Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta
An Academic Partner of Trinity College Dublin

Dr Deirdre Ward
Consultant in Inherited Cardiac Conditions

Unexplained Syncope in High Risk Patients

Syncope Training Day 2018
Mercer's Institute for Successful Aging

14th September 2018

Syncope and high risk

- Cardiac conditions not the most common cause, but associated with highest mortality
- Up to 16% of all cases presenting with syncope have a cardiac cause
  - especially with increasing age
- Initial assessment should focus on:
  - Is there evidence of risk associated?
  - Should this patient be admitted?
- Of secondary importance is determining:
  - The cause
  - Appropriate treatment

Conflicts and Sources

- No conflic
- Thanks to slides
- 2018 ESC and
  manager syncope in
  patients a
- 2018 ESC :hele Brignole
  & Angel M artj/ehy037
- Vincent P thorax,
  Nantes, France

ESC GUIDELINES

2018 ESC Guidelines for the diagnosis and management of syncope

The Task Force for the diagnosis and management of syncope of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)

Endorsed by: European Academy of Neurology (EAN), European Federation of Autonomic Societies (EFAS), European Federation of Internal Medicine (EFIM), European Union Geriatric Medicine Society (EUGMS), European Society of Emergency Medicine (EuSEM)

Authors/Task Force Members: Michele Brignole* (Chairperson) (Italy), Angel Moya* (Co-chairperson) (Spain), Frederik J. de Lange (The Netherlands), Jean-Claude Deharo (France), Perry M. Elliott (UK), Alessandra Fanciulli (Austria), Artur Fedorowski (Sweden), Raffaello Furlan (Italy), Rose Anne Kenny (Ireland), Alfonso Martín (Spain), Vincent Probst (France), Matthew J. Reed (UK), Ciara P. Rice (Ireland), Richard Sutton (Monaco), Andrea Ungar (Italy), and J. Gert van Dijk (The Netherlands)

Reducing incidence of syncope and potential SCD

- Appropriate therapy
  - Medication
    - largely unhelpful (except some hereditary conditions)
    - May be pro-arrhythmic
  - ICD
    - Low risk of device failure (? 1 per 300,000)
    - Significant risk of complications
      - Implant complications
      - Device recall
      - Lead and /or device revision
  - Surgical (or percutaneous) intervention
    - Aortic stenosis, HCM has a definite role
    - Reversal of cardiac ischaemia may have a role
    - Left cervical sympathetic denervation
- Identification of at-risk patients

- [
  (
- (

aght
versity
pital

Diagnostic criteria with initial evaluation

Recommendations	Class[a]	Level[b]
Reflex syncope and OH		
VVS is highly probable if syncope is precipitated by pain, fear, or standing, and is associated with typical progressive prodrome (pallor, sweating, and/or nausea).[5,12–17]	I	C
Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers, listed in Table 3.[4,5,17]	I	C
Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant significant OH.[18–24]	I	C
In the absence of the above criteria, reflex syncope and OH should be considered likely when the features that suggest reflex syncope or OH are present and the features that suggest cardiac syncope are absent (see Table 3).	IIa	C
Cardiac syncope		
Arrhythmic syncope is highly probable when the ECG shows[25–39]: • Persistent sinus bradycardia <40 b.p.m. or sinus pauses >3 s in awake state and in absence of physical training; • Mobitz II second- and third-degree AV block; • Alternating left and right BBB; • VT or rapid paroxysmal SVT; • Non-sustained episodes of polymorphic VT and long or short QT interval; or • Pacemaker or ICD malfunction with cardiac pauses.	I	C
Cardiac ischaemia-related syncope is confirmed when syncope presents with evidence of acute myocardial ischaemia with or without myocardial infarction.[25–28]	I	C
Syncope due to structural cardiopulmonary disorders is highly probable when syncope presents in patients with prolapsing atrial myxoma, left atrial ball thrombus, severe aortic stenosis, pulmonary embolus, or acute aortic dissection.	I	C
Additional advice and clinical perspectives		
The initial syncope evaluation, as described in this document, can define the cause of syncope in most patients. Strict adherence to the above definitions of VVS and situational reflex syncope, and of syncope due to OH, can be considered certain or highly likely irrespective of the presence of any other abnormal finding. In young subjects with unexplained syncope and no history of cardiac disease, no family history of sudden death, no supine syncope or syncope during sleep or exercise, no unusual triggers, and a normal ECG, the chance of cardiac syncope is very low. SCD rates in subjects <35 years amount to 1–3/100 000.		

AV = atrioventricular; BBB = bundle branch block; b.p.m. = beats per minute; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; OH = orthostatic hypotension; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VT = ventricular tachycardia; VVS = vasovagal syncope.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2018

Features that suggest increased risk

- History of IHD or heart failure
- Occurs during exertion (but not post exercise)
- Signs of heart failure or structural cardiac disease
- Abnormal ECG
- Occurs without warning - > 65 years
- Family history of hereditary cardiac condition or sudden cardiac death
- New or unexplained SOB (? PE)

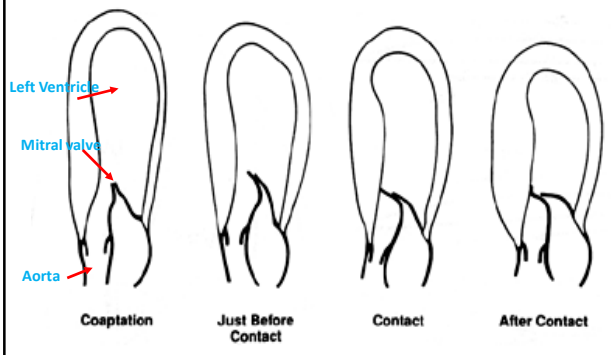
Hypertrophic Cardiomyopathy

- ☐ Left ventricular hypertrophy (concentric or asymmetric) in the absence of physiological cause
- ☐ HCM or HOCM
  - ◘ 25% have obstruction
- ☐ Genetic cause - Gene mutation in > 1 in 500 population
- ☐ Familial transmission in 90% of cases
- ☐ Sporadic in 10%
- ☐ 14 genes associated
  - ◘ Majority sarcomeric protein genes
  - ◘ Metabolic causes
    - ■ Fabry disease
    - ■ AMP Kinase
    - ■ Danon disease
  - ◘ Genetic test identifies cause approx 60% of affected cases

Syncope in HCM

- Mechanical obstruction
  - – Systolic anterior motion of AMVL causes gradient across LVOT
  - – Conditions of stress or exercise increase myocardial oxygen demand, increase gradient and reduce output (and coronary flow)
  - – Sometimes precipitated by post-prandial state or vasodilators (alcohol, GTN, phosphodiesterase inhibitors)

Left Ventricular Outflow Tract Obstruction (LVOTO)

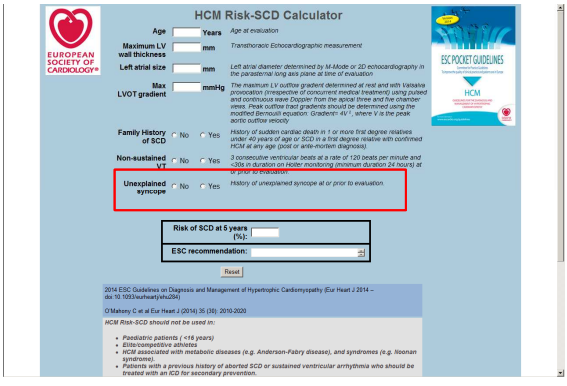


Syncope in HCM - Arrhythmia

- Conditions for arrhythmia in HCM
  - – Pro-arrhythmic substrate
    - Myofibre disarray
    - Fibrosis
  - – Trigger
    - Relative ischaemia
      - – Exercise (microvascular disease, mismatch supply and demand, LVOT obstruction)
      - – Arrhythmia (paroxysmal A Fib, SVT)
      - – Emotion

Arrhythmia and sudden death in HCM

- Overall 1% per year
- Higher rates in probands
- Lower rates in family screening services
- 9 - 50% of all sudden cardiac deaths aged 1-35 years
- Are high-risk patients identifiable?
- Is sudden death preventable?



ESC-hosted: http://www.doc2do.com/hcm/webHCM.html

Recommendations	Class	Level
Hypertrophic cardiomyopathy		
1. It is recommended that the decision for ICD implantation in patients with unexplained syncope is made according to the ESC HCM Risk-SCD score http://www.doc2do.com/hcm/webHCM.html	I	B
2. Instead of an ICD, an ILR may be considered in patients with recurrent episodes of unexplained syncope with systolic impairment but without a current indication for ICD.	IIa	C

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya
EHJ Doi:10.1093/eurheartj/ehy037

Familial DCM and arrhythmia

- Idiopathic DCM is familial in perhaps 25% of cases
- 100 different genetic causes, including sarcomeric mutations
  - Current gene panels offered are 28-96 genes
  - Cost (in Oxford) £1020 for index case
- Gene mutation identified 5-30%
  - Titin mutations may account for 25%
- Risk stratification as per SCD HeFT
  - NYHA Class II-III symptoms
  - LV ejection fraction ≤ 35%
- Only approx 20% of this population receive ICD therapy within 5 years of implant
- Recent studies (subgroup analysis DANISH, Sanjay Prasad et al this week's JACC Imaging) suggest presence of LGE (+/- Extent or location) the most reliable predictor of arrhythmia in non-ischaemic DCM

Special cases with DCM

- Higher arrhythmic risk with near-normal LV EF in
  - Lamin A/C disease (association of conduction disease and premature SCD +/- PAF)
  - Myotonic dystrophy
    - Presence of atrial arrhythmia (sustained atrial tachycardia, flutter or fibrillation)
    - severe ECG abnormality (PR ≥ 240 msec, QRS ≥ 120 msec, 2nd or 3rd degree A-V block)
    - Prolongation of A-H and H-V interval on EPS
  - Muscular dystrophies
  - LV variant ARVC

Recommendations	Class	Level
Left ventricular systolic dysfunction		
1. ICD therapy is recommended to reduce SCD in patients with symptomatic heart failure (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status	I	A
2. An ICD should be considered in patients with unexplained syncope with systolic impairment but without a current indication for ICD to reduce the risk of sudden death	IIa	C
3. Instead of an ICD, an ILR may be considered in patients with recurrent episodes of unexplained syncope with systolic impairment but without a current indication for ICD	IIb	C
Additional advice and clinical perspectives • The presence of syncope increases mortality irrespective of ICD implantation compared to patients without syncope. • Treatment of syncope is based on the specific cause of syncope whereas treatment for the underlying cardiomyopathy impacts on the long-term prognosis. • The decision to implant an ICD or to complete the investigation (e.g. ILR implantation) in patients with unexplained syncope depends on a global clinical evaluation of the patient's conditions, the potential benefit and harm of such therapy, and the presence of other risk factors for SCD.		

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya
EHJ Doi:10.1093/eurheartj/ehy037

Arrhythmogenic (right ventricular) cardiomyopathy (ARVC/D)

- Myocardial cell death and replacement with fat and fibrosis (causing arrhythmia and heart failure RV>LV)
- Inherited in > 50%
- Prevalence unknown – estimated at 1 in 5000 but may be more frequent
- Wide variation is penetrance and disease severity
- Risk of sudden death again ~ 1%/year
- 5 disease-causing desmosomal mutations known, accounting for 30-40% clinically diagnosed patients
- Diagnosis relies on TFC (originally 1994, revised 2010)
  - no gold standard for diagnosis

Sudden death in ARVC

- Initially thought to be 2% per year (pre-ICD)
- Family studies suggest overall incidence <<1% per year
- Risk stratification in ARVC
  - In USA clinical diagnosis usually considered indication for ICD
  - In Germany documented ventricular arrhythmia often treated pharmacologically
  - Clinical risk factors

Clinical risk factors ARVC

- Major morphological abnormalities of RV
  - Severe dilatation +/- systolic impairment +/- aneurysm
  - Significant LV involvement
  - Documented ventricular arrhythmia (especially if poorly tolerated haemodynamically)
  - Unexplained syncope
  - Strong family history SCD
- Pharmacological therapy
  - B-blockers no anti-arrhythmic benefit
  - Sotalol / amiodarone some benefit
- EPS and ablation – usually only post-ICD
- ICD may have higher complication rate in those with thinned and fibrosed RV (apex part of 'triangle of dysplasia')

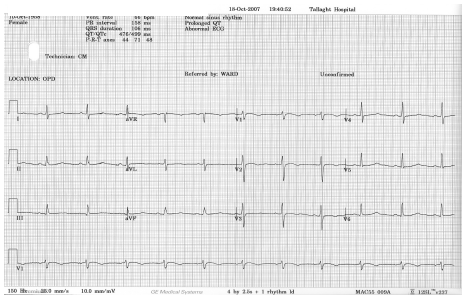
Recommendations	Class	Level
Arrhythmogenic right ventricular cardiomyopathy		
1. ICD implantation may be considered in patients with ARVC and a history of unexplained syncope.	IIb	C
2. Instead of an ICD, an ILR may be considered in patients with recurrent episodes of unexplained syncope but without a current indication for ICD.	IIa	C

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya
EHJ Doi:10.1093/eurheartj/ehy037

Long QT syndrome

- ☐ Prevalence may be 1 in 2000, Autosomal dominant
- ☐ Not detectable after death (unless DNA)
- ☐ Diagnosis
  - ◘ Abnormal T-wave morphology +/- QT prolongation
  - ◘ Inappropriate bradycardia for age
  - ◘ Inappropriate QT response to exercise (brisk standing)
- ☐ Genetic mutation detected in 60-80% (14 genes identified)
- ☐ Circumstances of arrhythmia may alter between types
  - ☐ LQT1 (KCNQ1) – events occur during exercise/emotion
  - ☐ LQT2 (KCNH2) – events occur when startled (telephone, alarm)
  - ☐ LQT3 (SCN5a) – events occur at rest / during sleep
- ☐ LQT1 patients more likely to be symptomatic (40%?) but self-limiting syncope more common
- ☐ SCD risk higher in LQT3, LQT2

LQT ECG



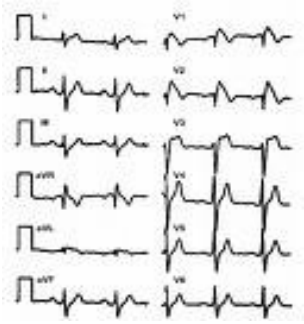
Recommendations	Class	Level
Long QT syndrome		
1. ICD implantation in addition to beta-blockers should be considered in LQTS patients who experience unexplained syncopea while receiving an adequate dose of beta-blockers.	IIa	B
2. Left cardiac sympathetic denervation should be considered in patients with symptomatic LQTS when: (a)beta-blockers are not effective, not tolerated, or are contraindicated; (b)ICD therapy is contraindicated or refused; or (c)when patients on beta-blockers with an ICD experience multiple shocks.	IIa	C
3. Instead of an ICD, an ILR may be considered in patients with recurrent episodes of unexplained syncope but without a current indication for ICD.	IIa	C

Additional advice
• Beta-blockers are recommended in all patients with a clinical diagno-sis of LQTS, with the possible exception of those with LQTS3 form.

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya
EHJ Doi:10.1093/eurheartj/ehy037

Brugada syndrome

- ☐ True prevalence unknown
- ☐ Ventricular arrhythmia (polymorphic VT) + ST elevation V1-V3
- ☐ South-East Asian males
- ☐ Events usually at rest/during sleep
- ☐ Sodium channel mutation found in 20%
  - ☐ 4 other genes recently discovered
- ☐ Characteristic ECG not always present at rest
  - ◘ May be unmasked by infusion of Na-channel inhibitors (Flecainide / Ajmalin)
- ☐ Management
  - ◘ VT stim
  - ◘ ICD



Risk stratification controversial

- Priori et al
  - High risk if :
    - Type 1 (coved pattern) present at rest
    - Syncope
- Brugada brothers
  - EP VT stimulation studies
    - Weak positive predictive value
    - Strong negative predictive value
- Management
  - ICD
  - No Med Rx
    - Quinidine may be effective at reducing arrhythmia (? Adjunct to ICD if frequent events)

Recommendations	Class	Level
Brugada syndrome		
1. ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and a history of unexplained syncope.	IIa	B
2. Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncopea who are at low risk of SCD, based on a multiparametric analysis that takes into account the other known risk factors for SCD.	IIa	C

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya
EHJ Doi:10.1093/eurheartj/ehy037

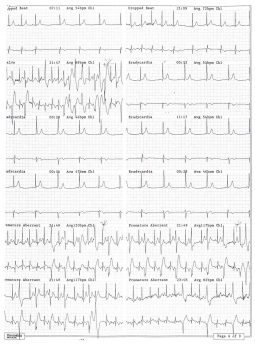
Other Forms

Due to a lack of studies examining unexplained syncope in other forms of inheritable arrhythmic diseases such as catecholaminergic polymorphic VT, early repolarization syndrome, and short QT syndrome, this Task Force is unable to give specific recommendations for the investigation and treatment of unexplained syncope.

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya
EHJ Doi:10.1093/eurheartj/ehy037

Catecholaminergic Polymorphic VT

- Syncope or sudden death during exercise / emotion
- ? 1 in 10,000 population
- Normal / near-normal resting ECG
- Bi-directional ectopy / VT when HR > 110/min
- 2 gene mutations identified (Ryanodine 2 receptor, Calsequestrin)
  - Disease of calcium handling
- Management
  - B-blockers (Nadolol may be most effective, very difficult to source in Ireland)
  - Avoid precipitant
  - ICD if events on-treatment (often high discharge rate)
  - Left Cervical Sympathetic Denervation



In summary

Tallaght University Hospital

- Cardiac conditions not the most common cause, but associated with highest mortality
- Up to 16% of all cases presenting with syncope have a cardiac cause (especially with increasing age)
- Initial assessment should focus on:
  - Is there evidence of risk associated?
  - Should this patient be admitted?
- Unexplained syncope in individuals with underlying cardiac conditions often indicates increased mortality risk
  - Should prompt consideration of ICD implant
  - ILR now included on syncope guidelines as reasonable option for individuals in whom features of underlying condition do not otherwise suggest ICD indicated