There have been many technical and pharmacological advances in the prophylaxis of cardiac arrest in recent decades. In adult patient populations, these advances have been complemented by many methodologically rigorous studies defining the risks of sudden cardiac arrest in targeted and epidemiologically well-defined study groups, most of which have identified cardiomyopathy (ischemic, dilated, nonischemic, or hypertrophic). This knowledge base has allowed a broad, evidence-based consensus to emerge in the form of policy guidelines regulating clinical practices aimed at reducing the risk of fatal cardiac arrest in adults with identified heart disease. By and large, those adults are identified by a program of primary-care surveillance for atherosclerotic disease consisting of well-defined management plans aimed at both preventing disease onset and progression and evaluating adults with potential cardiac symptoms.

The same is not true for apparently healthy pediatric patients. Children without known cardiovascular disease experience death from sudden cardiac arrest at rates several orders of magnitude lower than older populations with acquired heart disease, with estimates of incidence in the range of 0.5 to 4/100,000 children per year. The diseases principally responsible for these events, including hypertrophic cardiomyopathy, long QT syndrome, anomalous coronary arterial anatomy, and Wolff-Parkinson-White syndrome, are all rare causes of sudden death in adult populations, in large part because of the much higher prevalence of other diseases. Thus, risk models derived from adult populations are not clearly applicable to pediatric and adolescent patients without acquired heart disease. Although rare, sudden death in a child is a tragic and highly public event and results in a disproportionate number of years of healthy life lost. Accordingly, it is of considerable interest to society to determine whether a screening strategy can efficiently and effectively identify potentially affected children before their first cardiac event.

In this issue, Denchev et al use Markov modeling and Monte Carlo simulation techniques to perform a hypothetical cost-benefit analysis of one such screening approach. In particular, they attempt to address worries that the medical use of stimulant medicines has resulted in an excess number of sudden deaths in recent years. Such medicines are widely prescribed, with \( \approx 15 \) million prescriptions per year in the United States, but the epidemiological data obtained to date in postmarketing studies have failed to reliably identify an association or to prove the converse. Decision analysis would seem to be an ideal technique to clarify the issues in this case, and the authors’ question is simple: Is it cost-effective to perform cardiovascular screening for occult disease in healthy children who have been prescribed stimulant therapy for attention deficit hyperactivity disorder (ADHD)?

The components of the analyses that naturally develop from this question are far from straightforward. The authors have constructed a rigorous and well-reasoned model and have worked diligently both to find the best estimates available in the literature for population of the model parameters and to recognize some of the uncertainty inherent in some of those assumed parameters. Importantly, in addition to the effects of ADHD medications and the benefits of medical therapy for identified disease, the authors have included in their model additional beneficial effects realized by limiting sports participation in patients with heart disease. Much more on this critically important modeling decision is given below.

Their results include the following findings. First, cardiac screening of pediatric patients in this model is likely to be a cost-effective intervention if the societal acceptable cost threshold is $50,000 per quality-adjusted life-year. Second, history and physical examination screening are of negligible or even negative value in achieving this end; ECG screening will be almost identically sensitive and significantly more cost-effective. This is good news, but there is a catch: The model as it has been constructed is almost completely insensitive to the effects of ADHD medication on sudden death. In fact, the authors remark that setting the effect of medications to 0 (ie, stimulants caused no increase in sudden cardiac arrest) still yields a finding of cost-effectiveness of ECG screening. Absent any effect of stimulants on the incidence of cardiac arrest, a positive finding from the model suggests that any randomly selected group of patients—and not just those taking ADHD medications—would benefit from screening. If modeling the population effects of stimulant medication prescription is the whole point of the model, how can this be the case?

The most important data in this type of modeling exercise are the parameters used to populate the model, and careful assessment of their validity is fundamental to assessing the ranges and meaning of predicted outcomes. Parameters that
are well supported by published data form the foundations of the analysis; those for which values are poorly documented or pure expert guesswork should become the domain of explicit sensitivity analysis in which the effects of different assumptions on the outcome predictions of the model can be tested and demonstrated. This approach can be of enormous value for identifying and prioritizing gaps in our knowledge and determining the potential value of answering various questions about the populations and processes under study.

Parameter values that would enjoy a wide consensus on their accuracy and “reasonableness” in this case include the prevalence of occult heart disease in apparently healthy children and the cost of diagnostic procedures and encounters (chosen as the US Medicaid reimbursement rate). The sensitivity and specificity of diagnostic testing to identify these diseases in population screening are less well established and have somewhat broader margins of uncertainty. By far the biggest unknowns in this study, and those on which the model predications in fact hinge, are the pathophysiological effects of ADHD medications and athletic participation on the incidence of cardiac arrest in children who are intrinsically at risk.

As mentioned above, the epidemiological link between ADHD medication use and sudden death is unclear. What is known is that these medications cause small but significant increases in heart rate and blood pressure, by direct effect and/or by sympathetic activation. This in turn may be (and has been) hypothesized to predispose affected patients to cardiac events by promoting arrhythmic triggering events, altering myocardial electrophysiology, and/or reducing the physiological tolerance for otherwise self-terminating arrhythmias. The authors have made the assumption here that use of ADHD medications increases the low likelihood of cardiac arrest by a very modest 10%. Although this may be a reasonable estimate of ADHD drug effect, 1 case-control study suggests the possibility of an increase in risk with medication much greater than this, almost an order of magnitude greater than baseline. The authors have performed a formal sensitivity analysis of this parameter and demonstrated that, as expected, increasing the likelihood of adverse treatment effect also increases the cost-effectiveness of screening for the occult risk factor.

The link between sports participation and cardiac arrest in healthy children is somewhat more well established, with studies clearly suggesting that childhood cardiac arrests in modern societies can be correlated in some concrete ways with athletic activity. Unfortunately, although it may therefore seem like clinical “common sense” to prohibit sports for these patients, the extent to which we can prevent cardiac arrests in this manner and the countervailing costs of trying to do so are unclear. In the accompanying study, the parameter describing the importance of this intervention is derived from a single source, a regional Italian study by Corrado et al that developed a risk model for cardiac arrest in young adults demonstrating more frequent and early events in those who participated in competitive athletics. It is important to ask whether this parameter accurately or even realistically quantifies the beneficial effect of sports restriction. Thus, focusing some attention on the details of this study is critical to placing these findings in context.

The Corrado et al study was a clinicopathological analysis of long-term trends in sudden cardiac death in northeast Italy that identified the specified increased risk in athletes. There were 55 deaths among the 112 000 predominantly male athletes who were identified among a total of 1.4 million individuals ranging between 12 and 35 years of age. They ascribe competitive athletics a relative risk of 2.5 for cardiovascular causes of sudden cardiac arrest. The participation rate in athletics in this population was low (≈9%); in fact, most sudden deaths occurred in nonathletes. Subsequently, this investigative group identified the institution of centralized, universal cardiac screening program as the likely factor causal factor in a dramatic long-term decrease in the number of sudden deaths in that country experienced by young people.

Although these are significant findings, the causality of this association and the possibility of other unidentified contributing trends to this epidemiological observation fairly remain a matter for debate. Certainly, they are not adjusted for the effects of regular exercise on long-term risks of coronary disease, diabetes mellitus, and obesity, diseases for which childhood exercise may promote long-term benefits even while transiently increasing the risk of events for selected individuals. Of even greater importance in this case is the generalizability of these data and their specific applicability to the relevant population from the United States posited in this model. In Denchev and colleagues’ model, that population is younger, and American children are more likely to participate in sports and to have a different epidemiological pattern of heart disease than that seen in young Italian men. Additionally, the present model accepts that ECG screening alone is the source of case finding, whereas the Italian model uses physicians to perform a targeted annual preparticipation history, physical, and individually reviewed ECG, with additional testing readily available. In the Italian series, 4 of the 5 diseases with the highest relative risks (arrhythmogenic right ventricular cardiomyopathy, occult atherosclerotic disease, congenital coronary anomalies, and mitral valve prolapse) typically have normal resting ECGs, particularly in young people. The Italian approach does seem effective in identifying hypertrophic cardiomyopathy, but interestingly, the contribution of hypertrophic cardiomyopathy in young Italians to total cardiac arrests has been low, whereas it is the most common cause of unexpected death with athletics in the United States. In addition, although the Italian screening approach does identify ECG-targeted diseases such as Wolff-Parkinson-White and long QT syndromes, those diseases were notably rare in the athletic risk group, possibly because they had already been treated or excluded.

Based on the findings of the Corrado et al study, the present model assumes that the incremental adverse risk of sports participation for affected individuals is nearly 20 times greater than that modeled for medication effects in the median case (280% versus 110% risk increase for sports participation compared with ADHD medication use). The importance of sports restriction in this model can alternatively be compared with the assumed benefits of all forms of active treatment. This includes the use of β-blockade, ablation, implantable cardioverter-defibrillator therapy, surgery,
etc, which in combination are assumed by the model to lower the annual risk of death due to cardiac arrest from 1.5% to 0.97%, a reduction of \( \approx 35\%\). Thus, restriction from sports in this model is considered to be approximately twice as effective (and in the minimal modeled case, equally as effective) in reducing the likelihood of sudden death as all targeted medical therapies. It is clear that this parameter as selected is prone to become the principal driver of the findings of the model constructed so carefully here. We believe that this particular model choice is the “elephant in the room” in the present study, and given its large value relative to that proposed for the effect of medication, it is no surprise whatsoever that the effect of sports participation swamps the resultant analysis.

This is unfortunate. ECG test characteristics for the specific diseases of interest (Wolff-Parkinson-White, long QT syndrome, and hypertrophic cardiomyopathy) can be defined from the literature. Once these diseases are identified, many effective therapies and management strategies for risk reduction can be applied to patients with various identified disease, ranging from \( \beta \)-blocker therapy to ablation to implantable cardioverter-defibrillator therapy. Individualized plans can be made for sports and recreational activities. The authors propose a follow-up study on the value of screening before athletic participation. We believe that that would be appropriate and would, we think, highlight the great importance of establishing a complete and inclusive range of estimates for the adverse effects of sports participation on cardiac mortality in young people in American society. Importantly, such a study would also help to determine whether strategies of universal screening and/or screening targeted to athletes fall into the realm of cost-effective strategies according to current societal values.

With respect to the present study, it seems to us that the authors have concluded that even if the effect of ADHD medications themselves is small, the incidence of preventable cardiac arrest is sufficient to warrant screening and the principal benefit of this activity would be the incidental identification and restriction from athletic activity of children at risk. We are not certain that they have examined a complete range of plausible drug effects in their sensitivity analysis, and the conflation of this study with the question of sports participation confuses rather than clarifies the issue of ADHD as a standalone indication for screening. However, this is clearly an important first step to answering some contentious questions that are not easily addressed by direct observational studies and analysis of population-wide mortality and that will nonetheless have direct effect on pediatric public health policy.

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References

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Needle in a Haystack: Modeling the Incidence of Sudden Cardiac Arrest in Healthy Children

John K. Triedman and Mark E. Alexander

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