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REVIEW ARTICLE

Updated evidence on intracoronary abciximab in ST-elevation myocardial infarction: A systematic review and meta-analysis of randomized clinical trials

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Abstract

Background: *Intracoronary (IC) abciximab administration remains a promising approach aimed to increase a drug concentration in the target area and possibly improve clinical outcomes in the setting of ST-segment elevation myocardial infarction (STEMI). The goal of this literature review and meta-analysis is to update available knowledge comparing IC and intravenous (IV) abciximab administration in STEMI patients.*

Methods: *A total of 7 randomized clinical trials (RCTs) with a median follow-up of 3 months were included in the meta-analysis (n = 3311). All-cause mortality was selected as the primary end point while recurrent myocardial infarction (re-MI), target vessel revascularization (TVR) and major bleeding complications were the secondary end points.*

Results: *IC abciximab did not provide any benefits in terms of all-cause mortality as compared with IV abciximab (odds ratio [OR] 0.67; 95% confidence interval [CI] 0.34–1.34). However, this neutral effect was driven by the AIDA STEMI trial. The IC route was associated with a reduced rate of re-MI when compared with IV administration (OR 0.61; 95% CI 0.40–0.92) but the difference disappeared after one of the RCTs was excluded from the analysis. Both strategies were equal regarding TVR (OR 0.66; 95% CI 0.40–1.09) and major bleeding complications (OR 1.18; 95% CI 0.76–1.83).*

Conclusions: *Our updated meta-analysis shows that the clinical superiority of IC over IV abciximab administration in STEMI patients is no longer clear after the release of the AIDA STEMI trial results. Further research in high-risk STEMI patients is warranted to finally determine clinical advantages of IC* vs *IV abciximab administration.* (Cardiol J 2012; 19, 3: 230–242)

Key words: intracoronary abciximab, myocardial infarction, primary PCI

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Introduction

Therapy with glycoprotein (GP) IIb/IIIa receptor antagonist abciximab remains a widely implemented adjunctive strategy aimed to improve clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) [1–3]. Recent European guidelines on myocardial revascularization advise therapy with abciximab in STEMI patients with evidence of high intracoronary (IC) thrombus burden (class of recommendation IIa, level of evidence A) [1]. The standard abciximab administration regimen includes an intravenous (IV) bolus followed by a 12-h IV infusion. There are some theoretical advantages of IC abciximab administration over the IV route supported by data from some small single-center clinical studies in STEMI patients treated with pPCI. However, conflicting results regarding the effectiveness and safety of IC abciximab administration have been reported recently [4–7].

The aim of this systematic literature review and meta-analysis of randomized clinical trials (RCTs) is to update available knowledge comparing IC and IV abciximab administration in STEMI patients treated with pPCI with a special focus on the problem of inconsistency between recent reports.

A search covering the period from 1st January 1993 to 1st April 2012 was conducted by two independent investigators using PubMed, CENTRAL, Google Scholar and ClinicalTrials.gov 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 included. The following keywords were applied: "abciximab", "intracoronary administration", "primary PCI", "ST-elevation myocardial infarction" and "randomized trial". References of retrieved studies were searched manually for additional studies and reviews. No language restrictions were applied. Although we particularly focused on new studies [4, 7–10], long-term follow-ups of previously completed trials [5, 6] and recent meta-analyses [11–15], we also provide a background for our review presenting previous findings.

Why could IC abciximab administration possibly be superior to the IV route? Evidence from experimental studies

Abciximab 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 while adhesion and secretion are preserved [16–18]. Plasma concentration of abciximab available after an IV bolus and subsequent infusion is sufficient to develop effective decrease in platelet aggregation. In contrast to IV administration, the IC route results in much higher concentrations of abciximab within the culprit vessel, thus providing additional dose-dependent antithrombotic, and antiinflammatory effects [16, 19–24]. Desch et al. [8] sampling blood from the coronary sinus in STEMI patients have recently proved that a direct IC bolus injection results in a more pronounced local inhibition of platelet function and a higher degree of GP IIb/IIIa receptor occupancy compared with a standard IV bolus injection (median 93.5% [interquartile range 92.7––95.4] *vs* 74.0% [17.6–94.0]; p = 0.04). These data are in agreement with the latest observations from the ICE trial which demonstrated that IC when compared with IV bolus administration of eptifibatide, a competitive GP IIb/IIIa inhibitor, resulted in a higher local platelet GP IIb/IIIa receptor occupancy, which was associated with improved microvascular perfusion in patients undergoing urgent coronary stenting [25]. The difference in receptor occupancy between IC and IV administration of GP IIb/IIIa inhibitors had been assumed but demonstrated never before.

Marciniak et al. [20] 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. Inhibition of platelet-induced thrombin generation is an additional dose-dependent effect of abciximab resulting in a decreased release of platelet granules containing inhibitors of fibrinolysis such as plasminogen activator inhibitor-1 and α2-anti-plasmin [16]. High concentrations of abciximab 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 [26].

High local concentrations of abciximab obtainable with IC administration may result in some non-GP IIb/IIIa properties which 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 [16, 27, 28]. Interactions of abciximab with the Mac-1 leukocyte receptors and 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 [29–32].

All these mechanisms may play a role in reduction of reperfusion injury and a higher degree of myocardial salvage possibly translating into improvement in clinical outcome in patients treated with IC bolus of abciximab as compared with IV administration. This, however, was not confirmed in the recently published study evaluating the role of IC abciximab and bivalirudin on myocardial salvage and reperfusion injury in the porcine ischemia/ /reperfusion model [9]. Studied animals with myocardial infarction (MI) induced by balloon occlusion received IV bivalirudin and then five minutes prior to reperfusion, either a coronary downstream infusion of abciximab or saline. Similar size of the necrotic area in both groups as evaluated by histological assessment and biochemical marker concentrations is in line with comparable left ventricular ejection fraction (LVEF) at 48 h in abciximab- and saline-treated animals. However, the number of haemorrhagic infarctions detected by micro- and macroscopic evaluation tended to be higher in the abciximab-treated group (70 *vs* 20%; p = 0.07) [9]. The authors concluded that the lack of superiority of combined treatment with IC abciximab and peripheral bivalirudin over bivalirudin unaided in terms of myocardial salvage may be attributed to local abciximab-induced haemorrhage [9]. The fact that the infarct-related artery (IRA) was occluded with a balloon, rather than by a thrombus, presents a major limitation to this, otherwise elegant, experiment as it eliminated the risk of thrombus-related distal embolization, a key target of abciximab action in the STEMI setting.

Clinical studies overview before the AIDA STEMI trial

In a nonrandomized, retrospective study carried out in patients (n = 397) with a broad spectrum of acute coronary syndromes (ACS) published by Wohrle et al. [33] the incidence of major adverse cardiac events (MACE) including death, MI, and urgent revascularization was significantly lower in patients with IC compared with IV administration of abciximab (10.2 *vs* 20.2%; p < 0.008) at 30 days of follow-up. MACE occurred significantly less often after IC abciximab as compared with the IV use only in patients with pre-procedural TIMI 0/1 flow, but not with TIMI 2/3 flow [33].

In a retrospective study published by Kakkar et al. [34] in unselected patients (n = 173) undergoing coronary stenting and abciximab administration, the incidence of the 6-month composite endpoint of death or MI was significantly lower in the IC than in the IV bolus injection group (5.9 *vs* 13.9%; p < 0.04).

Bellandi et al. [35] reported a substantial reduction in the final infarct size assessed by single photon emission tomography (13.5 ± 11.2 *vs* 21.4 ± ± 12.7% of left ventricle [LV]; p < 0.044), leading to an improvement in LVEF (53.3 ± 9.5 *vs* 46.3 ± ± 10.7%; p < 0.035) at 1 month after pPCI with IC *vs* IV abciximab administration in consecutive patients with a first STEMI (n = 45) and pre-procedural IRA TIMI flow 0–1.

A significant improvement in coronary flow in the culprit vessel after IC abciximab administration (corrected TIMI frame count 48 ± 37 to 33 ± 33; p = 0.001) but not after IV delivery was observed by Romagnoli et al. [36] in patients with ACS undergoing urgent PCI. Interestingly, the acute decrease in the corrected TIMI frame count after IC bolus occurred in 37% of patients with *vs* 4% of those without a visible thrombus (p = 0.008).

Galache Osuna et al. [37] found considerably less post-procedural myocardial damage as assessed by troponin I and defined as an over 5-fold increase above the upper normal value (26 *vs* 51%; p < 0.05) in patients treated with an IC bolus of abciximab (n = 72) than in those receiving IV treatment (n = 65) in the setting of ACS treated with coronary angioplasty with stent implantation.

In the randomized LIPSIAbciximab-STEMI study published by Thiele et al. [38] the infarct size evaluated by magnetic resonance imaging was significantly smaller after IC (n = 77) compared with IV (n = 77) abciximab bolus administration. The extent of microvascular obstruction was smaller and ST-segment resolution was significantly more pronounced in the IC abciximab group. It should be underlined that IC *vs* IV abciximab bolus administration rendered greater clinical benefit in case of anterior MI, time from symptom onset to reperfusion > 4 h, as well as impaired TIMI flow and perfusion grades after pPCI [38]. A tendency, not quite reaching statistical significance, towards lower rates of the composite MACE (cardiac deaths, nonfatal reinfarctions, need for target vessel revascularization (TVR), new onset congestive heart failure) at 30 days follow-up was seen after IC *vs* IV abciximab administration (5.2 *vs* 15.6%, p = 0.06) [35]. As recently reported, the advantage of the IC strategy was maintained during long-term observation [6]. After 6 months of follow-up significantly smaller infarct size and less cases of LV remodeling were

observed in the IC abciximab group as compared with the standard IV treatment. Moreover, a significant recovery of LV function was exclusively observed in the IC abciximab group. These beneficial effects were also translated into a trend towards a reduced MACE rate in the IC abciximab group at 6-month follow-up (10 *vs* 21%, p = 0.07) [6].

Furthermore, a subanalysis of the LIPSIAbciximab-STEMI study [10] revealed that the incidence of aborted MI (≥ 50% ST-segment resolution and a lack of subsequent cardiac enzyme rise ≥ 2-fold the upper normal limit) was significantly higher in the IC than IV group.

Dominguez-Rodriguez et al. [39] showed a higher reduction in soluble CD40 ligand concentration after IC bolus abciximab administration as compared with the IV route in patients with STEMI undergoing thrombus aspiration during pPCI. CD40 ligand (CD40L) regarded as a unique molecule linking inflammation, thrombosis, and restenosis, is secreted by circulating aggregates of platelets and leukocytes. Soluble CD40 ligand binds to platelets via an αIIbβ3-dependent mechanism and triggers further platelet activation. Moreover, the IC strategy was associated with a significantly smaller infarct size when compared with IV bolus application. Due to the limited number of patients, no significant differences were detected in terms of clinical outcome at 30-day follow-up [39].

A *post hoc* analysis of the EASY trial performed by Bertrand et al. [40] showed no differences between patients receiving IC and IV bolus abciximab regarding the cardiac necrosis biomarkers (creatine kinase-MB, and troponin T) release or the clinical outcomes after uncomplicated transradial coronary stent implantation. However, it should be underlined that, according to the study protocol, STEMI patients were excluded.

A relevant improvement in myocardial reperfusion assessed as myocardial blush grade (MBG) 2/3 (76 *vs* 67%; p = 0.022) and a decrease of about 30% in the enzymatic infarct size (p = 0.008) were observed in the CICERO trial [41] in STEMI patients randomized to IC bolus application of abciximab (n = 271) given directly after thrombectomy compared with IV bolus administration (n = 263). However, the rates of complete ST-segment resolution (64 *vs* 62%; p = 0.562) were comparable between the groups. Furthermore, the study had insufficient power to detect significant differences in clinical events [41].

In the EASY-MI Study, STEMI patients who had been referred for pPCI within 6 h of symptom onset, were randomized to receive IC or IV abciximab bolus at a standard (0.25 mg/kg) or high dose (≥ 0.30 mg/kg) [42]. Aspiration thrombectomy was performed in 40% of the IC group and in 44% of those treated with IV bolus. Neither the higher dose nor IC abciximab bolus were associated with greater inhibition of platelet aggregation, improved acute or late results compared with the standard IV dosing and administration [42].

In a single-site, randomized study in STEMI patients (n = 355) undergoing pPCI Iversen et al. [43] reported significantly better results with IC *vs* IV abciximab in terms of mortality (1.1 *vs* 5.3%; p = 0.02), TVR (3.8 *vs* 9.4%; p = 0.03) and the composite end-point including all-cause death, MI and TVR (7.6 *vs* 19.4%; p = 0.001) within 30 days after randomization. Recently the authors have published results of 1-year follow-up. Benefits of IC abciximab administration regarding mortality (2.7 *vs* 10.0%; p = 0.004), TVR (7.6 *vs* 14.1%; p = 0.04) and the composite end-point (9.2 *vs* 20.6%; p = 0.002) were maintained at 1 year and the difference in the rates of MI (5.4 *vs* 11.8%; p = 0.03) became significant in favour of the IC route [43].

Some of the studies mentioned above failed to show any clinical advantage of IC administration of abciximab over the IV route [6, 30, 33–36, 38]. However, except for the EASY and EASY-MI trials [40, 42] characterized by low risk profiles of the studied populations, all other studies demonstrated improvements in 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) related to IC as compared with IV abciximab administration. It should be underlined that data from other studies strongly suggest superiority of IC over IV administration in high-risk STEMI patients, while the relative gain in the low risk population is questionable [5, 6, 33––39, 41, 43].

The bolus of abciximab is usually administered through the guiding catheter into the IRA. However, the use of a dedicated perfusion catheter — ClearWay RX Local Therapeutic Infusion Catheter (ClearWay, Atrium Medical Corp, Hudson, NH) facilitates local drug delivery resulting in obtaining a much higher drug concentration within the culprit artery since it prevents loss of abciximab in the aorta and a rapid wash out of the drug by the coronary flow. Prati et al. [44] tested the effectiveness of local abciximab delivery to the site of IC thrombus *vs* IC bolus infusion in patients with ACS undergoing coronary angioplasty in the COCTAIL

Study. Despite a low number of patients included (n = 50), encouraging results were obtained: a 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 significantly better short- (procedure-related MI: 10 *vs* 43%; p = 0.018) and long-term (MACE at 1 year: 5.9 *vs* 27.2%; p = 0.046) clinical outcome. 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 antiinflammatory effect [44].

Selective IC delivery of abciximab facilitated by the ClearWay catheter tested in the Crystal AMI trial was safe and produced higher myocardial blush scores (MBG of 3: 75 *vs* 45%) as well as a trend towards more significant ST-segment resolution (80 *vs* 70%) [45].

Meta-analyses before the AIDA STEMI trial

The available knowledge regarding the comparison of the IC abciximab regimen *vs* the IV standard route was summarized in six different meta-analyses [11–15, 46, 47].

All trials included in these meta-analyses have important limitations: all were carried as single-center studies with relatively low numbers of participants and only some of them were randomized. One of the meta-analyses mixed different clinical scenarios (STEMI and non-ST-elevation ACS) [46, 47] while two others assessed various GP IIb/IIIa inhibitors [12, 15]. Nevertheless, all meta-analyses provided valuable and clinically relevant information.

The meta-analysis by Hansen et al. [46] included data from five randomized and three retrospective studies, with a total number of 2,301 patients, including 997 with STEMI. Pooled data analysis demonstrated significantly reduced mortality (OR [95% CI] = 0.57 [0.35–0.94]; p = 0.028), and a trend toward reduction of MACE (OR [95% CI] = 0.62 [0.38–1.03]; p = 0.066) during up to 12 months of follow-up with IC *vs* IV abciximab. The significant reduction of MACE after 1 month of follow-up was exclusively limited to studies composed of STEMI patients [46].

The aim of the meta-analysis performed by Navarese et al. [11] and incorporating 6 randomized trials with a total number of 1246 participants, was to assess the clinical efficacy and safety of IC *vs* IV abciximab administration in STEMI patients undergoing primary angioplasty basing exclusively on randomized trials. At 30 days IC abciximab was associated with marked reductions in mortality (OR [95% CI] = 0.43 [0.20–0.94]; p = 0.03) and TVR (OR [95% CI] = 0.53 [0.29–0.99]; p = 0.05) as compared with IV abciximab, but no significant difference regarding the prevalence of recurrent MI was observed between the two strategies. Importantly, the clinical advantages of IC abciximab treatment were not associated with any excess of major bleeding complications [11].

Friedland et al. [12] searched for randomized studies comparing IC with IV administration of different GPIs (abciximab, eptifibatide, tirofiban) during coronary angioplasty. Ten randomized studies involving 1590 patients were included into the meta-analysis. Seven of these studies were composed only of STEMI patients while in the others the percentage of such patients ranged from 26% to 63%. One study examined eptifibatide, 2 others tested tirofiban while the 7 remaining studies investigated abciximab. No difference in terms of safety and tolerability of IC and IV administration was observed. Patients treated with IC administration of GP IIb/IIIa inhibitors were more likely to have complete reperfusion (TIMIgrade 3 flow) after the intervention (RR [95% CI] = 1.08 [1.02–1.15]). IC administration was also associated with a significant decrease in short-term (1 month to 3 months) TVR (RR [95% CI] = 0.54 [0.30–0.96]) as well as in short-term mortality (RR [95% CI] = 0.45 [0.23–0.90]). The difference in mortality was no longer significant in the mid-/long-term follow-up (≥ 6 months) [12].

Three other meta-analyses comparing IC *vs* IV abciximab administration in the setting of pPCI have been published recently [13–15]. Despite differences in their design as well as the characteristics of studies included [11–15, 46, 47], all meta-analyses present a consistent message, showing superiority of IC over IV administration of abciximab regarding clinical outcome.

AIDA STEMI trial: Lost battle or lost war?

Recently, long awaited results of the first multicenter, randomized, open-label, controlled trial testing whether IC abciximab bolus administration in comparison to standard IV application improves the clinical outcome of STEMI patients undergoing pPCI have been published [4]. According to the AIDA STEMI study protocol, the IC bolus delivered

Table 1. Results of the AIDA STEMI trial [4]

End point	IC abciximab	IV abciximab	P
Efficacy			
A composite of all-cause death, reinfarction, new congestive heart failure at 90 days	65/935 (7.0%)	71/932 (7.6%)	0.58
All-cause death at 90 days	42/935 (4.5%)	34/932 (3.6%)	0.36
Reinfarction at 90 days	17/935 (1.8%)	17/932 (1.8%)	0.99
New congestive heart failure at 90 days	22/935 (2.4%)	38/935 (4.1%)	0.04
Safety			
Bleedings according to the GUSTO definition at 90 days	131/985 (13.3%)	129/999 (12.9%)	0.63
Life-threatening/severe	26/985 (2.6%)	18/999 (1.8%)	
Moderate	26/985 (2.6%)	26/999 (2.6%)	
Mild	79/985 (8.0%)	85/999 (8.5%)	
Stroke in-hospital	5/985 (0.5%)	7/999 (0.6%)	0.7
Stent thrombosis according to the ARC definition	17/985 (1.7%)	20/999 (2.0%)	0.65
Definitive	5	12	
Probable	12	8	
Hemodynamic compromise during abciximab bolus	1/985 (0.1%)	6/999 (0.6%)	0.06
Life-threatening arrhythmia during pPCI	17/985 (1.7%)	21/999 (2.1%)	0.22

ARC — Academic Research Consortium; IC — intracoronary; IV — intravenous; pPCI — primary percutaneous coronary intervention

directly through the guiding catheter as well as the IV bolus were followed by an IV infusion of abciximab for 12 h [4]. Thrombectomy was used in about 20% of patients almost equally in both groups, particularly in lesions with high thrombus burden. The abciximab bolus was administered directly after penetration of the culprit lesion with the guiding wire to allow for high local concentrations of the antithrombotic agent at the thrombus and distal myocardium. No specific infusion balloons or perfusion catheters were used. The primary study endpoint was the composite of all-cause death, reinfarction, or new congestive heart failure within 90 days after randomization. The secondary endpoints were defined as: time to occurrence of combined clinical endpoint, TIMI-flow post pPCI, ST-segment resolution, infarct size assessed by creatine kinase-release. Safety outcome was evaluated on the basis of the occurrence of bleeding according to the GUSTO definition and life-threatening arrhythmia or hemodynamic compromise during the abciximab injection. The study population consisted of 2065 patients with a suspected STEMI enrolled at 30 centers in Germany [4]. With regard to previous studies and meta-analyses results, the AIDA STEMI trial was expected to confirm the superiority of IC over IV administration in STEMI patients treated with pPCI. The opposite was shown however (Table 1) [4]. The cumulative primary clinical end-point did not differ between the IC and IV groups. However, curves reflecting cumulative event-free survival had diverging directions in favour of the IC strategy, while after approximately 10–15 days they tended to converge. What could possibly be the explanation of this phenomenon? Since abciximab acts during the first hours after administration, it can be assumed that the gain of IC administration was obtained early after the procedure, but subsequently lost. Looking for the reason of the reversal of the initially observed tendency, one may speculate that those who gained most from IC abciximab are more prone to have cardiovascular events if the following antiplatelet therapy is insufficient. A reported tendency towards better outcomes with IC *vs* IV abciximab with prasugrel instead of clopidogrel as the following antiplatelet agent seems to support this hypothesis. Significantly better results obtained with IC administration of abciximab regarding the occurrence of heart failure are very difficult to interpret and they may be accidental as no difference between the compared strategies of treatment regarding the secondary end-points was observed. Both strategies were equally safe [4].

In the context of these disappointing results, some important comments should be made. Very low 90-days all-cause mortality (4.5 and 3.6% for IC and IV groups, respectively) along with only modestly impaired LV systolic function in most of the study patients (a median LVEF of 50% in both arms)

suggest that the majority of the population investigated in the AIDA STEMI trial was at low risk [4] while according to the existing data the superiority of IC over IV abciximab administration can be expected mainly in high risk populations. Although Thiele at al. [38] demonstrated in the LIPSIA pilot study that the beneficial effect of IC abciximab administration on infarct size and microvascular obstruction was mostly restricted to high risk subjects (anterior STEMI, impaired epicardial blood flow after pPCI, late hospital admission after symptom onset), they designed the AIDA STEMI trial as an all-comer study [4]. In our opinion, this approach was inappropriate as a significant relationship between a patient's risk profile and GP IIb/IIIa inhibitor — dependent benefits regarding mortality has been proven [48]. Therefore, no advantage of IC over IV abciximab administration should be assumed in low- and intermediate-risk STEMI patients where GP IIb/IIIa inhibitors do not improve the prognosis in general.

Furthermore, despite being the largest trial assessing clinical outcomes in patients treated with IC abciximab, the AIDA STEMI trial seems to be underpowered for the primary end point, as the event rate within 90 days in the IV arm as estimated by the investigators in the sample size calculation was 12% [4]. Similarly, a 4% absolute risk reduction for the primary end point associated with IC abciximab injection is probably overestimated when considering the risk profile of the study participants [4].

Hopefully, subgroup analyses of the trial might provide a substantial insight into the knowledge on subsets of patients who particularly benefit from IC abciximab administration. Such information would help to design future studies in this filed.

Updated meta-analysis of randomized clinical trials comparing IC and IV abciximab administration in STEMI

Due to the release of the AIDA STEMI trial results [4] and extended follow-ups of other studies [5, 6] we aimed to perform an updated meta-analysis of randomized trials (RCTs) comparing the clinical efficacy and safety of IC *vs* IV abciximab administration in STEMI patients treated with pPCI.

The methods were previously described in details [11]. Briefly, we conducted the present meta-analysis according to established methods, following the guidelines by the Cochrane Collaboration [49], and the PRISMA statement for reporting systematic reviews and meta-analyses in health care interventions [50]. A systematic investigation of all published and unpublished literature including oral presentations was performed as reported in the introduction section, to minimize the risk of a bias. The quality of included studies was appraised by two unblinded reviewers. Data were abstracted on prespecified forms by two independent investigators, neither involved in any of the retrieved studies. Divergences were resolved by discussion with a third investigator.

Citations were screened at the title/abstract level and retrieved as full reports. The inclusion criteria were: i) studies comparing IC *vs* IV administration of abciximab in ii) STEMI patients undergoing pPCI iii) RCTs. The main exclusion criteria included: 1) absence of comparator group and 2) observational not randomized studies.

All-cause mortality was selected as the primary end point while MI, TVR and major bleeding complications were the secondary end points. We performed a prespecified subanalysis of RCTs released before the AIDA STEMI trial.

Odds ratios (ORs) and 95% confidence intervals (95% CI) were computed from individual studies according to the intention-to-treat principle. Between-study heterogeneity was evaluated with the 2 test-based Q statistic and was considered statistically significant at a level of < 0.10 [50]. Pooled OR was calculated using a Fixed-Effect Model with the Mantel-Haenszel method. The DerSimonian and Laird Random Effect Model was used in case of significant heterogeneity and/or moderate or significant inconsistency ($> 50\%$) across the studies. The potential publication bias was examined by constructing a "funnel plot", in which sample size was plotted against ORs [51]. In addition, a mathematical estimate of asymmetry of this plot was provided by the linear regression approach [52]. Asymmetry was considered to be present if the intercept of the regression line deviated significantly from zero. All analyses were conducted using Review Manager version 5.1 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

After a systematic search 6562 citations were identified: 155 in the PubMed database, 206 in the CENTRAL database, 5770 in the Google Scholar database, and 431 in other databases. 6549 titles/abstracts were excluded as non-relevant. We found 13 trials fulfilling the inclusion criteria. Among them 6 studies were excluded according to explicit selection criteria: absence of a comparator group ($n = 1$), non-randomized studies ($n = 3$), duplicate reporting ($n = 1$), and lack of follow-up outcome data ($n = 1$). A total of seven RCTs were finally

included in the meta-analysis (n = 3311). The total numbers of patients were 1668 and 1643 in the IC and IV groups, respectively. However, results of the AIDA STEMI trial (n = 2065) include data for death and MI and for bleeding complications only for 1867 and 1984 patients, respectively. In case of clinical events reported within a particular study at different time points, the longest follow-up was accounted for in the analysis. Durations of follow-up periods of the studies included in our meta-analysis ranged from 1 month to 1 year with a median value of 3 months. Characteristics of the studies incorporated in the meta-analysis are presented in Table 2.

Seven studies reported all-cause mortality. In the overall cohort of patients there were a total of 120 deaths, 3.56% (56/1571) in the IC and 4.15% (64/1542) in the IV abciximab group. There was no evidence of publication bias as assessed by visual inspection of the funnel plot and confirmed by lack of significance in the Egger's test. Since significant heterogeneity among the included studies was found, we applied the DerSimonian and Laird Random Effect Model. In the overall population IC abciximab did not provide any benefits in terms of all-cause mortality compared with IV abciximab (Fig. 1). However, sensitivity analysis revealed that this neutral effect was driven by the AIDA STEMI trial, whereas data from other RCTs suggested reduced all-cause mortality associated with IC abciximab administration.

A total of 96 patients experienced recurrent MI. Overall comparison indicated the superiority of IC abciximab administration over the IV route in terms of reduction in recurrent MI (2.5 *vs* 3.88%): OR_{Fixed} [95% CI] = 0.61 [0.40–0.92]; p = 0.02 (Fig. 2). Sensitivity analysis demonstrated inconsistency of obtained results. After removal of the study by Iversen et al. [5, 43], the difference was no longer significant in favour of IC abciximab administration.

IC abciximab administration was comparable to the IV route considering its impact on the occurrence of TVR (Fig. 3) and major bleedings (Fig. 4). None of the studies influenced the overall results for both end points.

It is important to be aware of the drawbacks of our meta-analysis. If performed on individual patient's data it would certainly provide more detailed results, particularly by performing subgroup analyses. The inherent limitations of the studies incorporated into our meta-analysis include: a limited number of enrolled patients, variability of administration methods and various definitions of major bleedings.

Our updated meta-analysis shows that the clinical superiority of IC over IV abciximab administration in STEMI patients is no longer clear after the release of the AIDA STEMI trial results.

New insights from the INFUSE-AMI study

A considerable variability in the penetration of thrombectomy was observed in previously published studies. The thrombus aspiration combined with local administration of abciximab may exert a synergistic effect to reduce infarct size in STEMI patients undergoing pPCI. However, as both approaches are aimed to diminish thrombus burden, competitive effect could not be excluded [53].

Recently results of the INFUSE-AMI trial have been presented during the late-breaking clinical-trials session at the American College of Cardiology 2012 Scientific Sessions and have been simultaneously published online in the "Journal of the American Medical Association" [7]. This multicenter, open-label, controlled, single-blind randomized study tested the hypothesis that IC administration of abciximab bolus with or without thrombus aspiration before stent implantation compared with no infusion with or without thrombus aspiration reduces infarct size among patients undergoing pPCI for anterior STEMI who are treated with bivalirudin [7]. Four hundred fifty two high-risk STEMI patients with an extensive region of myocardium jeopardized due to occlusion of a proximal or mid-left anterior descending artery were enrolled. Subjects were randomized to one of the following 4 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) no IC abciximab and no thrombectomy. For IC administration of 0.25-mg/kg bolus of abciximab the ClearWay RX Local Therapeutic Infusion Catheter was used.

The primary end point of the study, infarct size at 30 days assessed by cardiac magnetic resonance imaging, was significantly reduced by bolus IC abciximab selectively delivered to the target area (median, 15.1%; interquartile range [IQR], 6.8–22.7%; n = 181, *vs* 17.9% [IQR, 10.3–25.4%]; n = 172; p = 0.03) but not by manual aspiration thrombectomy (median, 17.0% [IQR, 9.0–22.8%]; n = 174, *vs* 17.3% [IQR, 7.1–25.5%]; n = 179; p = 0.51) [7].

These findings confirm the usefulness of local IC abciximab infusion through the selective delivery catheter. The surprising lack of benefit with thrombus aspiration in the INFUSE-AMI trial warrants further investigation in large studies.

Table 2. Summary of studies comparing intracoronary *vs* intravenous abciximab administration in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention.

Author	Study name	Year of publication	Journal	Study design	Number of participants IC/IV	Symptom onset [h]	Additional thrombectomy IC/IV	Bolus of abciximab [0.25 mg/kg] followed by IV 12 h infusion [0.125 μg/kg/min] IC/IV	Reported follow-up [months]	End point	MBG at end of procedure (2-3) IC/IV	TIMI flow grade (3) after PCI IC/IV	In favour of	Definition of major bleeding
Thiele	LIPSIA	2008 2011	*Circulation Clin Res Cardiol*	Single-center, prospective, randomized, open-label	77/77	< 12	No/No	Yes/Yes	1 6	Clinical Surrogate	92.2%/ /80.5%	84.4%/ /85.7%	Neutral for clinical end point; IC administration beneficial for surrogate end point	Protocol
Dominguez--Rodriguez	–	2009	*Athero-sclerosis*	Single-center, prospective, randomized, open-label	25/25	< 6	Yes/Yes	Yes/Yes	1	Clinical Surrogate	NR	88%/ /68%	Neutral for clinical end point; IC administration beneficial for surrogate end point	Protocol
Gu	CICERO	2010	*Circulation*	Single-center, prospective, randomized, open-label	271/263	< 12	Yes (98%)/ /Yes (97%)	No/No	1	Clinical Surrogate	76%/ /67%	89%/ /86%	Neutral for clinical end point; IC administration beneficial for surrogate end point	TIMI
Bertrand	EASY-MI	2010	*Am J Cardiol*	Single-center, prospective, randomized, double-blind, placebo--controlled	53/52	< 6	Yes (40%)/ /Yes (44%)	Yes* or No/ /Yes or No	12	Clinical Surrogate	88%/ /75%	93%/ /90%	Neutral for clinical end point; neutral for surrogate end point	REPLACE
Dave	CRYSTAL AMI	2010	*Preliminary results*	Single-center, prospective, randomized	25/23	< 6	Yes (72%)/ /Yes (61%)	Yes/Yes	1	Surrogate Clinical	92%/ /86%	NR	A proof of concept study underpowered for end points	Protocol
Iversen	–	2011 2011	*J Interven Cardiol Cardiology*	Single-center, prospective, randomized, open-label	185/170	< 12	No/No	Yes/Yes	1 12	Clinical	NR	81%/ /73%	IC	Protocol
Thiele	AIDA STEMI	2012	*Lancet*	Multi-center, prospective, randomized, open-label, controlled	1032/1033	< 12	Yes (21%)/ /Yes (19%)	Yes/Yes	3	Clinical	NR	88.6%/ /89.0%	Neutral for clinical end point; neutral for surrogate end point	GUSTO

*Abciximab bolus dosage: standard dose — 0.25 mg/kg or high dose (≥ 0.30 mg/dL = 0.25 mg/kg + standard infusion amount); IC — intracoronary; IV — intravenous; MBG — myocardial blush grade; NR — not reported; STEMI — ST-segment elevation myocardial infarction

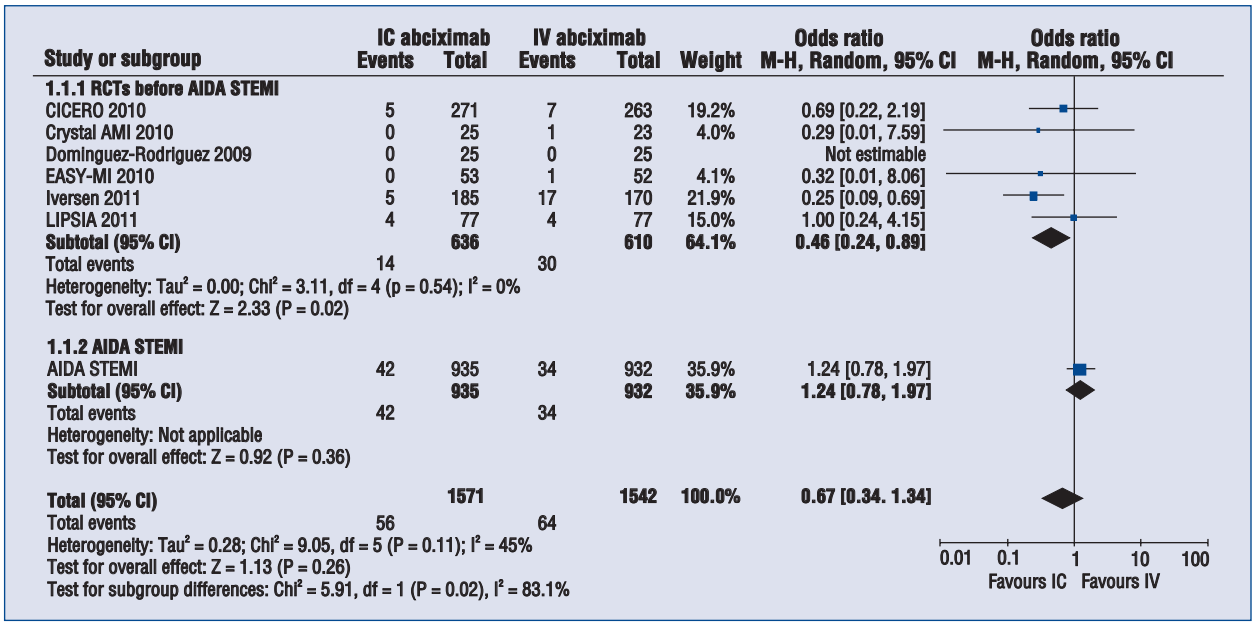

Figure 1. All-cause mortality in randomized clinical trials comparing intracoronary (IC) and intravenous (IV) abciximab administration in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. Results are presented as odds ratio (ORs) and their confidence interval (CIs). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial; RCT — randomized clinical trial.

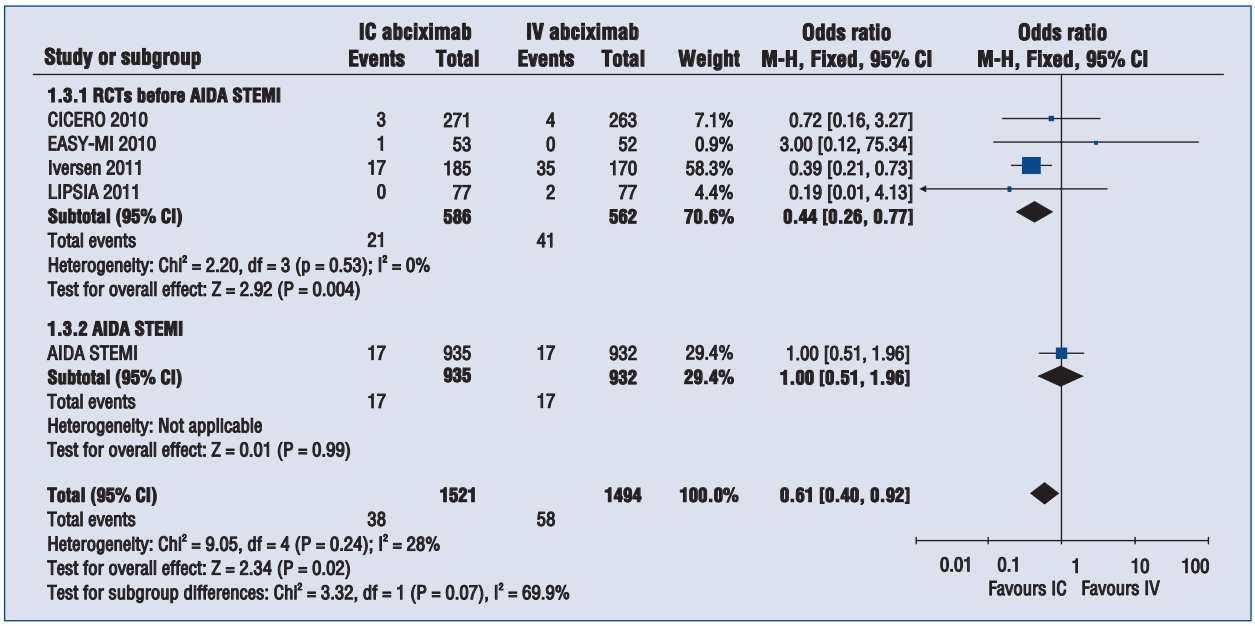

Figure 2. Recurrent myocardial infarction in randomized clinical trials comparing intracoronary (IC) and intravenous (IV) abciximab administration in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. Results are presented as odds ratio (ORs) and their confidence interval (CIs). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial; RCT — randomized clinical trial.

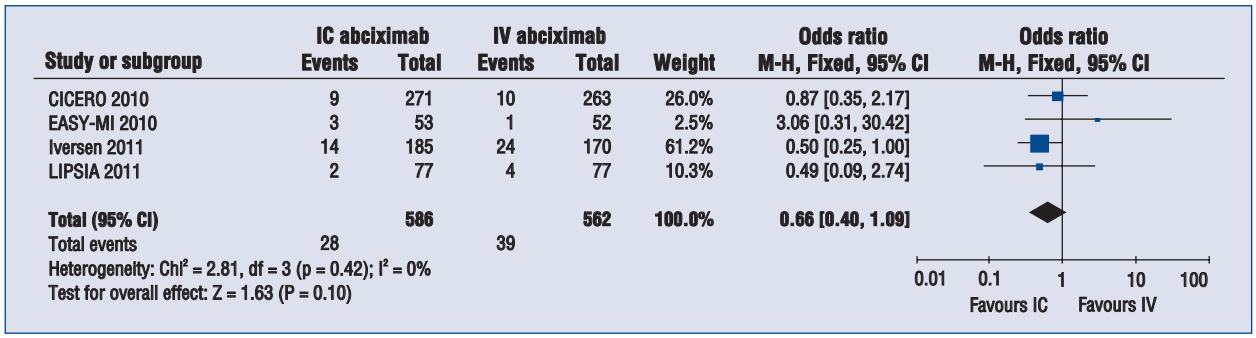

Figure 3. Target vessel revascularization in randomized clinical trials comparing intracoronary (IC) and intravenous (IV) abciximab administration in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. Results are presented as odds ratio (ORs) and their confidence interval (CIs). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial; RCT — randomized clinical trial.

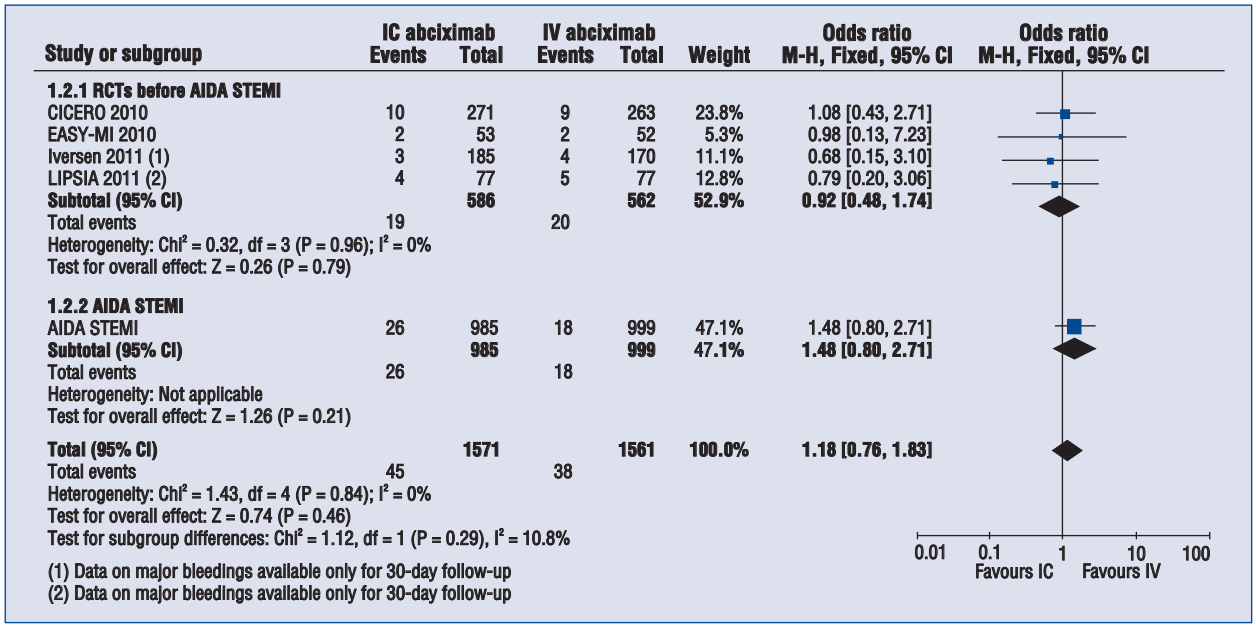

Figure 4. Major bleedings in randomized clinical trials comparing intracoronary (IC) and intravenous (IV) abciximab administration in segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. Results are presented as odds ratio (ORs) and their confidence interval (CIs). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial; RCT — randomized clinical trial.

Ongoing trials

The ongoing studies (ICAT [54], IC-Clearly [55], TOLEDO 1 [56], EASY-RESCUE [57]) are expected to answer several burning questions. Nevertheless not all important questions have still been addressed. Among high-risk patients with ACS, the early invasive strategy with selective downstream administration of GP IIb/IIIa inhibitors is the strategy of choice, whereas bivalirudin should be considered in patients at high risk for bleeding complications. Therefore, the combination of new inhibitors of $P2Y_{12}$ receptor and bivalirudin may appear an appealing strategy with maintained protection from ischemic events and potentially lower risk of bleeding complications in comparison to adjunctive therapy with GP IIb/IIIa inhibitors. The ongoing randomized trials will hopefully provide further insights on this issue.

Conclusions

The IC regimen remains an easy-to-use alternative to IV abciximab administration resulting in a higher drug concentration in the target area and potential additional dose-dependent antiplatelet, antithrombotic, and antiinflammatory effects. However, the IC route for abciximab administration cannot be currently recommended as the preferred option basing on the results of the AIDA STEMI trial and our updated meta-analysis. In our opinion, therapy with abciximab regardless the route of administration should be restricted to high-risk STEMI patients, particularly these with a visible thrombus impairing coronary blood flow. Furthermore, we believe that the negative results of the AIDA STEMI trial are driven by inappropriate inclusion criteria. As these data are in conflict with experimental studies and previous clinical trials, conduction of another adequately powered study enrolling exclusively high-risk participants with a high thrombus burden and large area at risk seems to be the only solution to finally determine the clinical efficacy and safety of IC abciximab administration in the STEMI setting. In addition, other issues that should be further addressed in future studies include: use of IC abciximab in combination with thrombectomy, role of selective delivery systems when compared with abciximab administration through the guiding catheter, necessity for a prolonged IV infusion of abciximab after IC bolus administration, and comparison between IC abciximab administration and bivalirudin with concomitant treatment with new inhibitors of the $P2Y_{12}$ receptor.

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References

1. Wijns W, Kolh P, Danchin N et al. Guidelines on myocardial revascularization. Eur Heart J, 2010; 31: 2501–2555.
2. Kushner FG, Hand M, Smith SC Jr et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2009; 54: 2205—2241.
3. Hagemeyer CE, Peter K. Targeting the platelet integrin GPIIb//IIIa. Curr Pharm Des, 2010; 16: 4119–4133.
4. Thiele H, Wöhrle J, Hambrecht R et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. Lancet, 2012; 379: 923–931.
5. Iversen AZ, Galatius S, Abildgaard U et al. Intracoronary Compared to Intravenous Abciximab in Patients with ST Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention Reduces Mortality, Target Vessel Revascularization and Reinfarction after 1 Year. Cardiology, 2011; 120: 43–49.
6. Eitel I, Friedenberger J, Fuernau G et al. Intracoronary versus intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: 6-month effects on infarct size and left ventricular function. The randomised Leipzig Immediate PercutaneouS Coronary Intervention Abciximab i.v. versus i.c. in ST--Elevation Myocardial Infarction Trial (LIPSIAbciximab-STEMI). Clin Res Cardiol, 2011; 100: 425–432.
7. Stone GW, Maehara A, Witzenbichler B et al. Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction: The INFUSE-AMI Randomized Trial. JAMA, 2012; DOI:10.1001/jama.2012.421.
8. Desch S, Siegemund A, Scholz U et al. Platelet inhibition and GP IIb/IIIa receptor occupancy by intracoronary versus intravenous bolus administration of abciximab in patients with ST-elevation myocardial infarction. Clin Res Cardiol, 2012; 101: 117–124.
9. Buszman PP, Wojakowski W, Milewski K et al. Controlled Reperfusion with Intravenous Bivalirudin and Intracoronary Abciximab Combination Therapy in the Porcine Myocardial Infarction Model. Thromb Res, 2011; DOI: 10.1016/j.thromres. 2011.10.020.
10. Eitel I, Desch S, Schindler K, Fuernau G, Schuler G, Thiele H. Aborted myocardial infarction in intracoronary compared with standard intravenous abciximab administration in patients undergoing primary percutaneous coronary intervention for ST--elevation myocardial infarction. Int J Cardiol, 2011; 153: 21–25.
11. Navarese EP, Kozinski M, Obonska K et al. Clinical efficacy and safety of intracoronary vs. intravenous abciximab administration in STEMI patients undergoing primary percutaneous coronary intervention: A meta-analysis of randomized trials. Platelets, 2011; DOI: 10.3109/09537104.2011.619602.
12. Friedland S, Eisenberg MJ, Shimony A. Meta-analysis of randomized controlled trials of intracoronary versus intravenous administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention for acute coronary syndrome. Am J Cardiol, 2011; 108: 1244–1251.
13. Shimada YJ, Nakra NC, Fox JT, Kanei Y. Meta-analysis of prospective randomized controlled trials comparing intracoronary versus intravenous abciximab in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol, 2012; 109: 624–628.
14. Piccolo R, Gu YL, Iversen AZ et al. Clinical impact of intracoronary abciximab in patients undergoing primary percutaneous coronary intervention: an individual patient data pooled analysis of randomised studies. Heart, 2012; DOI: 10.1136/heartjnl-2011--301101.
15. Wang Y, Wu B, Shu X. Meta-analysis of randomized controlled trials comparing intracoronary and intravenous administration of glycoprotein IIb/IIIa inhibitors in patients with ST-elevation myocardial infarction. Am J Cardiol, 2012; 109: 1124–1130.
16. Romagnoli E, Burzotta F, Trani C, Biondi-Zoccai GG, Giannico F, Crea F. Rationale for intracoronary administration of abciximab. J Thromb Thrombolysis, 2007; 23: 57–63.
17. Tcheng JE, Ellis SG, George BS et al. Pharmacodynamics of chimeric glycoprotein IIb/IIIa integrin antiplatelet antibody Fab 7E3 in high-risk coronary angioplasty. Circulation, 1994; 90: 1757–1764.
18. Mascelli MA, Lance ET, Damaraju L, Wagner CL, Weisman HF, Jordan RE. Pharmacodynamic profile of short-term abciximab treatment demonstrates prolonged platelet inhibition with gradual recovery from GPIIb/IIIa receptor blockade. Circulation, 1998; 97: 1680–1688.
19. Abernethy DR, Pezzullo J, Mascelli MA, Frederick B, Kleiman NS, Freedman J. Pharmacodynamics of abciximab during angioplasty: comparison to healthy subjects. Clin Pharmacol Ther, 2002; 71: 186–195.
20. Marciniak SJ Jr, Mascelli MA, Furman MI et al. An additional mechanism of action of abciximab: dispersal of newly formed platelet aggregates. Thromb Haemost, 2002; 87: 1020–1025.
21. Hantgan RR, Moussa SA. Inhibition of platelet-mediated clot retraction by integrin antagonists. Thromb Res, 1998; 89: 271–279.

22. Collet JP, Mishal Z, Soria J et al. Disaggregation of in vitro platelet--rich clots by abciximab increases fibrinogen exposure and promotes fibrinolysis. Arterioscler Thromb Vasc Biol, 2001; 21: 142–148.
23. Cox AD, Devine DV. Factor XIIIa binding to activated platelets is mediated through activation of glycoprotein IIb/IIIa. Blood, 1994; 83: 1006–1016.
24. Cohen I, Berk DL, White JG. The effect of peptides and monoclonal antibodies that bind to platelet glycoprotein IIb/IIIa complex on the development of clot tension. Blood, 1989; 73: 1880–1887.
25. Deibele AJ, Jennings LK, Tcheng JE, Neva C, Earhart AD, Gibson CM. Intracoronary eptifibatide bolus administration during percutaneous coronary revascularization for acute coronary syndromes with evaluation of platelet glycoprotein IIb/IIIa receptor occupancy and platelet function: the Intracoronary Eptifibatide (ICE) Trial. Circulation, 2010; 121: 784–791.
26. Reverter JC, Beguin S, Kessels H, Kumar R, Hemker HC, Coller BS. Inhibition of platelet-mediated, tissue factor-induced thrombin generation by the mouse/human chimeric 7E3 antibody. Potential implications for the effect of c7E3 Fab treatment on acute thrombosis and "clinical restenosis". J Clin Invest, 1996; 98: 863–874.
27. Tam SH, Sassoli PM, Jordan RE, Nakada MT. Abciximab (ReoPro, chimeric 7E3 Fab) demonstrates equivalent affinity and functional blockade of glycoprotein IIb/III and avb3 integrins. Circulation, 1998; 98: 1085–1091.
28. Byzova TV, Rabbani R, D'Souza SE, Plow EF. Role of integrin alpha(v) beta3 in vascular biology. Thromb Haemost, 1998; 80: 726–734.
29. Altieri DC, Edgington TS. A monoclonal antibody reacting with distinct adhesion molecules defines a transition in the functional state of the receptor CD11b/CD18 (Mac-1). J Immunol, 1988; 141: 2656–2660.
30. Neumann FJ, Zohlnhofer D, Fakhoury L, Ott I, Gawaz M, Schömig A. Effect of glycoprotein IIb/IIIa receptor blockade on platelet–leukocyte interaction and surface expression of the leukocyte integrin Mac-1 in acute myocardial infarction. J Am Coll Cardiol, 1999; 34: 1420–1426.
31. Pant S, Neupane P, Ramesh KC, Barakoti M. Post percutaneous coronary intervention antiplatelet therapy: Current perceptions, prospects and perplexity. Cardiol J, 2011; 18: 712–717.
32. Tompkins C, Henrikson CA. Optimal strategies for the management of antiplatelet and anticoagulation medications prior to cardiac device implantation. Cardiol J, 2011; 18: 103–109.
33. Wöhrle J, Grebe OC, Nusser T et al. Reduction of major adverse cardiac events with intracoronary compared with intravenous bolus application of abciximab in patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty. Circulation, 2003; 107: 1840–1843.
34. Kakkar AK, Moustapha A, Hanley HG et al. Comparison of intracoronary vs. intravenous administration of abciximab in coronary stenting. Catheter Cardiovasc Interv, 2004; 61: 31–34.
35. Bellandi F, Maioli M, Gallopin M, Toso A, Dabizzi RP. Increase of myocardial salvage and left ventricular function recovery with intracoronary abciximab downstream of the coronary occlusion in patients with acute myocardial infarction treated with primary coronary intervention. Catheter Cardiovasc Interv, 2004; 62: 186–192.
36. Romagnoli E, Burzotta F, Trani C et al. Angiographic evaluation of the effect of intracoronary abciximab administration in patients undergoing urgent PCI. Int J Cardiol, 2005; 105: 250–255.
37. Galache Osuna JG, Sánchez-Rubio J, Calvo I, Diarte JA, Lukic A, Placer LJ. Does intracoronary abciximab improve the outcome of percutaneous coronary interventions? A randomized controlled trial [in Spanish]. Rev Esp Cardiol, 2006; 59: 567–574.
38. Thiele H, Schindler K, Friedenberger J et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. Circulation, 2008; 118: 49–57.
39. Dominguez-Rodriguez A, Abreu-Gonzalez P, Avanzas P et al. Intracoronary versus intravenous abciximab administration in patients with ST-elevation myocardial infarction undergoing thrombus aspiration during primary percutaneous coronary intervention - Effects on soluble CD40 ligand concentrations. Atherosclerosis, 2009; 206: 523–527.
40. Bertrand OF, Rodés-Cabau J, Larose E et al. Effects of intracoronary compared to intravenous abciximab administration in patients undergoing transradial percutaneous coronary intervention: A subanalysis of the EASY trial. Int J Cardiol, 2009; 136: 165–170.
41. Gu YL, Kampinga MA, Wieringa WG et al. Intracoronary versus intravenous administration of abciximab in patients with ST--segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: the comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial. Circulation, 2010; 122: 2709–2717.
42. Bertrand OF, Rodés-Cabau J, Larose E et al. Intracoronary compared to intravenous Abciximab and high-dose bolus compared to standard dose in patients with ST-segment elevation myocardial infarction undergoing transradial primary percutaneous coronary intervention: a two-by-two factorial placebo-controlled randomized study. Am J Cardiol, 2010; 105: 1520–1527.
43. Iversen A, Abildgaard U, Galloe A et al. Intracoronary compared to intravenous bolus abciximab during primary percutaneous coronary intervention in ST-segment Elevation Myocardial Infarction (STEMI) patients reduces 30-day mortality and target vessel revascularization: a randomized trial. J Interv Cardiol, 2011; 24: 105–111.
44. Prati F, Capodanno D, Pawlowski T et al. Local delivery versus intracoronary infusion of abciximab in patients with acute coronary syndromes. J Am Coll Cardiol Cardiovasc Interv, 2010; 3: 928–934.
45. Dave RM. Improving outcome of STEMI PCI: Preliminary results of crystal AMI trial. http://www.clinicaltrialresults.org/ /Slides/CRYSTAL_Slides.ppt
46. Hansen PR, Iversen A, Abdulla J. Improved clinical outcomes with intracoronary compared to intravenous abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a systematic review and meta-analysis. J Invasive Cardiol, 2010; 22: 278–282.
47. Navarese EP, Koziński M, Pafundi T et al. Practical and updated guidelines on performing meta-analyses of non-randomized studies in interventional cardiology. Cardiol J, 2011; 18: 3–7.
48. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb/IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur Heart J, 2009; 30: 2705–2713.
49. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. www.cochrane.org/resources/handbook/ [updated June 2011].
50. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ, 2009; 339: b2700.
51. Fleiss JL. Analysis of data from multiclinic trials. Control Clin Trials, 1986; 7: 267–275.
52. Egger M, Smith GD. Bias in location and selection of studies. BMJ, 1998; 31: 61–66.
53. Kubica A, Kozinski M, Navarese EP, Grzesk G, Goch A, Kubica J. Intracoronary versus intravenous abciximab administration in STEMI patients: overview of current status and open questions. Curr Med Res Opin, 2011; 27: 2133–2144.
54. Efficacy of Combination of IntraCoronary Bolus Abciximab and Aspiration Thrombectomy in STEMI (ICAT). http://clinicaltrials.gov/ct2/show/NCT01404507?term=ICAT&rank=1.
55. Sardella G, Sangiorgi GM, Mancone M et al. A multicenter randomized study to evaluate intracoronary abciximab with the ClearWay catheter to improve outcomes with Lysis (IC ClearLy): trial study design and rationale. J Cardiovasc Med (Hagerstown), 2010; 11: 529–535.
56. Thrombus Aspiration for OcLuded Coronary Artery Enhanced With Distal Injection Of Abciximab (TOLEDO1). http://clinicaltrials.gov/ct2/show/NCT01383785?term=TOLEDO-1&rank=1.
57. A Randomized Trial of Early Discharge After Trans-radial Stenting of Coronary Arteries in Acute MI and Rescue-PCI (EASY--RESCUE). http://clinicaltrials.gov/ct2/show/NCT00440895?term= =EASY-RESCUE&rank=1.