

# Reduction in periprocedural enzyme elevation by abciximab after rotational atherectomy of type B<sub>2</sub> lesions: Results of the Rota ReoPro randomized trial

Annapoorna Kini, MD, MRCP, David Reich, MD, Jonathan D. Marmur, MD, FACC, Cristina A. Mitre, MD, and Samin K. Sharma, MD, FACC *New York, NY*

**Background** Abciximab has been shown to reduce ischemic complications and creatine kinase-myocardial band (CK-MB) elevation of both simple and complex coronary interventions. In addition to the procedural complications, one of the important mechanisms for CK-MB elevation after rotational atherectomy is an interaction between platelets and the atheromatous debris.

**Methods** This study was conducted to determine whether abciximab would limit the extent of periprocedural CK-MB release after rotational atherectomy of American Heart Association/American College of Cardiology type B<sub>2</sub> lesions in a double-blind, randomized, placebo-controlled manner. A total of 100 lesions in 100 patients were randomized with the primary end point being a CK-MB elevation of >16 U/L.

**Results** Procedural success was achieved in 100% in the abciximab arm compared with 98% in the placebo group with any CK-MB elevation >16 U/L of 8% in the abciximab versus 22% in the placebo group ( $P = .04$ ). The peak creatine phosphokinase level (units per liter) was  $102 \pm 14$  versus  $153 \pm 22$  ( $P = .05$ ) and the peak CK-MB level was  $12.8 \pm 1.8$  versus  $24.6 \pm 3.5$  ( $P = .06$ ) between the abciximab and placebo groups, respectively. Slow-flow or postprocedure chest pain occurred in 14% in the abciximab group versus 30% in the placebo group ( $P = .04$ ). There was 1 Q-wave myocardial infarction in the placebo arm and 1 nonhemorrhagic stroke in the abciximab group.

**Conclusions** Therefore the Rota ReoPro randomized trial revealed the benefit of abciximab during rotational atherectomy in reducing procedural morbidity and CK-MB elevation, and its routine use can be justified even in moderately complex lesions undergoing rotational atherectomy. (*Am Heart J* 2001;142:965-9.)

Blockade of the platelet glycoprotein (GP) IIb/IIIa receptors with abciximab has been demonstrated in 4 large-scale placebo-controlled trials to markedly reduce the incidence of acute ischemic complications in the setting of percutaneous coronary interventions (PCI).<sup>1-4</sup> These interventional trials did not include lesions treated with rotational atherectomy, a technique traditionally associated with slow-flow, distal embolization and persistent periprocedural chest pain leading to periprocedural creatine kinase-myocardial band (CK-MB) release.<sup>5-7</sup> The important mechanism of CK-MB elevation during rotational atherectomy is an interaction between platelets

and the atheromatous debris.<sup>8</sup> During ablation of the atherosclerotic plaque, the rotating burr exposes the vessel wall collagen, which in the presence of thrombin and other platelet agonists within the microenvironment activates the surrounding platelets.<sup>8</sup> Platelet activation initiates conformational change in the unactivated GP IIb/IIIa receptor, transforming it into an activated ligand-competent state and mediates the final common step leading to platelet aggregation responsible for various ischemic events during PCI.<sup>9</sup> Of the 3 available GP IIb/IIIa agents, abciximab, a monoclonal antibody, has been widely studied in various PCI settings by use of different interventional devices.<sup>9-13</sup> Abciximab and other small-molecule GP IIb/IIIa inhibitors have been evaluated in various types of clinical and angiographic settings and are now recommended in almost all PCIs. Abciximab administration during rotational atherectomy in type C and complex coronary lesions has been shown to be beneficial in reducing periprocedural CK-MB elevation.<sup>10-12</sup> Periprocedural CK-MB elevation after PCI has been associated with poor long-term survival, especially after balloon angioplasty, although with new devices the correlation between moderate CK-MB elevation (1-5 $\times$ ) and follow-

*From the Zena and Michael A. Wiener Cardiovascular Institute, Mt Sinai Hospital, New York, NY.*

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*Reprint requests: Samin K. Sharma, MD, Mt Sinai Hospital, Box 1030, One Gustave L. Levy Place, New York, NY 10029.*

*E-mail: samin.sharma@mssm.edu*

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up mortality has been controversial.<sup>14-16</sup> However, every effort should be made to prevent periprocedural CK-MB elevation.

The current study was conducted to evaluate whether abciximab therapy administered in a randomized, placebo-controlled manner would limit the extent of periprocedural CK-MB release after rotational atherectomy of moderately complex American College of Cardiology (ACC)/American Heart Association (AHA) type B<sub>2</sub> lesions.

## Methods

The study protocol was reviewed and approved by the Institutional Review Board of Mt Sinai Hospital. All patients enrolled in the study provided informed written consent.

### Study design

This was a randomized double-blind placebo-controlled study that included all patients who had planned rotational atherectomy of de novo lesions with more than one type B characteristic, in native vessel of any size. The ACC/AHA type B lesions included were ostial, tubular (10- to 20-mm length), eccentric, moderate tortuosity, moderate angulation (>45 degrees to <90 degrees), and irregular contour. Type B lesions with moderate to heavy calcification, total occlusion <3 months old, lesions containing thrombus, and bifurcation lesions were excluded. Other exclusion criteria were elevated CK-MB (>16 U/L) at baseline, unstable rest angina, restenotic lesion, or contraindication to abciximab use. All lesions undergoing elective PCI at Mt Sinai Hospital from June 1998 to April 1999 and suitable for rotational atherectomy were screened for inclusion and exclusion criteria, and 100 patients were randomized in the study.

### Procedural technique

All interventions were performed by conventional techniques and a standard antithrombotic strategy: aspirin 325 mg, intravenous heparin bolus (70 units/kg), and periodic boluses to keep the activated clotting time between 250 and 300 seconds and ticlopidine 500 mg if a stent was placed. Abciximab or placebo was administered in a double-blind manner as a bolus and a 12-hour infusion. All patients had baseline preprocedural CK and CK-MB measured. Baseline clinical, angiographic, and procedural characteristics were recorded in an interventional case report form. Rotational atherectomy was performed by a step-burr approach with short runs of ablation (<20 seconds each time) with burr speeds of 160,000 to 180,000 revolutions/min. After ablation, a low inflation pressure with a long balloon was used if a stent was not used. Stent implantation was performed according to conventional techniques of high-pressure deployment. After the procedure, 3 sets of cardiac enzymes were measured at 6- to 8-hour intervals and further if the levels were still rising. All patients were followed up in-hospital for any ischemic, vascular, and other clinical events.

### Definitions

Angiographic success is defined as <30% diameter obstruction after the procedure with Thrombolysis in Myocardial Infarction (TIMI) grade II or more flow at the end of the proce-

dure. Clinical success is angiographic success of at least one lesion with no major complication. Major complications include Q-wave myocardial infarction (MI) or postprocedure peak CK-MB >8× normal, emergency bypass surgery, in-hospital death, or disabling stroke. Procedural complications include transient abrupt closure, which is reversible complete closure of the treated vessel at anytime during PCI; acute closure (complete occlusion of the treated vessel with less than TIMI grade II flow at the end of PCI or before discharge); slow flow (delayed distal clearance of the dye in the absence of proximal dissection or spasm); distal thromboembolism (visible translucent filling defect or abrupt cutoff in the distal vessel); coronary spasm (focal or diffuse narrowing of vessel without any evident coronary dissection); side-branch closure after the procedure (less than TIMI grade III flow in a side branch of >1.0 mm diameter with normal flow before the procedure); coronary dissection (classified as National Heart, Lung, and Blood Institute [NHLBI] grade A, B, C, D, E, or F); coronary perforation (dye outside the vessel lumen: blush, extravasation, or free spilling in pericardium); prolonged hypotension (systolic blood pressure <80 mm Hg lasting for >5 minutes); and persistent chest pain (chest pain lasting for >30 minutes after the procedure).

Bleeding complications include major bleeding (drop in hemoglobin >5 g/dL or intracranial bleeding); minor bleeding (drop in hemoglobin >4 g/dL without any other bleeding source or >3 g/dL with other bleeding source or spontaneous nonvascular bleeding); and bleeding requiring transfusion.

CK-MB elevation was measured by immunoinhibition with the Johnson & Johnson Vitros 950 analyzer (Rochester, NY) with values <16 U/L normal and ≥16 U/L elevated, further subdivided in 3 categories (16-48 U/L = 1-3× normal, 49-80 U/L = 3-5× normal, and >80 U/L = >5× normal).

### Quantitative coronary angiography

A single experienced observer who was unaware of the purpose and outcome of the study independently performed quantitative angiographic analysis. Analysis was performed with the CMS Medis system (The Netherlands), and the end-diastolic frame revealing the most severe stenosis with the least amount of foreshortening and overlap was selected. The guiding catheter tip was used as the calibration standard. Angiographic views were obtained after routine injection of 100 to 200 μg of intracoronary nitroglycerin. Reference vessel diameter, percent diameter stenosis, minimal luminal diameter (MLD) before and after intervention, and lesion length were measured.

### Statistical analysis

The primary end point of the trial was the incidence of any CK-MB elevation above baseline between the 2 groups. All continuous variables are presented as the mean ± 1 SD and categorical variables are expressed as percentages. All data were stored in an Excel file and transferred to a statistical program. The two groups were compared by  $\chi^2$  analysis for the dichotomous variables and by analysis of variance (ANOVA) for continuous variables. A *P* value <.05 was considered significant.

## Results

A total of 100 patients were randomized in the study. Baseline characteristics were comparable between the

**Table I.** Baseline clinical characteristics

Variable	Abciximab (n = 50)	Placebo (n = 50)	P value
Age (y)	65 ± 12	63 ± 13	.62
Male (%)	38 (76)	37 (74)	.82
Hypertension (%)	20 (40)	24 (48)	.44
Diabetes mellitus (%)	12 (24)	14 (28)	.61
Hypercholesterolemia (%)	33 (66)	30 (60)	.50
Canadian Cardiovascular Society angina class (%)			
0-I	8 (16)	6 (12)	.58
II	30 (60)	28 (56)	.12
III-IV	12 (24)	16 (32)	.36
Prior myocardial infarction (%)	10 (20)	8 (16)	.58
Prior coronary artery bypass graft (%)	8 (16)	7 (14)	.72
Left ventricular ejection fraction (%)	44 ± 9	47 ± 8	.42
Multivessel disease (%)	12 (24)	11 (22)	.84

2 groups (Table D). Angiographic characteristics are shown in Table II; both groups had a similar number of type B characteristics (mean of 3.1) with comparable lesion lengths.

There was no significant difference in various procedural characteristics (Table III): the burr-to-artery ratio was 0.70 and a stent was implanted in 70% of cases. Quantitative coronary analysis data (Table III) revealed a mean vessel size of 2.5 mm with comparable preprocedure and postprocedure MLD. The procedural results (Table IV) revealed that angiographic success was 100% in the abciximab group and 96% in the placebo group because of 1 case of coronary perforation leading to acute closure and 1 case of acute closure out of the catheterization laboratory. The incidence of slow flow or postprocedure chest pain was lower in the abciximab group (14% vs 30%,  $P = .04$ ). Other important procedural variables were not different between the 2 groups. The clinical success (Table IV) was 98% in the abciximab group, with 1 patient having thrombotic disabling stroke later resulting in death, and 96% in the placebo arm, with 1 patient having coronary perforation leading to acute closure and 1 patient having a Q-wave MI from delayed acute closure. There was no urgent bypass surgery in both groups. Major and minor vascular complications were not different between the 2 groups.

#### Periprocedural CK-MB release (Table V)

Any CK-MB elevation >16 U/L, the primary end point of the trial, was 8% in the abciximab group versus 22% in the placebo group ( $P = .04$ ). Most of the CK-MB elevations were between 1 to 3 times normal. Peak creatine phosphokinase (units per liter) and peak total CK-MB (units per liter) were lower in the abciximab group

**Table II.** Angiographic characteristics

Variable	Abciximab (n = 50)	Placebo (n = 50)	P value
Vessel involved (%)			
Left anterior descending artery	30 (60)	28 (56)	.62
Left circumflex artery	8 (16)	9 (18)	.72
Right coronary artery	12 (24)	13 (26)	.76
Eccentric lesion (%)	32 (64)	35 (70)	.52
Complex/irregular contour (%)	6 (12)	6 (12)	1.0
Moderate angulation (%)	18 (36)	22 (44)	.42
Lesion length (%)	13 ± 4	13 ± 4	1.0
Mild-moderate calcification (%)	36 (72)	33 (66)	.52
Side branch in lesion (%)	10 (20)	12 (24)	.66
Mean No. of type B characteristics (%)	3.1 ± 1.2	3.1 ± 1.1	.82

( $102 \pm 14$  vs  $153 \pm 22$ ,  $P = .05$ , and  $12.4 \pm 1.8$  vs  $24.6 \pm 3.5$ ,  $P = .06$ , respectively).

## Discussion

Rotational atherectomy works by pulverizing the atherosclerotic plaque and is recommended in the treatment of long, bifurcation, and diffuse calcified lesions.<sup>7</sup> The debris created by the atherectomy device includes atheroma plus platelet aggregates that may clog the distal microcirculation, potentially causing hemodynamic and ischemic complications,<sup>8</sup> and are likely responsible for periprocedural CK-MB release.<sup>7-9</sup> Studies have shown that CK-MB elevation during rotational atherectomy can occur in up to 15% to 30%.<sup>5,16</sup> Periprocedural CK-MB elevation was associated with adverse long-term cardiac events during the era of balloon angioplasty,<sup>14,15</sup> but the relationship of a moderate level of CK-MB elevation (1-5 times) and poor long-term outcomes after new devices is controversial and may just be a marker of diffuse atherosclerosis; it occurs frequently with the newer devices.<sup>16</sup> Although the clinical importance of periprocedural CK-MB elevation after PCI with new devices is still controversial, attempts to prevent enzyme release should continue.

During PCI, damage to an atherosclerotic plaque results in exposure of adhesive glycoproteins and collagen. Subsequent platelet activation causes GP IIb/IIIa receptors to be expressed on the luminal surface, forming platelet aggregates, which in turn results in thrombus formation. These friable aggregates can embolize distally, causing microcirculatory plugging and resulting in slow flow.<sup>12,17</sup> One of the major factors limiting the short-term success of rotational atherectomy is the phenomenon of “no reflow” or “slow flow,” which often leads to hemodynamic compromise and other ischemic complications, including CK-MB release.<sup>6</sup> Various hypotheses have tried to explain the phenomenon

**Table III.** Procedural characteristics and quantitative coronary analysis

Variable	Abciximab (n = 50)	Placebo (n = 50)	P value
Mean No. of burrs	1.7 ± 0.4	1.6 ± 0.3	.32
Burr speed (revolutions/min)	168,000 ± 12,000	169,000 ± 11,000	.82
Maximal mean burr size (mm)	1.9 ± 0.2	1.8 ± 0.3	.32
Burr-to-artery ratio	0.70 ± 0.02	0.70 ± 0.03	.64
Duration of ablation (s)	210 ± 48	198 ± 62	.32
Stent implantation (%)	68	72	.24
Mean balloon size (mm)	2.75 ± 0.43	2.80 ± 0.36	.10
Maximal inflation pressure (atm)			
With stent	11 ± 3	12 ± 2	.92
Without stent	3 ± 2	3 ± 2	1.0
Mean balloon length (mm)	25 ± 6	26 ± 6	.92
Reference vessel diameter (mm)	2.47 ± 0.32	2.48 ± 0.31	.82
MLD, before procedure (mm)	0.29 ± 0.24	0.30 ± 0.26	.72
MLD, after rotational atherectomy (mm)	1.58 ± 0.18	1.56 ± 0.19	.74
MLD, after procedure (mm)	2.13 ± 0.22	2.15 ± 0.26	.64
Diameter stenosis, after procedure (%)	14 ± 9	13 ± 10	.64

**Table IV.** Procedural and clinical results

Variable	Abciximab (n = 50)	Placebo (n = 50)	P value
Procedural success (%)	50 (100)	49 (98)	.62
Acute closure (%)	0	1 (2)	.24
Transient closure (%)	1 (2)	3 (6)	.24
Slow flow (%)	4 (8)	8 (16)	.16
Postprocedure chest pain (%)	5 (10)	9 (18)	.12
Slow flow or chest pain (%)	7 (14)	15 (30)	.04
Side-branch closure (%)	2 (4)	4 (8)	.32
Spasm (%)	2 (4)	4 (8)	.32
NHLBI dissection A-C (%)	3 (6)	5 (10)	.42
Persistent hypotension (%)	2 (4)	4 (8)	.32
Perforation (%)	0	1 (2)	.24
Clinical success (%)	49 (98)	48 (96)	.52
Q-wave MI (%)	0	1 (2)	.24
Stroke (%)	1 (2)	0	.24
Bleeding complications (%)			
Major	1 (2)	0	.24
Minor	3 (6)	2 (4)	.62
Requiring transfusion	1 (2)	1 (2)	1.0

of “slow flow.” These include distal embolization of atheromatous debris as a result of ablation and local inflammatory response involving the injured endothelium.<sup>12</sup> Recent studies evaluating various burr speeds and platelet activation have shown that lower burr speeds (<150,000 revolutions/min) may decrease platelet activation compared with standard speeds (160,000-180,000 revolutions/min).<sup>18,19</sup>

Of particular interest are the data from the patients who underwent atherectomy in the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial and who received abciximab; these patients had significantly less angiographic “slow

**Table V.** Periprocedural cardiac enzymes elevation

Variable	Abciximab (n = 50)	Placebo (n = 50)	P value
Any CK-MB >16 U/L (%)*	4 (8)	11 (22)	.04
1-3× normal	3 (6)	8 (16)	
3-5× normal	1 (2)	1 (2)	
>5× normal	0	2 (4)	
Peak total CK-MB (U/L)	12.4 ± 1.8	24.6 ± 3.5	.06
Peak total creatine phosphokinase (U/L)	102 ± 14	153 ± 22	.05

\*Primary end point.

flow” compared with those receiving placebo.<sup>1</sup> Our study showed that, compared with placebo, the incidence of slow flow was lower in the abciximab group during rotational atherectomy, although it was not statistically significant because of small numbers. The impact of low speed or abciximab on slow-flow and CK-MB elevation was not evaluated in this trial.

Several hypotheses have been postulated for CK-MB release after PCI with newer devices: distal thromboembolism, slow flow, persistent chest pain, and side-branch closure.<sup>5,16</sup> Because platelet aggregation mediated by GP IIb/IIIa receptors has been identified to play a central role in these ischemic events, use of GP IIb/IIIa blockade during rotational atherectomy in the current trial has clearly demonstrated a significantly lower incidence of CK-MB release in moderately complex lesions by reducing the incidence of minor procedural events during PCI compared with placebo.<sup>8,12</sup> Other GP IIb/IIIa inhibitors, although not studied in this trial, are likely to exert a similar protective benefit of reducing platelet aggregation during rotational atherectomy.<sup>9-13,17</sup>

## Study limitations

An important limitation of the current study was the small sample size, although a significant difference in CK-MB elevation and minor procedural events were noted in favor of abciximab versus placebo. Careful review noted 3 protocol violations in randomization, but the study primary end point results remained unchanged even after exclusion of these patients.

## Clinical implications

Therefore an argument can be made for use of abciximab during rotational atherectomy, even in moderately complex lesions with few ACC/AHA B lesion characteristics because of its impact on significantly lowering the CK-MB release and minor procedural events. One of the important considerations in routine use of abciximab will be additional cost (equal to \$1350/case), but the reduction of minor procedural events and periprocedural CK-MB elevation may justify its routine use during rotational atherectomy.

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