Heart Failure Reviews (2019) 24:189–197
https://doi.org/10.1007/s10741-018-9752-6

Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical impact, and management

Lohit Garg[1] · Manasvi Gupta[2] · Syed Rafay Ali Sabzwari[1] · Sahil Agrawal[3] · Manyoo Agarwal[4] · Talha Nazir[1] · Jeffrey Gordon[1] · Babak Bozorgnia[1] · Matthew W. Martinez[1]

Published online: 19 November 2018

Abstract

Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiomyopathy characterized by left ventricular hypertrophy and spectrum of clinical manifestation. Atrial fibrillation (AF) is a common sustained arrhythmia in HCM patients and is primarily related to left atrial dilatation and remodeling. There are several clinical, electrocardiographic (ECG), and echocardiographic (ECHO) features that have been associated with development of AF in HCM patients; strongest predictors are left atrial size, age, and heart failure class. AF can lead to progressive functional decline, worsening heart failure and increased risk for systemic thromboembolism. The management of AF in HCM patient focuses on symptom alleviation (managed with rate and/or rhythm control methods) and prevention of complications such as thromboembolism (prevented with anticoagulation). Finally, recent evidence suggests that early rhythm control strategy may result in more favorable short- and long-term outcomes.

Keywords Atrial fibrillation · Hypertrophic cardiomyopathy · Treatment · Antiarrhythmic agents

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy due to mutation in one of the several sarcomere genes and transmitted in autosomal dominant pattern with variable penetrance [1, 2]. It is characterized by left ventricular hypertrophy (wall thickness > 13 mm on echocardiogram), usually asymmetric involving the septum, in the absence of abnormal loading conditions and other known phenocopies of HCM (e.g., Fabry disease, lysosomal-associated membrane protein-2 cardiomyopathy, or amyloidosis) [3–5]. The clinical presentation of HCM is heterogeneous and includes an asymptomatic state, heart failure syndrome due to diastolic dysfunction or left ventricular outflow (LVOT) obstruction, arrhythmias (atrial fibrillation and embolism), and sudden cardiac death [1, 6]. Atrial fibrillation (AF) is a very common sustained arrhythmia in HCM patients and is responsible for worsening symptoms and lifestyle [7, 8]. This review focuses on several aspects of AF in HCM patients with a focus on prevalence, clinical impact, and management.

Incidence and prevalence

HCM is the most common inherited cardiomyopathy with a population prevalence of up to 0.2% or 1 in 500 persons [7]. It is a common cause of exercise intolerance, heart failure, and sudden cardiac death in young patients. AF is the most common sustained arrhythmia in both HCM and general population. The prevalence of AF in HCM patients is four- to sixfold higher than the similarly aged general population. Several previous studies have reported an annual incidence of 2–4% and a lifetime prevalence of 20–30% with rates as high as 40% in HCM patients over the age of 70 years. A meta-analysis of 7381 patients reported an overall AF incidence of 3.08% per 100 patients per year and lifetime prevalence of 22.5% [9]. AF

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10741-018-9752-6) contains supplementary material, which is available to authorized users.

✉ Lohit Garg
garg.medicine@gmail.com

[1] Division of Cardiology, Lehigh Valley Health Network, 1200 S. Cedar Crest Blvd, Allentown, PA 18103, USA

[2] Maulana Azad Medical College, Delhi 110092, India

[3] Division of Cardiology, Brown University, Providence, RI 02903, USA

[4] Department of Internal Medicine, The University of Tennessee Health Science Center, Memphis, TN 38163, USA

is regarded a progressive arrhythmia in HCM patients with major clinical impact and tends to be paroxysmal in two-third of patients while the rest have persistent/permanent AF [8, 10].

Pathophysiology of AF in HCM

The genetic mutations in HCM leads to myofibril disarray and eventually left ventricular hypertrophy over time. The three most predominant mutations involving the sarcomeric proteins constitute 60% of the HCM cases, involving the beta-myosin heavy chain (MYH7), cardiac troponin T, and myosin-binding protein C [11]. A few studies have sought to understand the exact mechanism of AF in HCM. The development of AF in HCM patients is likely multifactorial, including genetic factors, structural abnormalities, and electrophysiological abnormalities. The missense mutation Arg663His in the MHY7 gene has been reported to be associated with greater risk of AF (47% prevalence over a follow-up period of 7 years) [12]. Polymorphisms in the angiotensin receptor gene (AGTR1) have also been linked to the development of AF in patients with HCM [13].

Hypertrophic cardiomyopathy is associated with diastolic dysfunction due to hypertrophied LV and reduced LV compliance. Diastolic dysfunction leads to elevated left ventricular end diastolic pressure (LVEDP) and increased afterload for left atrium (LA). This results in progressive dilatation and remodeling of LA causing structural and electrophysiological abnormalities. This is further exacerbated by LVOT obstruction and mitral regurgitation due to systolic anterior motion of the mitral valve [5, 14]. LA remodeling shortens the atrial refractory period and in turn increases the dispersion of repolarization. This can potentiate the ability of ectopic triggers to initiate AF (Fig. 1) [15, 16].

Furthermore, HCM itself can cause atrial myofibril disarray and atrial fibrosis that can serve as a substrate for AF by impairing intra-atrial conduction [15, 17, 18]. Finally other proposed mechanisms for AF in HCM includes atrial ischemia due to microvascular dysfunction, hypertrophy of muscle sleeves responsible for conduction from pulmonary vein triggers to LA, and the abnormal calcium handling resulting in triggered activities [16, 19, 20].

Risk factors for development of AF and detection in HCM

There are several clinical, electrocardiographic (ECG), and echocardiographic (ECHO) features that have been described in the literature as independent predictors for development of AF in HCM patients. The strongest independent predictors of those are left atrial size, age, and heart failure class.

The size of the LA is strongly associated with the development of AF in HCM patients. Different studies have used different cutoff of left atrial size to predict AF risk in HCM patients, but the most accepted size is anteroposterior diameter > 45 mm [8, 9]. In a meta-analysis of 7381 patients (33 studies), the LA diameter was 38 mm in HCM patients with sinus rhythm compared to 45 mm in patients with AF [9]. In another study of 480 patients, a LA diameter > 45 mm was significantly associated with higher risk of AF and is a part of the guidelines [8]. In European guidelines, 48-h ambulatory ECG monitoring is recommended every 6–12 months for AF detection in HCM patients who are in sinus rhythm and LA anteroposterior of greater than 45 mm (class IIa) [4]. The American guidelines on the other hand are less rigorous; 24-h ambulatory ECG monitoring could be considered in adults to detect asymptomatic AF in patients with enlarged LA (class IIb) [5]. More prolonged monitoring with event or implantable loop recorders might be required to increase the detection rate, especially in patients with intermittent symptoms [21].

Left atrial volume index (LAVI) provides more information about left atrial remodeling and is a better predictor of AF in HCM patients than LA diameter alone. In a study of 141 HCM patients, LAVI > 34 ml/m^2 identified patients at a risk of developing paroxysmal AF with a sensitivity and specificity of 80% and 73% respectively [22]. In another study of 427 HCM patients, LA emptying fraction < 38% and LA end-diastolic volume > 118 ml predicted future AF episodes in HCM patients [23]. However, it has been demonstrated that LA function are preserved until LAVI > 40 ml/m^2 [24]. These observation might lead to closer follow-up of HCM patients with LAVI > 40 ml/m^2 and reduced LA emptying fraction (Table 1).

Age is a well-known predictor of AF in general population and in HCM patients as well. Various study have identified age as a risk factor for development of AF and threshold ranging from > 40 to > 50 years are independently predictive of AF in HCM patients [8, 25]. Finally, NYHA class III/IV, moderate to severe mitral regurgitation, and LV ejection fraction < 50% have been associated with higher risk of AF in multiple studies [26, 27].

There have been several other structural factors based on cardiac imaging that have been observed to predict risk of AF. In a study of 1360 HCM patients, greater extent of septal hypertrophy on ECHO and/or cardiac magnetic resonance imaging (CMR) was associated with higher risk of AF [28]. In another study of 37 patients, HCM patients with AF had significantly more LGE than patients without AF. However, the predictive value of LGE was inferior to LA size [15]. LVOT obstruction in HCM is associated with worse outcomes but the evidence to predict AF is inconsistent. In a study of 3673 patients, AF was more common among patients with non-obstructive physiology [27].

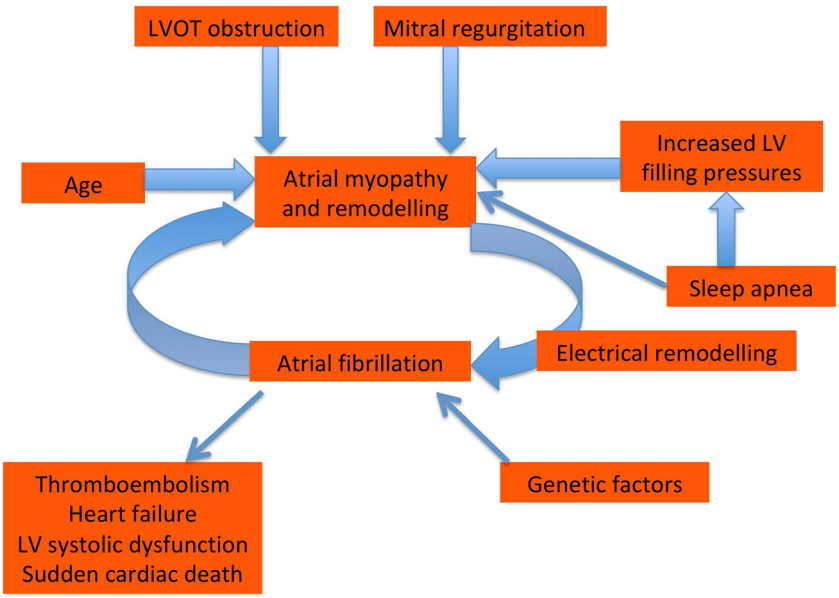

Fig. 1 Pathophysiology and clinical impact of atrial fibrillation in hypertrophic cardiomyopathy patients

Conversely, other studies have suggested that higher LVOT predicts risk of AF [13].

Abnormal atrial activation on electrocardiographic basis has been shown to predict risk of AF development. A study of 110 patients observed that HCM patients with signal averaged P wave > 140 ms are at higher risk of developing AF. It is more sensitive when combined with dilated LA > 40 mm [29]. Another study of 80 patients reported that P wave duration > 134.5 ms separated the patients with AF from controls with a sensitivity of 92% and specificity of 89%. They also reported that P wave dispersion value > 52.5 ms separated AF patients from controls with a sensitivity of 96%, and a specificity of 91% (Table 1) [30].

Clinical impact of AF

The development of AF in HCM patients has significant impact on quality of life and often is associated with functional decline. AF is associated with higher rates of symptomatic heart failure, thromboembolism, and mortality [31].

Symptoms of progressive heart failure were the major source of morbidity in this group. During AF, the loss of coordinated atrial contraction and rapid ventricular response leads to variable ventricular filling. This compounded with reduced LV compliance in hypertrophied ventricle can produce a wide range of hemodynamic consequences [10, 13]. HCM patients with LVOT obstruction can develop hypotension, presyncope, or syncope due to decreased cardiac output. In a study of 52 HCM patients, the acute onset of AF caused worsening symptoms in majority of patients with resolution of symptoms with return to normal sinus rhythm [10]. HCM patients with AF have a greater rate of progression to end stage heart failure. Finally, patients who develop AF experience deterioration in functional class, esp. those with LVOT obstruction. Of note, patients with paroxysmal AF have poor exercise tolerance despite being in normal rhythm at time of testing [32].

AF is an independent predictor of mortality in HCM patients and is associated with up to fourfold increased risk of death compared to sinus rhythm. The majority of cardiovascular deaths in AF group are related to thromboembolism and worsening heart failure. There are few cases of sudden cardiac death due to deterioration of AF into ventricular tachycardia, esp. in the presence of pre-excitation. In a study of 480 HCM patients, 107 developed AF during mean follow up of 9.1 years. The presence of AF was associated with significantly higher risk of mortality (3% versus 1%) in these patients. More so, patients who developed AF at younger age > 50 years were at highest risk of thromboembolism and carried worse prognosis [8]. In another study of 4248 HCM patients, those with AF had higher cardiovascular (10.9% AF versus 4.9%

Table 1 Predictors of atrial fibrillation in patients with hypertrophic cardiomyopathy

Predictors	Cutoff	Strength of evidence
Left atrial size	> 45 mm	OR = 3.4
Left atrial volume index	≥ 34 ml/m^2	ROC curve = 0.84
LA emptying fraction	< 38%	ROC curve = 0.754
LGE on MRI		ROC curve = 0.64
Septal hypertrophy		OR = 5.44
P-wave duration	≥ 140 ms	OR = 3.44
P-wave dispersion	≥ 52.5 ms	RR = 24

non-AF) and non-cardiovascular death (5.9% AF versus 3.2% non-AF) during follow-up period of 10 years [26].

Multiple studies have also documented that AF increases the risk of systemic thromboembolism (TE) in HCM patients. In a large meta-analysis of 7381 patients, the incidence of TE was 3.8% per year and overall prevalence was 27.1% [9]. In another study of 480 patients, the ischemic stroke was eight times more frequent in AF group compared to HCM patients without AF (21% AF; 2.6% non-AF) [8]. Thromboembolism risk in AF is unrelated to the type of AF (paroxysmal versus persistent) and number of paroxysms and cannot be predicted accurately using clinical prediction score like CHA_2DS_2-VASc [33].

Management of AF

Several studies have identified that lifestyle modifications like healthy eating and physical activity weight loss could reduce the incidence of AF, induce more AF remission, and also produce successful ablation outcomes [34]. Even though these studies have not specifically included HCM patients, we recommend that aggressive lifestyle modification along with treatment of underlying comorbidities like diabetes, hypertension, and sleep apnea should be undertaken to prevent AF.

Pharmacological treatment

Long-term complications of concern in determining management strategy for AF include stroke, tachycardia-induced cardiomyopathy, and worsening heart failure. The management of AF is, thereby, focused on two principles—symptom alleviation (managed with rate and/or rhythm control methods) and prevention of complications such as thromboembolism (prevented with anticoagulation). Current data from large randomized trials indicates equivalent outcome (in terms of quality of life and overall mortality) with both rate and rhythm control strategies for control of AF with marginally lower rates of cardiovascular death, admission for heart failure, thromboembolic event, severe bleeding, pacemaker implantation, or severe side effects from antiarrhythmic drugs in general population (Supplementary Table 1) [35, 36]. The limitation of this data lies in the general lack of sub-analysis of patients suffering from structural heart diseases. HCM, more specifically, involves dynamic obstruction of LV outflow that may make it difficult to extrapolate the little data that is available for AF in structural heart diseases. Physiologically, the LV dysfunction is predominantly diastolic in HCM that increases the dependence of LV outflow on synchronized atrial contraction occurring at normal rate. For this reason, despite the absence of definitive data on AF treatment in HOCM, expert opinion weighs in favor of rhythm control for long-term management with adequate anticoagulation [4, 5]. Rate control strategies may also be added to antiarrhythmic drugs to improve quality of life and prolong asymptomatic phases (Table 2).

Acute management

In the setting of new onset AF, rate control is often desired to provide symptomatic relief to the patient. This can be achieved by initiating oral beta-blocker or non-dihydropyridine calcium channel blockers (CCB). Transfer to an inpatient service and use of intravenous preparations is considered in patients experiencing severe symptoms of ischemia or heart failure or those in significant discomfort. Care should be taken to avoid these agents in case of pre-excitation or in setting of cardiogenic shock [3, 4].

For some patients, immediate conversion to sinus rhythm may be necessary and includes hemodynamic instability, actively progressing ischemia seen on ECG and inadequate response to intravenous beta-blockers and CCBs [3, 4]. Urgent cardioversion should be carried out when required, irrespective of anticoagulation status and although absence of anticoagulation is associated with risk of thromboembolism, it does not serve as a contraindication for cardioversion. If available, a transesophageal echocardiogram (TEE) can be performed to rule out thrombus in the left atrium before cardioversion. Pharmacologic cardioversion can also be considered, includes amiodarone, the preferred agent, with added benefit of delayed rate control (after 8–12 h later) when used intravenously. Class 1C antiarrhythmics like flecainide and propafenone, although more effective for cardioversion are associated with increased pro-arrhythmic effect in structural heart disease and should be avoided [37].

Vernakalant, an atrial selective antiarrhythmic, has shown promise in the AVRO trial and is recommended by the 2014 ESC guidelines for rapid and effective conversion of AF. However, limitation of availability of safety data in clinically significant structural heart disease precludes its use [38]. Ibutilide, an effective antiarrhythmic is recommended in countries where available, especially in setting of pre-excitation. Few studies have been performed to determine its role in HCM, thus restricting the use of the drug [39].

Chronic rate control

Despite a more widespread use for rhythm control methods in HCM patients with AF, exceptions include asymptomatic patients and those who cannot tolerate antiarrhythmic drugs due to their adverse effect profile. This group should be considered for rate control, given the lack of clear benefit from rhythm control. The preferred medications are oral non-dihydropyridine CCBs (verapamil/diltiazem) or beta-blockers (metoprolol, propranolol, atenolol, nadolol), individually or in combination. Calcium channel blockers, due to

Table 2 Summary of management of AF in HCM patients

Issue	Recommendation	Comments
Rate control	Beta-blockers and CCBs for acute and chronic rate control (class I)	Caution in patients with LV systolic dysfunction and cardiogenic shock.
Rhythm control	Amiodarone followed by disopyramide (class IIa)	In clinical practice, sotalol is preferred due to long-term side effects with other drugs.
Catheter ablation	Consider in patients with drug-refractory symptomatic AF, or unable to take antiarrhythmic (class IIa)	Early ablation strategy might be useful in young patients with normal-sized left atrium and/or paroxysmal AF.
Anticoagulation	Unless contraindicated, oral anticoagulation with VKA (INR 2–3) to prevent thromboembolism (class I)	Direct oral anticoagulant can be used a second-line therapy. CHA2DS2-VASc score is not validated and does not effectively predict stroke risk.

their negative inotropic action, should be avoided in patients with LV systolic failure [3, 4].

In critically ill patients, short-term intravenous amiodarone could be used for rate control. Dronedarone is a theoretical option for controlling rate in AF but existing data suggests its use in permanent AF is associated with worse outcomes [40]. Digoxin can be considered alone or in combination with beta-blockers or CCBs in the long-term management of permanent AF in patients presenting with symptoms of NYHA class II-IV, provided there is no significant LVOT obstruction (in which case the positive inotropic effect of the drug can do more harm) [41].

Of note, HCM patients who have failed rhythm control and for whom ablative procedures (as a consequence of comorbid conditions, advanced age) are contraindicated can be considered for AV nodal ablation with subsequent insertion of a dual chamber pacemaker if rate control methods are unsuccessful, assuming LVEF > 50%. In cases with LVEF < 50%, AV nodal ablation can be followed by either HIS bundle pacemaker or CRT pacemaker implantation [41, 42].

Chronic rhythm control

Once sinus rhythm is achieved, the goal of starting antiarrhythmic drug is to reduce the number and duration of AF recurrences. In short term, arrhythmia free phases allow patient to live a life of higher quality while in the long-term, natural progression from paroxysmal to persistent/permanent AF is prevented. Choice of antiarrhythmic drug in a given patient is guided by the duration of pharmacological treatment planned, patient characteristics like age and gender, existing comorbidities and the side effect profile of the drug.

Sotalol is the most commonly prescribed antiarrhythmic in otherwise young HCM patients with AF (Table 2). However, care should be taken to administer it under supervision for the purpose of monitoring QT prolongation that can occur over the first several doses. While sotalol is ineffective in cardioversion, long-term use is associated with lower rates of recurrence of AF and improved exercise tolerance [43]. Patients should be followed up regularly to monitor serum potassium, serum magnesium, electrocardiogram changes, and renal function [31, 43].

Similar to sotalol in terms of effect on QT prolongation, dofetilide is another IKr inhibitor that can be considered for rhythm control in patients with AF. In SAFIRE-D trial, rate of maintenance of sinus rhythm with dofetilide at 1 year was 58% compared to 25% in the placebo group [44]. Another trial studying the efficacy of dofetilide in patients with impaired LV function showed a higher rate at 1 year of dofetilide (78%) versus in placebo group (42%) [45]. Unfortunately, little work has been done on the use of dofetilide in HCM patients. A recent retrospective case review revealed that dofetilide was well tolerated in patients with AF and HOCM and it facilitated management of AF in 21/25 (84%) patients [46].

If a short duration of treatment is expected (in circumstances such as advanced age and imminent ablative procedure), amiodarone can be considered initially. Multiple RCTs have demonstrated the superiority of amiodarone over sotalol at 1-year follow-up [47, 48], but these studies did not specifically examine HCM patients. Additionally, long-term use of amiodarone is limited due to extracardiac side effects and increased mortality [48]. Short-term use with amiodarone can also be practiced only in a limited manner. A randomized trial demonstrated the episodic short-term use of amiodarone results in higher recurrences of AF with higher than expected morbidity and overall significantly higher rates of all-cause mortality and cardiovascular hospitalizations [49].

A close relative of amiodarone, dronedarone has a more tolerable side effect profile, enhanced exercise tolerance, and reduced mortality in paroxysmal and persistent AF. However, existing studies reveal that its use in permanent AF is associated with increased combined end point of MI, stroke, systemic embolism, and cardiovascular deaths [40]. Disopyramide, supplemented with AV node blocking drug like beta-blocker or CCB, is used to treat LVOT obstruction in HCM. An intention-to-treat meta-analysis suggested that this combination could maintain sinus rhythm for 2–3 years, but the protective effect gradually diminishes over time [26].

Non-pharmacologic rhythm control

Percutaneous catheter ablation is considered an effective treatment for atrial fibrillation. It could be considered for rhythm control in patients with drug-refractory symptomatic AF. Several studies have analyzed the role of catheter ablation in HCM patients for drug-refractory AF [20, 50, 51]. It aims to eradicate AF triggers and abnormal atrial substrate and can be achieved by pulmonary vein isolation (PVI). In the initial studies, PVI was reported to be a safe and effective therapy for drug-refractory AF, with good short-term results [20, 50]. In a study of 61 HCM patients, catheter ablation was successful with no recurrence of AF in 67% patients over 29-month follow-up. However, repeat procedure were required in 52% of patients and 54% patients were maintained on antiarrhythmic therapy. They observed that younger patients with small atrial size and mild symptoms had the best outcomes, likely due to lesser degrees of atrial myopathy and remodeling [20].

In a subsequent study including 43 HCM patients, PVI and posterior wall isolation alone, even though feasible and safe, was not effective in preventing late AF recurrence (> 1 year) in about 50% patients. They observed that non-PV triggers can be demonstrated in the majority of patients with late AF recurrence and more extensive ablation beyond PVI could result in significant improvement in the long-term AF free survival [51]. In a recently published meta-analysis including 15 observational studies, 45.5% of HCM patients were free from atrial arrhythmia during follow-up after a single catheter ablation. The success rate was increased to 66.1% overall with multiple procedures (71.8% in paroxysmal AF, and 47.5% in persistent/permanent AF). Without the use of antiarrhythmic drugs, the success rate was much lower at latest follow-up (32.9% with single procedure and 50.4% with multiple procedures). The major predictors of AF recurrence after catheter ablation was LA size, NYHA class III/IV, AF duration, non-PV triggers, and LV systolic dysfunction. The incidence of serious periprocedural complication was 5.1% and there was no death reported [52].

In another study, left atrial size was the major predictor of procedural success. They reported that outcomes in HCM patients with paroxysmal AF and normal sized atria (less degree of atrial myopathy and remodeling) were comparable to the non-HCM population [16]. This may suggest that an early and aggressive rhythm control strategy using catheter ablation in HCM patients might be more effective and will avoid long-term toxicities of antiarrhythmic medications. This approach is supported by recent studies reporting that a longer diagnosis-to-ablation time is associated with adverse LA remodeling and worse outcomes [53]. Also, AF ablation can result in significant reverse LA remodeling and improved outcomes [54].

The data about the efficacy of catheter ablation for AF in HCM patients are scarce and of modest quality. There is need for studies to evaluate the optimal energy source (radiofrequency versus cryoablation) and whether extensive ablation beyond PVI (posterior wall isolation, complex fractionated electrograms, rotors, ganglionic plexus, and non-PV triggers) would be more effective in treating AF. We recommend that catheter ablation should be considered for HCM patients with symptomatic drug-refractory AF, particularly younger patients with paroxysmal AF and smaller atria. The ablation strategy should be individualized and extensive ablation beyond PVI should be considered in HCM patients with persistent AF and who have had recurrent AF despite catheter ablation (Table 2).

In addition, there is some data suggesting the role of surgical ablation for AF. In a study of 68 HCM patients, who underwent surgical ablation during myectomy, 51% had freedom from AF after a single procedure at 35-month mean follow-up [55]. However, this procedure was associated with high rates of major complication (18%). Considering the limited data and high complication rate, we do not recommend stand-alone surgical ablation but concomitant MAZE procedure can be considered if septal myectomy or mitral valve replacement is indicated [56, 57].

Thromboembolic prophylaxis

Hypertrophic cardiomyopathy patients with AF are at substantial risk for thromboembolism (TE). Major guidelines strongly recommend long-term anticoagulation for TE prevention in HCM patients with AF [3, 4]. Anticoagulation with warfarin is known to be effective for stroke prevention compared to antiplatelet therapy in HCM patients [58, 59]. In a study of 4821 patients, warfarin use was associated with 54.8% stroke risk reduction compared to no therapy [33]. In patients with warfarin intolerability, difficult to maintain INR in therapeutic range, an oral direct thrombin inhibitor (Dabigatran) or factor Xa inhibitor (rivaroxaban/apixaban) is recommended despite under representation of HCM patients in randomized trials for the direct oral anticoagulants. However, based on observational data, guidelines have included both warfarin therapy (goal INR 2 to 3) and direct oral anticoagulants to be effective strategies for stroke prevention in HCM patients [3, 4]. In a small study of 52 HCM patients with AF, the use of amiodarone was associated with fewer embolic episodes [10]. No other antiarrhythmics have been studied or shown to reduce the risk of thromboembolism.

CHA2DS2-VASc score is commonly used for stroke risk stratification in AF; however, it is not validated and does not effectively predict stroke risk in HCM patients [33]. Therefore, current guidelines recommend that all HCM patients with even a single brief episode of AF should be treated with long-term anticoagulation, given the high risk of stroke [3, 4]. In patients, who cannot be prescribed anticoagulation due to high bleeding risk, left atrial appendage (LAA) occlusion procedures can be considered. However, HCM patients

are not included in the trials for LAA occlusion and not specifically studied [60]. LAA exclusion with surgical internal sutures or noncutting stapler could be considered during surgical myectomy. However, these procedures are mostly ineffective due to spontaneous recanalization of the LAA [61].

Hypertrophic cardiomyopathy patients presenting with stroke symptoms should be carefully monitored for AF as 7.4% of these have new onset AF at the time of event and 14.7% developed AF during evaluation after stroke [62]. We recommend that implantable loop recorders should be considered in patients with otherwise considered cryptogenic stroke [63].

Conclusion

Atrial fibrillation is the most common arrhythmia in HCM patients and is very poorly tolerated. It is related to several processes including genetic factors, left atrial structural, and electrical remodeling. AF in these patients is associated with worsening heart failure, functional decline, increased risk of thromboembolism, and increased mortality. We recommend an early and aggressive rhythm control strategy with long-term anticoagulation esp. in younger HCM patients to improve morbidity and mortality. Lastly, there is a need for larger, multicenter studies to specifically address the effective ablation strategy in HCM patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Maron BJ, Maron MS (2013) Hypertrophic cardiomyopathy. Lancet 381(9862):242–255. https://doi.org/10.1016/S0140-6736(12)60397-3.Epub2012Aug 6.Review.PubMedPMID: 22874472
2. Jacoby D, McKenna WJ (2012) Genetics of inherited cardiomyopathy. Eur Heart J 33(3):296–304
3. Olivotto I, d'Amati G, Basso C et al (2015) Defining phenotypes and disease progression in sarcomeric cardiomyopathies: contemporary role of clinical investigations. Cardiovasc Res 105(4):409–423
4. Authors/Task Force members, Elliott PM, Anastasakis A et al (2014) ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 35(39):2733–2779
5. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW (2011) American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 58(25):e212–e260
6. Marian AJ, Braunwald E (2017) Hypertrophic Cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res 121(7):749–770
7. MacIntyre C, Lakdawala NK (2016) Management of atrial fibrillation in hypertrophic cardiomyopathy. Circulation 133(19):1901–1905
8. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ (2001) Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 104(21):2517–2524
9. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM (2014) Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart 100(6):465–472
10. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ (1990) Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. J Am Coll Cardiol 15(6):1279–1285
11. Maron BJ, Maron MS, Semsarian C (2012) Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 60(8):705–715
12. Gruver EJ, Fatkin D, Dodds GA, Kisslo J, Maron BJ, Seidman JG, Seidman CE (1999) Familial hypertrophic cardiomyopathy and atrial fibrillation caused by Arg663His beta-cardiac myosin heavy chain mutation. Am J Cardiol 83(12A):13H–18H
13. Tuluce K, Tuluce SY (2015) Predictors of atrial fibrillation risk in hypertrophic cardiomyopathy. J Atr Fibrillation 7(5):1200
14. Nair AG, Fischer AG (2006) Atrial fibrillation in hypertrophic cardiomyopathy: mechanisms, embolic risk and prognosis. Anadolu Kardiyol Derg 6(Suppl 2):40–43
15. Papavassiliu T, Germans T, Flüchter S, Doesch C, Suriyakamar A, Haghi D, Süselbeck T, Wolpert C, Dinter D, Schoenberg SO, van Rossum AC (2009) Borggrefe M. CMR findings in patients with hypertrophic cardiomyopathy and atrial fibrillation. J Cardiovasc Magn Reson 11(34):34
16. Providencia R, Elliott P, Patel K, McCready J, Babu G, Srinivasan N, Bronis K, Papageorgiou N, Chow A, Rowland E, Lowe M, Segal OR, Lambiase PD (2016) Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. Heart 102(19):1533–1543
17. Ohtani K, Yutani C, Nagata S, Koretsune Y, Hori M, Kamada T (1995) High prevalence of atrial fibrosis in patients with dilated cardiomyopathy. J Am Coll Cardiol 25(5):1162–1169
18. Prinz C, Van Buuren F, Bogunovic N, Bitter T, Faber L, Horstkotte D (2012) In patients with hypertrophic cardiomyopathy myocardial fibrosis is associated with both left ventricular and left atrial dysfunction. Acta Cardiol 67(2):187–193
19. Alasady M, Shipp NJ, Brooks AG, Lim HS, Lau DH, Barlow D, Kuklik P, Worthley MI, Roberts-Thomson KC, Saint DA, Abhayaratna W, Sanders P (2013) Myocardial infarction and atrial fibrillation: importance of atrial ischemia. Circ Arrhythm Electrophysiol 6(4):738–745
20. Di Donna P, Olivotto I, Delcrè SD, Caponi D, Scaglione M, Nault I, Montefusco A, Girolami F, Cecchi F, Haissaguerre M, Gaita F (2010) Efficacy of catheter ablation for atrial fibrillation in

hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. Europace 12(3):347–355
21. Seet RC, Friedman PA, Rabinstein AA (2011) Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. Circulation 124(4):477–486
22. Tani T, Tanabe K, Ono M, Yamaguchi K, Okada M, Sumida T, Konda T, Fujii Y, Kawai J, Yagi T, Sato M, Ibuki M, Katayama M, Tamita K, Yamabe K, Yamamuro A, Nagai K, Shiratori K, Morioka S (2004) Left atrial volume and the risk of paroxysmal atrial fibrillation in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr 17:644–648
23. Maron BJ, Haas TS, Maron MS, Lesser JR, Browning JA, Chan RH, Olivotto I, Garberich RF, Schwartz RS (2014) Left atrial remodeling in hypertrophic cardiomyopathy and susceptibility markers for atrial fibrillation identified by cardiovascular magnetic resonance. Am J Cardiol 113(8):1394–1400
24. Tülüce K, Yakar Tülüce S, Yavuzgil O, İsayev E, Bilgin M, Akyıldız Akçay F, Nalbantgil S, Özerkan F (2014) The left atrial phasic functions and the relationship with plasma N-terminal pro-B-type natriuretic peptide levels and symptomatic states in patients with hypertrophic cardiomyopathy. Anadolu Kardiyol Derg 14(8): 719–727
25. Bauer F, Shiota T, White RD, Lever HM, Qin JX, Drinko J, Martin M, Tsujino H, Sitges M, Kim YJ, Thomas JD (2004) Determinant of left atrial dilation in patients with hypertrophic cardiomyopathy: a real-time 3-dimensional echocardiographic study. J Am Soc Echocardiogr 17(9):968–975
26. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, Garcia-Pavia P, McKenna WJ, Omar RZ, Elliott PM (2017) Hypertrophic cardiomyopathy outcomes investigators. Predictors of atrial fibrillation in hypertrophic cardiomyopathy. Heart 103(9):672–678
27. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ (2014) Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. J Am Heart Assoc 3(3):e001002
28. Park KM, Im SI, Kim EK, Lee SC, Park SJ, Kim JS, On YK (2016) Atrial fibrillation in hypertrophic cardiomyopathy: is the extent of septal hypertrophy important? PLoS One 11(6):e0156410
29. Cecchi F, Montereggi A, Olivotto I, Marconi P, Dolara A, Maron BJ (1997) Risk for atrial fibrillation in patients with hypertrophic cardiomyopathy assessed by signal averaged P wave duration. Heart 78(1):44–49
30. Ozdemir O, Soylu M, Demir AD, Topaloglu S, Alyan O, Turhan H, Bicer A, Kutuk E (2004) P-wave durations as a predictor for atrial fibrillation development in patients with hypertrophic cardiomyopathy. Int J Cardiol 94(2–3):163–166
31. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, Rastegar H, Estes NAM, Maron MS, Maron BJ (2017) Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. Circulation 136(25):2420–2436
32. Azarbal F, Singh M, Finocchiaro G, Le VV, Schnittger I, Wang P, Myers J, Ashley E, Perez M (2014) Exercise capacity and paroxysmal atrial fibrillation in patients with hypertrophic cardiomyopathy. Heart 100(8):624–630
33. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, Garcia-Pavia P, McKenna WJ, Omar RZ, Elliott PM (2015) Hypertrophic cardiomyopathy outcomes investigators. Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM risk-CVA). Eur J Heart Fail 17(8):837–845
34. Sabzwari SRA, Garg L, Lakkireddy D, Day J (2018) Ten lifestyle modification approaches to treat atrial fibrillation. Cureus 10(5): e2682
35. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD (2002) Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 347(23):1825–1833
36. Al-Khatib SM, NM ALP, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD, Povsic TJ, Raju SS, Shah B, Kosinski AS, AJ MB, Sanders GD (2014) Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. Ann Intern Med 160(11):760–773
37. Andrikopoulos GK, Pastromas S, Flecainide TS (2015) Current status and perspectives in arrhythmia management. World J Cardiol 7(2):76–85
38. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G (2011) AVRO investigators.. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. J Am Coll Cardiol 57(3):313–321
39. Oral H, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA, Morady F (1999) Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. N Engl J Med 340(24):1849–1854
40. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum Á, Blomström P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacrétaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbüchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsányi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH, PALLAS Investigators (2011) Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 365(24):2268–2276
41. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg 50(5):e1–e88
42. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, Bova Campbell K, Lee BK, Refaat MM, Saksena S, Fisher JD, Lakkireddy D (2018) ACC's electrophysiology council. His Bundle Pacing. J Am Coll Cardiol 72(8): 927–947
43. Tendera M, Wycisk A, Schneeweiss A, Poloński L, Wodniecki J (1993) Effect of sotalol on arrhythmias and exercise tolerance in patients with hypertrophic cardiomyopathy. Cardiology 82(5):335–342
44. Singh S, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M, Billing CB Jr (2000) Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. Circulation 102(19):2385–2390
45. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, Køber L, Sandøe E, Egstrup K, Agner E, Carlsen J, Videbaek J, Marchant B, Camm AJ (1999) Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish investigations of arrhythmia

and mortality on Dofetilide Study Group. N Engl J Med 341(12): 857–865
46. Moore JC, Trager L, Anzia LE, Saliba W, Bassiouny M, Bhargava M, Chung M, Desai M, Garberich R, Lever H, Lindsay BD, Sengupta J, Tchou P, Wazni O, Wilkoff BL (2018) Dofetilide for suppression of atrial fibrillation in hypertrophic cardiomyopathy: a case series and literature review. Pacing Clin Electrophysiol 41(4): 396–401
47. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD Jr, Raisch DW, Ezekowitz MD, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) investigators (2005) Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 352(18):1861–1872
48. Saksena S, Slee A, Waldo AL, Freemantle N, Reynolds M, Rosenberg Y, Rathod S, Grant S, Thomas E, Wyse DG (2011) Cardiovascular outcomes in the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management). An assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analyses. J Am Coll Cardiol 58(19):1975–1985
49. Ahmed S, Rienstra M, Crijns HJ, Links TP, Wiesfeld AC, Hillege HL, Bosker HA, Lok DJ, Van Veldhuisen DJ, Van Gelder IC, CONVERT Investigators (2008) Continuous vs episodic prophylactic treatment with amiodarone for the prevention of atrial fibrillation: a randomized trial. JAMA 300(15):1784–1792
50. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM, Rea RF, Shen WK, Powell BD, Ommen SR, Monahan KH, Haroldson JM, Packer DL (2008) Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol 19(10):1009–1014
51. Santangeli P, Di Biase L, Themistoclakis S, Raviele A, Schweikert RA, Lakkireddy D, Mohanty P, Bai R, Mohanty S, Pump A, Beheiry S, Hongo R, Sanchez JE, Gallinghouse GJ, Horton R, Dello Russo A, Casella M, Fassini G, Elayi CS, Burkhardt JD, Tondo C, Natale A (2013) Catheter ablation of atrial fibrillation in hypertrophic cardiomyopathy: long-term outcomes and mechanisms of arrhythmia recurrence. Circ Arrhythm Electrophysiol 6(6):1089–1094
52. Zhao DS, Shen Y, Zhang Q, Lin G, Lu YH, Chen BT, Shi LS, Huang JF, Lu HH (2016) Outcomes of catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a systematic review and meta-analysis. Europace 18(4):508–520
53. Hussein AA, Saliba WI, Barakat A, Bassiouny M, Chamsi-Pasha M, Al-Bawardy R, Hakim A, Tarakji K, Baranowski B, Cantillon D, Dresing T, Tchou P, Martin DO, Varma N, Bhargava M, Callahan T, Niebauer M, Kanj M, Chung M, Natale A, Lindsay BD, Wazni OM (2016) Radiofrequency ablation of persistent atrial fibrillation: diagnosis-to-ablation time, markers of pathways of atrial remodeling, and outcomes. Circ Arrhythm Electrophysiol 9(1): e003669
54. Walters TE, Nisbet A, Morris GM, Tan G, Mearns M, Teo E, Lewis N, Ng A, Gould P, Lee G, Joseph S, Morton JB, Zentner D, Sanders P, Kistler PM, Kalman JM (2016) Progression of atrial remodeling in patients with high-burden atrial fibrillation: implications for early ablative intervention. Heart Rhythm 13(2):331–339
55. Bassiouny M, Lindsay BD, Lever H, Saliba W, Klein A, Banna M, Abraham J, Shao M, Rickard J, Kanj M, Tchou P, Dresing T, Baranowski B, Bhargava M, Callahan T, Tarakji K, Cantillon D, Hussein A, Marc Gillinov A, Smedira NG, Wazni O (2015) Outcomes of nonpharmacologic treatment of atrial fibrillation in patients with hypertrophic cardiomyopathy. Heart Rhythm 12(7): 1438–1447
56. Chen MS, McCarthy PM, Lever HM, Smedira NG, Lytle BL (2004) Effectiveness of atrial fibrillation surgery in patients with hypertrophic cardiomyopathy. Am J Cardiol 93(3):373–375
57. Quintana E, Cox JL (2017) Surgical management of atrial fibrillation at the time of septal myectomy. Ann Cardiothorac Surg 6(4): 386–393
58. January CT, Wann LS, Alpert JS et al (2014) AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 130(23):e199
59. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, Casey SA, Gohman TE, Bongioanni S, Spirito P (2002) Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 39(2):301–307
60. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P, PROTECT AF Investigators (2009) Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 374(9689):534–542
61. Katz ES, Tsiamtsiouris T, Applebaum RM, Schwartzbard A, Tunick PA, Kronzon I (2000) Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. J Am Coll Cardiol 36(2):468–471
62. Haruki S, Minami Y, Hagiwara N (2016) Stroke and Embolic events in hypertrophic cardiomyopathy: risk stratification in patients without atrial fibrillation. Stroke 47(4):936–942. https://doi.org/10.1161/STROKEAHA.115.012130
63. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J, CRYSTAL AF Investigators (2014) Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 370(26): 2478–2486