**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

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<tr>
<th>Worksheet author(s)</th>
<th>Date Submitted for review:</th>
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<td>Prof. Dr. med. Hans-Richard Arntz</td>
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**Clinical question.**

In patients with suspected ACS/MI in prehospital and emergency department settings (P), does the use of IIB IIIA Inhibitors (I), compared with standard management (C), improve outcome (eg. chest pain resolution, infarct size, ekg resolution, survival to discharge, 30/60 d mortality) (O)?

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<th>Is this question addressing an intervention/therapy, prognosis or diagnosis? Addressing an intervention dealing</th>
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<td>State if this is a proposed new topic or revision of existing worksheet:</td>
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<td>Conflict of interest specific to this question: Dr. Arntz is coauthor in several scientific papers dealing with that question.</td>
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<td>Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? None</td>
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**Search strategy (including electronic databases searched).**

Search in Medline, EMBASE, Cochrane database for systematic reviews, AHA endnote master library using the text words glycoprotein IIb/IIIa inhibitor, abciximab, eptifibatide, tirofiban, acute coronary syndrome, myocardial infarction. Also review of the actual NSTE-ACS and STEMI guidelines (2007/2008) of the ACC/AHA and the ESC as well as the guidelines regarding PCI.

- **State inclusion and exclusion criteria**

  Duplicates, double publications, non-systematic reviews, letters, animal studies, comments and articles without available abstract were excluded. Thus the initially 4110 hits were reduced to 564 articles which were manually reviewed (by abstracts), leaving 58 articles for final review.

- **Number of articles/sources meeting criteria for further review:**

  53 articles meeting the criteria for randomized controlled trials, metaanalyses, reviews and registry data and clinical studies relevant to answer the posed question.
## Summary of evidence

### Evidence Supporting Clinical Question

| Good | | | | | |
|------|----|----|----|----|
| {CAPTURE 1997} C | {PRISM 1998} C | {PRISM-PLUS 1998} C | |
| {Boersma, 2002} C | {Bosch, 2001} E | {De Luca, 2005} C, E | {Dobrzynski, 2007} E |
| {De Luca, 2008} C | {Gibson, 2006} E | {Kandzari, 2004} E | {Montalescot, 2001} E |
| {Dobrzynski, 2007} E | | | {Ndrepepa, 2008} E |
| {De Luca, 2008} C | | | {Thiele, 2005} E |
| {Van't Hof, 2008} E | | | |
| {Dery, 2007} E | {Greenbaum, 2001} E | {Heestermans, 2009} B, E | |
| {Dudek, 2008} E | {Peterson, 2003} C | | {Gurbel, 2002} E |
| Fair | | | | |
| {Bellandi, 2006} E | {Bolognese, 2006} E | {Cutlip, 2003} E | {Dobrzynski, 2006} E |
| {De Luca, 2009} E | {Dieker, 2006} E | {Emre, 2006} E | {Godicke, 2005} E |
| {Gabriel, 2006} E | {Gyongyosi, 2004} E | {Lee, 2003} E | {Hassan, 2009} E |
| {Maioli, 2007} E | {Rakowski, 2006} E | {Thiele, 2005} E | |
| {Rakowski, 2007} E | {Thiele, 2006} E | | |
| {van 't Hof, 2003} E | {Xu, 2006} E | | |
| {Zeymer, 2005} E | | | |
| Poor | | | | |
| | | | | |
| 1 | 2 | 3 | 4 | 5 |

### Level of evidence

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

*Italics = Animal studies*
### Evidence Neutral to Clinical Question

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<td>{Pannu, 2008}C,E</td>
<td>{Roe, 2003}E</td>
<td>{Svensson, 200E6}</td>
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- A = Return of spontaneous circulation
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**Italics** = Animal studies

### Evidence Opposing Clinical Question

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- A = Return of spontaneous circulation
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**Italics** = Animal studies
REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

There are several major problems in interpreting studies on Gp IIb/IIIa receptor blockers in ACS pts.:

1) The number of studies dealing with the specific question of prehospital or emergency department use of Gp IIb/IIIa receptor inhibitors is limited. Moreover many of these specific studies are very small and have been performed in the early days of availability of this class of agents and are not applying alternative co-treatments. Consequently evaluation and answering the posed question predominantly relies on analogue interpretation i.e. in principal "early" vs "late" e.g. before transfer for PCI from a remote hospital to a PCI center, treatment started several hours before planned PCI in NSTE-ACS pts (initiation of treatment sometimes in the ED in other studies in the CCU to compared to deferred periprocedural treatment).

2) Some of the “early” studies use a combination of a (reduced dose) of a thrombolytic + Gp IIb/IIIa inhibitor as “early strategy”. Some of the studies have a strategy of facilitation of PCI with a Gp IIb/IIIa inhibitor comparing that strategy with a non-invasive approach.

3) A third problem is that the early studies which mostly tended to be in favor of using Gp IIb/IIIa inhibitors, were done without thienopyridine treatment – at least not using a high loading dose of thienopyridine as early as possible – with exceptions of the ON-TIME 2 study (van't Hof 2008 supporting the hypothesis) and the Early ACS trial (Giugliano 2009, opposing the hypothesis).

4) Results with Gp IIb/IIIa blockers from the early years may also become questioned since alternate/newer strategies for anticoagulation (i.e. bivalidurin) have been introduced and partially used in newer studies e.g. in the Early ACS trial (Giugliano 2009, opposing the hypothesis).

5) The majority of studies has been performed with abciximab which already by its mode of action (irreversible blockade of the Gp IIb/IIIa receptor) differs from eptifibatide and tirofiban.

On the background of these considerations and the relatively weak data (mostly “soft” surrogate endpoints) favouring the use of Gp IIb/IIIa blockers in general, a decisive judgement becomes even more difficult. Finally the increased risk for major bleedings with Gp IIb/IIIa blockers is of concern with respect to the worse outcomes reported with major bleedings in pts with ACS.

Acknowledgements:
Martina Weiland for preparing the worksheet
Citation List


In this large placebo controlled blinded randomized study on 1265 pts with unstable angina/NSTE-ACS in pts with angiographically documented severe coronary stenosis abciximab or placebo was infused for 18-24 hrs before PTCA and continued until 1 hr afterwards. The primary endpoint of death, myocardial infarction or urgent intervention for recurrent ischaemia at 30 days was less frequent in pts who received abciximab (11,3 %) compared to placebo (15,9 %) (p=0.012). Major bleeding with abciximab at 6 months, death, myocardial infarction or repeat intervention was observed in a similar frequency in both groups. This study shows that pre-treatment with abciximab before PCI in NSTE-ACS may improve at least short-term outcome (even if that regimen is not used anymore).
LOE1 supporting good


Randomized double blinded study on efficacy of 48 hrs tirofiban infusion without heparin or placebo in addition to heparin (3232 pts with NSTE-ACS in whom an early PCI was not planned) (PCI < 48 hrs 1,9 %). The primary endpoint of the composite of death, myocardial infarction or refractory ischemia at 48 hrs was 3,8 % with tirofiban vs 5,2 % with heparin p=0.01. At 30 day the composite endpoint with admission of re-admission for UAP was similar in the two groups (15,9 % with tirofiban vs 17,1 % with heparin p=0.34) but there was a trend to a lower rate of death plus MI and a reduced mortality with tirofiban (2,3 % vs 3,6 %) p=0.02) at 30 days. Major bleedings occurred a rate of 0,4 % in both groups.
LOE 1 supporting good


Double blinded randomized study on 1915 NSTE-ACS pts receiving tirofiban or placebo infusion for a mean of 71 hrs in addition to standard treatment with aspirin and heparin. Angiography (and PCI if indicated) was performed after 48 hrs of infusion. The study was stopped early because of lower mortality in the tirofiban group (1,1 % vs 4,6 %). Also the primary endpoint of death, MI or refractory ischemia at 7 days was lower with tirofiban at 30 days (18,5 % vs 22,3 %, p=0.03). Major bleedings did not differ significantly (4 % with tirofiban vs 3 % with placebo).
LOE 1 supporting good


Non randomized (retrospective?) study on 446 pts receiving abciximab at remote hospitals before transfer (n=138 early group) or just before PCI (n=308, late group). The transport time averaged 45 min. TIMI 2+3 flow was more prevalent in the early group (35 %) vs late (19 %), p< 0.001 as was the final TIMI flow 3 (91 vs 83 %, p=0.05). There were no differences in mortality and revascularisation rates.
LOE 3 supporting fair


Small randomized study on early (ED) and delayed (cath lab) treatment with abciximab in 55 pts presenting with STEMI (symptoms < 6 hrs) and planned PCI. TIMI flow grade as well as blush grade, corrected TIMI frame count and salvage index was in favour of early treatment.
LOE1 supporting fair

Metaanalysis of 6 major (> 1000 pts) randomized clinical trials on efficacy of glycoprotein IIb/IIIa inhibitors in pts with NSTE-ACS (total number of pts n=31402) who had no recommendation of early coronary vascularisation during study drug infusion. 30 days after randomisation the OR of death or MI was in 10,8 % of pts, on GP IIb/IIIa blockers compared to 11,8 % on placebo (OR 0,19 (95 CI 0,84-0,98)) (p=0.015). Major bleeding complications but not intracranial bleeding was increased with Gp IIb/IIIA inhibitors. It has to be stated that in the GUSTO 4 ACS study utilizing abciximab the rate of pts who died or had an myocardial infarction tended to be higher with abciximab to compared to placebo.

LOE 1 supporting good


Randomized study on 93 higher risk ACS pts undergoing PCI who received „upstream“ tirofiban (in the CCUI) for max 24 – 48 hrs before PCI or downstream tirofiban or abciximab at PCI. Upstream tirofiban resulted in less pts with TIMI 0/1 flow at angiography (28,1 % vs 66,7 % (tirofiban) and 71 % (abciximab)) and less troponin I release after PCI.

LOE1 supporting fair


Metaanalysis of 38 randomized controlled trials including 58495 pts with NSTE-ACS treated with Gp IIb/IIla beta blockers or placebo with regard to mortality at 30 days, myocardial infarction or bleeding rates. With PCI mortality at 30 days was reduced by 26 % (95 CI 0,58-0,94) but not at 6 months (OR 0,87, 95 %CI, 0,73-1,03). Death or MI was decreased both at 30 days (OR 0,67, 95 %CI 0,61-0,74) and at 6 months (OR 0,71 95 %CI 0,62-0,82) and severe bleeding was slightly increased (OR 1,38 95 %CI, 1,19-1,60). In pts treated conservatively (not PCI), Gp IIb/IIla blockers did not decrease mortality at 30 days or at 6 months, however death and MI was decreased at 30 days (OR 0,92 95 %CI 0,86-0,99) and 6 months (OR 0,88 95 %Cl 0,81-0,96) and severe bleeding was slightly increased (OR 1,27 95 %CI 1,12 – 1,44). These data were strongly suggestive of an existence of a positive interaction between PCI and the effect of Gp IIb/IIla blockers but do not consider the role of thienopyridines.

LOE 1 supporting good


Two phased randomized studies on pts with STEMI and the combination treatment of eptifibatide + t-PA (in phase A 25 or 50 mg dose of t-PA, in phase B pts were randomized to double dose bolus of eptifibatide, followed by 1,33 µg/kg/min infusion with t-PA up to 50 mg or another double bolus eptifibatide (180/90 mg, 10 minutes apart) and 2 µg/kg/min 50 mg t-PA compared with full-dose weight adjusted t-PA. The primary endpoint was TIMI flow grade 3 at first angiography (eventually followed by PCI in pts with a TIMI flow grade < 3). With similar incidences of death (or re-infarction or revascularisation at 30 days) (death 4 – 7 % in the different groups the best TIMI flow 3 grade perfusion at first angiography was achieved with double bolus eptifibatide and a 48 hrs infusion and half-dose t-PA. But also let to a high rate of major bleeding 6 – 11 % intracranial haemorrhages (1-3 %) compared to standard treatment with thrombolysis or PCI.

LOE 5 neutral good


LOE1 supporting fair

Substudy of a metaanalysis investigating outcome in diabetic STEMI pts with early vs late (periprocedural) Gp IIb/IIIa antagonist treatment resulting in a better pre and post procedural TIMI flow and less distal embolisation.

LOE 1  supporting, fair


Metaanalysis on 11 trials involving 27115 pts with STEMI who were randomly treated with or without abciximab and primary PCI or fibrinolysis as principal strategy, resulting in reduced 30 day re-infarction rate in all studies combined (2,1 % with abciximab vs 3,3 % without, p<0.001). Reduction in mortality however was only observed with abciximab treatment with PCI as reperfusion strategy at 30 days (2,4 % vs 3,4 %, p=0.047) and after 6 – 12 months (4,4 % vs 6,2 %, p=0.01).

LOE1  supporting good


Metaanalysis on individual pts data of studies investigating value of early pharmacological reperfusion with GP IIb/IIIa inhibitors between January 1990 and October 2007 (data from 11 out of 13 trials, including 1662 pts). TIMI 3 flow was more frequent before PCI with early Gp IIb/IIIa inhibitors (23 vs 13 %, p <0.0001), post-PI TIMI 3 flow 90 % vs 87,9 %, p=0.18) and myocardial blush grade 3 (49 % vs 45,8 %, p=0.18) were similar with and without pre-treatment. The rate of ST-segment resolution (> 70%) was significantly higher with early treatment. There was a significant difference in mortality between the whole group also early abciximab demonstrated improve survival as compared to late administration even after adjustment for clinical and angiographic confounding factors (p=0.05).

LOE1  supporting good


Substudy from the ESPRIT study in a subgroup of 901 patients who received a loading dose of thienopyridine before PCI. 123 received thienopyridine without loading dose and 1016 not being treated before PCI. The composite incidence of death or MI at 30 days was lower with a thienopyridine loading dose before PCI compared to the other groups combined (OR 0,71 (95 % CI, 0,52-0,99); p=0,042). The authors concluded that pre-treatment with thienopyridine lowers the rate of ischemic complications regardless of treatment with a Gp IIb/IIIA inhibitor, however, the effect of the Gp IIb/IIla receptor blockers was maintained irrespective of thienopyridine (treatment with ebtifibatide started only after hospital admission!)

LOE2  supporting good


Small and early terminated randomized study comparing on site fibrinolysis (and additional "liberal" rescue PCI if ST-resolution was < 60 % after 60 min) with abciximab facilitated PCI after transport to a PCI center (pts were randomized in smaller hospitals). Outcome regarding ST-segment resolution and clinical course tended to better with abciximab facilitated PCI.

LOE1  supporting fair


Preliminary data of a randomized study comparing on-site thrombolysis with transport to PCI with tirofiban in patients in STEMI (n=341), showing better outcome with transport to PCI with tirofiban. Final results were published in 2007 by the same authors confirming the preliminary data.

LOE 2  supporting fair

Final results on a study on 401 pts with STEMI presenting at community hospitals randomized to receive on site thrombolysis or transport with tirofiban (10 µg/kg bolus followed by 0.1 µg/kg(min infusion) to primary PCI (transfer time mean 122±36 min). Composite endpoint was total mortality; re-AMI and stroke during follow up. There was no difference in favour for transport + tirofiban to PCI (15.5 % vs 8 %, p=0.02) at 30 days and 21.5 vs 11.4 % p=0.06 at 1 year.

LOE 1 supporting good


Study on potential of early pharmacological reperfusion treatment (reduced dose of alteplase + abciximab + ASS + heparin) during a transportation time >90 min from a remote hospital to a PCI center, showing that successful treatment (TIMI flow 2+3 at first angiography achieved in 85.8 % of pts that treatment) predicts better post PCI TIMI flow, ejection fraction and improved 1-year outcome.

LOE4 supporting good


Large prematurely stopped randomized double blinded study comparing abciximab/half dose reteplase facilitated PCI with abciximab only facilitated PCI or primary PCI (treatment started in all groups after hospital admission!). The primary endpoint of all cause death, ventricular fibrillation more than 48 hrs after randomisation, cardiogenic shock or heart failure within 90 days occurred in 9.8 % in the combination facilitated PCI group, 10.5 % in the abciximab facilitated PCI group and 10.7 % in the primary PCI group (p=0.055) (90 day mortality rates were also different. Patients with a symptom duration of less than 12 hrs were randomized in the emergency room. The door to balloon time in hospitals performing PCI was 120 min (98 – 148 min), the door to balloon time in centers not performing PCI was 155 min (126 – 196 min). Thus, this study shows that neither combo lysis nor abciximab facilitated PCI with delay to PCI of about 2 hrs has influence of outcome.'

LOE1 Opposing good


Randomized study on 66 pts with AMI treated with tirofiban (usual dose) in the ED or at catheterisation. Primary endpoint was myocardial salvage as assessed with scintigraphy utilizing Tc 99 m sestamibi. The average door to balloon time was 53 min. ED treatment with tirofiban resulted in a higher rate of TIMI 3 flow (31 vs 12 %, p=0.04) and reduction in final infarction size (11.8 % vs 22.4 %). Also the composite of death, re-MI or rehospitalisation favoured the early group (6 % early vs 15 % late, p=0.06).

LOE1 supporting fair


Small study on eighty patients with STEMI and planned PCI randomized to receive standard dose abciximab in the emergency department or after angiography in the cath-lab. TIMI frame count was improved in patients treated early (23±10 vs 41±35, p=0.02). The study documents feasibility of early ED treatment for patients with STEMI and planned PCI.

LOE1 supporting fair

LOE1 supporting good


Randomised study in 9492 not-ST elevation ACS pts assigned for an invasive procedure receiving standard dose eptifibatide 12 hrs before angiography or placebo with provisional eptifibatide after PCI. There was no difference in the primary composite endpoints of death, MI, thrombolysis complications or urgent revascularisation at 96 hrs (also not in the single components) or the composite secondary endpoint of CV death or MI at day 30 (and the single components). Eptifibatide, however, led to a significantly higher rate of bleedings (minor and major and red cell transfusions.

LOE1 opposing good


Pooled analysis of 6 studies on early vs periprocedural treatment with abciximab. 260 pts received abciximab early (prehospital or shortly after hospital admission (partially ED)) and 342 pts at PCI. Early abciximab treatment resulted in a TIMI 2 + 3 flow grade in 42 % compared to 29 % in the late group (p=0.001). After PCI complete ST-resolution (> 70%) was present in 59 % of the early group pts and 41 % in the late group (p=0.03). There was a trend to better outcome regarding to composite endpoint of death, re-MI or repeat TV (7,3 % vs 9,7 %) and death alone (2,7 % vs 4,7 %).

LOE2 supporting fair


Substudy of the PURSUIT trial on eptifibatide or placebo on 429 pts transferred from non-PCI hospital to a PCI center during study drug infusion compared with 1987 pts who remained in the non-PCI hospital or were transferred after termination of study drug infusion (non-transfer pts). Patients after eptifibatide were transferred less frequently compared to placebo patients (16% vs 20%, p=0.014), transfer pts had more procedures, more pts died and more pts had a myocardial infarction compared to not transfer pts (21 vs 12 %, p=0.001). Irrespective of transfer status eptifibatide was associated with a reduction in death or MI trough 30 days, thus showing better outcome under all clinical conditions.

LOE2 supporting good


Substudy of the early pilot trial on 27 pts who received eptifibatide early in the emergency departments or late after 12 – 24 hrs (n=28) on 10 different platelet receptors and platelet aggregation (ADP induced). Measurement were performed 3,6, 12 and 24 hrs after randomisation. Platelet aggregation was rapidly inhibited by eptifibatide however no significant difference was seen in several platelet receptors. GP IIb/IIIa inhibitors (measured by PAC-1 the vitronectin receptor and the Gp Ib receptor were inhibited by eptifibatide. Thus, there was a rapid and profound inhibition of platelet aggregation however the platelet leukocyte aggregate formation (a marker of platelet activity) rises within 24 hrs despite eptifibatide treatment which may be a potential mechanism for microvascular obstruction.

LOE 5 supporting good


Small randomized study randomizing patients with STEMI to abciximab during the organisation phase for PCI or immediately before PCI. Time difference for abciximab between strategies was about 60 min. Several parameters as pre-PCI, ST-segment resolution (55 + 21 % vs 42 + 18 %, p=0.005) TIMI flow grade 3 (29 vs 7 %, p =0.0042) and corrected TIMI frame count (58 ± 32 vs 79 ± 28 %, p=0.018) were in favour of pre-treatment with abciximab, as was quantitative myocardial dye intensity and sharper increase of CK release and a QRS score
which indicated a smaller infarct size for pre-treatment.
LOE1 supporting fair


Open label study on 179 STEMI pts receiving an abciximab bolus in the ambulance or in the hospital resulting in an significantly higher rate of open IRA (TIMI 2+3) less 48 hrs CK release, a better ejection fraction at 90 days and a lower incidence of heart failure until day 210.
LOE1 supporting fair


A study combining data from a randomised open label study of STEMI pts receiving prehospital high-dose tirofiban or not (n=414) and the blinded randomised (prehospital tirofiban with an high initial bolus vs in-hospital treatment) On TIME-2 study (n=894).
LOE2 supporting good


Analysis of the data of the CRUSADE data base (n=65424) (CRUSADE being in initiative on improvement on treatment of pts with ACS) showing that only 1/3 of eligible NSTE-ACS pts received early Gp IIb/IIia inhibitorsat all, and that of those only 1/3 treatment was started already in the ED. Moreover use of Gp IIb/IIIA blockers was directed to lower risk pt. Cardiology care was the most significant factor for early use of a Gp IIb/IIia blocker
LOE4 neutral good


Review of all large studies on abciximab therapy in treatment of STEMI (n=3266 pts) treated with primary PCI with or without abciximab. Addition of abciximab reduced 30 day composite of death, re-infarction or urgent TVR with trends towards reduced 30 day mortality and reinfarction and a significantly reduction of TVR (OR 0.54, 95 % CI, 0.40-0.72). Similar results were achieved 6 months follow-up. Abciximab resulted in an increased likelihood and of major bleedings (OR 1.74, 95 % CI 1.11 -2.72).
LOE1 supporting good


2022 pts with non ST-elevation ACS were randomized to receive abciximab or placebo in addition to 600 mg clopidogrel given at least 2 hrs before intervention to all pts. Primary endpoint was the composite of death, MI or urgent TVR within 30 days which was reached in 8.9 % of the abciximab group compared to placebo with 11.9 % (RR reduction by 25 %) p=0.03, but no reduction in mortality alone was observed. An advantage for the combo treatment of clopidogrel and abciximab was only present in pts with elevated troponin levels.
LOE1 supporting good


In this open randomized controlled study 253 pts with STEMI referred to hospital without catheterisation facilities (n=186) and with cath facilities (n=67) (symptom duration < 12 hrs) received either the combo lysis of half-dose reteplase plus abciximab or abciximab alone and were then transferred to PCI. Primary endpoint was final infarct size as measured by Tc99m sestamibi between 5 and 10 days after randomization. The final infarct size of left ventricle was 13 % (3-28 %) in the Reteplase group compared to 11.5 % (2-26 %) in the abciximab alone group (p=0.81). There was no significant difference in a combined clinical endpoint of death, re-MI, or stroke within 6
months (6.4 % in the combo group and 4.7 % at the abciximab group). There was a trend to more bleedings (5.6 % in the combo group compared to abciximab alone, 1.6 %, p=0.16).

LOE1 neutral good


Meta-analysis on 11 randomized controlled studies published until 2004/2005 investigating Gp IIb/IIa receptor blocker facilitated PCI (n=9, n=1148 pts) and 2 studies (n=399 pts) with the combination lytic + Gp IIb/IIa blocker facilitated PCI with regard to ST-segment resolution, TIMI flow before and after PCI short term death and non-fatal MI urgent TVR and major bleedings (not all studies reporting all outcomes). Patients were included with a symptom duration of < 4 up to < 12 hrs in the different studies. Short term mortality was similar with both facilitation strategies: by Gp IIb/IIa blockers alone (3 % with treatment and placebo) and 4 % with combo facilitation vs 1 % with placebo respectively. There was a trend to better ST-segment resolution with Gp IIb/IIa receptor blockers and a significantly higher rate of initial TIMI 3 flow with Gp IIb/IIa facilitated as well as with combo facilitation compared to placebo before PCI. The effect on TIMI flow, however, was not more significant after PCI. It is concluded, that facilitation as used in these studies offers no benefit and should not be used outside the context of randomised studies.

LOE1 neutral good


Small randomized study on 100 pts with STEMI randomized to early administration of tirofiban in the ED or later administration in the cath lab. Early treatment with Tirofiban, i.e. 33 min (19 – 45 min) before angioplasty resulted in a higher rate of TIMI flow 3 (32 vs 10 %, p=0.007) and a higher TIMI 3 (32 % vs 6 %, p=0.001). Clinical outcome (peak CK, composite auf death, re-Mi, and re-hospitalisation as well as urgent TVR tended to be better with early treatment but was not significant).

LOE1 supporting fair


300 NSTE-ACS pts were randomized to receive upstream tirofiban (+ ASS + 600 mg clopidogrel + heparin < 48 hrs before PCI) or provisional abciximab at angio (as decided by the angiographer). PCI was performed in a total of 199 pts, 99 of these belonging to group 2. Of these 26 % received abciximab during PCI. There was no difference between the groups regarding clinical and biochemical outcomes i.e. release of cardiac markers.

LOE1 neutral fair


Randomized study on 210 patients with STEMI to receive abciximab in the ED (early group) or in the cath lab (late group). The primary endpoint of initial TIMI flow 3 rate was 24 % vs 10 %, p=0.01, blush grade 2 or 3 (15 % vs 6 %, p=0.02), gain in ejection fraction after 1 month was 8 ± 7 % vs 6 ± 7 %, p=0.02 favouring early abciximab treatment in the ED compared to periprocedural application.

LOE1 supporting fair


Double blinded randomized study on 300 STEMI pts who received abciximab or placebo before BMS-stenting showing that the primary composite endpoint of death, re-MI or urgent TVR occurred in 6 % of pts with abciximab and 14.6 % with placebo (p=0.01). This result was related to a better TIMI 3 flow at first angiography with abciximab. The most pronounced beneficial effect was seen in the subgroup of pts in whom study treatment was

**LOE 1** supporting good

Long term results from the ISAR-REACT 2 randomized study showing that the short term effect (30 days) was present also for one year i.e. specifically the reduction in re-infarction and TVR rates but not in mortality.

**LOE 1** supporting good


Metaanalysis on 5 studies (5303 pts, 2 studies in ACS pts, 3 studies in elective PCI) suggesting that addition of Gp IIb/IIa receptor blockers in pts with clopidogrel pre-treatment (375 – 600 mg) does not improve outcome (but increases bleeding rates with abciximab) in pts undergoing PCI.

**LOE 1** opposing good


Randomised open label study on 100 pts with STEMI and planned PCI treated with prehospital or periprocedural standard dose abciximab. There were neither differences in the initial or post-PCI TIMI flow, blush grades, maximal enzyme release nor differences in clinical outcome early or within 6 months after the index event.

**LOE 1** neutral, fair


Registry data on 60,770 pts with Non-ST-elevation MI from the NRMI 4 registry of 15379 pts received a Gp IIb/IIa inhibitor early after hospital admission (median 6 hrs after admission, average duration of infusion was 26.3 ± 18 hrs). Unadjusted in-hospital mortality was lower with early Gp IIb/IIa treatment (3.3 vs 9.6 %, p< 0.0001). This lower mortality was also remaining after adjusting for propensity of clinical factors hospital characteristic (treatment strategies) and was also lower for pts receiving PCI at any time (OR 0.85 (95% CI 0.76-0.95)) also after excluding all pts receiving cardiac catheterisation (OR 0.68 (95% CI, 0.6-0.78)) and even for those pts who died within the first 24 hrs of hospitalisation (OR 0.19 (95%CI, 0.83-1.01)).

**LOE 4** supporting good


**LOE 4** supporting fair


In the “EARLY” pilot trial 311 pts with NSTE-ACS were randomly assigned to double blinded therapy with
eptifibatide or placebo for 12 to 24 hrs initiated in the emergency department followed by crossover to open label eptifibatide with recommendation to performed PCI after cross over. PCI was performed in only 30 % of pts. Serial CK-MB and quantitative cardiac troponin T levels estimated during the first 24 hrs after initiation of treatment showed no difference between the treatment groups also there were no differences in clinical outcome within 72 hrs of observation or hospital discharge which ever came first.

LOE1 neutral fair


Randomized double blinded study on 7800 pts with NSTE-ACS who were not undergoing early revascularisation and were treated with abciximab for 24 hrs (n=2590) or 48 hrs (n=2612) or placebo. At 30 days 8 % of pts with 24 hrs abciximab infusion compared with 8 % on placebo died and with 48 hrs abciximab 9.1 % of pts died or had a myocardial infarction (OR 1.0 (95 %CUI, 083-1.24)) for difference between placebo and 24 hrs abciximab and 1.1 (0.94-1.34) for difference between placebo and 48 hrs abciximab). Bleeding rates were slightly increased with abciximab, especially when continued for 48 hrs). No benefits were seen in pts with abciximab. Any subgroup even not in those with raised troponin T or I. It is concluded that abciximab should not be used in pts with NSTE-ACS who do not have timely PCI.

LOE 1 opposing good


Randomized study on 9207 pts with moderate to higher risk on ST-elevation ACS undergoing an invasive treatment strategy who received either routine upstream or deferred selective Gp IIb/IIIa inhibitor at intervention. The composite endpoint of death, myocardial infarction or unplanned revascularisation for ischemia at 30 days occurred in 7.9 % of pts with deferred compared to 7.1 % of pts with upstream administration of a Gp IIb/IIIa blocker showing non inferiority of deferred Gp IIb/IIIa inhibitor use. Since Gp IIb/IIIa inhibitors were used more frequently for significantly longer duration with upstream initiation, there was a higher rate with major bleeding (6.1 % vs 4.9 %, p=0.001), showing a superiority (p=0.009) and p<0.001 for non-inferiority for upstream. use of Gp IIb/IIIa blockers. This concluded that the numerical increase in composite ischemia with deferred Gp IIb/IIIa inhibitors did not meet the criterion for non-inferiority and is offset by a significant reduction in major bleeding.

LOE1 neutral good


Randomized study a strategy of 4 arms in a 2 by 2 factorial design in 2082 pts with STEMI and a symptom duration < 12 hrs i.e. PTCA alone, PTCA + abciximab, stenting alone and stenting + abciximab. Normal flow was achieved with PCI in about 96 % of pts irrespective of strategy. A composite endpoint of death, re-infarction, disabling stroke and ischemia driven TVR occurred in 20 % after PTCA, 16.5 % after PTCA + abciximab, 11.5 % after stenting and 10.2 % after stenting + abciximab (p<0.001) (the differences due entirely to the rates to TVR: 15.7 % after PTCA 5.2 % after stenting + abciximab, p<0.001). It is concluded that stentimplantation with or without abciximab therapy should be considered as routine reperfusion strategy.

LOE1 neutral good


One year results of the ACUITY trial on 13819 pts with moderate to high risk NSTE-ACS treated with UFH or enoxaparin + Gp IIb/IIIa inhibitor, bivalirudin + Gp IIb/IIIa inhibitor or bivalirudin monotherapy. 4605 of the pts were randomized to receive of the routine upstream Gp IIb/IIIa inhibitors: 4602 pts deferred to selective Gp IIb/IIIa administration. The composite ischemia endpoint of death, myocardial infarction or unplanned revascularisation for ischemia at one year, occurred in 15.4 % in pts with heparin + Gp IIb/IIIa, 16 % with bivalirudin + Gp IIb/IIIa and 16.2 % with bivalirudin alone (n.s.). Mortality was in 3.9 % in the groups with Gp IIb/IIIa inhibitors and 3.8 % in the bivalirudin monotherapy group (p=n.s.). Composite ischemia occurred in 16.3 % of pts assigned to deferred Gp IIb/IIIa compared to 15.2 % with upstream administration (HR 1.08, 05 % CI, 0.97 – 1.2, p=0.15).

LOE1 neutral good

Randomized study on 7789 of 13819 pts with NSTE-ACS undergoing PCI who were treated with UFH or enoxaparin + Gp Iib/IIIa blockers (group 1), bivalirudin + Gp Iib/IIIa blocker (group 2) or bivalirudin alone (group 3). Primary outcome was the composite of death, MI or unplanned revascularisation for ischemia (ischemia endpoint), major bleeding and net clinical benefit (composite of ischemia and bleeding). The ischemia endpoint as well as bleeding revealed no significant differences between group 1 und 2 (ischemia group: 9 %, group 2: 8 %, p=0.16, major bleedings 8 % vs 7 % p=0.032 respectively). Also there was no significant difference between group 3 and group 1 regarding the ischemia outcome (9 % vs 8 %, p=0.45). However bleeding rates were significantly lower in group3 compared to group 1 (4 % vs 7 %, p<0.0001) resulting in a trend towards a better 30 day net clinical outcome (ischemia + bleedings) with bivalirudin alone (12 % group 3, 13 % group 1, p=0.057, CI 0.87 (0.75-1.00)).

LOE1 opposing good


Randomized study on 3602 STEMI pts with a symptom duration of less than 12 hrs to be treated with heparin + glycoprotein Gp Iib/IIIa inhibitors or bivalirudin alone for primary PCI. The two primary endpoints were major bleeding and the composite of major bleeding, death, re-infarction TVR for ischemia and stroke. Bivalirudin alone led to a reduced grade of the composite endpoint (9.2 % vs 12.1 %, RR 0.76, 95 CI 0.63-0.92, p=0.005) compared to heparin + Gp Iib/IIIa inhibitor due to a lower rate of major bleeding (4.9 % vs 8.3 %, RR 0.6, 95% CI, 0.46-0.77 p<0.001). Risk of acute stent thrombosis within 24 hours was increased at 24 hrs but not at 30 days with bivalirudin. Compared with heparin + Gp Iib/IIIa Bivalirudin resulted in a lower rate of death of cardiac cause (1.8 % vs 2.9 %, RR 0.62, 95 % CI 0.4 – 0.95, p=0.03) and all cause mortality (2.1 % vs 3.1 %, RR 0.66, 95 % CI, 0.44 – 1.0, p=0.047).

LOE1 opposing good


Randomized small study comparing prehospital fibrinolysis in pts with a symptom duration of less than 12 hrs to be treated with heparin + glycoprotein Gp Iib/IIIa inhibitors or abciximab facilitated PCI (symptom duration to PCI 202 min). ST-resolution > 50 % was not different at 120 min. At control angiography 5 – 7 days after randomisation TIMI 3 flow was present in 54 % of the fibrinolysis group and in 71 % of patients in the PCI group. At 30 days the composite of death, stroke, of re-MI was 8 % in the lytic and 3 % in the PCI group (p=n.s.).

LOE1 neutral fair


Substudy of the PRISM-Plus investigation on patients recruited in Canada in PCI hospitals (n=512) or non PCI-hospitals (n=322) showing that transfer with upstream treatment with tirofiban plus heparin is safe and achieved clinical benefits of tirofiban with and without transfer of pts with NSTE-ACS are similar.

LOE4 supporting fair


Randomized study comparing prehospital ½ dose reteplase lytic + abciximab (a standard bolus and 12 hrs infusion) with the same prehospital combo lytic regimen plus additional immediate facilitated PCI. Primary endpoint was infarct size assessed by delayed enhancement MR, secondary endpoints were 90 min ST resolution and the composite of death, Re-MI and stroke at 6 months. Infarct size was lower with facilitated PCI
(5.2 % (1.3 – 11.2 %)) compared to standard treatment after combo lytic with 10.4 % (3.4 – 16.3 %), p = 0.0001) as was complete (>70 %) ST-segment resolution (80 % vs 52 %, p<0.001). Also a trend in favour of facilitated PCI was observed for the composite clinical endpoint.

LOE1 supporting good


Randomized study comparing prehospital combination fibrinolysis (1/2 reteplase + abciximab, n=82) followed by routine treatment (including rescue PCI) and the same initial prehospital treatment with immediate "facilitated PCI" (n=82) and a routine primary PCI control group (n=136). The study shows that prehospital initiated facilitated PCI results in more complete ST-segment resolution (> 70% at 90 Min) in the "facilitated" group (80%) vs 52 % in the "combo lytic" group without immediate PCI and 52% with primary PCI. Clinical outcome (death, MI and stroke) was better with complete ST-resolution in this study as has been shown in other studies before.

LOE1 supporting fair


Data on 30830 NSTE-ACS pts of the CRUSADE registry who had upstream use of a Gp IIb/IIIA receptor blocker > 1 hr before PCI (43 % of pts) or periprocedural GP IIb/IIIA receptor blockers (57 % of pts). Immediate time from arrival to PCI was longer for pts who received Gp IIb/IIIA blockers (25.6 hrs) compared with pre-procedural Gp IIb/IIIA blockers (18.2 hrs). After adjusting for pts hospital characteristics there was no difference regarding death or MI but a lower incidence of unadjusted deaths or reinfarctions in patients who underwent PCI < 12 hrs from admission.

LOE4 neutral good


Randomized pilot study comparing early angiography (median delay 6 hrs, without tirofiban treatment) with delayed angiography (late group, median delay 50 hrs with 24 – 48 hrs tirofiban pre-treatment) in 229 NSTE-ACS pts and a symptom duration of < 24 hrs. Finally 130 pts underwent a PCI. No difference was observed in clinical outcome but total CK-MB release was lower and rate of patent coronary culprit vessel (TIMI 2+3) was higher (66 vs 59 %, p=0.05) with tirofiban pre-treatment.

LOE1 supporting fair


Randomized on 507 pts with STEMI receiving pre-hospital Tirofiban (early, 25 % in ambulance, 75 % in remote hospital) or at initiation of catheterisation (late). Time of treatment in the early group was 59 min before angiography, only pts with ability to perform PCI within 6 hrs after symptom onset were included. The total ischemic time in the early and late group was 196 and 199 minutes respectively. The primary endpoint was TIMI flow grade 3 at initial angiography, secondary endpoint were presence of thrombus at initial angiography and pre-PCI myocardial blush grade. There was an better blush grade 3 with Tirofiban (60 % vs 73 % the late group, p=0.002) and a higher rate of TIMI 2 or 3 flow grade (43 % with early treatment and 34 % with late treatment, p=0.04) but there was no difference in TIMI grade 3 flow (19 % early, 15 % late, p=0.22). Moreover there was no difference in TIMI 3 flow or myocardial blush grade post-PCI. Also the 1-year follow-up combined incidence of death or re-MI was identical in both groups (7 %). Thus, despite a lower prevalence of thrombus and a better myocardial perfusion pre-PCI, no beneficial effect was found post-PCI.

LOE1 neutral good

Randomized placebo-controlled, double blinded study on 984 pts with STEMI and a symptom duration < 24 hrs (median 76 min) receiving a high dose bolus (25 µg/kg followed by 0.15 µg/kg/min for 18 hrs) of tirofiban in an ambulance or in a non-PCI hospital in addition to 500 mg aspirin, 5000 U heparin and 600 mg clopidogrel. Primary endpoint was residual ST-segment deviation 1 hr after PCI (first angiography performed 55 min after start of treatment). ST-segment deviation 1 hr after PCI was significantly lower (3.6 ± 4.6 mm) with tirofiban vs 4.8 ± 6.3 mm with placebo (p=0.003) as well as before PCI (10.9 ± 9.2 mm vs 12.1 ± 9.4 mm respectively, p=0.028). There was also a significantly lower rate of the composite of death recurrent myocardial infarction urgent target vessel revascularisation or blinded bail-out use of study drug (p=0.02) with tirofiban pre-treatment, but neither for the single endpoints of dead, re-MI or urgent TVR nor the combination of these clinical endpoints. LOE1 supporting good


A small study on 158 AMI patients randomized to receive tirofiban before PCI in the emergency room or immediately before PCI in the cath-lab. The study showed that the TIMI 3 flow rate (23.1 % vs 10 %, p=0.032) at initial angiography in the "early group" was better than in the late group. After PCI angiographic results were similar. LOE1 supporting fair


102 pts with STEMI and a symptom duration < 12 hrs with planned PCI were randomly treated with early eptifibatide in the ED (early group) or optional eptifibatide at time of PCI (late group). The early group received eptifibatide in mean 45 min for angiography. The primary endpoint of TIMI 3 patency before PCI was observed in 34 % with early and 10 % with late treatment with eptifibatide (p=0.001). ST-resolution and TIMI 3 flow grade after PCI showed no difference as well as the composite of death, re-infarction, stroke or major bleeding until day 30. LOE1 supporting fair