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Review

Intracoronary versus intravenous abciximab administration in STEMI patients: overview of current status and open questions

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Abstract

Objectives:
To perform a systematic review to provide rationale for intracoronary (IC) abciximab administration in patients with ST-segment elevation myocardial infarction (STEMI), to summarize recent studies comparing IC vs. intravenous (IV) abciximab administration in this setting and to define questions that need to be answered in future trials determining the optimal abciximab regimen.

Methods:
A search covering the period from January 1993 to June 2011 was conducted by two independent investigators using MEDLINE, CENTRAL and Google Scholar databases. Proceedings from the scientific sessions of ACC, AHA, ESC, TCT and EuroPCR were also considered.

Results:
IC administration allows one to obtain a much higher concentration of abciximab than IV injection at the culprit lesion. Therefore it is hypothesized that IC abciximab administration provides more efficient GP IIb/IIIa receptor inhibition and more pronounced additional dose-dependent antiplatelet, antithrombotic, and anti-inflammatory effects when compared to the IV route. Numerous observational and randomized studies comparing IC vs. IV abciximab in STEMI patients indicated improvement in different surrogate end points (infarct size, obstruction of coronary microcirculation, ST segment resolution, inflammatory mediators and markers of platelet activation) related to IC administration. The evidence supporting clinical benefits associated with IC injection of abciximab comes from one randomized and several non-randomized trials as most of the studies were underpowered to assess clinical outcomes. No difference in bleeding complications was observed between IC and IV regimens. Issues that need to be addressed in future studies include: the use of IC abciximab in combination with thrombectomy, the role of selective delivery systems, and the necessity of a prolonged IV infusion of abciximab after IC bolus administration.

Conclusions:
An accumulating body of evidence suggests the superiority of IC over IV abciximab administration in STEMI patients. However, further trials are warranted to establish the optimal strategy of abciximab treatment in this setting.

Introduction

Primary percutaneous coronary intervention (PCI) with stent implantation is the mainstay of treatment for ST-segment elevation myocardial infarction (STEMI)[1,2]. In order to improve effectiveness of catheter-based reperfusion, an adjunctive glycoprotein (GP) IIb/IIIa receptor inhibitor, abciximab, was introduced into clinical practice[1,2]. Recent European guidelines on myocardial revascularization recommend therapy with abciximab in STEMI patients with

evidence of high intracoronary thrombus burden (class of recommendation IIa, level of evidence A)[1]. However, the guidelines do not specify the preferred route of abciximab administration[1,2]. Standard abciximab regimen includes an intravenous (IV) bolus followed by a 12-hour IV infusion.

The aim of this systematic review is to summarize available knowledge comparing intracoronary (IC) and IV abciximab administration in STEMI patients treated with primary PCI. Moreover, we attempt to define questions that need to be answered in future trials determining the optimal abciximab regimen in STEMI patients.

A search covering the period from January 1993 to June 2011 was conducted by two independent investigators using MEDLINE, CENTRAL and Google Scholar databases. Proceedings from the Scientific Sessions of the American College of Cardiology (http://www.acc.org), American Heart Association (http://www.aha.org), European Society of Cardiology (http://www.escardio.org), Transcatheter Cardiovascular Therapeutics (http://www.tctmd.com) and EuroPCR (http://www.europcr.com) were also considered. The following keywords were applied: 'abciximab', 'intracoronary administration', 'primary PCI', and 'ST-elevation myocardial infarction'. References of retrieved studies were searched manually for additional studies and reviews. No language restrictions were applied.

Mechanism of action

Abciximab is a chimeric Fab fragment of the monoclonal 7E3 IgG3 antibody (c7E3 Fab) derived from mouse immunization with human platelets[3]. It competitively binds to the GP IIb/IIIa receptor and prevents binding of fibrinogen and von Willebrand factor to activated platelets, and therefore blocks the final common pathway for platelet aggregation[3]. Abciximab is characterized by a short plasma half-life due to its rapid binding to exposed GP IIb/IIIa receptors on the surface of circulating platelets. This fact results in a strong inhibition of platelet aggregation, while adhesion and secretion are preserved[4,5].

Numerous factors may influence the efficacy of abciximab. Thrombocytosis, basal platelet activation, and agonist stimulation, i.e. thrombin, cause an increase in the number of available GPIIb/IIIa receptors leading to less platelet inhibition than expected[3,6,7].

Rationale for intracoronary abciximab administration

Several mechanisms should be considered to explain the supposed superiority of IC injection of abciximab over the IV route. Generally, the mechanisms could be divided into GP IIb/IIIa receptor-dependent and GP IIb/IIIa receptor-independent. Additional antiplatelet, antithrombotic, and anti-inflammatory effects of abciximab are dose-dependent (Figure 1).

Plasma concentration of available abciximab rapidly decreases after administration due to its rapid binding to the GP IIb/IIIa receptors. As soon as 10 minutes after bolus delivery of this compound, more than 80% of the GP receptors are occupied resulting in a decrease of platelet aggregation by 80%[3–5]. Because of the short plasma half-life of abciximab, its IV administration does not allow one to obtain a suitable concentration at the culprit lesion and in the coronary distal bed of the culprit vessel. In contrast to IV injection, IC route of administration allows one to obtain a much higher concentration within the coronary thrombus at the culprit lesion.

Not only does high local concentration of abciximab decrease platelet activity but it also results in the dissolution of existing platelet-rich thrombi at the ruptured plaque and dispersion of newly formed platelet aggregates reducing distal microembolization[8–10]. Marciniak *et al.*[8] have shown that abciximab at lower concentrations (1.5–3.0 μg/ml) prevents further aggregate formation; however, achieving concentrations ≥10 μg/ml results in an extensive dispersion of platelet aggregates.

The c7E3 Fab has properties which impede the formation and stability of clot structure by inhibition of binding of the coagulation enzyme, transglutaminase (factor XIIIa), to platelets[11], thereby diminishing crosslinking of both fibrin strands and α2-anti-plasmin to fibrin[9,12].

Inhibition of platelet-induced thrombin generation is an additional dose-dependent effect of abciximab resulting in a decreased release of platelet granule containing inhibitors of fibrinolysis such as plasminogen activator inhibitor-1 and α2-anti-plasmin[3].

Concentrations of abciximab that produce complete platelet disaggregation also inhibit thrombin–antithrombin complex formation, prothrombin fragment F1+2 generation, platelet-derived growth factor and platelet factor 4 release, as well as incorporation of thrombin into clots, and microparticle formation[13].

Furthermore, increased porosity of thrombus caused by c7E3 Fab allows penetration of endogenous fibrinolytic agents into the clot, thereby promoting more rapid and extensive spontaneous thrombolysis[10].

IC administration may also enhance the non-GP IIb/IIIa properties of abciximab that are mainly based on complex anti-inflammatory interactions. In contrast to other GP IIb/IIIa inhibitors, abciximab is a non-selective GP IIb/IIIa receptor antagonist. It also binds to vitronectin (avß3, CD51/CD61) expressed on endothelial and smooth muscle cells, monocytes, polymorphonuclear leukocytes, and T lymphocytes[3,14,15] and demonstrates affinity for the integrin Mac-1 (αMß2, CD11b/CD18) found on monocytes and neutrophils[16,17]. Interactions of abciximab

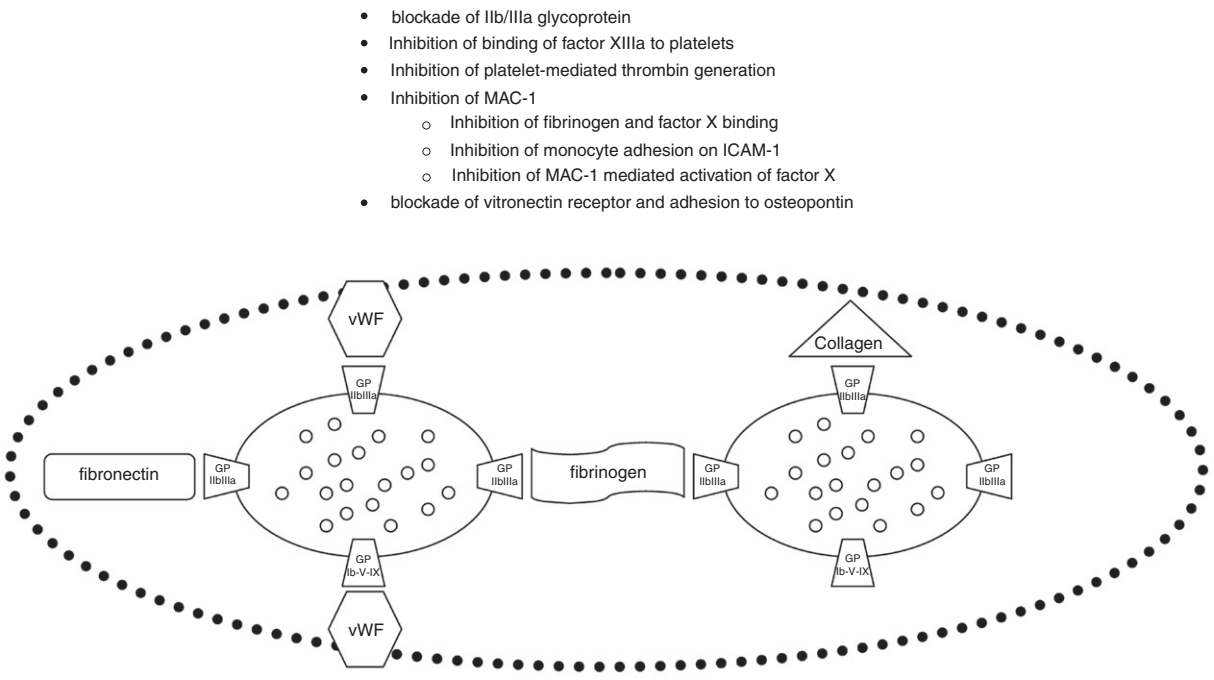

Figure 1. Mechanisms of abciximab action. GP IIb/IIIa – glycoprotein IIb/IIIa; ICAM-1 – intercellular adhesion molecule 1; vWF – von Willebrand factor..

with Mac-1 leukocyte receptors and sαVß3 vitronectin receptors on endothelial and smooth muscle cells are postulated to decrease the inflammatory response in the endothelium of the injured vessel, hence reducing further platelet aggregation. Reduction of smooth muscle cells migration preventing intimal hyperplasia on abciximab therapy was demonstrated in animal models[3,18]. In fact, a reduction in the rate of target vessel revascularizations in favour of abciximab was observed in the EPIC (16.5 vs. 22.3%; $p = 0.007$)[19] and the ISAR-SWEET (23.2 vs. 30.4%; $p = 0.03$)[20] trials. However, it was not confirmed in other clinical trials using prolonged GP IIb/IIIa receptor inhibition after PCI[3,21]. Vitronectin receptors on activated platelets have been implicated in both platelet adhesion to osteopontin present in atherosclerotic plaque and platelet-mediated thrombin generation[3,22]. Thus, abciximab provides a more potent inhibition of platelets due to a 'dual' receptor blockade (GP IIb/IIIa and avß3).

The leukocyte integrin Mac-1 binds heterogeneous ligands including inter-cellular adhesion molecule 1 (ICAM-1), fibrin, fibrinogen and factor X. Several studies demonstrated that the Mac-1 inhibition by abciximab is associated with interruption of the adhesive and migratory capability of leukocytes and reduction of tissue injury[23–26]. The interaction between c7E3 Fab and the integrin Mac-1 blocks the adhesion of monocytes to ICAM-1 and fibrin[27] and decreases thrombus deposition at the site of arterial injury by inhibiting the binding of factor X and its activation to factor Xa[28].

All these mechanisms may result in subsequent improvement in clinical outcome in patients treated with IC bolus of abciximab as compared to IV administration due to reduced reperfusion injury and a higher degree of myocardial salvage.

Overview of current status

Theoretical advantages of IC abciximab regimen over the IV route have led to clinical trials whose results with possible interpretations are summarized below.

Clinical studies assessing benefits of IC over IV abciximab administration in terms of surrogate endpoints

A clinically relevant improvement in myocardial reperfusion as assessed by myocardial blush grade (MBG 2 or 3: 76 vs. 67%; $p = 0.022$) was observed in the CICERO trial[29] in STEMI patients randomized to IC bolus of abciximab given directly after thrombectomy ($n = 271$) as compared to IV bolus administration ($n = 263$). This finding was in line with approximately 30% smaller infarct size in the IC group than in IV group as assessed by plasma concentration of creatine kinase (median 1214 [interquartile range 488–2184] vs. median 1746 [interquartile range 733–3383] U/L; $p = 0.008$), creatinine kinase-MB (median 154 [interquartile range 62–262] vs. median 232 [interquartile range 90–400] U/L; $p = 0.003$), and cardiac troponin T (median 3.03 [interquartile range 0.95–5.81] vs. median 4.36 [interquartile range 1.43–8.56] µg/L; $p = 0.008$). In contrast to some other studies[30–32], it was not confirmed

by the differences in complete ST-segment resolution (64 vs. 62 %; $p = 0.562$). The authors did not find any difference regarding ischemic events (major adverse cardiac events: 5.5 vs. 6.1%, $p = 0.786$) and bleeding complications (major bleedings: 3.7 vs. 3.4%; $p = 0.867$ and minor bleedings: 7.7 vs. 6.8%; $p = 0.688$, respectively) in the compared groups during 30-day follow-up. It is very likely that the benefit of intracoronary administration on myocardial reperfusion was offset by a relatively low clinical risk profile of patients and the routine use of thrombus aspiration in the study. Furthermore, although this study was the largest randomized trial conducted in this field, it had insufficient power to detect differences in ischemic and bleeding events[29].

Antagonists of GP IIb/IIIa have been reported to reduce concentration of soluble CD40 ligand (sCD40L) *in vitro*[3,33] and *in vivo*[34]. CD40L regarded as a unique molecule linking inflammation, thrombosis, and restenosis is secreted by circulating aggregates of platelets and leukocytes[35]. sCD40L binds to platelets via an $\alpha IIb\beta 3$-dependent mechanism and triggers further platelet activation[36,37]. Dominguez-Rodriguez *et al.*[38] compared the effects of IC ($n = 25$) vs. IV ($n = 25$) abciximab bolus administration on sCD40L levels in patients with STEMI undergoing thrombus aspiration during primary PCI. In the IC group, abciximab bolus was administrated after thrombectomy to improve abciximab penetration and allow its high concentration in the target region. IC abciximab administration was associated with a higher reduction in sCD40L concentration compared to IV administration (73.04 ± 12.21 vs. 99.92 ± 25.89 pg/mL; $p < 0.001$). This finding might be explained by the higher local levels of abciximab in the IC group, which may facilitate the diffusion of antibodies to platelets inside the flow-limiting thrombus, thus resulting in enhanced dissolution of thrombi and microemboli and further downstream of abciximab in the microcirculation. No-reflow phenomenon was observed in 12 and 32% of patients in the IC and IV groups ($p = 0.08$), respectively. Moreover, infarct size, as assessed by the peak of troponin I, was significantly lower in patients treated with IC as compared with IV bolus of abciximab (70 ± 32 vs. 95 ± 27 pg/mL; $p = 0.004$). This finding was associated with a trend towards improved myocardial perfusion as assessed by ST-segment resolution measured as a continuous variable (median 79.8 [interquartile range 64.7–100] vs. median 72.0 [interquartile range 43.2–85.5] %; $p = 0.09$). As anticipated, due to the limited number of patients, no significant differences were detected in terms of mortality, re-infarction, need for urgent or any revascularization at 30-day follow-up[38]. Finally, the authors hypothesized on a synergistic effect between thrombus aspiration and IC abciximab administration in patients with STEMI[38].

The aim of the randomized study published by Thiele *et al.*[32] was to assess the effects of IC vs. IV abciximab bolus administration followed by a 12-hour IV infusion on the occurrence of no-reflow phenomenon and infarct size assessed by contrast-enhancement magnetic resonance imaging. In the IC group, bolus administration was recommended after infarct-related artery recanalization by the PCI wire before balloon dilatation to allow high abciximab concentration in the target region. Thrombectomy was not used in this study. The infarct size evaluated by magnetic resonance imaging was significantly smaller after IC ($n = 77$) compared with IV ($n = 77$) abciximab bolus administration (median 15.1 [interquartile range 6.1–25.2] vs. median 23.4 [interquartile range 13.6–33.2] %; $p = 0.01$). Furthermore, there was a significantly lower infarct size in the IC group as assessed by the area under the curve of creatine kinase release (median 575 [interquartile range 359–863] vs. median 736 [interquartile range 416–1304] $\mu mol \times L^{-1} \times h^{-1}$; $p = 0.007$). Similarly, the extent of early microvascular obstruction was smaller in the IC than the IV group (median 2.1 [interquartile range 0.0–5.1] vs. median 4.3 [interquartile range 0.35–13.2]%; $p = 0.06$) and late (median 0.4 [interquartile range 0.0–1.8] vs. median 1.6 [interquartile range 0.03–5.0] %; $p = 0.04$). ST-segment resolution expressed as a continuous variable was also significantly more pronounced in the IC abciximab group (median 77.8 [interquartile range 66.7–100] vs. median 70.0 [interquartile range 45.2–83.5] %; $p = 0.006$). However, left ventricular ejection fraction and end-diastolic and end-systolic volume indexes as well as **thrombolysis** in myocardial infarction (TIMI) flow and TIMI perfusion grades did not differ between the compared groups. In contrast to ECG assessment reflecting improved tissue perfusion, TIMI flow and perfusion grades might not be sensitive enough to detect differences in the very early setting after abciximab bolus administration[32]. Patients with anterior myocardial infarction, those undergoing reperfusion >4 hours after symptom onset, as well as patients with impaired TIMI flow and perfusion grades after PCI had greater benefit from IC vs. IV abciximab bolus administration[32]. Improved myocardial perfusion in patients treated with IC abciximab resulted in better 30-day clinical outcome of borderline significance. The composite major adverse cardiac event (cardiac deaths, nonfatal reinfarctions, need for target vessel revascularization, new onset congestive heart failure) rate was 5.2% after IC and 15.6% after IV abciximab administration (relative risk 0.33; 95% confidence interval [CI] 0.09–1.05; $p = 0.06$)[32].

These data are in line with observations published by Romagnoli *et al.*[39] They performed a prospective assessment of angiographic effect of IC vs. IV abciximab bolus in patients with acute coronary syndromes undergoing urgent PCI. The corrected TIMI frame count (CTFC) significantly decreased immediately after IC abciximab administration in the culprit vessel (48 ± 37 to 33 ± 30; $p = 0.001$) but not in the non-culprit one (16 ± 7 to

16 ± 7; $p = 0.68$). In contrast, this improvement did not occur after IV delivery. Interestingly, the acute decrease in CTFC observed after IC administration of abciximab was present in 37% of patients with vs. 4% of those without a visible thrombus ($p = 0.008$)[39].

Bellandi *et al.*[40] reported results obtained in a population of consecutive patients with a first STEMI and infarct-related artery TIMI flow 0-1 undergoing primary PCI, randomly assigned to the IC ($n = 22$) or IV ($n = 23$) abciximab administration. Before starting PCI, patients received a bolus of abciximab either IC through a dual-lumen catheter (Multifunctional Probing) positioned below the occlusion, or IV. Bolus was followed by a 12-hr abciximab infusion in both groups. All patients underwent single photon emission computed tomography. Abciximab given IC resulted in a higher degree of myocardial salvage (20.4 ± 8.9 vs. 11.0 ± 7.5% of left ventricle; $p < 0.0001$) than the IV administration. This benefit was mainly related to a substantial reduction in the final infarct size (13.5 ± 11.2 vs. 21.4 ± 12.7% of left ventricle; $p < 0.044$), leading to an improvement in left ventricular ejection fraction (53.3 ± 9.5 vs. 46.3 ± 10.7%; $p < 0.035$) at 1 month after PCI[40].

A single-center prospective randomized trial aimed to evaluate the efficacy and safety of IC ($n = 72$) vs. IV ($n = 65$) administration of the abciximab bolus in patients undergoing coronary angioplasty with stent implantation was performed by Galache Osuna *et al.*[41]. The study included 57 patients with acute myocardial infarction and 80 with unstable angina. Considerably less post-procedural myocardial damage as assessed by troponin I was observed in the IC bolus group (an increase more than five times the upper limit for normal values: 26 vs. 51%; $p < 0.05$). Nevertheless, the clinical follow-up at 1 year did not reveal any difference in the incidence of major adverse cardiac events (8.5% in the IC group vs. 6.2% in the IV group; $p =$ ns) and major bleedings (detailed data not provided by the authors)[41].

The equivalence between abciximab bolus-only and abciximab bolus followed by a 12-hr infusion in a wide spectrum of patients after PCI was shown in the EASY trial[42]. However, it should be underlined that, according to the study protocol, patients with STEMI were excluded. A post hoc analysis of this trial was performed by Bertrand *et al.*[43]. Out of 1005 randomized patients undergoing a transradial coronary stent implantation, 208 received an IC and 797 received an IV abciximab bolus. Compared to IV abciximab administration, IC abciximab was not associated with less cardiac biomarkers release nor better clinical outcomes after uncomplicated transradial PCI[43].

Platelet aggregation inhibition (PAI) of ≥95% is associated with improved outcomes after PCI and GP IIb/IIIa inhibitor treatment. In the EASY-MI Study[44] 105 STEMI patients who had been referred for primary PCI within 6 hours of symptom onset were randomized to receive IC ($n = 53$) or IV ($n = 52$) abciximab bolus at a standard (0.25 mg/kg) or high dose (≥0.30 mg/kg). The primary end point of the trial was PAI measured at 10 minutes after the bolus of abciximab. The secondary end points included acute and 6-month outcomes using angiographic parameters, cardiac biomarkers, cardiovascular magnetic resonance imaging, and clinical variables. Aspiration thrombectomy was performed in 40% of the IC group patients and in 44% of the patients treated with IV bolus. At 10 minutes after the bolus, there was no difference in the proportion of patients with PAI ≥95% in the IC vs. IV (53 vs. 54%; $p = 1.00$) and the high-dose vs. standard-dose bolus groups (56 vs. 51%; $p = 0.70$). The TIMI flow grade and necrosis size, as assessed by cardiac biomarker measurement, were similar across the compared groups. The incidence of myocardial blush grade 2 and 3 was slightly higher in the IC group than in the IV group (88 vs. 75%, respectively; $p = 0.13$). Moreover, neither a higher dose nor IC abciximab bolus were associated with improved acute or late results compared to the standard IV dosing and administration[44].

Studies relating IC abciximab to improvement in clinical outcomes

A nonrandomized, retrospective comparison of the efficacy of IC ($n = 294$) and IV ($n = 109$) bolus of abciximab followed by 12 hours of IV infusion in patients with acute myocardial infarction ($n = 305$) or unstable angina ($n = 92$) was published by Wöhrle *et al.*[45]. At 30 days of follow-up, the incidence of major adverse cardiac events (MACE) including death, myocardial infarction, and urgent revascularization was significantly lower in patients with intracoronary compared with intravenous administration of abciximab (10.2 vs. 20.2%; $p < 0.008$). There was a significant interaction between the preprocedural TIMI flow, the application of abciximab, and the incidence of MACE. In patients with preprocedural TIMI 0/1 flow, MACE occurred significantly less often after IC abciximab, compared with the IV use (11.8 vs. 27.5%; $p < 0.002$). In contrast, the prevalence of MACE did not differ between the treatment strategies in patients with preprocedural TIMI 2/3 flow[45]. The authors did not report on bleeding events.

Another retrospective study published by Kakkar *et al.*[46] showed similar findings. In an unselected population of patients ($n = 173$; 31 patients with acute myocardial infarction) undergoing coronary stenting and abciximab administration, IC bolus ($n = 101$) injection was associated with a significantly lower 6-month composite endpoint of death or myocardial infarction (5.9 vs. 13.9%; $p < 0.04$) as compared to patients treated with IV bolus ($n = 72$). Major bleedings according to the TIMI definition were also less frequent in the IC group. However, the

difference did not reach statistical significance (4.0 vs. 8.3%; $p=0.32$). In both groups bolus was followed by a 12-hr IV infusion of abciximab[46].

In a single-site, randomized study Iversen *et al.*[47] assessed the efficacy and safety of IC ($n=185$) vs. IV ($n=170$) bolus of abciximab administered during primary PCI in STEMI patients and followed by a 12-hour IV infusion. Within 30 days after randomization significantly better results were observed in the IC group in terms of mortality (1.1 vs. 5.3%; $p=0.02$), target vessel revascularization (3.8 vs. 9.4%; $p=0.03$) and the composite end-point (target vessel revascularization, myocardial infarction or death: 7.6 vs. 19.4%; $p=0.001$). Since the total dose of abciximab was identical irrespective of the route of administration, as expected no differences concerning the safety of treatment (major and minor bleeding complications defined according to the study protocol: 1.6 vs. 2.4%; $p=0.62$ and 9.7 vs. 14.1%; $p=0.20$, respectively) between the groups were seen[47].

In the absence of results from large multicenter, randomized trials, a meta-analysis may provide clinically important information comparing results of two different strategies of treatment with abciximab – IC vs. IV. Data obtained from five randomized trials and three retrospective studies were analyzed by Hansen *et al.*[48]. The total number of 2301 patients, including 997 with STEMI, were incorporated in this meta-analysis. Pooled data analysis demonstrated significantly reduced mortality (odds ratio 0.57, 95% CI 0.35–0.94; $p=0.028$), and a trend toward a reduction of major adverse cardiac events (odds ratio 0.62, 95% CI 0.38–1.03; $p=0.066$) during up to 12 months of follow-up with IC vs. IV abciximab. A significant MACE reduction was observed after 1 month of follow-up exclusively in studies composed of patients with STEMI ($p<0.001$)[48]. Unfortunately, the authors did not assess bleeding complications.

Open questions

Results obtained in studies comparing IC and IV administration of abciximab in STEMI patients stand consistently in favor of the IC bolus in all studies[29,32,38,40,45–47] except one[44] (Table 1). Important limitations of these studies should be underlined: not all of the studies were randomized, all included relatively low numbers of patients, all were single-center, only some of them showed improvement in clinical outcome, while others revealed the superiority of IC administration only by assessment of different surrogate end points (infarct size assessed with biomarkers or imaging modalities, obstruction of coronary microcirculation evaluated by angiography or contrast-enhancement magnetic resonance, ST-segment resolution, markers of platelet activation), all were underpowered to assess bleeding complications as well as various bleeding definitions were applied.

In contrast to the superiority of IC vs. IV administration in high-risk STEMI patients, the relative gain in the low risk population is questionable.

Nevertheless, the answer to the question 'which way of abciximab administration is better?' seems to favor the IC route. However, before reaching a definitive conclusion further adequately powered, multi-center, randomized trials are warranted. Moreover, our knowledge concerning the optimal strategy of abciximab administration in STEMI patients is incomplete.

Several clinically relevant questions still remain unanswered:

- Does IC abciximab administration provide a better safety profile than the IV route?
- Can results of IC abciximab administration through the guiding catheter be further improved by the use of more selective delivery systems?
- Should IC abciximab be combined with thrombectomy?
- If so, should IC abciximab be administered before or rather after thrombectomy?
- Should the bolus of abciximab be followed by a prolonged IV infusion?

Below we discuss available knowledge regarding unanswered issues listed above and present design of several ongoing trials addressed to overcome some shortcomings of the previous studies.

Assessment of efficacy and safety profile of IC vs. IV abciximab administration

Limited number of participants and clinical events in completed studies precludes final conclusions regarding the safety and efficacy profile of IC vs. IV abciximab administration in the STEMI patients. Therefore the AIDA STEMI study[49] was designed. It is a randomized, multicenter, open-label, controlled trial designed to test whether IC abciximab bolus administration in comparison to standard IV application improves the clinical outcome of STEMI patients undergoing primary PCI. According to the study protocol a bolus of abciximab is followed by an IV infusion for 12 hours. In all patients, PCI of the infarct-related artery is performed according to standard procedures and the use of thrombectomy is strongly recommended in both groups, particularly in lesions with a high thrombus burden. The route of abciximab bolus delivery is the only difference between the compared groups. Abciximab bolus should be delivered directly after penetration of the culprit lesion with the PCI guiding wire to allow for high local concentrations of the antithrombotic agent at the thrombus and distal myocardium. No specific

Table 1. Summary of studies comparing intracoronary vs. intravenous abciximab administration in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention.

Authors	Year of publication	Study design	Number of participants IC/IV	Additional thrombectomy IC/IV	Bolus of abcximab followed by IV infusion IC/IV	Population	Efficacy end point/Result IC vs. IV	Safety end point/ Result IC vs. IV
Wöhrle *et al.*[45]	2003	Single-center, retrospective	294/109	No/No	Yes/Yes	STEMI/ NSTE-ACS	A composite of death, myocardial infarction, and urgent revascularization – in favor of IC administration	Bleeding events – not reported
Kakkar *et al.*[46]	2004	Single-center, retrospective	101/72	No/No	Yes/Yes	STEMI/ NSTE-ACS	A composite of death and myocardial infarction – in favor of IC administration	Major bleedings – neutral, numerically in favor of IC
Bellandi *et al.*[40]	2004	Single-center, prospective, randomized, open-label	22/23	No/No	Yes/Yes	STEMI	Ischemic events – not reported Myocardial salvage index assessed by SPECT – in favor of IC administration; Infarct size assessed by SPECT – in favor of IC administration; Left ventricular ejection fraction assessed by SPECT – in favor of IC administration	Bleeding events – not reported
Romagnoli *et al.*[39]	2005	Single-center, prospective, matched	37/37	No/No	Yes/Yes	STEMI/ NSTEACS	Corrected TIMI frame count in the culprit vessel – in favor of IC administration	Bleeding events – not reported
Galache Osuna *et al.*[41]	2006	Single-center, prospective, randomized, open-label	72/65	No/No	Yes/Yes	STEMI/ NSTE-ACS	A composite of death, myocardial infarction, repeat revascularization – neutral; Post-procedural myocardial damage assessed as an increase more than 5 times the upper limit for normal values of troponin I – in favor of IC administration	Major bleedings – neutral
Thiele *et al.*[32]	2008	Single-center, prospective, randomized, open-label	77/77	No/No	Yes/Yes	STEMI	A composite of cardiac death, myocardial infarction, target vessel revascularization and new onset congestive heart failure – in favor of IC administration of borderline significance; Infarct size evaluated by magnetic resonance – in favor of IC administration; Infarct size assessed by the area under the curve of creatine kinase release – in favor of IC administration;	Bleeding events – not reported

(*continued*)

Table 1. Continued.

Authors	Year of publication	Study design	Number of participants IC/IV	Additional thrombectomy IC/IV	Bolus of abciximab followed by IV infusion IC/IV	Population	Efficacy end point/Result IC vs. IV	Safety end point/ Result IC vs. IV
							Early and late microvascular obstruction evaluated by magnetic resonance – in favor of IC administration; ST-segment resolution – in favor of IC administration	
Dominguez-Rodriguez *et al.*[38]	2009	Single-center, prospective, randomized, open-label	25/25	Yes 100%/Yes 100%	Yes/Yes	STEMI	A composite of mortality, myocardial infarction and any revascularization – neutral Concentration of soluble CD40 ligand – in favor of IC administration; Infarct size assessed by the peak of troponin I release – in favor of IC administration	Bleeding events – not reported
Bertrand *et al.*[43]	2009	Post hoc analysis, single-center, prospective, randomized, open-label	208/797	No/No	Yes or No/ Yes or No	NSTE-ACS/ SA	A composite of death, myocardial infarction and target vessel revascularization – neutral; Infarct size assessed by the peak of biomarker release – neutral	Bleeding events – not reported
Gu *et al.*[29]	2010	Single-center, prospective, randomized, open-label	271/263	Yes 98%/Yes 97%	No/No	STEMI	A composite of cardiac mortality, myocardial infarction and target vessel revascularization – neutral; Myocardial blush grade – in favor of IC administration; Infarct size assessed by the peak of biomarker release – in favor of IC administration; Complete ST-segment resolution – neutral	Major bleedings – neutral; Minor bleedings – neutral
Bertrand *et al.*[44]	2010	Single-center, prospective, randomized, open-label	52/52	Yes 40%/Yes 44%	No/No	STEMI	Platelet aggregation inhibition $\geq$95% – neutral; Infarct size assessed by magnetic resonance and by the peak of biomarker release – neutral	Bleeding events – neutral but the study was underpowered to assess clinical outcomes

Iversen *et al.*[47]	2011	Single-center, prospective, randomized, open-label	185/170	No/No	Yes/Yes	STEMI	All cause-mortality – in favor of IC administration; Myocardial infarction – neutral; Target vessel revascularization – in favor of IC administration	Major bleedings – neutral, numerically in favor of IC administration; Minor bleedings – neutral, numerically in favor of IC administration

Detailed rates of end points are provided in the text.
IC – intracoronary; IV – intravenous; NSTE-ACS – non-ST-segment elevation acute coronary syndrome; SA – stable angina; SPECT – single photon emission computed tomography; STEMI – ST-segment elevation myocardial infarction.

infusion balloons or perfusion catheters are used. The primary efficacy end point of AIDA STEMI is the composite of all-cause mortality, recurrent myocardial infarction, or new onset congestive heart failure within 90 days of randomization. The primary safety outcome assessment will be major bleeding. The study population will consist of 1912 STEMI patients enrolled at 30 centers in Germany. Results of this trial are expected soon[49].

Selective delivery systems

A bolus of abciximab is usually administered through the guiding catheter into the infarct-related artery. However, this method of administration may not provide an optimal contact between the plaque components and abciximab, with the latter rapidly washed out by the coronary flow. Prati *et al.*[50] tested the effectiveness of local abciximab delivery to the site of IC thrombus vs. IC bolus infusion in patients with acute coronary syndromes undergoing PCI in the COCTAIL Study. For local IC delivery of abciximab a dedicated perfusion catheter – ClearWay RX Local Therapeutic Infusion Catheter (ClearWay, Atrium Medical Corp, Hudson, NH, USA) was applied. ClearWay is a low-profile, rapid-exchange therapeutic infusion catheter, indicated for localized perfusion of various diagnostic and therapeutic agents into the coronary and peripheral vasculature. The ClearWay therapeutic infusion catheter enables local drug delivery to reach approximately a 500-fold greater drug concentration vs. systemic delivery. Despite a low number of patients included ($n = 50$), very encouraging results were obtained. Significantly higher reduction of thrombus (mean percentage change of the thrombus score: 33.8 vs. 3.9%; $p = 0.002$) and superior corrected TIMI frame count (15.3 ± 10.2 vs. 21.1 ± 9.9; $p = 0.049$) were observed among patients of the local delivery group as compared with those of the IC infusion group. These benefits translated into better clinical outcome. Procedure-related myocardial infarction was observed in 10 and 43% ($p = 0.018$), while MACE at 1 year were observed in 5.9 and 27.2% of patients in the local delivery and intracoronary infusion groups, respectively ($p = 0.046$). These results strongly suggest that the use of the dedicated perfusion catheter leads to higher concentrations of abciximab within the thrombus, allowing for an additional antiplatelet, antithrombotic, and anti-inflammatory effect[50].

The effectiveness of an IC bolus of abciximab locally delivered using the ClearWay RX Local Therapeutic Infusion Catheter is also evaluated in the ongoing IC-Clearly Study[51]. The purpose of this randomized, open-label, multicenter trial is the comparison of a locally delivered bolus of abciximab with an IV bolus in STEMI patients with an angiographically visible thrombus (thrombus grade ≥ 2). The primary endpoint is infarct

size assessed by cardiac magnetic resonance. Clinical outcomes will be assessed for each patient at hospital discharge and at 30-day follow-up[51].

Recently preliminary results of the Crystal AMI trial have been presented[52]. In this single-center, prospectively randomized study the hypothesis that local IC delivery with ClearWay RX Local Therapeutic Infusion Catheter leads to more pronounced ST resolution, higher MBG, improved TIMI flow and smaller infarct size than IV abciximab in STEMI patients treated with primary PCI was tested. The majority of patients received manual thrombus aspiration in each study arm (65%). Because of a low number of patients enrolled in the study ($n = 50$), surrogate instead of clinical end points were chosen. Furthermore, the study was a pilot proof of concept trial, not powered to show statistical differences. Super-selective IC delivery of abciximab facilitated by the ClearWay catheter was safe and effective, and resulted in a better final TMI flow (TIMI 3: 96 vs. 82%; $p = 0.30$), higher MBG score (MBG of 3: 72 vs. 52%; $p = 0.15$), and more pronounced ST-segment resolution (80 vs. 70%; $p = 0.89$). Data regarding infarct size have not been presented so far.

Taking into account the reduction of the thrombus burden related to IC abciximab administration and the fact that this effect is probably even more pronounced by super-selective local delivery, such therapy may further facilitate the direct stenting approach. Direct stenting has been demonstrated to improve myocardial perfusion and to reduce risk of death and chronic heart failure in STEMI patients initially treated with fibrinolysis[53]. Thus it could be hypothesized that a greater use of primary stenting may be an additional positive effect of this therapy.

The application of thrombectomy in patients treated with IC abciximab

The question whether thrombus aspiration combined with local glycoprotein IIb/IIIa administration exerts a synergistic effect to reduce infarct size in STEMI patients undergoing primary PCI has not been answered yet. INFUSE-AMI is an ongoing, multicenter, open-label, controlled, single-blind randomized study testing the hypothesis that IC administration of an abciximab bolus with or without thrombus aspiration before stent implantation compared to no infusion with or without thrombus aspiration reduces infarct size among patients undergoing primary PCI for anterior STEMI who are treated with bivalirudin[54]. For IC administration the ClearWay RX Local Therapeutic Infusion Catheter is used. The study population consists of patients with anterior STEMI and an occlusion of proximal or mid-left anterior descending artery with TIMI 0, 1, or 2 grade flow undergoing primary PCI. Subjects are randomized to one of the following four arms: (1) local IC infusion of abciximab after thrombus aspiration, (2) local IC infusion of abciximab, without thrombectomy, (3) thrombus aspiration without IC abciximab, or (4) without IC abciximab and without thrombectomy. The primary end point is infarct size (percentage of total left ventricular mass) at 30 days measured by cardiac magnetic resonance imaging. Other secondary end points include microvascular obstruction assessed with cardiac magnetic resonance imaging at 5 days, ST-segment resolution, angiographic myocardial perfusion, thrombus burden, angiographic complications, and clinical events through 1-year follow-up[54].

The most beneficial sequence of administration of IC bolus of abciximab – i.e. before or after thrombectomy – should be defined in future studies.

The necessity of a prolonged IV infusion of abciximab after IC bolus administration

Results of the EASY trial proving the equivalence between abciximab bolus-only and abciximab bolus followed by a 12-h infusion in patients with unstable or stable angina treated with PCI are not automatically valid for the STEMI population[42]. From the pathophysiological point of view the potent antiplatelet action of abciximab is more important in STEMI, as the thrombus burden is usually much higher as compared to both stable and unstable angina. Moreover, prolonged IV infusion may be of higher importance in patients treated with IV bolus because of a more potent abciximab action due to its higher concentration in the culprit vessel with IC vs. IV bolus. Thus the question concerning the necessity of a prolonged IV infusion subsequent to the initial bolus of abciximab in STEMI patients is still waiting for the final answer.

Conclusions

An accumulating body of evidence suggests the superiority of IC over IV abciximab administration in STEMI patients treated with primary PCI. However, further trials are warranted to establish the optimal strategy of abciximab treatment in this setting.

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A.K., M.K., E.P.N., G.G., A.G., and J.K. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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