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Evidence from the evaluation of athletes aiming the exclusion of sudden cardiac death

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Index

Abstract

Introduction: Sudden cardiac death (SCD) in young athletes is a devastating and highly discussed event, nowadays. The aim of the preparticipation screening is to identify athletes with underlying cardiovascular disease who may be at increased risk of SCD during sports. This review article aims to provide an extensive critical analysis of the subject and tries to appeal to consensus regarding the best medical approach.

Methods: A literature search was performed in PubMed database using the keywords: sudden death, sudden cardiac death, sudden cardiac arrest, athlete, young athlete, screening. From an initial search of 525 articles, only 65 articles were left, to which 20 more were added after analysis of the bibliographical references of each, resulting in a database with 85 articles for review.

Results: Currently, there are two distinct models in the evaluation of athletes, with or without using the electrocardiogram (ECG). Although low sensitivity and specificity in detecting underlying cardiovascular anomalies based solely on history and physical examination has already been proven, the benefits of adding ECG to pre-participation screening (PPS) for reducing sudden death lacks evidence. The introduction of new ECG interpretation criteria has reduced the false-positive (6%) rate and thus increased its cost-effectiveness, although resulting in a high number of unnecessary disqualifications of athletes. The diagnosis of silent cardiovascular conditions is considered beneficial by many athletes, being able to make their own decision of keep practising sports with full knowledge of risks.

Conclusion: The incidence of sudden cardiac death is increasing as studies become more robust and with fewer bias. The evaluation of an athlete can not be limited to the H&P. It is fundamental to reach a consensus on proper education for sports physicians and proper evaluation of athletes. It is important to understand the need to transform decades of information and innovation into practical action aimed at a common good: Athlete's quality of life.

Keywords: sudden cardiac death; athlete; preparticipation screening.

Introduction

Young trained athletes are often considered role-models and the healthiest segment of our society [1]. Thus, it is difficult to accept how suddenly and tragically they can be victimized by underlying heart conditions [2]. Sudden cardiac death (SCD) in athletes occurs because of the existence of silent and assymptomatic cardiovascular disorders which, during effort, may cause a certain instability of the heart leading to ventricular tachycardia and/or fibrillation [3]. Sudden death in young competitive athletes has captured the cardiovascular medicine attention in the last 40 years, particularly with the deaths of several top-level athletes due to a wide variety of cardiovascular conditions [4]

Nowadays, SCD is known as the leading medical cause of death in athletes during exercise in the playing field [5]. However, due to an inexistent homogeneous data collection method, the incidence of SCD could range from 1:23 000 to 1:917 000 athletes per year [6]. Despite this fact, a preparticipation screening program (PPS) in athletes prior to competition is globally endorsed by many sports and cardiologic societies in order to identify cardiovascular abnormalities that may put the athlete at unmeasured risk of sudden death or injury [7].

Innovative results were reported from Veneto, Italy, that have emphasized the value of 12-lead electrocardiography (combined with history and physical examination) as part of the annual screening process that is required for all Italian athletes since the early 1980's, which resulted in a reduction of SCD rate [8]. This study caused controversy and similar studies, in Israel and USA, were carried out contradicting the Italian results and stating that ECG has no ability to decrease SCD [9] [10].

Despite all the confrontation of arguments throughout the years, there is no consensus on the most effective and cost-efficient diagnostic method to deal with athletes and families´ at risk of SCD.

The objective of this review was to perform an extensive critical evaluation of studies on SCD in athletes, assess the quality of evidence on which the medical community is standing, and whether the screening methods are cost-effective and capable of improving prognosis.

Materials and methods

A literature search was performed in PubMed database using the keywords: sudden death, sudden cardiac death, sudden cardiac arrest, athlete, young athlete, screening. Articles were reviewed with the objective of finding articles focused on the current methods of screening in athletes and its importance in reducing the incidence/risk of sudden cardiac death. Expert opinions, consensus statements, journal articles, meta-analysis, reviews and systematic reviews were included in this article review.

Articles were then reviewed and excluded if they were not published in English, in the last 10 years and if they did not focus on screening young athletes from 12-35 years or if there was no mention of SCD. Thus, articles referring non-cardiac sudden death, targeting a >35-year old athlete population or general population were left out of our study.

The original literature search found 525 articles. 525 articles were submitted to the exclusion criteria and 212 were left based on the fact that were published in English in the last 10 years targeting an athelete population from 12-35 years-old. Then, the remaining 212 articles were reviewed based on the capacity to fullfil the purpose of this review, aiming the actual incidence and causes of SCD, screening of young athletes, its actual controversy and the worldwide implications of inexistent national screening programs for athletes. This research/investigation resulted in the exclusion of 147 articles, making reference to treatment of athletes who suffered SCD (60), disregarding primary prevention (47) and focusing only on secondary/third prevention methods (40). Only 65 articles left as database through this process. However, 20 more articles were added after reviewing the reference list from the 65 articles, reaching a final number of 85 articles that constituted the starting point of this review article.

Our study set diferent objetives that are dealt separately by topics: incidence and causes of SCD in young athletes (12-35 years-old), current screening recommendations, the heterogeneity of diagnostic capacity in screening methods, false-positive rates, cost-effectiveness, the need for screening methods and its impact in reducing SCD and report the positive or negative outcome of such approach in an athlete's life.

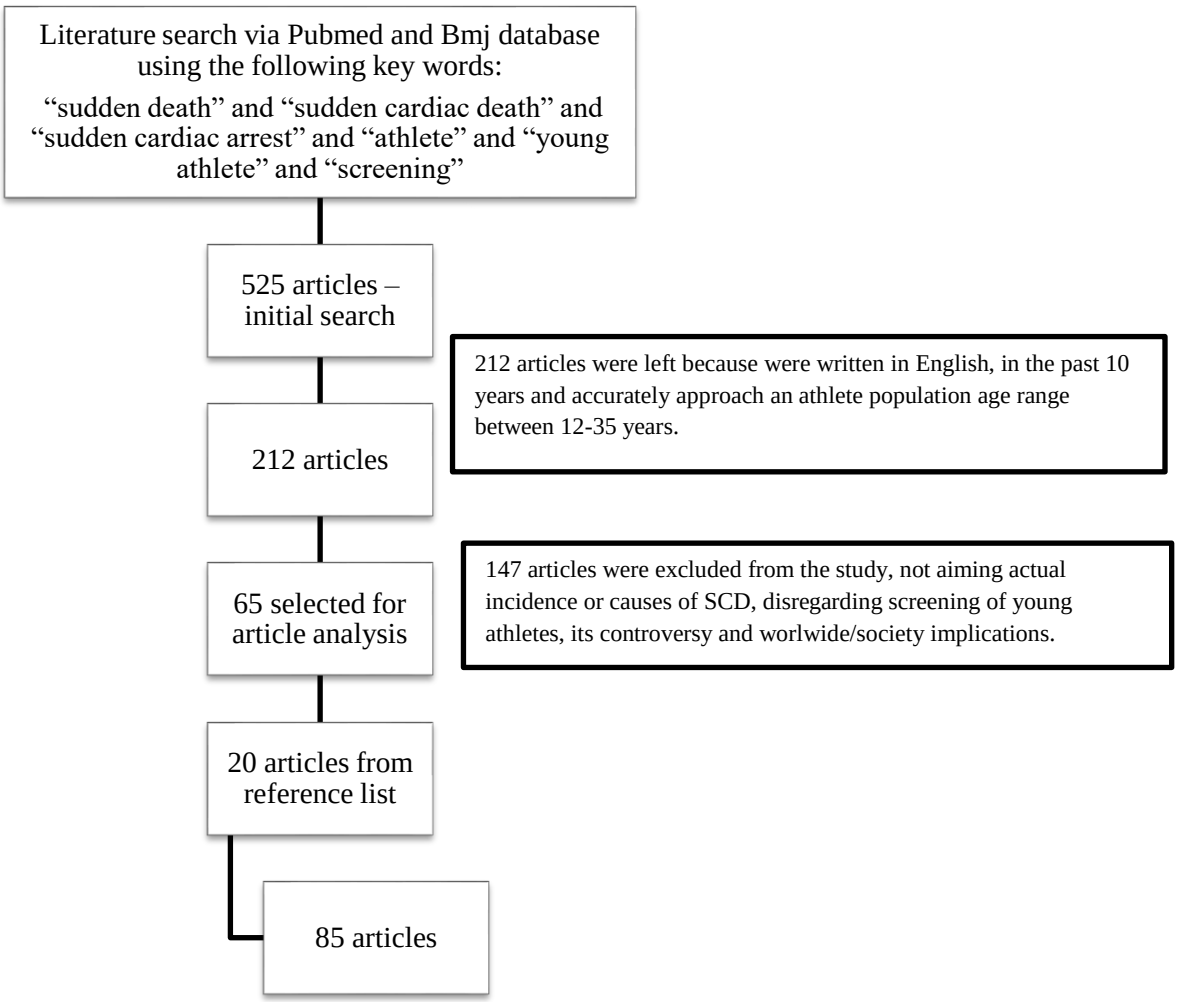

Figure 1 Study selection process

Results

Why support screening?

Physical exercise brings benefits in terms of promoting health, specifically cardiovascular fitness. However, exercise can make previously silent cardiovascular conditions become potentially fatal [11]. Data referring to Italian studies report a 2.8-fold higher risk of SCD among athletes compared to their non-athletic counterparts [8]. In order to support and implement a screening program to prevent SCD in young athletes, first, it needs to be proved that the incidence of SCD is higher in athletes than in general population.

Although it has been a widely discussed topic in the last decades, it was only in 1996 that the first results on SCD incidence were reported with a rate of about 1:300 000 person-years in a 10-year survey [6]. Later, it took place an exponencial growth of studies and published articles that estimated the rate of SCD in different countries, and raised awareness for SCD in young athletes.

The pioneer countries that tried to give voice to the problem of SCD are definitely the United States and Italy, with an ever-increasing contribution from other countries, such as Israel and Denmark [9] [12]. The Italian landmark study in Veneto [13], a small region in Italy, included young people and athletes between 12 and 35 years of age screened, and reported alarming data for the incidence of sudden cardiac death around 3,6:100 000 athletes-year on a pre-screening period. The authors reported 55 SCDs in screened athletes and 265 SCDs in unscreened nonathletes during the study period. The annual incidence of SCD decreased by 89%, but the incidence of SCD among the nonathletes, who were not screened, did not differ significantly. The odds risk of SCD in the prescreening period was 0,56 and decreased to 0,21 in the late screening period. The decline in SCD was due to a more accurate diagnose of cardiomyopathies, and an increasing identification of arrythmogenic right ventricular cardiomyopathy (ARVC) in

athletes and their sports disqualification. Furthermore, the implementation of the first major prospective study, a national mandatory reporting system of SCD, lead to a more accurate estimate of SCD events in the athlete population [13].

One of the largest studies on SCD in athletes was based on the collected information by the US Registry for Sudden Death in Athletes (URSDA) and conducted by Maron et al from 1980 to 2006, showing an incidence of SCD of about 0,6:100 000 athletes-year, much lower than the Italian one [14]. In 2010, Holst et al reported a rate of SCD of 1,2:100 000 athletes-year in athletes and young people aged 12-35 [12]. The Israeli study included athletes between the ages of 12 and 44 years and reported a rate in SCD of 2,6:100 000 athletes-year [9] (figure 2).

More recent American studies have focused on college and high-school young athletes, showing higher values than the initial estimates in the USA, but still on a retrospective basis. Harmon et al was able to ensemble information from the Parent Heart Watch and NCAA (National Collegiate Athletic Association) database from 2004 to 2008 and obtained a rate of sudden death of 2,3:100 000 athletes-year [15] (Figure 2). Maron et al performed a new study between 2002-2011, based on the USRSDA (United States registry of sudden death in athletes) and NCAA, obtaining an incidence of 1,6:100 000 athletes-year [16] (Figure 2). More recently Harmon conducted a study between 2003-2013 with data taken from the NCAA demonstrating an incidence of 1,9:100 000 athletes-year [17] (Figure 2). Plus, two retrospective studies in american high-schools Maron reported a rate of 0,7:100 000 on a 25 year survey, while Harmon reported a rate of 1,7:100 000 athletes-year on a 6 year survey. [18] [6]

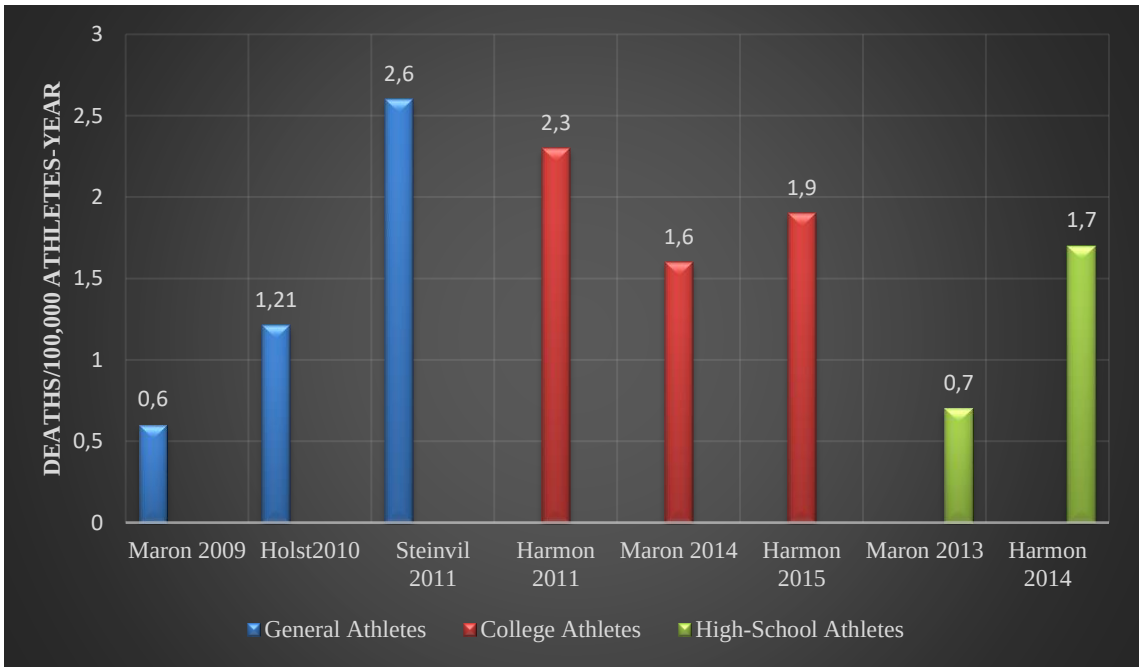

Figure 2 Incidence studies in general, college and high-school athletes [6] [14] [12] [9] [15] [16] [17] [18]

One of the major setbacks pointed out in the Italian experience is related to the assumptions made in considering a high incidence rate of 3,6:100 000, during a prescreening era from 1979 to 1980 in an athlete population. It is also unclear that data from such a homogeneous cohort in Southern Europe would translate to mixed and heterogeneous population such as the one in the United States [19] (Table 1). Danish and Israeli studies attempt to reproduce the Italian study, however presented main limitations as they based their case identification on media research, thus underestimating the rate of SCD events. [20] (Table 1) It is noteworthy that the low SCD incidence in studies including high-school athletes were due to retrospective cohorts based on catastrophic insurance claims and registries with an uncertain denominator. (Table 1) High-school incidences are more difficult to interpret and the limitations of incidence studies need to be aknowledge. The current incidence rates focus on a fraction of the day (school hours), accounting SCD during a limited amount of sports activities and relying on media reports. (Table 1) [6]

Variability in incidence rates is largely due to different methodologies including case identification, population denominators and the inclusion of only SCD events, excluding SCA from incidence calculations. Reports from Italy suggest that the incidence of SCD in athletes is higher than initial estimates, but probably not as high as it was previously claimed, taking in consideration that the world population is heterogeneous and not homogeneous as Veneto population. [19]

The final purpose of implementing screening strategies in young athletes, is defined by the American Heart Association (AHA) as "the ultimate objective of preparticipation screening for athletes is the detection of silent cardiovascular abnormalities that can lead to SCD"[21], so taking into account age range in the overall studies, a incidence of 2:100 000 athletes-year seems a reasonable estimate, keeping in mind the reports from retrospective cohort studies and the only prospective study performed in Veneto, Italy.[6] Furthermore, the authors presented several high risk findings of SCD: male athletes, basketball players and African-American athletes. [6]

	Study design	Case identification	SCD or SCA+SCD	Pros	Cons
Corrado (2003)	Prospetive cohort	Mandatory death reporting	SCD	Prospective cohort with a national mandatory death reporting system.	Only related to SCD. Short duration of pre-screening era and its missing data.
Maron (2009)	Retrospective cohort	USRSDA	SCA+SCD	Data assembled in a large, informative and registry format. Considering SCA+SCD.	Retrospective cohort. Considering only deaths that come to public domain and only during exercise. Ascertainment bias with uncertain denominators. Deaths may have been modestly underestimated.
Holst (2010)	Retrospective cohort	Review of death certificates	SCD	Improvement in identification through death certificates and autopsy reports. An appropriate age range to SCD study.	Retrospective cohort. Only related to SCD. Using population statistics as a denominator. The primary weakness was accurately identify athletes from the reduced information

Steinvil (2011)	Retrospective cohort	Two Israeli newspapers	SCD	Trying to replicate the study performed in Veneto, Italy.	Retrospective search of two newspapers, inclusion of a 24-year interval with variable media attention to athlete SCD, the broad age range with rates of SCD largely influenced by inclusion of older athletes and the imprecise denominator.
Harmon (2011)	Retrospective cohort	Parent Heart Watch database, NCAA resolutions list, Insurance claims	SCD	Narrow and well-defined age range. First study with SCD rates reporting sex and ethnic were known.	Retrospective search including data from insurance claims, with underestimation of SCD and imprecise denominator. Considering only SCD cases.
Maron (2014)	Retrospective cohort	USRSDA and NCAA resolutions list	SCD	Comparison of 2 research database.	Retrospective cohort in the absence of a mandatory reporting database leads inevitably to na underestimation of SCD cases. Considering only SCD cases.
Harmon (2015)	Retrospective cohort	USRSDA, Parent Heart Watch database, NCAA resolutions list	SCA+SCD	3 different data resources including SCA+SCD.	Retrospective cohort. Some SCD cases were likely to be missed, the heavily trust in autopsy reports. It is unknown the absolute number of athletes who were included.
Maron (2013)	Retrospective cohort	USRSDA	SCA+SCD	Including all deaths (SCA+SCD) not necessarily limited to those occurring in a particular sport.	Retrospective cohort. Metodological limitations of incidence studies in high school athletes must be acknowledged, for exemple, focus on a fraction of the day (school hours).
Harmon (2014)	Retrospective cohort	Media reports	SCA+SCD	Including all deaths (SCA+SCD)	Retrospective cohort with media reports for case identification and metodological limitations.

Table 1 Pros and cons of incidence studies in general, college and high-school athletes.

However, it is perhaps the prevalence of cardiovascular diseases with the potential to cause sudden death in athletes of greater relevance in the rigorous choice of screening techniques compared to the incidence of sudden death. And while the rate of sudden death incidence has shown very disparate values from several studies, the prevalence of cardiovascular disease and its potentially lethal risk has consistently fluctuated between 0.3-0.6% of the cohorts (table 2). In other words, 1 out of 300-600 athletes has a silent and unknown cardiovascular condition that put them at risk of SCD. [22]

Prevalence of cardiovascular diseases with potential risk of SCD in young athletes.		
Reference	Population	Prevalence (%)
•Maron	•Estimative in 1435 young competitive athletes	•0,3%
•Wilson	•2720 young athletes and children (10-17) in United Kingdom	•0,3%
•Baggish	•510 USA college athletes	•0,6%

Table 2 Prevalence of cardiovascular diseases with potencial risk of SCD in young athletes [23] [24] [25]

What is being screened?

Structural	Electric	Acquired
Hypertrophic Cardiomiopathy (HCM)	Wolff-Parkinson-White syndrome (WPW)	Infection (Myocarditis)
Arritmogenic Right Ventricular Cardiomiopathy (ARVC)	Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	Trauma (Commotio Cordis)
Congenital Coronary Anomalies (CAA)	Brugada Syndrome (BrS)	Drugs and stimulants
Marfan Syndrome	Long QT Syndrome (LQTS)	
Mitral Valve Prolapse (MVP)	Short QT Syndrome (SQTS)	
Aortic Rupture/Dilated aorta		

Figure 3 Major causes of sudden cardiac death in athletes [23]

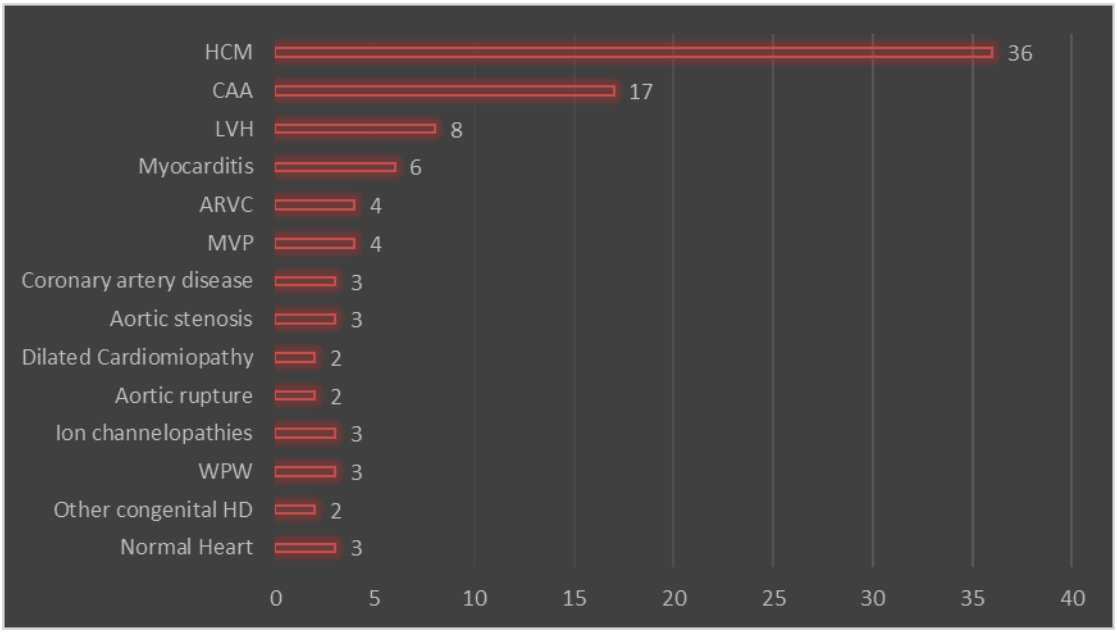

Figure 4 Adapted from Kerkhof et al. : Frequency of SCDs caused by cardiac condition (%) [26] *ion channelopathies=brugada syndrome, long QT syndrome, short QT syndrome and catecholaminergic polymorphic ventricular tachycardia*

There are multiple causes of sudden death in athletes. While for athletes aged 35 and over the main cause is atherosclerotic coronary disease, in younger individuals younger than 35 years, genetic and acquired cardiovascular abnormalities are the most common, where cardiomyopathies and coronary arteries anomalies gain special relevance. For athletes with structurally abnormal hearts, hypertrophic cardiomyopathy (HCM) has been, by far, the most common etiology reported in the USA with a frequency between 30 to 50%, whereas arrhythmogenic right ventricular dysplasia (ARVD) represents about a quarter of deaths reported in Italian studies. [27] [8] There are other pathologies that increase the risk of SCD related to physical exercise such as coronary artery anomalies, myocarditis, dilated cardiomyopathy and aortic stenosis. There are rarer non-arrhythmic pathologies associated with SCD, such as the spontaneous rupture of the aorta in a context of Marfan syndrome or a bicuspid aortic valve. Furthermore, sudden blunt, nonpenetrating and innocuous-appearing trauma to the anterior chest may result in sudden death from ventricular fibrillation, usually denominated *commotio cordis* [5] [28]. Some studies report the existence of 2 to 5% of young athletes SCD with structurally normal hearts. However, according to more recent data from these autopsy-negative sudden unexplained deaths (SUD), a possible significant cause of SCD in young athletes may be inherited arrhythmia syndromes and ion channel disorders, such as long QT syndrome (LQTS), short QT syndrome, Brugada syndrome, or familial catecholaminergic polymorphic ventricular tachycardia (CPVT). [29] [17]

A retrospective study between 2003 and 2013 conducted in college athletes reported that 25% of athletes who suffered sudden death had a structurally normal heart, and HCM was present in only 8% of the cases [17] . Reports from Denmark show that the most common finding related to SCD is a structurally normal heart (27%), while only 7% of the deaths were associated with HCM [12] Similar reports have found between 1996 and 2008, 23% of deaths were associated with a structurally normal heart, whereas only 11% were due to HCM [29]. The prevalence of ion

channel disorders, as a cause of SCD in athletes, may be underestimated, as autopsy-negative SUD represents a substantially larger proportion of theses cases.

The knowledge of the main causes of sudden death was a considerable acomplishment with an international recognition of its importance. More importantly, considering that the primary objective of athlete screening is to identify underlying cardiovascular conditions in order to reduce the athlete's risk of SCD, it is crucial to know which techniques are capable of recognizing it, in an accurate and reliable way, the anomalies that subsequently lead to the diagnosis of these disease. (Figure 4)

History and physical examinantion (H&P) has limited effectiveness in the detection of occult and potentially life-threatening cardiac disorders [30]. Recently, AHA reaffirmed their position regarding the current use of H&P as the only screening method. Although this American model is cheap and pragmatic, with sensitivity values as low as 6%. The majority of competitive athletes (60-80%) are assymptomatic before SCD, and most diseases related to SCD are not related with physical signs [30]. Furthermore, family history is usually absent since diseases like HCM or LQTS have low event rates [31]. Nonetheless, Wilson et al determined that 2,5% of H&P positive results required further testing, and in 9 cases H&P had 0% sensitivity to detect potentially lethal cardiovascular disease. [24]

The addition of a 12-lead ECG has potential for detecting athletes with electrophysiological cardiac disease, as LQTS, BS and WPW syndrome. [24] This might be relevant since an increasing number of sports-related SCDs, are associated to ion channel disorders. Although non-invasive cardiac imaging modalities are the gold standard for cardiomyopathies (HCM and ARVC), it is known that 90% of athletes with HCM and at least 50% with ARVC will have an abnormal ECG. ECG is nearly five times mores sensitive than medical questions and 10 times more sensitive than physical examination [32]. Despite being a

method with good diagnostic performance, diseases of the aorta and coronary arteries are not well detected by ECG, which represents a main flaw taking into account that those diseases comprise more than 16% of SCD in athletes.[32]

Ecocardiogram (Echo) was recently used in PPS performed by cardiologists who concluded that the addition of Echo improves the diagnostic capacity and efectiveness of screening programs.[33] In a recent study, Rizzo et al. stated that Echo not only confirms diagnoses related to electrocardiographic abnormalities, but also found anomalies not present in the ECG, such as bicuspid aortic valves, atrial septum defects, and mitral valve prolapse, [34] which represent a reduced percentage of causes of sudden death. In a study of about 3100 athletes, 56 abnormal Echos were reported, and only 2 were concordant with HCM. However, the ECG in these athletes was also abnormal, which would consequently lead to a referral to imaging techniques.[21] Echo has higher sensitivity and greater specificity than ECG in the diagnosis of structural cardiac anomalies,[35] however, it is unlikely that the diagnostic capacity gain will influence SCD in young athletes.[36]

	H&P	ECG	ECHO
HCM	Detect high false positive and false-negative	Detect high false-positive and low false-negative	Detect low false-positive and false-negative
CAA	Undetectable	Difficult detection	Detect low false positive and high false-negative
ARVD	Undetectable	Detect low false-positive and high false-negative	Detect low false-positive and false-negative
DILATED CM	Undetectable	Detect high false-positive and false negative	Detect low false positive and false negative
WPW	Undetectable	Detect low false-positive and false negative	Undetectable
LQTS	Detect high false-positive and false-negative	Detect low false-postive and high false-negative	Undetectable
BRS	Detect high false-positive and false-negative	Detect low false-positive and high false-negative	Undetectable
CPVT	Detect high false-positive and false-negative	Detect low false-positive and high false-negative	Undetectable

Figure 4 Adapted from Kerkhof et al. : Summary of the diagnostic capacity of screening tests; H&P – history and physical examination; ECG-electrocardiogram; ECHO – echocardiogram; HCM – hypertrophic cardiomyopathy; CAA – coronary artery anomalies; ARVD – arrythmogenic right ventricular dysplasia; CM – cardiomyopathy; WPW – Wolff-Parkinson-White; LQTS – long QT syndrome; BRS – Brugada syndrome; CPVT – catecholaminergic polymorphic ventricular tachycardia. [26]

Screening Athletes: Where do we stand?

Athlete's Heart

There are two main types of exercise, endurance and strength, and most sports are a combination of both. Athlete's cardiovascular system is considerably different, both structurally and functionally, depending on the type of exercise they endorse. And, as in the general population, each athlete responds differently to cardiovascular conditioning.[33]

In about 50% of athletes, physical exercise causes a cardiac remodeling, which is considered a normal and physiological change of the heart. Although it is a physiological process, it can cause anomalies in the electrocardiographic pattern in 40% of the athletes.[33] Despite that, there is no evidence that these changes in cardiac remodeling have a negative impact on athlete's prognosis, the ECG abnormal findings may hamper the clinical profile of the screened athletes.[33]

HCM is one of the most prevalent cardiac disorder responsible for SCD, and the differentiation from the physiological findings in an "athlete's heart" can be ascertain through the use of ECG and ECHO techniques, also from cardiopulmonary exercise test (CPET) and cardiac magnetic resonance (CMR) [28] as displayed in Figure 5, with the presence of a problematic grey zone that can mislead some diagnoses.

"Athlete's Heart"	Grey Zone	HCM
Assymptomatic; Isolated voltage criteria for LVH on ECG; LV dilatation (>55cm) with preserved LV function; Normal RV function	LV wall thickness of 13-15mm	Symptoms + family history; Pathological Q waves, ST-segment depression, LBBB or T-wave inversion in inferior/lateral leads; ASH, LV cavity <45mm, LA enlargement & abnormal diastolic filling; Peak VO2 max <50ml/kg/min on CPET CMR: delayed gadolinium enhancement

Figure 5 Adapted from Chandra et al. : Diference between "athlete's heart" findings and HCM pathologycal findings. ASH=asymmetrical septal hipertrophy; CMR=cardiac magetic ressonance; CPET= cardiopulmonary exercise test; LV=left ventricular; RV=right ventricular; LBBB= left bundle branch block [28]

The majority of cardiac conditions related to SCD are suspected or identified by anomalies in a 12-ECG screening method. Despite this increased ability to detect silent cardiovascular pathologies, the ECG has reduced ability in detecting abnormalities in the coronary arteries, premature coronary atherosclerosis and aortopathies. Nevertheless, cardiomyopathies such as HCM may present as normal ECG. Importantly, it is essential to have an appropriate knowledge about the physiological cardiac adaptations resulting from physical exercise. [37](Table 3)

Normal ECG finding	Definition
Increased isolated QRS voltage	Isolated QRS voltage criteria for left (SV1 + RV5 or RV6 >3.5 mV) or right ventricular hypertrophy (RV1 + SV5 or SV6 >1.1 mV); **Except → QRS voltage criteria for LVH occuring with any non-voltage criteria for LVH such as left atrial enlargement, left axis deviation, ST segment depression, T-wave inversion or pathological Q waves.**
Incomplete RBBB	rSR0 pattern in lead V1 and a qRS pattern in lead V6 with QRS duration <120 ms
Early repolarization	J-point elevation, ST-segment elevation, J waves, or terminal QRS slurring in the inferior and/or lateral leads
Black athlete repolarization variant	J-point elevation and convex ('domed') ST-segment elevation followed by T-wave inversion in leads V1–V4 in black athletes
Juvenile T-wave pattern	T-wave inversion V1–V3 in athletes age <16 yrs
Sinus bradycardia	>30 beats/min
Sinus arrythmia	Heart rate variation with respiration: rate increases during inspiration and decreases during expiration
Ectopic atrial rhythm	P waves are a different morphology compared with the sinus P-wave, such as negative P waves in the inferior leads ('low atrial rhythm')
Junctional escape rhythm	QRS rate is faster than the resting P-wave or sinus rate and typically <100 beats/min with narrow QRS complex unless the baseline QRS is conducted with aberrancy
1º AV block	PR interval 200–400 ms
Mobitz Type I (Wenckebach) 2º AV block	PR interval progressively lengthens until there is a non-conducted P-wave with no QRS complex; the first PR interval after the dropped beat is shorter than the last conducted PR interval

Table 3 Adapted from Seattle Criteria: Exercise-related ECG findings [37]

AV= atrioventricular block; ECG=electrocardiogram; PVC=premature ventricular contraction; RBBB=right bundle branch block; LVH= left ventricular hipertrophy

Isolated QRS voltage criteria for LVH may be present in <2% of athletes with HCM, but in the absence of other ECG markers or clinical symptoms related to cardiovascular pathology, those ECG findings are considered physiological adaptions and do not need further evaluation [37]. An early repolarization pattern (Figure 6)[37] is common in healthy people, including young athletes, male and black ethnicity. There has been reports from a possible association between early repolarization and the potential risk of ventricular fibrillation (VF), but up until now there is not enough data to support such correlation. Notwithstanding, the pattern isolated early repolarization without clinical features of cardiac condition is considered benign[38]. More than two thirds of black athletes report repolarization variant due to physical exercise (Figure 7)[37] and should not be seen as a criteria for further investigation in the absence of any other cardiac markers.[37] Sinus bradycardia and sinus arrhytmia in the absence of adittional symptoms are a normal variant in highly competitive athletes and should not be seen as major concern, because anomalies of rhythm and bradycardia should disappear after the onset of physical activity.[37]

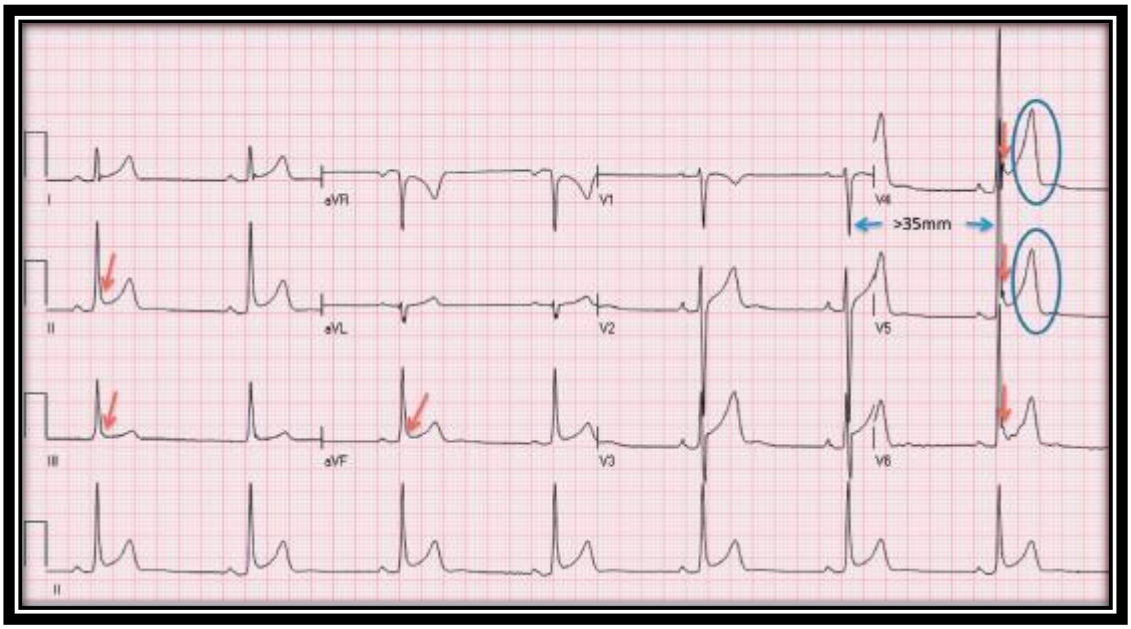

Figure 6 Adapted from International Recommendations for Electrocardiographic interpretation in athletes: Early repolarization changes in an athlete; electrocardiogram of a 29 year-old male soccer player showing sinus bradycardia (44 beats/min), early repolarization in I,II,aVF,V2 to V6 (arrows), voltage criteria for left ventricular hipertrophy and tal, peaked T waves (circles). These are common, training related findings in athletes. [37]

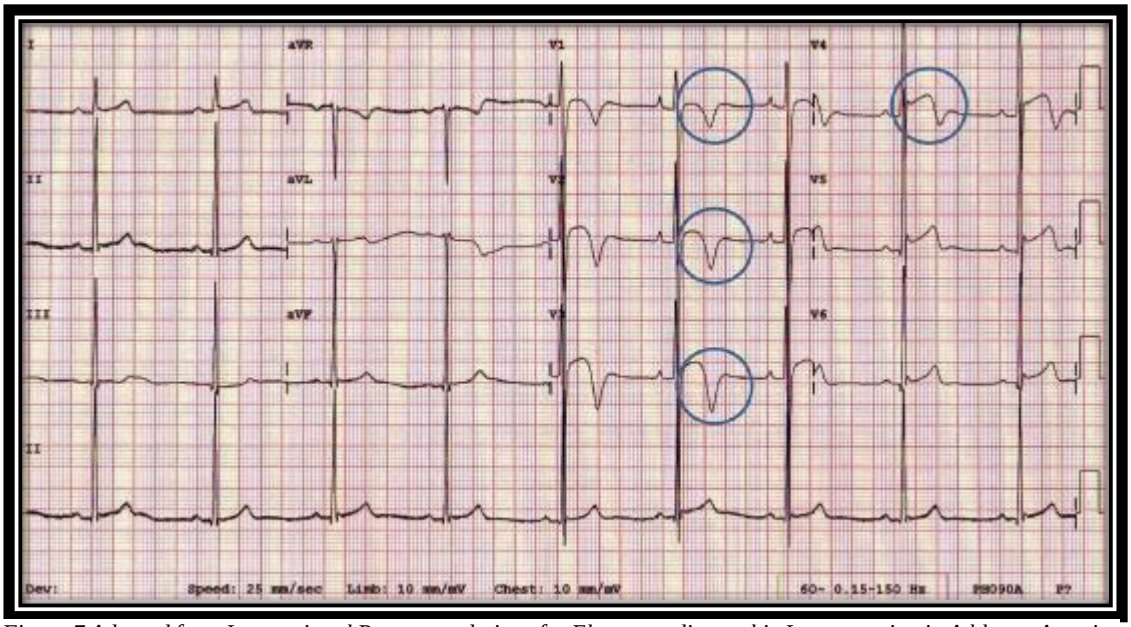

Figure 7 Adapted from International Recommendations for Electrocardiographic Interpretation in Athletes: Anterior Repolarization Changes in a Black Athlete; Electrocardiogram from a black athlete demonstrating voltage criteria for left ventricular hipertrophy, J-point elevation, and convex ('domed') ST-segment elevation followed by T-wave inversion in V1 to V4 (circles). Normal repolarization pattern in black athletes [37]

Current Recommendations

History and Physical examination

Although SCD in sport is a relatively rare event, the social impact of these events, the loss of decades of quality-life years, and the ability to detect and manage cardiac pathologies related to SCD have motivated national authorities throughout the world to support the preparticipation cardiovascular screening. Physical activity appears to increase the risk of sudden death in athletes who have underlying cardiovascular pathology that has not been previously diagnosed. [23]Additionally, about 60-80% of sudden deaths in athletes emerges in the absence of any previous symptoms. [20 39]

The protocol approved by the AHA includes a 14-point history and physical examination. By scrutinizing this small questionnaire, we have about 7 elements for the athlete's personal history, 3 family history elements and 4 physical exam elements, but because this 14-item questionnaire is relatively recent, many of the studies reported here used as reference an

old AHA questionnaire of only 12 elements. Although recommended by the AHA, several studies have demonstrated that medical and family history together with the physical examination have a limited effectiveness in detecting cardiovascular pathologies that predispose young athletes to sudden death. [3] More recently, the AHA and the American College of Cardiology (ACC) have reaffirmed that there is no evidence to support the need for a more thorough assessment in athletes and exclude non-athletes from this equation [40] The model adopted in USA is cheap and simple, however, the 12-element form of AHA is outperformed by ECG [5]. It would be necessary to have 1000 positive questionnaires to identify 1 athlete with a relevant cardiac condition, while 15 abnormal ECGs would suffice to identify a relevant cardiac disorder [41]. Several studies report that history and physical examination protocol (H&P) can appropriately detect up to 33% of silent cardiovascular anomalies [25]. Nonetheless, methods of screening based exclusively on history and physical examination will entail a high number of false negatives, as well as false hopes for some athletes who in fact are at risk due to a significant cardiac pathology. [31] Furthermore, the questionnaire implemented by the AHA produces a high number of positive results during the screening. About 25% of athletes who are screened with this method are referred for further cardiovascular assessment and in a national context, this amounts to about 2.5 million athletes who would undergo further evaluation, which contrasts clearly with the reduced values of both the incidence of SCD and the prevalence of potentially lethal cardiovascular diseases. [31]

Table 4 Adapted from Maron et al. : The 14-item AHA recommendations for PPS of competitive athletes [40]
Medical personal history Chest pain, discomfort, tightness/pressure related to exertion; Unexplained syncope/near syncope (not of neurocardiogenic origin); particularly relevant associated with physical exertion; Excessive exertional and unexplained dyspnea/fatigue, associated with exercise; Previous recognition of heart murmur; Elevated systemic blood pressure; Previous restriction from participation in sports;* Previous testing for the heart ordered by a physician because of family history;*
Family history Premature death (sudden and unexpected) <50years of age attributable to heart disease in ≥1 relative; Disability due to heart disease in a close relative with <50 years; Hypertrophic or dilated cardiomyopathy, LQTS, or other ion cannelopathies in family members;
Physical examination Heart murmur (auscultation should be performed with the patient in the supine and standing position, in an effort to identify more clearly the presence of murmurs associated with dynamic obstruction of the left ventricular outflow tract) Femoral pulses to exclude aortic coarctation; Physical stigmas of Marfan syndrome; Brachial artery blood pressure (with the patient seated) in both arms.
***new additons to the 12-item questionnaire

Does ECG improve the detection of cardiovascular diseases?

The AHA, although recognizing some of the benefits from ECG over H&P, stated that the systematic use of ECG in the prevention of SCD was extremely costly and not feasible, finding that legal and ethical concerns were the main barriers to the development of such a program [40]

The ECG is considered the most effective method of screening for the detection of cardiovascular disease, when performed by experienced and competent clinicians [20 27 42]. In a systematic review conducted by Harmon et al, it is stated that ECG has 5 times more sensitivity than current medical questions, it is 10 times more sensitive than physical examination and has a higher positive likelihood ratio and a lower false-positive rate than H&P [32]. It has increased performance for screening cardiovascular anomalies in the case of primary electrical diseases, ion channelopathies and cardiomyopathies, which commonly present annomalies in the ECG and therefore can be routinely diagnosed through this method. Additionally, nearly 95% of HCM athletes have ECG abnormalities. [27]

A recent study in 510 athletes showed that the inclusion of ECG at routine screening with H&P led to a considerable increase in the detection of cardiac abnormalities (confirmed by echocardiogram) from 5/11 to 10/11, resulting in a sensitivity increase of about 90.9%. [25] However, using the traditional ECG interpretation criteria, false-positive values were higher than those of H&P alone (16.9% vs 5.5%), thus reducing its specificity to 82.7%. Consequently, the medical community argue for a revision of the ECG criteria to reduce the number of false positives, which inevitably has consequences for athletes and healthcare costs. [25] All of the above has led to the endorsement of the ECG screening of athletes by the European Society of Cardiology (ESC), and International Olympic Committee (IOC) [43 44]. The rest-ECG criteria is not capable of detecting athletes with congenital alterations of the coronary arteries or

premature coronary artery disease, thus about 25% of those affected with a potentially fatal condition would remain undetected [45]

Major concerns have arisen regarding the high number of false positives reported by some studies if ECG was included in the screening. False positives produce a large number of additional exams, making the entire screening and decision-making process more complex and more expensive. Therefore, efforts have been made to improve the original ECG interpretation criteria of athletes in order to increase the specificity of the test without compromising its sensitivity. [46]

Recent studies have shown that the workforce that was intended to interpret the ECGs of athletes could not do so effectively and accurately, leading necessarily to a high rate of false positives and consequently to a high number of unnecessary secondary evaluations. [47] Thus, in 2010, the European Society of Cardiology (ESC) introduced new interpretation criteria that differentiate physical-related physiological abnormalities from uncommon abnormalities that were unrelated to exercise, which they tried to replicate in a group of 1005 ECGs of young trained athletes resulting in a increase of 70% in specificity, keeping the same sensitivity and decreasing the number of false-positives from 40% to 11%. [44] The explanation to such an increase in ECG specificity is primarily due to the young athletes with voltage criteria for left ventricular (LV) hipertrohy and early repolarization anomalies, having also helped maintaining the sensitivity for screening potentially lethal cardiovascular conditions. The Seattle criteria (2013) [47]improved ECG interpretation by improving definitions and providing more restrict cut-off values to long QT interval and intraventricular conduction delay, with innovating reference values for anomalies and recommended clinical management. [46] In 2015, a study by Riding et al [48] proposed to assess and compare the accuracy of their own "Refined criteria" against ESC 2010 criteria and 2013 Seattle criteria in a study with Arabic, Caucasian and Black athletes. Table 5 compares the 3 proposed criteria, regarding several cardiac anomalies.

ECG anomaly	ESC recommendations (2010)	Seattle Criteria (2013)	Refined Criteria (2015)
Left atrial enlargement	Negative portion of the P-wave in lead V1 ≥0.1 mV in depth and ≥40 ms in duration	Prolonged P-wave duration of >120 ms in leads I or II with negative portion of the P-wave ≥0.1 mV in depth and ≥40 ms in duration in lead V1	As ESC
Right atrial enlargement	P-wave amplitude ≥2.5 mm in leads II, III or aVF	As ESC	As ESC
Left QRS-axis deviation	−30° to −90°	As ESC	As ESC
Right QRS-axis deviation	>115°	>120º	As ESC
RV hipertrophy	Sum of R-wave in V1 and S-wave in V5 or V6 ≥1.05 mV	Sum of R-wave in V1 and S-wave in V5>1.05 mV and right axis deviation >120°	As ESC
Corrected QT interval	>440 ms (men) and >460 ms (women)	>470 ms (men) and 480 ms (women)	As Seattle
Complete LBBB	QRS ≥120 ms predominantly negative QRS complex in lead V1 (QS or rS), and upright monophasic R-wave in leads I and V6	As ESC	As ESC
Complete RBBB	RSR pattern in anterior precordial leads with QRS duration ≥120 ms	Irrelevant	As ESC
Intraventricular conduction delay	Any QRS duration>120 ms including RBBB and LBBB	Any QRS duration ≥140 ms or complete LBBB	As ESC

Pathological Q wave	>0.4 mV deep in any lead except III, aVR	>0.3 mV deep and/or >40 ms duration in ≥2 leads except III and aVR	≥40 ms in duration or ≥25% of the height of the ensuing R-wave
T wave inversion	≥2 mm in ≥2 adjacent leads (deep) or 'minor' in ≥2 leads	>1 mm in depth in two or more leads V2−6, II and aVF or I and aVL (excludes III, aVR and V1)	As Seattle
ST segment depression	≥0.5 mm deep in ≥2 leads	As ESC	As ESC
Ventricular pre-excitation	PR interval <120 ms with or without delta wave	PR interval <120 ms with delta wave	As Seattle

Table 5 Adapted from Riding et al.: Electrocardiographic parameters to define ECG anomalies. LBBB=left bundle branch block; RBBB=right bundle branch block; ms=miliseconds; mV=milivolts; mm=milimeters [48]

In this study, athletes that were screened positive with ECG needed to undergo ecocardiographic evaluation. Subsequently to the identification of 10 pathological cases in asian, black and caucasian athletes (7 HCM and 3 WPW), the authors calculated the sensitivity and specificity of the three ECG criteria. (Figure 6) Compared to ESC 2010 criteria, Seattle Criteria has an improved specificity from 76,6% to 87,5%, while the "Refined Criteria" are highlighted with an increase of specificity to 94%, however no external validation has been made yet. All the pathologic cases were identified by the three screening protocols with 100% sensitivity. [48]

	ESC 2010 criteria	Seattle criteria	"Refined criteria"
Specificity	76,6%	87,5%	94%
Sensitivity	100%	100%	100%
Positive predictive value	2,4%	4,5%	8,9%

Table 6 Adapted from Riding et al.: Sensitivity, specificity and positive predictive value of three screening protocols. ESC=european society of cardiology[48]

Although the number of false positives has decreased with the Seattle criteria to 11% (Zorzi), the false positive rate is about 6%. [32] In addition, it is important to remember that not all causes of sudden death have an abnormal ECG, and we must take into account the significant number of false negatives and their impact in SCD risk stratification and prognosis. For example, about 10% of HCM cases [49] will have a negative ECG. Futhermore, the improvement of the ECG criteria in order to reduce the false-positive rate, will statistically cause an increase in the false-negative rate and an uknown impact in new SCD cases.

Is there a role for Ecocardiography in athletes screening?

Echocardiography is considered the most practical technique in the detection of cardiac structural defects.[50] Currently, the use of echocardiography as a primary screening technique in asymptomatic athletes is controversial, among other reasons is the fact that the routine use of echocardiogram would not be cost-effective [33] [51]. However, this noninvasive screening technique may be of extreme importance in the evaluation of athletes with abnormal ECG. [33] [51] Echocardiography is not suitable for the diagnosis of arrhythmogenic abnormalities, such as ion channelopathies or Wolf-Parkinson-White syndrome, which may ultimately lead to SCD. On the other hand, echocardiography can identify important pathologies such as anomalous coronary arteries, aortic root dilatation and cardiomyopathy in the absence of an abnormal

electrocardiogram. However, its diagnostic performance is limited in asymptomatic athletes with normal physical examination and ECG. [50]

Riding et al. found that the systemic use of echocardiography in cardiovascular PPS almost doubled financial costs compared to a 12-lead ECG-led program with echocardiogram reserved as a follow-up modality[52]: 10 athletes had cardiac disease related to SCD, and those 10 athletes had an abnormal rest-ECG. Echocardiography alone was unable to increase the diagnosis of pathology associated with SCD, merely helped to clarify and confirm HCM diagnoses.[52] This study showed that using echocardiography as a second-line screening tool would have resulted in a reduction of about 47% in program costs without compromising the diagnoses of potentially fatal pathologies for athletes. [52]

The Early Screening for Cardiac Abnormalities with Preparticipation Echocardiography (ESCAPE) was developed in 2012. [53] [54]The study's methodology consisted of a portable echocardiograph use by a frontline physician (PEFP), having specific echocardiographic windows to allow the direct visualization of different cardiac anatomic regions that are generally associated with SCD. An evaluation of 61 athletes was made through H&P, ECG (ESC 2010 criteria) and portable echocardiography performed by a sports physician, to verify the presence of HCM and dilation of the aortic root. The study demonstrated that their approach through PEFP reduced the referral of screened athletes to cardiologists by 33% than a detailed analysis through H&P and ECG screening. In conclusion, Kerkhof et al found that performing a portable echocardiogram allowed a more accurate screening for structural abnormalities and in a more cost-effective way than a full echocardiogram performed by a senior cardiologist. Notwithstanding, further studies are needed to corroborate those findings, especially in the diagnostic capacity of HCM. [33] [26]

Thus, adding echocardiography will allow physicians to more accurately identify a greater number of pathologies, but is unlikely to affect SCD in young athletes. Its current role is in a secondary assessment of symptomatic athletes, with abnomal H&P or ECG [36] and is unlikely to be part of a national screening program of SCD in sports.[36]

Cost implications and considerations

Costs and cost-effectiveness are an important part of the development of any screening program. The cost-effectiveness estimates depend largely on the specificity and sensitivity of the screening method itself, as well as the prevalence of the disease. A medical intervention to be considered cost-effective should cost less than $ 50,000 per quality-adjusted life-year gained. [27] The topic of cost-effectiveness is the cornerstone of SCD screening, namely the cost-effectiveness of ECG screening to the use of H&P alone. [55] Initial studies reported that the use of ECG in screening programs was not cost effective, since SCD has a very low incidence and a high rate of false positives was showed when traditional ECG screening criteria were still being used. [39] Nonetheless, more recent studies have shown that screening with H&P alone is the least cost-effective strategy ($ 119,000 per life-year saved) due to its low sensitivity and specificity and that ECG implementation at preparticipation screening or its use alone has the ability to satisfy the cost-effectiveness standards ($42,000 per life year saved). [27,56] From Wheeler's point of view, the inclusion of ECG results in an incremental of sensitivity (30% to 75%) towards the suspicion of cardiovascular disorders. The ability to recommend athletes for secondary evaluation and to identify athletes at risk was determinant (Table 7).

Strategy (cost-effectiveness assuming no screening as baseline)	Athletes Recommended for Secondary Testing, (n=)	Identified Athletes at Increased Risk for SCD, (n=)	Cases of SCD in Athletes, (n=)
• No screening	0	0	1100
• H&P	117 000	6700	1010
• ECG+H&P	123 000	30 200	670
Cost effectiveness assuming H&P as baseline	Athletes Recommended for Secondary Testing, (n=)	Identified Athletes at Increased Risk for SCD, (n=)	Cases of SCD in Athletes, (n=)
• ECG+H&P	96 000	23 500	670

Table 7 Adapted from Wheeler et al. : Comparing Methods of Cardiovascular Screening to Prevent SCD in Student-Athletes n=number of athletes; H&P=history and physical examination; ECG=electrocardiogram; SCD=sudden cardiac death [56]

However, in this study, it was instituted an initial price for ECG of $5, which is the designed price when performed by a stablished infrastructure of trained volunteer physicians. The cost- per life year saved would be increased if it was taken into consideration that an ECG in an office setting would cost $19-40. Furthermore, the original analysis did not account the cost of follow-up testing such as echocardiograms and cardiac magnetic resonance (CMR), usually done in secondary athlete evaluation. [19]

Preparticipation screening of student-athletes for cardiovascular disease using a single, appropriately interpreted ECG and cardiovascular-focused history and physical examination has an acceptable cost-effectiveness ratio of $76 000 per life-year saved, compared with a strategy of no screening. [56]

Another study on cost-effectiveness analysis was carried out by Schoenbaum et al. The incremental cost-effectiveness (ICE) for H&P plus the ECG was $ 68,800 per quality-adjusted life-year (QALY), while ICE with the use of ECG alone was $ 37,700 per QALY. [57]

More recently, Menafoglio et al [58] conducted a study in 1070 Swiss athletes using history, physical examination and resting ECG (2010 criteria of the ESC) and reported a cost per athlete of $152 and $14,802 per abnormal finding. The results of this study suggest that ECG screening can be feasible and reasonably priced considering the modern ECG interpretation criteria.

Despite the above studies, the use of ECG as a universal screening method is far from a reality. Halkin et al [59] projected the costs of a 20-year screening program for young athletes in the USA, based on the Corrado Italian study. [13] It was estimated that there are about 8.5 million young athletes, which would cost the health system around $2.5-3.4 billion per year, something between $51 and $69 billion in 20 years, leading to a substantial economic burden to the healthcare system. These results were based on an incidence of SCD of 4 per 100,000 athletes-year, with a cost per ECG of 39 dollars, arguing that the cost per ECG advocated by Wheeler et al would only make sense in the presence of a well-built infrastructure with volunteer and experienced medical / technical staff. [59] [19]

Another implication in the costs of a screening program is the time interval in which the screening should be performed. A single ECG in an athlete may fail to detect a cardiac anomaly in development, thus the need to repeat the same exam in subsequent years is needed, which would double or triple the initial cost estimate. At last, the long-term cost-benefit analysis should also take into consideration the athletes falsely labelled as positive, which disqualifies them to practicing competite sports. In addition to withdrawing the pleasure from sports, it can influence the possibility of employment in the sports sector, and thus, lose several years due to unnecessary disqualifications. [19]

Are Imaging Cardiac and genetic strategies an important breakthrough?

Cardiac magnetic resonance (CMR) is considered one of the biggest promises in the cardiac evaluation of athletes. [51] Recently, there has been an increase in the diagnosis of cardiomyopathies not only in athletes, but also in their relatives, corroborating the increased diagnostic capacity provided by CMR. It can be performed to assess cardiac function or to enhance abnormal cardiac tissue and fibrosis with delayed gadolinium enhancement (DGE). Despite its advantages, there is little information on its casuistic effect, in addition to reports that DGE is identified in healthy athletes. [51] In the case of normal ECHO but with high pathological suspicion, resorting to CMR seems the most accurate approach, since it allows for a more detailed analysis of myocardial areas that may be difficult to ascertain with conventional echocardiography techniques. [60] Further investigation of the healthy athlete's CMR values is needed in order to extrapolate these values to identify athletes with cardiac abnormalities. [51]

As noted above, the pathologies that may potentially cause SCD have an important hereditary component. In this sense, information about the diagnosis of hereditary cardiac pathologies has appeared in the last years through genetic testing (DNA-basis). [60] However the diagnosis of cardiac conditions such as HCM, Marfan syndrome, LQTS and other ion channelopathies has been performed through routine clinical examination techniques. Currently, due to its expensive and complex methodology and its heterogeneity of characteristics, the inclusion of genetic tests is not easily practicable on a clinical basis, much less its application among the young athlete population. [61] However this genetic testing could help characterize diseases such as HCM and LQTS for optimum treatment. [2]

Pre-participation screening programme – does it save lives?

Pre-participation screening allows the identification of high-risk assymptomatic athletes, enables the diagnose of potentially lethal cardiovascular abnormalities and, in the end, protects them from the SCD risk. [62] To authentically assess whether screening can reduce the number of sudden cardiac death in young athletes, it would require a randomized controlled trial. At present, this study is not expected to occur in following years.

There are only two major prospective studies that compare mortality rates before and after a national screening program is implemented. In the Italian study [13], a dramatic reduction in mortality was demonstrated comparing the years prior to the screening program and the years thereafter. There was a SCD reduction of about 89% from the pre-screening period and the post-screening period, and it should be safeguarded that this reduction was not observed in the non-athlete population. This long-term experience was the only study to provide data that allegedly proved that PPS prior to the onset of symptoms may alter the course of cardiovascular pathology in athletes and improve their prognosis. [63 64]

An Israeli study conducted a few years later,[9] with the goal of comparing death rates before and after a national screening program, failed to show any benefit from the screening program. This study extended the pre-screening period and did not find a significant difference in the mortality between the period before or after the implementation of the national screening program. As a result, Steinvil et al [9]criticised and suggested that the Italian results were fraudulent, due to the existence of a very short pre-screening period. The fact that in the Italian study there was no unscreened control population, the decline in mortality may have been due to improved resuscitation techniques or due to an increase in the proportion of female athletes, which are associated with a lower risk of sudden cardiac death.[9] Nonetheless, the Israeli study

methodology was also harshly criticised, as the data was collected from media reports instead of using a national database such as the Italian study. [9] [64]

Another study, conducted by Maron et al for 23 years in Minnesota high-schools, reported a lower rate of sudden death than the rates established in both previous studies. [10] The ECG was not part of the screening method in the United States during this period, which may suggest that no screening method or the simpler screening method of USA could be as effective as the Italian national program. [9] [10] The inclusion of ECG in the USA remains a financial issue, stating that a 20 years screening program would save about 4813 athletes with an average cost of $10.6-14.4 million per life saved, being unbearable for a national healthcare system. [59]

Is medical prevention a reliable solution for athletes?

An accurate diagnosis of potentially fatal conditions is the fundamental starting point for a targeted treatment. [2] When we are faced with a diagnosis of HCM, medication with beta-blockers may be planned, or an implantation of an implantable cardioverter defibrillator (ICD) in patients at high risk or with history of SCD. [2] Arrythmias in cardiac conditions such as WPW and some cases of HCM or ARVC may rely in ablation therapy as the solution to interrupt the ectopic foci. Regarding channelopathies (Brugada syndrome, CPVT and long QT syndrome) may be treated with beta-blockers and/or antiarrhythmic agents depending on their specific phenotype. [2] However, the adverse effects associated with medical therapies may be higher than the risk of SCD. [65] Ablative procedures are associated with a rate of 5-8% of complications, which may lead to the need of pacemaker. [66] The insertion of automated implanted defibrillators can lead to numerous complications at a rate of 11,5%, associated with a death risk of 1 in 500 insertions in athletes. The number of deaths in structurally normal hearts is increasing and sometimes the diagnosis of an electrical disorder such as WPW syndrome can be seen as an

important achievement, however, the associated risks of an athlete undergoing electrophysiological studies may be higher than the appearance of SCD as the first manifestation of the syndrome. [67]

The American Heart Association and American College of Cardiology have assumed that the practice of competitive sports is possible in athletes with channelopathies, taking proper precautions such as establishing good hydration and electrolytic supply, as well as the existence of well-stablished emergency plans [68]

Knowledge about the consequences of ICD in athletes has improved substantially with the presence of multiple centers with multinational registration. No adverse effects have been reported such as: tachyarrhythmias during or after physical exercise or any type of injury resulting from syncope or shock during sports. This type of information shows that athletes can perform sports without the conditioning related to injury or loss of function of the ICD. [69]

Is sports disqualification the more reasonable way?

The main objective of screening is the identification of underlying cardiovascular disease at risk for SCD, with the aim of reducing the risk through medical procedures and lifestyle modification, such as restriction/disqualification of competitive sports activity. The medical impact of the diagnosis of an unknown cardiovascular disease can be extremely beneficial, however disqualification from competitive sports activity cannot be considered an effective preventive strategy for all athletes. It would be unwise to think that all disqualified athletes will deprive themselves of any kind of physical activity, and knowing that there is no cut-off to consider safe physical exercise, there are reports of athletes who eventually die because they kept exercising against medical advice. [42] [70]

In an analysis of about 184 deaths with HCM, only 19% of deaths were related to physical exercise. In most cases of sudden death during exercise, diagnosis is rarely achieved. In this way, it is extremely important to diagnose this type of cardiac pathology before any fatal arrythmic event, perhaps implementing preventive measures such as ICD implantation. [71]

Furthermore, particular attention should be paid to psychological well-being, which has often been discarded, and which may have important implications in the outcome of medical evaluation. Reporting to an athlete that he has a potentially fatal cardiac anomaly and that needs to be removed permanently from sports is an extremely delicate subject. The risk of psychological morbidity is extremely high in disqualified athletes, as it implies an involuntary change, which many of them are not prepared to take. Involvement of parents, coaches, or other important people in the athlete's life from the beggining can be critical in creating an athlete support network. [70]

Over the last few years, medical practice has allowed greater involvement of its patients in decisions regarding their diagnosis and treatment, leaving behind the traditional approach

where the doctor has the last word. This concept of "empowerment" regarding the eligibility or disqualification of athletes with underlying cardiovascular anomalies has been little explored and its importance undervalued. The goal is to give athletes a central role in a decision that will define their future. It is essential that the accompanying physician gives all information regarding the natural history of the disease, treatment options and knowledge about areas of uncertainty as well as the eventual risk of sudden death, but ultimately the athlete's will should prevail irrespective of the physical and psychological risk due to persistence of the sporting activity or a possible restriction. With this new concept is intended the establishment of a more dynamic and close relationship between the athlete and the medical services, allowing a more continuous follow-up and improve the survival of these athletes in case some more serious event occurs. [72]

Time for action

The implementation of ECG in cardiovascular screening of athletes must be based on the existence of a solid infrastructure composed of physicians trained in sports cardiology, with the ability to interpret an ECG conveniently according to modern athlete-specific criteria.[20] Chandra et al. [28] stated that due to the overlap of alterations between athlete's heart and a pathological condition, it is fundamental that the evaluation of the athletes is performed by sports doctors with experience in dealing with complex phenotypic expressions. The ultimate goal is to create a workforce capable of differentiating whether the findings in an athlete are normal or abnormal. [28] The need and benefits of teaching clinicians was recently proven in a study [30], comparing the answers between primary care physicians and cardiologists regarding ECGs from healthy athletes mixed with ECGs associated with potentially fatal cardiac conditions. In a first phase, physicians correctly categorized 74% of the ECGs and the cardiologists 85%. In a second stage, using ECG interpretation criteria, the ability to properly

recognize abnormal and normal ECGs increased exponentially in both groups with 91% for physicians and 96% for cardiologists. As this study has shown, the existence of more formal training programs will lead to an improvement in the ability to detect abnormal ECG findings.[30]

Despite all the importance given to primary prevention, it is crucial to bear in mind that not all cardiac abnormalities that can culminate in SCD are identified by screening, and that sudden cardiac arrest (SCA) will continue to be part of sporting. In the presence of a sudden cardiac arrest, their survival could be improved by the presence of trained and experienced medical personnel able to recognize these episodes and to promptly initiate cardiopulmonary resuscitation. The creation of an emergency medical plan (EMP) and early access to an automated external defibrillator (AED) may improve the outcome of these SCD episodes in athletes. [28]

A recent study by Drezner et al [73] demonstrated for the first time, an improvement in the survival rate for young athletes who have suffered cardiac arrest if early defibrillation is achieved. Twenty-three of the 36 athletes who suffered SCA (64%) survived including 9 of 14 athletes and 14 of 22 non-athletes. Although it is a retrospective study, it is the first major report to prove that the consistente use of on-site-AED in schools plays a very important role in aborting sudden cardiac arrest.

As long as there are no practical guidelines for SCD, the availability of AED and public access defibrillator (PAD) are two of the most appropriate strategies to reduce SCD in athletes.[74]

Discussion

Sudden death in competitive young athletes has become one of the topics with greater visibility, attracting a great public interest within communities and especially the medical community. There has been a great deal of discussion around the impact on public health and the best method of screening to identify the causes responsible for these tragic events.

Much time has been expended in conducting studies to reach the true values of the incidence of SCD, prevalence of cardiovascular pathologies and their potentially fatal risk, in order to generalize and institute a worldwide practice of protecting athletes. However, there is a large variability in incidence rates due to large differences in the methodology of the various studies, not only in case identification but also in the inclusion and exclusion of cases. SCD rates have varied abruptly, although recent studies [6] with a more consistent and superior methodological quality have found rates ranging from 1: 40000 to 1: 80000 athletes-year. Nonetheless, a true understanding of SCD incidence rates and etiology is critical to ensure efficacy, value, and cost-effectiveness in implementing screening programs in athletes.

The causes of sudden death have been the object of study in the last 35 years, from which time unexplained deaths by internationally renowned athletes began to emerge. Studies in Italy and USA [13] [10] have found that a structurally abnormal heart associated with HCM or ARVD, as well as coronary artery anomalies, would be important causes of SCD. However, a recent study from Denmark [12] have shown different results, reporting that structurally normal or autopsy-negative hearts are found at a similar or sometimes higher rate than previously reported. The latter may make it imperative to carry out studies with standardized autopsy criteria, in order to provide clarification of SCD etiologies and choose the appropriate screening methods.

The goal of screening techniques is the early detection of potentially lethal cardiovascular disorders in order to reduce the risk of SCD. For this to happen, it is fundamental to standardize ECG interpretation criteria in order to homogenize the evaluation of our athletes. The evaluation of electrocardiographic abnormalities that increase the suspicion of potentially fatal cardiac pathology, such as the presence of T-wave inversion in the lateral or inferolateral leads is associated with potential cardiac pathologies such as HCM and ARVC, creating the need for a subsequent assessment through ECHO or CMR. [37] However, not only the athletes with abnormal electrocardiographic findings need a tighter control over their cardiac function and activity. Patients with criteria for isolated left ventricular hypertrophy may be present in <2% of athletes with hypertrophic cardiomyopathy, and special reference must be made in athletes who present a left ventricular thickness between 13-15 mm. In relation to athletes with early repolarization (ER) criteria, despite considered a common finding in athletes (22-43%) [75] and relatively benign, studies have reported an increase in the prevalence of ER in athletes who survived SCA. [76]

However, there is insufficient evidence to confirm that PPS is able to identify athletes who are truly at risk and to prevent SCD. No SCD-related study has shown that a PPS based on H&P can detect athletes at risk and prevent / reduce sudden death. [5] The addition of the ECG to H&P greatly increases the screening sensitivity in the detection of cardiac anomalies, with less false positives rates and increment of cost effectiveness, despite all the criticism. [30] Currently, only the Italian study demonstrated that ECG screening leads to a reduction in SCD. [13] Similar screening studies showed no significant impact in athletes' prognosis, in fact, there is a need for further investigation to prove undoubtedly the increment value of adding ECG to screening protocol.

The main current dilemma is no longer the need to implement a screening program, but rather, what is the most evidence-based protocol, taking into account benefits and risks, cost-

effectiveness and feasibility, leading to an early disease detection to reduce the morbidity and mortality of the athletes.

No screening method is capable of detecting all causes of cardiovascular disease or eliminating all cases of sudden death.[40] Taking into account the information presented in this article, it seems that the ECG is a fast and acessible method to evaluate young athletes, it is cost-effective and has high sensitivity and specificity, which no other screening method has presented until now. One of the main obstacles to definitively generalize ECG screening as a viable screening technique is the costs involved. When the value required for a medical intervention to be successful surpasses $ 50,000 QALY, conducting a national screening program becomes impractical, since after H & P and the ECG a whole secondary evaluation is mandatory to establish a diagnosis and risk stratify. Limitations and obstacles to the inclusion of ECG are legitimate and must not be seen as a door that closes, but as a window that opens with a view to greater sporting responsibility at community and family level.

Despite all the controversy, the need to carry out a H&P oriented to exclude cardiovascular disease is globally recognized. Furthemore, there is an ethical need to inform athletes and their families about the limitations of H & P, moreove, athletes should not be deprived of an ECG or secondary evaluation because of financial reasons. It is therefore vital that universities, secondary schools and sports federations come forward and ensure that their athletes have access to the best screening methods to prevent SCD. In order to uniformize athletes screening, we propose a simple algorithm that uses H&P and ECG as first line risk stratificators and echocardiogram in secondary evaluation. (Figure 8).

The benefits of pre-participation screening go beyond the detection of athletes with inherited heart disease because it triggers a cascade assessment of their family members, allowing them to expand the goal of screening, identifying relatives at risk, and eventually

saving lives. [8]About 30-40% of SCD have a hereditary component, regardless of the presence of structural anomalies. In this sense, it may be necessary to carry out molecular or genetic tests in addition to routine clinical cardiac evaluations in first degree relatives, in order to demonstrate potential complications and risks inherent to these cardiac abnormalities. [77] Genetic tests are especially important in the evaluation of "complex" cases in which the distinction between the athlete's heart and cardiac pathology is difficult with traditional exams.

In the 21st century, tragic events such as those mentioned above, also devastate young people in non-competitive sports such as recreational sport or gymnasium-based sports. Although an increased risk of SCD is documented in athletes participating in competitive sport, it is imperative that sport institutions and communities become aware of SCD risk is not only seen in high-intensity sports. Also, it is necessary to change the paradigm that if an athlete is diagnosed with a potentially fatal cardiac pathology, he / she must necessarily adopt a sedentary life full of restrictions. Perhaps we have invested more time understanding the cardiac conditions that cause SCD, than to ascertain the dangers associated with its diagnosis. [71]

An early study [71] reported that the majority of athletes with a potentially life threatening condition (HCM) die at rest and without any relation to exercise, so disqualification from sports activity seems not to be the answer. The goal should not be to disqualify athletes so that they die at home or when practicing recreational sports. The athletes' opinion, concerns and awareness of the SCD risk shoud also be taken into account in the final medical decision. The concept of "patient empowerment" should be part of the routine evaluation of athletes, since the role of medicine, when there is no consensual diagnostic or treatment approach, is to give information about the causes of the disease and how we can prevent possible consequences to occur, the final decision will be made by the athlete.

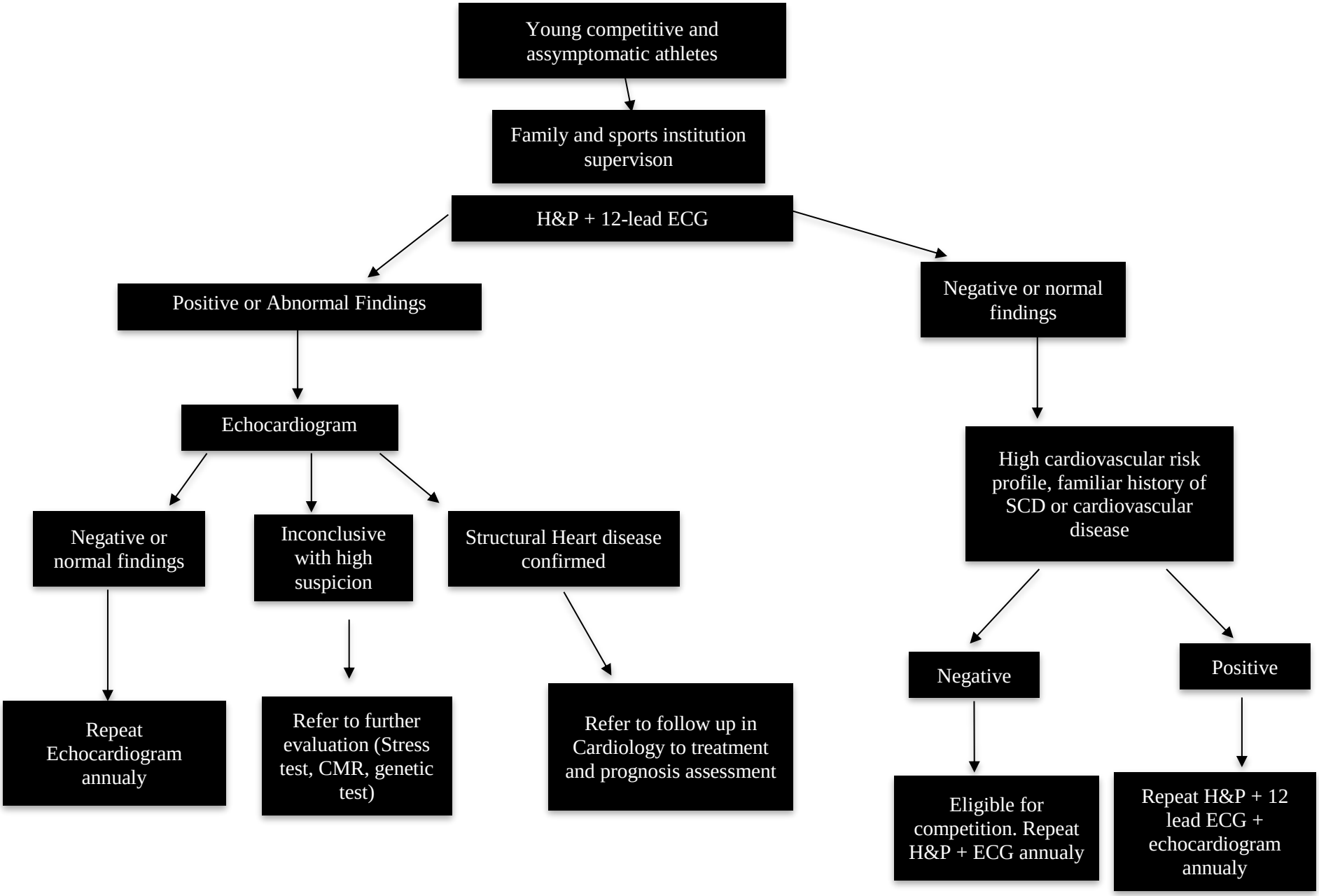

Figure 8: Flowchart providing an algorithm for a sequential evaluation of young asymptomatic athletes, using different screening methods.

Conclusion

Sudden death in athletes is a socially devastating and catastrophic event, associated with a myriad of causes. The PPS was one of the first and most important steps to combat this scourge. Based on all the advances to date, the inclusion of the ECG in the screening of athletes is increasingly a reality adopted by several sports societies. However, there should be a permanent attention to the need to implement national and legal screening programs which should focus on what can really help clinicians improve athlete screening. It could be done through education, infrastructure building and standardization of interpretation criteria to distinguish the athlete's heart from pathological findings.

On July 8, 2017, Abdelhak Nouri, a 20-year-old Ajax player, suffered a sudden cardiac arrest on the field and despite being assisted, the time for his ressuscitation was too long and caused him irreversible brain damage that will prevent him from practicing football for the rest of his life. This is one of many cases that continue to occur in the world of sport, despite the relevance given to PPS techniques whose value remains unclear. Complementary well-defined secondary prevention programs may cover a larger number of athletes and improve their survival.

The financial and social benefits of conducting PPS are very clear and real, it is fundamental to transpose from theory to practice all the knowledge gathered until today, in order to interrupt this gap. It’s also consensual that more data and information is nedded, and the discussion will continue to increase and will remain for many more years, from where no more answers will come, if nobody takes action. [78]

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