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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

The REOPEN-AMI Study (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction)

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Objectives This study sought to assess whether intracoronary adenosine or nitroprusside following thrombus aspiration (TA) is superior to TA alone for the prevention of microvascular obstruction (MVO) in ST-segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI).

Background MVO, due to its multifactorial pathogenesis, still occurs after TA in a sizeable portion of patients.

Methods We performed a placebo-controlled, randomized, open-label, blind-examination, multicenter trial. A total of 240 STEMI patients with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1 were randomly allocated 1:1:1 to receive adenosine (n = 80), nitroprusside (n = 80), or saline (n = 80) given distal to the occluded site after TA. The primary endpoint was the incidence of ST-segment resolution (STR) >70% on surface electrocardiogram at 90 min after PCI. Secondary endpoints were angiographic MVO incidence (TIMI flow grade ≤2 or 3 with a myocardial blush grade <2) and major adverse cardiac event (MACE) rate at 30 days as a composite of cardiac death, myocardial infarction, target lesion revascularization, and heart failure requiring hospitalization.

Results STR >70% occurred in in 71% of adenosine-treated patients, in 54% of nitroprusside-treated patients, and in 51% of saline-treated patients (p = 0.009 and p = 0.75, respectively, vs. saline). Angiographic MVO occurred in 18% of adenosine-treated patients, in 24% of nitroprusside-treated patients, and in 30% of saline-treated patients (p = 0.06 and p = 0.37, respectively, vs. saline). MACE occurred in 10%, 14%, and 20% of patients, respectively (p = 0.08 and p = 0.29 vs. saline).

Conclusions In STEMI patients treated by PCI and TA, the additional intracoronary administration of adenosine, but not that of nitroprusside, results in a significant improvement of MVO, as assessed by STR. (J Am Coll Cardiol Intv 2013;6:580–9) © 2013 by the American College of Cardiology Foundation

The prompt reopening of the infarct-related artery (IRA) by primary percutaneous coronary intervention (PPCI) is the main therapeutic goal in patients with ST-segment elevation myocardial infarction (STEMI) (1). Yet, in about 30% to 50% of patients, microvascular obstruction (MVO) reduces the beneficial effects of a successful recanalization of the IRA (2). The prevention of MVO has been an intense field of clinical research in the past (3,4), with a renewed interest in the last few years (5,6). Interestingly, in the TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study) trial, thrombus aspiration (TA) before stent implantation, as compared with standard PPCI, improved the rate of complete resolution of ST-segment elevation, a validated index of reperfusion (6). Of note, 90% of patients were treated by intravenous (IV) abciximab, which has been previously shown to lower the incidence of MVO (7). However, in this study, complete resolution of ST-segment elevation was not obtained in 44% of patients despite TA, and it did not translate into a reduction of infarct size (6). This is not surprising because the pathogenesis of MVO after PPCI is multifactorial, and ischemia–reperfusion injury plays a key role (8).

Drugs able to dilate the microcirculation, such as adenosine (9,10) or nitroprusside (11), might limit reperfusion injury. Both drugs have been investigated in previous studies (12–21), but study results are conflicting because of small sample size, inadequate drug dosage, or lack of glycoprotein IIb/IIIa administration or TA. Thus, we have carried out a trial aimed at establishing whether high doses of intracoronary adenosine or nitroprusside improve myocardial perfusion in patients undergoing primary or rescue PCI for STEMI and treated by glycoprotein IIb/IIIa antagonists and TA (1).

Methods

Study design and population. The REOPEN-AMI (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction) trial is a placebo-controlled, randomized, open-label, blind-examination (PROBE), multicenter trial of the effects of intracoronary adenosine or nitroprusside on MVO in patients undergoing primary or rescue PCI and TA and glycoprotein IIb/IIIa antagonist administration (22). Six hospitals in Italy enrolled patients from September 2008 to September 2011, with enrollment starting after local ethics committee approval. Informed consent was obtained on admission for each patient enrolled in the study. Inclusion criteria were symptom onset <12 h before enrollment, ST-segment elevation of at least 2 mm in 2 or more contiguous leads, and Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1 at baseline angiography. Exclusion criteria were age <18 years, previous STEMI in the same territory of current admission, cardiogenic shock, pregnancy, history of renal failure (serum creatinine >3 mg/dl), contraindications to contrast agents or other study medications, paced rhythm, frequent ventricular ectopy, left bundle branch block, pre-excitation or other conditions or artifacts interfering with interpretation of the ST segment, culprit lesion located in a bypass graft, stent thrombosis, unidentified culprit lesion, and left main disease.

Randomization and treatment. All PPCI patients received aspirin (250 mg IV), clopidogrel (600 mg orally) in the emergency department, whereas IV bolus administration of abciximab (0.25 mg/kg) and heparin (5,000 IU) was performed before PCI. A 12-h infusion of abciximab followed the bolus.

In rescue PCI patients, a weight-adjusted single IV dose of tenecteplase was given, ranging from 30 mg in patients <60 kg to 50 mg in those weighing ≥90 kg. Simultaneously, a 60 U/kg bolus of unfractionated heparin was administered up to a maximum of 4,000 U followed by a 24-h infusion of 12 U/kg/h (up to a maximum of 1,000 U/h), with an initial adjustment to maintain an activated partial thromboplastin time 1.5 to 2 times the upper normal limit. All patients received 300 mg of clopidogrel, whereas IV bolus administration of abciximab (0.25 mg/kg) was performed before PCI, whereas a 12-h infusion of abciximab followed the bolus. Thus, all patients, underwent abciximab administration.

If eligible at the completion of diagnostic angiography, the patient was randomized either to intracoronary adenosine (120 μg as fast bolus followed by 2 mg given in 33 ml of saline over 2 min as slow bolus), nitroprusside (60 μg as fast bolus followed by 100 μg given in 33 ml of 5% glucose over 2 min as slow bolus), or placebo (2 ml of heparinized saline as fast

Abbreviations and Acronyms

AV = atrioventricular
CI = confidence interval
CK = creatine kinase
ECG = electrocardiogram
IRA = infarct-related artery
IV = intravenous
MACE = major adverse cardiac event(s)
MVO = microvascular obstruction
PCI = percutaneous coronary intervention
PPCI = primary percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
STR = ST-segment resolution
TA = thrombus aspiration
TIMI = Thrombolysis In Myocardial Infarction

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bolus followed by 33 ml of heparinized saline given over 2 min as slow bolus). Randomization took place through an envelope opened by a trainee, so that a 1:1:1 ratio was achieved. Envelopes were arranged in a sequence for treatment assignment, and the number of patients to be enrolled by each center was decided at the start of the study (see the Online Appendix for the number of patients enrolled by each center). The nursing personnel were then asked to prepare the study drugs. Both opening of the envelope and drug preparation were performed after diagnostic angiography to establish eligibility. TA was performed after wire crossing. The device used for manual TA was left to the policy of each catheterization laboratory (all manual TA devices were 6-F compatible). After TA, the device was removed, flushed with saline, reintroduced into the culprit vessel, advancing the tip beyond the occlusion site, and then used for selective administration of study drugs. Drugs were infused into the IRA only if distal vessels were visualized after aspiration. Otherwise, balloon pre-dilation was allowed before drug administration. If, for mechanical reasons, the TA device could not be advanced into the culprit vessel, drug administration was performed through the guiding catheter after balloon pre-dilation. Acute side effects were recorded by the interventional cardiologist during and after the infusion into the IRA. In case of transient atrioventricular (AV) block, the operator was allowed to restart the infusion after a few seconds in order to provide the full dose of the drugs. In case of persistent AV block, the operator was allowed to insert a temporary pacing catheter in order to complete drug administration.

Study endpoints, assessment of outcomes, and definitions. The primary endpoint was the rate, evaluated by visual assessment, of ST-segment resolution (STR) >70% on surface electrocardiogram (ECG) at 90 min after PCI. Secondary endpoints were the rate of angiographic MVO (TIMI flow grade ≤2 or 3 with a myocardial blush grade <2) and of major adverse cardiac events (MACE) at 30 days as a composite of cardiac death, myocardial infarction, target lesion revascularization, and heart failure requiring hospitalization. Furthermore, the rate of combined MVO (concordance of lack of STR and angiographic MVO) was compared between treatment groups and placebo (23). Enzymatic infarct size defined as the peak of creatine kinase (CK), CK-MB, and troponin T (TnT) was also assessed. Details about the study endpoint assessment are reported in the Online Appendix.

Statistical analysis. The following parameters were used for the sample size calculation, using Statcalc (EpiInfo 3.5.1, Centers for Disease Control and Prevention, Atlanta, Georgia): power of 0.8, significance level of 0.025, allocation ratio of 1:1 with a common control, but 2 treatments, and an effect size to be detected of 0.25, improvement of the primary endpoint by 25%, which was obtained considering a STR of 45% in the placebo group (24), and an STR of 70% in the treatment groups. Because the minimum sample size requested was 237 patients, we decided to enroll up to 240 patients.

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 Fischer exact test, as appropriate. The Student *t* test or Mann-Whitney *U* test were used for the comparison of continuous variables, as appropriate. A per-protocol analysis regarding the primary endpoint was performed after excluding patients with TA failure. Subgroup analysis according to main clinical and angiographic data was also performed by means of logistic regression analysis with formal test for interaction. 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. The software SPSS 17.0 (SPSS Italia, Florence, Italy) was used for all statistical analyses with the exception of subgroup analysis performed with STATA 10.1 (StataCorp LP, College Station, Texas).

Results

Study population. During the study period, 471 patients were considered for inclusion and 240 patients were enrolled according to eligibility criteria (Fig. 1). Patients enrolled were randomized to adenosine (80 patients), nitroprusside (80 patients), or saline (80 patients) after TA. Clinical and angiographic characteristics were similar in patients treated by adenosine or nitroprusside as compared with those treated by saline after TA (Table 1).

Procedural data and complications. Procedural data and intraprocedural complications are shown in Table 2. Procedural data were similar in patients treated by adenosine or nitroprusside as compared with those treated by saline. TA failed and drugs or saline was infused through the guiding catheter in 8 patients treated by adenosine, in 9 patients treated by nitroprusside, and in 7 patients treated by saline (p = 0.98 and p = 0.79 vs. saline, respectively). The rates of transient AV block not requiring pacing were higher in patients treated by adenosine as compared with those treated by saline, without, however, reaching the statistical significance level of the study (13% vs. 3%, p = 0.03) (Table 2). The rates of severe hypotension requiring vasopressor drugs or intra-aortic balloon pump support were similar in patients treated by nitroprusside and in those treated by saline (8% vs. 6%, p = 0.56) (Table 2).

Myocardial reperfusion and peak enzymatic release. Data regarding myocardial reperfusion and peak enzyme levels are shown in Table 3. STR >70% occurred in 71% of patients treated by adenosine, in 54% of patients treated by nitroprusside, and in 51% of patients treated by saline (risk ratio:

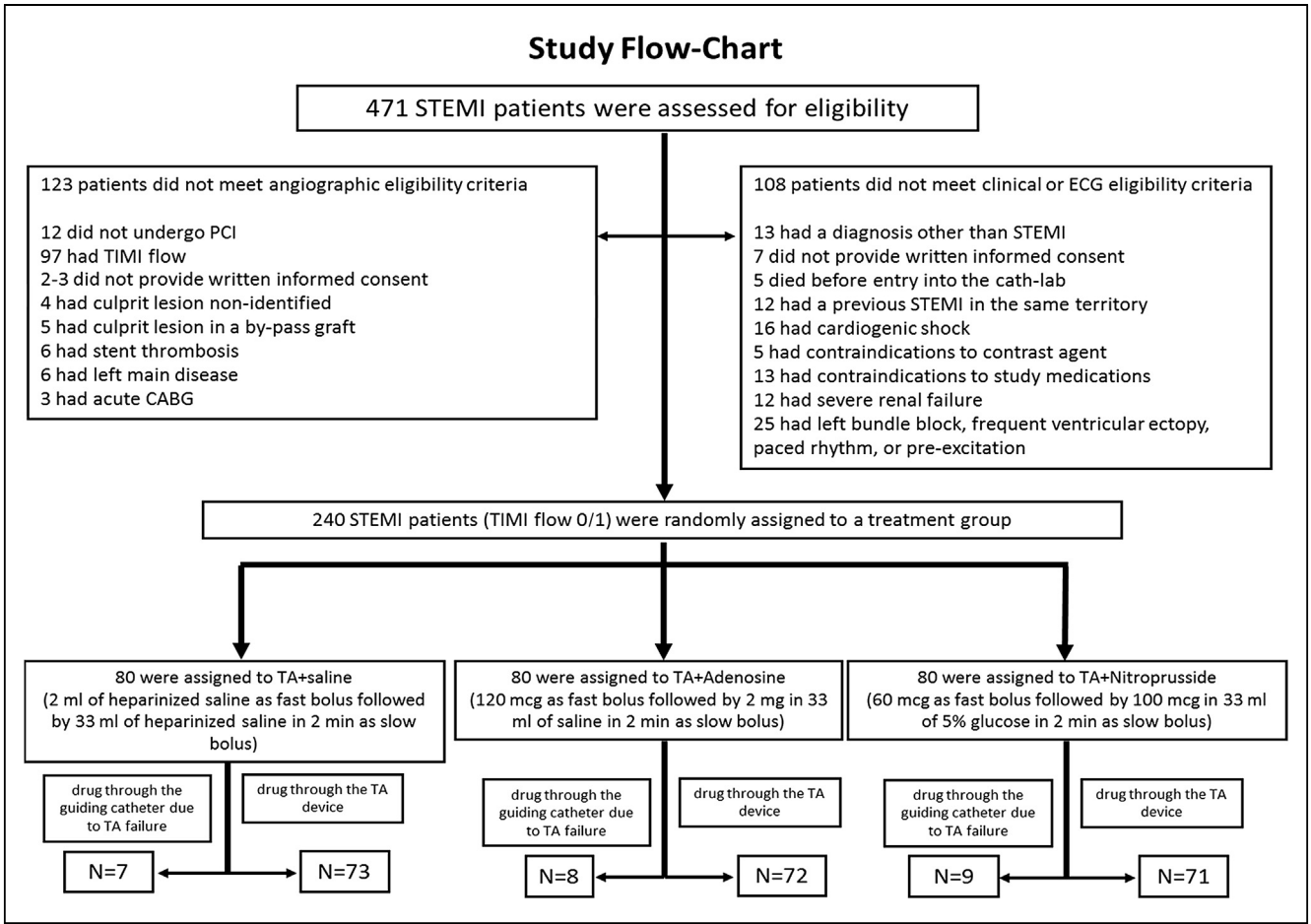

Figure 1. Randomization Flow Chart

During the study period, 471 patients were considered for inclusion and 240 STEMI patients with TIMI flow grade 0/1 were enrolled according to eligibility criteria and randomly allocated 1:1:1 to receive adenosine (n = 80), nitroprusside (n = 80), or saline (n = 80) given distal to the occluded site after TA. CABG = coronary artery bypass graft; ECG = electrocardiogram; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TA = thrombus aspiration; TIMI = Thrombolysis In Myocardial Infarction.

1.39; 95% confidence interval [CI]: 1.07 to 1.79; p = 0.009, and risk ratio: 1.04; 95% CI: 0.78 to 1.40; p = 0.75, adenosine or nitroprusside vs. saline, respectively) (Fig. 2A). Of note, after excluding patients with TA failure, STR >70% occurred in 76% of patients treated by adenosine, in 56% of patients treated by nitroprusside, and in 52% of patients treated by saline (risk ratio: 1.46; 95% CI: 1.13 to 1.89; p = 0.003, and risk ratio: 1.08; 95% CI: 0.80 to 1.46; p = 0.62, adenosine or nitroprusside vs. saline, respectively). Angiographic MVO occurred in 18% of patients treated by adenosine, in 24% of patients treated by nitroprusside, and in 30% of patients treated by saline (risk ratio: 0.58; 95% CI: 0.32 to 1.04; p = 0.06, and risk ratio: 0.79; 95% CI: 0.47 to 1.32; p = 0.37, adenosine or nitroprusside vs. saline, respectively) (Fig. 2B). Combined angiographic and ECG MVO occurred in 8% of patients treated by adenosine, in 13% of patients treated by nitroprusside, and in 18% of patients treated by saline (risk ratio: 0.42; 95% CI: 0.17 to 1.05; p = 0.057, and risk ratio 0.71; 95% CI: 0.33 to 1.51; p = 0.37, adenosine or nitroprusside vs. saline, respectively) (Fig. 2C). Peak CK-MB and TnT levels were lower in patients treated by adenosine as compared with those treated by saline (p = 0.002 and p = 0.01, respectively), whereas they were similar between patients treated by nitroprusside as compared with those treated by saline (p = 0.99 and p = 0.69, respectively).

There was no evidence that the benefit with regard to the primary endpoint was heterogeneous among baseline levels of pre-specified covariates. There was no significant interaction for any subgroups (Fig. 3).

Clinical outcome. Clinical outcome at 30 days is shown in Table 4. MACE occurred in 10% of patients treated by adenosine, in 14% of patients treated by nitroprusside, and in 20% of patients treated by saline (risk ratio: 0.5; 95% CI: 0.22 to 1.10; p = 0.08, and risk ratio: 0.68; 95% CI: 0.34 to 1.38; p = 0.29, adenosine or nitroprusside vs. saline, respectively).

Table 1. Baseline Characteristics of the Patients According to Treatment Group

Characteristics	Adenosine (n = 80)	Nitroprusside (n = 80)	Saline (n = 80)	p Value*	p Value†
Clinical					
Age, yrs	63 ± 11	63 ± 10	64 ± 13	0.70	0.51
Male	62 (78)	59 (74)	59 (74)	0.71	0.99
Hypertension	43 (54)	43 (54)	48 (60)	0.52	0.52
Current smoking	48 (60)	43 (54)	45 (56)	0.75	0.87
Diabetes	20 (25)	22 (28)	17 (21)	0.71	0.46
Hypercholesterolemia	20 (25)	20 (25)	17 (21)	0.71	0.71
Family history of CAD	26 (33)	27 (34)	23 (28)	0.73	0.61
Previous CAD	16 (20)	13 (16)	19 (24)	0.71	0.32
Previous PCI	7 (9)	7 (9)	11 (14)	0.45	0.37
Previous CABG	2 (3)	1 (1)	4 (5)	0.68	0.45
Pre-infarction angina	22 (28)	20 (25)	19 (24)	0.72	0.99
Rescue PCI	2 (3)	3 (4)	2 (3)	0.99	0.98
Killip class 3	11 (14)	8 (10)	9 (11)	0.80	0.60
Total ischemic time, min	277 ± 223	278 ± 221	280 ± 205	0.93	0.95
BMI, kg/m^2	26 ± 2.2	26 ± 2.4	26 ± 2.3	0.45	0.52
SBP, mm Hg	148 ± 24	150 ± 23	150 ± 24	0.55	0.92
DBP, mm Hg	84 ± 15	87 ± 14	87 ± 15	0.29	0.90
HR, beats/min	69 ± 19	70 ± 20	68 ± 20	0.63	0.46
Cr clearance, ml/min/1.73 m^2	62 ± 15	65 ± 13	64 ± 15	0.31	0.63
Glycemia, mg/dl	118 ± 43	123 ± 52	120 ± 47	0.77	0.72
Therapy on admission					
Aspirin	24 (30)	26 (33)	24 (30)	0.98	0.86
Beta-blockers	14 (18)	17 (21)	17 (21)	0.69	0.99
Ace-inhibitors/AII blockers	17 (21)	13 (16)	15 (19)	0.84	0.84
Statins	11 (14)	10 (13)	10 (13)	0.98	1.00
Angiographic					
Number of diseased vessels					
1	35 (44)	35 (44)	38 (48)		
2	24 (30)	28 (35)	24 (30)	0.84	0.80
3	21 (26)	17 (21)	18 (23)		
Infarct-related vessel					
LAD	37 (46)	42 (53)	36 (45)		
LCX	13 (16)	15 (19)	11 (14)	0.83	0.26
RCA	30 (38)	23 (29)	33 (41)		
TIMI flow grade 0	72 (90)	67 (84)	65 (81)	0.18	0.84
Thrombus score 4/5	77 (96)	69 (86)	70 (88)	0.08	0.98
Proximal vessel segment	40 (50)	32 (40)	40 (50)	0.99	0.27

Values are mean ± SD or n (%). *Adenosine versus saline. †Nitroprusside versus saline.

ACE-inhibitors/AII blockers = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; Cr clearance = creatinine clearance; DBP = diastolic blood pressure; HR = heart rate; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; SBP = systolic blood pressure; TA = thrombus aspiration; TIMI = Thrombolysis In Myocardial Infarction.

Discussion

The results of our randomized trial show that the intracoronary administration of a high dose of adenosine, but not that of a high dose of nitroprusside, given selectively into the IRA, improves microvascular perfusion in the setting of PPCI, as assessed by STR, whereas the improvement of angiographic MVO and clinical outcome does not reach statistical significance.

Adenosine is an endogenous nucleoside characterized by a short half-life (<2 s) and by pleiotropic effects (9,10,25,26). First, it is a potent direct vasodilator of coronary microcirculation through stimulation of A2 receptors (27). Second, it exhibits anti-inflammatory properties against neutrophils (28) and inhibits platelet aggregation (29). Third, adenosine mimics ischemic pre-conditioning and limits reperfusion injury (25,26,30). Fourth, it exhibits antiapoptotic effects and

Table 2. Procedural Data and Intraprocedural Complications According to Treatment Group

Characteristics	Adenosine (n = 80)	Nitroprusside (n = 80)	Saline (n = 80)	p Value*	p Value†
Procedural data					
Femoral approach	32 (40)	32 (40)	27 (34)	0.51	0.51
TA failure	8 (10)	9 (11)	7 (9)	0.98	0.79
Direct stenting after TA	37 (46)	41 (51)	33 (41)	0.63	0.27
DES implantation	32 (40)	30 (38)	30 (38)	0.87	0.98
Number of stents	1.3 ± 0.6	1.4 ± 0.5	1.4 ± 0.5	0.49	0.88
Length of stented segment, mm	23.8 ± 7.2	25.1 ± 10	24.7 ± 7.0	0.57	0.78
Diameter of stented segment, mm	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	0.85	0.91
Post-dilation	39 (49)	41 (51)	42 (53)	0.75	0.98
Intraprocedural complications					
Transient AV block not requiring pacing	10 (13)	1 (1)	2 (3)	0.03	0.98
AV block requiring pacing for drug infusion	1 (1)	0	0	0.98	1.00
Transient hypotension not requiring vasopressor drugs or IABP	1 (1)	4 (5)	2 (3)	0.98	0.68
Hypotension requiring vasopressor drugs or IABP,	4 (5)	8 (8)	5 (6)	0.98	0.56
Ventricular tachycardia/fibrillation	2 (3)	2 (2)	2 (3)	1.00	1.00
Chest pain/dyspnea during study administration	3 (4)	1 (1)	1 (1)	0.62	1.00
Angiographically visible distal embolization	9 (11)	7 (8)	9 (11)	1.00	0.79

Values are n (%) or mean ± SD. *Adenosine versus saline. †Nitroprusside versus saline.
AV = atrioventricular; DES = drug-eluting stent; IABP = intra-aortic balloon pump; TA = thrombus aspiration.

may stimulate angiogenesis (10,31). All these effects are mediated by the stimulation of cell surface receptors, including the well-known electrophysiological and algogenic effects (10,25,26,32). Of note, although the vasodilatory, electrophysiological, and algogenic effects of adenosine are short-lived, the remaining effects are prolonged because they are related to the activation of intracellular metabolites or even modulation of gene expression (25–27). The high doses of adenosine administered to our patients are probably high enough to stimulate all adenosine receptors, thus activating all pleiotropic effects potentially protective in the setting of MVO (25–27). Furthermore, due to the short half-life of both drugs, a bolus and infusion regimen was chosen in order to allow a more sustained vasodilation. Of note, STR was improved by adenosine more than were angiographic indexes of reperfusion, thus suggesting that effects lasting more than those related to vasodilatation may be involved in the beneficial role of adenosine. Interestingly, lack of STR and angiographic MVO have been shown to have independent prognostic value after reperfusion (23), because they may reflect different pathogenetic mechanisms. In particular, angiographic data seem to reflect alteration of the microcirculation, whereas ECG data seem to reflect also the myocardial involvement during reperfusion that needs time to appear (33). Adenosine with its pleiotropic effects may probably antagonize both players.

Our results are in keeping with those of previous smaller studies that used high intracoronary doses of adenosine

Table 3. Angiographic, Electrocardiographic, and Enzymatic Data According to Treatment Group

Characteristics	Adenosine (n = 80)	Nitroprusside (n = 80)	Saline (n = 80)	p Value*	p Value†
Baseline ST-segment elevation	1.9 ± 1.1	1.9 ± 1.0	1.9 ± 1.1	0.82	0.87
STR >70%‡	57 (71)	43 (54)	41 (51)	0.009	0.75
Residual ST-segment elevation at 90 min	0.5 ± 0.2	0.7 ± 0.4	0.9 ± 0.4	0.001	0.39
Time from the last dye to ECG	91 ± 8	92 ± 7	93 ± 5	0.83	0.85
Final TIMI flow grade <3	7 (9)	8 (10)	8 (10)	0.28	1.00
Final MBG 0–1	10 (13)	14 (18)	19 (24)	0.06	0.43
Final cTFC	13.0 ± 3.7	15.2 ± 4.2	21.1 ± 14.1	<0.001	<0.001
Peak CK, mg/dl	799 (365–1234)	952 (560–1667)	973 (462–2445)	0.001	0.42
Peak CK-MB, ng/ml	78.7 (45.3–112.1)	123.1 (65.5–213.2)	116.6 (37.9–218.9)	0.002	0.99
Peak troponin, ng/ml	7.73 (3.01–9.97)	8.52 (1.94–21.05)	12.06 (2.42–16.54)	0.01	0.69

Values are mean ± SD, median (interquartile range), or n (%). *Adenosine versus saline. †Nitroprusside versus saline. ‡Primary endpoint.
CK = creatine kinase; CK-MB = creatine kinase-MB; cTFC = corrected Thrombolysis In Myocardial Infarction frame count; MBG = myocardial blush grade; STR = ST-segment resolution; other abbreviations as in Table 1.

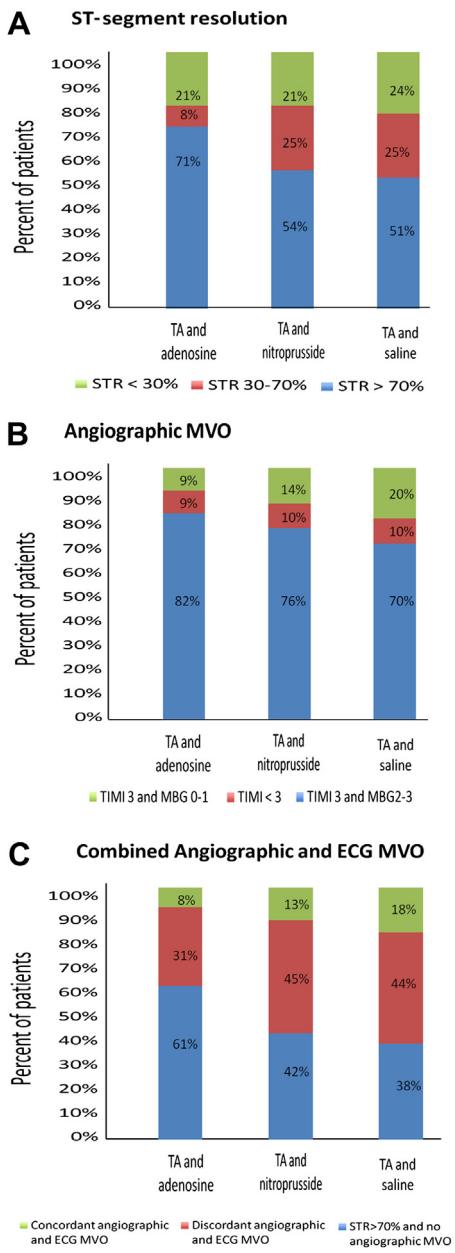

Figure 2. Myocardial Reperfusion Data on Electrocardiography According to the Treatment Group

(A) The percentages of patients are shown according to the degree of ST-segment resolution (STR): STR <30%; STR 30% to 70%, or STR>70%. **(B)** The percentages of patients are shown according to TIMI flow grade 3 and myocardial blush grade (MBG) 2 to 3, TIMI <3, or TIMI = 3 and MBG 0 to 1. **(C)** The percentages of patients are shown according to concordance of angiography and ECG for lack of MVO (both STR >70% and no angiographic MVO); discordance of angiography and ECG for MVO (either STR<70% or angiographic MVO); concordance of angiography and ECG for presence of MVO (both STR <70% and angiographic MVO). MVO = microvascular obstruction; other abbreviations as in Figure 1.

showing an improvement of various indexes of reperfusion (13–16). Our results differ, however, from those of the AMISTAD I (34) and II (35) (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up I and II) trials with IV adenosine and of 2 recent studies with intracoronary adenosine. The AMISTAD II trial (35), in particular, failed to show an improvement of the primary combined endpoint of death and hospitalization for heart failure after 6 months of IV adenosine. However, many differences exist between our study and the AMISTAD studies. Indeed, thrombolysis was used in all patients of the AMISTAD I trial and in nearly 60% of patients of the AMISTAD II trial, with no patient treated by glycoprotein IIb/IIIa inhibitors. Furthermore, adenosine was used with an IV approach, and it was often infused after thrombolysis (50% of patients did not receive adenosine before thrombolysis had begun in the AMISTAD I study). Finally, data about indexes of reperfusion are not provided; the authors chose to assess final scintigrafic infarct size in a subset of patients (197 patients from the AMISTAD I trial and 243 from the AMISTAD II trial). Of note, a reduction of infarct size was observed in those patients treated by high-dose IV adenosine (70 μg/kg/min), especially when the area at risk was high, and a reduction in mortality was shown for patients treated <3 h in a substudy of the AMISTAD II trial (36), suggesting probably that high-dose IV adenosine may have beneficial effects, especially when structural alterations of the microcirculation have not occurred.

More recently, in a study carried out in 448 patients, Fokkema et al. (17) failed to find a beneficial effect of intracoronary adenosine given after TA on both angiographic and ECG indexes of myocardial reperfusion. However, the dose of adenosine (240 μg) was much smaller than that used in our study; furthermore, adenosine was injected through the guiding catheter, thus further reducing the effective drug concentration in the IRA. Interestingly, in our study, adenosine was superior to placebo in regard to the primary endpoint after also excluding those patients who received the drugs through the guiding catheter due to TA failure.

Similarly, in a study carried out in 112 patients, Desmet et al. (18) failed to show a reduction in MVO or an increase in myocardial salvage, as assessed by cardiac magnetic resonance by using high doses of intracoronary adenosine (4 mg) distal to the occlusion site of the culprit lesion. However, adenosine was injected without previous TA and before balloon dilation, thus distal embolization could have overridden the protective effect of adenosine. Of note, IV adenosine given before revascularization failed to improve clinical outcome in the AMISTAD II study (35). Taken together, these studies suggest that only high doses of adenosine reaching coronary microcirculation in the IRA territory immediately after flow restoration are able to improve MVO, as assessed by STR.

Our subgroup analysis shows an homogeneous effect of adenosine in all explored subgroups, thus confirming the

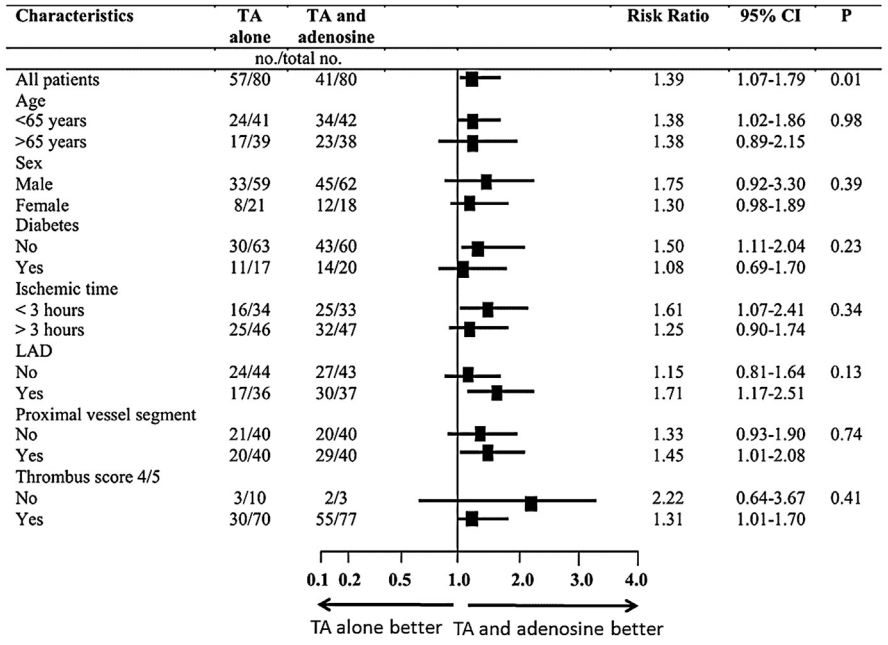

Figure 3. Risk Ratio for the Primary Endpoint, According to Pre-Specified Clinical or Angiographic Subgroups

Numbers in the TA alone and the TA and adenosine columns refer to patients that reached the primary endpoint over the entire number of patients of each treatment group. The p for interaction is reported. CI = confidence interval; LAD = left anterior descending coronary artery; TA = thrombus aspiration.

robustness of its beneficial effects in the overall population. Notably, despite the high doses, adenosine administration in our study was safe; in particular, the episodes of AV block were infrequent and transient, thus allowing the operators to complete its infusion in all patients.

In our study, we failed to show a beneficial effect of nitroprusside on MVO. This finding is consistent with that of the only randomized study, previously performed by Amit et al. (21) who injected 60 μg of nitroprusside before balloon dilation and distal to the occlusion site in 98 patients. Although in our study we used higher doses of nitroprusside, we failed to show improvement of indexes of MVO. The causes of lack of efficacy can be multiple. First, nitroprusside was given concurrently with glycoprotein IIb/IIIa inhibitors, thus its antiplatelet effects (37) might have been overridden by that conferred by abciximab. Second, doses of nitroprusside may have been inadequate. Indeed, some studies suggest that nitroprusside may improve coronary flow by increasing the dose up to 700 μg in the attempt to reverse angiographic MVO (19). The safety of such high doses has not been tested, however, in large trials. Finally, nitroprusside does not exhibit the several pleiotropic effects of adenosine that may play a critical role in patients at risk of MVO.

Table 4. Clinical Outcome According to Treatment Group

Characteristics	Adenosine (n = 80)	Nitroprusside (n = 80)	Saline (n = 80)	p Value*	p Value†
Death	2 (3)	2 (3)	3 (4)	0.98	0.98
MI	1 (1)	2 (3)	3 (4)	0.62	0.98
TLR	4 (5)	5 (6)	6 (8)	0.75	0.98
HF	1 (1)	2 (3)	4 (5)	0.37	0.68
MACE	8 (10)	11 (14)	16 (20)	0.08	0.29
Any bleeding	12 (15)	12 (15)	12 (15)	0.99	0.99
GUSTO bleeding classification					
Severe	1 (1)	2 (3)	1 (1)	0.99	0.98
Moderate	2 (3)	2 (3)	3 (4)	0.98	0.98
Minor	9 (11)	8 (10)	8 (10)	0.98	0.99

Values are n (%). *Adenosine versus saline. †Nitroprusside versus saline.

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HF = heart failure; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization.

Study limitations. Ours is an open-label study, enrolling a small number of patients, which may have been underpowered for some statistical associations. In particular, our study was not powered to provide information on clinical endpoints. The inclusion of patients with ischemic time up to 12 h may have blunted the protective effects of adenosine, as ischemic cell death has already occurred. This is consistent with the substudy of the AMISTAD II trial mentioned in the previous text (36) and with the results of our subgroup analysis, which showed a greater STR in patients presenting <3 h of symptom onset. Furthermore, the inclusion of patients treated by rescue PCI may have diluted the

beneficial effects of adenosine on STR, because rescue patients may have a window of thrombolytic-induced reperfusion with reperfusion injury having already occurred at the time of adenosine administration. However, we included 7 rescue patients only. Thus, the impact of such a variable on our results should be trivial. Additionally, the lack of cardiac magnetic resonance evaluation of both MVO and infarct size is an important limitation of the study. However, ECG indexes of MVO have been shown to correlate with those provided by cardiac magnetic resonance, whereas angiographic indexes have a less robust correlation, the reason why we chose STR as the primary endpoint of our study (38,39). The high rate of ineligible patients is another limitation of our study; however, we aimed to include patients presenting with TIMI flow grade 0/1 on admission who are known to be those at highest risk of MVO. The role of intracoronary drugs in the prevention of MVO in patients with open vessels and TIMI flow grade 2/3 may be a matter of future studies. Moreover, we were not able to evaluate the interaction between thrombus burden and therapies against MVO. Indeed, we performed thrombus score assessment before wiring the vessel, thus possibly underestimating thrombus burden in occluded vessels (40). Finally, when we designed the study, the use of bivalirudin plus bail-out glycoprotein IIb/IIIA inhibitors was not a Class I recommendation, thus our strategy should be compared against this regimen.

Conclusions

The incidence of MVO after PPCI may be lowered by the use of glycoprotein IIb/IIIa antagonists (41) and by the addition of manual TA (6,24). The results of the present study show that the additional intracoronary administration of a high dose of adenosine may further improve STR up to 70%. Future larger studies with clinical endpoints are warranted to confirm the benefit of intracoronary administration of a high dose of adenosine in addition to glycoprotein IIb/IIIa antagonist administration and TA in the setting of PPCI or rescue PCI.

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Key Words: IIb/IIIa antagonists ■ intracoronary adenosine ■ intracoronary nitroprusside ■ manual thrombus aspiration ■ primary percutaneous coronary intervention ■ ST-segment elevation myocardial infarction.

APPENDIX

For an expanded Methods section, please see the online version of this paper.