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

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Key Words
Abciximab · Intracoronary administration · Intravenous administration · ST segment elevation myocardial infarction · Primary percutaneous coronary intervention

Abstract
Objectives: Administration of the glycoprotein IIb/IIIa inhibitor abciximab to patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) improves outcome. Data have suggested that an intracoronary (IC) bolus might be superior to the standard intravenous (IV) administration. We have previously reported reduced short-term mortality and need for target vessel revascularization (TVR) with the IC route. We now present long-term data from our randomized trial on IC versus IV abciximab in pPCI-treated STEMI patients. Methods: A total of 355 pPCI-treated STEMI patients were randomized to either IC or IV bolus abciximab followed by a 12-hour IV infusion. Patients were followed for 1 year to observe mortality, TVR or myocardial infarction (MI) and the combination of these. Results: The two treatment arms (IV, n = 170; IC, n = 185) were similar with regard to baseline characteristics. Mortality was reduced from 10% in the IV group to 2.7% in the IC group (p = 0.004). TVR and MI were also reduced with IC administration (TVR: 14.1 vs. 7.6%, p = 0.04; MI: 11.8 vs. 5.4%, p = 0.03). Consequently, patients in the IC treatment arm had a relative risk reduction of 55% for the combined endpoint after 1 year (p = 0.002) compared to the IV treatment arm. Conclusions: In pPCI-treated STEMI patients treated with abciximab, IC bolus administration resulted in a significant reduction in mortality, TVR and MI compared to IV bolus administration.

Introduction
The glycoprotein IIb/IIIa inhibitor (GPI) abciximab has been shown in several randomized trials to reduce major adverse cardiac events (MACEs) in invasively treated patients with acute coronary syndrome (ACS) [1–3]. Even after optimizing other factors that influence the outcome after ACS, such as shortening of symptom-to-balloon time, development of new stent types and drugs, abciximab reduces adverse outcomes even further [4–6].
This is particularly important in high-risk ACS patients, since they have a 1-year mortality rate of approximately 10% and a 25% risk of developing heart failure [7].

Hence, abciximab is a well-established adjunctive therapy in most international guidelines concerning revascularization of patients with ACS [8, 9]. These recommendations are made on the basis of studies using an intravenous (IV) bolus of abciximab. However, since abciximab binds with very high affinity to circulating activated platelets, only a limited fraction of the drug actually reaches the infarct-related coronary thrombus that caused the coronary in patients with ST segment elevation myocardial infarction (STEMI) [10, 11]. Delivering abciximab directly into the coronary artery provides a higher local concentration of the drug and subsequently a higher degree of local platelet inhibition and possibly thrombus dispersal [12, 13]. Lately, studies have shown intracoronary (IC) administration of abciximab to be superior to IV administration with respect to surrogate parameters such as improved myocardial perfusion, reduction of infarct size and microvascular obstruction [14–16]. Also, some studies have shown an effect on MACEs in favor of the IC route [17–19]. However, most data on this alternative route of administration come from retrospective or small randomized studies.

We have previously shown that IC administration of abciximab is superior to IV administration with respect to short-term (30-day) mortality and need for target vessel revascularization (TVR) in STEMI patients treated with primary percutaneous coronary intervention (pPCI) [20]. However, the long-term effect on clinical outcome after IC administration of abciximab is not known. We now present 1-year follow-up data from our randomized clinical trial evaluating the effect on MACEs of IC versus IV abciximab in STEMI patients treated with pPCI.

### Methods

#### Study Population

Patients were eligible for inclusion if they fulfilled all of the following criteria: (1) age >18 years; (2) STEMI treated with pPCI (symptom duration <12h, ST segment elevation in two contiguous leads of ≥2 mm in V1–V3 or ≥1 mm in other leads), and (3) indication for abciximab (e.g. type C/B2 lesion [21], high thrombus burden, no/slow reflow) at the discretion of the operator. Patients were excluded if any of the following were present: (1) ongoing bleeding; (2) recent stroke; (3) major surgery within the previous 2 months; (4) known bleeding disorder; (5) pregnancy, or (6) allergy to abciximab. Patients were enrolled between 2006 and 2008. The data presented in table 1 were prospectively collected and entered in a dedicated database. All patients gave written in-
formed consent. The study was approved by the local ethics committee and the Danish Medicines Agency and carried out in con-
cordance with the Second Helsinki Declaration and Good Clinical Practice requirements. The study is registered at clinicaltrials.
gov (NCT00685464).

Randomization and Treatment
This was a randomized, open label, single-center trial. Ran-
domization was performed by using sealed, opaque envelopes
which were opened if patients fulfilled all the inclusion criteria and
none of the exclusion criteria and the patients had given written
informed consent. Treatment was subsequently initiated with ei-
ther an IC or IV bolus of abciximab at a dose of 0.25 mg/kg body
weight followed by a 12-hour IV infusion of abciximab at a dose of
0.125 μg/kg body weight/min, with a maximum of 10 μg/min. The
IC bolus of abciximab was delivered via the guiding catheter after
wire penetration, whereas the IV bolus was administered into a
peripheral vein, both manually and over 2–4 min after filtering of
the drug. The GPI of use in our center is Reo-Pro® (Eli Lilly, Den-
mark). All patients were pretreated according to national guide-
lines with 300–500 mg of aspirin, 300–600 mg of clo-
pidogrel and 10,000 IU of unfractionated heparin IV, which was supplemented
if activated cloting time was less than 250 s during PCI. Patients
were discharged on lifelong aspirin 75 mg/day, clo-
pidogrel 75 mg/day for a minimum of 12 months, β-blockers, angiotensin-con-
verting enzyme inhibitors and statins, as recommended in current
guidelines. Echocardiography was performed during the hospital
stay to estimate left ventricular ejection fraction.

Endpoint Definition and Follow-Up
Endpoints were defined according to the Academic Research
Consortium proposals, i.e. mortality, TVR, reinfarction (myocar-
dial infarction, MI) and the combination of the three [22]. We
have previously reported a similar effect of abciximab on short-
term bleeding complications regardless of administration route,
and this aspect will not be discussed further [20]. Follow-up was
performed after 30 days and 1 year. Patients were contacted by
telephone, subsidiarily by letter. No patients were lost to follow-
up. All possible events were confirmed by checking hospital
source data. Assessment of the study endpoints was performed
blinded by the endpoint committee.

Statistical Analysis
The preassumption of a 50% reduction (from 10 to 5%) in the
combined endpoint, blinded to the randomization, after 30 days
was fulfilled, with an average event rate of 7.5% among the 355
patients included and a risk of type 2 error of 20%. Patients were
subsequently followed for 1 year. Differences in demographic and
angiographic data were evaluated using the
χ² test for frequencies
and Student’s unpaired t test or the Mann-Whitney test for other
variables. Due to balanced distribution of baseline data between
the two groups, no adjusted analyses were performed. Kaplan-
Meier plots for the endpoints in the two groups were compared
using the log rank test. Two-sided p values <0.05 were considered
statistically significant. All analyses were performed with SPSS,
version 17 (SPSS Inc., Chicago, Ill., USA).

Fig. 1. Kaplan-Meier plots showing the endpoints. Differences between groups (IC vs. IV) were assessed by log
rank p values after 30 days and 1 year. Cum. = Cumulative.
Results

Of the 355 patients included, 170 were randomized to an IV bolus of abciximab and 185 to an IC bolus. Randomization was well balanced, since no differences in baseline characteristics were seen (table 1). The only difference noted was in the proportion of patients achieving post-PCI Thrombolysis in Myocardial Infarction (TIMI) flow 3 in favor of IC abciximab, although this was not statically significant. Notably, approximately 80% of patients were men, which is not representative of a real-life STEMI population.

Cumulative event rates for all endpoints are shown in figure 1. For all four endpoints, a significant reduction in favor of IC bolus abciximab was seen after 1 year. Mortality was reduced from 10% in the IV group to 2.7% in the IC group (log rank p value 0.004). Also, the risk of TVR and MI was reduced in favor of IC administration (TVR: 14.1 vs. 7.6%, log rank p value 0.04; MI: 11.8 vs. 5.4%, log rank p value 0.03). This conferred a relative risk reduction of 55% (and an absolute risk reduction of 11.4%) for the combined endpoint from 20.6% in the IV group to 9.2% in the IC group (log rank p value 0.002).

Data on differences after 30 days are also shown. These analyses revealed that the benefits of IC abciximab compared to IV abciximab seen after 1 year were generally similar to differences seen after 30 days, except for MI, where the short-term risk reduction was not found to be statistically significant. Thus, the relative risk reduction in mortality after 30 days was almost 80%, and after 1 year it was slightly lower (73%; absolute risk reduction of 7.3%). The risk of TVR was reduced by 60% after 30 days, which was diminished to 46% after 1 year (absolute risk reduction of 6.5%). The insignificant relative risk reduction in MI of 43% after 30 days increased to 55% (absolute risk reduction of 6.4%) after 1 year, which was statistically significant. Consequently, the relative risk reduction in the combined endpoint in favor of IC abciximab was unchanged, with a 60% reduction after 30 days and 55% after 1 year.

Discussion

In this randomized trial comparing IC to IV bolus administration of abciximab during pPCI we found a surprising reduction of more than 50% in the 1-year combined endpoint of mortality, TVR and MI. To our knowledge, this trial is the first to show a significant long-term effect on clinical endpoints of IC versus IV bolus abciximab. Other studies have shown benefits of IC over IV abciximab on surrogate parameters [14–16]. However, these studies were too small to detect any effect on clinical endpoints, and yet others have been retrospective.

Some aspects of our results need to be commented on. Most of the demographic data resemble those from a real-life clinical setting. However, only 12% of patients had diabetes and 50% were smokers. These numbers are consistent with the background prevalence in Europe. Also, echocardiography showed a mean left ventricular ejection fraction of 40%, which does not necessarily indicate that patients suffered from congestive heart failure, but rather that some degree of myocardial stunning might have occurred.

The relative risk reductions observed in our study were high, and one should bear in mind that only a limited number of endpoints account for these differences. Nevertheless, all analyses gave highly significant results. The 10% mortality seen in the IV group was expected, but the 2.7% mortality in the IC group was certainly lower than anticipated. The need for TVR within the first year after randomization was 14.1 and 7.6% for the IV and IC group, respectively. All revascularizations were symptom driven, since follow-up coronary angiography was not planned as part of the study design. Patients with lesions in the nonculprit artery, which was not treated during the index PCI, underwent a staged PCI. This was not categorized as an endpoint. The risk of recurrent MI was 11.8% in the IV group, which is higher than expected. In the IC group, this risk was reduced by more than 50%. Overall, patients treated via the IV route had a somewhat higher risk of experiencing the endpoints compared to other trials on STEMI patients treated with pPCI. Conversely, patients treated via the IC route had low comparable event rates. This is probably due to the high complexity of the lesions treated. Interestingly, the recently published Comparison of Intracoronary versus Intravenous Abciximab Administration during Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction (CICERO) trial did not find any differences between IC and IV bolus administration with regard to clinical endpoints [23, 24]. This might be explained by differences in inclusion criteria. We included high-risk patients, e.g. type C/B2 lesions, high thrombus burden and no/slow reflow. These criteria render our study population at high risk of adverse outcomes. In contrast, the patients in the CICERO trial, although they had STEMI, showed somewhat less severe baseline characteristics. Only half of the patients had TIMI flow grade 0 at baseline, compared to 75% in our population. Also, patients in CICERO were eligible
for inclusion irrespective of lesion complexity. Finally, thrombus aspiration and a bolus-only strategy were utilized in almost all patients in CICERO and in no patients in our trial. This discrepancy between our results and the CICERO trial emphasizes an important aspect, namely the importance of selecting the right treatment for the right patient. Treatment with abciximab should be reserved for those with high-risk coronary lesions, in whom it has been shown to reduce MACES, and this aspect should be taken into account when extrapolating our results to populations with other characteristics.

When we reported the short-term outcome of our trial, we described some of the mechanisms thought to be responsible for the superiority of the IC route compared to the IV route, which has been reported before [25]. In brief, we divided the mechanisms into two groups: (1) GPI platelet receptor-dependent and (2) GPI platelet receptor-independent effects. The former mechanism is responsible for the displacement of the platelet-platelet bridging ligand, fibrinogen, which can be obtained by the high local concentration achieved through IC delivery of abciximab. These properties are thought to act as a thrombolytic effect [10–13, 26, 27]. The platelet-independent mechanism of abciximab relies on the anti-inflammatory effects of abciximab, namely through binding to receptors on leukocytes (the MAC-1 receptor) and endothelial and smooth muscle cells (the αVβ3 vitronectin receptor), which might decrease the intimal hyperplasia and late lumen loss [28, 29]. The above explanations are not fully understood and have not been unequivocally proven. We speculated that if our 1-year results showed an even more pronounced benefit of IC versus IV abciximab, this might have been explained by GPI platelet receptor-independent effects. However, our results imply that the beneficial effect of IC compared to IV administration of abciximab occurs within the first month. Thus, we believe the GPI platelet receptor-dependent effect to be predominantly responsible for our results, which is in line with the short life span of platelets.

We believe our results add valuable knowledge to the discussion on IC versus IV administration of abciximab. Others have shown improvement in myocardial function and salvage and yet others have shown superiority of the IC route in retrospective studies. The future perspectives are exciting. Ongoing trials are using dedicated delivery catheters (Clearway RX system) to optimize the delivery of abciximab near the thrombus [30]. Others are using thrombus aspiration in combination with IC abciximab administration [31], and yet others are using the transradial approach to minimize bleeding complications [32].

Also, this adds to the discussion on whether to initiate abciximab treatment ‘upstream’ or in the cath lab. Should IC administration of abciximab become the preferred route, ‘upstream’ administration before coronary angiography would by nature not be possible. We await data from the above trials to see whether the trend might shift from IV to IC bolus abciximab administration in STEMI patients. Moreover, data on bivalirudin, a direct thrombin inhibitor, are promising. However, most studies have compared bivalirudin to IV administered GPs with no significant effect on clinical outcome but reduced bleeding complications in the bivalirudin arm [33, 34], and one trial showed a reduction in cardiac death in favor of bivalirudin compared to IV administered GPI [35]. Thus, future studies might consider using IC administration of GPs when designing trials comparing GPs to other antiplatelet drugs.

In conclusion, IC bolus administration of abciximab in STEMI patients with high-risk coronary lesions treated with pPCI is superior to IV administration with respect to mortality, TVR and MI.

Study Limitations

Although the design of our study was randomized and no differences were observed between the baseline characteristics of our groups, we cannot rule out the possibility that some unmeasured characteristics were different in the two groups. Neither can we rule out that our study might be underpowered and consequently the results might be ‘by chance’, but our short-term results were pooled and confirmed in a meta-analysis [17]. We chose not to blind the operator or the patient to the treatment, since we believed that the clinical endpoints could not be influenced by such blinding. However, all endpoints were assessed blinded to group assignment. Patients were pretreated with a fixed dose of 10,000 IU of unfractionated heparin according to current national guidelines. This is not in line with US guidelines. We chose to evaluate clinical endpoints rather than imaging or biomarker parameters which have been investigated before with results indicating a superior effect of IC abciximab. It would be interesting to study the effect of IC abciximab on the release of microRNAs, for example, which have proven to correlate strongly to myocardial damage after STEMI [36].

Also, thrombectomy was not performed in any patients. This treatment modality was not considered standard during the inclusion period at our center, but we acknowledge that the use of thrombectomy is becoming more common and the combination of IC abciximab and
thrombectomy might yield different results. In addition, our inclusion criteria were rather stringent. Only patients who fulfilled our institution’s indications for adjunctive therapy with abciximab were included. Thus, our results should be interpreted in this context.

Conflict of Interest

The authors have no financial or personal conflicts of interest or associations with industry to declare. Eli Lilly, Denmark, which manufactures the GPI used in this trial, had no financial or scientific involvement in the trial.

References


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