j.cjca.2023.06.415.
[23] M. Aguilar, 'Should We Be Looking at the Forest or the Trees? Postoperative Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy', *Canadian Journal of Cardiology*, vol. 39, no. 12, pp. 1938–1940, Dec. 2023, doi: 10.1016/j.cjca.2023.09.029.
[24] M. A. Losi *et al.*, 'Prediction of incident atrial fibrillation in hypertrophic cardiomyopathy', *Int J Cardiol*, vol. 395, p. 131575, Jan. 2024, doi: 10.1016/j.ijcard.2023.131575.
[25] P. Debonnaire *et al.*, 'Left Atrial Size and Function in Hypertrophic Cardiomyopathy Patients and Risk of New-Onset Atrial Fibrillation', *Circ Arrhythm Electrophysiol*, vol. 10, no. 2, Feb. 2017, doi: 10.1161/CIRCEP.116.004052.
[26] T. Tani *et al.*, 'Left atrial volume and the risk of paroxysmal atrial fibrillation in patients with hypertrophic cardiomyopathy', *Journal of the American Society of Echocardiography*, vol. 17, no. 6, pp. 644–648, Jun. 2004, doi: 10.1016/j.echo.2004.02.010.
[27] M. C. Meucci *et al.*, 'Left atrioventricular coupling index in hypertrophic cardiomyopathy and risk of new-onset atrial fibrillation', *Int J Cardiol*, vol. 363, pp. 87–93, Sep. 2022, doi: 10.1016/j.ijcard.2022.06.017.
[28] K. C. Siontis, J. B. Geske, K. Ong, R. A. Nishimura, S. R. Ommen, and B. J. Gersh, 'Atrial Fibrillation in Hypertrophic Cardiomyopathy: Prevalence, Clinical Correlations, and Mortality in a Large High-Risk Population', *J Am Heart Assoc*, vol. 3, no. 3, May 2014, doi: 10.1161/JAHA.114.001002.
[29] M.-A. Losi *et al.*, 'Determinants of atrial fibrillation development in patients with hypertrophic cardiomyopathy', *Am J Cardiol*, vol. 94, no. 7, pp. 895–900, Oct. 2004, doi: 10.1016/j.amjcard.2004.06.024.

[30] B. Essayagh *et al.*, 'Left atrial dysfunction as marker of poor outcome in patients with hypertrophic cardiomyopathy', *Arch Cardiovasc Dis*, vol. 114, no. 2, pp. 96–104, Feb. 2021, doi: 10.1016/j.acvd.2020.06.004.

[31] C. Tjahjadi *et al.*, 'Assessment of left atrial electro-mechanical delay to predict atrial fibrillation in hypertrophic cardiomyopathy', *Eur Heart J Cardiovasc Imaging*, vol. 22, no. 5, pp. 589–596, Apr. 2021, doi: 10.1093/ehjci/jeaa174.

[32] S. Sivalokanathan *et al.*, 'Hypertrophic Cardiomyopathy Patients With Paroxysmal Atrial Fibrillation Have a High Burden of Left Atrial Fibrosis by Cardiac Magnetic Resonance Imaging', *JACC Clin Electrophysiol*, vol. 5, no. 3, pp. 364–375, Mar. 2019, doi: 10.1016/j.jacep.2018.10.016.

[33] S. S. Kuppahally *et al.*, 'Left Atrial Strain and Strain Rate in Patients With Paroxysmal and Persistent Atrial Fibrillation', *Circ Cardiovasc Imaging*, vol. 3, no. 3, pp. 231–239, May 2010, doi: 10.1161/CIRCIMAGING.109.865683.

[34] K. Ghafouri, K. B. Franke, F. S. Foo, and M. K. Stiles, 'Clinical utility of cardiac magnetic resonance imaging to assess the left atrium before catheter ablation for atrial fibrillation - A systematic review and meta-analysis', *Int J Cardiol*, vol. 339, pp. 192–202, Sep. 2021, doi: 10.1016/j.ijcard.2021.07.030.

[35] C. Bongini *et al.*, 'Impact of Genotype on the Occurrence of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy', *Am J Cardiol*, vol. 117, no. 7, pp. 1151–1159, Apr. 2016, doi: 10.1016/j.amjcard.2015.12.058.

[36] S.-P. Lee *et al.*, 'Incident Atrial Fibrillation Is Associated With *MYH7* Sarcomeric Gene Variation in Hypertrophic Cardiomyopathy', *Circ Heart Fail*, vol. 11, no. 9, Sep. 2018, doi: 10.1161/CIRCHEARTFAILURE.118.005191.

[37] R. Coppini *et al.*, 'Clinical Phenotype and Outcome of Hypertrophic Cardiomyopathy Associated With Thin-Filament Gene Mutations', *J Am Coll Cardiol*, vol. 64, no. 24, pp. 2589–2600, Dec. 2014, doi: 10.1016/j.jacc.2014.09.059.

[38] E. Orenes-Pinero *et al.*, 'Prognostic value of two polymorphisms in non-sarcomeric genes for the development of atrial fibrillation in patients with hypertrophic cardiomyopathy', *QJM*, vol. 107, no. 8, pp. 613–621, Aug. 2014, doi: 10.1093/qjmed/hcu046.

[39] '2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy', *Eur Heart J*, vol. 35, no. 39, pp. 2733–2779, Oct. 2014, doi: 10.1093/eurheartj/ehu284.

[40] R. T. Carrick *et al.*, 'Development and Validation of a Clinical Predictive Model for Identifying Hypertrophic Cardiomyopathy Patients at Risk for Atrial Fibrillation: The HCM-AF Score', *Circ Arrhythm Electrophysiol*, vol. 14, no. 6, Jun. 2021, doi: 10.1161/CIRCEP.120.009796.

[41] R. Providencia *et al.*, 'Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis', *Heart*, vol. 102, no. 19, pp. 1533–1543, Oct. 2016, doi: 10.1136/heartjnl-2016-309406.

[42] F. Cecchi, A. Montereggi, I. Olivotto, P. Marconi, A. Dolara, and B. J. Maron, 'Risk for atrial fibrillation in patients with hypertrophic cardiomyopathy assessed by signal averaged P wave duration.', *Heart*, vol. 78, no. 1, pp. 44–49, Jul. 1997, doi: 10.1136/hrt.78.1.44.

[43] M. Efremidis *et al.*, 'Atrial substrate characterization in patients with atrial fibrillation and hypertrophic cardiomyopathy: Evidence for an extensive fibrotic disease', *J Electrocardiol*, vol. 69, pp. 87–92, Nov. 2021, doi: 10.1016/j.jelectrocard.2021.06.001.

[44] D. J. Philipson, F. Rader, and R. J. Siegel, 'Risk factors for atrial fibrillation in hypertrophic cardiomyopathy', *Eur J Prev Cardiol*, vol. 28, no. 6, pp. 658–665, May 2021, doi: 10.1177/2047487319828474.

[45] Y. Guo, G. Y. H. Lip, and S. Apostolakis, 'Inflammation in Atrial Fibrillation', *J Am Coll Cardiol*, vol. 60, no. 22, pp. 2263–2270, Dec. 2012, doi: 10.1016/j.jacc.2012.04.063.

[46] L. Liu *et al.*, 'Associations Between Multiple Circulating Biomarkers and the Presence of Atrial Fibrillation in Hypertrophic Cardiomyopathy with or Without Left Ventricular Outflow Tract Obstruction', *Int Heart J*, vol. 60, no. 2, pp. 327–335, Mar. 2019, doi: 10.1536/ihj.18-438.

[47] T. Watson, E. Shantsila, and G. Y. Lip, 'Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited', *The Lancet*, vol. 373, no. 9658, pp. 155–166, Jan. 2009, doi: 10.1016/S0140-6736(09)60040-4.

[48] A. Bernardini *et al.*, 'Atrial Dysfunction Assessed by Cardiac Magnetic Resonance as an Early Marker of Fabry Cardiomyopathy', *JACC Cardiovasc Imaging*, vol. 13, no. 10, pp. 2262–2264, Oct. 2020, doi: 10.1016/j.jcmg.2020.05.011.

[49] F. Cappelli *et al.*, 'Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation', *Amyloid*, vol. 28, no. 1, pp. 12–18, Jan. 2021, doi: 10.1080/13506129.2020.1798922.

[50] H. R. Khan *et al.*, 'Left Atrial Function Predicts Atrial Arrhythmia Recurrence Following Ablation of Long-Standing Persistent Atrial Fibrillation', *Circ Cardiovasc Imaging*, vol. 16, no. 6, Jun. 2023, doi: 10.1161/CIRCIMAGING.123.015352.

[51] B. Raman *et al.*, 'Incremental value of left atrial booster and reservoir strain in predicting atrial fibrillation in patients with hypertrophic cardiomyopathy: a cardiovascular magnetic resonance study', *Journal of Cardiovascular Magnetic Resonance*, vol. 23, no. 1, p. 109, Dec. 2021, doi: 10.1186/s12968-021-00793-6.

[52] T. Zegkos *et al.*, 'The predictive value of left ventricular and left atrial mechanics for atrial fibrillation and heart failure in hypertrophic cardiomyopathy: a prospective cohort study', *Int J Cardiovasc Imaging*, vol. 37, no. 9, pp. 2679–2690, Sep. 2021, doi: 10.1007/s10554-021-02232-0.

[53] T. Zegkos *et al.*, 'Left Atrial Myopathy is Associated With Exercise Incapacity and Ventilatory Inefficiency in Hypertrophic Cardiomyopathy', *Heart Lung Circ*, vol. 32, no. 2, pp. 215–223, Feb. 2023, doi: 10.1016/j.hlc.2022.10.002.

[54] V. T. Truong *et al.*, 'Normal left atrial strain and strain rate using cardiac magnetic resonance feature tracking in healthy volunteers', *Eur Heart J Cardiovasc Imaging*, Jun. 2019, doi: 10.1093/ehjci/jez157.

[55] M. Markl, D. C. Lee, J. Ng, M. Carr, J. Carr, and J. J. Goldberger, 'Left Atrial 4-Dimensional Flow Magnetic Resonance Imaging', *Invest Radiol*, vol. 51, no. 3, pp. 147–154, Mar. 2016, doi: 10.1097/RLI.0000000000000219.

[56] J. B. Geske, P. Sorajja, R. A. Nishimura, and S. R. Ommen, 'The Relationship of Left Atrial Volume and Left Atrial Pressure in Patients With Hypertrophic Cardiomyopathy: An Echocardiographic and Cardiac Catheterization Study', *Journal of the American Society of Echocardiography*, vol. 22, no. 8, pp. 961–966, Aug. 2009, doi: 10.1016/j.echo.2009.05.003.

[57] H. Farhad *et al.*, 'Left Atrial structure and function in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy', *Journal of Cardiovascular Magnetic Resonance*, vol. 19, no. 1, p. 107, Dec. 2017, doi: 10.1186/s12968-017-0420-0.

[58] F. Girolami *et al.*, 'Novel α-Actinin 2 Variant Associated With Familial Hypertrophic Cardiomyopathy and Juvenile Atrial Arrhythmias', *Circ Cardiovasc Genet*, vol. 7, no. 6, pp. 741–750, Dec. 2014, doi: 10.1161/CIRCGENETICS.113.000486.

[59] G. Hindricks *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)', *Eur Heart J*, vol. 42, no. 5, pp. 373–498, Feb. 2021, doi: 10.1093/eurheartj/ehaa612.

[60] E. Arbelo *et al.*, '2023 ESC Guidelines for the management of cardiomyopathies', *Eur Heart J*, vol. 44, no. 37, pp. 3503–3626, Oct. 2023, doi: 10.1093/eurheartj/ehad194.

[61] P. A. Noseworthy, X. Yao, N. D. Shah, and B. J. Gersh, 'Stroke and Bleeding Risks in NOAC- and Warfarin-Treated Patients With Hypertrophic Cardiomyopathy and Atrial Fibrillation', *J Am Coll Cardiol*, vol. 67, no. 25, pp. 3020–3021, Jun. 2016, doi: 10.1016/j.jacc.2016.04.026.

[62] F. Dominguez *et al.*, 'Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation', *Int J Cardiol*, vol. 248, pp. 232–238, Dec. 2017, doi: 10.1016/j.ijcard.2017.08.010.

[63] H. Jung *et al.*, 'Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation With Hypertrophic Cardiomyopathy', *Chest*, vol. 155, no. 2, pp. 354–363, Feb. 2019, doi: 10.1016/j.chest.2018.11.009.

[64] F. Cappelli *et al.*, 'Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation', *Amyloid*, vol. 0, no. 0, pp. 1–7, 2020, doi: 10.1080/13506129.2020.1798922.

[65] J. M. Smit *et al.*, 'Anatomical Characteristics of the Left Atrium and Left Atrial Appendage in Relation to the Risk of Stroke in Patients With Versus Without Atrial Fibrillation', *Circ Arrhythm Electrophysiol*, vol. 14, no. 8, Aug. 2021, doi: 10.1161/CIRCEP.121.009777.

[66] R. O. Bonow *et al.*, 'Atrial systole and left ventricular filling in hypertrophic cardiomyopathy: Effect of verapamil', *Am J Cardiol*, vol. 51, no. 8, pp. 1386–1391, May 1983, doi: 10.1016/0002-9149(83)90317-X.

[67] D. L. Glancy, K. P. O'Brien, H. K. Gold, and S. E. Epstein, 'Atrial fibrillation in patients with idiopathic hypertrophic subaortic stenosis', *Heart*, vol. 32, no. 5, pp. 652–659, Sep. 1970, doi: 10.1136/hrt.32.5.652.

[68] W. J. Stafford, R. G. Trohman, M. Bilsker, L. Zaman, A. Castellanos, and R. J. Myerburg, 'Cardiac arrest in an adolescent with atrial fibrillation and hypertrophic cardiomyopathy', *J Am Coll Cardiol*, vol. 7, no. 3, pp. 701–704, Mar. 1986, doi: 10.1016/S0735-1097(86)80484-3.

[69] A. J. Furlan, A. R. Craciun, N. R. Raju, and N. Hart, 'Cerebrovascular complications associated with idiopathic hypertrophic subaortic stenosis.', *Stroke*, vol. 15, no. 2, pp. 282–284, Mar. 1984, doi: 10.1161/01.STR.15.2.282.

[70] C. A. S. Miller *et al.*, 'Safety, Side Effects and Relative Efficacy of Medications for Rhythm Control of Atrial Fibrillation in Hypertrophic Cardiomyopathy', *Am J Cardiol*, vol. 123, no. 11, pp. 1859–1862, Jun. 2019, doi: 10.1016/j.amjcard.2019.02.051.

[71] E. Ammirati, R. Contri, R. Coppini, F. Cecchi, M. Frigerio, and I. Olivotto, 'Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives', *Eur J Heart Fail*, vol. 18, no. 9, pp. 1106–1118, Sep. 2016, doi: 10.1002/ejhf.541.

[72] C. Ferrantini *et al.*, 'Late sodium current inhibitors to treat exercise-induced obstruction in hypertrophic cardiomyopathy: an in vitro study in human myocardium', *Br J Pharmacol*, vol. 175, no. 13, pp. 2635–2652, 2018, doi: 10.1111/bph.14223.

[73] S. Haruki, Y. Minami, A. Suzuki, and N. Hagiwara, 'Effects of flecainide on left ventricular pressure gradient and symptoms in obstructive hypertrophic cardiomyopathy: a comparison of flecainide and disopyramide', *Heart Vessels*, vol. 30, no. 5, pp. 604–610, Sep. 2015, doi: 10.1007/s00380-014-0534-3.

[74] J. C. Moore *et al.*, 'Dofetilide for suppression of atrial fibrillation in hypertrophic cardiomyopathy: A case series and literature review', *Pacing and Clinical Electrophysiology*, vol. 41, no. 4, pp. 396–401, Apr. 2018, doi: 10.1111/pace.13310.

[75] G. Hindricks *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*, vol. 42, no. 5, pp. 373–498, Feb. 2021, doi: 10.1093/EURHEARTJ/EHAA612.

[76] B. J. Maron *et al.*, 'Left Atrial Remodeling in Hypertrophic Cardiomyopathy and Susceptibility Markers for Atrial Fibrillation Identified by Cardiovascular Magnetic Resonance', *Am J Cardiol*, vol. 113, no. 8, pp. 1394–1400, Apr. 2014, doi: 10.1016/j.amjcard.2013.12.045.

[77] J. W. McCready *et al.*, 'Predictors of recurrence following radiofrequency ablation for persistent atrial fibrillation', *Europace*, vol. 13, no. 3, pp. 355–361, Mar. 2011, doi: 10.1093/europace/euq434.

[78] F. Gaita *et al.*, 'Usefulness and Safety of Transcatheter Ablation of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy', *Am J Cardiol*, vol. 99, no. 11, pp. 1575–1581, Jun. 2007, doi: 10.1016/j.amjcard.2006.12.087.

[79] P. Santangeli *et al.*, 'Catheter Ablation of Atrial Fibrillation in Hypertrophic Cardiomyopathy', *Circ Arrhythm Electrophysiol*, vol. 6, no. 6, pp. 1089–1094, Dec. 2013, doi: 10.1161/CIRCEP.113.000339.

[80] X. Chen *et al.*, 'Long-term outcome of catheter ablation for atrial fibrillation in patients with apical hypertrophic cardiomyopathy', *J Cardiovasc Electrophysiol*, vol. 29, no. 7, pp. 951–957, Jul. 2018, doi: 10.1111/jce.13645.

[81] S. Wen *et al.*, 'Depolarization and repolarization parameters on ECG predict recurrence after atrial fibrillation ablation in patients with hypertrophic cardiomyopathy', *J Cardiovasc Electrophysiol*, vol. 30, no. 11, pp. 2405–2413, Nov. 2019, doi: 10.1111/jce.14137.

[82] A. Creta *et al.*, 'Catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a European observational multicentre study', *EP Europace*, vol. 23, no. 9, pp. 1409–1417, Sep. 2021, doi: 10.1093/europace/euab022.

[83] D. Castagno *et al.*, 'Transcatheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy: Long-term results and clinical outcomes', *J Cardiovasc Electrophysiol*, vol. 32, no. 3, pp. 657–666, Mar. 2021, doi: 10.1111/jce.14880.

[84] F. Faraz *et al.*, 'Efficacy of Catheter Ablation for Atrial Fibrillation in Hypertrophic Cardiomyopathy: A Systematic Review and Meta-Analysis', *Curr Probl Cardiol*, vol. 48, no. 3, p. 101524, Mar. 2023, doi: 10.1016/j.cpcardiol.2022.101524.

[85] A. Latif *et al.*, 'Catheter ablation of atrial fibrillation in hypertrophic cardiomyopathy: A proportional meta-analysis and systematic review of single-arm studies', *Heart Rhythm O2*, vol. 4, no. 4, pp. 258–267, Apr. 2023, doi: 10.1016/j.hroo.2023.01.002.

[86] T. J. BUNCH *et al.*, 'Substrate and Procedural Predictors of Outcomes After Catheter Ablation for Atrial Fibrillation in Patients with Hypertrophic Cardiomyopathy', *J Cardiovasc Electrophysiol*, vol. 19, no. 10, pp. 1009–1014, Oct. 2008, doi: 10.1111/j.1540-8167.2008.01192.x.

[87] E. Lapenna *et al.*, 'Mid-term outcomes of concomitant surgical ablation of atrial fibrillation in patients undergoing cardiac surgery for hypertrophic cardiomyopathy†', *European Journal of Cardio-Thoracic Surgery*, vol. 51, no. 6, pp. 1112–1118, Jun. 2017, doi: 10.1093/ejcts/ezx017.

[88] A. Bogachev-Prokophiev *et al.*, 'Mitral valve repair or replacement in hypertrophic obstructive cardiomyopathy: A prospective randomized study', *Interact Cardiovasc Thorac Surg*, vol. 25, no. 3, pp. 356–362, Sep. 2017, doi: 10.1093/icvts/ivx152.

[89] D. R. Talreja *et al.*, 'Alcohol septal ablation versus surgical septal myectomy', *J Am Coll Cardiol*, vol. 44, no. 12, pp. 2329–2332, Dec. 2004, doi: 10.1016/j.jacc.2004.09.036.

[90] C. Butcher *et al.*, 'Atrioventricular nodal ablation is an effective management strategy for atrial fibrillation in patients with hypertrophic cardiomyopathy', *Heart Rhythm*, Aug. 2023, doi: 10.1016/j.hrthm.2023.08.028.

[91] I. Olivotto *et al.*, 'Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial.', *Lancet*, vol. 396, no. 10253, pp. 759–769, Sep. 2020, doi: 10.1016/S0140-6736(20)31792-X.

[92] M. S. Maron *et al.*, 'Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy', *J Am Coll Cardiol*, vol. 81, no. 1, pp. 34–45, Jan. 2023, doi: 10.1016/j.jacc.2022.10.020.

[93] C. Y. Ho *et al.*, 'Evaluation of Mavacamten in Symptomatic Patients With Nonobstructive Hypertrophic Cardiomyopathy', *J Am Coll Cardiol*, vol. 75, no. 21, pp. 2649–2660, Jun. 2020, doi: 10.1016/j.jacc.2020.03.064.

[94] S. M. Hegde *et al.*, 'Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy', *J Am Coll Cardiol*, vol. 78, no. 25, pp. 2518–2532, Dec. 2021, doi: 10.1016/j.jacc.2021.09.1381.

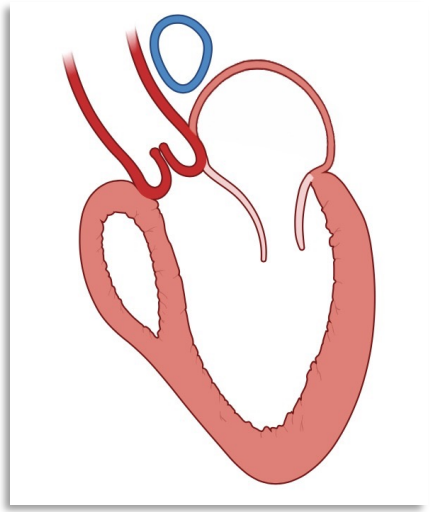
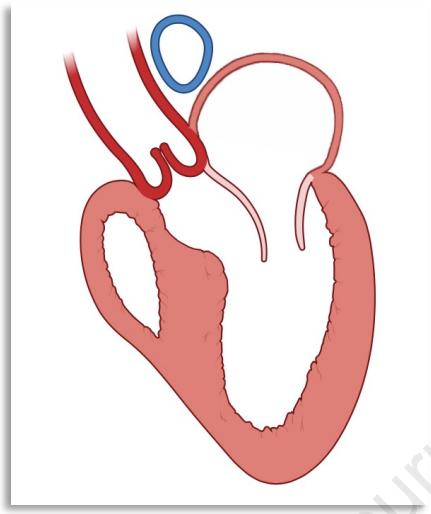
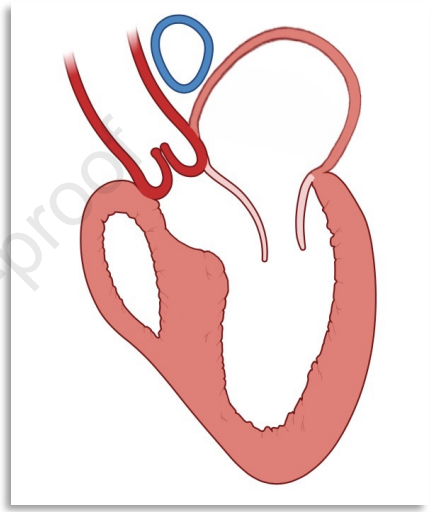
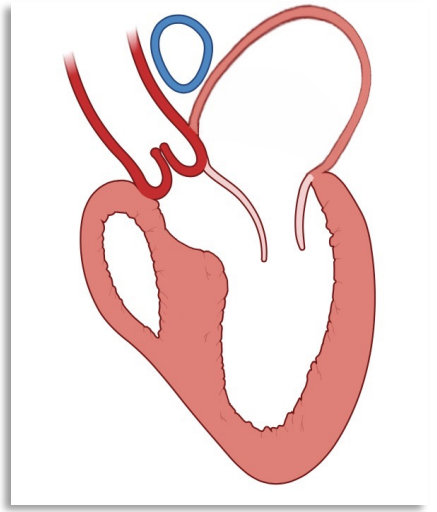
[95] P. C. Cremer *et al.*, 'Myosin Inhibition and Left Ventricular Diastolic Function in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy: Insights From the VALOR-HCM Study', *Circ Cardiovasc Imaging*, vol. 15, no. 12, Dec. 2022, doi: 10.1161/CIRCIMAGING.122.014986.

[96] P. Wessly, G. E. Lazzara, J. M. Buergler, and S. F. Nagueh, 'Early Observations on Effects of Mavacamten on Left Atrial Function in Obstructive Hypertrophic Cardiomyopathy Patients', *JACC Cardiovasc Imaging*, vol. 16, no. 12, pp. 1633–1634, Dec. 2023, doi: 10.1016/j.jcmg.2023.06.008.

[97] S. Saberi *et al.*, 'Mavacamten Favorably Impacts Cardiac Structure in Obstructive Hypertrophic Cardiomyopathy', *Circulation*, vol. 143, no. 6, pp. 606–608, Feb. 2021, doi: 10.1161/CIRCULATIONAHA.120.052359.

[98] S. M. Hegde *et al.*, 'Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy', *J Am Coll Cardiol*, vol. 78, no. 25, pp. 2518–2532, Dec. 2021, doi: 10.1016/j.jacc.2021.09.1381.

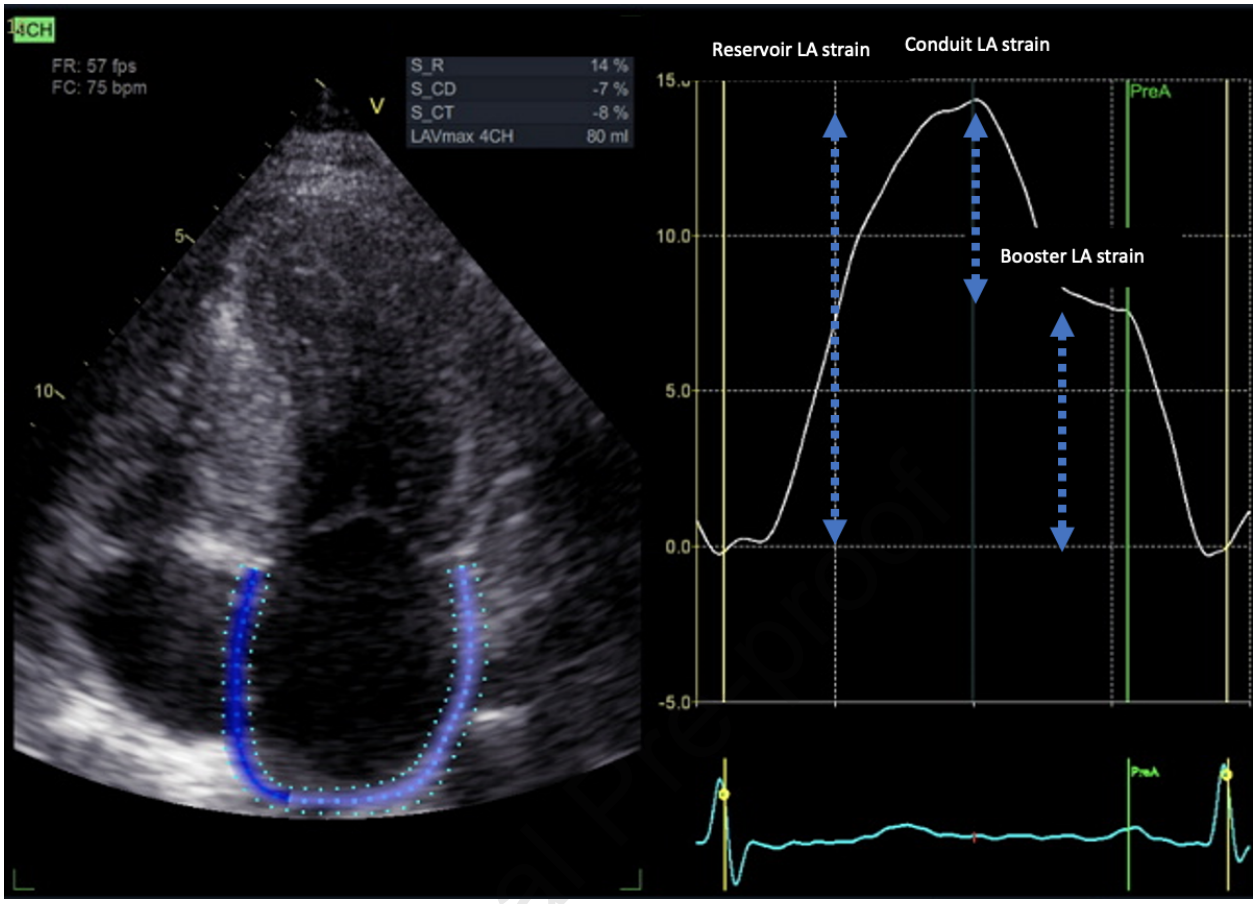
Spectrum of left atrial myopathy in HCM

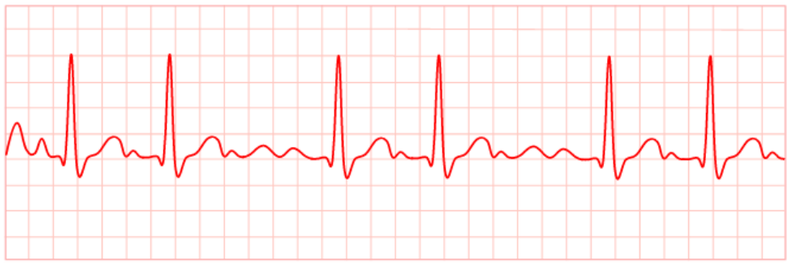
Pre-clinical HCM	Classic Phenotype HCM	Adverse Remodeling HCM	End-stage HCM
			
LA Pressure	±	+	++	+++
LV Diastolic Dysfunction	±	+	++	+++
LACI	±	+	++	+++
LA Dilatation	Genetic Forms	+	++	+++

LA myopathy

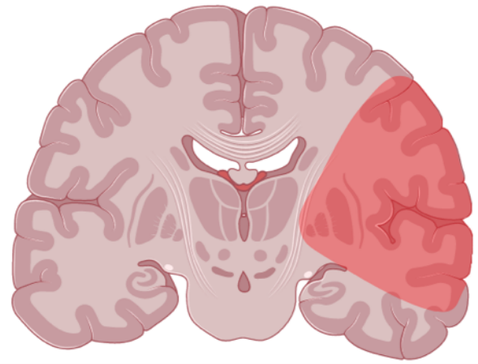
Incident AF

LA Reservoir Strain

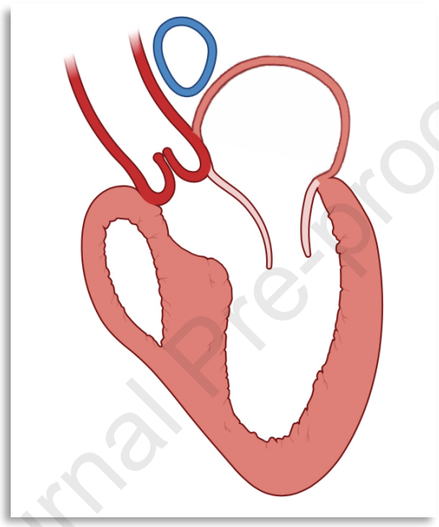




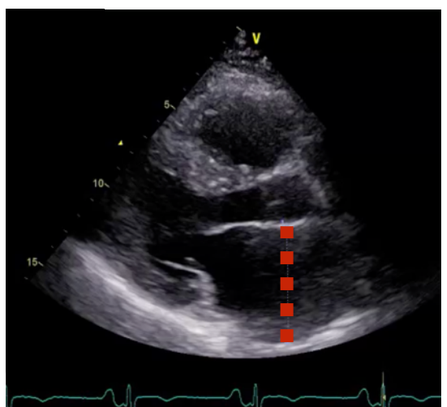
atrial fibrillation



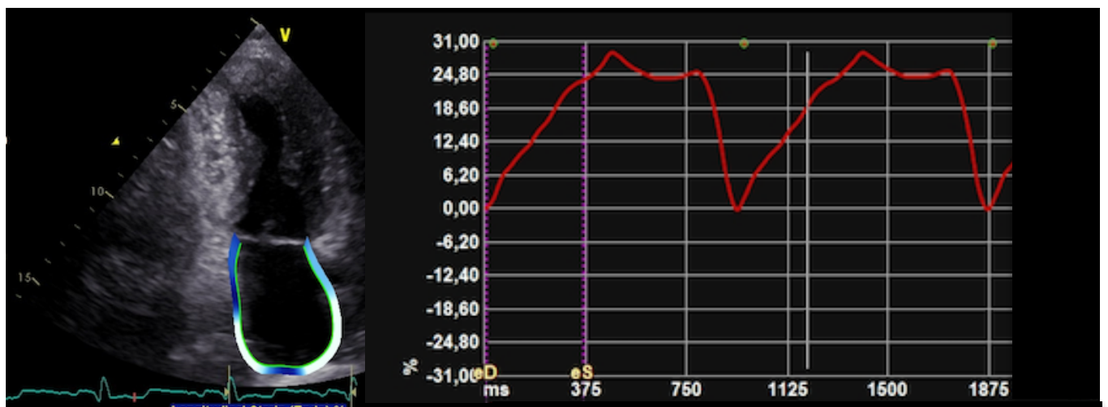
stroke



HCM



LA enlargement



impaired LA strain