sinus node dysfunction. Second, total power (i.e., a quantitative measure of heart rate variability) was similar both in patients with early recurrence and in subjects who maintained sinus rhythm.

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**Over-AVID Subgroup Analysis**

Given the extensive time, effort and expense involved in performing large-scale clinical trials, there is a natural tendency to perform subgroup analyses on the accumulated data subsequent to termination of the trial. Assmann et al. (1) recently stated: “Subgroup analyses are particularly prone to overinterpretation, and one is tempted to suggest “don’t do it” (or at least “don’t believe it”) for many trials, but this suggestion is probably contrary to human nature.” The report by Hallstrom et al. (2), a subgroup analysis of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial (3), falls into the category of “don’t believe it.”

The hypothesis of this substudy is reasonable—there may be subgroups of AVID patients who do not benefit from an implantable defibrillator as opposed to amiodarone therapy. Based on their data, the authors (2) conclude that the lowest-risk sextile is a subgroup in which implantable defibrillators may not offer benefit. However, this conclusion is faulty as the design of this substudy forces the outcome to be negative.

The AVID trial (3) evaluated whether the strategy of antiarrhythmic drug therapy versus implantable defibrillator therapy is better for treating patients with hemodynamically significant ventricular tachycardia or ventricular fibrillation. In designing the study, the investigators (4) concluded that a sample size of 1,200 patients was required to demonstrate the predicted benefit. The trial was terminated early, after only 1,096 patients were enrolled, because the analysis revealed that the difference in the primary outcome variable had crossed the statistical boundary for early termination. In the current report (3), the analysis of relative benefit between antiarrhythmic drugs and the implantable defibrillator relies on a sample size that is one-sixth the total sample size of the AVID trial. In addition to the small sample size, the subgroup being investigated is the group of patients in which the event rate and mortality is lowest. In subgroups with lower event rates, the difference between event rates in the two treatment groups typically decreases and a larger sample size is required to demonstrate that the difference is significant. It is misleading to suggest that one could demonstrate a difference in survival in the lowest-risk sextile with the sample size that is available.

Study sample size is typically chosen so that the power of the study or the probability of detecting the postulated difference is high, typically in the 80% to 90% range. The calculated power of this AVID substudy is 5.5% (calculated using a sample size of 106 patients, two year mortality of 11% [which was the observed mortality], a 25% reduction in mortality to 8.25% by one of the treatments), a value substantially less than the 80% to 90% value used in designing a trial. This means that there was only a minimal chance that this report could have demonstrated a difference between the two therapies even if implantable defibrillators or amiodarone reduced mortality by as much as 25%.

These substudy results should be interpreted as inadequate to answer the question posed by the investigators. The data are consistent with no benefit of implantable defibrillator over amiodarone therapy, with a benefit of implantable defibrillator therapy over amiodarone therapy and with a benefit of amiodarone therapy over implantable defibrillator therapy. In contrast, the clinical characteristics that identify the low risk sextile are interesting. A suggestion that the cost-effectiveness in this low risk sextile may be less favorable than in the other sextiles may also be valid. However, only properly designed clinical trials will be able to address the question of which therapy is appropriate or better in patients who have a low arrhythmia risk. Until such studies are performed, one can only conclude based upon the AVID trial that the strategy of implantable defibrillator therapy has a survival benefit compared to the strategy of antiarrhythmic drug therapy (amiodarone) in patients who have suffered either ventricular fibrillation or hemodynamically significant ventricular tachycardia.

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**REPLY**

We agree with Goldberger et al. that subgroup analyses are prone to overinterpretation. One must be very cautious in dealing with subgroup analyses, particularly when they are post hoc (ours was a priori), based on essentially randomly defined subgroups (ours was
based on a prespecified mechanistic “dose response” relationship, and the result is based on lack of significance (if our null hypothesis had been that there was no treatment effect in the lowest sextile, not being able to reject the null would probably be a low-power issue [Goldberger et al.’s power calculations are, in fact, based on this null hypothesis]—however, our null hypothesis was that the treatment effect would be the same in all sextiles, and we were able to reject this null hypothesis with an, admittedly marginal, significance of 0.05).

Thus, while we would not disagree with Goldberger and colleagues’ caution “don’t believe it,” we might also caution “don’t disbelieve it.”

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Congenital Coronary Artery Anomalies: Diagnosable, Premortem?

Dr. Pelliccia’s recent sage editorial comment on congenital coronary artery anomalies (CCAA) (1) establishes an authoritative impetus for the creation of an international registry of youths with CCAA concomitant with a researched analysis of their clinical profile and mode of noninvasive identification. The enormity of this challenge is well appreciated on learning that in 20% of cases wrong sinus coronary malformations are implicated as the cause of catastrophic unexpected death in young people on the athletic field.

Dr. Pelliccia’s summaries of the admirable presentation by Davis et al. (2), and his citations of the literature review and conclusions of Basso and colleagues (3), instill in the undersigned a warranted enthusiasm and expectation for the noninvasive clinical and electrocardiographic identification of wrong sinus coronary artery anomalies, as has been accomplished for individuals with an anomalous left coronary artery from the pulmonary trunk. Both studies emphasize the importance of a history of exertional chest pain or syncope as a marker of potential sudden death, alerting physicians to the possibility of CCAA in the young athlete. In their report, Basso et al. (3) determined that 37% of the competitive athletes were asymptomatic antemortem, and in their literature review of patients with CCAA (among both athletes and nonathletes), Basso et al. found 94% of subjects were symptomatic, and, most importantly, 72% complained of angina, syncope, or dyspnea, on exertion. In this study cohort of young competitive athletes dying suddenly, we are informed that a premortem electrocardiogram (ECG) was normal in all but two of nine patients; however, the configurations of the ventricular ectopy demonstrated by the two Italian professional athletes were unfortunately not clarified (3). In their literature search of the 18 patients under 35 years of age, Basso et al. showed that the ECG was reportedly abnormal in 50% of patients and the stress test positive in 22% (3).

In the four patients identified by Davis et al. (2), two possessed abnormal electrocardiography, one demonstrating ventricular ectopy of right ventricular origin. Sudden death in these patients is presumably due to ventricular tachyarrhythmia, consequent upon vasospasm induced by endothelial injury, or an electrically unstable myocardial cicatrix. The athlete with an anomalous origin of the left coronary artery from the pulmonary trunk is much more readily

![Figure 1. Anomalous origin of the left coronary artery from the pulmonary trunk. Q-waves and biphasic T-waves in the anterolateral leads I, aVL, V4, V5, and V6, suggestive of anterolateral injury in a 14-year-old male Caucasian. Negative U-waves are graphed and there is ST segment elevation in lead V4. Kindness of Dr. Gary Webb, Director, Toronto Congenital Cardiac Centre for Adults, Toronto General Hospital.](image-url)