Syncope in hypertrophic cardiomyopathy (part II): An expert consensus statement on the diagnosis and management

Michele Brignole [a,*], Franco Cecchi [a], Aris Anastasakis [b], Lia Crotti [a,p], Jean Claude Deharo [c,o], Perry M. Elliott [d], Artur Fedorowski [e], Juan Pablo Kaski [f], Giuseppe Limongelli [g], Martin S. Maron [h], Iacopo Olivotto [i], Steve R. Ommen [j], Gianfranco Parati [k], Win Shen [l], Andrea Ungar [m], Arthur Wilde [n]

[a] IRCCS Istituto Auxologico Italiano, Dept of Cardiology, Hospital S. Luca, Milan, Italy
[b] Unit of Inherited and Rare Cardiovascular Diseases, Onassis Cardiac Surgery Centre, Kallithea, Greece
[c] Hôpitaux de Marseille, Centre Hospitalier Universitaire La Timone, Service de Cardiologie, Marseille, France
[d] Institute of Cardiological Sciences, University College London, UK
[e] Dept. of Cardiology, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden
[f] Institute of Cardiovascular Science, University College London and Great Ormond Street Hospital, London, UK
[g] Department of Translational Medical Sciences, University of Campania "Luigi VanvitellI", AO Dei Colli-Monaldi Hospital, Naples, Italy
[h] HCM Center, Lahey Hospital and Medical Center, Burlington, MA, USA
[i] Meyer Children Hospital, Department of Experimental and Clinical Medicine, University of Florence, Italy
[j] Medicine, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA
[k] IRCCS Istituto Auxologico Italiano, Dept of Cardiology, University of Milano Bicocca, Milan, Italy
[l] Mayo Clinic Arizona, Phoenix, AZ, USA
[m] Division of Geriatric and Intensive Care Medicine, Azienda Ospedaliero Universitaria Careggi, Department of Experimental and Clinical Medicine, University of Florence andFlorence, Italy
[n] Heart Centre, Department of Cardiology, Amsterdam Universitair Medische Centra, Amsterdam,location AMC, the Netherlands
[o] Aix Marseille Université, C2VN, Marseille, France
[p] Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

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ABSTRACT

Syncopal events in patients with hypertrophic cardiomyopathy (HCM) are of concern as they are a vital consideration in algorithms for risk stratification for sudden cardiac death (SCD) and ICD implantation. However, the cause of syncope is often under-investigated and/or unexplained. Current syncope guidelines do not provide a detailed definition of unexplained syncope.

To address this important gap, an international panel of experts in the field of both syncope and HCM wrote a consensus document with the aim of providing practical guidance for the diagnosis and management of syncope in patients with HCM.

1. Introduction

Syncopal events in patients with hypertrophic cardiomyopathy (HCM) are of concern as they are a vital consideration in algorithms for

risk stratification for sudden cardiac death (SCD) and ICD implantation. However, the cause of syncope is often under-investigated and/or un-explained. In a recent systematic review and metanalysis of relevant publications from 1973 to 2021, syncope was reported by 15.8% (3.452

of 21.791) HCM patients [1]. 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 (relative risk of 1.99). Syncope was considered unexplained in 91% of cases [1].

Current HCM management guidelines consider syncope that is not explained by non-life threatening mechanisms as a major risk factor in SCD risk assessment. The European Society of Cardiology (ESC) 2014 HCM guidelines [2] use the terminology "unexplained non-vasovagal syncope", while the 2020 American Heart Association (AHA)/ American College of Cardiology (ACC) HCM guidelines [3] described this as "syncope suspected by clinical history to be arrhythmic" and "unexplained syncope". Neither guideline provides detailed definitions of how to evaluate and categorize syncopal events such that the appropriate events are used in the risk factor algorithms [4–7].

Also current syncope guidelines do not provide a detailed definition of unexplained syncope. The 2017 American Heart Association (AHA)/ American College of Cardiology (ACC) and the 2018 European Society of Cardiology (ESC) syncope guidelines [8] defined unexplained syncope as "syncope for which a cause is undetermined after an initial evaluation that is deemed appropriate by the experienced healthcare provider". The initial evaluation usually includes, but is not limited to, a thorough history, physical examination, and ECG". The consequence is uncertainty regarding the therapeutic decision, and specifically in the case of patients with HCM, whether or not to recommend an ICD.

Notably, while "unexplained syncope" is associated with subsequent cardiac arrest, ICDs often do not prevent recurrent syncope especially if the underlying mechanism is not a ventricular arrhythmia which may impact the quality of life [9]. Patients with obstructive HCM are particularly sensitive to changes in preload and afterload that can accompany hypovolaemia, severe anemia, use of vasodilators and diuretics and are thus more prone to syncope under such conditions. Understanding the underlying mechanism of syncope is a prerequisite for preventing recurrences, but a systematic approach to diagnostic assessment to identify the cause of syncope is currently underused [1].

To address this important gap, the two senior authors of the above-mentioned systematic review and metanalysis [1] invited an international panel of experts in the field of both syncope and HCM to write a consensus document with the aim of providing practical guidance for the diagnosis and management of syncope in patients with HCM.

2. Method

The chairmen (FC and MB) developed a draft algorithm for the management of syncope in a patient with HCM and nominated the panel of experts in March 2022. The members were selected based on their international reputation as having been involved in previous guidelines (see Appendix). A plenary remote video conference was organized in April 2022 during which the panel members were asked to review the algorithm by adding comments, explanations, and new proposals. In June 2022 a second draft of the document was prepared based on the received feed-back. Finally, a plenary conference was organized in Florence on July 8, 2022, during which a consensus was achieved. The final document was written accordingly and approved by the panel on July 31, 2022, and submitted for publication.

3. Algorithms for the diagnosis and management of syncope in a patient with HCM

The panel of experts recommend the algorithm for the diagnosis of syncope in a patient with HCM shown in the Fig. 1.

Unexplained syncope is defined in those patients in whom, after the initial evaluation and those additional tests deemed appropriate by an experienced healthcare provider, no condition reported in sections 4 B (non-cardiac syncope) and 4C (cardiac syncope unrelated to risk for SCD) is met (*see below*).

Once the aetiology of the syncopal event is ascertained, then appropriate treatment to prevent recurrence can be initiated. In the case of "unexplained syncope", as defined above, the event is considered as a risk factor for SCD in the ESC (Fig. 2 A) and AHA/ACC guidelines (Fig. 2 B) flow charts for risk stratification and guidance to ICD implantation.

A validated clinical risk tool (HCM Risk-SCD) that estimates the 5-year risk of SCD in adults with HCM [5,6] can be found on www.HCMRisk-SCD. The AHA/ACC HCM SCD Risk Algorithm can be accessed at https://professional.heart.org/en/guidelines-and-statements/hcm-risk-calculator. A similar risk score has been developed for paediatric patients (HCMRisk-Kids) [7] and can be accessed at www.HCM
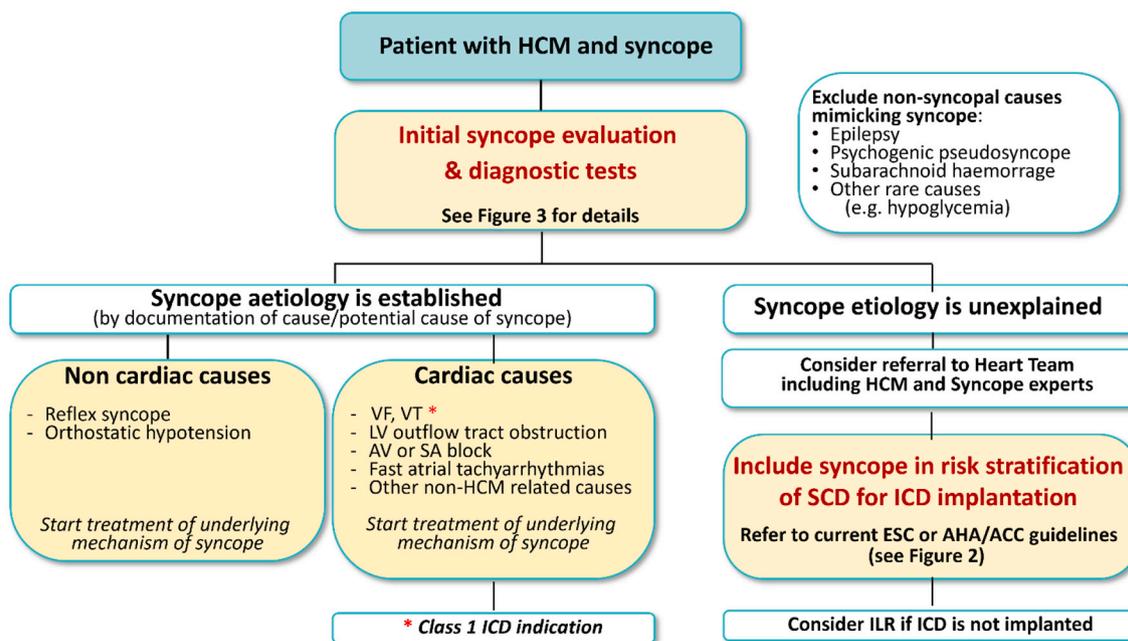

Fig. 1. Algorithms for the diagnosis of syncope in patients with HCM.
Abbreviations: HCM = hypertrophic cardiomyopathy; VF = ventricular fibrillation; VT = ventricular tachycardia; SCD = sudden cardiac death; AV = atrioventricular; SA = sinoatrial

A)   ESC guidelines algorithm
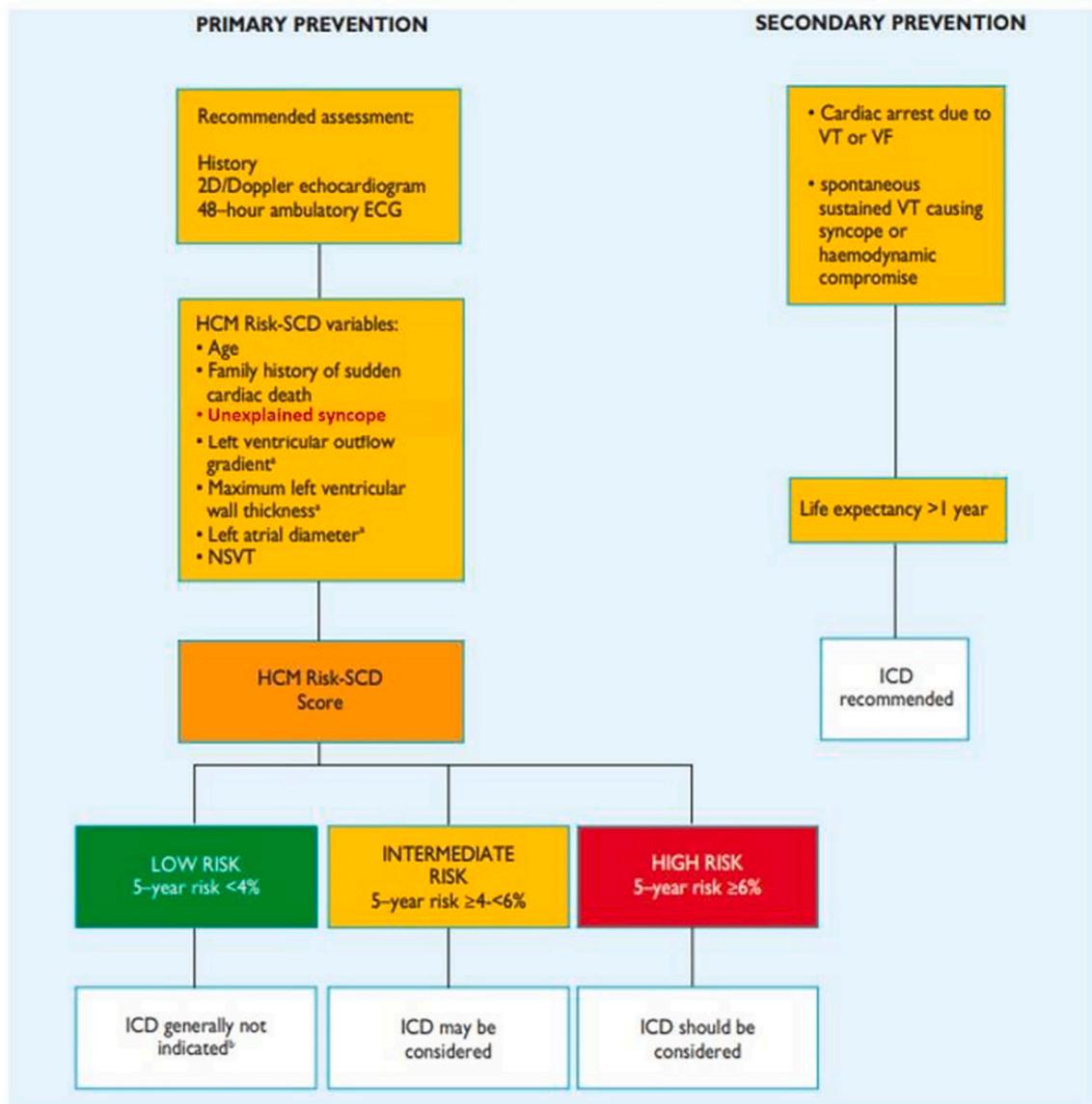
Fig. 2. Flow charts of the ESC guidelines (Panel A) and of the AHA/ACC guidelines (Panel B).
Abbreviations: HCM = hypertrophic cardiomyopathy; VF = ventricular fibrillation; VT = ventricular tachycardia; SCD = sudden cardiac death; NSVT = non-sustained ventricular tachycardia; CMR = cardiovascular magnetic resonance; EF = ejection fraction; FH = family history; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy

Risk-Kids.

HCM Risk-SCD variables included in the HCM Risk-SCD are:

- Age.
- Family history of sudden cardiac death.
- Unexplained syncope.
- Left ventricular outflow gradient.
- Maximum left ventricular wall thickness.
- Left atrial diameter.
- Non-sustained ventricular tachycardia.

4. Practical guidance for the diagnosis and management of syncope

4.1. Work-up for assessment of syncope in HCM patients

The proposed work up for patients with HCM and syncope is shown in Fig. 3.

In accordance with current HCM guidelines, all patients with HCM should have a comprehensive medical history, physical examination (including standing BP measurement), echocardiogram, ECG, and 24–48-h ambulatory Holter ECG monitoring or similar devices able to provide continuous ECG monitoring; the role of intermittent event recorders, e.g., Apple watch, FitBit, KardiaMobile, etc. in risk stratification has not yet been established. The history and the circumstances of the event guide the appropriate evaluation and treatment. If heart rhythm

B)   AHA/ACC guidelines algorithm
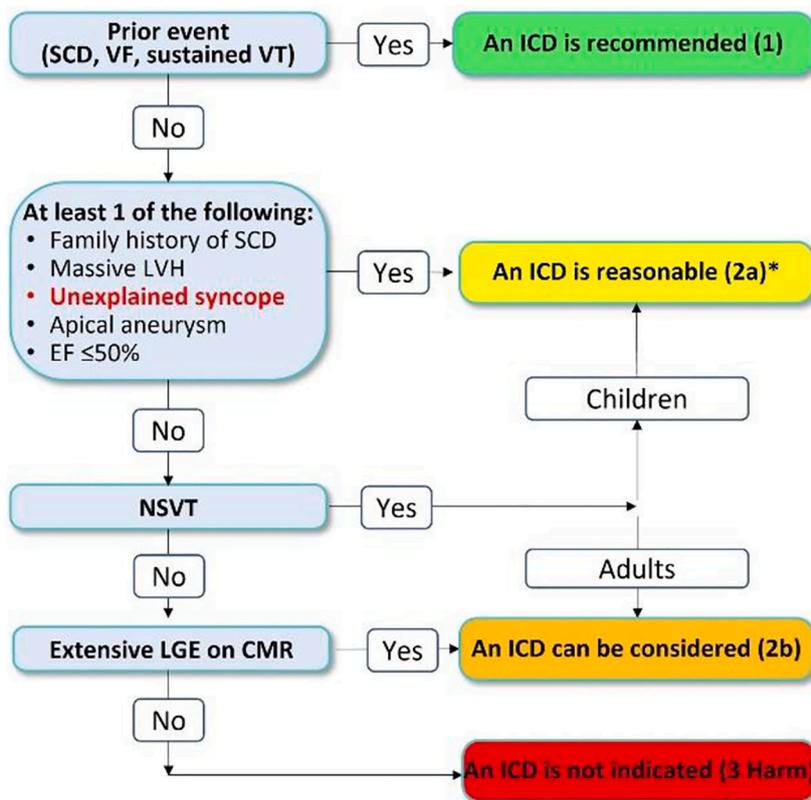
* The 5-year SCD risk score can be estimated as part of the shared decision-making

Fig. 2. (*continued*).

abnormalities capable of causing syncope (e.g., advanced atrioventricular block, bradycardia, sustained ventricular tachycardia, or paroxysmal atrial fibrillation) are documented, then appropriate treatment is initiated. In patients in whom the event is clearly attributable to a reflex mechanism or autonomic failure (see Table 1A), an extensive test panel may be unnecessary. Similarly, significant left ventricle outflow tract obstruction (LVOTO) (i.e, peak instantaneous gradient >50 mmHg at rest or with provocation) is a likely cause of syncope when it is triggered by transient hypotension due to hypovolemia or systemic vasodilatation as may occur when standing abruptly, during prolonged standing or effort, or when there is reflex-mediated vasodilation

The guiding concepts of this proposed evaluation are that if the history and initial testing do not clearly identify reflex or LVOTO-mediated mechanism, then that syncopal event is considered "unexplained" and represents a risk marker.

If the history implicates LVOTO as a major contributing factor, exercise echocardiography is reasonable if the patient is not already known to have significant resting or provokable gradient (e.g., > 50 mmHg).

If reflex syncope or orthostatic hypotension are suspected in patients without the immediate diagnosis at initial evaluation, further cardiovascular autonomic function tests could be performed:

- Active standing test
- 24-h ambulatory blood pressure monitoring (ABPM),
- Tilt testing
- Carotid sinus massage (in patients >40-year-old)

- Implantable loop recorder (if the above tests were not diagnostic) to document a syncopal recurrence or a life-threatening event

In some cases, these tests may also help guide therapy.

Other tests such as cardiac MRI or electrophysiologic testing may be considered in selected patients, most often in the context of an experienced multi-disciplinary team that includes specialists in both HCM and syncope.

The decision to admit the patient for rapid investigation is influenced by local organization. Generally, hospitalization can be justified in case of syncope without prodromes or supine or occurring during exercise. In the other cases high-priority out-of-hospital investigation may be preferred if there is an access to a syncope expert/unit.

Once the diagnosis has been established, the treatment of underlying syncope mechanisms should be started according to syncope guidelines recommendations [8,9].

Example Case 1: A middle aged man with HCM experiences syncope while seated during a conversation with his wife. The patient doesn't not recall any symptoms prior waking up on the floor. His wife noted that just prior to his faint, his speech slowed mildly, and he simply slumped sideways. She helped lower him to the floor where he regained consciousness in about a minute. This is a worrisome syncopal event. Even if this patient has LVOTO, the fact that there was no rapid posture change or triggering event (e.g., reflex mediated hypotension) would make it unlikely that the LVOTO was the proximate cause for the event. Prolonged ambulatory ECG monitoring (including implantable loop recorder) is reasonable, but this event would be considered
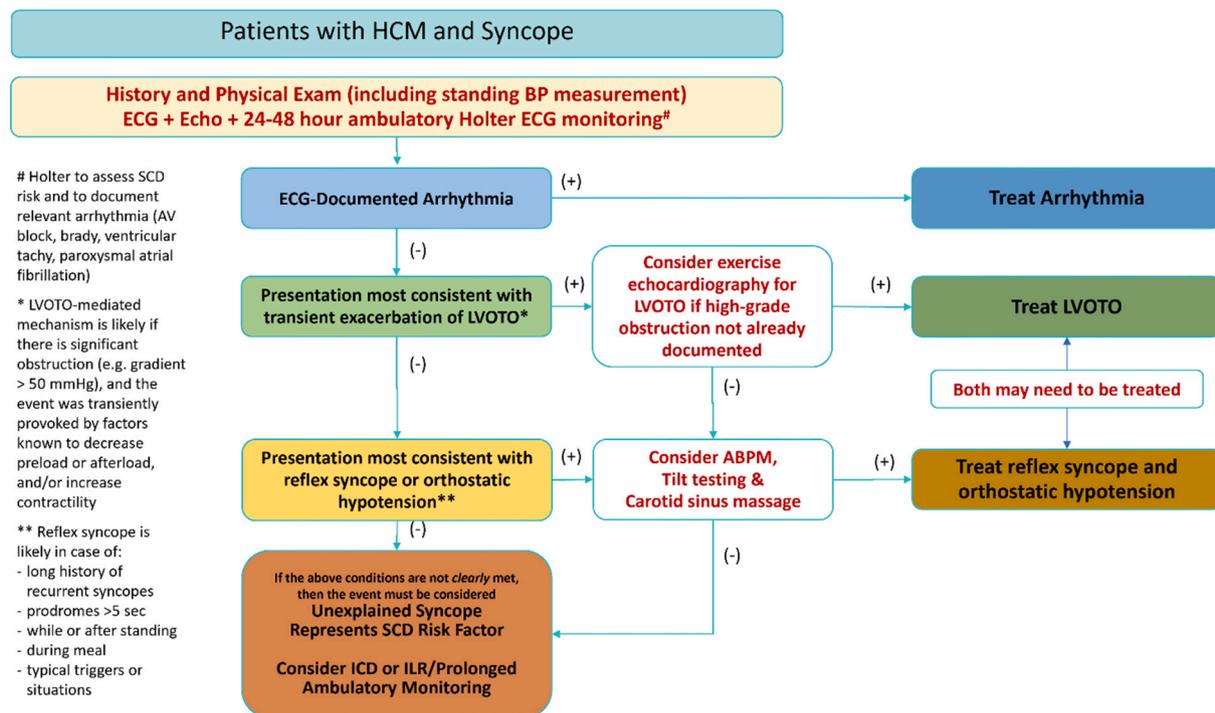
Fig. 3. Proposed evaluation for patients with HCM and a syncopal episode.
Abbreviations: HCM = hypertrophic cardiomyopathy; LVOTO = left ventricle outflow tract obstruction; ABPM = 24-h ambulatory blood pressure monitoring; SCD = sudden cardiac death; ILR = implantable loop recorder

"unexplained", and would be considered a SCD risk marker unless the ECG monitoring demonstrates an arrhythmia that coincides with similar symptoms and is not ventricular in origin.

Example Case 2: A young man with known obstructive HCM with a resting LVOT gradient of 50 mmHg had a syncopal event during phlebotomy. He described becoming sweaty, warm, and nauseated prior to the loss of consciousness. He regained consciousness and returned to baseline quickly when placed in the supine position. The history is prototypical for reflex syncope and measures to avoid the triggering circumstances should be addressed. The LVOTO predisposed this patient to full loss of consciousness with the reflex vasodilation, and perhaps needs more treatment as well; importantly, this event is not considered as a risk marker for SCD and would not be included in risk assessment tools.

Example Case 3: A woman with resting LVOTO of 50 mmHg experienced syncope at the beach. After skipping breakfast, the patient napped on the beach, and had a syncopal episode when she stood up abruptly. The only prodrome was sense of weakness in the legs and darkening vision. She had had 2 previous syncopal episodes with similar characteristics in upright position. In this case, the posture change suggests a hypotension-mediated exacerbation of LVOTO as the mechanism for the event. Here, the exact mechanism of the faint should be further investigated by means of ABPM and autonomic tests aimed to find a mechanism-guided therapy and prevent recurrences, which includes medical therapy to minimize LVOTO. Should the syncope be the first episode, ABPM and autonomic tests might be not needed. This event is also not considered as a risk for SCD.

Example Case 4: A 30-year-old man with non-obstructive HCM experienced syncope while climbing the stairs of the metro. He fell and reported a mild trauma. He denied palpitations before the faint. He had an episode of dizziness some time ago while performing a sudden effort. His echocardiogram showed 20 mm septal thickness and an enlarged left atrium of 55 ml/m^2. No LVOT gradient was detected at rest or with provocation. The cardiac MRI showed patchy late gadolinium enhancement in the hypertrophic zones. No significant arrhythmias

were present during 24-h Holter monitoring and during stress test. His father and an uncle are alive and suffer from HCM. Here, the exact mechanism of the faint is unexplained. This places in a dilemma: primary cardiac arrhythmia or reflex syncope? According to the flow chart in the Fig. 3 autonomic testing is the next step. If a reflex mechanism is established, the mechanism specific treatment should be started. If no autonomic problem can be established, then the case represents an SCD risk marker with a 5 yr risk = 6–7%, so ICD generally is indicated (Class 2A indication by ESC and ACC/AHA criteria). If the patient opts not to get an ICD, then a long-term monitoring by an ILR is also reasonable.

Table 1A

Class I diagnostic criteria of non-cardiac syncope (reflex and orthostatic hypotension).

Diagnostic criteria with initial evaluation
  Vasovagal syncope is highly probable if syncope is precipitated by pain or fear or standing, and is associated with typical progressive prodrome (pallor, sweating, nausea).
  Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers, listed in Table 3.
  Syncope due to orthostatic hypotension is confirmed when syncope occurs while standing and there is concomitant orthostatic hypotension.
Carotid sinus syndrome
  Carotid sinus syndrome is confirmed if carotid sinus massage causes bradycardia (asystole) and/or hypotension that reproduces spontaneous symptoms, and patients have clinical features compatible with a reflex mechanism of syncope.
Active standing
  Syncope due to orthostatic hypotension is confirmed when there is a fall in systolic blood pressure from baseline value ≥20 mmHg or diastolic blood pressure ≥ 10 mmHg or a decrease in systolic blood pressure to <90 mmHg that reproduces spontaneous symptoms.
Electrocardiographic monitoring
  The absence of arrhythmia during syncope excludes arrhythmic syncope.
Exercise testing
  Reflex syncope is confirmed when syncope is reproduced immediately after exercise in the presence of severe hypotension.

Table 1B

Class II diagnostic criteria of reflex syncope, orthostatic hypotension (OH), postural orthostatic tachycardia syndrome (POTS) and psychogenic pseudo-syncope (PPS).

Tilt testing
Reflex syncope, OH, POTS, or PPS should be considered likely if tilt testing reproduces symptoms along with the characteristic circulatory pattern of these conditions

4.2. Conditions in which the diagnosis of non-cardiac syncope (reflex syncope or orthostatic hypotension) is established (low risk related to syncope)

The 2017 AHA/ACC and the 2018 ESC syncope guidelines [8,9] have defined those situations in which a diagnosis of non-cardiac syncope can be considered established (Tables 1A and 1B):

4.3. Other conditions in which the diagnosis of syncope is unrelated to the risk of sudden death (low risk related to syncope)

As any structural heart disease, HCM can be complicated by cardiac syncope that not necessarily is life-threatening and by non-cardiac syncope.

Arrhythmic syncope not due to ventricular tachyarrhythmias should be suspected [8,9], but need confirmation by further investigations (electrophysiological study, prolonged ECG monitoring) in case of (Table 2):

- Syncope during exertion or when supine
- Sudden onset palpitation immediately followed by syncope
- Bifascicular block
- Mobitz I second-degree AV block and 1 degree AV block with markedly prolonged PR interval
- Asymptomatic mild inappropriate sinus bradycardia (40–50 b.p.m.) or slow atrial fibrillation (40–50 b.p.m.)

Examples of non-cardiac causes of syncope, often in combination among them, are listed in Table 3.

4.4. Syncope in paediatric HCM

The prevalence of unexplained syncope in paediatric HCM cohorts varies from 3.1% in the PRIMaCY cohort [10] to 9.9% in the large multicentric International Paediatric Hypertrophic Cardiomyopathy

Table 2

Diagnostic criteria of cardiac syncope not caused by ventricular arrhythmias.

Arrhythmic cardiac syncope
Syncope due to sick sinus syndrome is established when persistent sinus bradycardia <40 b.p.m. or sinus pause >3 s is documented on ECG in awake state and in absence of physical training.
Syncope due to AV block is established when Mobitz II second- and third-degree AV block or alternating left and right BBB is documented on ECG
Alternating left and right BBB;
Syncope due to atrial or ventricular paroxysmal tachyarrhythmias is established when syncope is documented to occur at the onset of rapid atrial or ventricular tachyarrhythmias
Non-arrhythmic cardiac syncope
Cardiac ischaemia-related syncope is confirmed when syncope presents with evidence of acute myocardial ischaemia with or without myocardial infarction
Syncope due to structural cardiopulmonary disorders is highly probable when syncope presents in patients with:

- outflow tract obstruction,
- prolapsing atrial myxoma,
- left atrial ball thrombus,
- severe aortic stenosis,
- pulmonary embolus,
- acute aortic dissection.

Table 3

Diagnostic criteria of non-life-threatening non-cardiac syncope.

Dehydration, volume depletion
Significant anemia, bleeding
Drug-induced severe hypotension

Consortium [7]. As in adults, putative mechanisms for syncope in childhood HCM may include supraventricular and ventricular arrhythmias, failure to increase cardiac output during stress, abnormal blood pressure response during exercise, impaired baroreflex sensitivity and worsening left ventricular outflow tract obstruction [11].

The occurrence of syncope is a major risk factor for SCD in children with HCM. In a metanalysis of paediatric populations with HCM that included patients under 18 years of age, unexplained syncope was statistically associated with SCD with a hazard ratio of 1.89 [12]. This risk increased markedly to a hazard ratio of 7.4 in a younger population (mean age 9.8 years) with a history of unexplained syncope within previous 6 months [10]. Even if the prevalence of unexplained syncope is lower (6.1%) in preadolescent population (age < 12 years), the long-term outcome did not differ by age of presentation [13]. All the above-cited articles did not provide a definition of unexplained syncope. Based on the results of paediatric populations, a paediatric risk stratification tool (HCM Risk-Kids), which includes unexplained syncope among the variables of risk, was developed similar to the adult risk stratification tool [7]. The HCMRisk-Kids prediction model has been externally validated in large and geographically different childhood populations including 3 multicentre external validation cohorts [14–16]. An alternative risk shore has also been recently published which largely overlap with HCMRisk-Kids score [10].

The work-up for assessment of syncope shown in Fig. 3 should be used also for children. Reflex syncope is the most frequent cause of syncope also in children and should be investigated as in adults. However, some tests for the diagnosis of reflex syncope may be not feasible in younger children and their interpretation may be doubtful due to the lack of data regarding their diagnostic accuracy. Exercise stress echocardiography should be considered in children with HCM old enough to use the equipment to unmask an underlying LVOTO. For the above limitations, implantable loop recorder (ILR) has become widely used in children. ILR should be considered in children with HCM and risk factors for SCD, when the aetiologic work-up of syncope is inconclusive and where the identification of an arrhythmic cause would warrant ICD implantation. In these cases, the possible complications of ICD implantations should be weighed against the risk of arrhythmic episodes and the discussion of the multidisciplinary syncope and HCM Heart Team should consider at the same level ICD and ILR implantation.

Example case 5: An 8-year old child with HCM presents to the ED with a history of syncope after he stood up abruptly during his summer holidays. He had a family history of HCM and his father had undergone ICD implantation for primary prevention. His echocardiogram showed a maximal left ventricular wall thickness of 18 mm (z score + 13,2), a left atrial diameter of 21 mm (z score − 1.46) and, on exercise stress echocardiography, he showed a LVOTO with a gradient of 35 mmHg. His Holter monitoring did not show any episodes of NSVT. In this patient, clinical evaluation points to reflex syncope, but ABPM and head-up tilt test could not be performed due to the younger age. In this patient the estimated HCMRisk-Kids score prior to the syncopal episode was 4.76%. The score would be 7.22 if syncope were potentially arrhythmic. The multidisciplinary syncope and HCM Heart Team should consider at the same level ICD and ILR implantation after careful discussion of concomitant risk factors and the risk of device-related complications.

4.5. Multidisciplinary Syncope and HCM Heart Team and Shared Decision with the Patient

The decision to implant an ICD or to complete the investigations (e.g.

ILR implantation) in HCM patients with unexplained syncope depends on the overall global clinical evaluation of the patient's condition, the potential benefit and harm of such therapy, and the presence of other risk factors for SCD. It should not be based solely on pre-specified risk scores, as that does not support the concept of patient autonomy and shared decision making. The risk score is invaluable in communicating the magnitude of risk, and for identifying broad categories of risk. Individual patients, however, have their own understanding and the level of risk tolerance that must be integral to the final decision.

The panel of experts agree on the need of a strict collaboration between experts in HCM and experts in syncope and support the idea of creating a multidisciplinary syncope and HCM Heart Team in any referral hospital for HCM patients, which could be consulted for clinical decision making (Fig. 1).

Appendix A. Writing Committee Members and their affiliations

Name	Affiliation	Email address	Remark
Anastasakis Aris	Unit of Inherited and Rare Cardiovascular Diseases, Onassis Cardiac Surgery Centre, Kallithea, Greece.	anastasakisaris@gmail.com	Member, 2014 ESC HCM guidelines
Brignole Michele	IRCCS Istituto Auxologico Italiano, Dept of Cardiology, Hospital S. Luca, Milan, Italy	mbrignole@outlook.it	Chair, 2018 ESC Syncope guidelines
Cecchi Franco	IRCCS Istituto Auxologico Italiano, Dept of Cardiology, Hospital S. Luca, Milan, Italy	francocecchi337@gmail.com	Member, 2014 ESC HCM guidelines
Crotti Lia	IRCCS Istituto Auxologico Italiano, Dept of Cardiology, Hospital S. Luca, Milan, Italy	l.crotti@auxologico.it	Member of ERN and EHRA)/HRS/APHRS/LAHRS Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases
Deharo Jean Claude	Hôpitaux de Marseille, Centre Hospitalier Universitaire La Timone, Service de Cardiologie, Marseille, France and Aix Marseille Université, C2VN, Marseille, France	jeanclaude.deharo@ap-hm.fr	Member, 2018 ESC Syncope Guidelines
Elliott Perry	Institute of Cardiological Sciences, University College London, UK	perry.elliott@ucl.ac.uk	Chair, 2014 ESC HCM guidelines Member, 2020 AHA/ACC HCM guidelines
Fedorowski Artur	Dept. of Cardiology, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden	artur.fedorowski@ki.se	Member, 2018 ESC Syncope Guidelines
Kaski Juan Pablo	Institute of Cardiovascular Science, University College London and Great Ormond Street Hospital, London, UK	j.kaski@ucl.ac.uk	Chair, 2023 ESC Cardiomyopathy guidelines
Limongelli Giuseppe	Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", AO Dei Colli-Monaldi Hospital, Naples, Italy.	limongelligiuseppe@libero.it	Member of ERN; Member, 2014 ESC HCM guidelines
Maron Martin S	HCM Center, Lahey Hospital and Medical Center, Burlington, MA, USA.	mmaron@tuftsmedicalcenter.org	Member, 2020 AHA/ACC HCM guidelines
Olivotto Iacopo	Meyer Children Hospital, Department of Experimental and Clinical Medicine, University of Florence, Italy	iacopo.olivotto@unifi.it	Member, 2019 EAPC Recommendations for sports participation in athletes with cardiomyopathies, myocarditis and pericarditis.
Ommen Steve R	Professor of Medicine, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA	ommen.steve@mayo.edu	Chair, 2020 AHA/ACC HCM guidelines
Parati Gianfranco	IRCCS Istituto Auxologico Italiano, Dept of Cardiology, and University of Milano Bicocca, Milan, Italy	gianfranco.parati@unimib.it	Member, 2018 ESC/ESH Hypertension guidelines
Shen Win	Mayo Clinic Arizona, Phoenix, AZ, USA	wshen@mayo.edu	Chair, 2017 AHA/ACC Syncope guidelines
Ungar Andrea	Division of Geriatric and Intensive Care Medicine, Azienda Ospedaliero Universitaria Careggi, Department of Experimental and Clinical Medicine, University of Florence andFlorence, Italy	andrea.ungar@unifi.it	Member, 2018 ESC Syncope Guidelines
Wilde Arthur	Heart Centre, Department of Cardiology, Amsterdam Universitair Medische Centra, Amsterdam,location AMC, The Netherlands	a.a.wilde@amsterdamumc.nl	Member, ERN 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families

ERN: 'Member of the European Reference Network for rare, low prevalence and complex diseases of the heart: ERN GUARD-Heart' (ERN GUARDHEART; http://guardheart.ern-net.eu).

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