EDITORIAL COMMENT

Abciximab During Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

Intracoronary, Intravenous, or Not at All?*

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The intravenous (IV) route is the standard way to administer abciximab to patients during percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), but pharmacokinetic principles predict that the intracoronary (IC) route would be better. Because of the short half-life of abciximab and its avid binding to multiple integrin types during the first pass through the systemic circulation, less drug may reach exposed IIb/IIIa epitopes on activated platelets within the culprit lesion after IV bolus than after direct IC administration (1). Supporting

this concept, a small mechanistic study of 16 patients with STEMI (2) showed that IC abciximab compared with IV abciximab produced immediately higher IIb/IIIa receptor occupancy in platelets sampled in coronary sinus blood (94% vs. 74%). Thirty minutes later, however, no difference in receptor occupancy was seen (93% vs. 92%). Whether IC abciximab can reduce infarct size or improve clinical outcomes has been evaluated in several clinical trials.

IC abciximab versus no abciximab. In the INFUSE-AMI (Intracoronary Abciximab Infusion and Aspiration Thrombectomy in Patients Undergoing Percutaneous Coronary Intervention for Anterior ST-Segment Elevation Myocardial Infarction) trial, 452 patients within 4 h of STEMI caused by proximal or mid left anterior descending artery occlusion undergoing primary PCI were randomized to bolus IC abciximab delivered locally into the culprit lesion or to no abciximab (3). The use of bolus IC abciximab

compared with no abciximab produced a significant reduction in the primary endpoint of infarct size at 30 days (15.1% vs. 17.9% of the left ventricle), as assessed with cardiac magnetic resonance (CMR) imaging.

IC abciximab versus IV abciximab. Another trial using a different protocol arrived at a different primary conclusion (Table 1). In the AIDA STEMI (Abciximab Intracoronary versus intravenous Drug Application in ST-Elevation Myocardial Infarction) trial (4), 2,065 all comers within 12 h of STEMI were randomized to bolus IC abciximab (plus IV infusion) or to bolus IV abciximab (plus IV infusion). The use of bolus IC abciximab compared with bolus IV abciximab produced no improvement in the primary endpoint of death, new myocardial infarction (MI), or heart failure at 90 days (7.0% vs. 7.6%), as compared with those randomized to IV abciximab.

A systematic analysis, embedded in the AIDA-STEMI report (4), of 8 randomized trials including 3,158 patients, also reported that the use of IC abciximab compared with IV abciximab produced no difference in death (risk ratio: 0.9; 95% confidence interval: 0.5 to 1.5) or MI (risk ratio: 0.8; 95% confidence interval: 0.5 to 1.4).

Infarct size after IC versus IV abciximab. A report of a substudy of the AIDA-STEMI trial, which appears in this issue of the *Journal* (5), provides additional information about the role of IC abciximab. In 795 patients, Eitel et al. (5) performed CMR within 1 week to compare infarct size after IC or IV abciximab. The investigators found that the use of IC abciximab compared with IV abciximab produced no difference in infarct size (16% vs. 17% of the left ventricle).

Is infarct size an appropriate endpoint? Recent studies suggest that infarct size measured by CMR is a stronger predictor of outcomes after MI than ejection fraction or other measures of left ventricular function (6). The question of whether infarct size is an appropriate surrogate for clinical outcomes can be explored by reviewing the CMR findings in recent studies. In the AIDA-STEMI substudy (5), patients with major adverse cardiac events (MACE) had larger infarcts than those without MACE (24% vs. 16% of the left ventricle), suggesting that CMR measurements of infarct size have prognostic value.

In the INFUSE-AMI trial (3), infarct size could not be correlated with clinical outcomes because only 2 of 31 patients (6.5%) with MACE underwent CMR imaging at 30 days. The primary results of the INFUSE-AMI trial can be analyzed, however, to determine whether the reduction in infarct size seen with IC abciximab corresponded to improved clinical outcomes. Although the observed 16% reduction in infarct size was less than the 25% reduction prospectively defined as clinically meaningful (3,5), the difference in infarct size after IC abciximab compared with no abciximab reached statistical significance (p = 0.03) but was not associated with a reduction in major adverse cardiac or cerebrovascular events (4.8% vs. 3.2%) (3), suggesting

Table 1	Trial Comparisons			
	INFUSE-AMI Trial (3)		**AIDA-STEMI Trial (4,5)**	
Protocols				
Indication	Anterior STEMI <4 h		STEMI <12 h	
Adjunctive anticoagulant	Bivalirudin		Heparin	
No.	229	223	1,032	1,033
Treatment comparison	IC abciximab	No abciximab	IC abciximab	IV abciximab
IC administration	Local infusion	—	Guide catheter	—
IV abciximab infusion	No	No	Yes	Yes
Outcomes				
Primary endpoint	Infarct size measured by CMR		All-cause mortality, recurrent MI, or HF within 90 days	
Main results	Positive		Negative	
Timing of CMR, d	30		7	
No. undergoing CMR	181	172	394	401
Infarct size (% of LV)	15	18*	16	17
Timing of death rates, days	30		90	
Death rates, (%)	3.5	2.3	4.5	3.6

*p = 0.03.

CMR = cardiac magnetic resonance; HF = heart failure; IC = intracoronary; IV = intravenous; LV = left ventricle; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

that CMR measurements in this setting had limited prognostic value. Fortunately, the clinical endpoints in the INFUSE-AMI trial (3), the AIDA-STEMI trial (4,5), and several other recent trials (7–10) help to define the role of abciximab in current practice.

Drug therapy during PCI for STEMI. Refinements in the use of oral antiplatelet agents (7–9) and bivalirudin (10) have narrowed the indications for abciximab during PCI for STEMI. The decision to use abciximab, an inhibitor of platelet aggregation, can be guided in part by the adequacy of concurrent therapy with aspirin and $P2Y_{12}$ receptor blockers, which are inhibitors of separate pathways for platelet activation. Stressing the critical role of oral antiplatelet agents, the 2013 American College of Cardiology Foundation/American Heart Association guideline (11) recommends aspirin and $P2Y_{12}$ receptor blockers for all patients undergoing PCI for STEMI, with either unfractionated heparin or bivalirudin (Class of Recommendation I).

Oral aspirin is absorbed rapidly, predominantly from the upper small intestine, and appreciable concentrations appear in plasma within 30 min (12). True resistance to aspirin is either rare or nonexistent in normal individuals (13), but delayed or reduced gastrointestinal absorption may lead to a condition known as aspirin pseudoresistance (13).

Pre-treatment with clopidogrel probably reduces mortality in patients with STEMI. It was shown in a meta-analysis (7) that administering clopidogrel before PCI for STEMI has been associated with a lower incidence of death than administering the drug later (1.28% vs. 2.54%, p = 0.04). Clopidogrel resistance is well described, but studies have now documented that both prasugrel and ticagrelor may also have a delayed onset of platelet inhibition during STEMI (14). Slowed gastrointestinal absorption or an intensely thrombotic milieu may retard the onset of platelet inhibition in this setting (14). The 2013 American College of Cardiology Foundation/American Heart Association guideline (11) now recommends IV abciximab for selected patients with STEMI receiving unfractionated heparin (Class of Recommendation IIa) and states that IC abciximab may be reasonable in limited circumstances (Class of Recommendation IIb).

Practical approaches. Abciximab should be used when aspirin and $P2Y_{12}$ receptor blockers might fail or cannot be given before PCI for STEMI. When emesis prevents the ingestion of oral antiplatelet agents or when cardiogenic shock, low output, or diabetic gastroparesis impairs gastrointestinal absorption, particularly in treatment-naïve patients, abciximab may be indicated during PCI for STEMI. In high-risk situations such as stent thrombosis or extensive intracoronary thrombus, IC abciximab may be preferable to IV abciximab. When IC abciximab is selected, a technical pearl is to convert an aspiration-thrombectomy catheter to a drug-infusion system by disconnecting the suction syringe and pushing a bolus of abciximab through the aspiration ports. Local delivery is preferable to guide-catheter infusion, which tends to blow drug back into the aorta or send it preferentially into the lower resistance circuit of nonculprit coronary arterial branches. In either case, it is reassuring to see that local delivery (3) and guide-catheter infusion (4) both constitute safe approaches for administering abciximab.

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