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Review

Syncope in hypertrophic cardiomyopathy (part I): An updated systematic review and meta-analysis

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ABSTRACT

Aims: To describe the proportion of patients with syncope among those affected by hypertrophic cardiomyopathy (HCM) and the relevance of syncope as risk factor for sudden cardiac death and life-threatening arrhythmic events.

Method and results: Systematic review of original articles that assessed syncope in HCM patients. Literature search of PubMed including all English publications from 1973 to 2021.We found 57 articles for a total of 21.791 patients; of these, 14 studies reported on arrhythmic events in the follow-up. Syncope was reported in 15.8% (3.452 of 21.791) patients. It was considered unexplained in 91% of cases. Life-threatening arrhythmic events occurred in 3.6% of non-syncopal patients and in 7.7% of syncopal patients during a mean follow-up of 5.6 years. A relative risk of 1.99 (95%CI 1.39 to 2.86) was estimated for syncope patients by the random effect model using Haldane continuity correction for 0 events.

Conclusions: In the current practice, the cause of syncope remained unexplained in most patients affected by HCM. The management of patients seems mainly driven by risk stratification rather than identification of the aetiology of syncope. There is a need of precise instructions how to apply the recommendations of current guidelines to this disease, which tests are indicated and how to interpret their findings.
The protocol was registered in Prospero (ID: 275963).

1. Background

Syncope is a challenging condition in patients with hypertrophic cardiomyopathy (HCM) as several causes are potentially involved, including arrhythmias (rapid atrial and ventricular tachy-arrhythmias, sinoatrial or atrioventricular block), low output states (outflow tract obstruction, reduced preload leading to underfilling) and abnormal cardiac and vascular reflexes (orthostatic hypotension, neurally-mediated reflexes). Unexplained syncope in HCM is an established risk factor for sudden cardiac death (SCD) [1,2]. Identifying the mechanism of syncope is important for preventing SCD as well as syncopal recurrence, which may lead to severe consequences like secondary trauma, lifestyle changes, social and medical costs.

The aim of this systematic review is to describe the proportion of syncope in the HCM population, its relevance as a risk factor for SCD and the incidence of life-threatening arrhythmic events in the follow-up of syncopal HCM cohorts in comparison with non-syncopal one. Moreover, we will assess the diagnostic yield and the use of the diagnostic tests, which are reported for the diagnosis of unexplained syncope.

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2. Methods

2.1. Search strategy and eligibility criteria

We performed a systematic review of original articles that assessed syncope in HCM patients. The protocol was registered in Prospero (ID: 275963). A comprehensive literature search of PubMed including all English publications from 1973 to 2021 was performed using the Medical Subject Headings search terms "hypertrophic cardiomyopathy" and "syncope." From the initial 232 results, we excluded editorial letters, comments, reviews, systematic reviews, case reports, practical guidelines and replicated populations from the same authors. We found 51 articles that assessed syncope at initial evaluation in HCM population [3–53] and we included 9 additional articles from personal files [2,54–61]. The PRISMA flow diagram depicts the flow of information through the different phases of the systematic review (Supplementary Fig. 1). Overall, we analysed 57 articles for a total of 21,791 patients (Supplementary Table 1). Of these, only 14 studies reported on arrhythmic events in the follow-up (Supplementary Table 2), and 26 studies reported the results of diagnostic tests (Supplementary Table 3).

2.2. Selection studies and data extraction

Two authors (MG and CF) independently screened titles and abstracts and reviewed the full text of potentially relevant studies. They discussed questionable studies to agree on their possible inclusion in the present analysis.

For each included study we extracted the following information: authors, publication year, study location, number subjects with history of syncope, total sample size, mean age, percentage of male patients, type of diagnostic tools (documented or no clear data), mean follow-up duration syncope subjects with and without SCD, no syncope subjects with and without SCD, association estimate (Risk relative - RR) and relative 95% Confidence Intervals (95% CI) between the history of syncope and arrhythmic events risk, use of adjustment approach for the association estimate. When adjusted or raw association estimate was not available, we calculated it.

2.3. Statistics

We performed a meta-analysis of syncope proportion (ratio between number subjects with history of syncope and total sample size) using a one-step approach based on generalized linear mixed models (GLMMs). This approach overcomes the limits of traditional transformations of proportions (e.g log, logit, arcsine, and Freeman–Tukey double-arcsine) taking into account for within-study uncertainties, which are especially critical for small sample sizes and rare events and does not require corrections for zero counts. GLMMs do not need any data transformations at the study level because they directly model event counts with binomial likelihoods, and use a specific link function to transform latent true proportions to a linear scale [62]. In the forest plot we reported the original point estimates and relative 95% confidence intervals (95% CI) and the GLMM overall proportion. This last could be interpreted as the median proportion from multiple studies. Presence of publication bias was evaluated by means of funnel plot inspection. We built the funnel plot as suggested by Hunter et al. [63] plotting the study size against the log odds of proportion. Moreover, a meta-regression was performed to identify subject and study-characteristics useful to explain the variability in published syncope proportions.

Finally, we estimated the pooled risk relative (RR) and the corresponding 95% CI between the history of syncope and arrhythmic events risk. This estimate was obtained according to Der Simonian and Laird's method [64] pooling all available RR and pooling by duration of follow-up (more or less of 4 years). Statistical heterogeneity among association estimates was evaluated by means of I^2 of Higgins, varying from 0 to 100%. High values of this index (more than >75%) suggest high heterogeneity [65]. In presence of 0 events in one or both exposure groups, the continuity correction of Haldane [66] was used. As sensitivity analysis we applied other three continuity correction methods (Carter, TACC and Pettigrew [67]. Results were considered statistically significant when two-tailed *p*-value was lower than 0.05. All analyses were performed with R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Prevalence and prognosis

Syncope was reported in 15.8% (3452 of 21,791) of patients. It was considered unexplained in 91% of cases, while in the remaining 9% the aetiology was heterogeneous, as it was attributed to left ventricular outflow tract (LVOT) obstruction (3.3%), abnormal blood pressure/vascular response or neurally mediated (2.4%), ventricular arrhythmias (3.0%), supra-ventricular arrhythmias (0.8%) and conduction disturbances (0.1%) (Fig. 1).

The forest plot in Supplementary Fig. 2 reports the syncope proportion and its 95% CI for each study. The overall proportion estimated by GLMM is 22.4% (95% CI 18.9 to 26.4). The meta-regression model included the following variables: i) age mean, ii) percentage male, iii) published year (⟨2000,2000−2010,⟩ 2010), geographic area (Europe, Asia, North America, Multicenter), total sample size, diagnostic tools (documented, no clear data). High percentage of males, recent publication years and presence of documented for syncope diagnosis was statistically significant associated to low syncope proportion. Funnel plot reported in Supplementary Fig. 3 did not show a strong asymmetry of estimates although we cannot exclude the presence of publication bias.

3.2. Life-threatening arrhythmic events

Raw data of arrhythmic events were assessed in 14 articles for a total of 9834 patients, 1357 of whom (13,8%) with a history of syncope. An implantable cardioverter-defibrillator (ICD) had been implanted in 1191 (12.2%) patients. In 7 studies (total 319 patients), an ICD had been implanted in 172 (54%) patients with a history of syncope and in 147 (46%) patients without a history of syncope. The other studies report an overall incidence of ICD of 9.2%, but they do not report the prevalence in patients with syncope (Supplementary Table 2).

Life-threatening arrhythmic events defined as SCD or appropriate ICD shocks occurred in 3.6% of non-syncopal patients and in 7.7% of syncopal ones during a mean follow-up of 5.6 years (Table 1). The overall relative risk for syncope patient, estimated by the random effect model using Haldane continuity correction for 0 events, was 1.99 (95% CI 1.39 to 2.86) (Fig. 2). The sensitivity analysis shows similar pooled RR using Carter continuity correction methods (2.01, 1.40 to 2.89) (Supplementary Fig. 4), TACC continuity correction methods (2.05, 1.51 to 2.79), (Supplementary Fig. 5) and Pettigrew continuity correction methods (1.99, 1.39 to 2.87), (Supplementary Fig. 6).

3.3. Diagnostic tests

A total of 26 studies (among the 60 eligible, see Supplementary Fig. 1) reported the results of the most common diagnostic tests used in the management of unexplained syncope (see Supplementary Table 3). The pooled findings are reported in Table 2. Surprisingly, no study reported data on carotid sinus massage, stress echocardiography or implantable loop recorder (ILR) despite these tests are considered among the most useful for the assessment of syncope [68].

4. Discussion

From this overview, several considerations can be drawn that are

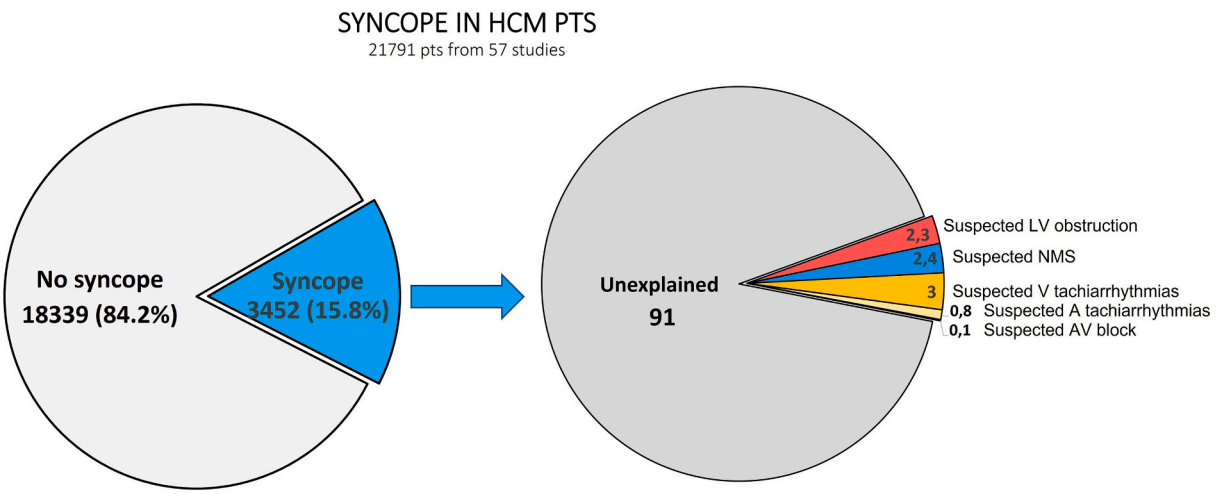

Fig. 1. Prevalence of syncope in HCM population and its aetiology.

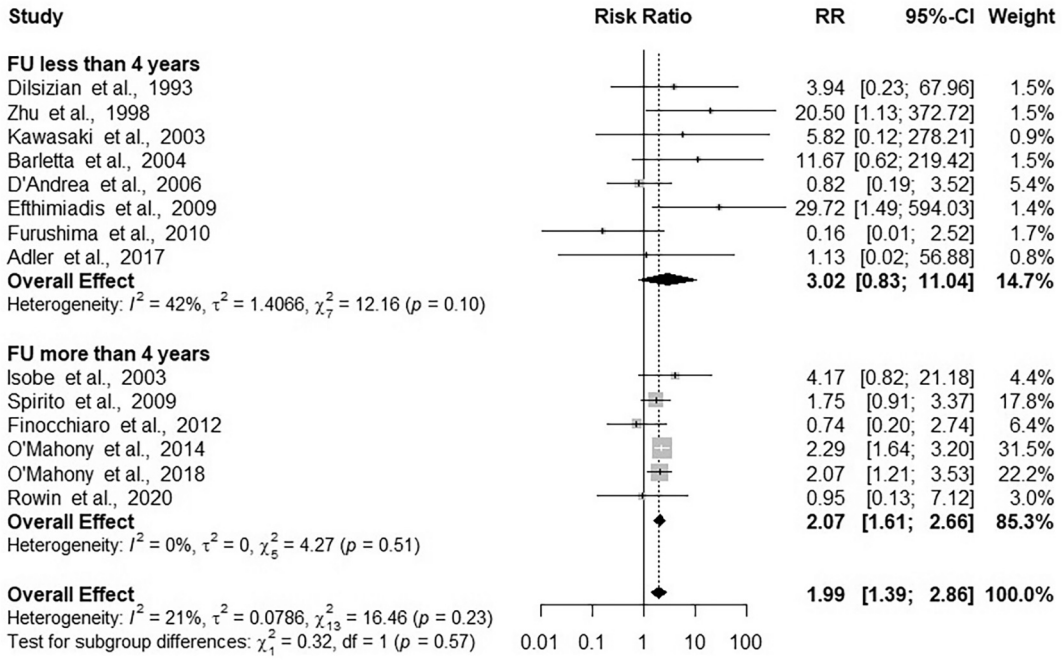

Fig. 2. Relative risk for syncope patient estimated by the random effect model using Haldane continuity correction for 0 events. Studies with a mean follow-up less than 4 years were analysed separately from those with a follow-up longer than 4 years.

useful for a better understanding of the cause and management of syncope in patients with HCM and future research planning.

4.1. Syncope in HCM and in the general population

In HCM syncope is reported in nearly 16% of the patients and therefore it seems to be no more frequent than in the general population which is approximately 25% in the age range of HCM patients of this study [68]. However, the very low rate of reflex aetiology raises the suspicion of an under-reporting of this aetiology.

4.2. Syncope as risk factor for sudden cardiac death

In the present study, SCD events were twice more frequent in HCM patients with syncope, compared with those without (7.7% versus 3.6% respectively) and syncope was associated with almost a double risk of life-threatening arrhythmias (RR 1.99, 95%CI 1.39 to 2.86). These results confirm and validate unexplained syncope as an important risk factor, which is included both in the HCM Risk-SCD calculator [1,2] and in the algorithm for ICD patient selection of the recent 2020 AHA/ACC HCM guidelines [69].

Surprisingly, syncope was reported as unexplained in the vast majority of patients (91%). It is likely that the cause of syncope in many such cases was under-diagnosed. This point has obvious practical implications A more precise diagnosis of syncope should have been useful to better stratify the risk, ruling out the risk of arrhythmic events in some and increasing the risk estimate in others. Moreover, the absence of an established diagnosis raises the question whether syncope has a direct causal effect on SCD or it is only an indirect risk marker which reflects a more severe cardiac disease [70].

4.3. Unexplained syncope

The fact that syncope remained unexplained in a such a high

Table 1
Raw data of life-threatening arrhythmic events in 14 HCM studies that reported data for patients with and without a history of syncope.

Reference	Pts	FU (years)	Mean age	No syncope		Syncope	
				Patients	Events	Patients	Events
Rowin et al., 2020	146	5,8	16	129	9	17	1
O'Mahony et al., 2014	3703	5,9	52	3229	56	474	17
Adler et al., 2017	168	1,3	59	154	0	14	0
O'Mahony et al., 2018	3675	5,7	48	3168	146	507	52
Finocchiaro et al., 2012	84	8,5	43	50	6	34	3
Furushima et al., 2010	66	0,8	55	55	14	11	0
Efthimiadis et al., 2009	123	2,9	52	106	0	17	2
Spirito et al., 2009	1511	5,6	46	1306	61	205	13
D'Andrea et al., 2006	123	4	39	99	10	24	2
Barletta et al.,2004	28	0,75	44	20	0	8	2
Kawasaki et al., 2003	73	2,3	52	63	0	10	0
Isobe et al., 2003	58	10,4	51	50	3	8	2
Zhu et al., 1998	53	3,9	42	40	0	13	3
Dilsizian et al., 1993	23	0,4	17	8	0	15	8
Total	9834	5,6	49	8477	305 (3.6%)	1357	105 (7.7%)

Table 2
Diagnostic yield of most frequent tests performed in 26 HCM studies that reported data on syncope assessment.

Test	Patients tested	Sustained VT/ FV	Non-sustained VT	Low output states	Angina/ ischemia	Sick sinus syndrome	AV conduction disease	Reflex syncope response
1–7 day ECG monitoring	384	2 (0.5%)	118 (31%)				1 (0%)	
Exercise test	360	3 (0.8%)		2 (1%)	6 (1.7%)			49 (14%)
EPS	229	72 (31%)	9 (3.9%)			34 (15%)	27 (12%)	
Tilt testing	81							21 (26%)
Coronary angiography	37				0 (0%)			

ECG = electrocardiogram; EPS = electrophysiology study; VT = ventricular tachycardia; VF = ventricular fibrillation; AV = atrio-ventricular.

percentage warrants further consideration. There are several possible explanations:

i. Physicians were well aware of the multifactorial mechanisms that may lead to syncope in patients with HCM. The precise mechanism may not be identified despite the use of multiple diagnostic tests. Thus, they prudentially preferred to classify syncope as unexplained.
ii. Scarce availability of most necessary tests for syncope evaluation might be considered especially in older studies.
iii. Physicians were concerned on the low sensitivity and specificity of the diagnostic tests. They refrained to perform an extensive diagnostic assessment, which, even when described, very rarely showed a cause-effect relationship. The documentation of a sustained VT was uncommon and was frequently associated with left ventricular apical aneurysm [71]. Syncope due to severe LVOT obstruction was induced during exercise test in only 1% of patients (Table 2). Stress echocardiography may be able to reproduce LVOT obstruction [72], but it has never been reported in the assessment of patients with unexplained syncope. In the absence of a causal relationship, most diagnosis remained uncertain. Non-sustained VT is a known risk factor, and it could be documented by ambulatory ECG monitoring in about one third of patients, but its prevalence was similar in patients with and without syncope, making uncertain a direct causal relationship [45]. Although by tilt testing, reflex syncope was identified in about one fourth of the patients, its role is also debated [1,19,49,73–75]. Owing to its supposed low specificity, tilt testing was considered not superior to clinical history for the diagnosis of reflex syncope. The presence of asymptomatic sinus node dysfunction [76], conduction abnormalities [77–79] or atrial tachyarrhythmias [80,81] was rarely reported and it was not necessarily considered the cause of syncope.
iv. HCM physicians mainly focused on SCD prevention, with a minor interest in performing a comprehensive evaluation aimed to understand the exact mechanism of syncope or to prevent syncopal recurrences and atrial tachyarrhythmias [80,81].
v. Surprisingly, no study reported data on ILR and on carotid sinus massage in HCM patients with syncope, despite these tests are considered among the most useful for the diagnosis of syncope [66]. Admittedly, the studies were predominantly done prior to the widespread use of ILRs. ILR was actually used in two case reports [82,83]; in both ILR was able to demonstrate a causal relationship between symptoms and arrhythmia and to guide the mechanism-specific therapy. ILR was also recently used in 25 HCM patients who had a combination of symptoms (e.g., recurrent presyncope, palpitations), presence of myocardial fibrosis and/or an intermediate risk for SCD (5-year risk of SCD $\geq$ 4 to <6%) [84]. During a mean of 17 months of follow-up, ILR detected atrial fibrillation and supraventricular arrhythmias in 5 patients, sinus node dysfunction leading to pacemaker implantation in one patient and non-sustained VT leading to implantation of ICD for primary prevention in 2 patients.

In non-HCM patients aged >40 years who had syncope compatible with a reflex mechanism, carotid sinus syndrome accounted for 8.8% of its causes [68]. In non-HCM patients with unexplained syncope, prolonged ECG monitoring by means of an ILR was able to provide a diagnosis in 35% - 46% of cases [68]. Both the 2014 ESC HCM guidelines [1] and the 2018 ESC guidelines on syncope [68] recommend ILR in patients with HCM and recurrent episodes of unexplained syncope (class IIa, LoE C).

4.4. Syncope recurrence and quality of life

Recurrence of syncope is a clinical and social problem especially in older patients as it is usually more severe than in younger people. It may

significantly impact individuals' quality of life, functional autonomy, and prognosis. Data regarding syncopal recurrences during follow-up are scarce. ICD follow-up studies are mainly focused on SCD and ICD appropriate or non-appropriate discharge, and syncopal recurrences are rarely reported during follow-up. There is an urgent need to increase diagnostic capabilities and collect follow-up data.

5. Conclusions

The assessment of the causes of syncope in HCM is often a challenge for clinicians and cardiologists as misdiagnosis may have serious consequences. In the current practice, the cause of syncope remained unexplained in most patients affected by HCM. It seems that the management of syncope in HCM was mainly driven by risk stratification of SCD. While ESC 2014 HCM guidelines [1] gave suggestions and recommendations for the assessment of syncope, the most recent 2020 AHA/ACC HCM guidelines [69] consider unexplained syncope as a risk factor for SCD and ICD selection, being less focused on etiological diagnosis.

Syncope is likely to recur and may impact on quality of life and morbidity even if it is not caused by a life-threatening arrhythmia. Therefore, understanding its mechanism is a pre-requisite for preventing recurrences. In the current practice of HCM patients, diagnostic assessment identified a mechanism in a minority of subjects, while the positive findings of diagnostic tests were poorly correlated with SCD or ICD discharge.

Therefore, we feel there is a need of precise instructions how to apply the recommendations of current guidelines to this disease, which tests are indicated and how to interpret their findings. In part II, an ad hoc consensus of experts in HCM and in syncope will propose a practical algorithm tailored for the diagnosis and management of syncope in patients with HCM.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.03.028.

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Data availability statement

Anonymized data can be made available to qualified investigators on reasonable request.

Declaration of Competing Interest

None.

References

[1] P.M. Elliott, A. Anastasakis, M.A. Borger, M. Borggrefe, F. Cecchi, P. Charron, 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) (2014) 2733–2779 (Epub 2014/09/01).

[2] C. O'Mahony, F. Jichi, M. Pavlou, L. Monserrat, A. Anastasakis, C. Rapezzi, et al., A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD), Eur. Heart J. 35 (30) (2014) 2010–2020 (Epub 2013/10/16).

[3] E.J. Rowin, A. Sridharan, C. Madias, C. Firely, B. Koethe, M.S. Link, et al., Prediction and prevention of sudden death in young patients (<20 years) with hypertrophic cardiomyopathy, Am. J. Cardiol. 128 (2020) 75–83 (Epub 2020/07/12).

[4] A. Pelliccia, S. Caselli, M. Pelliccia, M.B. Musumeci, E. Lemme, F.M. Di Paolo, et al., Clinical outcomes in adult athletes with hypertrophic cardiomyopathy: a 7-year follow-up study, Br. J. Sports Med. 54 (16) (2020) 1008–1012 (Epub 2020/06/14).

[5] S. Wang, H. Cui, C. Zhu, R. Wu, L. Meng, Q. Yu, et al., Obstructive sleep apnea causes impairment of the carotid artery in patients with hypertrophic obstructive cardiomyopathy, Respir. Med. 150 (2019) 107–112 (Epub 2019/04/10).

[6] C. Song, Y. Guo, X. Zheng, J. Lu, X. Fang, S. Wang, et al., Prognostic significance and risk of atrial fibrillation of Wolff-Parkinson-White syndrome in patients with hypertrophic cardiomyopathy, Am. J. Cardiol. 122 (9) (2018) 1546–1550 (Epub 2018/09/12).

[7] M. Avanesov, J. Münch, J. Weinrich, L. Well, D. Säring, C. Stehning, et al., Prediction of the estimated 5-year risk of sudden cardiac death and syncope or non-sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy using late gadolinium enhancement and extracellular volume CMR, Eur. Radiol. 27 (12) (2017) 5136–5145 (Epub 2017/06/16).

[8] A. Adler, D. Fourey, A. Weissler-Snir, W. Hindieh, R.H. Chan, M.H. Gollob, et al., Safety of outpatient initiation of disopyramide for obstructive hypertrophic cardiomyopathy patients, J. Am. Heart Assoc. 6 (6) (2017) (Epub 2017/05/28).

[9] L.L. Sorensen, H.Y. Liang, A. Pinheiro, A. Hilser, V. Dimaano, N.T. Olsen, et al., Safety profile and utility of treadmill exercise in patients with high-gradient hypertrophic cardiomyopathy, Am. Heart J. 184 (2017) 47–54 (Epub 2016/11/29).

[10] S. An, C. Fan, L. Yan, C. Cai, Y. Yang, S. Zhai, et al., Comparison of long-term outcome between apical and asymmetric septal hypertrophic cardiomyopathy, Cardiology 136 (2) (2017) 108–114 (Epub 2016/09/07).

[11] E. Biagini, C. Pazzi, I. Olivotto, B. Musumeci, G. Limongelli, G. Boriani, et al., Usefulness of electrocardiographic patterns at presentation to predict long-term risk of cardiac death in patients with hypertrophic cardiomyopathy, Am. J. Cardiol. 118 (3) (2016) 432–439 (Epub 2016/06/13).

[12] T.H. Lynge, B. Risgaard, R. Jabbari, C. Glinge, H. Bundgaard, B. Maron, et al., Cardiac symptoms before sudden cardiac death caused by hypertrophic cardiomyopathy: a nationwide study among the young in Denmark, Europace 18 (12) (2016) 1801–1808 (Epub 2016/01/30).

[13] Y. Amano, K. Aita, F. Yamada, M. Kitamura, S. Kumita, Distribution and clinical significance of high signal intensity of the myocardium on T2-weighted images in 2 phenotypes of hypertrophic cardiomyopathy, J. Comput. Assist. Tomogr. 39 (6) (2015) 951–955 (Epub 2015/10/16).

[14] Ç. Güleç, N. Abacı, F. Bayrak, E. Kömürcü Bayrak, G. Kahveci, C. Güven, et al., Association between non-coding polymorphisms of HOPX gene and syncope in hypertrophic cardiomyopathy, Anadolu Kardiyol. Derg. 14 (7) (2014) 617–624 (Epub 2014/07/19).

[15] C. Cai, F.J. Duan, Y.J. Yang, X.Y. Guo, Y.L. Liu, Y.Q. Liu, et al., Comparison of the prevalence, clinical features, and long-term outcomes of midventricular hypertrophy vs apical phenotype in patients with hypertrophic cardiomyopathy, Can. J. Cardiol. 30 (4) (2014) 441–447 (Epub 2014/01/29).

[16] B. Yashiro, Y. Minami, Y. Terajima, N. Hagiwara, Prognostic difference between paroxysmal and non-paroxysmal atrial fibrillation in patients with hypertrophic cardiomyopathy, J. Cardiol. 63 (6) (2014) 432–437 (Epub 2013/11/28).

[17] M. Baran, W. Szczepanski, A. Bossowski, Syncope in children and adolescents living in north-eastern Poland - scope of causes, Adv. Med. Sci. 58 (2) (2013) 326–330 (Epub 2013/08/21).

[18] H. Samardhi, D.L. Walters, C. Raffel, S. Rateesh, C. Harley, D. Burstow, et al., The long-term outcomes of transcoronary ablation of septal hypertrophy compared to surgical myectomy in patients with symptomatic hypertrophic obstructive cardiomyopathy, Catheter. Cardiovasc. Interv. 83 (2) (2014) 270–277 (Epub 2013/07/23).

[19] M.F. Macatrão-Costa, E. Arteaga-Fernandez, F.S. de Brito, F. Darrieux, S.L. de Melo, M. Scanavacca, et al., Evaluation of the autonomic function in patients with hypertrophic cardiomyopathy with and without syncope, Arq. Bras. Cardiol. 100 (2) (2013) 180–186 (Epub 2013/03/19).

[20] N.M. Orme, P. Sorajja, J.A. Dearani, H.V. Schaff, B.J. Gersh, S.R. Ommen, Comparison of surgical septal myectomy to medical therapy alone in patients with hypertrophic cardiomyopathy and syncope, Am. J. Cardiol. 111 (3) (2013) 388–392 (Epub 2012/11/22).

[21] G. Finocchiaro, B. Pinamonti, M. Merlo, F. Brun, G. Barbati, G. Sinagra, Prognostic role of clinical presentation in symptomatic patients with hypertrophic cardiomyopathy, J. Cardiovasc. Med. (Hagerstown) 13 (12) (2012) 810–818 (Epub 2012/08/14).

[22] P.P. Dimitrow, L. Chojnowska, T. Rudzinski, W. Piotrowski, L. Ziólkowska, A. Wojtarowicz, et al., Sudden death in hypertrophic cardiomyopathy: old risk factors re-assessed in a new model of maximalized follow-up, Eur. Heart J. 31 (24) (2010) 3084–3093 (Epub 2010/09/17).

[23] H. Furushima, M. Chinushi, K. Iijima, A. Sanada, D. Izumi, Y. Hosaka, et al., Ventricular tachyarrhythmia associated with hypertrophic cardiomyopathy: incidence, prognosis, and relation to type of hypertrophy, J. Cardiovasc. Electrophysiol. 21 (9) (2010) 991–999 (Epub 2010/05/22).

[24] M. Haghjoo, B. Faghfurian, M. Taherpour, A.F. Fazelifar, S. Mohammadzadeh, A. Alizadeh, et al., Predictors of syncope in patients with hypertrophic cardiomyopathy, Pacing Clin. Electrophysiol. 32 (5) (2009) 642–647 (Epub 2009/05/09).

[25] P. Spirito, C. Autore, C. Rapezzi, P. Bernabò, R. Badagliacca, M.S. Maron, et al., Syncope and risk of sudden death in hypertrophic cardiomyopathy, Circulation 119 (13) (2009) 1703–1710 (Epub 2009/03/25).

[26] K. Prasad, L. Williams, R. Campbell, P.M. Elliott, W.J. McKenna, M. Frenneaux, Episodic syncope in hypertrophic cardiomyopathy: evidence for inappropriate vasodilation, Heart 94 (10) (2008) 1312–1317 (Epub 2008/07/26).

[27] R. Thaman, J.R. Gimeno, R.T. Murphy, T. Kubo, B. Sachdev, J. Mogensen, et al., Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy, Heart 91 (7) (2005) 920–925 (Epub 2005/06/17).

[28] G. Barletta, C. Lazzeri, F. Franchi, R. Del Bene, A. Michelucci, Hypertrophic cardiomyopathy: electrical abnormalities detected by the extended-length ECG and their relation to syncope, Int. J. Cardiol. 97 (1) (2004) 43–48 (Epub 2004/09/01).

[29] S. Cuomo, F. Marciano, M.L. Migaux, F. Finizio, E. Pezzella, M.A. Losi, et al., Abnormal QT interval variability in patients with hypertrophic cardiomyopathy:

can syncope be predicted? J. Electrocardiol. 37 (2) (2004) 113–119 (Epub 2004/05/06).
[30] T. Kawasaki, A. Azuma, T. Sakatani, M. Hadase, T. Kamitani, S. Kawasaki, et al., Prognostic value of heart rate variability in patients with hypertrophic cardiomyopathy, J. Electrocardiol. 36 (4) (2003) 333–338 (Epub 2003/12/09).
[31] N. Isobe, T. Toyama, K. Taniguchi, S. Oshima, S. Kubota, T. Suzuki, et al., Failure to raise blood pressure during exercise is a poor prognostic sign in patients with hypertrophic non-obstructive cardiomyopathy, Circ. J. 67 (3) (2003) 191–194 (Epub 2003/02/27).
[32] F. Manganelli, S. Betocchi, Q. Ciampi, G. Storto, M.A. Losi, A. Violante, et al., Comparison of hemodynamic adaptation to orthostatic stress in patients with hypertrophic cardiomyopathy with or without syncope and in vasovagal syncope, Am. J. Cardiol. 89 (12) (2002) 1405–1410 (Epub 2002/06/14).
[33] M.H. Park, D.M. Gilligan, N.L. Bernardo, O. Topaz, Symptomatic hypertrophic obstructive cardiomyopathy: the role of dual-chamber pacing, Angiology 50 (2) (1999) 87–94 (Epub 1999/03/04).
[34] G. Yi, K. Prasad, P. Elliott, S. Sharma, X. Guo, W.J. McKenna, et al., T wave complexity in patients with hypertrophic cardiomyopathy, Pacing Clin. Electrophysiol. 21 (11 Pt 2) (1998) 2382–2386 (Epub 1998/11/24).
[35] H.L. Thomson, J. Morris-Thurgood, J. Atherton, W.J. McKenna, M.P. Frenneaux, Reflex responses of venous capacitance vessels in patients with hypertrophic cardiomyopathy, Clin. Sci. (Lond.) 94 (4) (1998) 339–346 (Epub 1998/06/26).
[36] D.W. Zhu, H. Sun, R. Hill, R. Roberts, The value of electrophysiology study and prophylactic implantation of cardioverter defibrillator in patients with hypertrophic cardiomyopathy, Pacing Clin. Electrophysiol. 21 (1 Pt 2) (1998) 299–302 (Epub 1998/02/25).
[37] R. Lorenzoni, R. Gistri, F. Cecchi, I. Olivotto, G. Chiriatti, P. Elliott, et al., Syncope and ventricular arrhythmias in hypertrophic cardiomyopathy are not related to the derangement of coronary microvascular function, Eur. Heart J. 18 (12) (1997) 1946–1950 (Epub 1998/02/03).
[38] B. Brembilla-Perrot, A. Jacquot, D. Beurrier, L. Jacquemin, Hypertrophic cardiomyopathy: value of atrial programmed electrical stimulation in patients with or without syncope with special reference to the role of atrial arrhythmias, Int. J. Cardiol. 59 (1) (1997) 47–56 (Epub 1997/03/01).
[39] M. Nakatani, Y. Yokota, M. Yokoyama, Acute hemodynamic deterioration during rapid atrial pacing in patients with hypertrophic cardiomyopathy, Clin. Cardiol. 19 (5) (1996) 385–392 (Epub 1996/05/01).
[40] D.M. Gilligan, P. Nihoyannopoulos, A. Fletcher, E. Sbarouni, A. Dritsas, C. M. Oakley, Symptoms of hypertrophic cardiomyopathy, with special emphasis on syncope and postprandial exacerbation of symptoms, Clin. Cardiol. 19 (5) (1996) 371–378 (Epub 1996/05/01).
[41] R.C. Saumarez, A.K. Slade, A.A. Grace, N. Sadoul, A.J. Camm, W.J. McKenna, The significance of paced electrogram fractionation in hypertrophic cardiomyopathy. A prospective study, Circulation 91 (11) (1995) 2762–2768 (Epub 1995/06/01).
[42] J.F. Sneddon, A. Slade, H. Seo, A.J. Camm, W.J. McKenna, Assessment of the diagnostic value of head-up tilt testing in the evaluation of syncope in hypertrophic cardiomyopathy, Am. J. Cardiol. 73 (8) (1994) 601–604 (Epub 1994/03/15).
[43] V. Dilsizian, R.O. Bonow, S.E. Epstein, L. Fananapazir, Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 22 (3) (1993) 796–804 (Epub 1993/09/01).
[44] F. Alfonso, P. Nihoyannopoulos, J. Stewart, S. Dickie, R. Lemery, W.J. McKenna, Clinical significance of giant negative T waves in hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 15 (5) (1990) 965–971 (Epub 1990/04/01).
[45] C.A. Nienaber, S. Hiller, R.P. Spielmann, M. Geiger, K.H. Kuck, Syncope in hypertrophic cardiomyopathy: multivariate analysis of prognostic determinants, J. Am. Coll. Cardiol. 15 (5) (1990) 948–955 (Epub 1990/04/01).
[46] V.K. Bahl, U. Kaul, V. Dev, M.L. Bhatia, Electrophysiologic evaluation of patients with hypertrophic cardiomyopathy, Int. J. Cardiol. 25 (1) (1989) 87–92 (Epub 1989/10/01).
[47] K.H. Kuck, K.P. Kunze, M. Schlüter, C.A. Nienaber, A. Costard, Programmed electrical stimulation in hypertrophic cardiomyopathy. Results in patients with and without cardiac arrest or syncope, Eur. Heart J. 9 (2) (1988) 177–185 (Epub 1988/02/01).
[48] W.A. Schiavone, J.D. Maloney, H.M. Lever, L.W. Castle, R. Sterba, V. Morant, Electrophysiologic studies of patients with hypertrophic cardiomyopathy presenting with syncope of undetermined etiology, Pacing Clin. Electrophysiol. 9 (4) (1986) 476–481 (Epub 1986/07/01).
[49] L. Fananapazir, C.M. Tracy, M.B. Leon, J.B. Winkler, R.O. Cannon 3rd, R.O. Bonow, et al., Electrophysiologic abnormalities in patients with hypertrophic cardiomyopathy. A consecutive analysis in 155 patients, Circulation 80 (5) (1989) 1259–1268 (Epub 1989/11/01).
[50] P.R. Kowey, R. Eisenberg, T.R. Engel, Sustained arrhythmias in hypertrophic obstructive cardiomyopathy, N. Engl. J. Med. 310 (24) (1984) 1566–1569 (Epub 1984/06/14).
[51] M.I. Canedo, M.J. Frank, A.M. Abdulla, Rhythm disturbances in hypertrophic cardiomyopathy: prevalence, relation to symptoms and management, Am. J. Cardiol. 45 (4) (1980) 848–855 (Epub 1980/04/01).
[52] D.D. Savage, S.F. Seides, B.J. Maron, D.J. Myers, S.E. Epstein, Prevalence of arrhythmias during 24-hour electrocardiographic monitoring and exercise testing in patients with obstructive and nonobstructive hypertrophic cardiomyopathy, Circulation 59 (5) (1979) 866–875 (Epub 1979/05/01).
[53] M.J. Frank, A.M. Abdulla, M.I. Canedo, R.E. Saylors, Long-term medical management of hypertrophic obstructive cardiomyopathy, Am. J. Cardiol. 42 (6) (1978) 993–1001 (Epub 1978/12/01).
[54] C. O'Mahony, F. Jichi, S.R. Ommen, I. Christiaans, E. Arbustini, P. Garcia-Pavia, et al., International external validation study of the 2014 European Society of Cardiology Guidelines on sudden cardiac death prevention in hypertrophic cardiomyopathy (EVIDENCE-HCM), Circulation 137 (10) (2018) 1015–1023 (Epub 2017/12/02).
[55] J.R. Gimeno, M. Tomé-Esteban, C. Lofiego, J. Hurtado, A. Pantazis, B. Mist, et al., Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy, Eur. Heart J. 30 (21) (2009) 2599–2605 (Epub 2009/08/20).
[56] G.K. Efthimiadis, C. Pliakos, E.D. Pagourelias, D.G. Parcharidou, G. Giannakoulas, V. Kamperidis, et al., Identification of high risk patients with hypertrophic cardiomyopathy in a northern Greek population, Cardiovasc. Ultrasound 7 (2009) 37 (Epub 2009/07/28).
[57] A. D'Andrea, P. Caso, S. Severino, S. Cuomo, G. Capozzi, P. Calabrò, et al., Prognostic value of intra-left ventricular electromechanical asynchrony in patients with hypertrophic cardiomyopathy, Eur. Heart J. 27 (11) (2006) 1311–1318 (Epub 2005/12/21).
[58] P.M. Elliott, J.R. Gimeno, M.T. Tomé, J. Shah, D. Ward, R. Thaman, et al., Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy, Eur. Heart J. 27 (16) (2006) 1933–1941 (Epub 2006/06/07).
[59] F. Cecchi, I. Olivotto, S. Betocchi, C. Rapezzi, M.R. Conte, G. Sinagra, et al., The Italian Registry for hypertrophic cardiomyopathy: a nationwide survey, Am. Heart J. 150 (5) (2005) 947–954 (Epub 2005/11/18).
[60] M.J. Kofflard, F.J. Ten Cate, C. van der Lee, R.T. van Domburg, Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration, J. Am. Coll. Cardiol. 41 (6) (2003) 987–993 (Epub 2003/03/26).
[61] L. Monserrat, P.M. Elliott, J.R. Gimeno, S. Sharma, M. Penas-Lado, W.J. McKenna, Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients, J. Am. Coll. Cardiol. 42 (5) (2003) 873–879 (Epub 2003/09/06).
[62] L. Lin, H. Chu, Meta-analysis of proportions using generalized linear mixed models, Epidemiology 31 (5) (2020) 713–717 (Epub 2020/07/14).
[63] J.P. Hunter, A. Saratzis, A.J. Sutton, R.H. Boucher, R.D. Sayers, M.J. Bown, In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias, J. Clin. Epidemiol. 67 (8) (2014) 897–903 (Epub 2014/05/06).
[64] R. Der Simonian, N. Laird, Meta-analysis in clinical trials, Control. Clin. Trials 7 (1986) 177–188.
[65] J.P.T. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (2002) 1539–1573.
[66] J.B. Haldane, The estimation and significance of the logarithm of a ratio of frequencies, Ann. Hum. Genet. 20 (1956) 309–311.
[67] J.J. Wei, E.X. Lin, J.D. Shi, K. Yang, Z.L. Hu, X.T. Zeng, T.J. Tong, Meta-analysis with zero-event studies: a comparative study with application to COVID-19 data, Mil. Med. Res. 8 (2021) 41.
[68] M. Brignole, A. Moya, F.J. de Lange, J.C. Deharo, P.M. Elliott, A. Fanciulli, et al., 2018 ESC Guidelines for the diagnosis and management of syncope, Eur. Heart J. 39 (21) (2018) 1883–1948 (Epub 2018/03/22).
[69] S.R. Ommen, S. Mital, M.A. Burke, S.M. Day, A. Deswal, P. Elliott, et al., 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 76 (25) (2020 Dec 22) 3022–3055.
[70] G. Mascia, I. Olivotto, J. Brugada, E. Arbelo, P. Di Donna, R. Della Bona, et al., Sport practice in hypertrophic cardiomyopathy: running to stand still? Int. J. Cardiol. 345 (2021) 77–82 (Epub 2021/10/19).
[71] F. Alfonso, M.P. Frenneaux, W.J. McKenna, Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm, Br. Heart J. 61 (2) (1989) 178–181 (Epub 1989/02/01).
[72] J.S. Shah, M.T. Esteban, R. Thaman, R. Sharma, B. Mist, A. Pantazis, et al., Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy, Heart 94 (10) (2008) 1288–1294 (Epub 2007/11/23).
[73] D.M. Gilligan, P. Nihoyannopoulos, W.L. Chan, C.M. Oakley, Investigation of a hemodynamic basis for syncope in hypertrophic cardiomyopathy. Use of a head-up tilt test, Circulation 85 (6) (1992) 2140–2148 (Epub 1992/06/01).
[74] K.K. Lim, B.J. Maron, B.P. Knight, Successful catheter ablation of hemodynamically unstable monomorphic ventricular tachycardia in a patient with hypertrophic cardiomyopathy and apical aneurysm, J. Cardiovasc. Electrophysiol. 20 (4) (2009) 445–447 (Epub 2008/12/05).
[75] K. Inada, J. Seiler, K.C. Roberts-Thomson, D. Steven, J. Rosman, R.M. John, et al., Substrate characterization and catheter ablation for monomorphic ventricular tachycardia in patients with apical hypertrophic cardiomyopathy, J. Cardiovasc. Electrophysiol. 22 (1) (2011) 41–48 (Epub 2010/09/03).
[76] R. Barriales-Villa, R. Centurión-Inda, X. Fernández-Fernández, M.F. Ortiz, L. Pérez-Alvarez, I. Rodríguez García, et al., Severe cardiac conduction disturbances and pacemaker implantation in patients with hypertrophic cardiomyopathy, Rev. Esp. Cardiol. 63 (8) (2010) 985–988 (Epub 2010/08/27).
[77] M. Tamura, K. Harada, T. Ito, M. Enoki, G. Takada, Abrupt aggravation of atrioventricular block and syncope in hypertrophic cardiomyopathy, Arch. Dis. Child. 73 (6) (1995) 536–537 (Epub 1995/12/01).
[78] M. Yesil, S. Bayata, I. Susam, H. Dinçkal, N. Postaci, Rare association of hypertrophic cardiomyopathy and complete atrioventricular block with prompt disappearance of outflow gradient after DDD pacing, Europace 1 (4) (1999) 280–282 (Epub 2001/02/28).

[79] K.L. Rosen, R.W. Cameron, P.J. Bigham, S.R. Neish, Hypertrophic cardiomyopathy presenting with 3rd-degree atrioventricular block, Tex. Heart Inst. J. 24 (4) (1997) 372–375 (Epub 1997/01/01).
[80] I. Olivotto, F. Cecchi, S.A. Casey, A. Dolara, J.H. Traverse, B.J. Maron, Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy, Circulation 104 (21) (2001) 2517–2524 (Epub 2001/11/21).
[81] K. Robinson, M.P. Frenneaux, B. Stockins, G. Karatasakis, J.D. Poloniecki, W. J. McKenna, Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study, J. Am. Coll. Cardiol. 15 (6) (1990) 1279–1285 (Epub 1990/05/01).
[82] E.G. Arkolaki, E.N. Simantirakis, S.I. Chrysostomakis, P.E. Vardas, Appropriate management of syncope in a patient with hypertrophic cardiomyopathy: rationale behind long-term cardiac rhythm monitoring, Hell. J. Cardiol. 50 (2) (2009 Mar–Apr) 144–146.
[83] M.B. Musumeci, P. Spirito, F.M. Cauti, C. Autore, High risk for sudden death identified by electrocardiographic loop recording in a patient with hypertrophic cardiomyopathy without major risk factors, Am. J. Cardiol. 107 (10) (2011) 1558–1560.
[84] R. Sakhi, R. Huurman, D.A.M.J. Theuns, A.F.L. Schinkel, A. Assaf, T. Szili-Torok, et al., Incremental value of an insertable cardiac monitor in patients with hypertrophic cardiomyopathy with low or intermediate risk for sudden cardiac death, Cardiology 146 (2) (2021) 207–212.