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Local Delivery Versus Intracoronary Infusion of Abciximab in Patients With Acute Coronary Syndromes

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Objectives We investigated whether local abciximab delivery to the site of intracoronary thrombus is more effective than intracoronary bolus infusion in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention and downstream clopidogrel administration.

Background The intracoronary route of administration does not allow an optimal contact between the plaque components and abciximab, which is rapidly washed out by the coronary flow.

Methods A total of 50 patients with ACS and a significant lesion in the culprit artery indicative of local thrombosis were randomly assigned to receive local intracoronary delivery of abciximab through a dedicated perfusion catheter or intracoronary infusion through the guiding catheter. The primary end point was the change in thrombus score after angioplasty by optical coherence tomography.

Results After the intervention, the mean percentage change of the thrombus score was significantly higher among patients of the local delivery group compared with those of the intracoronary infusion group (33.8% vs. 3.9%, $p = 0.002$). Post-procedural corrected Thrombolysis in Myocardial Infarction frame count was shorter in the local delivery group compared with the intracoronary infusion group (15.3 ± 10.2 vs. 21.1 ± 9.9, $p = 0.049$). Procedure-related myocardial infarction was observed in 10% and 43% of patients in the local delivery and intracoronary infusion groups, respectively ($p = 0.018$). At 1 year, MACE were observed in 5.9% and 27.2% of patients in the local delivery and intracoronary infusion groups, respectively ($p = 0.046$).

Conclusions Local intracoronary delivery of abciximab by means of a dedicated perfusion catheter reduces thrombus burden with the potential to improve coronary microcirculation. (J Am Coll Cardiol Intv 2010;3:928–34) © 2010 by the American College of Cardiology Foundation

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Most acute coronary syndromes (ACS) are caused by a thrombus superimposed on a disrupted atherosclerotic plaque leading to sudden complete or partial obstruction of an epicardial coronary artery (1). Percutaneous coronary intervention (PCI) is a well-established therapy for patients presenting with ACS (2,3). However, a proportion of patients treated with PCI experience distal embolization and microvascular obstruction when the clot is mechanically dislodged and sent downstream, and this event is associated with diminished myocardial perfusion and increased mortality (4–6).

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Adjunctive antiplatelet therapy with the glycoprotein IIb/IIIa receptor inhibitor abciximab improves epicardial and tissue-level perfusion as well as clinical outcomes of patients undergoing PCI (7–11). Intracoronary administration of abciximab is associated with additional benefits compared with intravenous bolus application (12,13). On the downside, the intracoronary route of administration does not allow an optimal contact between the plaque components and the drug, which is rapidly washed out by the coronary flow.

The ClearwayRX Therapeutic Perfusion Catheter (Atrium Medical Corporation, Hudson, New Hampshire) is a micro-porous balloon catheter that acts as a low-pressure irrigating system for localized perfusion of therapeutic agents into the coronary vasculature. We investigated whether local abciximab delivery to the site of thrombus through the ClearwayRX catheter is more effective than intracoronary infusion through the guiding catheter in ACS patients undergoing PCI.

Methods

Study design and patient selection. The COCTAIL (ClearwayRx System to reduce intracoronary thrombus in patients with acute coronary syndromes according to Optical Coherence Tomography after Abciximab Intracoronary Local infusion) study was a randomized, open label, multicenter trial with blinded assessment of the study end points. Local institutional ethical committees approved the study protocol, and all participating patients provided informed consent. The authors wrote the manuscript and vouch for the completeness and accuracy of the data gathering and analysis. The sponsor had no role in study design, data collection, or editing of the final manuscript.

Details on the study protocol have been previously reported (14). Briefly, the study population consisted of patients with unstable angina/non–ST-segment elevation myocardial infarction in which an invasive approach was planned and patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI. Due to safety reasons, patients with STEMI were not randomized if the infarct-related artery was totally occluded. Other key exclusion criteria are listed in Table 1. Patients were randomized if they had a significant lesion in the culprit artery indicative of local thrombosis or haziness suggestive of thrombus. Randomized patients entered the final analysis if they had a thrombus score ≥50 according to the optical coherence tomography (OCT) core laboratory.

Randomization and treatment. Before PCI, patients were randomly assigned to receive local delivery of abciximab through the ClearwayRX catheter or intracoronary infusion of abciximab via the guiding catheter, with the use of a randomization scheme devised and implemented by the study statistician.

All patients underwent baseline angiography and OCT assessment before abciximab administration. Patients in the local delivery group received an intracoronary bolus dose of abciximab (0.25 mg/kg) delivered with the perfusion catheter, whereas patients in the control-group received the same intracoronary bolus dose of abciximab delivered through the guiding catheter.

Abbreviations and Acronyms

ACS = acute coronary syndrome
OCT = optical coherence tomography
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis in Myocardial Infarction

Both groups received post-procedural infusion of abciximab for the ensuing 12 h at the dosage of 0.125 μg/kg/min. All patients received aspirin 81 to 325 mg orally as soon as possible and daily thereafter, a clopidogrel 600-mg loading dose after the completion of PCI and 75 mg for at least 30 days after randomization (or up to 1 year in case of drug-eluting stent implantation), and unfractionated heparin bolus of 40 U/kg (maximum 3,000 U) with dose adjustment to maintain activated clotting time 200 to 250 s during the procedure.

End points and definitions. The primary end point was the change of the thrombus burden defined by the thrombus score, as detailed in the following text. Secondary end points were post-procedural corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (15), myocardial blush grade (16), procedure-related myocardial infarction (MI), and 30-day and 1-year rates of major adverse cardiac events (MACE). MACE were defined as the composite of death from any cause, re-infarction, or target lesion revascularization. Procedure-related MI was diagnosed if the creatine kinase-myocardial band level increased to twice the upper limit of normal or twice the last non-normalized measurement (17).

Coronary angiography was performed before and after the PCI. The OCT image acquisition was performed before and after abciximab administration to document changes in the thrombus score. The M2 and M3 OCT systems

Table 1. Key Exclusion Criteria

Myocardial ischemia precipitated by a condition other than atherosclerotic disease
Use of a fibrinolytic agent within 14 days before randomization
Use of abciximab or any other glycoprotein IIb/IIIa inhibitor within 30 days before randomization
Suspected active internal bleeding or history of hemorrhagic diathesis
Major surgery, biopsy of a parenchimal organ, eye surgery, or serious trauma within 6 weeks before randomization
Gastrointestinal or genitourinary bleeding of clinical significance within 6 weeks before randomization
History of cerebrovascular accident or transient ischemic attack within the previous 2 yrs or any cerebrovascular accident with a residual neurological deficit
Administration of oral anticoagulants within 7 days before randomization unless prothrombin time 1.2 or less times control (or international normalized ratio ≤1.4) or ongoing treatment with oral anticoagulant
Known current platelet count <100,000 cells/μl
Intracranial neoplasm, arteriovenous malformation, aneurysm, or aneurysm repair
Known allergy to abciximab or other murine proteins
Known positive pregnancy test for women of childbearing age

(LightLab Imaging, Inc., Westford, Massachusetts) were used according to the nonocclusive technique, as previously described (18–21). Briefly, the image wire was positioned in the target vessel, distal to the culprit lesion, and pulled back at 2 or 3 mm/s speed. Pull-back was performed during simultaneous hand-made injection of Iodinoxanol 370 (Visipaque, GE Healthcare, Cork, Ireland) from the guiding catheter at an infusion rate based on the runoff of the artery and the online assessment of the OCT image quality. To ensure performance of the post-drug infusion acquisition in the same segment, the image wire was not removed after the baseline assessment. Offline core laboratory analysis identified matching cross-sections on the basis of anatomical landmarks or lumen morphology. Patients with wrong matched cross-sections were excluded from the analysis.

Thrombus score grading was based on the semi-quantitative assessment of thrombus (number of involved quadrants in the cross-sectional OCT images) and the longitudinal extension of the thrombus itself (14). By applying this method, in each cross-section, a thrombus was classified as absent or subtending 1, 2, 3, or 4 quadrants. Hence, the score was calculated as the sum of each cross-section score (Fig. 1). Thrombi were identified by OCT as masses protruding into the vessel lumen and discontinuous from the surface of the vessel wall.

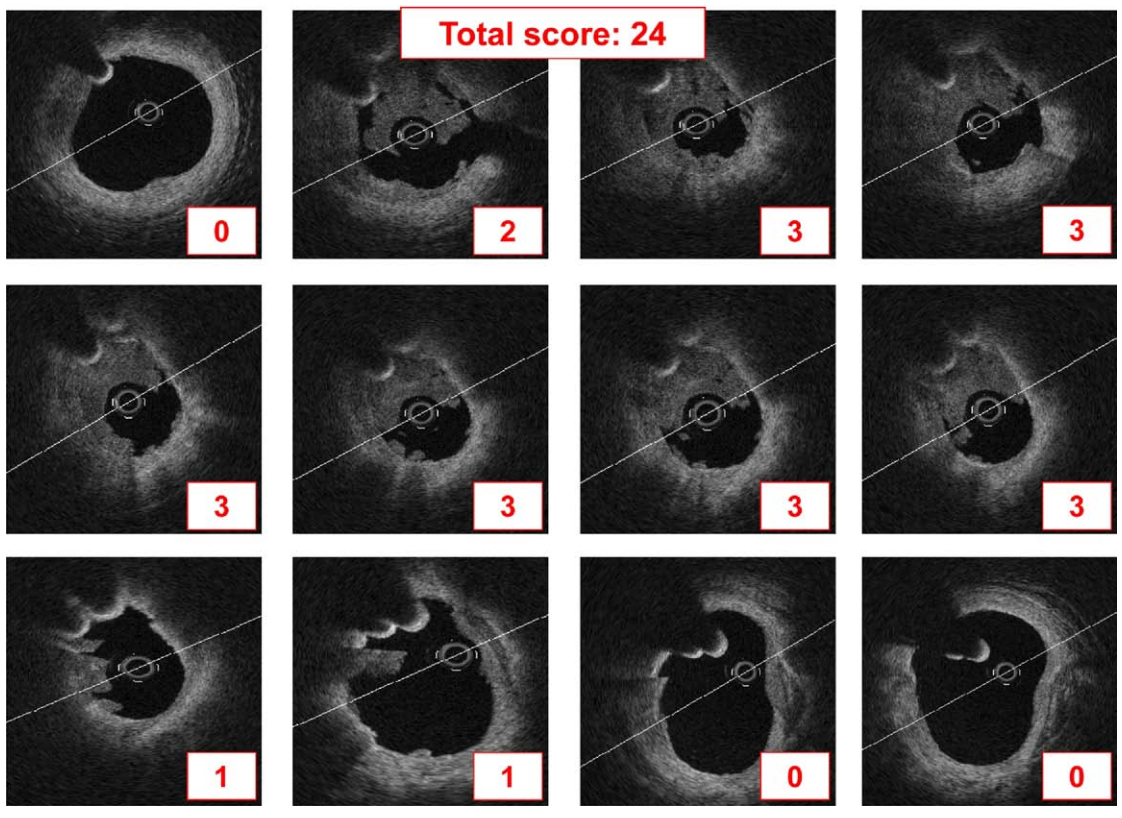

Figure 1. Thrombus Score

Case example of thrombus score calculation in a patient excluded from the final analysis due to thrombus score <50.

Statistical analysis. We estimated that we would have to enroll 40 patients to achieve a power of 80%, with a 2-sided significance level of 0.05, to detect a 25% difference in the primary end point reduction in patients who underwent local abciximab delivery through the perfusion catheter as compared with those who underwent intracoronary bolus administration through the guiding catheter.

All data were processed with SPSS version 15 (SPSS, Inc., Chicago, Illinois). Categorical variables were presented as counts and percentages and compared by means of the chi-square test or Fisher exact test when at least 25% of values showed an expected cell frequency below 5. Continuous variables were normally distributed and therefore presented as mean ± SD and compared by Student unpaired *t* test for between-group comparison and paired *t* test for within-group comparison. The Levene test was used to evaluate the homogeneity of the variances. For all analyses, a 2-sided p value <0.05 was considered statistically significant.

Results

Study population. During the study period, 50 of 87 screened patients at 3 sites in Europe matched the eligibility criteria and, before PCI, were randomly assigned to undergo local delivery of abciximab through the perfusion catheter (n = 25) or intracoronary delivery of abciximab through the guiding catheter (n = 25) (Fig. 2). The baseline clinical characteristics, including age and cardiovascular risk factors, were well-balanced in the 2 arms of the study (Table 2). A STEMI was the clinical presentation in 40% of patients in the local delivery group and 36% of patients in the intracoronary infusion group. A total of 43% of patients in the local delivery group and 40% of those in the intracoronary infusion group had left anterior descending coronary artery disease. Minimal lumen diameter, reference vessel diameter, and stenosis diameter before intervention did not differ between the study groups (Table 3). After the intervention, the mean residual diameter stenosis was lower in the local delivery group compared with the intracoronary infusion group (5.9 ± 3.3 vs. 11.2 ± 9.1, p = 0.022).

Thrombus burden. In the local delivery group, no failure to advance the device across the culprit lesion was observed. Thrombus score changes were assessed in 41 of the 50 randomized patients (82%). Nine patients (5 in the local delivery group and 4 in the intracoronary infusion group) were excluded for the reasons listed in Figure 2. Clinical characteristics of these patients did not significantly differ from those of patients randomized and included in the final analysis. Patients excluded from the final analysis were followed up at 12 months from the index procedure with only 1 target lesion revascularization reported in the intracoronary infusion group at 9 months (p = 0.444).

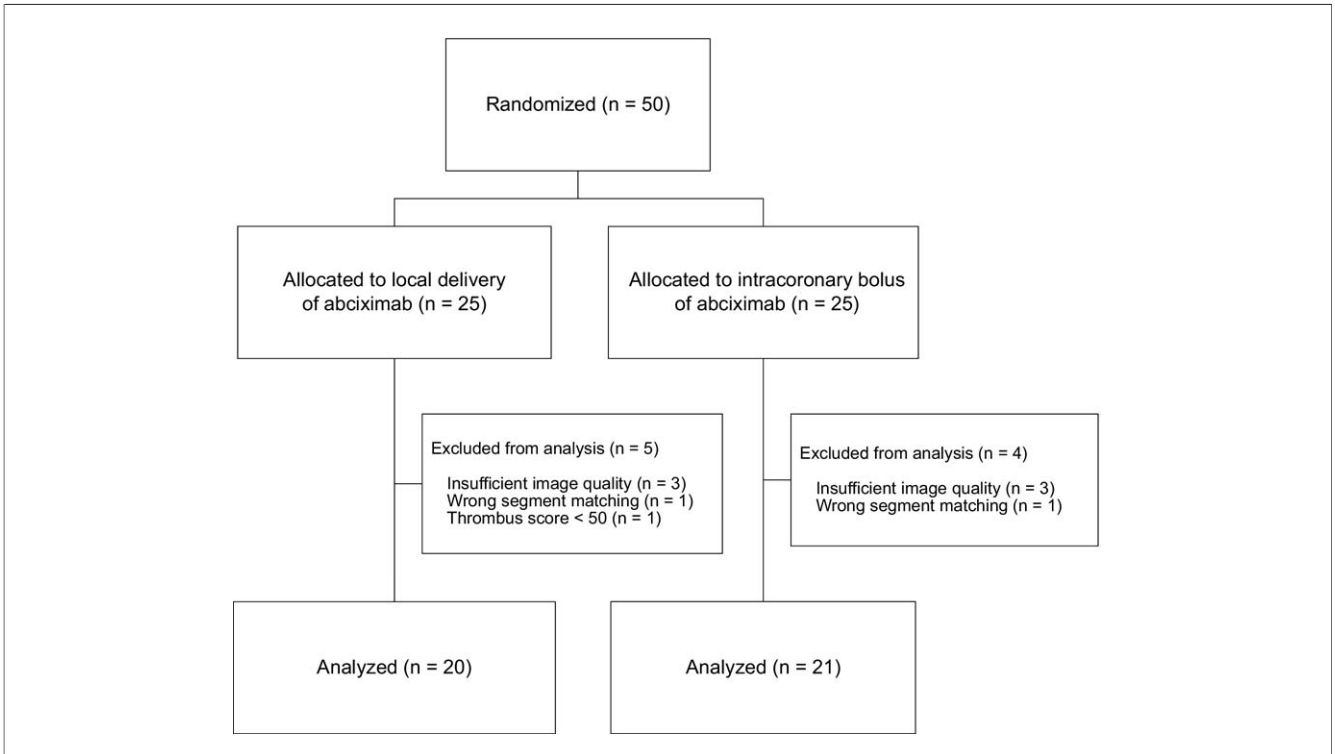

Figure 2. Study Flow Chart

Nine randomized patients did not enter the final analysis, because of insufficient image quality, wrong segment matching, or thrombus score <50.

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Table 2. Baseline Clinical Characteristics

	Intracoronary Abciximab Through the Perfusion Catheter (n = 25)	Intracoronary Abciximab Through the Guiding Catheter (n = 25)	p Value
Age	62.7 ± 9.2	64.4 ± 10.3	0.544
Male	18 (72)	17 (68)	0.758
Hypertension	19 (76)	18 (72)	0.747
Diabetes mellitus	9 (36)	7 (28)	0.544
Hyperlipidemia	14 (56)	16 (64)	0.564
Smoking	12 (48)	8 (32)	0.248
Family history	8 (32)	5 (20)	0.333
Prior MI	4 (16)	3 (12)	1.000
Prior CABG	2 (8)	1 (4)	1.000
Clinical presentation			0.816
Unstable angina	3 (12)	2 (8)	
NSTEMI	12 (48)	14 (56)	
STEMI	10 (40)	9 (36)	
Target vessel			0.789
LMT	1 (4)	0 (0)	
LAD	9 (36)	10 (40)	
LCX	9 (36)	9 (36)	
RCA	6 (24)	6 (24)	

Values are expressed as mean ± SD or n (%).

CABG = coronary artery bypass graft; LAD = left anterior descending; LCX = left circumflex; LMT = left main trunk; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

In the overall study population, thrombus scores at baseline and after the procedure were 98.3 ± 50.0 and 77.1 ± 48.9, respectively. The absolute thrombotic burden defined by the thrombus score was similar at baseline between patients in the local delivery group and those in the intracoronary infusion group (106.8 ± 50.0 vs. 90.5 ± 48.4, p = 0.272). After the procedure, the thrombus score was 68.8 ± 44.8 in the local delivery group and 85.4 ± 52.7 in the intracoronary infusion group (p = 0.393). As a result, the absolute change of the thrombus score after the procedure was significant in the local delivery group and not significant in the intracoronary infusion group (Fig. 3). Accordingly, the mean percentage change of the thrombus score (primary end point) was significantly higher among patients of the local delivery group compared with those of the intracoronary infusion group (33.8% vs. 3.9%, p = 0.002).

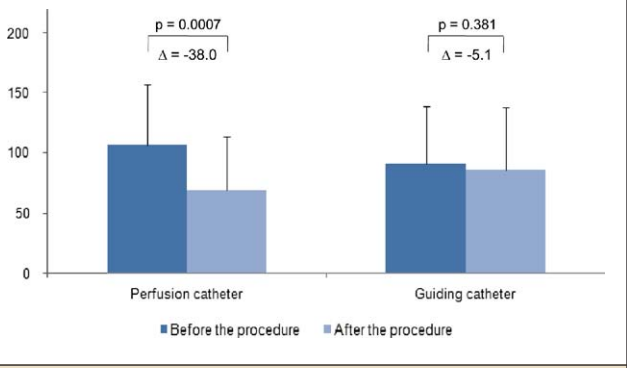

Figure 3. Pre-Procedural and Post-Procedural Thrombus Scores

Differences of thrombus score between patients who received local abciximab delivery and those who received intracoronary infusion through the guiding catheter. In the local delivery group, thrombus score significantly varied after the procedure.

Myocardial reperfusion and 30-day clinical outcome. In the local delivery group, the post-procedural corrected TIMI frame count was shorter compared with the intracoronary infusion group (15.3 ± 10.2 vs. 21.1 ± 9.9, p = 0.049). A myocardial blush grade of 0 or 1 occurred in no patients of the local delivery group and in 5.9% patients of the intracoronary infusion group (Fig. 4). Post-procedural mean myocardial blush grade did not differ between groups (2.78 ± 0.43 vs. 2.59 ± 0.62, p = 0.303). However,

Table 3. Procedural Profile and Results of Quantitative Coronary Angiography

	Intracoronary Abciximab Through the Perfusion Catheter (n = 25)	Intracoronary Abciximab Through the Guiding Catheter (n = 25)	p Value
Minimal lumen diameter, mm			
Before angioplasty	0.57 ± 0.38	0.61 ± 0.33	0.779
After angioplasty	2.64 ± 0.34	2.49 ± 0.38	0.201
Reference vessel diameter, mm			
Before angioplasty	2.55 ± 0.52	2.49 ± 0.42	0.617
After angioplasty	2.82 ± 0.40	2.82 ± 0.37	0.921
Diameter stenosis, %			
Before angioplasty	78.7 ± 11.5	75.2 ± 13.5	0.444
After angioplasty	5.94 ± 3.27	11.21 ± 9.07	0.022

Values are expressed as mean ± SD.

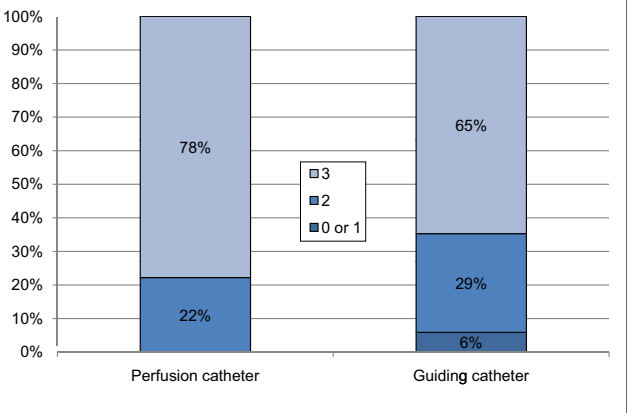

Figure 4. Myocardial Blush Grade According to Treatment Group

The percentages of patients are shown according to myocardial blush grade on the angiogram.

procedure-related MI was detected in 10% of patients in the local delivery group and 43% of patients in the intracoronary infusion group ($p = 0.018$).

There were no clinical events at 30 days in either group. Conversely, at 1 year, MACE were observed in 5.9% of patients in the local delivery group versus 27.2% of those in the intracoronary infusion group ($p = 0.046$), driven by a higher rate of target lesion revascularization in the intracoronary infusion group compared with the local delivery group (21.6% vs. 5.9%, $p = 0.126$).

Discussion

The results of this randomized trial show that, in patients with ACS and evidence of thrombus in the culprit lesion undergoing PCI and downstream clopidogrel administration, local delivery of abciximab at the site of the atherothrombotic plaque through a dedicated catheter yields a greater dissolution of the thrombus burden than conventional intracoronary bolus administration. In particular, patients who received abciximab through the perfusion catheter had an almost 30% higher change of thrombus score after infusion compared with those in the control group, as described by OCT. Importantly, these patients also had a lower degree of post-procedural stenosis, improved myocardial perfusion as expressed by the corrected TIMI frame count, and lower rates of procedure-related MI and 1-year MACE. Overall, these findings suggest the efficacy of local drug delivery to enhance the contact of abciximab with the plaque components and imply that the wash-out of the drug is 1 of the potential mechanisms to explain why rates of slow flow remain high in lesions with high thrombotic burden, despite intracoronary abciximab administration via the guiding catheter.

The interest in combining pharmacological and catheter-based invasive therapies to lower the frequency of suboptimal myocardial reperfusion after PCI has encouraged the development of various devices to protect the microcirculation. The ClearwayRX Therapeutic Perfusion Catheter acts as a low-pressure irrigating system for localized perfusion of therapeutic agents at high concentrations into the coronary and peripheral vasculature. Mechanical features of the delivery catheter are maximized to allow improved drug delivery throughout the entire length of the balloon by prolonging the "residence time" of the drug (drug stays in contact longer with the thrombotic lesion before being washed away) and by facilitating the diffusion of the antibody to platelets inside flow-limiting thrombi. This might result in improved dissolution of thrombi and microemboli at the culprit lesion and in the distal vessel territory.

Importantly, because the study aimed to assess differences related to the route of drug administration, the protocol required the use of perfusion devices slightly undersized with respect to the luminal diameter of the vessel, on the basis of OCT assessment. This was necessary to avoid the potential for thrombus dislodgement due to the use of the perfusion balloon, which could make it difficult to discriminate between therapeutic effect of local abciximab delivery and reduced thrombus volume due to the mechanical action of the device. The potential for a Dotter effect was also limited or avoided by careful sizing of the perfusion catheter on the basis of OCT.

This is, to the best of our knowledge, the first study that uses OCT to grade thrombotic burden in the setting of PCI. Thrombus score was graded with a pre-specified definition developed ad hoc and adapted for OCT. Although OCT is an optimal technique for thrombus visualization, due to its high-resolution modality—which allows detailed imaging of the superficial components of the atherosclerotic plaque (21)—one might argue that thrombus dislodgement could be caused by wire insertion and thereby affect the study results. However, it has been demonstrated that the amount of thrombus dislodged due to wire crossing is trivial, because the vast majority of thrombus embolization is caused by percutaneous transcatheter coronary angioplasty and stenting (22). In this study, the minimal additional risk caused by thrombus dislodgement due to wire crossing was offset because all the procedures were accomplished with intracoronary abciximab administration. This is in agreement with the observation that only 1 patient experienced post-procedural myocardial blush grade <2 in the intracoronary infusion group, and no patients had early clinical events at 30 days. In addition, patients in the local delivery group experienced lower rates of procedure-related MI.

Study limitations. The COCTAIL study was a phase IIb trial, which aimed to investigate the efficacy of a novel system to enhance intracoronary abciximab delivery. Despite 9 of 50 patients being randomized, treated, and then excluded from the analysis mainly due to insufficient image quality or wrong segment matching, the study was powered for assessing differences relevant to the primary end point. However, the potential for introducing bias by excluding patients who were randomized cannot be entirely ruled out. Therefore, caution should be applied when interpreting the study results. The study was not powered to address secondary end points, which have been provided to guide the interpretation of the primary results. Also, information on clinical outcomes, which are pivotal to prompt the use of a novel investigated device into clinical practice, are limited by the small sample size. The INFUSE AMI (INFUSE - Anterior Myocardial Infarction) trial (NCT00976521), which is currently recruiting participants, will randomize 452 patients with a 2×2 factorial design to investigate the combined role of local infusion of abciximab and thrombus aspiration. This study will provide more evidence to support (or discourage) the implementation of a comprehensive multi-targeted mechanical and pharmacological approach as

a strategy aimed to increase the magnitude of the angiographic benefit and put it significantly on the clinical level.

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Key Words: abciximab ■ acute coronary syndromes ■ perfusion balloon.