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AMISTAD Trials: Possible Reasons for Lack of Success

Results of the Acute Myocardial Infarction STudy of ADenosine (AMISTAD II) trial were recently reported by Ross et al. (1). As in the AMISTAD I trial (2), most of the conclusions were at best equivocal, although subgroup analysis each time suggested adenosine might be useful as an adjunct to reperfusion therapy in certain patients with acute myocardial infarction. Thus the hope was raised that a more targeted trial might yield a significant difference between placebo and treatment groups. Although this possibility is real, we would like to offer an alternative hypothesis. Contrary to the twice-repeated assertion by the investigators that “adenosine...has consistently provided myocardial protection from ischemic injury in animal models,” the ability of adenosine administered at or shortly before reperfusion to provide cardioprotection against infarction is indeed quite controversial. There are certainly some studies which report that adenosine at reperfusion can decrease infarct size in various animal models, and some of these experimental investigations are acknowledged by Ross et al. (1). However, it is notable that two of the references cited by the researchers to justify their conclusion have been misquoted. Yao and Gross (3) and Thornton et al. (4) found protection when adenosine or an adenosine agonist was used as a preconditioning agent.

Furthermore, Thornton et al. (4) actually observed that when N6-(2-phenylisopropyl) adenosine (PIA) was infused at reperfusion, it had no cardioprotective effect despite its effectiveness when applied as a pretreatment. Also, numerous other preclinical studies have been unable to document an effect of authentic adenosine (5–8) at reperfusion on infarct size. Therefore, it is possible that both the inability to demonstrate a significant effect of adenosine at reperfusion in patients and the inconsistent preclinical results are because adenosine given at reperfusion simply does not protect the heart.

In the two AMISTAD trials it was reported that infarct size was significantly diminished in those patients with anterior wall myocardial infarction who were treated with adenosine. Although this observation is potentially important and noteworthy, a technical limitation diminishes the significance of the data. It has been recognized for many years that a major determinant of infarct size is the size of the region at risk. In fact, no experimental study of infarct size limitation would be accepted for publication if the size of the risk region were not quantitated and used to normalize the measurement of infarct size. It is recognized that it is difficult, but not impossible, to obtain these data in clinical studies because scans must be recorded both before and after the intervention. Reliance on absolute infarct size as a percentage of the left ventricle—despite the many reasonable correlations between this parameter and measures of ventricular function and clinical outcome, without normalization for the size of the region at risk—can yield incorrect conclusions. And this difficulty is perhaps best highlighted by the very different measurements of infarction in patients treated with placebo: 45% in the AMISTAD I study and 27% in the AMISTAD II study.

REFERENCES


REPLY

We thank Drs. Cohen and Downey for their interest in our report on treatment of anterior myocardial infarction with adenosine (1). We do not agree that we misquoted Yao and Gross (2) and Thornton et al. (3) with respect to the cardioprotective effects of adenosine. The Thornton et al. study was cited, with others, in stating that “adenosine has consistently provided myocardial protection from ischemic injury.” The Yao and Gross study (2) supports the statement that “adenosine and adenosine agonists are myocardial protectants.” We did not say that this protection was specifically related to the time of reperfusion, as implied. The reduction in infarct size may have been related also to other salutary effects of adenosine. In many patients the drug was on board during at least part of the time of coronary occlusion, and thus it might have a protective effect during ischemia. Certainly, in those receiving thrombolytic therapy, there was a time lag between administration of the lytic and when reperfusion was complete. Thus, it is possible that adenosine played a protective role during this time of continuing ischemia.

We do not agree that the difference in infarct size in the AMISTAD I and AMISTAD II studies somehow imputes the reliability of the single-photon emission computed tomography data in the AMISTAD II study. The validity of SPECT infarct
size measurement is well-established (4) on the basis of multiple lines of scientific evidence. We agree that myocardium at risk is highly variable and a major determinant of infarct size in both animal models and humans. The absence of measurement of myocardium at risk will reduce power (i.e., increase the likelihood of a type II [beta] statistical error). However, the estimates reported in our paper of a type I (alpha) statistical error for infarct size remain valid. In the AMISTAD I study (5), myocardium at risk was measured in a subset of patients. In anterior infarcts, adenosine showed similar benefit using either myocardial salvage index \((p = 0.015)\) or infarct size \((p = 0.014)\). Other randomized trials that have measured myocardium at risk and infarct size \((6,7)\) have reported similar significant differences using either infarct size or salvage index as an end point.

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Statins and Antioxidant Vitamins: Should Co-Administration Be Avoided?

In the interesting study by Arad et al. (1), co-administration of atorvastatin (20 mg/day) and high-dose antioxidant vitamins C (1 g/day) and E (1,600 IU/day) failed to decrease the progression of coronary artery calcification, whereas a borderline decrease of cardiovascular events was observed. Based on the fact that previous studies have shown that statins do decrease both the progression of coronary artery calcification and cardiovascular events (2), the investigators proposed that the atorvastatin dosage they used was low, and they suggested that their population was not large enough to detect any differences. However, another possibility might be considered: The results of the present study may reflect a negative effect of antioxidant vitamins (especially vitamins C and E), which could interfere with lipoprotein metabolism, preventing the statin-induced increase of high-density lipoprotein (HDL)-2 subtraction, as has been proposed in the past (3). Indeed, in a study by Brown et al. (4), it was shown that co-administration of statin and antioxidant vitamins C and E partly prevents the beneficial effects of statins on cardiovascular outcome. Additionally, we (5) have recently demonstrated that, although low-dose atorvastatin treatment (10 mg/day) improves endothelial function in patients with ischemic heart disease, this effect is abolished when vitamin E (400 IU/day) is co-administered. Therefore, further studies examining the effect of atorvastatin 10 to 20 mg/day alone on the progression of coronary artery calcification and clinical events are required before any conclusion is made.

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REFERENCES


REPLY

As Dr. Tousoulis and colleagues point out, the design of the St. Francis Heart Study Randomized Clinical Trial (two cells of a 2 × 2 factorial) does not permit a definitive conclusion as to whether statins alone retard the progression of coronary calcification. However, there are other reasons to believe that statins do not reduce the rate of coronary calcification, or, if they do, that said