ECG Screening for Sudden Cardiac Death in Children and Adolescents: Is it Money Well Spent? Is There an Optimal Age for Screening?

Running title: Saul et al.; ECG screening for SCD in children

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Journal Subject Codes: [5] Arrhythmias, clinical electrophysiology, drugs; [121] Primary prevention; [171] Electrocardiology; [41] Pediatric and congenital heart disease, including cardiovascular surgery; [100] Health policy and outcome research

Key words: cardiomyopathy; Editorials; pediatrics; QT interval electrocardiography; screening; sudden death
Sudden cardiac death (SCD) in otherwise healthy children is tragic. Increasing attention has been paid to preventing these untimely events, particularly with regard to cardiac causes, as these are the most common, though not the exclusive causes. Interest has centered around sports participation, as about 25% of such events occur at this time\(^1\), and the use of ADHD medication which may or may not precipitate SCD in susceptible individuals. A recent NHLBI panel evaluated the evidence base for addressing the prevention of SCD, and found too many gaps in evidence to formulate general recommendations for SCD prevention in the young\(^2\). Particular concerns surround lack of knowledge of the true incidence of SCD, absence of a pilot ECG screening program to test the effectiveness of various screening methodologies, identification of the most effective screening strategy (the most useful screening method, and selective screening in high risk individuals vs. universal screening at a specific age), and limited knowledge of the impact of a screening program on the both the quality of life and clinical outcomes of the asymptomatic individuals and families screened. The report states “before a significant public health investment is made in large scale ECG screening, it would be ideal to empirically demonstrate a link between screening and improved health outcomes.”

To fill a critical gap in the evidence, Leslie and colleagues\(^3\) have performed a detailed analysis of the cost and benefits of combined history, physical and electrocardiographic (ECG) screening for the more common causes of sudden cardiac death (SCD) in children age 8, who are initiating stimulant therapy for attention deficit hyperactivity disorder (ADHD), and adolescents age 14, who are participating in high school sports. Although their analyses and algorithms are necessarily complex, they have attempted to focus the problem by limiting screening to the two time points and populations described above, and prevention of SCD from 3 conditions: hypertrophic cardiomyopathy (HCM), Wolff-Parkinson-White syndrome (WPW) syndrome, and
the long QT syndrome (LQTS). These restrictions were used not only to simplify the analysis and interpretation, but also because they are the most common causes of SCD in childhood. The data available to parameterize the model is much more robust than for other rarer conditions. In contrast to some previous analyses in overlapping populations, the investigators found that the incremental cost-effectiveness of screening was high at between $91,000 (age 14 screening) and $204,000 (age 8 screening) per life-year saved. The estimates were most sensitive to the following parameters: disease prevalence, baseline mortality, and the relative risk of mortality due to stimulant medication use and sports participation.

The authors are to be lauded for addressing the many complexities of screening in their model. One strength of the study is the use of ranges of estimates for many of the model parameters. This overcomes the problem of picking a single, potentially incorrect, value and provides a range that can provide guidance in the absence of complete outcomes data. The authors have been reasonably conservative in estimating the parameters for their model. However, they have not included estimates of increased non-cardiac causes of mortality in untreated ADHD patients. If included, the true cost of screening might be considerably higher than the estimates Leslie et al.3 derived. For instance, the results for the ADHD stimulant population are highly dependent on the presumption that mortality is increased by stimulant therapy (relative risk > 1.0); however, the literature suggest this may not be true4-6.

For LQTS, the authors have used a low prevalence rate for LQTS of 7/100,000 as the central parameter for their model in 14 year olds, significantly below what may be the best data from Schwartz et al.7, who estimated a prevalence in neonates at about 1/2500 (40/100,000). The important point here is that the estimate in 8 and 14 year olds may be appropriately low, because
by the age of 8, many, if not most LQTS patients who will present in childhood have either presented with disease or died as a consequence of it.

### Screening for LQTS in Neonates

An alternative age to screen for LQTS is infancy. Based on molecular autopsy data, about 10 to 15% of Sudden Infant Death Syndrome (SIDS) deaths are due to LQTS \(^8,9\). The rates of SIDS are carefully tracked by almost all developed countries, and vary from about 0.7-1.0/1000 \(^10,11\). The rate of unexplained SCD secondary to LQTS alone in the infant population would thus be about 0.1/1000 (10/100,000), which is between 2 and 12 times the total SCD rate estimates for children 1-18 years of age in the United States (0.8 to 6/100,000) \(^3\), about 5 times the rate in NCAA athletes (2.3/100,000), and comparable to the highest risk NCAA group of basketball players (8.8:100,000) \(^12\). These infant data also suggest that almost as many infants have SCD from LQTS alone each year (about 400) as all school age children from all other causes (500-1000).

The value of ECG screening in the neonatal population has been addressed prospectively as well in two different Italian studies \(^7,13\). Taken together, the data from these studies plus the available literature suggest that most of the LQTS cases which lead to SIDS can indeed be identified by ECG screening performed during the neonatal period; however, the best methodology and age (0-2 days vs. 14-28 days) for screening remain unclear. Additional questions important for a neonatal ECG screening program are related to effectiveness and cost in preventing SCD during infancy and later in life. A cost-effectiveness analysis using the data from the Italian studies \(^7,13\) estimated a relatively low cost per life-year saved at 11,740 Euros (about $17,000) using health care cost estimates from the Italian National Health System \(^14\). Although there are a number of issues in this analysis which have been questioned due to
potential cultural and cost differences in the United States compared to Italy and Europe\textsuperscript{15}, the cost estimate is far below that estimated by Leslie et al \textsuperscript{3}, and well below the usual cutoff for a screening or therapy to be considered effective.

**HCM in Adolescents**

HCM in the United States \textsuperscript{16} and ARVD in Italy \textsuperscript{17} are the most common cardiac findings in adolescents and young adults with SCD, are rarely a cause of SCD under the age of 12 years, and can be identified with ECG screening or clinical findings in these age groups. These observations support the findings of Leslie et al \textsuperscript{3} that screening at age 14 is closer to being considered cost effective. A complicating issue is that the literature suggests that the prevalence of HCM may be as high as 1 in 500 \textsuperscript{18}, and yet the rate of SCD in adolescents from HCM is on the order of 0.3/100,000/year. \textsuperscript{16} Thus, for every 600 identified cases of HCM in late adolescence only 1/year is destined to die from SCD during adolescence. If screening took place at age 14, for every 600 HCM patients identified, a total of 8 will have SCD (1.3\%) by age 21 (1/year for 8 years). If case finding is that high, it is critical to determine the financial and personal cost of restricting and treating 77 cases of HCM who will never have an event for every one case that will.

**The Health Effects of ADHD Therapy and Sports Participation**

A further limitation of the debate relates to the potential health benefits of both ADHD medication and sports participation. The current debate on ADHD medication and potential cardiac complications has not generally accounted for all cause morbidity and mortality related to ADHD in the absence of stimulant medication use. For example, children and adolescents with ADHD are at increased risk for general trauma and being involved in auto accidents, risks which are significantly higher than cardiovascular event rates, and are known to be substantially
reduced with treatment \textsuperscript{19-21}. Thus, not treating a significant percentage of children who meet indications could lead to significantly increased non-cardiac events not only in ADHD patients, but also in the “bystanders” impacted by the higher rate of serious accidents, perhaps much greater than the lives saved by not prescribing the medication.

A focus on screening sports participants could indirectly limit participation in these activities and deflect from other more prevalent public health issues. Risk of sudden death on the athletic field is a much smaller problem than the current obesity epidemic. A general increase in sports participation or physical activity may have a larger health benefit than the potential rare sudden event related to this participation \textsuperscript{22}. From a public health standpoint, with a smoking prevalence of 15\%, for every 100,000 children screened about 15,000 will become smokers, preventing 10 of these from smoking will add about 70 life years. (http://www.cdc.gov/Features/YouthTobaccoUse). Both tobacco use and obesity are associated with sudden death in adults \textsuperscript{23,24}.

**Other Possible Prevention Strategies**

Identification of high risk individuals is an important medical strategy; however, a population based prevention strategy for sudden death could also be considered. For example, placement of defibrillators in schools may provide emergency treatment for many affected children and have the added benefit of providing a lifesaving treatment for adults as well. Currently, many more adults are resuscitated in schools with defibrillators than are children \textsuperscript{25}. Since many of the conditions under consideration are genetic, cascade screening of families of resuscitated children could also be initiated leading to more efficient case identification.

In summary, Leslie et al \textsuperscript{3} have filled a critical gap in the evidence for screening to prevent SCD in children and adolescents, particularly by demonstrating the high cost of currently
proposed prevention strategies. Preventing a significant portion of SCD in the young might require: 1) a neonatal screen for primary arrhythmia conditions like LQTS, as opposed to screening selectively the population who require ADHD medications, and 2) a universal adolescent screen to identify the ECG abnormalities present with structural heart disease, rather than a selective screening of sports participants. Before embarking on such a strategy, further research to fill in evidence gaps identified by the recent NIH report is critical. We have tried to emphasize the larger context that needs to be considered in approaching this issue, including discussion of the best age to screen, the health benefits of ADHD medication and sports participation, and the potential role of effective treatments at the point of SCD events as an alternative to incurring the high costs of screening.

Conflict of Interest Disclosures: None

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Circulation. published online May 3, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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