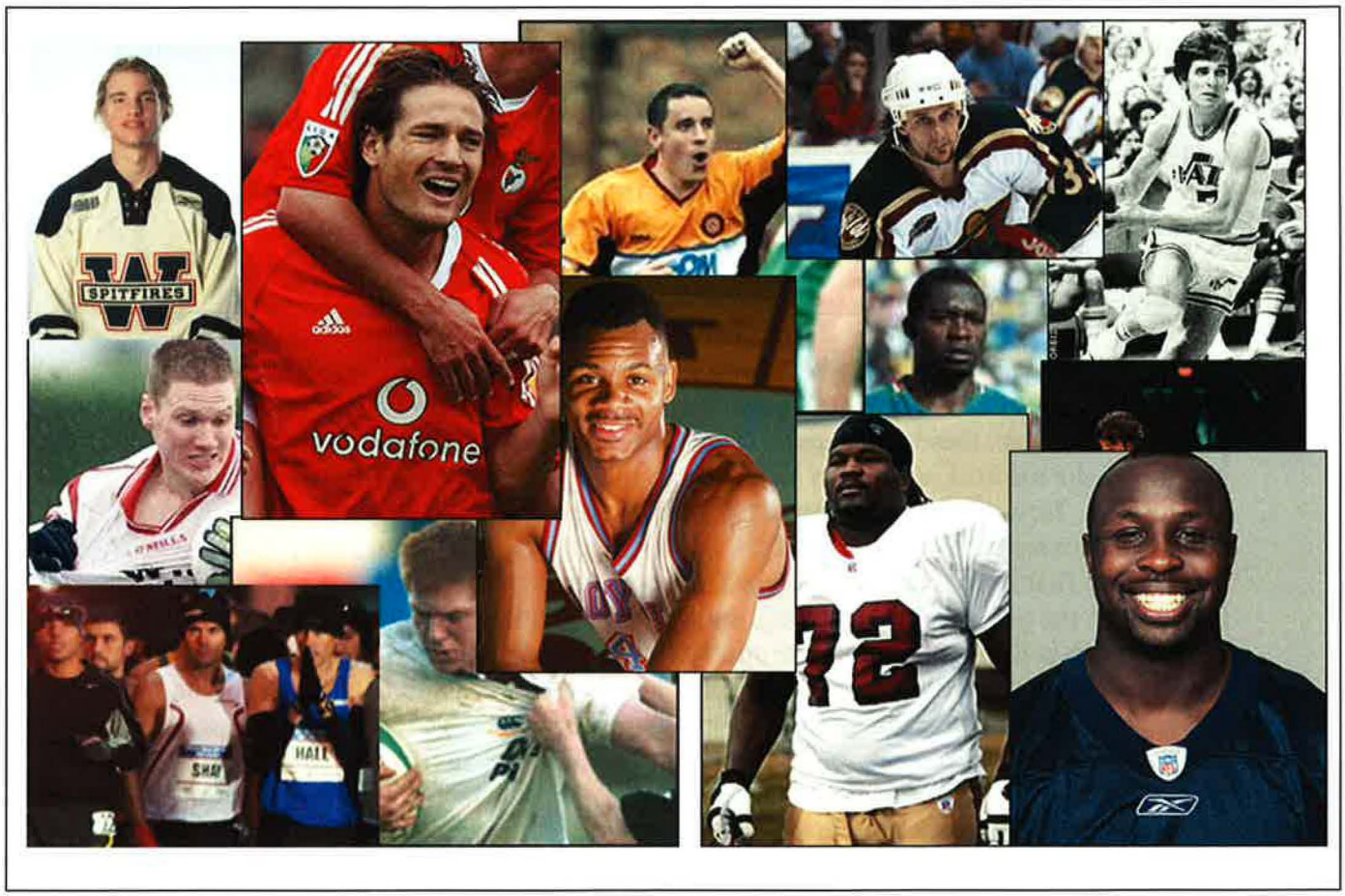
Prevention of Sudden Cardiac Death During Sports Using ECG Screening: Life Saving Preventive Medicine or Ineffective Economic Disaster?



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Introduction

The sudden death of a competitive athlete stirs great emotion among family, fans, and the media. Because such athletes are generally young and vigorous with many years of productive life lost, these unfortunate events have generated powerful interest among the public and the medical profession regarding what could have been done to prevent the catastrophe. However the best paradigm to screen apparently healthy young athletes is highly controversial. On one side of the issue, experts from the American Heart Association first in 1996 and again in 2007 recommended that a 12-point evaluation focusing on the presence of symptoms during exercise and a family history of sudden cardiac death is the most appropriate strategy[2]. Conversely, the European Society of Cardiology has forcefully recommended that an electrocardiogram (ECG) be included as part of the screening process[3]. These divergent opinions have generated an intense, emotive, and at times acrimonious debate[4] among medical professionals and the lay public. Unfortunately, there are no direct comparisons of screening strategies with, vs. without an ECG component. This lack of data is not a minor issue since estimates of the cost of implementing an ECG based screening program in the United States alone have been as high as $2 billion, more than the entire budget of UT Southwestern Medical Center (~1.5 billion), and equivalent to the yearly budgets for NIH Institutes such as NIDDK (~ $2 billion); NHLBI (~ $3 billion) or the combination of NIA/NINDS/NIDCR (~ $2 billion). These costs are staggering given the current debate involving health care access in America. Nevertheless, numerous communities are moving forward with ECG based screening programs despite lack of direct evidence supporting this practice[5]. Given the extraordinary economic and personal cost of such programs as well as the tragic loss of a young athlete, it is essential that high quality objective evidence rather than emotion guide policy.

Causes of Sudden Death During Sports

Sudden death (SCD) during sports has always been a cause for consternation, at least in part because athletes are supposed to represent the healthiest segment of our society. In 1980, Maron et al published the first systematic compilation of sudden deaths in young athletes and demonstrated that the majority are caused by inherited cardiac abnormalities [6]. In the United States, repeated efforts to examine this issue by Maron ([7-9] and others [10] have confirmed this finding. Fig 1 shows the most recent estimate of the causes of SCD in athletes in the US[9], with the most common diagnosis being hypertrophic cardiomyopathy (HCM), and the second being coronary anomalies. A few additional points are worth making: 1) the majority (80%) of these sports related sudden deaths occurred during intense physical exertion, either during practice or competition, though a significant minority occurred at other times (20%); 2) over a nearly 30 year period of tracking SCD during sports, the highest number of absolute events during any given year was 76, with an average of 66/year. By comparison, this number is ~ half the number of people killed in car accidents each day, (takes about 4-5 days to accumulate this number for teenagers alone…) and less than the number killed by lightening strikes; 3) it should be noted that in the US, there is not mandatory reporting of athletic deaths so the identification of cases occurred by systematic examination of media reports, which may underestimate the total number. This underestimation however is likely to be small however and it is safe to say that the absolute number of deaths per year is <100; 4) African-Americans tended to be over-represented in these deaths (36%), especially those with HCM, and women were under-represented (11%)[9]; 5) although the absolute number of participants is hard to determine, reasonable estimates from national sporting organizations, accounting for multiple sport athletes consistently estimates 10-11 million sports participants < 40 years old per year[9, 10]. If these estimates are correct, the incidence of SCD in the most recent 6 years of reporting (2001-2006) was 0.61/100,000 person years.

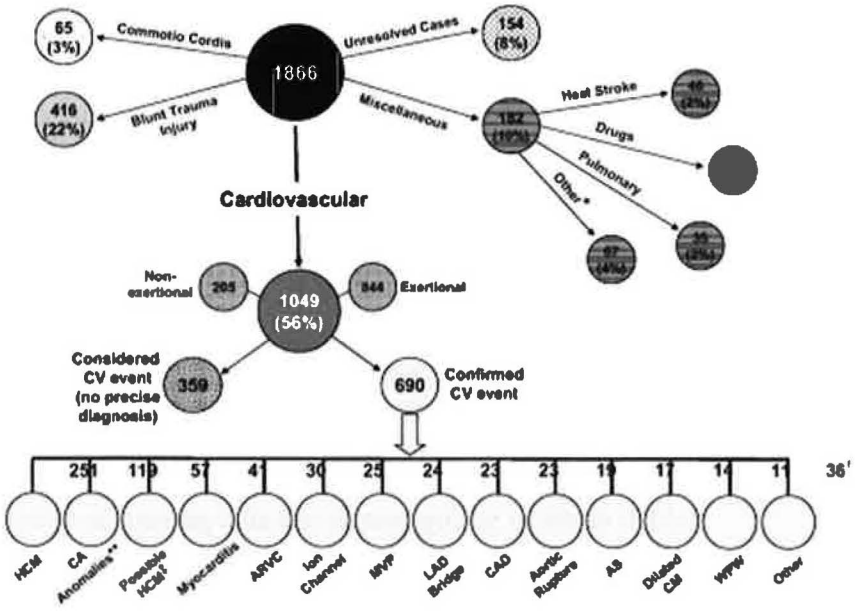

Fig 1 from Maron, 2009

For the sake of this discussion, "young" athletes are defined as those under the age of 35-40. For athletes 40 or over, the vast majority of deaths are caused by coronary artery disease which of course cannot be detected by a routine ECG. Indeed, even the second most common cause of SCD in young athletes, namely coronary anomalies (specifically

the origin of the left coronary artery coming off the right sinus of Valsalva and coursing between the aorta and pulmonary artery) cannot be detected by a resting ECG. It is also important to emphasize that there are many other causes of death during sports that will not be prevented by the use of a screening ECG and that are equally tragic including (but not limited to): comotio cordis, head trauma, intracranial aneurysms, dissecting aortic aneurysms (as a complication of Marfan's syndrome), heat injury, and even sickle cell crisis[9]. The best estimates are that ~25% of all sports related deaths are due to non-cardiovascular causes. [9, 10]

Etiology Varies by Geography

In Europe however, particularly the Veneto region of northern Italy where much of the data regarding ECG screening originates, the etiologies of sudden death in athletes are somewhat different with a much greater presence of right ventricular cardiomyopathy than HCM[11]. The term ARVC was proposed in 1977 and reported to be a cause of sudden death during exercise in the early 1980s[12]. Similarly high numbers of ARVC causing sudden death in young people are also present in other Mediterranean countries such as Spain[13] suggesting that there may be a specific regional genetic susceptibility to this syndrome.[12].

So Can these Conditions Be Detected in Asymptomatic Athletes?

For athletes with known cardiovascular disease, there are extensive guidelines developed over the past 25 years to limit the risk of death during sports [14, 15]. However detecting the presence of potentially life threatening disease in asymptomatic athletes is much more problematic. Indeed, many small screening studies, even using advanced clinical tools like echocardiography have failed to detect significant numbers of athletes at risk.[16, 17]. Most recently, a small cross-sectional study among 510 Harvard competitive collegiate athletes using modern echo techniques identified one patient with pulmonic stenosis which had been detected on physical exam, one with presumed post-viral myocarditis, and one patient with possible hypertrophic cardiomyopathy (0.6% of the total) who were ultimately excluded from sports participation; the total number of false positives was 17% based on ECG findings alone[18].

The Key Components of an Effective Screening Program

The World Health Organization has established the Wilson – Jungner criteria for appraising the validity of a screening programme. These criteria were initially proposed in 1968 and included the following:

The Wilson-Jungner criteria for appraising the validity of a screening programme (WHO 1968)

1). The condition being screened for should be an important health problem
2). The natural history of the condition should be well understood

3). There should be a detectable early stage (*with effective preventive measures/treatments*)
4). Treatment at an early stage should be of more benefit than at a later stage (*with evidence of better outcomes*)
5). A suitable test should be devised for the early stage
6). The test should be acceptable
7). Intervals for repeating the test should be determined
8). Adequate health service provision should be made for the extra clinical workload resulting from screening
9). The risks, both physical and psychological, should be less than the benefits
10).The costs should be balanced against the benefits

In 2003, these criteria were updated (WHO 2003) to include the following:

The condition
1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage. 3.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.
The test
5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested for, should be clearly set out.
The treatment
10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimized in all healthcare providers prior to participation in a screening programme.
The screening programme
13. There should be evidence from high-quality randomized controlled trials that the screening programme is effective in reducing mortality or morbidity.
14. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (for example, Down's syndrome and cystic fibrosis

carrier screening), there must be evidence from high-quality trials that the test accurately measures risk.
15. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
16. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially. and ethically acceptable to health professionals and the public.
17. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
18. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money).
19. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
20. Adequate staffing and facilities for testing, diagnosis, treatment, and programme management should be available prior to the commencement of the screening programme.
21. All other options for managing the condition should have been considered (for example, improving treatment and providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
22. Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.
23. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
24. If screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members.

Let me call your attention to numbers **6, 12, 13, 17, 18, 20, and 22** which are especially germane (and problematic) to widespread adoption of ECG screening for participation in competitive sports.

Italy vs the United States

In 1982, a national screening program was initiated in Italy based on Italian law which mandated that every individual participating in competitive sports undergo a systematic medical evaluation including an ECG based on the ability of the ECG to detect some (but not all) of the conditions primarily responsible for SCD in athletes[1]. The major long term results of this program were published in

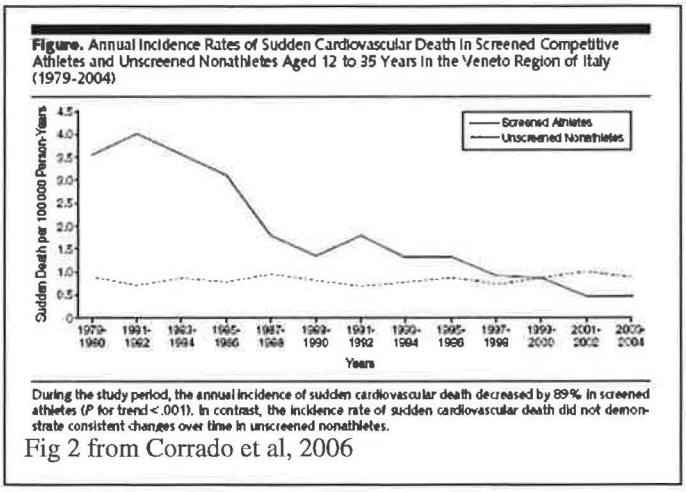

Fig 2 from Corrado et al, 2006

JAMA recently and the authors suggested that the data were compelling in favor of ECG screening reducing the risk of death during sports[1]. The key figure from this paper is reproduced in figure 2. Based on these data, the European Society of Cardiology came out with strong recommendations that the ECG should be a standard component of the pre-participation evaluation of all athletes.[3] Other organizations such as the International Olympic Committee have followed suit[19]despite the fact that screening efforts focused on elite athletes have been particularly unfruitful, perhaps because the underlying cardiovascular conditions such as HCM are not conducive to elite sports participation[20].

However there are numerous problems with this data set that were elaborated in an accompanying editorial by Levine and Thompson[21]: a) it was not a controlled comparison of the screening vs nonscreening of athletes; b) this study did not evaluate the routine use of ECGs compared with more limited screening based on history and physical examination; c) there are important differences in disease prevalence between Italy and other countries; d) the initial rate of death during sports in Italy seems quite high compared to other studies (perhaps due to the unrecognized high prevalence of RVC). Moreover racial differences among athletes from different countries may have important implications for screening tests involving ECG[22] or echo[23]; e) the death rates following implementation of the Italian screening law are actually quite close to those observed in the US without screening[10]; f) the screening of Italian athletes is performed by specifically trained physicians with a specialized skill set; g) 7% false positive rate and 2% disqualification rate are staggering with extraordinary economic implications for larger countries like the United States. It is likely that the desire to reduce risk as low as possible led to the exclusion of athletes NOT at risk; h) risk-benefit ratio of interventions is NOT known in asymptomatic patients. Based in part on these concerns, a task force from the American Heart Association revisited their recommendations for pre-participation screening of athletes, and once again recommended the 12-element history and physical without an ECG (fig 3)[2].

TABLE. The 12-Element AHA Recommendations for Preparticipation Cardiovascular Screening of Competitive Athletes

Medical history*
- Personal history
  1. Exertional chest pain/discomfort
  2. Unexplained syncope/near-syncope†
  3. Excessive exertional and unexplained dyspnea/fatigue, associated with exercise
  4. Prior recognition of a heart murmur
  5. Elevated systemic blood pressure
- Family history
  6. Premature death (sudden and unexpected, or otherwise) before age 50 years due to heart disease, in ≥1 relative
  7. Disability from heart disease in a close relative <50 years of age
  8. Specific knowledge of certain cardiac conditions in family members: hypertrophic or dilated cardiomyopathy, long-QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrhythmias

Physical examination
- 9. Heart murmur‡
- 10. Femoral pulses to exclude aortic coarctation
- 11. Physical stigmata of Marfan syndrome
- 12. Brachial artery blood pressure (sitting position)§

*Parental verification is recommended for high school and middle school athletes.
†Judged not to be neurocardiogenic (vasovagal); of particular concern when related to exertion

Fig 3

Fig4

Box 1 A list of electrocardiography patterns considered to represent a potentially serious cardiac disorder

ECG pattern
- Inverted T waves (more negative than −0.2 mV) in any lead except aVR, V1 and III
- Left ventricular hypertrophy (Romhilt–Estes)
- ST segment depression
- Voltage criteria for increased left atria
- Left axis deviation and one other abnormality
- Pathological Q wave patterns
- Prolonged QT interval
- Epsilon waves
- Right ventricular hypertrophy with ST segment depression in leads V1 to V3
- Complete bundle branch block

It should be noted that the European Society of Cardiology has recently revised their guidelines for ECG interpretation attempting to reduce the false positive rate of ECGs that has been reported to be as high as 40% for competitive athletes in the Italian experience[24]. By excluding athletes

with only voltage criteria for LVH or early repolarization abnormalities from being considered "abnormal", they reduced the false positive rate considerably[25]. A simplified diagram of these modified criteria[26] is shown in fig 4.

As a follow up to the publication of the Italian data, Maron and colleagues examined the SCD rates during sports in Minnesota, which has a population about the size of the Veneto region of northern Italy, with a similar number of competitive athletes[27]. Over the same years of comparison, Minnesota, which uses the AHA recommendations of history and physical exam only, had virtually the same number of sudden deaths during sports as Veneto, Italy (11 vs 12 from 1993 – 2004).

The most recent data (not yet published…) in this debate come from Israel, where following a rash of SCDs during sport in 1995-96, passed a national law similar to the Italians mandating both and ECG and stress testing for all athletes before participation in competitive sports. Dr. Sami Viskin from Tel Aviv has given me permission to present his data to you which I can only show in slide form. These data show that the incidence of SCD during sports for the decade following the implementation of this law was no different than the incidence for the decade following the law[28] providing some counterweight to the Italian data. It should be acknowledged however that both the Minnesota and the Israel case ascertainment was by news reports. Only the Italian data are derived from mandatory reporting of sports related deaths.

Costs of Screening

The last issue that needs to be addressed is the costs associated with screening. These are difficult to calculate since they include not only the cost of the ECG (and its interpretation in a litigious society like the United States), but all the downstream costs of secondary testing including echo, MRI, exercise testing, monitoring, and therapy. Psychological and emotional costs associated with putting large numbers of adolescents and their families through complex and expensive tests are particularly difficult to quantitate. Finally, the end-result of this process assumes that asymptomatic athletes are protected against sudden death

Table 2. Cardiovascular Conditions Causing Disqualification From Competitive Sports in 879 Athletes Over 2 Consecutive Screening Periods (1982-1992 and 1993-2004) at the Center for Sports Medicine in Padua, Italy

Cardiovascular Causes of Disqualification	No. (%) of Disqualified Athletes			P Value
	Total Study Period (1982-2004)	Early Screening Period (1982-1992)	Late screening Period (1993-2004)	
Total No. screened*	42 386	22 312	20074	
Total No. disqualified†	879 (2.0)	455 (2.0)	424 (2.1)	
Rhythm and conduction abnormalities	345 (39.0)	166 (36.0)	179 (42.2)	.13
Ventricular arrhythmias	173 (19.6)	81 (18.0)	92 (21.6)	.20
Supraventricular arrhythmias	73 (8.3)	39 (8.6)	34 (8.0)	.66
Wolff-Parkinson-White syndrome	55 (6.3)	29 (6.3)	26 (6.1)	.88
LBBB or RBBB and LAD	26 (3.0)	8 (1.7)	18 (4.2)	.10
2nd-degree atrioventricular block	13 (1.5)	7 (1.5)	6 (1.4)	.89
Long QT syndrome	5 (0.6)	2 (0.4)	3 (0.7)	.69
Systemic hypertension	205 (23.0)	118 (25.9)	87 (20.5)	.06
Valvular disease, including MVP	184 (21.0)	106 (23.3)	78 (18.4)	.09
Cardiomyopathies	60 (6.8)	20 (4.4)	40 (9.4)	.005
Hypertrophic	30 (3.4)	14 (3.0)	16 (3.8)	.50
Arrhythmogenic right ventricular	16 (1.8)	2 (0.4)	14 (3.3)	.004
Dilated	14 (1.6)	4 (0.9)	10 (2.4)	.21
Coronary artery disease	11 (1.3)	2 (0.4)	9 (2.1)	.06
Other‡	74 (8.4)	43 (9.5)	31 (7.3)	.42

Abbreviations: LAD, left axis deviation; LBBB, left bundle-branch block; MVP, mitral valve prolapse; RBBB, right bundle-branch block.
*All athletes were screened at the Center for Sports Medicine in Padua, Italy, between 1982 and 2004.
†A total of 721 males and 158 females (age range, 12-35 years; mean [SD] age, 18.9 [5] years; median, 17 years) comprised the disqualified athletes for the total study period; 382 males and 73 females (age range, 12-35 years; mean [SD] age, 19.1 [4] years; median, 17 years) comprised the disqualified athletes for the early screening period; and 339 males and 85 females (age range, 12-35 years; mean [SD] age, 18.6 [5] years; median, 17 years) comprised the disqualified athletes for the late screening period.
‡Includes congenital heart disease, vascular disease, rheumatic disease, and pericarditis.

Fig 5: From Corrado et al[1]

at some point in their lives by identifying the conditions associated with SCD during sports. This assumption requires a huge leap of faith in the absence of prospective data because asymptomatic individuals may have a different natural history than those who present to medical attention and whose risk is usually identified in clinical studies. For example, in the Italian data, it is quite clear that over the course of the screening program, patients with RVC were identified and kept out of sport, perhaps with life saving consequences. However a closer examination of some of the other conditions suggests that in fact virtually no patients with long QT syndrome were protected, nor was there a significant reduction in the risk of death from HCM (see figure 5). Moreover, there is the implicit assumption that therapy, such as implantable defibrillators is life-saving in this asymptomatic population. Given the growing awareness of the marked life-long complications associated with implanting these devices in young people[29, 30] this assumption must be tested explicitly before committing a young person to such therapy.

As far as cost calculation is concerned, the AHA panel calculated the cost of implementing an ECG screening program of nearly $2 billion[2]. As noted above, this figure is more than the entire budget of UT Southwestern Medical Center (~1.5 billion), and equivalent to the yearly budgets for NIH Institutes such as NIDDK (~ $2 billion); NHLBI (~3 billion) or the combination of NIA/NINDS/NIDCR (~ 2 billion). These costs are staggering given the current debate involving health care access in America. More recently, a group at Stanford has attempted a more sophisticated cost-benefit analysis of such a screening program[31]. Many of the cost and outcome assumptions associated with this analysis are highly debatable (i.e. $5 for an ECG, and $171 for an echocardiogram). Most importantly, although the authors claim a cost effectiveness ratio of $43,000 per life-year saved (using a very high threshold for assuming a "positive ECG"), they still calculated a total incremental cost of performing an ECG as part of a screening strategy of $737 million assuming screening of 3.7 million athletes (and assuming a single life-time screening per athlete of only high-school and collegiate athletes). For more realistic costs associated with these tests, and applying it to the entire population of ~10 million young athletes, these costs approach the $2 billion predicted by the AHA panel, and pushed the cost effectiveness ratio to $174,000 per life-year saved[31].

Final Thoughts

The best approach to screen young athletes to prevent sudden death during competitive sports is a hotly debated topic that will continue to generate controversy until definitive, prospective studies are performed. It is important to emphasize that even if disease is identified in asymptomatic individuals, it is a huge leap of faith, and quite paternalistic to exclude such individuals from participation in sports with the assumption that we are preventing them from adverse events. Particularly for older athletes, we have argued that the right of any athlete to assume risk, especially unknown risk, should be left to discussions between the physician, the athlete, and the family[32], though others have argued strongly otherwise[33]. Recent unpublished data from the NCAA (Dave Klossner, Ph.D., personal communication) emphasize clearly that the largest number of student-athlete deaths are caused by accident and trauma – not death on the playing field. Indeed, if deaths in the course of transportation to competitive events are considered as "sudden

death during sports", it is clear that public health dollars would be better spent improving the safety of transportation for young athletes rather than on ECG screening and its consequences.

It is clear that ECG screening can certainly aid in screening athletes, and will prevent some sudden cardiac deaths. Any athlete who wants the security of a screening ECG and is prepared to accept the downstream work up that may ensue should have every right to ask for one to be performed by their primary care or screening physician, and pay for it out of their own health care dollars. However mandating ECG screening for all athletes represents a huge societal burden and ignores the fact that: a) many athletes who would never have a problem are excluded; b) the cost (both financial and psychological) of screening large populations where most abnormal tests will be "false positive" may be quite large; and c) the outcome of disease intervention in asymptomatic patients is not as clear as we would like it to be, and d) all deaths cannot be prevented.

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