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CORRESPONDENCE

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Left Ventricular Remodeling and 1-Year Clinical Follow-Up of the REOPEN-AMI Trial

To the Editor: In about 30% to 50% of patients with ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI), microvascular obstruction (MVO) reduces the beneficial effects of a successful recanalization of the infarct-related artery (1). The open-label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction (REOPEN-AMI [Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction] study) showed that the intracoronary administration of a high dose of adenosine, but not of a high dose of nitroprusside, given selectively into the infarct-related artery after thrombus aspiration, improved MVO, as assessed by ST-segment resolution (2). We present here left ventricular remodeling data and the 1-year clinical outcomes of patients enrolled in the REOPEN-AMI study (2).

Six hospitals in Italy enrolled patients from September 2008 to September 2011. Details of the study design have been previously reported (2). Briefly, a total of 240 STEMI patients presenting with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1 were randomly allocated 1:1:1 to receive adenosine (120 μg as fast bolus followed by 2 mg given in 33 ml of saline over 2 min as slow bolus, n = 80), nitroprusside (60 μg as fast bolus followed by 100 μg given in 33 ml of 5% glucose over 2 min as slow bolus, n = 80), or saline (2 ml of heparinized saline as fast bolus followed by 33 ml of heparinized saline given over 2 min as slow bolus,n = 80) distal to the occluded site after thrombus aspiration. Of note, among included patients, 7 patients undergoing rescue PCI were also enrolled (n = 2 in the adenosine group, n = 3 in the nitroprusside group, and n = 2 in the saline group).

The primary endpoint was the incidence of ST-segment resolution >70% on surface electrocardiogram at 90 min after PCI. In this study, we report pre-specified secondary endpoint data about the major adverse cardiac event (MACE) rate at 1-year clinical follow-up (FU) as a composite of cardiac death, myocardial infarction, target lesion revascularization, and heart failure requiring hospitalization and the rate of left ventricular remodeling at 1-year echocardiographic FU, defined as an increase in end-diastolic volume ≥20%, based on repeated measurements in individual patients and on the upper 95% confidence limit of the intraobserver variability (3).

Data distribution was assessed by the Kolmogorov-Smirnov test. Variables that did not follow a normal distribution were expressed as medians and interquartile ranges, whereas other continuous variables were expressed as mean ± SD; categorical variables were expressed as proportions. Comparison between categorical variables was done using the chi-square test or Fisher's exact test, as

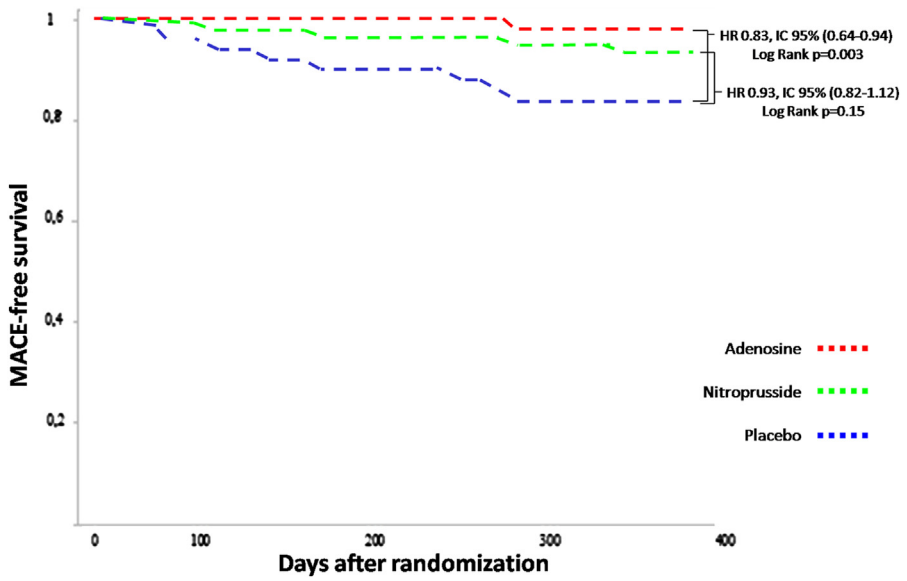

Figure 1 MACE-Free Survival Kaplan-Meier Curves According to Treatment Groups

Adenosine-treated patients had a better MACE-free survival curve when compared with those treated by placebo (log-rank p = 0.003), whereas nitroprusside-treated patients had a similar MACE-free survival curve when compared with those treated by placebo (log-rank p = 0.15). CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s).

appropriate. The Student *t*-test or Mann-Whitney *U* test was used for the comparison of continuous variables, as appropriate. Data have been analyzed according to the intention-to-treat principle. Two-sided tests were used, and a p value <0.025 (using the Bonferroni adjustment, alpha level/number of comparison: 0.05/2) was the statistical significance level. MACE curves using the Kaplan-Meier methods were produced for treatment group and compared by the log-rank test. The software SPSS version 17.0 (SPSS Italia, Florence, Italy) was used for all statistical analyses.

One-year FU was complete in all but 5 of 240 patients (2 patients in the adenosine group, 1 patient in the nitroprusside group, and 2 patients in the placebo group). As in the main study, demographics, cardiovascular risk factors, ischemic times, Killip classes and discharge therapy did not differ significantly among treatment groups (p = NS, data not shown). Of note, compliance with therapy at FU was nearly 90% for all drugs and was similar among treatment groups (p = NS). Baseline end-diastolic and end-systolic left ventricular volumes were similar between adenosine-treated patients (105 ± 19 ml and 62 ± 15 ml, respectively) or nitroprusside-treated patients (107 ± 21 ml and 64 ± 16 ml, respectively) and saline-treated patients (104 ± 20 ml and 65 ± 15 ml, respectively), p = 0.59, p = 0.42, p = 0.48, p = 0.68, respectively), with no significant differences between adenosine- and nitroprusside-treated patients (p = 0.57 and p = 0.61, respectively). However, at 1-year echocardiographic FU, the left ventricular remodeling rate occurred less frequently in the adenosine-treated patients as compared with the placebo-treated patients (6% vs. 23%, p = 0.006), whereas it was similar between nitroprusside- and placebo-treated patients (18% vs. 23%, p = 0.43), and tended to be less frequent in the adenosine-treated patients as compared with the nitroprusside-treated patients (p = 0.07). The MACE rate at 1-year FU was significantly lower in the adenosine group (2 deaths, 1 myocardial infarction, 6 target-lesion revascularizations, 1 heart failure) as compared with the placebo group (4 deaths, 5 myocardial infarctions, 7 target-lesion revascularizations, 7 heart failures) (13% vs. 31%, p = 0.01), whereas it was similar between the nitroprusside (3 deaths, 4 myocardial infarctions, 7 target–lesion revascularizations, 3 heart failures) and the placebo groups (21% vs. 31%, p = 0.21) and between the adenosine and the nitroprusside groups (p = 0.21). Of note, hospitalization for heart failure tended to occur less frequently in the adenosine group as compared with the placebo group (1% vs. 9%, p = 0.06). Kaplan-Meier curves for MACE-free survival according to treatment allocation are shown in Figure 1.

In this study, we showed that high-dose intracoronary adenosine administration in patients with STEMI undergoing primary PCI is associated with improved clinical outcomes after 1 year, mainly because of a reduction in hospitalization for heart failure and less left ventricular negative remodeling (with a statistical power of 99% for adenosine vs. saline and 95% for nitroprusside vs. saline). Because this effect was borderline after 1 month (2), it suggests that the beneficial effects of adenosine on clinical outcomes need more time in order to be demonstrated, as adenosine may have an impact on the rate of left ventricular remodeling (4) after STEMI. The adenosine-related improvements of left ventricular remodeling and clinical outcome are probably due to its effects on MVO and infarct size. Indeed, both reductions of MVO and infarct size have been related to improved clinical outcome (1). Multiple cardioprotective effects of adenosine have been reported, including its potent direct vasodilatory effect on the coronary microcirculation, its anti-inflammatory properties against neutrophils, and its ability to inhibit platelet aggregation, to stimulate angiogenesis, and to mimic ischemic pre-conditioning, thus probably accounting for the beneficial effects observed in this trial (5). In particular, on the basis of these effects, left ventricular remodeling improvement may be related to a better healing process of a smaller infarct area in adenosine-treated patients (suggested also by the smaller enzymatic infarct size observed in the main study for adenosine-treated patients). This study is not powered, however, to demonstrate a mortality benefit, thus further studies should test larger populations for the impact of intracoronary adenosine after thrombus aspiration in STEMI on survival.

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Incidence of Sudden Cardiac Arrest in Minnesota High School Student Athletes

The Limitations of Catastrophic Insurance Claims

To the Editor: An accurate understanding of the incidence of cardiovascular events in athletes is central to the development and