WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

J R Skinner **Rani Robson**	Initial separate WS A&B discussed in Orlando Nov 2010 Updated combined WS based on WSE, E3, TF feedback and discussion with pediatric WSA on similar topic- submitted 28 January 2010.

Clinical question.

In apparently healthy children and young adults (P), does the presence of any warning signs available to the lay person or health care professional (e.g. syncope, family history) (I), as opposed to their absence (C), predict an increased risk of sudden cardiac death (O)? (Exclude screening in sportsmen and patients with known ischaemic heart disease).

Is this question addressing an intervention/therapy, prognosis or diagnosis? **Prognosis**
State if this is a proposed new topic or revision of existing worksheet: **New topic**

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? **No**

Search strategy (including electronic databases searched).

***General points**:*
*Heart conditions listed below predispose to risk of sudden death in the Young (SUDY). Therefore any symptom or sign which predates **either** SUDY/Cardiac arrest/resuscitated cardiac arrest **or** diagnosis of these conditions effectively predicts risk of sudden death. (*
Long QT syndrome, CPVT, Brugada, HCM, DCM, ARVC, WPW, Congenital Coronary arterial anomalies.

Warning signs can be in
a) the family history (eg FHx of SUDY/SIDS/SUDEP of one of the familial conditions above or
b) in the clinical history/presentation (syncope/palpitations/seizure/drowning in strong swimmer/ RTA while driving on a straight road.

*Since these people are all outwardly normal and usually have a normal physical exam- the warning signs are **not clinical signs** but rather **symptoms and family history**.*

Pubmed: "sudden, death, cardiac" AND "palpitations" OR "syncope" as MeSH OR "family history"
"Risk Factors"[Mesh] AND "Death, Sudden, Cardiac"[Mesh]
"seizures sudden death"
SUDEP
"Prevalence"[Mesh] AND Chest pain AND Sudden Death
Medline: "sudden, death, cardiac" AND "risk factor" OR "syncope" OR "palpitations" as MeSH (headings or abstract)
Cochrane reviews (database of systemic reviews), DARE (through Cochrane), Cochrane clinical trials, DARE (direct search): "sudden, death, cardiac" as MeSH
EMBASE: "sudden, death, cardiac" AND "risk factor" as MeSH
Forward searching using Google scholar, hand searching of citations

- State inclusion and exclusion criteria

Limitations:
Medline: Age (child 7-12, adolescent 13-17, Adult 18-64), Human, English, Journal articles only,
EMBASE: Human and Age: Groups School Child 7 to 12 years or Adolescent 13 to 17 years or Adult 18 to 64 years and English Language and Publication Types: Journal
Exclusions:
Animal studies, Reports of single cases, reviews, editorials, all papers not relating to prodromal symptoms

- Number of articles/sources meeting criteria for further review:

49 studies met criteria for further review. Of these, 2 were LOE P1, 2 LOE P3, 6 LOE P4 and 39 LOE P5.

Summary of evidence

Evidence Supporting Clinical Question

Good				**Gimino, 2009 K Tan, 2005 K**	**Brugada, 2003 B Calkins, 1995 N4 Colivicchi, 2003 HM Dalal, 2005 A Flicker, 1998 N3a Goldenburg, 2008 BI Hobbs, 2006 B Johnson, 2009 N3b Kaufman, 2008 BI Kofflard, 2003 AFM MacCormack, 2009 N3b Probst, 2007 N1 Skinner, 2004 N3b Sopontammarak, 2003 N7 Sumitomo, 2003 A**
Fair			**Colman, 2009 N4**	**Behr, 2008 A Brothers, 2008 K Nava, 2000 A**	**Basso, 2000 A Colivicchi, 2004 N4 Drory, 1991 C Elliott, 2000 GHC Hulot, 2004 AE Linzer, 1994 N3b Oh, 1999 MHJ Opeskin, 2003 N3a Priori, 2002 B Spirito, 2009 AE Wisten (p143-149), 2005 A***
Poor					**Akerman, 1999 N5 Amital, 2004 C* Bromberg, 1996 N6 Corrado, 2001 A Kramer, 1988 C* Martin, 1997 ML Quigley, 2005 A Tester, 2004 N2a/b Tester, 2005 N5 Wisten, 2002 A***
	P1	**P2**	**P3**	**P4**	**P5**
Level of evidence					

A = Symptoms as a predictor of SCD
B = Symptoms as a predictor of SCD or aborted cardiac arrest
C = Symptoms as a predictor of SD (any cause)
D = Life style as a predictor of SCD
E = Sudden cardiac death (SCD)
F = Cardiac death (SCD or heart failure)
G = Sudden death (SD) (any cause – non-traumatic)
H = Death (any cause)
I = SCD or aborted cardiac arrest
J = Cardiac cause of syncope
K = Disease associated with SCD
L = All cause mortality or arrhythmias
M = Symptoms as a predictor of death (all cause)
N1 = Syncope associated with risk of SCD among cohort of inherited heart disease subjects
N2 = SUDY autopsy series a – indicated presence of inherited heart disease b – indicated presence of warning signs.
N3=Seizure disorders a) have increased risk of SUDY b)Arrhythmic conditions (LQTS) misdiagnosed as seizure disorder
N4= type of syncope indicates cardiac arrhythmia
N5=drowning/near drowning sometimes due to LQTS or CPVT
N6= palpitations may indicate risk of SCD
N7=congenital sensorineural deafness associate with risk of LQTS
* = *Overlapping patients*

Evidence Neutral to Clinical question

Good					
Fair			**Wisten, 2005 (p137-142) C***		**Costantino, 2008 MH Massin, 2004 N4 Peters, 2007 H**
Poor	**Tanaka, 2006 E**				
	P1	**P2**	**P3**	**P4**	**P5**
Level of evidence					

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Evidence Opposing Clinical Question

Good				**Callenbach, 2001 N3a**	
Fair	**Wilson, 2007 J**				
Poor					
	P1	**P2**	**P3**	**P4**	**P5**
Level of evidence					

A = Symptoms as a predictor of SCD
B = Symptoms as a predictor of SCD or aborted cardiac arrest
C = Symptoms as a predictor of SD (any cause)
D = Life style as a predictor of SCD
E = Sudden cardiac death (SCD)
F = Cardiac death (SCD or heart failure)
G = Sudden death (SD) (any cause – non-traumatic)
H = Death (any cause)
I = SCD or aborted cardiac arrest
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REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

DISCUSSION: Sudden cardiac death (SCD) in the young is a rare but catastrophic event. Estimates of the incidence SCD in the young (<40 years old) range from 0.4 to 3 per 100,000 person years. SCD is notoriously difficult to prevent as it is often the first manifestation of cardiac disease in an individual at risk. Since survival rates from out-of-hospital cardiac arrests remain poor, primary prevention is the key to reducing the incidence of SCD. With the advent of effective therapies (such as internal cardiac defibrillators) for some of the most common causes of SCD, there is increased pressure for mechanisms of identifying those at increased risk. Due to the overall small number of individuals at risk of SCD, prospective cardiac assessment of the general population is not feasible.

Many sudden deaths in the young occur during or shortly after exercise with vigorous exertion thought to act as a trigger in those with risk of SCD. In one study, the risk of SCD was 2.1 in 100,000 athletes per year compared with 0.7 in 100,000 non-athletes. As a result, competitive athletes are being targeted for cardiac screening. As the percentage of the general population considered "athletes" is small; the greatest number of SCD occurs within non-athletes. In addition to athletes, the targeting of other high-risk subgroups such as patients with cardiac symptoms, relatives of SCD victims and relatives of patients with a cardiac disorder known to predispose to SCD should also be considered.

Sudden Cardiac Death is defined as a witnessed natural unexpected death due to cardiac causes occurring within 1 hour after onset of symptoms in a previously healthy person, or an un-witnessed natural unexpected death of a person observed to be well 24 hours prior to being found dead. Causes of sudden cardiovascular deaths in the young can be subdivided into:

1) Structural/functional: cardiomyopathies (including hypertrophic cardiomyopathy – HCM), coronary artery anomalies, myocarditis, endocarditis, obstructive coronary artery disease, valvular disease, congenital heart disease.
2) Electrical: Long QT syndrome, Short QT syndrome, WPW, Brugada syndrome, congenital heart block, catecholaminergic VT and arrhythmogenic right ventricular cardiomyopathy (ARVC)

Studies relevant to examining the presence of warning signs predisposing to a risk of SCD in apparently healthy children and young adults can be subdivided into the following categories, which are discussed below:

1) Studies examining the risk of SCD in those experiencing specific symptoms
2) Screening of healthy children and young adults for cardiac diseases predisposing to SCD
3) Autopsy studies examining the prodromal symptoms of victims of SCD
4) Studies examining the consequences to an individuals risk of SCD if they have a family history of SCD or a family member with a cardiac disease associated with SCD
5) Studies examining the risk profile of patients with known cardiac disorders predisposing them to SCD.
6) Studies investigating the lifestyle differences in victims of SCD

It is important to note that this worksheet is not examining the value of screening the general population or indeed high risk populations such as those with a family history of SCD or those with a known underlying disease with a pre-disposition to SCD. None-the-less, information gained from studies involving such patients is likely to be of some value in developing an evidence base for warning signs in the otherwise fit and healthy population of children and young adults.

1) Risk associated with specific cardiac symptoms

Studies of the prognostic value of symptoms in predicting sudden cardiac death in the young are few and are generally restricted to cohorts of patients who are registered with an inherited heart disease.

Syncope:

There is evidence mostly from adult literature that syncope of a certain type should lead to a suspicion of arrhythmogenic cardiac disease which of itself predisposes to risk of SCD. The American Heart Association and European Society of cardiology guidelines on syncope agree broadly on the nature of syncope that should raise suspicion of cardiac disease:

Family history of premature sudden death
Familial heart disease,
Syncope during exercise and in particular during swimming,
Syncope while supine or sleeping (usually presenting as a seizure),
Syncope preceded by chest pain or palpitations.

Reassuringly, syncope in Children presenting to A&E is can be as low as 2% cardiac in origin (Calkins, 1995). There is evidence, however, that the nature of syncope is key in ascertaining what types of syncope which are suspicious of underlying arrhythmic cardiac disease. In one LOE P3 study (Colman, 2009) the nature of syncope experienced by patients with LQTS was compared to young adults presenting to A&E with syncope and patients with known vasovagal syncope. A family history of syncope or SCD, palpitations as a symptom, supine syncope and syncope associated with exercise and emotional stress were more common in patients with LQTS.

There are two adult studies (therefore LOE P5) which examined the nature of syncope in older adults as a predictor of a sinister cardiac origin. Oh et al (1999) examined 497 patients with syncope (>16 years old) presenting via inpatient admission, ED visits or outpatient visits to one center. Details of 19 associated symptoms and comorbidities were obtained. 222 patients were allocated a cause of syncope from history and physical

examination alone. In the remaining 275 patients, the absence of nausea & vomiting before syncope (OR 7.1, 95% CI 1.6-33.3) and ECG abnormalities (OR 23.5, 95% CI 7.0-78.7) were the only independent predictors of arrhythmic syncope. Underlying cardiac disease was the only predictor of 1-year mortality (OR 7.7, 95% CI 1.6-36.4, OR 13.5, 95% CI 2.6-70.5). No symptom remained as independent predictor for 1-year mortality or syncope recurrence. (Symptoms assessed included dizziness, diaphoresis, nausea and/or vomiting, generalised weakness, visual changes, flushing, dyspnoea, headache, chest pain, abdominal pain, palpitations, tingling, vertigo, lethargy, confusion, in continence, aura, neurological deficits, pruritus, or tonic/clonic movements.) Importantly, with regards to mortality, all cause mortality rather than SCD was examined. In the cohort of 275 patients, 24 died at 1 year, 11 with a cardiac cause (although no information was provided on incidence of SCD). In addition, the mean age of the cohort studied was 57 (range 17-94). The other study (Calkins, 1995) identified the duration of warning signs prior to syncope of < 5 seconds (P value <0.001) and less then 2 episodes (P value 0.001) were predictors of syncope due to VT or AV block as opposed to neurocardiogenic.

Arrhythmic cardiac conditions, in particular Long QT syndrome, can be misdiagnosed as seizure disorders. One third of those ultimately diagnosed with Long QT syndrome have been misdiagnosed as seizure disorder prior to the correct diagnosis. The prevalence of inherited heart disease among those diagnosed with seizure disorders in childhood is not clear from the literature, but seizures which should raise suspicion are those which:

are recalcitrant to treatment,
occur at night,
are precipitated by exercise,
are preceded by syncope.

Water related syncope or near drowning in a capable swimmer is suspicions of Long QT syndrome or CPVT. In a case series of two drowned children with negative autopsy, Tester (2005) found RyR2 mutations (i.e. they died from CPVT). The first child had prior history of syncope. This study proves that some cases of drowning due CPVT, however the denominator remains unknown.

Data are few on the predictive value of palpitations or chest pain, though in clinical practice these tended to be benign. The exceptions are anginal chest pain with exertion (which requires imaging to exclude HCM and coronary arterial abnormalities) and palpitations associated with syncope.

2) Screening

Two studies examined the efficacy of screening young, apparently healthy, individuals with a view to identifying those with inherited cardiac pathologies (and therefore risk of SCD)

Wilson et. al (2008) used personal symptom and family history questionnaires alongside resting ECG and physical examination in a cohort of 2720 junior athletes and physically active schoolchildren. Symptoms considered to be suggestive of a possible underlying cardiovascular disorder included repetitive syncope during exercise, prolonged palpitations, sustained chest pain and unexplained sudden death in a first degree relative <35 years old. Of the 2720 participants, 9 were diagnosed with a disease associated with sudden cardiac death. The ECG screening data identified all 9 children with potentially serious cardiovascular conditions; none of these children were symptomatic or had a family history of note.

In 1973, a national screening system in children looking for cardiovascular disease was introduced in Japan. Tanaka et. al. (2006) prospectively assessed the cardiovascular screening program for all students entering year 7 and then again at year 10 in the city of Kagoshima, Japan. A total of 37,807 subjects were evaluated at both screening stages. Screening involved an ECG (paper speed 25 mm per second) and a questionnaire regarding any cardiac history of heart murmurs, cardiac diseases (including Kawasaki disease and congenital heart defects) and cardiac symptoms (syncope, chest pain, irregular heart beat or palpitations on exertion, shortness of breath) as well as any family history of sudden death <40 year olds. Subjects with abnormal ECG or history of cardiac disease were examined further by physical examination and if needed CXR, ETT, ECHO. According to the to the questionnaire, 632 students were previously diagnosed with cardiovascular disease by their family doctor and of all the 7^{th} and 10^{th} grade students, 975 and 901 showed abnormal findings in the primary screening respectively. A total of 1876 students (2.7% of 37,807) participated in secondary screening. 9 Students (0.024%) (6 of whom were non-athletes) were identified as having significant cardiac disease potentially predisposing them to risk of SCD. Of these, 5 had HCM, 1 LV dilatation, 1 had WPW with tachycardic episodes, 1 primary pulmonary hypertension, 1 had Long QT syndrome with torsade de pointes. Three sudden deaths occurred during the study period; one student was from the high-risk group. Of the 3 deaths, all were boys with no history of syncopal attacks and no family history of SCD. One 14-year-old boy was identified with HCM during screening and died while jogging. He had been disqualified from participating in competitive sport. The remaining 2 SCD patients had normal ECGs. No autopsies were performed. Of the cohort, 497 were identified as “low-risk” subjects although further clarification of what this means was not provided. Unfortunately, no information was provided on the relationship between symptoms and ECG findings at initial screening and the subsequent diagnosis of cardiac disorders. As a result, no comment on the usefulness of cardiac symptoms, family history or ECG in screening can be made.

3) Autopsy studies

There were 8 case series (LOE P4) examining the prodromal symptoms of victims of SD (Amital, 2004. Basso, 2000. Corrado, 2000. Drory, 1991, Kramer, 1988. Quigley, 2005. Wisten, 2002. Wisten, 2005 p137. Wisten, 2005 p143). Prodromal symptoms were sought by examining the medical records, coroners report and from interviewing relatives. All of these retrospective studies run a significant risk of bias through symptom over-reporting by relatives and under-reporting in medical and coroners reports. Prodromal symptoms (Syncope, palpitations, chest pain, dyspnoea and/or flu-like symptoms) were reported in 12% (Quigley, 2005) - 57% (Wisten, 2005 p143-149) of victims of SCD.

Syncope/presyncope was the most common symptom reported. In a Swedish cohort of 15-35 year olds (162 individuals) having suffered SCD, 31% complained of syncope/presyncope, 17% palpitations, 14% chest pain, 7% fatigue, 3% flu-like illness and 2% dyspnoea prior to death

(Wisten, 2005 p143-149). In 74 who sought medical attention for their symptoms (half of these did so within 6 months of death) only 32 had an ECG (24 were pathological). 8 of these individuals were diagnosed with a cardiac disorder prior to death.

One study reported only 12% of patients complaining of prodromal symptoms (1.3% complained of syncope) (Quigley, 2005). However, details regarding previous relevant symptoms were obtained from the Dublin City Coroners' records. No attempt was made to obtain information from other sources such as hospital doctors, relatives, GP.

In a study examining the prodromal symptoms in victims of SCD caused by anomalous coronary arteries, chest pain occurred in 19% (exertional in 3/5) and syncope in 15% (exertional in ¾) (Bass, 2000). Drory et. al. (1991) in a cohort of 162 SD (all cause) reported that no patients under the age of 20 died of atherosclertic coronary artery disease, however, 24% of patients aged 20 – 29 years old and 58% of >30 year olds died of atherosclertotic coronary artery disease. The most frequent prodromal symptom reported in >20 year olds were chest pain (25%).

4) Family History

Many cardiac diseases associated with SCD in the young are known to have genetic inheritance (HCM, Idiopathic dilated cardiomyopathy, Left ventricular non-compaction, LQTS, Brugada, SQTS, ARVD/C) and the prevalence of family disease in these conditions is high. Systematic family screening can identify asymptomatic affected patients who could be at risk of SCD (Brothers, 2008. Gimeno, 2009). In a dedicated cardiac screening clinic, familial screening was offered to a total of 2,329 relatives of a patients with an inherited cardiac disease over a 5 year period. 222 affected relatives were identified, 129 of whom were newly diagnosed (Gimeno, 2009). Even in victims of Sudden Arrhythmic Death Syndrome or Sudden Unexplained Death, in whom a specific cardiac disease is not diagnosed at routine autopsy, screening of relatives provided a high yield of diagnoses of syndromes associated with SCD (Behr, 2008. Tan, 2005).

There is contradictory data on whether patients with a syndrome associated with SCD are at increased risk of SCD or aborted cardiac arrest if they have a history of SCD in a first degree relative. In a study (368 patients) identifying patients at high risk of SD in HCM, there was a significant pairwise interaction in the Cox model between a family history of SD and syncope, which when considered together resulted in an increased risk of SD (Elliott, 2000).

5) Populations with cardiac disorders predisposing them to a risk of SCD

There are a number of studies which identify risk profiles in patients already diagnosed with a cardiac condition associated with SCD (Brugada, 2003. Elliott, 2000. Goldenberg, 2008. Hobbs, 2006. Hulot, 2004. Kofflard, 2003. Nava, 2000. Peters, 2007. Priori, 2002. Spirito, 2009. Sumitomo, 2003). The majority of these studies were allocated LOE P5 as they analysed the warning signs of a subset of individuals already known to be at risk of SCD, and in addition the majority of these studies looked at all cause cardiac death (including heart failure). Those studies analysing symptoms prior to the diagnosis of a cardiac condition were allocated LOE P4.

Syncope (cardiac or without prodrome) was invariably identified as an independent risk of increased death in patients with HCM, Catecholaminergic polymorphic VT, LQTS, ARVD/C and Brugada Syndrome (along with ECG and Echocardiographic features specific to the disease being evaluated). Recent syncope (within 2 years) was a significantly stronger risk than distant syncopal episodes, as was recurrent syncope. Caution must be applied when extrapolating these results in order to assess the risk profile in apparently healthy young individuals. No other symptom was identified as an independent risk factor for SCD in these patients with cardiac conditions.

Importantly, in many studies identifying risk profiles in patients with a known cardiac condition, investigation for cause of syncope was a common route to the diagnosis of the cardiac condition associated with SCD.

6) Lifestyle

One study examined the association between lifestyle and SCD in the young, comparing a cohort of individuals who had suffered SCD (162 individuals) with an age matched control population (2131 individuals) (Wisten, 2005 p137-142). This study found no discernable difference with regards to lifestyle factors, including athletic activities, in these two groups.

Acknowledgements:

Citation List

Ackerman MJ, **Tester DJ**, **Porter CJ**. **Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. Mayo Clin Proc. 1999;74(11):1088-94.**

LOE P5, poor, supportive. Retrospective cohort of LQTS pts with swimming triggered syncope/drowning-strong link (100%) LQT1.

Amital H, Glikson M, Burstein M, Afek A, Sinnreich R, Weiss Y, Israeli V. Clinical characteristics of unexpected death among young enlisted military personnel: results of a three-decade retrospective surveillance. Chest, August 2004, vol./is. 126/2(528-33), 0012-3692

LOE P5, supportive, poor. The cause of cardiac death In under 30 year olds (total 41) included, IHD 10%, Myocarditis 34%, HCM 24%, Dilated cardiomyopathy 2%, Marfans syndrome 5%, Anomalous left coronary artery 2%, Corrected Tetrallogy of Fallot 2%, Mitral valve prolapse 7% and conduction abnomalities 12%. 20% of deaths were of unknown cause in the under 30 year old group.
Symptoms were available for only a subsection of the study cohort although further details are not provided. Syncope occurred in 2 cases of HCM (17%), in 1 cases of myocarditis (6%), 1 case of conduction abnormality (17%), and in 1 case of IHD (3%). 16% of patients with unknown cause of death experienced syncope. In total 19 patients experienced syncope prior to death (13%). Chest pain preceded death in 10 (34%) cases of IHD, 3 (25%) HCM, 2 (13%) cases of myocarditis, and in 1 (100%) of anomalous coronary artery. 24% of all deaths occurred within 6 hours of vigorous physical activity.
Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. J Am Coll Cardiol. 2000 May;35(6):1493-501.

LOE P5, supportive, fair. All patients in this study were either competitive athletes or participated in sport requiring systematic training and regular competition.

Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tome Esteban MT, Rowland E, Jeffery S, McKenna WJ. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. Eur Heart J. 2008 Jul;29(13):1670-80. Epub 2008 May 27.

LOE P4, supportive, fair. Affected first degree relatives were similar to unaffected first degree relatives exept that they were more likely to report a cardiac symptom, especially syncope (diagnosis present 20%, diagnosis abscent 4% - $p<0.001$). 2/3 SADS victims were young males and the majority died at rest or during sleep (63%). Half suffered antecedent symptoms that were rarely assessed (syncope 19%) and never diagnosed as being due to cardiac disease and there was a family history of premature sudden death in 30%.

Bromberg BI, Lindsay BD, Cain ME, Cox JL. Impact of clinical history and electrophysiologic characterization of accessory pathways on management strategies to reduce sudden death among children with Wolff-Parkinson-White syndrome. J Am Coll Cardiol. 1996;27(3):690-5

LOE P5, supportive, poor. Retrospective cohort study of 60 children with WPW, shows that children with WPW can present first with cardiac arrest and many have a history of SVT type palpitations. (Implication is children with syncope/palpitations should have an ECG). Palpitations may reveal a life threatening condition in children.

Brothers, J. A., P. Stephens, et al. (2008). Anomalous aortic origin of a coronary artery with an interarterial course: should family screening be routine? J Am Coll Cardiol 51(21): 2062-2064.

LOE P4, supportive, good

Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation. 2003 Dec 23;108(25):3092-6. Epub 2003 Nov 17.

LOE P5, supportive, good. Of the cohort patients, 124 were initially identified as having Brugada Syndrome during investigations for syncope of unknown origin, 170 were undergoing routine ECG screening and 253 were identified during screening of family members with the syndrome. Age at diagnosis was 41+/- 15 years. In 302 individuals, a family history of sudden cardiac death was present.

Calkins H, Shyr Y, Frumin H, Schork A, Morady F. The value of the clinical history in the differentiation of syncope due to ventricular tachycardia, atrioventricular block, and neurocardiogenic syncope. Am J Med. 1995 Apr;98(4):365-73.

LOE P5, supportive, good. All adults' rather then young adults and children. Assessing value of clinical history in diagnosing cause of syncope prospectively obtained from 80pts with syncope, symptoms lasting >5 seconds prior, and presence of nausea, warmth, diaphoresis, light headedness, palpitations, and fatigue post syncope indicate neurocardiogenic rather than cardiac.

Callenbach PM, Westendorp RG, Geerts AT, Arts WF, Peeters EA, van Donselaar CA, Peters AC, Stroink H, Brouwer OF. Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood. Pediatrics. 2001 Jun;107(6):1259-63.

LOE P4, against, good. Prospective cohort study of children with seizures. The nine deaths (of 472 children) all occurred in those with definite cerebral abnormality rather than the others.

Colivicchi, F., F. Ammirati, et al. (2003). Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. Eur Heart J 24(9): 811-819.

LOE P5, supportive, good. Derivation and validation of CDR on a split population sample. The primary end point of the study was death from any cause within 21 months of the initial evaluation in the ED (which occoured in 11.5% of the derivation cohort). Death was considered cardiovascular in 58% of these, non-cardiovascular in 9.6% and unknown origin in 32.4%. No sub-analysis specifying SCD was made. The mean age of the derivation cohort was 59.9 +/- 24.3. 34% had a history of hypertension, 29% had a clinical history of cardiovascular disease and 12% had a history of DM. This study was allocated a LOE P5 as its cohorts were not apparently healthy young adults and children and there was no extrapolation of risk of SCD in the outcome.

Colivicchi F, Ammirati F, Santini M. Epidemiology and prognostic implications of syncope in young competing athletes. Eur Heart J. 2004 Oct;25(19):1749-53.

LOE P5, supportive, fair. Large Prospective cohort study, of 7568 athletes. (474) 6.2% had a history of syncope. Only those with exertional syncope were investigated (4)- 2 had pathology, 4 did not. Syncope in athletes is rarely dangerous, but exertional syncope may be. Weakness is that not all cases with syncope underwent investigation, some may have had e.g. LQTS/WPW.

Colman N, Bakker A, Linzer M, Reitsma JB, Wieling W, Wilde AA. Value of history-taking in syncope patients: in whom to suspect long QT syndrome? Europace. 2009 Jul;11(7):937-43. Epub 2009 May 29.

LOE P3, supportive, fair. Retrospective cohort study.

Corrado D, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. Cardiovascular Research, May 2001, vol./is. 50/2(399-408), 0008-6363

LOE P5, poor, supportive. This study commented on symptoms experienced by patients prior to SCD, however, the objective of the study was to further differentiate the cause of death. No information was given on how clinical information of SCD victims such as family history, sport activity, prior symptoms and pre-mortal cardiac investigations were obtained.
33% of patients subsequently diagnosed with myocarditis experienced a flu-like illness 2-15 days prior to death, 7% experienced syncope, 4% experienced chest pain. Of patients diagnosed with ARVC, 33% had a family history of premature sudden death, 78% experienced palpitations, 44% experienced syncope. 18 patients had congenital accessory pathway, 6 (33%) with a history of SVT which was associated with syncope in 2. 6 patients had acquired conduction system disease leading to heart block. 2 (33%) of these patients experienced previous syncope and 1 pre-syncope. Of the 16 patients with no evidence of structural heart disease 13% complained of previous syncope and palpitations.

Costantino G, Perego F, Dipaola F, Borella M, Galli A, Cantoni G, Dell'Orto S, Dassi S, Filardo N, Duca PG, Montano N, Furlan R; STePS Investigators. Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: results from the STePS (Short-Term Prognosis of Syncope) study. J Am Coll Cardiol. 2008 Jan 22;51(3):276-83.

LOE P5, neutral, fair. Cohort of patients >18 years old. Average age 59 +/- 22, with 194 patients (29%) between the ages of 18-44. 10 patients were lost to 1 year follow-up.
Multivariate analysis found that absence of symptoms prior to syncope, an abnormal ECG and male gender were independent risk factors for adverse outcomes at 10 days after presenting with syncope. None of these adverse outcomes were SCD. At 1 year 3 patients had Sudden Death (0.4%), 16 patients had death unknown cause (2.4%) and 21 had death from other causes (3.1%). Risk factors for adverse outcomes at 1 year included aged older than 65, co-existence at presentation of neoplasm, cerebrovascular diseases, structural heart disease or ventricular arrhythmias.

Dalal D, Nasir K, Bomma C, Prakasa K, Tandri H, Piccini J, Roguin A, Tichnell C, James C, Russell SD, Judge DP, Abraham T, Spevak PJ, Bluemke DA, Calkins H. Arrhythmogenic right ventricular dysplasia: a United States experience. Circulation, December 2005, vol./is. 112/25(3823-32), 1524-4539

LOE P5, supportive, good. Patient's medical history was gained from both review of the medical records and by interview of the patients and their relatives. 8 of the 31 patients diagnosed with ARVD/C at autopsy had

symptoms before death. 5 of these patients experienced 1 or more episodes of syncope. The median time between presentation and death in these 8 patients was 1.5 (range 0-4 years). 3 study patients diagnosed with ARVD whilst alive subsequently died (2 SCD and 1 due to heart failure). All 3 had one or more episodes of syncope. Among patients with ARVC, palpitations, syncope and death are common presenting feature of ARVC. No comparison to control population incidence.

Drory Y, Turetz Y, Hiss Y, Lev B, Fisman EZ, Pines A, Kramer MR. Sudden unexpected death in persons less than 40 years of age. Am J Cardiol. 1991 Nov 15;68(13):1388-92.

LOE P5, supportive. Syncope was infrequently reported in all 3 age groups (2-4%).

Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000 Dec;36(7):2212-8.

LOE P5, fair, supportive. Retrospective case series of patients with known HCM. Study did not look at symptoms experienced prior to diagnosis (therefore allocated LOE P5).
Patient cohort was between 14-65 with mean age at diagnosis 33 +/- 14. 34% of patients were less than 30 years old. Recruitment was from a registry of patients at a tertiary referral centre with mean follow up 3.6 +/- 2.5 years.
A history of syncope was included only if it happened within the 12 months preceding patients first review at the tertiary centre. Family history of sudden death was defined as sudden cardiac death in two or more first-degree relatives <40 years old.
6% of the cohort of patients had SCD with 7.3% having cardiac death (SCD & heart failure). Of the 22 patients with SCD, 15 (68%) were <40 years old.
In isolation SCD and FHSD were not statistically significant independent risk factors for SCD. In combination they were a strong independent risk factor (RR 5.3, 95% CI 1.9-14.9).

Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, Belau PG. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology. 1998 Nov;51(5):1270-4.

LOE P5, supportive, good. Population based study retrospective of SUDEP.. Aged 14 to 44 years. The incidence of SUDEP was 0.35 per 1,000 person-years. SUDEP was responsible for 1.7% of deaths in this cohort. SUDEP is a rare cause of death in the epilepsy population but exceeds the expected rate of sudden death in the general population by nearly 24 times.

Gimeno, J. R., J. Lacunza, et al. (2009). Penetrance and risk profile in inherited cardiac diseases studied in a dedicated screening clinic. Am J Cardiol 104(3): 406-410.

LOE P4, supportive, good

Goldenberg I, Moss AJ, Peterson DR, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Priori SG, Qi M, Schwartz PJ, Towbin JA,

Vincent GM, Zhang L. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. Circulation, April 2008, vol./is. 117/17(2184-91), 1524-4539

LOE P5, supportive, good. Aborted cardiac arrest and SCD were evaluated together.

Hobbs JB, Peterson DR, Moss AJ, McNitt S, Zareba W, Goldenberg I, Qi M, Robinson JL, Sauer AJ, Ackerman MJ, Benhorin J, Kaufman ES, Locati EH, Napolitano C, Priori SG, Towbin JA, Vincent GM, Zhang L. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. JAMA, September 2006, vol./is. 296/10(1249-54), 1538-3598

LOE P5, supportive, good. Syncope was defined as a transient loss of consciousness that was abrupt in onset and offset. Individuals were included in the study if they were on the registry with either 1) QTc >450ms, 2) QTc from 420-450ms with syncope before age 10, 3) QTC from 420–450ms with an LQTS mutation by genetic testing.
This study analysed risk in patients with known LQT syndrome between the ages of 10-20. It therefore does not analyse risk factors associated with SCD in apparently healthy children and young adults.
The highest risk of aborted cardiac arrest or SCD was in the group with syncope (especially recent syncope defined as 1 or 2 episodes in the last 2 years) or those with a QTc greater then 530ms.

Hulot, J. S., X. Jouven, et al. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation, 2004, 110(14): 1879-1884.

LOE P5, Supportive, fair. Mean age at onset of symptoms was 31.8 +/- 14.4 years. Palpitations were described by 2/3 of the patients, a history of syncope by 1/3 and atypical chest pain by ¼. A history of at least 1 episode of LBBB VT was observed in 78.5% of patients and represented the first symptom in 39%. An aborted cardiac arrest was observed in 17 patients as the first manifestation of the disease. The ECG was spontaneously abnormal in 83.9% of patients.
Left ventricular failure was defined as LVEF <40%. 92% of patients were treated with anti-arrhythmic therapy.

Johnson JN, Hofman N, Haglund CM, Cascino GD, Wilde AA, Ackerman MJ. Identification of a possible pathogenic link between congenital long QT syndrome and epilepsy. Neurology. 2009 Jan 20;72(3):224-31. Epub 2008 Nov 26.

LOE P5, supportive, good. Among pts diagnosed with LQTS Seizure phenotype identified in 29% of probands. LQT 2 over-represented (47% of probands, vs 22% and 25%, 1 and 3). Positive association of seizure and LQTS level 3 retrospective cohort study.

Kaufman, E. S., S. McNitt, et al. (2008). Risk of death in the long QT syndrome when a sibling has died. Heart Rhythm 5(6): 831-836.

LOE P5, supportive, good

Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. 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. 2003 Mar 19;41(6):987-93.

LOE P5, good, supportive. Retrospective case series of patients with known HCM. Study did not look at symptoms experienced prior to diagnosis (therefore allocated LOE P5). The mean age at diagnosis was 37+/- 17 years. Mean age at endpoint of SCD 44 +/- 15.
49% of patients had a positive family history of HCM, 23% reported a sudden death in a first degree relative age <40 years old. Patients reported the following symptoms; dyspnoea (36%), syncope (19%), palpitations (19%).
In this cohort of treated patients (only 1 patient had an ICD) the annual SCD mortality was 0.6% and annual cardiac mortality (SCD and heart failure) was 0.6%.
Only syncope was an independent predictor for SCD (RR 4.3, 95% CI 1.8-5.9).

Kramer MR, Drori Y, Lev B. Sudden death in young soldiers. High incidence of syncope prior to death. Chest. 1988 Feb;93(2):345-7.

LOE P5, supportive, poor. Retrospective analysis of all non-traumatic deaths of soldiers aged 17-30. Deaths related to previous underlying disease such as asthma and epilepsy were excluded. Information on cause of death and prodromal symptoms were gained from all medical records, records of investigation committees and autopsy reports.
Of patients with syncope prior to SD, 2 (33%) died of HCM (total of 6 cohort patients died of HCM), (both patients had exertional syncope), 3 (100%) had heat stroke (all 3 had exertional syncope), 1 (14%) had Myocarditis and 6 (60%) had unknown cause of death. In addition to syncope and chest pain, 7% of patients complained of palpitations 2 weeks to 8 months prior to death.
No statistical analysis was undertaken. No definition of syncope or chest pain was provided. Population likely to be pre-screened although no detail on this.

Linzer M, Grubb BP, Ho S, Ramakrishnan L, Bromfield E, Estes NA 3rd. Cardiovascular causes of loss of consciousness in patients with presumed epilepsy: a cause of the increased sudden death rate in people with epilepsy? Am J Med. 1994 Feb;96(2):146-54.

LOE P4, supportive, fair. Case series of 12 misdiagnosed seizure disorders. Some pts labelled as epileptic have potentially lethal cardiac arrhythmias.

MacCormick JM, McAlister H, Crawford J, French JK, Crozier I, Shelling AN, Eddy CA, Rees MI, Skinner JR. Misdiagnosis of long QT syndrome as epilepsy at first presentation. Ann Emerg Med. 2009 Jul;54(1):26-32. Epub 2009 Mar 12.

LOE P5, supportive, good. Retrospective cohort study of pts diagnosed genetically with LQTS, mostly children and young adults 5 of 31 were diagnosed as epileptic. Level of evidence 3, seizures, especially nocturnal ones, can be due LQTS and misdiagnosed as epilepsy.

Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. Annals of Emergency Medicine, April 1997, vol./is. 29/4(459-66), 0196-0644

LOE P2, supportive, poor. This study examined patients presenting to ED with all cause syncope. The proportion of patients who were subsequently diagnosed as having presented with cardiac syncope were 31% in the derivation cohort and 17% in the validation cohort. The mean age in the derivation cohort was 57.3 (Range 15-90) and in the validation cohort 56.1 (Range 18-94). 27% of the derivation cohort were <45 years old and 30% of the validation cohort were <45 years old.

Arrhythmias (as included in the study outcome) were defined as VT (3 or more beats), sinus pauses of 2 seconds or longer and those pauses that were symptomatic; symptomatic sinus bradycardia; SVT with symptoms or associated with hypotension (BP <90mmHg), AF with slow ventricular response (RR interval >3 seconds); compete atrioventricular block; Mobitz II; and evidence of pacemaker malfunction. Ventricular arrhythmias (VA) included a past history of frequent (more than 10 per hour), repetitive (2 or more consecutive), or multifocal PVC's.
As the study outcome was not SCD it was allocated LOE P5 rather than P2

Massin MM, Bourguignont A, Coremans C, Comté L, Lepage P, Gérard P. Syncope in pediatric patients presenting to an emergency department. J Pediatr. 2004 Aug;145(2):223-8.

LOE P5, neutral, fair. Prospective series. 2% of syncope to paediatric A and E was of cardiac cause.

Nava A, **Bauce B**, **Basso C**, **Muriago M**, **Rampazzo A**, **Villanova C**, **Daliento L**, **Buja G**, **Corrado D**, **Danieli GA**, **Thiene G**. **Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol. 2000 Dec;36(7):2226-33**

LOE P4, supportive, fair. This study examined a selection of families known to be affected by ARVD/C in an isolated geographical region.
The mean age of the 19 probands who died suddenly was 27 +/- 10.5 years. Nine pro-bands had a previous history of syncope (47%). By comparing clinical data from the 19 pro-bands who died suddenly and the 132 living affected patients there was a statistically significant difference in terms of previous history of syncope (42% vs 18%, p<0.001).

Oh JH, Hanusa BH, Kapoor WN. Do symptoms predict cardiac arrhythmias and mortality in patients with syncope? Arch Intern Med. 1999 Feb 22;159(4):375-80

LOE P5, fair, supportive. This study showed that symptoms associated with syncope were not useful in predicting those at risk of Sudden Cardiac Death. Underlying cardiac disease was the only predictor of 1-year mortality (OR 7.7, 95% CI 1.6-36.4, OR 13.5, 95% CI 2.6-70.5). The absence of nausea & vomiting before syncope (OR 7.1, 95% CI 1.6-33.3) and ECG abnormalities (OR 23.5, 95% CI 7.0-78.7) were the only independent predictors of arrhythmic syncope.
The cohort analysed had a mean age of 57 years (hence LOE P5) and only patients aged 18 and older were recruited into the study. Electrophysiologic studies were not performed on all patients and patients given a diagnosis of the cause of syncope at initial history and examination did not undergo any further testing. 99% of patients were followed up for at least 1 year.

Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. Seizure. 2003 Oct;12(7):456-64.

LOE P5, supportive, fair. Prospective controlled study of SUDEP shows more prevalent among younger people found dead in bed with evidence of terminal seizure. No correlation to seizure frequency. Not proven link to SCD, but similarities to dead in bed (esp LQT) noted. Nocturnal seizures young people, risk of death.

Peters S. **Long-term follow-up and risk assessment of arrhythmogenic right ventricular dysplasia/cardiomyopathy: personal experience from different primary and tertiary centres. Journal of Cardiovascular Medicine, July 2007, vol./is. 8/7(521-6), 1558-2027**

LOE P5, neutral, poor. Retrospective trial with no case controls. Large cohort of cases (considering how rare ARVD/C is) with multicentre recruitment. Patients with unrecognised ARVD/C and those whose first presentation with ARVD/C was SCD were not included in the study. The single author systematically reviewed the study outcomes in all 313 cases. The review method was inconsistent using any of questionnaire, telephone interview or direct consultation. Left ventricular dysfunction was measured by 2D ECHO in all patients. Cases of unexplained SCD in family members under the age of 35 years were found in 5 families (Total of 313 patients in the study, although no comment on the number of families represented). During the follow-up period (mean period 8.5 years, range 2.5-18) SCD occurred in 5 patients (1.6%) – annual rate of 0.2%. There were 27 adequate terminations of ventricular arrhythmias by implantable ICD. All SCD and ventricular arrhythmia terminations were found exclusively in 166 patients with documented ventricular arrhythmias and syncope – event rate totalled 19%. In all 5 patients with SCD 100% had preceding syncope (risk factor, univariate analysis OR 3.49, 95%CI 1.35-7.63), Left ventricular dysfunction was found in 4 cases (80%) and family history was found in 1 patient (20%).
Left ventricaular dysfunction was found to be the only statistically significant risk factor of SCD in patients with known ARVD/C(OR 14.68, 95% CI 2.67-49.68 – univariate analysis). The study was not powered to find statistical significance in preceding syncope or family history of SCD.
21 patients suffered aborted SCD before the diagnosis of ARVD/C was made. A careful history ruled out any symptoms before this event (method of history taking not specified).

Priori, S. G., C. Napolitano, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation, 2002,105(11): 1342-1347.

LOE P5, supportive, fair. A history of syncope was present in 34 or 200 patients (17%), and 8 of these 34 patients had a cardiac arrest (23.5%). A history of syncope produced an 85% specificity and 36% sensitivity in identifying cardiac arrest victims in this cohort. A family history of unexplained sudden death produced a 22% sensitivity and 65% specificity in this cohort. The mean age at cardiac event was 33+/- 13 years.

Probst V, Denjoy I, Meregalli PG, Amirault JC, Sacher F, Mansourati J, Babuty D, Villain E, Victor J, Schott JJ, Lupoglazoff JM, Mabo P, Veltmann C, Jesel L, Chevalier P, Clur SA,Haissaguerre M, Wolpert C, Le Marec H, Wilde AA. Clinical aspects and prognosis of Brugada syndrome in children. Circulation. 2007 Apr 17;115(15):2042-8. Epub 2007 Apr 2.

LOE P5, supportive, good. Among a population of children (<16 yrs) with Brugada syndrome, one third presented with syncope, and half of these with syncope during fever. Retrospective cohort study.

Quigley F, Greene M, O'Connor D, Kelly F. A survey of the causes of sudden cardiac death in the under 35-year-age group. Irish Medical Journal, September 2005, vol./is. 98/8(232-5), 0332-3102

LOE P5, supportive, poor. Aim of study is to establish incidence and cause of sudden cardiac death rather than to identify warning signs. However, details regarding previous relevant symptoms were obtained from the Dublin City Coroners' records. No attempt was made to obtain information from other sources such as hospital doctors, relatives, GP. Prodromal symptoms were reported in 9 (12.5%) cases. Chest pain in 4 (causes of death in 2 coronary artery disease, in 1 aortic rupture, in 1 Mafan's syndrome), Flu like symptoms in 2 (cause of death in both = Myocarditis), Syncope in 1 (cause of death unknown), sore throat in 1 (cause of death unknown), "felt un-well" in 1 (cause of death hypertrophic cardiomyopathy).

Skinner JR, Chong B, Fawkner M, Webster DR, Hegde M. Use of the newborn screening card to define cause of death in a 12-year-old diagnosed with epilepsy. J Paediatr Child Health. 2004 Nov;40(11):651-3.

LOE P5, supportive, good. A case 12 yr old diagnosed at PM to be epilepsy found to be LQTS by mol genetics. Final proof that misdiagnosis of LQTS as epilepsy can result in death.

Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barilla CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation, April 2009, vol./is. 119/13(1703-10), 1524-4539

LOE P5, supportive, fair. Detailed descriptions of the features and circumstances related to each syncopal event were systematically obtained. All patients were recruited from tertiary referral centers. VF interrupted by the discharged of an ICD was regarded as equivalent to sudden death.
147 (10%) of patients were <18 years old. During a follow-up of 6.5 +/- 5.7 years, 15 (10%) died suddenly. Of the 147 patients, 7 (5%) had unexplained syncope before initial evaluation, 3 of whom died suddenly. Of these young patients with unexplained syncope, mortality for sudden death was 120/1000 person years (95% CI 24.4 to 351.4) compared with 13/1000 person-years (95% CI 6.7 to 22.6) in those without unexplained syncope.
Neural mediated syncope was not associated with a risk of Sudden Death.

Sopontammarak S, Khongphatthanayothin A, Sa-Nguanchua P. Prevalence of idiopathic long QT syndrome in congenital sensori-neural hearing loss students of Songkhla School for the Deaf. J Med Assoc Thai. 2003 Dec;86(12):1149-55.

LOE P5, supportive, good. Prospective cohort study of 276 children with congenital sensory neural deafness. Prevalence LQTS 0.7%

Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, Saito A, Kurosaki K, Jouo K, Koujiro M, Konishi S, Matsuoka S, Oono T, Hayakawa S, Miura M, Ushinohama H, Shibata T, Niimura I. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart, January 2003, vol./is. 89/1(66-70), 1468-201X

LOE P5, supportive, good. It is implied but not stated clearly that syncope in these patients occurred during exercise or during sympathetic activation. 93% of the patients in this study experienced syncope or cardiac arrest. On exercise testing, exertion induced CPVT in all patients, but unless CPVT deteriorated into VF , syncope did not occur.

Tan, H. L., N. Hofman, et al. (2005). "Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives." Circulation 112(2): 207-213.

LOE P4, supportive, good

Tanaka Y, Yoshinaga M, Anan R, Tanaka Y, Nomura Y, Oku S, Nishi S, Kawano Y, Tei C, Arima K. Usefulness and cost effectiveness of cardiovascular screening of young adolescents. Med Sci Sports Exerc. 2006 Jan;38(1):2-6.

LOE P1, Neutral, poor. A total of 69,033 students were enrolled in this study. The screening involved an ECG (paper speed 25 mm per second) and a questionnaire regarding any cardiac history of heart murmurs, cardiac diseases (including Kawasaki disease and congenital heart defects) and cardiac symptoms (syncope, chest pain, irregular heart beat or palpitations on exertion, shortness of breath) as well as any family history of sudden death <40 year olds. Subjects with abnormal ECG or history of cardiac disease were examined further by physical examination and if needed CXR, ETT, ECHO.
According to the questionnaire, 632 students were previously diagnosed with cardiovascular disease by their family doctor and of all the 7th and 10th grade students, 975 and 901 showed abnormal findings in the primary screening respectively. A total of 1876 students (2.7% of 37,807) participated in secondary screening.
9 Students (0.024%) were identified as having significant cardiac disease potentially predisposing them to risk of SCD. Of these, 5 had HCM, 1 LV dilatation, 1 had WPW with tachycardic episodes, 1 primary pulmonary hypertension, 1 had Long QT syndrome with torsade de pointes.
Of the 3 deaths, all were boys with no history of syncopal attacks and no family history of SCD. One 14 year old boy was identified with HCM during screening and died while jogging. He had been disqualified from participating in competitive sport. The remaining 2 SCD patients had normal ECGs. No autopsies were performed.
Of the cohort, 497 were identified as "low-risk" subjects although further clarification of what this means was not provided. No analysis was provided on the relationship between symptoms and ECG findings at initial screening and the subsequent diagnosis of a significant cardiac disease.
There is the potential for geographical/genetic bias as this study was located solely in one city in Japan. HCM was identified in only 0.013% of this population, however in the USA, HCM has been shown to be present in approximately 0.17% of young adults screened by 2D ECHO.

Tester DJ, Spoon DB, Valdivia HH, Makielski JC, Ackerman MJ. Targeted mutational analysis of the RyR2-encoded cardiac ryanodine receptor in sudden unexplained death: a molecular autopsy of 49 medical examiner/coroner's cases. Mayo Clin Proc. 2004 Nov;79(11):1380-4.

LOE P5, supportive, poor. Molecular autopsy Case series of 49. CPVT a significant cause of SUDY. Age 2-34. History of symptoms before SCD only in 1 of 7, but 3 of 7 (43%) had a positive family history of young sudden death. Commonest cause of SUDY in teenagers. Where history known, 3 of 4 died during exertion, one with emotion. Poor as only half of cases had symptoms and family history documented.

Tester DJ, Kopplin LJ, Creighton W, Burke AP, Ackerman MJ. Pathogenesis of unexplained drowning: new insights from a molecular autopsy. Mayo Clin Proc. 2005 May;80(5):596-600.

LOE P5, supportive, weak. Case series where two children drowned, negative autopsy, they found RyR2 mutations, i.e. they died from CPVT. First child had h/o syncope prior. Proves that some cases of drowning due CPVT, denominator unknown. Weak only because there were no more than 2 cases in the case series.

Wilson MG, Basavarajaiah S, Whyte GP, Cox S, Loosemore M, Sharma S. Efficacy of personal symptom and family history questionnaires when screening for inherited cardiac pathologies: the role of electrocardiography. Br J Sports Med. 2008 Mar;42(3):207-11. Epub 2007 Aug 23

LOE P1, against, fair.
Trial outcome was diagnosis of inherited cardiac pathologies with the potential to cause SCD rather then SCD per se. Prospective screening of selected children (national and international junior athletes and physically active school children). All athletes were screened, however active school children were invited to screening producing a potential recruitment bias. Only those with symptoms and/or abnormal examination findings and/or ECG abnormalities were further evaluated for inherited cardiac pathologies. All physical examinations and analysis of ECG's were undertaken by a Consultant Cardiologist.
Symptoms evaluated (as they were considered to be suggestive of possible underlying cardiovascular disorder) included repetitive syncope during exercise, prolonged periods of palpitations, sustained chest pain and unexplained sudden death in a first degree relative < age 35. Of the participants screened, 4% required further examination because of an abnormal ECG and/or positive questionnaire.
***None of the participants diagnosed with a disease associated with SCD were symptomatic.** Ominous symptoms, such as repeated syncope during exercise (2.6% of cohort), all produced negative findings.*

Wisten A, Forsberg H, Krantz P, Messner T. Sudden cardiac death in 15-35-year olds in Sweden during 1992-99. Journal of Internal Medicine, December 2002, vol./is. 252/6(529-36), 0954-6820

LOE P5, supportive, poor. Retrospective case series. The reliability of the national database of forensic medicine "Rattsbase" was compared the The Swedish Death Registry for one of the trial years (1995). 20% of cases of SCD were not found in the Rattsbase database. Information on pre-mortal cardiac related symptoms were collected using police records, medical records and in many cases interviews with family members (no information given on method/approach to family interview). The study included patients with known congenital or valvular heart disease (5.5%) but excluded analysing symptoms in this group.
In 50% of patients, pre-mortal cardiac-related symptoms (chest pain, dizziness, syncope, palpitations and/or dyspnoea) were noticed. A sub-analysis of the frequency of the various symptoms or their definitions was not provided.
2.7 times more men than women died from SCD during the 8-year survey period.

Wisten A, Messner T. Young Swedish patients with sudden cardiac death have a lifestyle very similar to a control population. Scandinavian Cardiovascular Journal, July 2005, vol./is. 39/3(137-42), 1401-7431

LOE P3, neutral, fair. Study specifically analysed allergy, medication, BMI, smoking and physical activity and food habits. Information was gathered from 85% of the case control group.

Wisten A, Messner T. Symptoms preceding sudden cardiac death in the young are common but often misinterpreted. Scandinavian Cardiovascular Journal, July 2005, vol./is. 39/3(143-9), 1401-7431

LOE P5, supportive, fair. 79% of SCD victims relatives accepted to participate in supplying information during interview for the study. Syncope/presyncope, palpitations, chest pain and dyspnoea were counted irrespective of when in the individuals life they occurred. Symptoms of infections and/or fatigue only if they were experienced within 2 months prior to death.
Syncope was experienced by 36(22%) of individuals and presyncope by 6 (4%) between 6 hours and 6 years of death. Chest pain was experienced by 14% of individuals between 0 hours and 2 years of death. Palpitations were experienced by 12% of individuals 0 hours to 9 months preceding death. Dyspnoea was an uncommon main symptom but sometimes occurred together with syncope or palpitations. Fatigue was reported in 33% of individuals, mainly as a coexisting symptom.
46% of the study group sought medical advice because of symptoms, with half of these within 6 months prior to death. 32 out of 74 (43%) of patients seeking medical advice had a 12 lead ECG taken. 24 (75%) were pathological. 8 cardiac diagnoses were made in these individuals including HCM (3), LQTS (1), ARVC (1),

DCM (1), WPW (1), MI (1). None of these patients had an ICD. In 6 individuals congenital heart disease had been diagnosed in childhood.
26 (16%) of individuals in the study group there was hereditiy of SCD or a condition that could lead to SCD in a first degree relative.
Chest pain was more common in persons >30 (18/60 vs 6/102, p<0.001). Syncope/presyncope was more common in the age group <30 (35 vs 7, p=0.002)