Echocardiography in Risk Assessment of Patients with Hypertrophic Cardiomyopathy - A Systematic Review

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetically transmitted cardiomyopathy with a long life expectancy in most patients, but with potentially devastating outcomes caused by sudden cardiac death (SCD). The aim of this review was to summarize echocardiographic studies in risk stratification for SCD. PubMed searches were performed by the following search string “hypertrophic cardiomyopathy” and “echocardiography.” The retrieved papers independently screened the records for inclusion and exclusion criteria according to PRISMA guidelines. A total of 841 papers were originally retrieved by searching the database, of which 26 articles were finally included in this systematic review. Ten out of eleven studies showed an association between large left atrium (LA) size and poor outcome or higher risk of arrhythmia. The majority of the studies assessed LA size by measuring LA volume. Significant discrepancies between echocardiography and cardiac magnetic resonance (CMR) were found in four out of six studies comparing left ventricle wall thickness (LVWT) and in two studies comparing LV mass. However, good correlation was seen between real-time 3D echocardiography (RL3DE) and CMR in four studies measuring LVWT and LV mass. Three studies found that systolic dysfunction evaluated by wall motion were predictors of poor outcome, but left-ventricular outflow tract (LVOT) obstruction was not. In conclusion, LA size should be assessed by volume instead of diameter on echocardiography. CMR and RT3DE might be more accurate methods to evaluate LVWT compared to echocardiography. LVOT obstruction as a predictor of outcome is questionable.

Keywords: echocardiography, hypertrophic cardiomyopathy, implantable cardioverter-defibrillator, risk stratification, sudden cardiac death.

Abstract

Hypertrophic cardiomyopathy (HCM) is the most common genetically transmitted cardiomyopathy [1]. The prevalence in the general population is approximately 1:500-1000 or as high as 1:350 if genotypes are included [1]. Shortness of breath, especially at exercise is the major limitation for these patients but chest discomfort, dizziness, syncope, and palpitations are frequently reported [1]. The heterogeneity of the clinical course is well known. Most patients have a long life expectancy but death caused by stroke, heart failure, and sudden cardiac death (SCD) even in the young remains a sobering risk [2]. Despite growing awareness of the devastation caused by SCD in young HCM patients, it is crucial to remember that SCD can occur at any age.

Ventricular fibrillation (VF) and ventricular tachycardia (VT) are the major arrhythmias resulting in death, even though lethal bradycardia also occurs. An implantable cardioverter-defibrillator (ICD) is highly effective in terminating ventricular tachyarrhythmias and is used in both secondary and primary prevention [3,4]. Survivors of cardiac arrest due to VF or VT with hemodynamic compromise are eligible for secondary prevention of SCD [1]. Primary prevention, i.e. those deemed at increased risk but without a known life-threatening arrhythmia, requires careful clinical judgment. ICD therapy may be lifesaving, but complications are non-negligible: inappropriate shocks and complications requiring surgery. ICD leads are prone to damage and 20% fail within 10 years. Health-related quality of life deteriorates in HCM patients with ICD and some ICD patients report adverse life experience due to the device [5,6].

In the 2011 American College of Cardiology (ACC) Foundation /American Heart Association (AHA)
guideline. SCD risk stratification was proposed for primary prevention based on the following five risk factors: non-sustained ventricular tachycardia (NSVT), severe left ventricular hypertrophy (\(\geq 30\) mm), family history of SCD, unexplained syncope, and an abnormal blood pressure response to exercise [7]. Patients with primary prevention ICDs with one or more of these risk factors experienced appropriate ICD therapy at a rate of 5% per year, indicating a much higher risk of SCD in some individuals and the importance of selecting patients at high risk [4].

A validation study was conducted for the 2003 ACC/European Society of Cardiology (ESC) and 2011 ACC/AHA risk stratification and treatment algorithms for SCD in patients with HCM [7-9]. There are several shortcomings in the original algorithm, with limited power to discriminate high-risk from low-risk individuals [1]. All factors are regarded as dichotomous and oversimplified without taking several other considerations into account.

Therefore, a novel clinical risk prediction model for SCD in HCM was developed from a retrospective, multicenter longitudinal cohort study of 3,65 patients (HCM risk-SCD). Age, maximal left ventricular wall thickness (LVWT), left atrial (LA) diameter, left-ventricular outflow tract (LVOT) gradient, family history of SCD, NSVT, and unexplained syncope were associated with SCD/appropriate ICD therapy [10].

While the HCM Risk-SCD risk stratification algorithm has been criticized[11], the risk prediction model has so far been validated by several studies [12,13] and is endorsed by the ESC. HCM-EVIDENCE, including 3,703 patients from 14 centers, showed an excellent prognostic accuracy of the HCM Risk-SCD calculator, especially in the high-risk group [10]. However, of the 1,524 patients with <4% SCD-risk in five years, 16 patients experienced SCD, indicating that for every 95 patients not implanted with an ICD, one patient could die of SCD within five years.

The absolute low risk of SCD and the clinical heterogeneity of HCM make it difficult to identify all patients at high risk of SCD. The implantation of an ICD only in patients with a high HCM risk-SCD score may result in unexpected SCD. Although several risk factors for SCD have been identified and are part of guidelines, improved sensitivity and specificity are warranted. Echocardiographic findings are part of the current guidelines, but the underlying evidence needs to be scrutinized in order to possibly improve risk assessment.

The role of cardiac imaging in HCM is constantly evolving. On an individual level, pitfalls and limitations in the interpretation of cardiac imaging might lead to less precise clinical decision-making. Therefore, the decision to offer the patient an ICD should be based on evidence and awareness of the underlying studies.

**Objectives**

The aim of this review was to summarize echocardiographic studies in risk stratification for sudden cardiac death in patients with hypertrophic cardiomyopathy.

**METHODS**

**Literature search**

The present systematic review was performed by searches in the database PubMed. Searches were limited to English language, human species and time of publication (published between January 2007 and February 2018). The database was searched by the following search string “hypertrophic cardiomyopathy” and “echocardiography.”

**Inclusion and exclusion criteria**

Studies that evaluated the association of specific cardiac imaging findings and outcomes of patients with HCM were included. Studies based on children and adolescents were excluded. All journal articles, reviews and case reports were excluded.

**Selection of studies**

The studies generated by the search were screened independently by title or abstract, for methodology, inclusion and exclusion criteria. The full texts of the retrieved articles after the first screening were scrutinized to inspect whether data on the topic of interest were included. Any disagreement was resolved by the authors through discussion. Reference lists of the selected articles were searched for sources of potentially relevant information. The flow of papers through the search and selection process was summarized in a flow chart inspired by PRISMA flow diagram (Figure 1).

**Report of outcomes**

The reported outcome measurements including comparisons and statistical hypothesis testing when appropriate: hazard ratio (HR) with confidence interval (CI), correlation coefficient \(r\), and a two-sided \(p\)-value.

**RESULTS**

The final extracted 26 papers are summarized below, with regard to the following echocardiographic parameters: LA diameter, LVWT, and maximum LVOT gradient.

**Left atrium**

The ESC HCM Risk-SCD calculator published in 2014 includes the LA diameter determined by M-mode or 2D echocardiography in the parasternal long-axis view [4]. However, LA size is not included in the ACC/AHA guideline from 2011.
Assessing LA size by diameter

In our search, we found four studies that measured the LA diameter when assessing LA size. Gimeno et al. [14] did a single-center prospective study on 1,380 HCM patients who underwent exercise testing. In a multivariable analysis, larger LA diameter (p = 0.03) and larger maximal LVWT (p = 0.009) were associated with NSVT. Notably, NSVT was also associated with increased risk of SCD or resuscitated ventricular arrhythmia (p = 0.049).

Finocchiaro et al. [15] also measured the LA diameter in a prospective study with 84 HCM patients and a median follow-up of 102 (53–187) months. Multivariable analysis revealed that heart failure and LA diameter were independent predictors of overall mortality or heart transplant, with a hazard ratio (HR) of 1.83 for every 1 mm increase of the LA diameter. (95% CI 1.16–2.89, p = 0.009).

Kubo et al. [16] compared two different subgroups in 80 patients with apical HCM. The two apical subgroups were defined according to morphologic patterns. The “pure-apical” form had hypertrophy (≥15 mm) confined to the LV apex below the papillary muscle level. The “distal-dominant” form, on the other hand, had apical hypertrophy extended to the interventricular septum without basal septal hypertrophy. The study found that the distal dominant subtype had a significantly larger LA diameter (43 mm vs. 39 mm; p = 0.003). The event-free rate of cardiovascular events in patients with the distal-dominant form was significantly worse (log-rank p = 0.012) than that in patients with the pure-apical form (the mean follow-up period in the pure-apical and distal-dominant groups was 5.4±5.1 and 4.3±4.9 years, respectively). Cardiovascular events were defined as SCD (including resuscitated cardiac arrest), heart failure related death, stroke related death and major morbidity events (including hospitalization for heart failure, stroke, and sustained VT). This study only included patients with apical HCM and compared the subgroups with each other, which limits the possibility to apply these findings to HCM patients in general.

On the contrary, Correia et al. [17] found no association between LA diameter and the prevalence of NSVT on Holter-monitoring in a cohort of 32 HCM patients.

Assessing LA size by volume

In four studies [18-21] LA size was assessed through measuring LA volume instead of LA diameter. All of these studies found an association between LA volume and outcome.

Choi et al. [18] also studied different subtypes in patients with apical HCM, but assessed LA size by measuring volume instead of diameter. HCM patients (n=182) were divided into three apical subtypes according to patterns of hypertrophy: pure focal (n=81) with hypertrophy confined to one or two apical segments, pure diffuse (n=70) with hypertrophy in more than two apical segments, and mixed type (n=31) with hypertrophy coexistent of the interventricular septum not extending to basal segments.

The incidence of atrial fibrillation (AF) and LA volume corrected for body mass area (LAVi) was significantly different among subtypes. The mixed type had the highest incidence of AF and the highest LAVi, indicating that enlarged LA volume is associated with AF.

Moon et al. [19] examined a cohort of 454 patients with apical HCM. Multivariable analysis reported that LAVi was an independent predictor of major cardiovascular events, defined as unplanned hospitalization because of heart failure, stroke, or cardiovascular mortality, with a HR of 1.01 for each 1 mL/m² increase of LAVi (95% CI 1.00-1.03, p < 0.047).

Yang et al. [20] on the other hand, included 81 HCM patients without the apical form. The multivariable analysis showed that increased LAVi was an independent predictor of cardiovascular death and other cardiovascular events (5 SCD, 7 heart failure hospitalizations, and 5 strokes). An increase of 5 mL/m² in LAVi was associated with outcome, hazard ratio (HR) 1.28 (95% confidence interval [CI] 1.10-1.48, p < 0.01). LAVi > 39 mL/m² had a HR of 8.19 for cardiovascular events (p < 0.01).

Hiemstra et al. [21] showed, in a prospective cohort study on 427 HCM patients, LAVi to be an independent predictor (multivariable analysis) of the combined end point of all-cause mortality, heart transplantation, aborted SCD, and appropriate ICD therapy (HR 4.27; 95% CI 2.35–7.74, p < 0.001).

Assessing LA size both by diameter and volume

Three studies [22-24] measured both LA diameter and volume. Two of these studies compared the two methods of assessing LV size and their association to outcome.

Candan et al. [22] divided 63 HCM patients into two groups: 17 with appropriate ICD therapy compared to 46 without appropriate ICD therapy. No significant differences were found in LA diameter, NSVT or LVOT gradient between groups. Interestingly, in patients with appropriate ICD therapy, a larger LAVi (p = 0.005) was observed. However, multivariable analysis did not determine LAVi to be a significant independent predictor of appropriate ICD therapy.

Tani et al. [23] examined 107 HCM patients (without LVOT obstruction and heart failure) and found that LAVi was significantly larger in patients with a...
cumulative endpoint of stroke, sudden death and congestive heart failure (n=24) than those without (LAVi: 40.1±15.4 vs. 31.5±8.7 mL/mm², p = 0.0009; maximum LA volume: 64.3±25.0 vs. 51.9±16.0 mL, p = 0.005; minimum LA volume: 33.9±15.1 vs. 26.2±10.9 mL, p = 0.008). Interestingly, there were no significant differences in the other echocardiographic parameters (LV dimension, interventricular septum, ejection fraction, E/A ratio, deceleration time). Moreover, there were no significant differences in LA diameter between the two groups, suggesting that measurement of the left atrial size by volume instead of diameter is a more sensitive method to measure LA size. The outcome group also had a significantly greater number of patients with severe mitral regurgitation, which could cause the greater LA volumes. In the outcome group there were more patients with hypertension and AF, which could confound interpretation.

Girasis et al. [24] also assessed LA size both by diameter and volume, comparing 30 HCM patients with paroxysmal AF to 25 HCM patients without known AF. Maximal LA volume and LAVi, was increased in the AF-group; however, the difference was not statistically significant (p = 0.07 and 0.09, respectively). The LA diameter, on the other hand, both in absolute measure and indexed to body surface area, was significantly increased in the AF-group (p = 0.001 for both parameters). Furthermore, the peak strain rate of the LA lateral wall was significantly decreased in the reservoir phase in the AF-group.

**Left atrial appendage**

Yakar et al. [25] studied the function of the left atrium appendage (LAA) and the prevalence of LAA-thrombus in 62 HCM patients with sinus rhythm, normal LV ejection fraction and without episodes of AF. Transesophageal echocardiography detected LAA thrombus formations in 8%. Compared to 53 age- and sex-matched controls, patients with HCM showed decreased LAA function (depressed Doppler tissue imaging emptying and filling velocities of the LAA wall and the velocities of LAA flow). The impairment was independent of age, LV mass, and the presence and degree of LV diastolic dysfunction and could predispose patients with HCM to thromboembolic events.

**Summary**

In total, 12 articles studied the left atrium in HCM patients. All studies except one studied LA size. All but one study showed an association between large LA size and poor outcome and/or higher risk of arrhythmia. The majority of the studies assessed LA size by measuring LA volume instead of LA diameter. One study compared the two methods and found that LA volume predicted outcome, whereas LA diameter did not. One study compared HCM patients with and without paroxysmal AF and found differences in both LA diameter and volume between the two groups, however the difference in LAVi failed to reach significance. One study focused on the LAA and found a decreased LAA function in HCM patients, which could explain thrombus formation and a higher risk of thromboembolic events.

**Left ventricular wall thickness**

LVWT is a known risk factor for SCD and is included in the HCM Risk-SCD calculator. LV mass is also associated with increased risk for SCD and other adverse cardiovascular events [26,27]. Although it is not included as a risk factor in the HCM Risk-SCD calculator.

Three studies showed that LVWT was significantly increased in patients with NSVT. The optimal modality for LVWT assessment remains to be clarified. We found 10 studies comparing the use of echocardiography and cardiac magnetic resonance (CMR) imaging in the measurement of LVWT and LV mass.

**LVWT associated with NSVT**

Gimeno et al. [14] studied 1,380 HCM patients with a mean follow-up of 54±49 months. All patients underwent exercise testing, 24-hour Holter monitoring and echocardiography. NSVT during exercise was associated with larger LA diameter (47.3 vs. 43.7 mm, p = 0.03) and larger maximal LVWT (22.6 vs. 19.5 mm, p = 0.009), according to multivariable analysis. Notably, exercise-induced NSVT was also independently associated with increased risk of SCD or resuscitated ventricular arrhythmia (HR 3.14; 95% CI 1.29–7.61, p = 0.01).

Di Salvo et al. [28] compared 93 HCM patients with 30 patients with LV hypertrophy due to hypertension. In the HCM-group, 24 had at least one episode of NSVT on 24-hour Holter monitoring. LVWT was significantly increased in HCM patients with NSVT compared to HCM patients without NSVT (22±6 mm vs. 19±5 mm, p = 0.03). LV mass was comparable between groups (125±21 g/m² vs. 126±16 g/m², p = non-significant).

Correia et al. [17] compared 32 HCM patients with or without NSVT on Holter-monitoring. Patients with NSVT (n=9, 28 %) had higher maximal LVWT on echocardiography (23.6 mm vs. 19.4 mm, p = 0.027).

**LVWT measured by echocardiography compared to CMR**

Corona-Villalobos et al. [29] studied 72 HCM (basal or mid-septal) patients of whom 47 underwent contrast echocardiography. Mean maximal interventricular septal WT was larger when measured by echocardiography compared to CMR: LVOT plane (1.1±3.4 mm, p = 0.009) and short axis plane (1.7±3.8 mm, p = 0.0003). Increasing differences were seen with increasing hypertrophy. Instead, when contrast
echocardiography was used for these measurements, no differences were observed.

Bois et al. [30] performed a study on 618 HCM patients. The median difference of LVWT was 3.0 mm between echocardiography and CMR. Echocardiography either overestimated (25% of cases) or underestimated (63% of cases) LVWT compared to CMR. Mean difference in measured LVWT using echocardiography and CMR was greater in the group with massive HCM (> 30 mm) than in the group with less wall thickness (p < 0.001). The fact that investigators were unblinded may have affected the interpretation.

Hindieh et al. [31] examined 195 HCM patients. Echocardiography underestimated (33%) or overestimated (60%) maximal LVWT in the majority of patients (93%) compared to CMR. Half of the patients had > 10% difference in measurements between modalities, and, interestingly, 16% had differences affecting the diagnostic (15 mm) or prognostic (30 mm) thresholds.

Phelan et al. [32] also found that CMR assessment of septal LVWT differed significantly from echocardiography and transesophageal echocardiography in 90 HCM patients, with lower measurements seen with CMR. Furthermore, the intra-observer variability was significantly lower with CMR vs. echocardiography in variability analysis, but no difference in inter-observer variability was seen between the techniques. There was significantly lower intra-observer variability with CMR vs. echocardiography (p < 0.01 for both), but no difference in inter-observer variability.

Romano et al. [33] found in 39 HCM patients that maximal LVWT measured by echocardiography was correlated to that measured by CMR (r = 0.755, p = 0.001). Furthermore, there was a significant correlation between echocardiographically assessed LVWT and LV mass (r = 0.420, p = 0.008) as well as LV mass-index derived by CMR (r = 0.467, p = 0.003). However, a considerable number of patients (31%) had incomplete LV anatomic characterization by echocardiography due to difficult visualization of the LV apex and the anterolateral free wall.

Bicudo et al. [34] found in 20 HCM patients that there was an agreement between real time 3D echocardiography (RT3DE) and CMR (Rc = 0.90; 95% CI 0.87-0.91) for determining linear measurements of LVWT, and between 2D echocardiography and CMR (Rc = 0.85; 95% CI 0.82-0.88). There was also an agreement between RT3DE and CMR for determining LV mass (Rc = 0.96; 95% CI 0.91-0.99) with a linear correlation (r = 0.97; 95% CI 0.91-0.99; p < 0.0001). This would suggest that RT3DE is a superior method compared to 2D echocardiography. The good agreement between RT3DE and CMR in measurements concerning LVWT and LV mass suggests that RT3DE might be an alternative to CMR, when CMR is contraindicated, too costly, or otherwise not available.

Chang et al. [35] also studied the correlation between LV mass measured by RT3DE and CMR, enrolling 69 HCM (46% apical) patients. The study showed a correlation between LV mass measured by RT3DE and CMR (r = 0.86, p < 0.0001). LV mass determined by M-mode and 2D echocardiography was less correlated with CMR (r = 0.48, p = 0.01, and r = 0.71, p < 0.001), respectively.

The study also showed that LV mass measured by RT3DE was more accurate in non-apical form. One limitation is the fact that two patients were excluded due to poor image quality on RT3DE, indicating that not everyone is suitable for echocardiographic examination due to poor acoustic windows and poor image quality.

Avegliano et al. [36] did a similar study on 48 HCM patients but with different subtypes of HCM; 25 nonobstructive septal hypertrophy, 15 obstructive septal hypertrophy, and 8 apical hypertrophy. The study found that LV mass obtained by RT3DE had a good concordance with CMR, provided high RT3DE image quality (n = 20, 42%) and moderate image quality (n = 15, 31%), with a high Lin’s coefficient (0.76) and a correlation index of 0.78 with an upper limit of 23.4 g and a lower limit of 21.5 g. On the other hand, when echocardiographic image quality was poor (n = 13, 27%), the correlation between LV mass by RT3DE and CMR was low with a low Lin’s coefficient (0.043). The correlation between LV mass by M-mode and CMR was also poor (301±110 g by echocardiography vs. 187±49 g by CMR (Rc = 0.17, p = 0.0002).

Valente et al. [37] compared echocardiography to CMR in 40 genopositive HCM patients without LV hypertrophy (LVWT 9.7±1.8 mm). Diagnostic agreement between the two methods was seen in 36 of 40 patients without hypertrophy, although CMR measurements of LVWT were on average 19% lower than echocardiography. Nevertheless, in 4 of 40 patients CMR demonstrated mild hypertrophy (12.6–14 mm) that was not assessed by echocardiography.

Summary
Significant discrepancies between echocardiography and CMR were found in four [29-32] of the six studies comparing LVWT measurements in HCM patients and in the two studies [35,36] comparing LV mass measured by echocardiography (M-mode) and CMR. Increasing differences were seen with increasing hypertrophy with lower LVWT measured by CMR. One study found discrepancies between echocardiography and CMR
when measuring LVWT on sarcomere carriers without echocardiographic hypertrophy [37]. In contrast, one study found a correlation [33] and one study found satisfactory agreement [34] between LVWT measured by echocardiography and CMR. Good correlation between RL3DE and CMR was also seen in one study comparing LVWT measurements [34], and 3 studies comparing LV mass measurements [34-36], but only when echocardiographic image quality was good to adequate.

**Left ventricular outflow tract obstruction and exercise**

**Echocardiography**

Exercise echocardiography has mainly been used to measure a dynamic LVOT gradient and blood pressure response. The maximum LVOT gradient determined at rest and with Valsalva provocation using pulsed and continuous wave Doppler from the apical three and five chamber views is used in the HCM Risk-SCD calculator.

Finnochiaro et al. [15] identified in a multivariable analysis LVOT gradient > 30 mmHg at rest (hazard ratio [HR] 2.56; 95% CI 1.27-5.14, p = 0.009), and LVOT gradient > 30 mmHg during stress (HR 4.96; 95% CI 1.81-13.61, p = 0.002), to be independent predictors of outcome (septal reduction) in patients with latent obstruction.

Ciampi et al. [38] analyzed 706 HCM patients from six centers with a median follow-up of 49 months (first quartile, 26; third quartile 74) with the following cumulative outcome (n=180): all-cause mortality (n=40), heart transplantations, sustained VT, heart failure, and AF. New wall motion abnormality (NWMA) and impaired coronary flow velocity reserve (CFVR ≤ 2.0) was significantly related to outcome (NWMA relative risk [RR] 2.29, 95% CI 1.62–3.27 and CFVR reduction RR 5.09, 95% CI 2.66–9.73). Interestingly, clinical/ hemodynamic criteria (i.e. symptoms, exercise-induced hypotension, and exercise-induced LVOT obstruction) did not predict outcome (RR 0.97, 95% CI 0.97–1.28).

Peteiro et al. [39] studied 239 HCM patients with a median follow up of 4.1±2.6 years with regard to a composite endpoint (n=19) of cardiac death, cardiac transplantation, appropriate ICD therapy, cardiac transplant, stroke in the context of atrial fibrillation/flutter, myocardial infarction, sustained VT or hospitalization due to heart failure. All patients underwent echocardiography at rest and after treadmill exercise. NWMA were more frequent in patients who reached any endpoint (32% vs. 6%, p< 0.001). At multivariable analysis, LVWT (HR 1.13; 95% CI 1.05–1.21, p = 0.002) and resting wall motion score index (HR 21.6; 95% CI 2.38-196.1, p = 0.006) were independent predictors whereas LVOT obstruction was not.

Peteiro et al. [40] did another study but on 148 HCM patients with the same endpoints as above and a follow-up of 7.1±2.7 years. Wall motion score index (WMSI) on exercise echocardiography was an independent multivariable predictor (HR = 404; CI 95% 12-13.681, p = 0.001). There was no association between exercise LVOT gradient and wall motion abnormalities, or between LVOT gradient and the cumulative endpoint.

**Exercise capacity as a predictor of outcome**

Desai et al. [41] showed in 426 asymptomatic HCM patients that exercise capacity rather than LVOT-gradient or blood pressure response predicted outcome (all-cause mortality, appropriate ICD therapy, aborted SCD or admission for heart failure). Exercise capacity was defined as the achieved percentage of predicted metabolic equivalent of tasks (METs) according to the Veterans Affairs cohort formula for men (predicted METs = 19 – [0.15 x age]) and for women the St. James Take Heart Project formula (predicted METs = 14.7 – [0.13 x age]). The mean follow-up was 8.7±3 years. The event rate was 1% in patients achieving >100% of predicted METs compared to 12% in patients achieving <85 % of predicted METs.

**Summary**

The search generated one study [15] that identified LVOT gradient > 30 mmHg to be an independent predictor of outcome in multivariable analysis. However, the endpoint was clinical deterioration leading to septal reduction and not SCD. Interestingly, three studies [38-40] found that NWMA and WMSI were predictors of poor outcome, but LVOT obstruction was not. Another study [41] showed that exercise capacity predicted outcome, whereas LVOT gradient did not. This indicates that NWMA rather than LVOT obstruction used in the HCM Risk-SCD Calculator could be a predictor of SCD.

**Discussion**

The ESC HCM Risk-SCD calculator includes three echocardiographic parameters: LA diameter, maximum left ventricular wall thickness, and maximum left ventricular outflow gradient.

The ESC HCM Risk-SCD calculator recommends assessing LA size by measuring the LA diameter determined by M-mode or 2D echocardiography in the parasternal long-axis view [10]. However, to be able to derive volume from diameter, one must assume that the LA is spherical in shape, which may not always be the case. Furthermore, when the LA enlarges, it is often not an isotropic enlargement [42-44]. Several studies have shown that the diameter frequently does not represent an accurate estimation of LA size and have suggested that LA...
volume should be used instead [42,45,46]. When it comes to assessing LA volume and remodeling in clinical practice, the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend measurement of LA volume [47]. Based on these findings it might be advised to include LA volume instead of LA diameter in upcoming guidelines.

While CMR is generally considered the “gold standard” in evaluating LV geometry, its routine use in clinical practice is limited because it is expensive and not widely available. Echocardiography is a simple, repeatable, and inexpensive tool often used for LV assessment, including LVWT. However, several studies have shown large discrepancies in LVWT measurements obtained by echocardiography compared to CMR. This is of clinical importance as they affect diagnostic thresholds and prognosis. CMR may provide the more accurate assessment of LVWT measurements and help to reduce misclassification when assessing risk according to the HCM Risk-SCD calculator.

On the other hand, RT3DE is rapidly gaining appreciation as a tool to measure LVWT and LV mass, and several studies have proved it superior to 2D echocardiography. It is suggested that in HCM patients, an asymmetric LV morphology contributes to the inaccuracies of 2D echocardiography LV mass estimations compared to CMR [35]. RT3DE resolves the asymmetry and thus the discrepancies are smaller between RT3DE and CMR. However, the method is limited to images of high or adequate quality.

Echocardiography has been the standard modality assessing LVWT. Even so, echocardiography is highly user dependent, and small measurement errors may influence the risk score and possibly impact the clinical decision about the use of an ICD. In some patients, poor acoustic windows make it difficult to obtain accurate LVWT values. CMR has a superb spatial resolution and may complement echocardiography for these patients.

Even though recent studies indicate that RT3DE and CMR might be more accurate and should be considered when LVWT measurements affect diagnostic thresholds and prognosis, it is important to note that current diagnostic and prognostic values are based on studies that used echocardiography. Because of discrepancies in measurements between modalities, new reference values need to be established for RT3DE and CMR.

LVOT obstruction was not a predictor of outcome in our review. The LVOT-obstruction gradient is highly dynamic depending on several physiologic parameters [48]. Recent studies indicate that predictors of outcome are new wall motion abnormalities, wall motion score index, and exercise capacity.

**Limitations**

HCM is characterized by its heterogeneity. The disease manifestation includes diverse phenotypic expressions. Typically, studies only account for predictors at baseline and the longitudinal modifiers are unknown. In addition, there is significant ethnic diversity, i.e. the apical form is more prevalent in Asian populations. This might limit generalization to the Western population, where asymmetric septal hypertrophy is more common.

Several of the studies are subject to statistical error, due to small sample size. Furthermore, follow-up durations varied widely among the studies and most HCM patients live a long time with the condition.

The endpoints differ between studies and often include composite endpoints. That implies that the associations with SCD are not necessarily proven. Often appropriate ICD therapy is used as a surrogate for SCD, however not all aborted arrhythmias would have led to SCD as many ventricular arrhythmias are self-terminated [49].

Based on the lack of uniform predictors and outcome measurements, a meta-analysis seems impossible. Future large studies with prospective outcome measurements are warranted. Ongoing initiatives with large registries would be helpful.
Fig-1: PRISMA search flow diagram
**CONCLUSION**

According to recent studies, LA size should be assessed by volume instead of diameter on echocardiography. Compared to echocardiography, CMR and RT3DE might be more accurate methods to evaluate LVWT. LVOT obstruction as a predictor of outcome is questionable.

**Strengths and limitations of this study**

- The hypertrophic cardiomyopathy (HCM) disease manifestation includes diverse phenotypic expressions. Typically, studies only account for predictors at baseline and the longitudinal modifiers are unknown.
- Several of the studies are subject to statistical error, due to small sample size.
- Follow-up durations varied widely among the studies and most HCM patients live a long time with the condition.
- The endpoints differ between studies and often include composite endpoints.
- Based on the lack of uniform predictors and outcome measurements, a formal meta-analysis seems impossible.

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**Author contributions**

Nicolette Mankovsky Hult: data collection, data analysis, major writing of the manuscript. Jonny Nordström: design, data analysis, critical revision, project co-management

Peter Magnusson: project idea, design, data analysis, writing of the manuscript, project management

All authors approved the manuscript for submission.

**Conflicts of interest**

Peter Magnusson: speakers fee/grant from Abbott, Bayer, Boehringer Ingelheim, Novo Nordisk, and Pfizer.

**Table 1: Studies included in review**

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<th>First Author</th>
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<th>Title</th>
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<th>Study type</th>
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<td>Utility of Real Time 3D Echocardiography for the Assessment of Left Ventricular Mass in Patients with Hypertrophic Cardiomyopathy: Comparison with Cardiac Magnetic Resonance</td>
<td>Argentina</td>
<td>Prospective</td>
<td>48 HCM: 25 NOHCM 15 OHCM 8 ApHCM</td>
<td>LVM obtained by RT3DE had a high correlation with LVM measured by CMR, but only when the quality of the echocardiographic images was high or adequate. When echocardiographic image quality was low, the correlation between LVM by RT3DE and CMR was poor. There was poor correlation between LVM by M-mode and CMR.</td>
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<tr>
<td>Author(s)</td>
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<tr>
<td>Bicudo[34]</td>
<td>2008</td>
<td>Value of Real Time Three-Dimensional Echocardiography in Patients with Hypertrophic Cardiomyopathy: Comparison with Two-Dimensional Echocardiography and Magnetic Resonance Imaging</td>
<td>Brazil</td>
<td>Prospective</td>
<td>20 HCM</td>
<td>Excellent agreement between RT3DE and CMR for linear measurements of LVWT (Rc = 0.90; 95% CI 0.87-0.91) and LVM (Rc= 0.96; 95% CI 0.91-0.99). Satisfactory agreement between echocardiography and CMR (Re = 0.85; 95% CI 0.82-0.88).</td>
</tr>
<tr>
<td>Bois[30]</td>
<td>2017</td>
<td>Comparison of Maximal Wall Thickness in Hypertrophic Cardiomyopathy Differs Between Magnetic Resonance Imaging and Transthoracic Echocardiography</td>
<td>USA</td>
<td>Retrospective</td>
<td>618 HCM</td>
<td>Discrepancy between the techniques for maximal reported LVWT assessment. Mean difference in measured LVWT using echocardiography and CMR was greater in the group with massive HCM (&gt; 30 mm) than the group with less wall thickness (p &lt; 0.001).</td>
</tr>
<tr>
<td>Candan[22]</td>
<td>2017</td>
<td>Mechanical dispersion and global longitudinal strain by speckle tracking echocardiography: Predictors of appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy.</td>
<td>Turkey</td>
<td>Case control</td>
<td>63 HCM with ICD (17 with ICD-therapy)</td>
<td>Median follow-up period of 3 years (21.5±6.9 months). High SCD-risk score, longer mechanical dispersion, lower GLPS and LAVi (p = 0.005) was associated with poor outcome.</td>
</tr>
<tr>
<td>Chang[35]</td>
<td>2013</td>
<td>Assessment of left ventricular mass in hypertrophic cardiomyopathy by real-time three-dimensional echocardiography using single-beat capture image</td>
<td>Korea</td>
<td>Prospective</td>
<td>69 HCM</td>
<td>RT3DE measurement of LVM more accurate (r=0.86, p = 0.0001) than 2D (r = 0.71, p &lt; 0.001) or M-mode (r = 0.48, p = 0.01) when compared to CMR.</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Study Details</td>
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<td>Endpoint Findings</td>
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<td>Choi[18]</td>
<td>2008</td>
<td>Phenotypic spectrum and clinical characteristics of apical hypertrophic cardiomyopathy: multicenter echo-Doppler study.</td>
<td>Korea</td>
<td>Prospective</td>
<td>ApHCM 3 subtypes: Incidence of atrial fibrillation and LAVi were significantly different among subtypes. Peak systolic and diastolic mitral annular velocities were also significantly different.</td>
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<tr>
<td>Ciampi[38]</td>
<td>2016</td>
<td>Prognostic role of stress echocardiography in hypertrophic cardiomyopathy: The International Stress Echo Registry</td>
<td>International SE data-bank (Italy, Spain, Portugal, Serbia)</td>
<td>Retrospective</td>
<td>706 HCM Ischemia-related end-points on exercise echocardiography (CFVR reduction (RR 5.09, 95% CI 2.66–9.73) and NWMA (RR 2.29; 95% CI 1.62–3.27)) showed greater predictive accuracy than hemodynamic endpoints (RR 0.97, 95% CI 0.97–1.28).</td>
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<tr>
<td>Corona-Villalobos[29]</td>
<td>2016</td>
<td>Left ventricular wall thickness in patients with hypertrophic cardiomyopathy: a comparison between cardiac magnetic resonance imaging and echocardiography</td>
<td>USA</td>
<td>Retrospective</td>
<td>72 HCM, 52 CECHO Echocardiography measures greater LVWT compared to CMR (LVOT plane (1.1±3.4 mm, p = 0.009) and short axis plane (1.7±3.8 mm, p = 0.0003)), with the largest differences in moderate to severe hypertrophy (affecting the diagnostic thresholds and prognosis). Contrast echocardiography more closely approximates CMR measurements of LVWT (p &lt; 0.001).</td>
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<tr>
<td>Correia[17]</td>
<td>2011</td>
<td>Longitudinal left ventricular strain in hypertrophic cardiomyopathy: correlation with non-sustained ventricular tachycardia.</td>
<td>Portugal</td>
<td>Prospective</td>
<td>32 HCM HCM patients with or without NSVT on Holter-monitoring were compared. Patients with NSVT (n=9, 28%) had higher maximal LVWT on echocardiography (23.6 mm vs. 19.4 mm, p = 0.027). Mean follow-up of 22.3 months.</td>
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<tr>
<td>Desai[41]</td>
<td>2014</td>
<td>Exercise echocardiography in asymptomatic HCM: exercise capacity, and not LV outflow tract gradient predicts long-term outcomes.</td>
<td>USA</td>
<td>Case control</td>
<td>426 HCM Mean follow up 8.7±3 years. Exercise stress testing provides risk stratification, with a low event rate (1%) in patients achieving &gt;100% of predicted METs compared to 12 % in patients achieving &lt;85 %. LVOT-gradient did not predict outcome (p = 0.08).</td>
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<tr>
<td>Di Salvo [28]</td>
<td>2010</td>
<td>Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy and new ultrasonic derived parameters</td>
<td>Italy</td>
<td>Case control</td>
<td>93 HCM 30 controls (with hypertension) LVWT was significantly increased in patients with NSVT compared to patients without NSVT (22±6 mm vs. 19±5 mm, p = 0.03. However, LVM was comparable between the groups.</td>
<td></td>
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<tr>
<td>Finocchiaro [15]</td>
<td>2012</td>
<td>Prognostic role of clinical presentation in symptomatic patients with hypertrophic cardiomyopathy</td>
<td>Italy</td>
<td>Prospective</td>
<td>84 HCM Heart failure and left atrium diameter at diagnosis showed incremental prognostic power compared to echocardiographic Doppler assessment of left ventricular systolic and diastolic dysfunction. HR of 1.83 for every 1 mm increase of the LA diameter: (95% CI 1.16–2.89, p = 0.009).</td>
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<tr>
<td>Gimeno [14]</td>
<td>2009</td>
<td>Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy.</td>
<td>UK</td>
<td>Prospective</td>
<td>1,380 HCM Larger LA diameter (p = 0.03) and larger maximal LVWT (p = 0.009) was associated with NSVT. NSVT was also associated with increased risk of SCD or resuscitated ventricular arrhythmia (p = 0.049).</td>
<td></td>
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<tr>
<td>Girasis [24]</td>
<td>2013</td>
<td>Patients with hypertrophic cardiomyopathy at risk for paroxysmal atrial fibrillation: advanced echocardiographic evaluation of the left atrium combined with non-invasive P-wave analysis</td>
<td>Greece</td>
<td>Retrospective</td>
<td>30 HCM PAF; (32 HCM-controls, 25 controls) Compared with HCM controls, in HCM-PAF patients, LA diameter was significantly enlarged (LADAP: 46.1±5.9 vs. 40.0±4.7 mm, P, 0.001), peak strain rate of the LA lateral wall in the reservoir phase was significantly decreased (LAT peak SR-S: 1.93±0.51 vs. 2.55±0.83 s²1, p = 0.01), and P-wave duration in the Z-lead was significantly prolonged (P-durZ: 106.9±24.6 vs. 86.2±14.3 ms, P, 0.001).</td>
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<tr>
<td>Hiemstra [21]</td>
<td>2017</td>
<td>Global Longitudinal Strain and Left Atrial Volume Index Provide Incremental Prognostic Value in Patients With Hypertrophic Cardiomyopathy.</td>
<td>Netherlands</td>
<td>Prospective</td>
<td>427 HCM Multivariate analysis revealed LAVi to be an independent risk factor for adverse outcome. (HR 4.27; 95% CI 2.35–7.74, p &lt; 0.001).</td>
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<td>Hindieh [31]</td>
<td>2017</td>
<td>Discrepant Measurements of Maximal Left Ventricular Wall Thickness Between Cardiac Magnetic Resonance Imaging and Echocardiography in Patients With Hypertrophic Cardiomyopathy</td>
<td>Canada</td>
<td>Retrospective</td>
<td>195 HCM</td>
<td>In 31 (15.9%) patients, measurement discrepancy occurred at diagnostic (15 mm) or prognostic (30 mm) cut-offs. Half of the patients had &gt; 10% difference in measurements between modalities.</td>
</tr>
<tr>
<td>Kubo [16]</td>
<td>2009</td>
<td>Clinical profiles of hypertrophic cardiomyopathy with apical phenotype—comparison of pure-apical form and distal-dominant form</td>
<td>Japan</td>
<td>Retrospective</td>
<td>80 apHCM:51 pure, 29 distal</td>
<td>Follow-up period in the pure-apical and distal-dominant groups was 5.4±5.1 and 4.3±4.9 years respectively. Distal dominant group was more symptomatic, had larger LA diameter (43 mm vs. 39 mm, p = 0.003) and more events (log-rank p = 0.012) compared to pure apical form.</td>
</tr>
<tr>
<td>Moon[19]</td>
<td>2011</td>
<td>Clinical and echocardiographic predictors of outcomes in patients with apical hypertrophic cardiomyopathy</td>
<td>Korea</td>
<td>Prospective</td>
<td>454 ApHCM</td>
<td>The clinical outcomes of patients with apical HCM were less benign in older patients and in those with hypertension or diabetes. In addition, LAVi, Sa velocity, and E/Ea ratio were predictors of a poor prognosis in patients with apical HCM. HR of 1.01 for each 1 ml/m² increase of LAVi (95% CI 1.00-1.03, p &lt; 0.047).</td>
</tr>
<tr>
<td>Peteiro [39]</td>
<td>2012</td>
<td>Prognostic Value of Exercise Echocardiography in Patients with Hypertrophic Cardiomyopathy</td>
<td>Spain</td>
<td>Prospective</td>
<td>239 HCM</td>
<td>LVWT (p = 0.002) and resting WMSi (p = 0.006) were independent predictors of hard events. LVOT obstruction was not associated with either endpoint.</td>
</tr>
<tr>
<td>Peteiro [40]</td>
<td>2015</td>
<td>Exercise echocardiography and cardiac magnetic resonance imaging to predict outcome in patients with hypertrophic cardiomyopathy</td>
<td>Spain</td>
<td>Prospective</td>
<td>148 HCM</td>
<td>Follow-up of 7.1±2.7 years. Wall motion score index (WMSi) on exercise echocardiography was an independent multivariable predictor (HR = 404; CI 95% 12-13,681, p = 0.001). There was no association between exercise LVOT gradient and the cumulative end-point.</td>
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<th>Reference</th>
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<th>Study Design</th>
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<th>Summary</th>
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<tbody>
<tr>
<td>Phelan[16]</td>
<td>2017</td>
<td>Comparison of Ventricular Septal Measurements in Hypertrophic Cardiomyopathy Patients Who Underwent Surgical Myectomy Using Multimodality Imaging and Implications for Diagnosis and Management.</td>
<td>USA</td>
<td>Prospective</td>
<td>90</td>
<td>CMR assessment of septal LVWT differed significantly from echocardiography (8%) and trans esophageal echocardiography (13%), with lower measurement seen with CMR (both p &lt; 0.001).</td>
</tr>
<tr>
<td>Romano[33]</td>
<td>2008</td>
<td>Evaluation of the left ventricular anatomy in hypertrophic cardiomyopathy: comparison between echocardiography and cardiac magnetic resonance imaging.</td>
<td>Italy</td>
<td>Retrospective</td>
<td>39</td>
<td>Maximal LVWT on echocardiography was correlated to LVWT on CMR (r = 0.755, p = 0.001). There was a significant correlation between echocardiographically assessed LVWT and LV mass (r = 0.420, p = 0.008) as well as LV mass-index derived by CMR (r = 0.467, p = 0.003).</td>
</tr>
<tr>
<td>Tani[23]</td>
<td>2011</td>
<td>Left atrial volume predicts adverse cardiac and cerebrovascular events in patients with hypertrophic cardiomyopathy.</td>
<td>Japan</td>
<td>Prospective</td>
<td>102</td>
<td>Maximum LAV, minimum LAV, and LAVi corrected for body surface area were significantly larger in HCM patients that reached endpoint compared to those who did not. (LAVi: 40.1±15.4 vs. 31.5±8.7 ml/mm², p = 0.0009; maximum LA volume: 64.3±25.0 vs. 51.9±16.0 ml, p = 0.005; minimum LA volume: 33.9±15.1 vs. 26.2±10.9 ml, p = 0.008).</td>
</tr>
<tr>
<td>Valente [37]</td>
<td>2013</td>
<td>Comparison of echocardiographic and cardiac magnetic resonance imaging in hypertrophic cardiomyopathy sarcomere mutation carriers without left ventricular hypertrophy.</td>
<td>USA</td>
<td>Prospective</td>
<td>40 gene-carriers</td>
<td>CMR identified mild hypertrophy in 10% of mutation carriers with normal echocardiographically assessed wall thickness.</td>
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</tbody>
</table>
### References


3. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Cardiak [25] 2010 Assessment of Left Atrial Appendage Function during Sinus Rhythm in Patients with Hypertrophic Cardiomyopathy: Transesophageal Echocardiography and Tissue Doppler Study Turkey Case control 62 HCM 53 controls LAA thrombus formation was not rare (8%) in this patient population (sinus rhythm). The significantly depressed LAA filling and emptying velocities in SR may predispose patients with HCM to thromboembolic events.

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<th>Sample Size</th>
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<tbody>
<tr>
<td>Yakar[25]</td>
<td>2010</td>
<td>Assesment of Left Atrial Appendage Function during Sinus Rhythm in Patients with Hypertrophic Cardiomyopathy: Transesophageal Echocardiography and Tissue Doppler Study</td>
<td>Turkey</td>
<td>Case control</td>
<td>62 HCM 53 controls</td>
<td>LAA thrombus formation was not rare (8%) in this patient population (sinus rhythm). The significantly depressed LAA filling and emptying velocities in SR may predispose patients with HCM to thromboembolic events.</td>
</tr>
<tr>
<td>Yang[20]</td>
<td>2009</td>
<td>Left Atrial Volume Index: A Predictor of Adverse Outcome in Patients With Hypertrophic Cardiomyopathy</td>
<td>Korea</td>
<td>Prospective</td>
<td>81 non-apical HCM</td>
<td>Univariate analysis showed that older age, atrial fibrillation, elevated E/E ratio, increased left atrial (LA) volume index, presence of mitral regurgitation grade &gt; 2 NYHA class III or IV, and LGE ≥6% were associated with cardiovascular events. In multivariate Cox regression analysis, increased LA volume index was found to be an independent predictor of cardiovascular events (for each 5 mL/m² increase, HR 1.28; 95% CI, 1.10-1.48; p &lt; 0.01). Increased LA volume index was also revealed to be an independent predictor for cardiovascular events other than death (for each 5 mL/m² increase, hazard ratio, 1.44; 95% confidence interval, 1.12-1.83; p &lt; 0.01).</td>
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ApHCM - apical hypertrophic cardiomyopathy; CI - confidence interval; CMR - cardiac magnetic resonance; HCM - hypertrophic cardiomyopathy; HR - hazard ratio; LA - left atrium; LAA - left atrial appendage; LAV - left atrial volume; LAVi - left atrium volume index; LVED - left ventricle end diastolic; LVES - left ventricle end systolic; LVM - left ventricle mass; LVOT – left ventricle outflow tract; LVWT - left ventricle wall thickness; NOHCM - nonobstructive hypertrophic cardiomyopathy; NWMA - new wall motion abnormality; OHCM - obstructive hypertrophic cardiomyopathy; PAF - paroxysmal atrial fibrillation; RR - relative risk; RT3DE - real time 3D echocardiography; SCD - sudden cardiac death; WMSi - wall motion score index


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