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Prevention of sudden cardiac death in children and young adults☆,☆☆

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ABSTRACT

In the present review, we summarize current approaches to the prevention of sudden cardiac death (SCD) in children and young adults, focusing on age <35 years. SCD in the young is rare, but devastating from the societal perspective. While coronary artery disease is the main etiology of SCD in the older age groups, conditions such as cardiomyopathies and electrical channelopathies are more likely to be found in the young. In the majority of younger cases, cardiac arrest can be the first recognized manifestation of the underlying cardiac pathology, although some have experienced cardiovascular symptoms prior to the SCD. Since identification of a cardiac disease is pivotal for implementation of appropriate prevention, measures such as electrocardiographic screening in subpopulations such as athletes have been proposed. However, these efforts are impeded by the large number of individuals needed to test in order to find one with cardiac disease, leading to significant rates of false positive findings and high costs. When a high-risk cardiac condition is identified in a young person, measures of lifestyle modification, appropriate medical treatment and ICD implantation in selected individuals based on risk stratification are warranted. Nevertheless, the benefits of lifelong ICD therapy need to be balanced with long-term complications and quality of life.

1. Magnitude of the problem

Sudden cardiac death (SCD) in a young person is a rare but devastating event for the family and also for the community. The estimated incidence of pediatric and young adult SCD has varied in the published literature due to differences in age range as well as in methods for SCD adjudication. If children of age less than one year are excluded [1,2], recent estimates of SCD incidence for age 1 to 35 years have ranged from 0.8–2.8 per 100,000 person-years [3–5]. However, the actual burden of SCD is disproportionately larger among the young, due to significantly more years of potential life lost in this population [6]. The incidence of SCD in children and young adults also varies depending on age and sex. At age one to four, children have a higher incidence of SCD than those aged 5–10 years who represent the age group at lowest risk. After 15 years of age the incidence of SCD starts to progressively increase, with those aged 31–35 years having up to 10 times higher incidence than age 1–10 years [7]. Epidemiological studies have also consistently demonstrated that SCD is significantly more prevalent among males compared to females, by a factor of approximately 2:1 (3–5).

2. Etiologies of SCD in the young

The cardiac abnormalities underlying SCD in children and adolescents include congenital heart disease, coronary artery anomalies, myocarditis, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, left ventricular non-compaction cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC) and ion channelopathies such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome [3–5,8–10]. The estimated prevalence rates of these conditions vary widely in the general population. For example, overall prevalence of HCM is estimated to be 1 per 500 [11] and LQTS around 1 per 2500 persons [12]. The etiologies of SCD are different depending on the age group. In the majority of children aged 1–4 years (if those with severe congenital heart disease are excluded), the heart is structurally normal and SCD is presumably due to primary electrical disorders. In contrast, structural heart disease begins to dominate in older children and young adults [4,8]. Coronary artery disease (CAD) accounts for the great majority of SCD burden in middle-aged and elderly patients [13], but premature CAD is also the major cause of SCD in young adults aged over 25 years [8]. In a pooled clinico-pathological series in the general population <40 years old, premature CAD was responsible for 31%, myocarditis for 9%, and left ventricular hypertrophy and hypertrophic cardiomyopathy (HCM) each

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for 8% of SCD [10]. In up to 30–40% of cases, the autopsy does not reveal any cardiac structural abnormalities [3,14,15], pointing to a primary electrical disorder such as LQTS, CPVT or Brugada syndrome [5,9,16].

3. Strategies for SCD prevention

Since CAD accounts for the great majority of SCA cases in the adult population, modification of CAD risk factors and treatment of acute and chronic manifestations also impacts SCD burden at the population level [17]. Moreover, among high-risk subjects such as those with severely reduced left ventricular ejection fraction (LVEF), optimal medical heart failure therapy together with implantable cardioverter-defibrillators (ICDs) in selected high-risk patients has demonstrated clear survival benefit [18]. However, among under age 35 years and especially among children and adolescents, these approaches to SCD prevention have only limited relevance due to the significantly different spectrum of underlying etiologies. Advances in emergency medical care are an important part of improving survival from cardiac arrest, and efforts to improve measures such as bystander cardiopulmonary resuscitation (CPR) and early defibrillation are likely to improve outcomes [19,20]. However, even with ongoing advances in resuscitation, survival rates from SCA have plateaued, demanding other, more pre-emptive approaches to prevent SCD in the general population [21].

3.1. Prevention of coronary artery disease

The atherosclerotic process begins early in life, and the presence of cardiovascular risk factors in childhood and adolescence are associated with worse cardiometabolic health in adulthood [22–24]. This strongly suggests that pursuit of optimal cardiovascular health in childhood, i.e. primordial prevention, is important in preventing cardiovascular events in adulthood. In particular, identification and treatment of individuals at high risk of developing premature CAD, such as those with familial hypercholesterolemia [25], is likely to reduce CAD-related SCD burden in the young adult population where premature CAD is a major cause of SCD [8].

3.2. General cardiac screening

Since cardiac arrest is often the first recognized symptom of an underlying cardiac condition in the young, there has been a longstanding interest in the concept of cardiovascular screening. The intent would be to prospectively identify or raise suspicion of a previously unrecognized cardiac disease capable of causing SCD in a previously asymptomatic subject. For the affected individuals identified with screening, there would thus be a window of opportunity for interventions aimed at preventing SCD. Among the possible preventive steps would be avoidance of strenuous physical activity or disqualification from competitive sports, appropriate medical therapy for the cardiac disease (such as beta blockers in LQTS and CPVT) and primary prevention ICD therapy for selected patients at highest risk. Several different screening programs have been proposed for different populations, or for subgroups such as athletes considered to be at high risk of SCD. In fact, pre-participation screening of athletes for underlying cardiovascular disease is either mandatory or under discussion in several countries [26]. However, most cardiac arrests occur at rest or during light activity [5], and definitive evidence for the benefits compared to costs and potential harm of these approaches to SCD preventions is still lacking [26]. History and physical examination alone are relatively ineffective in identifying subjects at elevated risk [27], so using a standard 12-lead electrocardiogram (ECG) based screening to detect underlying cardiac pathology has been a major focus of potential screening strategies [28]. The resting 12-lead ECG is reasonably sensitive in diagnosing several of the SCD etiologies such as HCM, LQTS, Brugada syndrome, ARVC and Wolff-Parkinson-White syndrome, but the positive predictive value of ECG for true cardiac pathology is generally low, leading to a need for screening substantial numbers to effectively diagnose or exclude underlying cardiovascular disease [26,28]. For example, anterior T-wave inversions in the right precordial leads are a characteristic finding in ARVC, but in the general population this ECG phenomenon carries a benign prognosis and is rarely associated with cardiac pathology [29,30].

The number of abnormal ECG findings identified via screening depends on the diagnostic criteria utilized, as well as the population of interest. Children and adolescents are particularly challenging in this respect due to alterations in electrocardiographic depolarization and repolarization patterns during aging and growth. Race and sex affect ECG as well, and certain ECG patterns such as anterior T-wave inversions are much more common in black athletes compared to whites [31]. According to a recent study, ECGs of up to one fifth of young non-athletes and a third of athletes were judged to be pathological on the bases of the criteria presented in a 2010 European Society of Cardiology document [32,33]. Due to the aforementioned challenges, the cost of ECG screening in pediatric or young populations are relatively high compared to potential benefits [34], and systematic mass screenings of athletes or young people from the general population are not generally recommended [26,35].

3.3. Screening of relatives

In contrast to broad screening efforts aimed at a large segment of the general population, screening of the family members of an individual with potentially hereditable cardiac disease represents a more focused and widely accepted way of identifying those with a high likelihood of having cardiac pathology [36]. In many institutions, testing of family members is part of routine clinical practice for the relatives of patients with potentially inheritable cardiac disease. This approach is a relatively effective approach for identifying affected individuals. For example, a study from New Zealand demonstrated that using a national registry for LQTS, an average of 2 affected family members could be identified per proband [37]. In the case of a SCD event in the young, identification of affected family members depends largely on detection or exclusion of a structural cardiac disease at the autopsy. In the absence of structural abnormalities, genetic testing of the deceased, so called molecular autopsy, may be helpful in identifying an inheritable genetic disease in the diseased. This can subsequently lead to testing of the surviving family members and enables initiation of appropriate therapy in the affected relatives [9]. In general, molecular autopsy has revealed a clinically relevant cardiac gene mutation such as mutation associated with LQTS or CPVT in approximately one-third of subjects with unexplained SCD [5,38]. If a specific cardiac diagnosis is determined for the deceased, comprehensive clinical assessment of families with SUD inheritable heart disease may lead to a diagnosis in 18–53% of cases, long QT syndrome being the most common finding [9,39,40].

3.4. Warning symptoms

Another group that may benefit from aggressive diagnostic approach are those who present with cardiac symptoms prior to their SCD. Aborted cardiac arrest represents a symptom that is highly predictive of future SCD, and it is presently a well-recognized indication for ICD therapy [41]. In addition, several studies have demonstrated that most children and young adults with SCD have experienced at least some cardiovascular symptoms prior to the cardiac arrest [42–45]. Symptoms such as chest pain, palpitations and dyspnea are non-specific, but many experience potentially serious symptoms; for example, over one fourth of cardiac arrest victims have reported syncope or pre-syncope prior to SCD [42,43]. In many cases, these symptoms are brought to the attention of health care providers, but may not have been recognized as warning signs of an underlying life-threatening cardiac disease [42]. However, if prodromal symptoms preceding cardiac arrest lead to a 911 call, data from Oregon Sudden Unexpected Death study has demonstrated in an adult population that survival is over 5-

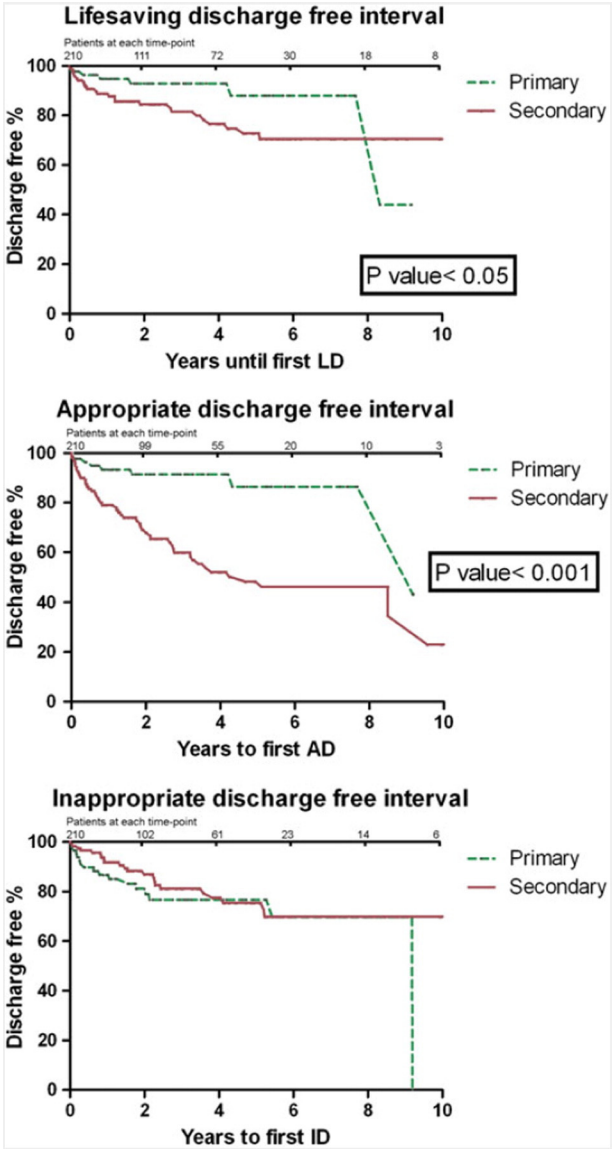

Fig. 1. Outcomes of children and young adults age <30 years, after implantation of primary prevention vs secondary prevention ICD 1992–2007 [55]. Re-printed with permission.

fold higher among those who requested emergency medical services compared to those who did not call 911 [46].

Especially in children, symptoms can often be vague and difficult to pinpoint, and optimal diagnostic approaches in such patients have yet to be determined. However, detailed clinical investigation including a 12-lead ECG is probably warranted for most young patients with suspected cardiovascular symptoms. The ECG is a relatively sensitive method for identifying individuals with abnormalities for a further evaluation; for example, over 80% of SCD patients with a final diagnosis of ARVC or HCM have had abnormal ECG findings prior to the SCD [47]. The positive predictive value of abnormal ECG patterns is likely to increase in subgroups with higher prevalence of cardiac disease (as is expected among those with cardiovascular symptoms) compared to the general population, making it more effective than unselected screening. However, this approach would require wide efforts to educate general practitioners and family doctors on the importance of obtaining the ECG in the appropriate patient. Also subtle ECG changes may be difficult to detect, although automated analyses generated by diagnostic algorithms of modern ECG machines are likely to be increasingly useful tools for this purpose [48]. For some conditions that increase risk of SCD, for example congenital coronary artery anomalies, the 12-lead ECG, stress ECG and echocardiography are unlikely to be abnormal [49] and additional imaging such as cardiac CT and MRI are needed to make a diagnosis and perform corrective surgery [50]. Furthermore, focusing on the population with likely cardiac symptoms will miss the significant number of young SCD patients who don't complain of their symptoms or seek medical attention prior to the arrest. Therefore, further research is needed in order to identify the optimal combination of clinical and ECG risk markers for recognizing patients at imminent risk of SCD.

3.5. Bystander CPR and early defibrillation

In the event of out-of-hospital cardiac arrest, bystander CPR and early access to automated external defibrillators (AEDs) can affect survival outcomes. There is emerging evidence that the ongoing attempts to increase bystander CPR together with wider implementation of public access defibrillator programs are likely to significantly improve cardiac arrest survival among the young [19,20,51,52]. Targeted CPR education for family members of subjects at high risk of SCD is a reasonable approach and could potentially improve outcomes, although definitive evidence for the benefits of this approach is still awaited [53].

4. Risk stratification and primary prevention ICD therapy in established cardiac disease

Identification of a cardiac disease substrate, whether in relatives of the proband or by cardiac screening of a population sub-group, is the key to improved prevention [14]. However, only a small minority of young SCD patients have a cardiovascular disease diagnosed prior to their cardiac arrest. For example, in a Danish study of children age 1–18 only 18% of all SCD cases had cardiac abnormalities, mostly congenital cardiac disease, diagnosed during their lifetime [45]. When a high-risk cardiac diagnosis is established, specific preventive measures, including ICD therapy in selected patients, can be undertaken. Utilization of ICDs for primary prevention of SCD in children has been increasing and is roughly equivalent to the proportion of secondary prevention ICDs, but overall, children still account for only a very small percentage of overall ICD recipients [41]. The largest sub-group of young patients with ICDs are those with primary electrical cardiac disease (approximately 40%), followed by those with cardiomyopathies and congenital heart disease (approximately 30% each) [54,55]. There are few randomized trials conducted among pediatric patients and subjects with congenital heart disease, but retrospective analyses have demonstrated the efficacy of ICD therapy in children, with an approximately 25% of patients receiving appropriate shocks from the device [56]. Substantially higher rates of appropriate therapy are observed in patients implanted

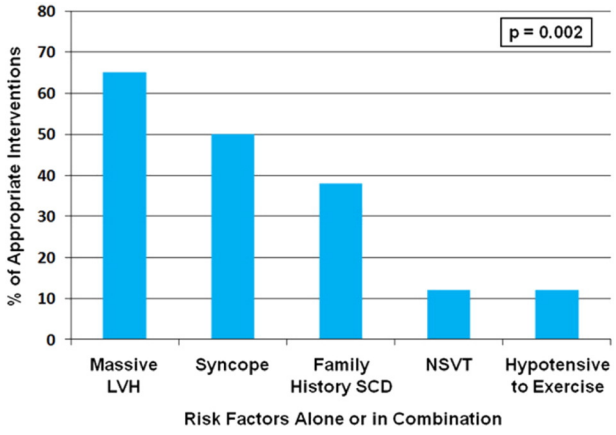

Fig. 2. Distribution of primary prevention risk factors in age <20-year-old hypertrophic cardiomyopathy patients with an appropriate ICD intervention [57]. Re-printed with permission.

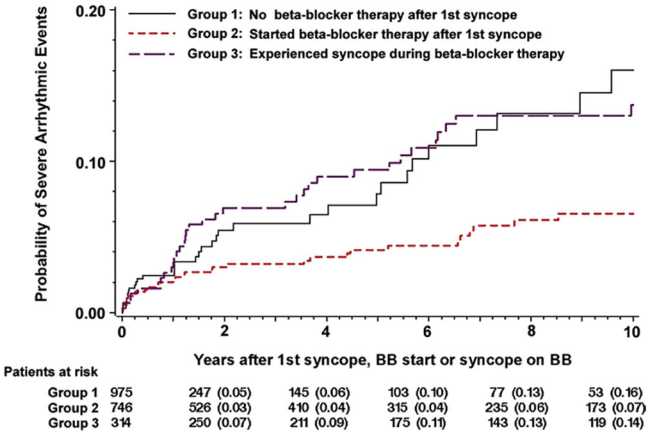

Fig. 3. Risk of severe arrhythmic events after first syncope in LQTS according to beta-blocker therapy status [61]. Re-printed with permission.

for secondary prevention indications compared to primary prevention [55,57] (Fig. 1).

The recommendations for use of ICDs are generally not age-specific, so for pediatric patients the guidelines are similar to adults. ICD therapy for secondary prevention is indicated for survivors of cardiac arrest or hemodynamically unstable ventricular tachycardia (VT) without clearly reversible cause such as Wolff-Parkinson-White syndrome with pre-excited atrial fibrillation, or myocarditis [58]. Those with structural heart disease who experience sustained hemodynamically stable VT should also generally receive an ICD for secondary prevention. As for adults, primary prevention ICD therapy is generally recommended for young patients with severely reduced LVEF <30–35% [41].

In addition, for some conditions such as HCM, ARVC, LQTS, CPVT and Brugada syndrome, specific guidelines for SCD preventive measures such as lifestyle modifications and use of medications and device therapy exist and can be followed also in pediatric and adolescent patients [41,58–60]. In HCM, prior cardiac arrest or sustained VT, extreme left ventricular hypertrophy, syncope, family history of HCM-related SCD and abnormal blood pressure response to exercise or non-sustained VTs (when manifesting together with other risk modifiers) are risk factors for cardiac arrest that warrant consideration of a primary prevention ICD also for pediatric patients [57,59] (Fig. 2). In LQTS patients, in addition to lifestyle changes such as avoidance of QT-prolonging drugs and arrhythmia triggers, beta-blockers are the mainstay of prevention for those with a history of syncope and for those having significantly prolonged QTc interval [61] (Fig. 3). In LQTS, ICD therapy should be reserved only for those who experience recurrent syncopal episodes or VT while on beta-blockers [60]. Similarly, for CPVT patients, implantation of an ICD is recommended only for those who have syncopal episodes or bidirectional/polymorphic VT while on beta-blocker therapy [60]. In Brugada syndrome, besides cardiac arrest survivors and those with sustained VT, patients with a history of syncope judged to be caused by ventricular arrhythmias are likely to benefit from ICD implantation [60].

4.1. Additional considerations regarding ICD therapy

The impact of receiving an ICD may be considerably greater for a young person than for older individuals, highlighting the need to carefully balance the risks and adverse effects of these devices with potential survival benefit. Many of the youngest patients outgrow the length of their intra-cardiac leads and outlive the functionality of their devices. As a consequence, a large subgroup will manifest with long-term problems related to the ICD, requiring not just generator changes but also lead replacements, revisions or extractions. Inappropriate device therapy is not uncommon among the young (Fig. 1), and is usually a significant adverse event for patients, with major psychological impact and clinical implications. Data from several US pediatric centers demonstrated that inappropriate shocks occur in approximately 20% of

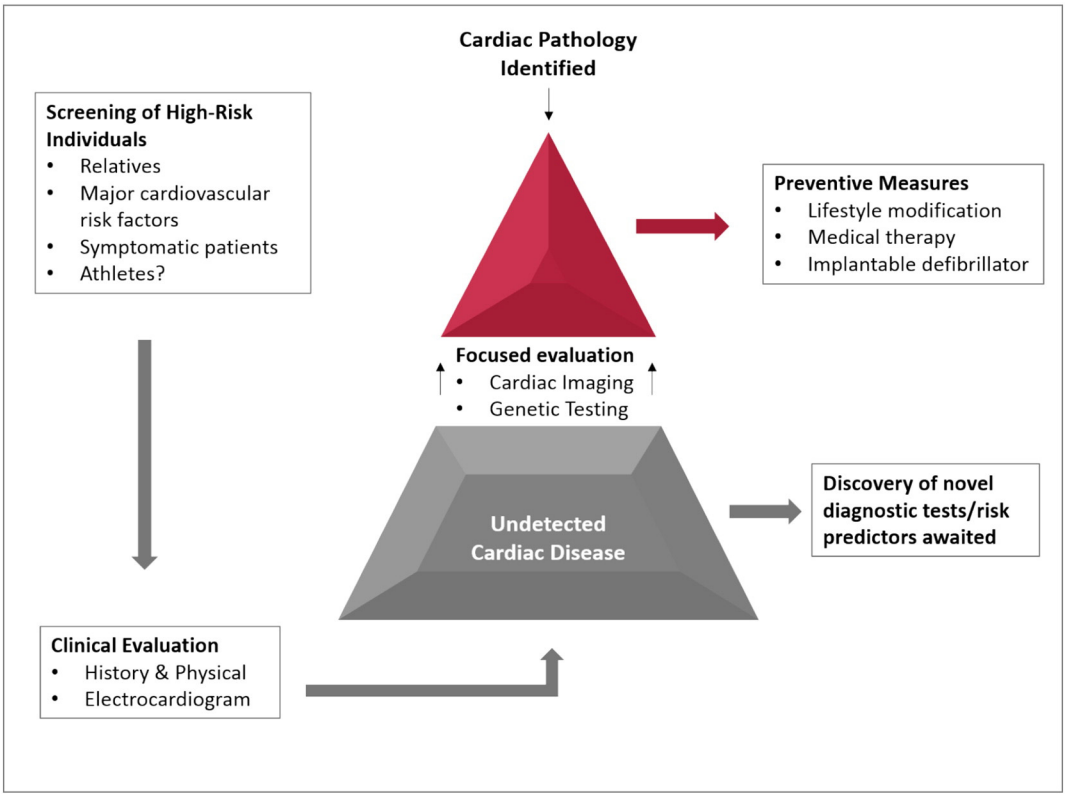

Fig. 4. Current and future approaches to sudden cardiac arrest prevention in the young.

patients with an ICD, with a mean of six inappropriate shocks per patient [56]. Most of the inappropriate therapies are attributable to lead failure, followed by supraventricular tachycardias and over-sensing [56,62,63]. Consequently, the subcutaneous ICD has recently emerged as an appealing alternative to the intra-cardiac device for a carefully selected subgroup of patients [64]. In addition, for some patients at potentially high risk of SCD but not meeting definite indications for implantation of a permanent ICD, the wearable cardioverter-defibrillator can be a short-term solution [65,66].

5. Conclusions

Prevention of SCD in the young remains a significant challenge, and widespread screening efforts for underlying causes are unlikely to be feasible due the low prevalence of this tragic event. Targeted screening for subgroups at highest risk, such as relatives of SCD victims or of those with hereditable cardiac disease capable of causing SCD, in addition to individuals with cardiac symptoms, are likely to provide the highest yield. However, this approach fails to identify a large proportion of young SCD patients, so novel risk markers and tools are needed in order to better recognize asymptomatic subjects with underlying potentially life-threatening cardiac pathology (Fig. 4). If a cardiac diagnosis can be established, optimal preventive measures such as lifestyle adaptation, medical therapy and ICD implantation for those at highest risk should be implemented. However, ICD therapy needs to be balanced with potential long-term adverse effects and complications, and further research is needed to more clearly identify those who are most likely to benefit from an ICD.

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