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Review Article

Sudden death in young athletes: Is it preventable?

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ABSTRACT

Sudden death in young athletes is a rare but always dramatic condition. Unlike all other rare diseases, the estimate of its real incidence is made complex not only because of the uncertain number of correctly identified cases (numerator) but also because of the uncertain estimation of the real number of the reference population, the athletes (denominator). New elements of complexity are also emerging with regard to prevention. The current two pillars of prevention are pre-participation screening (proactive strategy) and promoting use / access to the automated external defibrillator (reactive strategy). The standardization of procedures implemented over the past two decades for pre-participation screening can now allow us to assess the impact of this approach. The result is complex to evaluate. While screening may allow the identification of conditions potentially associated with SDA, and therefore the adoption of specific treatments, in about 0.4% of screened subjects, a single study investigated the yield in terms of mortality showing a positive predictive value of 4.7% with 25% sensitivity. Conversely, the reactive strategy appears considerably effective, due to the widespread use of the automated external defibrillators in sports facilities, calling for a homogeneous implementation worldwide. On a broader perspective, the vast attention devoted to SDA prevention in the world of sports represents a major driver for transfer of a reactive prevention strategy to the general population.

1. Introduction

Sudden deaths in athletes (SDA) are rare but devastating events, with huge social impact and vast echo in the media. Elite athletes are contemporary icons epitomizing health and success, promoting positive lifestyles and penetrating the daily lives of fans and their families. Although SDA is a rare event, recent data suggests that it is probably more common than previously thought. Incidence estimation is limited by difficulties in identifying the cases (numerator), a condition shared with all other rare diseases, and in estimating the true number of athlete population (denominator). In the last two decades, awareness of the pathological conditions responsible for SDA has dictated the development of proactive prevention strategies based on pre-participation screening. Such strategies have been paralleled by a progressive diffusion of automated external defibrillators (AEDs), which is at the core of the complementary, reactive strategy. The present review aims to reappraise available evidence the epidemiology and underlying causes of SDA, and to critically revise these two preventive approaches.

2. Estimation of SCD incidence

Incidence estimation requires a numerator (identified cases) and a denominator (reference population). As is usually the case with all rare events, case identification is a challenge in itself, due to several reasons, such as lack of mandatory reporting, selective exclusion from reporting of cases based on time and site of the event and variable inclusion of non-lethal as well as lethal cardiac events. The second major challenge is the correct identification of the reference population (denominator). Differently from other rare disease, the denominator of SDA is not the general population but the athletic community. The definition and

Abbreviations: ACC, American College of Cardiology; AED, automated external defibrillator; AHA, American Heart Association; ARVC, arrhythmogenic right ventricular cardiomyopathy; CPR, cardiopulmonary resuscitation; ESC, European Society of Cardiology; FIFA, Fédération Internationale de Football Association; HCM, hypertrophic cardiomyopathy; IDCs, implantable cardioverter-defibrillators; NCAA, National Collegiate Athletic Association; PAD, public access defibrillation; SADS, sudden arrhythmic death syndrome; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SDA, sudden death in athlete; USRSDA, United States National Registry of Sudden Death in Athletes; VF, ventricular fibrillation; VT, ventricular tachycardia.

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selection criteria adopted may therefore importantly affect the final estimate. Knowledge of the methodology adopted to estimate both the numerator and the denominator in the various studies is therefore necessary when comparing different estimations (Table 1) (1-21), as an incorrect reading may lead to an equivocal interpretation of the data.

With regard to the identification of the events, eliminating non-cardiac etiologies such as accidental deaths, significantly changes the ratios and can skew results making entities appear more or less common. Importantly, underreporting inevitably leads to an underestimation of SDA incidence. This is evident even in major, well-curated registries. The largest currently active is the United States National Registry of Sudden Death in Athletes (USRSDA), established in 1980 at the Minneapolis Heart Institute Foundation [7]. USRSDA prospectively collects data on the field deaths of young athletes engaged in team or individual sports requiring regular training and participation in athletics competitions [7]. Deaths occurring in club or intramural sports, or resulting from automobile accidents, cancer, and other systemic diseases are not included. USRSDA adopts a variety of sources to identify the study population by targeted searches: (a) LexisNexis archival informational database with searchable access to authoritative news, legal, and public records; (b) National Collegiate Athletic Association Memorial Resolutions List; (c) news media accounts systematically assembled through Burrelle's Information Services (Livingston, NJ); (d) internet search engines (eg, Google, Yahoo); (e) reports from the US Consumer Product Safety Commission (Washington, DC); (f) records of the National Center for Catastrophic Sports Injury Research (University of North Carolina, Chapel Hill, NC); (g) reports submitted to the Registry through personal contact with physicians, attorneys, coroners/medical examiners, schools, and patient advocacy/support organizations[7]. As in most similar studies (Table 1), the primary source of information are media searches, electronic databases, self-reports, that is, next-of-kin, and insurance claims. Media searches are adopted because SDA is often publicized in national or local media. Interestingly, when looking at the time distribution of SDA in USRSDA reports [7], the number of cases identified increased steadily by approximately 6% annually as media search strategies have gradually improved. In particular, a sharp increase in SDA incidence is evident after 1994 [7] when the numerator was drastically increased by the birth of Google, providing a drastic increase in access to newspapers and media. However, even sophisticated media surveys have important limitations. In a retrospective cohort study from Denmark, only 20% of SDA identified by death certificates were found through extensive media search [9]. In a retrospective cohort study of high-profile athletes from US colleges, media reports identified only 56% of total cases [10]. Media reports are even less reliable in identifying SDA among low-profile athletes (younger athletes, female athletes and unprofitable sports). A complementary approach involves insurance claim consultation, which has the advantage of relying on huge, nationwide databases. Nevertheless, insurance claims usually only provide information on deaths occurring during competitive or school-sponsored sporting events and do not include SDA during individual activities and unofficial practices. In fact, catastrophic insurance claims missed 80% of SDA cases in a study that used an internal reporting facility for the National Collegiate Athletic Association (NCAA) [22].

Therefore, incidence assessments based on media reports and catastrophic insurance claims, as well as other methods adopted in retrospective studies, all underestimate SDA in the community. This is evident when we consider the low rates of these reports with the only prospective study, investigating a large cohort of soccer players [17] (Table 1).

SDA incidence is strongly influenced by the estimation of the denominator, i.e. the population under consideration. Differently from other rare diseases, where the denominator is the resident population, estimating the reference athlete population is a challenging task. The most accurate estimates of incidence can be calculated in pre-specified cohorts with well-defined demographics [17]. This is challenging when trying to process nationwide data, as estimating the overall number of athletes based on population statistics, spanning broad age ranges and multiple demographic areas, is fraught with potential error. In the USRSDA, for example, the denominator (i.e. the number of athlete-years) was estimated by considering the number of athletes participating in competitions as obtained from the National Federation of State High School Associations and the NCAA [7,23] for all organized amateur and competitive sports. In the US, the final approximated number is of 10.7 million participants per year for subjects younger than 39 years [7,16]. Additionally, some studies may examine sudden deaths

Table 1
Studies reporting incidence of sudden death in athletes.

Authors	Year	Deaths	Deaths/100.000 athlete-years	Case identification	Population	Age Range
Van Camp et al. [1]	1995	100	0.33	Media reports, National Center for Catastrophic Sport Injury Research database	High school-college athletes	17-24
Maron et al. [2]	1996	134	-	US Registry for Sudden Death in Athletes	High school athletes	12-40
Maron et al. [3]	1998	3	0.46	Insurance claims	High school students	16-17
Corrado et al. [4]	2003	55	0.87	Media reports, death reporting	Athletes	12-35
Drezner et al. [5]	2005	5	1.49	Questionnare to trainer (survey)	College athletes	
Corrado et al. [6]	2006	55	1.87	Sport medicine data base	Athletes and young people	
Maron et al. [7]	2009	690	0.61	US Registry for Sudden Death in Athletes	Athletes	8-39
Drezner et al. [8]	2009	14	2.17	School cross-sectional survey	High school athletes	14-17
Holst et al. [9]	2010	470	1.20	Death certificate	Athletes and young people	12-35
Harmon et al. [10]	2011	37	2.28	NCAA, Media reports, Insurance claims	College athletes	18-26
Marijon et al.[11]	2011	50	0.98	Media reports/autopsy/medical records	Competitive athletes	10-35
Steinvil et al. [12]	2011	24	2.60	Media reports	Athletes	12-44
Roberts and Stovitz [13]	2013	4	0.24	Insurance program	High school athletes	12-19
Drezner et al. [14]	2014	7	0.65	Media reports	High school	14-18
Harmon et al. [15]	2014	35	1.86	Media reports	High school athletes	14-18
Maron et al. [16]	2014		1.20	US Registry for Sudden Death in Athletes	College athletes	17-26
Malhotra et al. [17]	2018	8	6.75	Prospective study	Athletes	15-17
Risgaard et al. [18]	2019	44	0.47	Sports-related death in Denmark (2007-2009)	Competitive athletes	12-35
Bohm et al. [19]	2020	240	0.12	Media reports, Registry, Forensic	Non elite athletes, recreational sport	10-79
Tchanana et al. [20]	2020	27	1.70	Multisource surveillance system	Recreational sports in general population	15-38
Sollazzo et al. [21]	2021	98	0.47	Google search	Competitive and non competitive athletes	-

as opposed to all deaths in a population [7,16].

Finally, SDA estimates may be influenced by legislative changes modifying the prevention procedures adopted in the state or region of interest. In 1982, a mandatory screening program for all athletes was implemented in Italy. In the Veneto region, the initial SDA rate was 1: 28,000 from 1979 to 1981 [4] and dropped to 1:250,000 in 2006 [6]. Such drastic reduction, interpreted as a measure of the effectiveness of the program, is however also a direct consequence of the increase in denominator, because of the substantially greater number of athletes screened after 1982. Collectively, these considerations highlight the need for continued efforts aimed at understanding the true epidemiology of SDA, by using more reliable and sophisticated indicators.

3. From epidemiology to the search for the SDA cause

Knowing the predisposing causes of an event and its precipitating factors can be the basis for effective prevention. A virtuous example is exercise-associated hyponatremia, which, in the last 20 years, has affected 5 marathon runners with extensive media coverage [24–26]. Exercise-associated hyponatremia was initially described in the 1980s in endurance athletes [27,28], and overdrinking beyond thirst and non-osmotic arginine vasopressin release were recognized as the most common etiologic factors. Specific studies were subsequently conducted during the 2002 Boston Marathon [29] and 2006 London Marathon [30] showing that 13.0% and 12.5% of finishers, respectively, suffered from asymptomatic hyponatremia. On this basis, sports medicine has pursued three main prevention strategies with (a) the promotion of the use of small boluses of hypertonic solutions and the dissemination of protocols for acute treatment [31]; (b) the launch of educational programs for marathon organizers (recommendation to drink according to thirst, while fixed ranges of fluid intake are now recognized as inappropriate; reduced availability of fluids along the routes of exercise; monitoring of weight changes during exercise; recognition of the signs and symptoms of exercise-associated hyponatremia as well as the need for immediate medical attention) [32,33]; (c) and, last but not least, the extension of surveillance strategies to other populations at risk (e.g. soldiers operating in the hot climates, fire and rescue services) [34].

In the case of cardiac deaths, the most frequent cause of SDA, the search for the causes started with simple epidemiological observations. SDA risk was reported to be higher in young (10 to 35 years old) competitive athletes than in noncompetitive sports participants (relative risk 4.5, 95% CI 2.3 to 8.7) [11]. Middle-aged men performing nonelite competitive or recreational sports were consistently reported to be at the greatest risk of SDA [11,19], which is not surprising considering the growing number of older individuals participating in competitive sports and the age-related prevalence of atherosclerotic cardiovascular diseases. Indeed, in the adult-master athlete, the most common identified cause of SDA is coronary artery disease (CAD) [11,19,35]. Furthermore, the incidence of SDA is 6 to 30 times lower in female athletes compared to males [2,11,23,36–38]. The incidence is expressed per million participants, making the contribution of gender variations in the participation rate to sport unlikely. Although the duration or level of exertion during each session may differ between men and women, a sex-related risk of inherent CAD could play a role. In young victims, CAD is a rare finding, and other structural abnormalities predisposing to arrhythmic death are the most frequent substrates of SDA [39], including hypertrophic cardiomyopathy (HCM) [37], congenital coronary artery anomalies, arrhythmogenic right ventricular cardiomyopathy (ARVC). In patients with normal hearts at autopsy, long QT syndrome and other ion channel diseases may be found by genetic investigation [40]. Notably, studies conducted in the US mainly identified HCM, coronary anomalies and myocarditis [1,7,41], while in Europe ARVC seems to represent the most common cause of SDA [4,42]. Regardless of these regional discrepancies, which may reflects true epidemiological and differences but also methodological differences in the attribution of diagnoses [4], early identification of substrates at risk became a main target for prevention.

Implantable cardioverter-defibrillators (ICDs) represented a major breakthrough at the beginning of the 2000s, allowing effective prevention of sudden death in high-risk individuals. Nevertheless, even the most accurate screening strategy will not be sensitive enough to identify all subjects at risk of SDA. In addition, even when cardiac abnormalities are identified, these are often mild in competitive athletes, and rarely suggestive of a high-risk individual profile requiring an ICD. With specific regard to ARVC, Kirchhof et al. [43] were the first to report that the macroscopically detectable changes, both at cardiac magnetic resonance and endomyocardial biopsy, may develop later than functional changes and arrhythmogenic propensity. In these individuals, physical exercise has been clearly identified as a strong determinant of phenotypic expression, arrhythmic risk and disease progression [44]. Thus, while conditions such as HCM is often detected at preparticipation evaluation [4], ARVC, can be missed both at screening and at pathological investigations [4]. In athletes with ARVC, the ECG is abnormal (allowing effective pre-participation screening) in 55% to 75% of cases [45–47]. However, it is rarely associated with cardiomegaly or evidence of ventricular dysfunction, and affected hearts may appear normal at screening visits [4,48]. A definitive diagnosis requires adequate sampling of myocardial tissue and careful histological examination. Furthermore, sudden cardiac death can occur in complete absence of underlying structural or functional heart disease. Finocchiaro et al. [35], in a registry of SDA in the UK collected between 1994 and 2014, found that sudden arrhythmic death syndrome (SADS) was the most prevalent cause of death in young athletes (70% Caucasian), followed by left ventricular hypertrophy and/or fibrosis and ARVC, while HCM and coronary artery anomalies were less frequent [35]. More precisely, a structurally normal heart accounted for 42% of the overall cohort (56% under 18 years and 26% over 35 years) [35]. Such high prevalence was partly explained by a possible referral bias because the national center might have received mainly complex cases of uncertain diagnosis while cases of simple diagnosis were resolved at the first level centers [35]. However, structurally normal hearts are also prevalent in U.S. SDA cohorts, i.e. 31% in collegiate athletes and 41% in young military personnel. These findings underscore the importance of inherited arrhythmia syndromes as a major cause of SCD in young athletes [49, 50]. Overall, rather that discouraging systematic evaluation of adolescents and young people embarking in sports activity, current knowledge should stimulate constant improvement and standardization of preparticipation cardiovascular screening strategies [51–54].

4. Prevention strategies

4.1. Proactive strategy with preparticipation screening

Comprehensive and thorough evaluation prior to participation in competitions is the current proactive strategy for SDA prevention. History and physical examination are the first step, and the AHA in 2014 released a 14-element cardiovascular screening checklist for congenital and genetic heart disease in young athletes (Table 2) [51]. At the discretion of the examiner, a positive response or finding in any one or more of the 14 items may be judged sufficient to trigger a comprehensive cardiovascular evaluation in which ECG, echocardiography and stress testing may be performed. The European Society of Cardiology (ESC) and the International Olympic Committee endorse universal use of the ECG, whereas the American College of Cardiology (ACC) and the American Heart Association (AHA) support selective use of ECG. While the cost-effectiveness of the ECG continues to fuel debates at various levels, it is clear that discriminating between training-related and pathologic ECG changes may be challenging even for experts. Recommendations for ECG interpretation in the athlete have been firstly published by the ESC in 2005 [55], to reduce the false positive rate of ECGs, and reviewed in 2010 [56] with the aim to distinguish ECG findings attributable to exercise training from those associated with

Table 2
The 14-element cardiovascular screening checklist for congenital and genetic heart disease in young athletes recommended by the American Heart Associations.

Personal history
Chest pain/discomfort/tightness/pressure related to exertion
Unexplained syncope/near-syncope
Excessive exertional and unexplained dyspnea/fatigue or palpitations
Prior recognition of a heart murmur
Elevated systemic blood pressure
Prior restriction from participation in sports
Prior testing for the heart, ordered by a physician
Family history
Premature death (sudden and unexpected, or otherwise) before age 50
Disability from heart disease in close relative <50 y of age
Hypertrophic or dilated cardiomyopathy, long-QT syndrome, or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias
Physical examination
Heart murmur
Femoral pulses to exclude aortic coarctation
Physical stigmata of Marfan syndrome
Brachial artery blood pressure (sitting position)

heart disease. In this last document, red flags requiring more advanced cardiac work-up were defined including non-Group 1 T-wave inversions, ST-segment depression, pathological Q waves, left atrial enlargement, left axis deviation/left anterior hemiblock, right axis deviation/left posterior hemiblock, right ventricular hypertrophy, ventricular pre-excitation, complete left or right bundle branch block, long- or short-QT interval, and Brugada-like early repolarization [56]. Using ESC criteria, mainly based on Caucasian athletes, black athletes were 2.5 times more likely to have an abnormal ECG, a figure that did not correlate with the likelihood of underlying cardiac disease in these individuals [53,57]. The Stanford criteria, published in 2011, modified the ESC criteria [58] and in February 2012, an international group of experts met in Seattle, further revising the ECG guidelines for athletes aged 14 to 35 years [52]. To solve the major ethnic limitations of these three sets of criteria, still largely based on Caucasians, a 2nd International ECG Summit convened in Seattle and produced the refined international criteria still in use today [54]. How to improve screening procedures further is a continued topic of debate. The use of echocardiography is controversial, whereas the introduction of advanced MRI-based preparticipation screening strategies, triggered by clinical red flags, is currently under investigations [59,60].

In Italy the pre-participation assessment protocol (PPE) for competitive athletes, established by law in 1982 [61] includes medical history, physical examination, visual acuity test, resting 12-lead ECG, ECG stress testing, spirometry and urine dipstick. Second-line investigations include 24 h ECG monitoring (including a training session) and echocardiography. Third-line examinations such as cardiac magnetic resonance imaging or coronary angiography / computed tomography are reserved for selected cases. For this provision of law, screening in Italy (1) is repeated every year, (2) is charged to the NHS until the age of 18, and (3) if the condition is deemed incompatible with safe competitive sporting practice, the athlete is disqualified, temporarily (if curative treatment was available) or permanent. The decision is binding but the athlete has the right to appeal to a multidisciplinary regional commission [62].

What is the optimal strategy to prevent SCD in the athlete is a matter of continuous debate and every sport cardiologist may use the available data to support his/her own belief. The standardization of screening procedures recently allowed to investigate screening performance. The first question is how many athletes with conditions potentially associated with SCD can be detected at preparticipation screening. Interestingly, well-designed studies performed in different populations of young athletes showed a similar yield (Table 3). The final detection of HCM, dilated cardiomyopathy, ARVC, coronary-artery anomalies, bicuspid aortic valve-associated disease, long-QT syndrome,

Table 3
Conditions potentially associated with sudden cardiac death detected at preparticipation screening

	Screened athletes n	Conditions potentially associated with SCD* n (%)
History[&], Physical Examination, ECG[$]		
Riding et al. [53] 2015	2,491	9 (0.36 %)
History, Physical Examination, ECG[$], Exercise stress testing		
Vessella et al. [62] 2020	5,910	18 (0.30%)
Zorzi et al. [65] 2020	10,985	54 (0.49%)
Sarto et al. [66] 2021	15,127	62 (0.42%)
History[&], Physical Examination, ECG[$], ECHO		
Malhotra et al. [17] 2018	11,168	42 (0.38 %)
Williams et al. [63] 2019	3,620	16 (0.44 %)
Calo'et al. [67] 2019	2,261	9 (0.39 %)

* hypertrophic cardiomyopathy; dilated cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy; coronary-artery anomalies; bicuspid aortic valve-associated disease; long-QT syndrome; Wolff–Parkinson–White ECG pattern.
& Football Association Pre-Cardiac Screening Health Questionnaire.
$ ESC, Seattle, refined, and international criteria.

Wolff–Parkinson–White occurred in 0.36% [53] to 0.44% [63] of screened athletes. Exercise stress test, required by the Italian law, is diagnostically relevant to record premature ventricular complexes in the young [64] and ischemic heart disease in master athletes although the rate of detection of conditions potentially associated with SCD was not modified [62,65,66]. Calo` et al. [67] suggest that echocardiography may uncover additional cardiac disease, but report a rate of disease (0.39%) similar to the Malhotra (0.38%) [17] and Williams studies (0.44%) [63], emphasizing the consistency of this estimate. The second, and most important question, is the sensitivity and positive predictive value of screening versus SDA. To answer the question prospective studies are needed, following screened cohorts over time. Because SDA incidence is low, these cohorts must be large, screening procedures highly standardized, the follow-up adequately long and pathology investigations performed on all victims. A single study published in 2018 [17] respected all these characteristics with a screened cohort of 11,168 adolescent athletes (mean age of 16.4±1.2 years, 95% male), participating in the English Football Association screening program, with a longitudinal mean follow-up of 10.6±8.3 years. Overall, 42 athletes were found to be affected by conditions potentially associated with SCD (0.38%) at screening visit and all received interventions according to current guidelines. In particular, 8 athletes with a diagnosis of cardiomyopathy and 3 with long-QT syndrome were advised against participation in competitive soccer. During follow-up, 23 deaths were recorded. Autopsy data showed that cardiac disorders accounted for 8 deaths (35%), all of which were sudden and occurred during exercise (6.8 per 100,000 athletes) with a mean time between screening and sudden death of 6.8 years. Overall, 40 out of the 42 athletes affected by conditions potentially associated with SCD were alive at the end of the study period. Two of the 8 SCDs were athletes with a diagnosis of HCM who continued to compete despite medical advice and died subsequently during intensive exercise. Conversely, 6 out of the 8 SCDs were due to cardiomyopathies (n=5) or to sudden arrhythmic death syndrome (n=1) that had not been detected at baseline [17]. The study is very important notwithstanding limitations related with the procedure adopted in Great Britain. The main ones are that it was a once only screening at the age of 16 and that the athletes kept their final decision to follow medical advice or not.

An epidemiologist would expect a low impact of proactive strategy with a low preparticipation screening effectiveness due to the low incidence of SDA. Indeed, the yield of the screening program in terms of mortality produced a positive predictive value of 4.7% with a 25%

sensitivity [17].

On the other hand, the potential psychosocial implications associated with sports screening is now emerging. False-positive results may cause unnecessary restrictions from sports leading to emotional stress for young athletes and their families [68,69]. Furthermore, even when a diagnosis is correct, total abolition of exercise and sports participation is detrimental for youth, low-risk individuals. National guidelines based on expert opinion discourage participation in high intensity competitive sports of subjects with conditions at potential risk, such as cardiomyopathies [70]. However, the risk is not homogeneous. While vigorous exercise may accelerate phenotype development and arrhythmic propensity in ARVC [71], HCM patients seem to benefit from a tailored physical activity [72]. The recently published ESC guidelines in sports cardiology and the updated AHA/ACC guidelines in the management and treatment of HCM [73,74] advocate light to moderate exercise in all individuals with HCM and provide more liberal recommendations for competitive sports in individuals who are deemed to be at low risk. Most individuals with HCM may also engage in recreational sports of low to moderate intensity and competitive sports of low intensity [75]. It is now well recognized that a sedentary lifestyle has a detrimental effect in all individuals with HCM. All able patients with HCM should adhere to the current minimal physical activity recommendations, while others should perform symptom-limited physical activity [72,75]. Notwithstanding low to moderate intensity exercise is now suggested in international guidelines for HCM[73,74,76], many physicians still recommend extremely conservative physical activity restrictions, or patients themselves choose to be sedentary due to fear of events [77–79] despite a negative impact on their quality of life [72] and a high prevalence of overweight/obesity [80,81]. Thus, on the one hand overdiagnosis should be carefully avoided in screening programs (by referring athletes to tertiary center when doubts persist), and, on the other, athletes with a definite diagnosis of heart disease should be advised regarding alternative, low intensity exercise programs tailored to their conditions [75].

Ultimately it is important to recognize that screening young people, especially if they are not (or not yet) elite athletes, has considerable individual and societal costs and may have cons as well as pros, in the face of its low predictive power. It should also be noted that, in jurisdictions without established screening programs, risk of sudden death during competitive sport is virtually identical to that in jurisdictions where systematic screening is undertaken (Table 1). Thus, consensus regarding the ideal screening procedure and target population for proactive SDA prevention is far from established.

4.2. *Reactive strategies with the automated external defibrillator*

Cardiopulmonary resuscitation, a reactive strategy preventing cardiac arrest from sudden death, appears to offer an effective, tested and established method for preventing SDA. This strategy requires the direct involvement of different social sectors rather than single professionals. Survival from sudden cardiac arrest (SCA) is mainly affected by the time interval from cardiac arrest to cardiopulmonary resuscitation, with a decline in survival of approximately 10% for every minute that defibrillation is delayed [82,83]. Very high survival rates can be obtained with implementation of systematic protocols for response during in-the-field cardiac arrest, appropriate training, and public education. Survival following SCA can be significantly improved by involving lay and non-professional rescuers in cardiopulmonary resuscitation (CPR) and the use of AED through public access defibrillation programs specifically designed to reduce the time interval from SCA to shock delivery [5,84,85]. Survival for out-of-hospital SCA doubled when non-professional rescuers were trained and equipped with AEDs compared to CPR alone [86,87]. The placement of AEDs in schools and at athletic venues has become the cornerstone of emergency response planning and the prevention of SCD in young athletes [8,88–90]. A clear advantage of this reactive strategy is the possibility of resuscitating spectators as well as athletes. This point clearly emerged from prospective observational study involving 2149 high schools in the US between 2009 and 2011 [91]. Fifty-nine cases of SCA were confirmed during the study period including 26 (44%) cases in students and 33 (56%) in adults; 55 (93%) events were witnessed and 54 (92%) received prompt cardiopulmonary resuscitation (CPR) [91]. Having AEDs on-site at sporting facilities and in schools increases SCA survival to over 80% [91]. Approximately 1 in 70 high schools had a SCA on campus each year, nearly half of these events in students or student-athletes and survival rates were higher in schools with an emergency action plan for SCA versus those without (79% vs 44%; OR 4.6), and if an onsite AED was used versus an offsite AED provided by emergency services (80% vs 50%; OR 4.0) [91]. A 2019 investigation of mobile responders equipped with AEDs during road races in Japan reported 100% survival in 28 participants with witnessed SCA in which the mean time to CPR was 0.8 min and the mean time to AED shock was 2.2 min [92]. AEDs are safe to use and come with simple instructions including voice and visual prompts that can be followed by any trained or untrained responder. The AED will not provide a shock to the heart unless ventricular tachycardia (VT) or ventricular fibrillation (VF) is detected. Training should include a review of the signs of SCA considering also possible distractors which might contribute to rescue delay due to misinterpretation of symptoms (eyes open / rolled back; seizure-like activity; agonal respirations with periodic chest/abdominal movements; falsely assuming a pulse) [93]. Notably, when developing an emergency action plan, atypical sporting equipment (full pads or helmet), or sporting venue (involving large geographical area including rowing, cycling, open water swimming, Nordic and downhill skiing, surfing, and distance running events) should all be considered in order to allow rapid resuscitation as a priority [93]. Community education in basic life support is important. In a French 5-year prospective registry of SCA during sport, regions with the highest levels of bystander resuscitation had the best survival rates at admission and hospital discharge [94].

Promotion of CPR training and AED access to bystanders, the main basis of effective reactive strategies, require the commitment of sports federations, of the individual countries hosting the sporting events, with a direct involvement of local stakeholders and policy makers. To date, global results are less than satisfying. However, the Fédération Internationale de Football Association (FIFA) has worked extensively in the field of the prevention of SCD [95,96]. In 2014 FIFA established a registry of SCD/SCA (Sudden Death Registry, FIFA-SDR) in football players worldwide, both at professional and amateur level [97]. SCD was defined as death occurring during football-specific exercise (warm up, training, match) or within 1 h after cessation of activity, deaths being recorded by media monitoring, confidential web-based data platform and data synchronization with existing national Sudden Death Registries [97]. The recently published first report included data of 617 players who were victims of SCD/SCA worldwide from 2014 to 2018 [97]. As expected, compared with an overall survival rate of 23% (142 of 617 players), survival was better when prompt cardiopulmonary resuscitation (CPR) was performed by lay persons (35%), CPR-trained staff (50%) and the use of an automated external defibrillator (AED) by CPR-trained staff (85%). Interestingly, 81% of delayed CPR (with inactivity until the arrival of paramedics or first responders) were due to misinterpretation of symptoms or unawareness [97]. Regular CPR training of football players and staff with direct access to AEDs is a recommended measure to turn SCA into a more frequently survived event, with success rates up to 85% at the global level [97]. Finally, immediate availability of an automated external defibrillator (AED) could be potentially life-saving for cardiac patients that are not detected during pre-participation screening, representing a safety net for the inaccuracies of the proactive strategy in athletes.

4.3. *What is the collective impact of proactive and reactive strategies?*

Proactive (ie, preparticipation screening) and reactive (CPR/AED)

strategies, are currently both implemented albeit to varying degrees in different countries and regions. Although the final collective impact has yet to be assessed systematically, a recent study performed in France [98] provides some interesting insight on the power of combining these two approaches. In France, medical assessment is mandatory since March 1999 in order to participate in competitive sports and/or obtain a sports license [99]. The modalities of preparticipation screening were published in 2009 by the French Society of Cardiology [100]. In middle-aged/senior individuals engaged in leisure time sports activities, implementation of the position stand from the European Association of Cardiovascular Prevention and Rehabilitation is recommended in France since 2011 [101]. However, it is not mandatory, and is left to the discretion of the treating physician. In a study assessing the temporal trends of SDA incidence, management, and survival in the Greater Paris area, the incidence of SrSCA remained stable over a series of 6 successive 2-year periods between 2005 and 2018 (6.24 vs 7.00 per million inhabitants/y; P=0.51). Conversely, across study periods the frequency of bystander CPR initiation (34.9%-94.7%; $P < 0.001$) and public AED use (1.6%-28.8%; $P<0.006$) rose steadily. Likewise, SDA survival increased from 23.8% to 66.7% ($P <0.001$) clearly indicating that the chain of survival has succeeded in its main goal [98]. Although the sports medicine recommendations took a significant turn in France in 2009/2011 [99,100], leading to an increase in screening rate, the extent and modalities of its implementation among recreational sport participants was not specifically assessed. Considering the trends for a higher rate of sports participation rate observed over the last decade, it is possible that screening prevented an increase in SrSCA incidence in the global population, as might have been expected given the increased participation. However, the stable incidence of SrSCA over time suggests the need for further improvement in screening strategies and emphasize the value of public education in basic life support [98].

5. Conclusions

Recent data indicate that the real incidence of SDA is higher than previously thought, and prevention remains challenging. Current screening programs have a low yield, with a positive predictive value of 4.7% and a 25% sensitivity. However, performance of pre-participation screening cannot be based solely on the yield of events, as it leads to the identification of, and potentially effective intervention on, about 4-5 subjects out of 1000 affected by conditions potentially at risk. To date, however, the most relevant impact on SDA prevention comes from the reactive strategy based on the widespread use of the AED, calling for systematic implementation worldwide in the world of sports. Spectators of a football match require emergency intervention more often than athletes. On a broader perspective, the vast attention devoted by society to the world of sport can be a very useful driver to allow the transfer of a reactive prevention strategy to the general population.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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