On the use of abciximab in percutaneous coronary intervention

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THE 6 ORIGINAL PAPERS ARE

Paper I Iversen A, Galatius S, Jensen JS. The optimal route of administration of the glycoprotein IIb/IIIa receptor antagonist Abciximab: Intravenous versus intracoronary. A review. Curr Cardiol Rev. 2008;4: 293-299.

Paper II Iversen A, Abildgaard U, Galloe A, Hansen PR, Galatius S, Madsen JK, Engstroem T, Pedersen S, Jensen KS, Jensen JS. Intracoronary Compared to Intravenous Bolus Abciximab During Primary Percutaneous Coronary Intervention in STEMI Patients Reduces 30-days Mortality and Target Vessel Revascularization.
A Randomized Trial. J Interv Cardiol. 2011;24: 105-111

Paper III Iversen AZ, Galatius S, Abildgaard U, Galloe A, Hansen PR, Jensen JS. Intracoronary compared to intravenous abciximab in STEMI patients undergoing primary percutaneous coronary intervention reduces mortality, target vessel revascularization and re-infarction after 1 year.
Long-term follow-up from a randomized trial.
Submitted.

Paper IV Iversen AZ, Pedersen S, Jons C, Mogelvang R, Galatius S, Galloe A, Abildgaard U, Hansen PR, Madsen JK, Jensen JS. Impact of abciximab in diabetes patients with acute coronary syndrome who undergo percutaneous coronary intervention: Results from a high-volume single center registry.
J Invasive Cardiol. 2011;23: 21-26.

Paper V Iversen AZ, Galatius S, Pedersen S, Madsen JK. Jensen JS. Impact of abciximab in the elderly patients with high risk acute coronary syndrome who undergo percutaneous coronary intervention.
Drugs & Aging. 2011;28: 1-10.

Paper VI Iversen AZ, Galatius S, Pedersen S, Abildgaard U, Jensen JS. Mortality reduction with administration of abciximab during primary PCI is confined to STEMI patients with complex lesions.
Submitted.

ABBREVIATIONS

ACS = Acute Coronary Syndrome
BMI = Body Mass Index
BMS = Bare Metal Stent
CAG = Coronary Angiography
CI = Confidence Interval
CVD = Cardio Vascular Disease
DES = Drug Eluting Stent
DM = Diabetes Mellitus
GCP = Good Clinical Practice
GPI = Glycoprotein IIb/IIIa Inhibitor
HR = Hazard Ratio
IC = Intracoronary
IV = Intravenous
IQR = Interquartile Range
LOE = Level of Evidence
MACE = Major Adverse Cardiac Events
MI = Myocardial Infarction
NSTEMI = Non-ST-segment Elevation Myocardial Infarction
PAI = Platelet Aggregation Inhibition
PCI = Percutaneous Coronary Intervention
RCT = Randomized Clinical Trial
GCP = Good Clinical Practice
STEMI = ST-segment Elevation Myocardial Infarction
TIMI = Thrombolysis In Myocardial Infarction
TVR = Target Vessel Revascularization
UAP = Unstable Angina Pectoris

ACRONYMS

AIDA STEMI	Abciximab Intracoronary versus intravenously Drug Application in STEMI trial.
BRAVE-3	Bavarian Reperfusion Alternatives Evaluation-3 study.
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial.
CAPTURE	C7E3 Fab Anti Platelet Therapy in Unstable REfractory trial.
CICERO	Comparison of Intracoronary versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction trial.
EPIC	Evaluation of 7E3 for the prevention of Ischemic Complication study.
EPILOG	Evaluation in PTCA to Improve Long-Term Outcome with abciximab GP IIb/IIIa Blockage study.
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibitor for Stenting study.
ISAR-REACT 2	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 trial.
ISAR-SWEET	Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a superior Way to Eliminate Elevated Thrombotic Risk in Diabetics study.

Part I
INTRODUCTION

1.1 Historical perspective

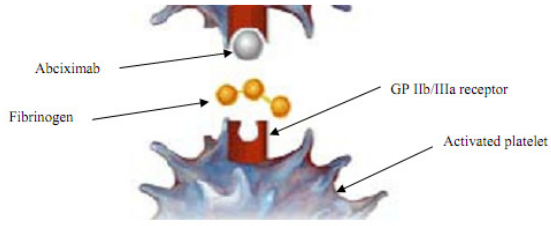
Since the introduction of the glycoprotein IIb/IIIa inhibitors (GPI) in the early 1990ies, three agents have been marketed, namely the two small molecule GPI, eptifibatide and tirofiban and one large molecule GPI, abciximab. These agents are used as adjunctive antiplatelet therapy in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI). Abciximab has been tested in several randomized clinical trials (RCT) in multiple settings. A pooled analysis of three of the earliest studies (EPIC [1, 2], EPOLOG [3] and EPISTENT [4, 5]) comprising both high- and low risk ACS patients, showed an almost 50 % reduction of the composite endpoint of mortality, need of target vessel revascularization (TVR) and recurrent myocardial infarction (MI) in favor of abciximab treatment [6]. This led to a general acceptance of abciximab as a rational choice of adjunctive antiplatelet therapy in ACS [7]. However, other types of stents and classes of drugs that inhibit platelets have emerged during the last two decades which might have changed the efficacy of abciximab. Trials have evaluated abciximab in the context of additional P2Y12 antagonists with conflicting result. The BRAVE-3 trial, which included patients with ST-segment elevation MI (STEMI), did not show any additional effect of up-stream abciximab when administered in addition to 600 mg of clopidogrel [8]. In contrast to this, The ISAR-REACT 2 trial found a beneficial short term effect of abciximab on top of clopidogrel among non-ST-segment elevation MI (NSTEMI) patients, though confined to those with elevated biomarkers [9, 10]. Meta-analyses have subsequently shown a reduction in adverse outcome in favor of abciximab, but also that the higher the risk profile, the larger the benefit [11]. This has resulted in changes in international guidelines over the last decade [12, 13]. Whereas routinely and up-stream use of abciximab was encouraged in the earlier guidelines [7], it is now recommended that abciximab should be reserved for those with high thrombus burden and in bail-out situations [12, 13]. The latest concerns on the use of abciximab regard the route of administration. It is currently being investigated whether intracoronary bolus administration confers additional benefits compared to the standard intravenous administration. This novel route of administration is however, not mentioned in the current guidelines. Also, data indicating different efficacy of abciximab in specific subgroups of patients have emerged. Furthermore, introduction of direct thrombin inhibitors, such as bivalirudin, and newer P2Y12 inhibitors, such as prasugrel and ticlopidine, have changed the use and indication for abciximab and will probably continue to do so.

1.2 Mechanism of action

One of the most pivotal events in ACS is the formation of the intracoronary thrombus, preceded by a rupture or erosion of the vulnerable plaque [14-16]. Through several complex pathways the thrombus is formed as a mesh of fibrinogen interlinked platelets in which red blood cells are captured. If the thrombotic activity is extensive one would expect the resultant thrombus to be totally occlusive and result in STEMI. In case of NSTEMI or unstable angina pectoris (UAP), some thrombus is expected to be present, although less extensive.

The main action of abciximab, a Fab fragment of the chimeric human-murine monoclonal antibody 7E3, is the irreversible binding to the glycoprotein IIb/IIIa receptor (GP) expressed on the surface of the platelet [17].As parts of ACS platelets are activated – a state in which an up-regulation of the surface GPs occurs. Through binding of abciximab to those receptors and thus preventing cross-binding of platelets via fibrinogen, the aggregation of platelets and hence thrombus formation is diminished, Figure 1.

Figure 1. Showing how abciximab prevents cross-binding between activated platelets and fibrinogen



In addition to the mechanisms directly related to inhibition of the platelet bound GP, abciximab also exerts other effects. In short these rely on inhibition of some of the inflammatory components that is induced following an ACS [18]. The mechanisms will be discussed in more detail in the following sections of the thesis in relation to the specific papers in which the mechanism is of relevance.

1.3 Objectives

As the short historical review above shows, abciximab has moved from widely used to a more targeted use. Also, abciximab is currently undergoing evaluation to test whether optimization of the administration route, timing of delivery and identification of subgroups who might have additional benefit, can further improve the efficacy of abciximab use.
In order to elucidate these aspects we have performed a randomized trial and three observational registry studies.

For clarity, presentation of the 6 papers included, is divided into 2 parts:

Part II
Optimal administration route of abciximab.
The purpose of this section is to investigate whether intracoronary administration of bolus abciximab is superior to intravenous administration in STEMI patients treated with pPCI.
This section is based on paper I-III.

Part III
Differences in the effect of abciximab in three subgroups of patients.
The purpose of this section is to describe the influence of diabetes mellitus (DM), age and lesion type on the efficacy of abciximab.
This section is based on paper IV-VI.

Part II
OPTIMAL ADMINISTRATION OF ABCIXIMAB. A RANDOMIZED STUDY

2.1 Background

The glycoprotein IIb/IIIa inhibitor abciximab was approved for IV use in the early 1990ies.
In 1999 the first case reports were published on IC administration [18, 19]. Later – and continuing – several studies investigating the possible superiority of IC bolus administration have been published. In paper I, we have summarized the studies evaluating IC versus IV bolus abciximab until 2008 when it was published.
These studies were either retrospective, measuring non-clinical parameters, or underpowered to detect any differences in clinical endpoints. See Table 2, paper I.
Since then a number of studies have been published with contradicting results. Latest the CICERO trial showed no effect on clinical endpoints with IC compared to IV bolus abciximab in a low risk STEMI population [20, 21]. Overall, data have suggested that IC compared to IV bolus abciximab improves myocardial function following PCI, but no study have yet been able to show an effect on the clinical endpoints of mortality, TVR, or MI.
The rationale for the possible superiority of IC bolus administration must be sought in the mechanisms of action of abciximab. As described before in this thesis, abciximab binds with very high affinity to GP receptors on the surface of the activated platelets, thereby preventing binding of von Willebrand factor and especially fibrinogen, the bridging ligand between platelets in a thrombus. By doing so, abciximab blocks the final pathway of platelet aggregation [22]. Hence, platelet aggregation inhibition (PAI) is one of the pivotal elements in prevention and treatment of thrombotic coronary artery disease. IV administration of abciximab in standard dose is known to confer a PAI of ≥ 80 % which is meant to be sufficient to prevent further platelet aggregation [23]. However, studies have suggested that only a limited proportion of patients reach a sufficient PAI and that PAI ≥ 95 % lead to even better clinical outcome [24, 25]. By delivering abciximab IC and hence obtain a higher local drug concentration it is believed, that a higher PAI is reached. Furthermore, in vitro studies have shown that a very high local abciximab concentration might disrupt the platelet-fibrinogen linkage and thus have the ability to disaggregate the thrombus [26-28]. This is believed to improve the outcome. Evidence of improvement in outcome by IC administration on surrogate parameters is becoming more and more convincing. However, evidence of improvement in clinical outcome is not as clear.

2.2 Objectives

In the present studies we sought to evaluate the short- and long-term effect of IC versus IV bolus abciximab on clinical endpoints among high risk STEMI patients treated with pPCI. Also, risk of short-term bleeding complications was assessed.

2.3 Methods

Study design:
Is described in detail in the method sections in paper II and III. Summarized, this is a randomized, open-label, single-center trial. Patients included had STEMI and were treated with pPCI. Furthermore, they had to have indication for adjuvant treatment with abciximab, which was decides at the operators' discretion (typically type C/B2 lesion, high thrombus burden, no/slow reflow) and no contraindications for abciximab. The data presented in Table 1 were prospectively collected and entered in a dedicated database. Randomization was performed by using sealed, opaque envelopes to either IC or IV bolus of abciximab in a dose of 0.25 mg/kg body weight followed by a 12-hour IV infusion of abciximab in a dose of 0.125 μg/kg body weight/min with a maximum of 10 μg/min. IC bolus of abciximab was delivered via the guiding catheter, whereas the IV bolus was administered into a peripheral vein, both after filtering of the drug. The drug of use in our centre is Reo-Pro® (Eli Lilly, Denmark, who had no financial or scientific involvement in the trial). All patients received pre- and post-treatment according to national guidelines.

Endpoint definition and follow-up:
The primary endpoints were defined according to the Academic Research Consortium (ARC) proposals, i.e. mortality, TVR, re-infarction (MI), and the combination of the three [29]. Secondary endpoints were bleeding complications. Follow-up was performed after 30 days and 1 year. Patients were contacted by telephone, subsidiary by letter. All possible events were confirmed by checking hospital source data. Assessment of the study endpoints was done blinded by the endpoint committee.

Statistical analysis:
The assumption of a 50 % reduction (from 10% to 5 %) in the combined endpoint after 30 days could be fulfilled with an average event rate of 7.5 % among 355 patients included. Hence the study was un-blinded and data analyzed for short term outcome with a risk of type 2 error of 20 %. Patients were subsequently followed for 1 year. Differences in demographic and angiographic data were evaluated using $\chi 2$-test for frequencies and Students unpaired t-test or Mann-Whitney test for continuous 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 log rank test. Two-sided p-values < 0.05 were considered statistically

significant. All analyses were performed with SPSS version 17 (SPSS Inc., Chicago, Illinois, USA).

2.4 Main results

Short-term outcome (30-days) is presented in paper II.
Long-term outcome (1-year) is presented in paper III.
A total of 355 pPCI-treated STEMI patients treated with adjuvant abciximab were included from 2006 to 2008. Of those 185 patients were randomized to IC administration and 170 patients to IV administration of bolus abciximab. Baseline characteristics were well balanced between assignment groups. See Table 1.
Despite the selected nature of our study population, variables describing known risk factors were as expected from a contemporary Danish STEMI population. Of interest, it should be noticed that the majority of patients had complex coronary lesions (type B/C constituted > 90 %) and had pre-PCI TIMI flow 0 (in average 75 %), thus indicating high risk lesions. There was a trend towards higher restoration of normal TIMI flow post-PCI in the IC group (p=0.08) although this was not a prespecified endpoint.
Event rates after 30 days showed a significant reduction in mortality and the risk of TVR in favor of the IC administration. Despite a more than 40 % relative reduction in the risk of recurrent MI, this was not statistically significant. The composite endpoint was also highly significant reduced from almost 20 % in the IV group to nearly 8 % in the IC group (Figure 2).

Table 1. Showing demographic and procedural characteristics stratified by assignment group

	Intracoronary abciximab (n=185)	Intravenous abciximab (n=170)	p-value
Demographic data			
Age, years, median(IQR)	62 (54-71)	62 (54-71)	0.77
Male gender, %	82	79	0.69
Hypertension, %	40	40	1.00
Hyperlipidemia, %	43	39	0.52
Diabetes mellitus, %	14	11	0.34
Current smokers, %	50	52	0.67
BMI, kg/m^2 (±SD)	27 (±4)	26 (±5)	0.28
Family history of CVD, %	38	32	0.22
Prior PCI, %	19	18	0.79
LVEF, %, mean (±SD)	38 (±12)	40 (±)	0.34
Procedural data			
Culprit lesion, %			
LMS	0	0	
LAD	48	51	
Cx	8	9	0.53
RCA	43	40	
Vein graft	1	0	
No of vessels diseased, %			
1	65	70	
2	23	18	0.49
3	12	12	
Lesion type, %			
A	8	6	
B	34	27	0.23
C	58	67	
Stent type, %			
POBA	4	6	
BMS	16	16	0.80
DES	80	78	
Pre-PCI TIMI flow, %			
0	72	78	
1	10	12	0.12
2	9	3	
3	9	7	
Post-PCI TIMI flow, %			
0	1	2	
1	4	7	0.33
2	14	18	
3	81	73	0.08

From Iversen et al. Submitted. Paper III

The secondary endpoint, namely bleeding complications, showed no differences between assignment groups.
As planned from study start all patients were followed for 1 year. No patients were lost to follow-up. Again, we observed a significant reduction in favor of the IC administration for the endpoints mortality, TVR and the composite endpoint. In addition, the risk of recurrent MI was now found to be significantly reduced in favor of the IC group.
Thus, the risk of reaching the combined endpoint within 1 year from randomization was reduced from 20 % in the IV group to 10 % in the IC group (log rank p-value 0.002)(Figure 3).
The reduction in endpoints observed after 1 year of follow-up both absolutely and relatively were similar to those observed after 30 days, and indicates firstly that the positive effect of IC abciximab administration is obtained on short-term and secondly, that the effect is sustained on long-term, at least 360 days.

Figure 2. 30-days event rate

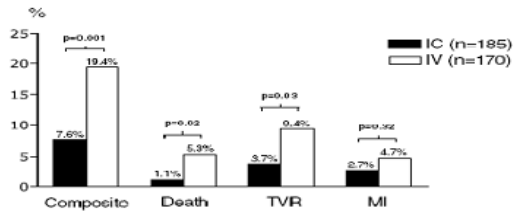


Figure 1. Event rates at 30 days (n = 355). Bar chart showing proportions reaching primary end-points within 30 days from randomization. P-values are calculated by chi-squared test. IC = intracoronary; IV = intravenous. Composite = MI, TVR or death; TVR = target vessel revascularization; MI = myocardial infarction. Numbers reaching end-points were (IC/IV), composite (14/33), death (2/9), TVR (7/16), MI (5/8).

From Iversen et al. J Interv Cardiol. 2011. Paper II

2.5 Discussion

The main finding from this study was the significant reduction in the four clinical endpoints: mortality, TVR, MI, and the composite of those, in favor of the IC administration. This clinical effect has never been shown before in a population as large as ours. Several aspect regarding our method and results need to be commented.
Firstly, our study was designed in accordance to current guidelines and treatment recommendations. Since then, the use of abciximab has changed from a broader to a more restricted use and new antiplatelet agents (P2Y12 and direct thrombin inhibitors) have been introduced. Also, new catheters for more targeted IC drug delivery are being tested and thrombus aspiration, distal protection, and transradial access has become an integrated modality in many centers. Thus, our results must be interpreted in this context. Several studies have shown improvement in non-clinical parameters in favor of the IC administration [30-34]. However, no studies have yet proved this to translate into improvement in clinical outcome. Latest, the CICERO trial showed improvement in infarct size, but no effect on clinical endpoints, despite their larger number of patients enrolled (n=534) [21]. We believe that the most important reason why we, in contrast to others, were able to detect a clinical relevant difference in endpoints between the two administration routes relies on differences in the selection of patients. We included only high risk STEMI patients with indication for adjuvant therapy with abciximab i.e. high thrombus burden and high degree of complexity in the coronary lesion. In the CICERO trial only 50 % of patients had a TIMI 0 prior to PCI and all patients, regardless of lesion complexity, were eligible for inclusion. Indeed, a metaanalysis that we are currently conducting in collaboration with an Italian group on a patient level shows that the benefit of IC abciximab is confined to the high risk STEMI patients. Also, a metaanalysis conducted on numbers of events only, showed a reduction in both MACE and mortality in favor of IC administration [35].
In paper II, we speculated whether the differences in endpoints between groups observed after 30 days, would further increase during the first year from randomization. If so, this might have been explained by the GPI platelet receptor independent effect of abciximab, mainly the anti-inflammatory actions. However, this

seemed not to be the case, but importantly the beneficial effect obtained during the first 30 days was sustained until 1 year.

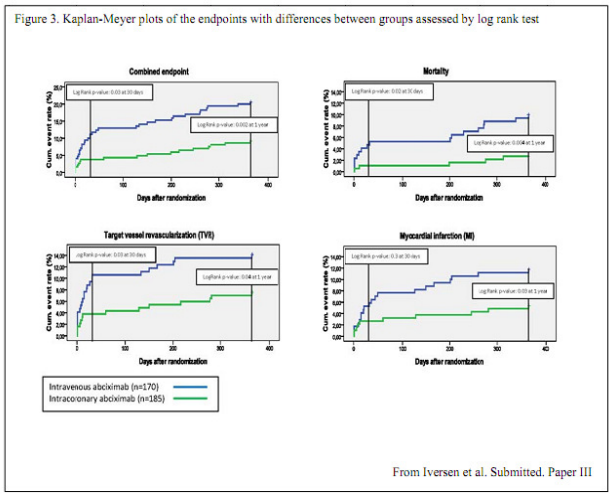


Figure 3. Kaplan-Meyer plots of the endpoints with differences between groups assessed by log rank test

From Iversen et al. Submitted. Paper III

2.6 Study limitations

Despite the randomized nature of our study and that no differences between the assignments groups were observed, we cannot rule out the possibility that some unmeasured characteristics were different in the two groups as it is the case in any randomized trial. Neither can we rule out that our study might be underpowered. Nevertheless, we found a consistent reduction in the endpoints over time. Should our study be underpowered, we would primarily face the risk of a type II error, which obviously is not the case for the primary endpoints after 1 year. However, it could be the case for MI and bleeding complications in our 30-days follow-up.

Another topic that might be of concern is the unblended nature of the administration route. We chose not to blind the operator or the patients, since we believed that the clinical endpoints could not be influenced by such blinding. Importantly, all endpoints were assessed blinded and unaware of group assignment. Also, the inclusion criteria we used must be accounted for. The criteria for abciximab at our center are quite stringent compared to a general use in STEMI patients and might thus not resemble those used elsewhere. This is not only expressing the ambiguous recommendations in international guidelines, but also a reflection of the fact that we wanted to include patients with the highest risk of adverse outcome, since we believed they would benefit the most from the abciximab treatment.

2.7 Conclusion

Results from this study, one of the largest yet conducted, indicates that IC bolus abciximab administered to high risk STEMI patients during pPCI, is superior to IV bolus administration with regards to short-term mortality, TVR and MI. This effect appears to sustain on the long-term and to be without any side effects.

2.8 Perspectives

The results from our trial adds to the body of evidence that IC bolus administration of abciximab in high risk STEMI patient treated with pPCI is superior to IV administration. However, larger studies must confirm our findings. We are awaiting the results from the AIDA STEMI trial, which plan to enroll 2,000 patients [36]. Also, the new concept of more targeted delivery with the ClearwayRx catheter system is being tested and data already published are promising [37]. Even though the use of abciximab might partly be substituted by other small molecule GPIs and direct thrombin inhibitors in the future for some indications in ACS, we still believe that abciximab plays an important role as adjuvant therapy in PCI in high risk patients. Future studies testing new agents against abciximab must consider using the IC administration in these patients. Finally, we believe that future guidelines need to consider the possibility of IC abciximab administration in high risk STEMI patients.

Part III
DIFFERENCES IN THE EFFECT OF ABCIXIMAB IN 3 SUBGROUPS OF PATIENTS. THREE REGISTER STUDIES.

3.1 Background

Abciximab treatment with PCI and in ACS has been extensively investigated in several RCTs. However, new treatment strategies have been developed since the first trials and are still evolving. This has led to changes in the recommendations by both the European Society of Cardiology and the American societies of cardiology. Also, patients in RCTs do not necessarily resemble patients treated under real-life conditions [38]. We have aimed to evaluate the possible benefit of abciximab treatment in specific subgroups only sparsely mentioned in the international guidelines.

Firstly, we wished to evaluate the effect of abciximab in patients with diabetes mellitus (DM) (paper IV). Earlier studies have suggested that diabetic patients might have an incremental benefit of abciximab compared to patients without DM [39-41]. Since DM, which is a known risk factor for CVD, is becoming more prevalent and is known to confer a higher risk of adverse outcome after ACS, this subgroup of patients needs special attention [42-45]. Several cellular mechanisms are thought to account for the higher risk of adverse outcome in DM patients [46-49]. Platelets in DM patients are known to exhibit increased ability to aggregate and adhere to each other. Moreover, in DM patients, platelets are easier activated (and thus, exhibit surface GP receptors) and levels of fibrinogen are heightened. With this in mind, it would be logical to aggressively inactivate platelets by GPIs in diabetic patients. However, not all studies have confirmed such an incremental effect in this specific subgroup of patients.

Secondly, we wished to assess if an age-dependent effect of abciximab exists (paper V). Since age is the most powerful independent predictor of adverse outcome in ACS patients and increase in the future ACS population, treatment with adjuvant therapies, such as abciximab, is of particular interest. However, the possible benefit of abciximab on cardiac events (less MI and TVR) should be weighed against the possible side-effects, in this case bleeding complications, which will be higher in elderly [50]. Previous studies have reported conflicting results on the efficacy of abciximab among the elderly [51-55]. Furthermore, RCT rarely include elderly patients and our knowledge on the effect of abciximab in the elderly is largely based on extrapolation from results among the younger patients [56].

Thirdly, we wanted to assess if the type of lesion found on CAG would influence the effect of abciximab in STEMI patients (paper VI). In the latest guidelines on revascularization, abciximab is recommended to patients with high risk lesions and high intracoronary thrombus burden [12, 13]. At the same time, ongoing studies are testing the thesis that ´early´ abciximab initiation (upstream) is superior to in ´cath-lab´ (downstream) [57-59].

Currently, upstream abciximab is not recommended. The consequence of upstream abciximab administration, would by nature be, that the lesion complexity would not be known at the time of abciximab initiation. We hypothesized that the effects of abciximab (inhibition of thrombus formation and propagation) would only confer a clinical benefit in the presence of complex lesions with high thrombus burden [11, 60].

3.2 Objectives

In the following three studies we sought to evaluate whether the benefits of abciximab differs in three distinct subgroups of patients with ACS, namely among patients with diabetes, patients of different ages, and in patients with different types of lesions, studied in registries attempting to mirror real life patients.

3.3 Methods

Study populations:

Results from the three papers in this part of the thesis arose by merging data from the following databases:

The P-base: A local PCI-registry at Gentofte University Hospital, which holds information on baseline-, angiographic- and treatment characteristics. Data were entered at the time of the procedure. Also, this database was used for validation of the endpoints TVR and reinfarction.

The Danish National Board of Health´s National Patient Registry (Lands Patient Registret): This registry holds information on ICD-10 and ICD-10-PCS (discharge diagnosis and procedure codes, respectively) on a patient level.

The National Person Identification Registry (CPR Registret): This registry holds information on vital status (alive, dead or emigrated).

All Danish citizens are provided with a unique person registration number at birth which enables us to link all diagnoses with subsequent treatment and follow-up data. In addition, all possible endpoints found in the registries mentioned were validated by cross-checking with hospital source data in the OPUS Work-place 2005® CSC, Scandihealth system.

Definitions:

In paper IV and V, all patients with ACS were included. In paper VI, only patients with STEMI were included.

ACS was defined as one of the following:

STEMI: presence of chest pain for >30 minutes and <12 hours and cumulative persistent ST-segment elevation >4 mm in at least 2 contiguous precordial ECG-leads or >2 mm in at least two or more contiguous limb ECG-leads.

NSTEMI: chest pain, positive cardiac biomarkers (Troponin T/I and/or creatine kinase MB (CKMB)), and/or ST-segment depression in two contiguous leads of ≥0.5 mm or inverted T waves ≥1.0 mm.

Unstable angina pectoris (UAP): chest pain, and ST-segment depression in two contiguous leads of ≥0.5 mm or inverted T waves ≥1.0 mm.

In all three papers, the following definitions on baseline- and angiographic data were used:

Diabetes was defined as use of anti-diabetic medication (oral and/or insulin) on admission.

Hypertension was defined as use of blood pressure-lowering drugs on admission.

Hypercholesterolemia was defined as use of lipid-lowering drugs on admission.

Multi-vessel disease was defined as 2- or 3 vessel-disease

Complex/high risk lesions were defined as type C/B2-lesions, visible thrombus, or no/slow reflow.

Endpoints:

According to the recommendations made by the Academic Research Consortium [29] the following endpoints were chosen:

-Mortality
-TVR
-Reinfarction
-Composite of the three above

Follow-up was 3 years in paper IV and 1 year in paper V and VI. Data were collected between January 2003 and November 2008

Statistics:

Baseline characteristics were compared using χ2-test for frequencies and Student´s unpaired t-test or Mann-Whitney´s test for continuous variables. Tests for interaction were performed between DM status (paper IV), age (paper V), and lesion type (paper VI) and use of abciximab for end points.

Since all three variables (DM status, age and lesion type) showed statistical significant interaction with use of abciximab, patients were subsequently stratified to ± DM (paper IV), age < 70 or ≥ 70 years (paper V), and simple/complex lesion (paper VI), besides use of abciximab.

Unadjusted Kaplan-Meier plots stratified by the relevant variable and use of abciximab were constructed for the four endpoints and differences compared with log rank test. In addition, for each investigated variable (DM, age and lesion type) hazard ratios (HR) were calculated using Cox proportional hazard regression analyses. In order to maintain a robust model only 1 variable per each 10 events was allowed in the multivariable analyses. In the statistical analyses, p-values <0.05 were considered of statistical significance. SPSS for Windows version 17.0 (SPSS, Inc., Chicago, Illinois) was used.

3.4 Main results

Paper IV: Abciximab in diabetic ACS patients

We identified 5,003 patients with ACS in our registries. Of those, 629 patients (12.6 %) had been diagnosed with DM at the time of the index procedure.

In short, severe comorbidity and risk factors known to be predictive of adverse outcome were more prevalent among patients with DM.

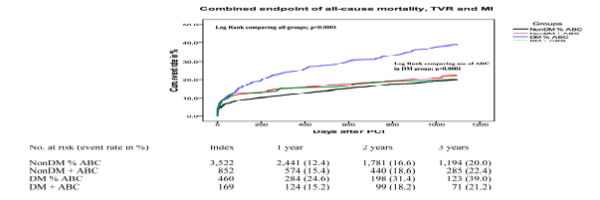
Also, the use of abciximab was more prevalent among patients with DM compared to patients without DM. Patients with DM who were treated with abciximab compared to those who were not, showed more severe angiographic characteristics and hence an a priori higher risk of adverse outcome.

In the unadjusted analyses, treatment with abciximab in DM patients reduced the mortality and need of TVR (and hence, the risk of reaching the composite endpoint, also including MI) to a level comparable to patients without DM. Figure 4 (and Figure 1a-d, paper IV). After adjustment for conventional baseline and angiographic variables (Table 1, paper IV) analyses showed, that even though DM patients treated with abciximab had an a priori higher risk of adverse outcome assessed by baseline characteristics, their risk of reaching the four endpoints was not significantly different from the reference group (patients without DM, who were not treated with abciximab).

Importantly and in contrast, patients with DM who were not treated with abciximab showed a HR of app. 1.5, 4.0 and 2.0 for mortality, TVR and MI, respectively, compared to the reference group. This conferred a doubling in the risk of the composite

endpoint among DM patients not treated with abciximab compared to a HR of 1.0 among DM patients treated with abciximab (Figure 2, paper IV). Looking at the DM group alone, adjusted analyses showed HR of 0.53 and 0.30 for mortality and TVR, respectively, in favor of treating patients with ACS and DM with abciximab (Figure 3, paper IV).

Figure 4. Kaplan-Meier plot of unadjusted long-term outcome in patients with and without DM, receiving and not receiving abciximab



From Iversen et al. J Invasive Cardiol. 2011. Paper IV

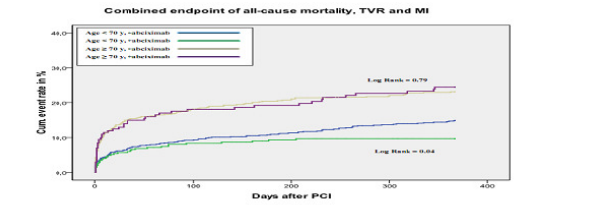
Paper V: Abciximab in elderly ACS patients

We identified 2,068 ACS patients with high risk coronary lesions on CAG. Of those, 870 patients (42 %) were ≥ 70 years of age. In short, both the younger (< 70 years of age) and the elderly (≥ 70 years of age) treated with abciximab more often had STEMI and their total stent length was longer, thus suggesting a higher risk of adverse outcome.

Unadjusted analyses revealed a significant mortality benefit in favor of abciximab treatment for the younger patients, whereas such an effect was not present among the elderly. No differences were observed for TVR and MI regardless of age and abciximab treatment. Still, the mortality benefit of abciximab treatment among the younger conferred a reduction in the composite endpoint, but not in the elderly. Figure 5 (and Figure 2a-b, paper V)

Also, after adjustment for conventional baseline and angiographic variables – including age (Table 1 and 2, paper V) analyses showed that whereas abciximab reduced mortality and the composite endpoint (also including TVR and MI) among the younger, no such effect was seen among the elderly (Figure 1, paper V).

Figure 5. Kaplan-Meier plot of unadjusted long-term outcome in patients < 70 and ≥ 70 years of age, receiving and not receiving abciximab



From Iversen et al. Drugs & Aging. 2011. Paper V

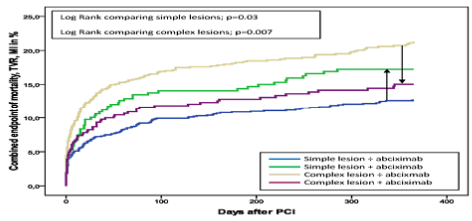
Paper VI: Abciximab in STEMI patients with simple or complex coronary lesions

We identified 2,935 STEMI patients treated with pPCI. Of those, 1.382 patients (47 %) had a complex lesion on CAG. In general, those with complex lesions had more severe risk factors and showed more severe angiographic characteristics (Table 1, paper VI). Stratified by lesion type (simple vs. complex) and use of abciximab, the 2x2 groups emerging were in general similar, when looking at baseline characteristics, except for the prevalence of DM, which was more prevalent among those treated with abciximab (Table 2, paper VI).

Unadjusted analyses showed a highly significant mortality reduction in favor of abciximab among patients with complex lesions. The opposite was the case in patients with simple lesions. Despite the finding that no differences were observed for TVR and MI in any of the groups, the mortality effect translated into a similar and significant effect on the composite endpoint. Figure 6 (and Figure 1a-d, paper VI).

Still, after adjustment for conventional baseline and angiographic variables (Table 1 and 2, paper VI) mortality and the composite endpoint were still less frequent among patients with complex lesions treated with abciximab (HR 0.62 and 0.71, respectively). The opposite effect was observed among patients with simple lesions. Again, the effect of abciximab was neutral with regards to TVR and MI in both groups (Figure 2, paper VI).

Figure 6. Kaplan-Meier plot of unadjusted long-term outcome in patients with simple and complex lesions, receiving and not receiving abciximab



From Iversen et al. Submitted. Paper VI

3.5 Discussion

Paper IV: Abciximab in diabetic ACS patients

In this paper we report a reduction in adverse outcome in diabetic patients with ACS treated with abciximab compared to those who were not. Data on this subject have been investigated before, but results are inconsistent. In a metaanalysis of data from EPIC, EPILOG and EPISTENT by Bhatt et al [39], abciximab treatment conferred a reduction in MI and mortality (as we did) among diabetic patients. However, patient selection and concomitant non-contemporary treatment makes comparison with historical trials difficult. In the newer ISAR-SWEET trial the risk of TVR was reduced with abciximab among low-to-intermediate risk patients with DM [61]. Although our population does not resemble the ISAR-SWEET population entirely, since we investigated only patients with ACS, this result is consistent with our finding, namely the marked reduction in TVR. Besides the different nature of the above mentioned studies (RCTs) and our study (observational), also the difference in prevalence of DM needs to be commented. Typically, the prevalence of DM in RCTs is estimated to one in four. In our study only one in eight were classified as having diabetes. Firstly, the background prevalence of DM in a contemporary Danish population is lower than in a similar US population [62]. Secondly, since patients enrolled in RCTs undergo extensive biochemical testing some patients might be diagnosed with DM, at the time of inclusion. In our study, only patients diagnosed with DM and treated with anti-diabetic agents at the time of index PCI were classified as having DM. Thus, we might have missed some DM patients not yet diagnosed. However, the (inter)-cellular changes in DM patients which make the treatment with GPIs logically attractive probably need to have been present for some time in order to gain the incremental effect of abciximab. These DM induced changes rely mainly on

alteration of the properties of platelets and changes in the coagulation pathway, which overall leads to increased risk of thrombosis and restenosis [46, 63]. For further details, refer to the designated section in paper IV.
Adjuvant abciximab treatment in diabetic patients with ACS was in general recommended for years [64]. However, with the introduction of new and high-dose antiplatelet regimen, this treatment is no longer as strongly recommended in guidelines. Results from the present study, although observational, strongly support the use of abciximab in diabetic patients with ACS treated with PCI, also in a modern and contemporary setup for ACS patients.

Paper V: Abciximab in elderly ACS patients

In this paper we report a reduction in adverse outcome in high risk ACS patients treated with abciximab, but only among patients younger than 70 years of age. No such beneficial effect was observed among the elderly (≥ 70 years of age). The mechanisms that might be responsible for our findings are not entirely clear. As for the diabetes patients, elderly are known to exhibit increased platelet reactivity [65]. Logically, abciximab should then show incremental effect among the elderly, which is contradictory to our findings. On the other hand, elderly are also known to have impaired microcirculation due to changes in endothelial function and nitric oxide production [66, 67]. Thus, abciximab administration in the elderly patients might not be sufficient to overcome these age-dependent changes. An alternative interpretation of our results might be, that the elderly who were actually treated with abciximab, had their a priori risk of adverse outcome reduced from ultra high risk to high risk due to the adjuvant treatment. This is suggested by the fact that some baseline data, predictive of adverse outcome were more prevalent among the elderly patients treated with abciximab. E.g. STEMI was more prevalent and total stent length was longer in the abciximab treated group. Finally, the lack of mortality benefit among the elderly treated with abciximab compared those elderly not treated might be due to the increased bleeding risk which is a known side effect of abciximab, especially in the elderly [50]. Bleeding is closely related to mortality [53], but unfortunately we do not have access to data on bleeding complications or causes of death, and thus cannot draw such a conclusion.
Nevertheless, our results are interesting, since the elderly are only rarely included in RCTs. However, subgroup analyses on the elderly from earlier studies have reported conflicting results. Mak et al earlier reported similar benefit in the younger and elderly in a pooled analysis from EPIC, EPISTENT, EPILOG, and CAPTURE [53], whereas more contemporary data from the ISAR-REACT-2 [9] and CADILLAC trials [52] suggest the same lack of benefit in the elderly as we report. Thus, our results do not answer the question whether abciximab is beneficial or harmful in the elderly, but merely adds to the evidence that administration of GPI should in particular not be initiated without weighing the benefits against the possible disadvantages in this subgroup.

Paper VI: Abciximab in STEMI patients with simple or complex coronary lesions

In this paper we report a reduction in adverse outcome in STEMI patients treated with abciximab, but only in those with complex lesions. No such beneficial effect was observed among those with simple lesions. Actually, those with complex lesions who were treated with abciximab had their risk of adverse outcome reduced to a risk similar to all those with simple lesions irrespective of abciximab treatment, despite the more severe risk factor profile and worse angiographic characteristics in the abciximab treated patients with complex lesions. Our adjusted analyses showed that lesion complexity was an independent predictor of both mortality and the composite endpoint. Surprisingly, we found that those with simple lesions who were treated with abciximab showed increased mortality compared to those with simple lesions not treated. At our institution abciximab treatment in patients with simple lesions is only given in bail-out situations and thus a simple procedure may have turned into a complex procure (in cases of high degree of microembolization, dissection etc.). These patients might have benefitted from the abciximab treatment and would have had an even worse outcome, had they not been treated. This might explain the excess mortality and there may not be a causal relationship with use of abciximab. A more likely causal relationship exists among patients with complex lesions as they were treated with abciximab specifically because of their high-risk lesion. Still we found marked lower mortality among those treated with abciximab compared to those with complex lesions not treated with abciximab. Since the action of abciximab relies mainly on inhibition of thrombus formation and propagation [23, 68, 69], and possibly also some degree of thrombus disaggregation [26, 27, 70], only in the cases where thrombus is actually present, one can expect an effect of abciximab. If thrombus is not present, the effect will be absent and the treatment might even be harmful, with the side effects of abciximab in mind, and will outweigh the potential benefit [71].
Our results raise important issues in the discussion of the optimal timing and patient selection in abciximab administration. In the former guidelines on interventional cardiology it was recommended that abciximab should be started ´as early as possible before primary PCI´ [7]. The most up-to-date guidelines have rephrased this to´…at the time of primary PCI… in selected patients´ [13]. However, the guidelines do not specify how to ´select´ these patients. Our data suggest that one of the selection criteria should be the complexity of the lesion (and diabetes, as shown in paper IV). Consequently, if treatment with abciximab should be targeted to those who have complex and not simple coronary lesions, a diagnostic angiogram must be performed before administration of abciximab, and hence the upstream strategy is not recommendable. Also, a number of studies (including paper II and III) have shown intracoronary administration of abciximab to be superior to intravenous administration [35]. If indeed the administration route of choice should be intracoronary, abciximab can by nature only be administered when the patient is in the catheterization laboratory as a peri-procedural treatment.

3.6 Study limitations

The three papers constituting this part of the thesis were based on registries. This approach has several advantages, such as a large number of unselected patients, but also some inherent limitations. Specifically, in paper IV and VI, the main limitation is the risk of ´confounding by indication´, whereas a major limitation in paper V is the missing information on bleeding complications. These limitations are described in detail in the manuscripts. Please, also refer to Part IV – General considerations on study designs.

3.7 Conclusion

In these three registry studies, we aimed to evaluate the efficacy of abciximab among specific subgroups of ACS patients, namely diabetics, elderly and patients with complex lesions. We found evidence of better outcome with abciximab treatment in ACS patients with either diabetes or complex lesions, but not among

the elderly where the effect appeared neutral. In summary, our data suggest that abciximab is recommendable in ACS patients with diabetes and complex lesions, but should only be administered after careful considerations to the elderly.

3.8 Perspectives

The results from this part of the thesis add knowledge on how to target the treatment with abciximab to patients with high risk ACS. We believe this is of importance, since other strategies on platelet inhibition have reduced the risk of adverse outcome among low-to-intermediate risk ACS patients to a level where abciximab might be superfluous. This is supported by the decrease in use of abciximab seen over the last years. However, we also believe that high-risk ACS patients might still benefit from this potent GPI, but the treatment should be reserved for those who in fact are at high risk of adverse outcome. Thus, routinely use of abciximab, regardless of risk factor profile is not supported by our data.

Part IV
GENERAL CONSIDERATIONS ON STUDY DESIGN

4.1 Introduction

This PhD thesis is based on both a randomized trial and 3 retrospective observational studies. Both designs have their own inherent advantages and disadvantages. Below, some considerations on the strengths and limitations in the two types of studies are shortly outlined. Specific limitations regarding each paper are also discussed prior in this thesis and in the papers on which it is based. In general, several considerations must be made before deciding on a specific study design. RCTs, although serving as the gold standard under many circumstances (for instance, RCTs are almost mandatory for a given treatment to receive LOE A/B recommendation in international guidelines), are sometimes not economically and time wise feasible. An alternative to RCTs is the observational studies that can be either retrospective or prospective. In case of the latter, again time might be an issue. Our observational studies were of retrospective nature and thus taking advantage of being quick and cheap to perform – and in addition to include a large number of patients with comprehensively described baseline characteristics and long follow-up time. Such types of studies can furthermore be the basis of metaanalyses and give rise to future RCTs. Hence, both types of study design have their eligibility but must be interpreted in the context in which they have been conducted.

4.2 Randomized clinical studies

Strengths:

If conducted optimally, the groups investigated differ only with respect to their treatment, thus minimizing the risk of bias.
If the study population is adequately large, distribution of unmeasured variables can be assumed to be equally distributed between the groups.
Thus, RCTs are regarded as the gold standard in medical research.

Limitations:

RCTs are time consuming, both with regards to planning and completion. Also, patients must be followed for some time before final conclusions can be drawn. In our study, we prespecified analyses after 30 days and 1 year in order to assess our hypotheses on platelet GP IIb/IIIa dependent and independent mechanisms.
In order to obtain high statistical power a sufficient number of patients must be included. In the calculation of patients needed to obtain that power, one must estimate the expected reduction in endpoints. We anticipated a 50 % reduction in the composite endpoint in favor of the IC route based on prior published data. However, these data were derived from observational register studies or small non-randomized studies. Nevertheless it proved that our assumption was correct, since we found a 60 % relative risk reduction in the composite endpoint after 30 days.
In the assessment of a possible benefit from a new treatment strategy in a RCT, the issue of blinding is essential. In our study, neither the patient nor the operator was blinded. We believe our choice of endpoints (that is the patient oriented: death, TVR and MI), justify why we did not double-blind our study. We did not expect that knowledge of assignment group in any way could influence outcome measured on such hard clinical endpoints.
RCTs seldom mirrors real life populations – and one must be aware of extrapolation when interpreting results from RCTs. Thus our inclusion criteria were quite strict and the positive results in our study should be interpreted in that context and should not be extrapolated into a broad ACS population. This is indeed supported by the conflicting results recently published [21]. However, metaanalyses on the highest at risk STEMI patients confirm our findings [11].

4.3 Register studies

Strengths:

Retrospective observational studies are able to detect small, but clinical significant differences between groups quickly and with limited resources, compared to RCTs.
Observational studies reflect real-life settings to a higher degree than RCTs, which makes the generalization more straightforward.
Observational studies often provide new information/questions that can be evaluated in future RCTs.

Limitations:

In all three papers the risk of sample selection bias is present. For each paper, we chose a population in which we believed the hypotheses would be tested most relevant. Thus, in paper IV all patients with ACS were included to evaluate if the presence of one specific disease, diabetes mellitus, was predictive of the efficacy of abciximab; in paper V patients with ACS who had high risk lesions were included to evaluate the impact of age; and finally, in paper VI only patients with STEMI were included to estimate the impact of lesion complexity in abciximab treatment. With the above mentioned differences in population characteristics it is obvious that our results must be interpreted in the context in which they have been evaluated. For instance, the lack of benefit of abciximab observed among the elderly patients with ACS and high risk lesions in paper V, might not necessarily translate into a similar lack of effect in a group of STEMI patients with low risk lesions. In general, care should be taken not to extrapolate results from analyses of a specific group of patients into a generalized population.
All baseline data were derived from our local PCI-registry, the P-base. This database serves primarily as a hospital source file, but is also used for research. Data are entered in a fixed interface just prior to or after the PCI. Some data are describing the procedure and yet others are based on the history of the patient. The latter might therefore underestimate the true prevalence of risk factors. This might partly explain the relatively low prevalence of DM in our populations. Also, the prevalence of prior MI and PCI was quite low. In register studies, only data that are actually collected

can be entered in subsequent analyses. Thus, some differences in characteristics might exist that we do not know about, since these data were never collected. We have tried to overcome these possible shortcomings in the validity of the data, by crosschecking our data with the National Patient Registry and further searching in the OPUS work-place system. For example, in paper IV the variable ´DM´ was of special interest. In order to optimize the validity of this variable, we performed an additional search in the National Patient Registry for the DM diagnosis. Thereby, some patients that were not initially categorized as diabetics appeared. However, we wished only to include patients who had DM at the time of the index procure and thus a time restriction was applied to our search. Furthermore, patient's hospital files were then searched to confirm the diagnosis. By performing this extensive work of validation we believe our baseline data to be of sufficient quality.

Also in the assessment of endpoints we recognize, that some validation issues might exist. Data on mortality was retrieved from the National Person Identification Registry and it is not likely that patients were misclassified in this registry. In all three papers we report all-cause mortality. Our results might have been strengthened if we had been able to report only cardiac mortality. However, we did not have access to data from The Register of Causes of Death. It is more likely that a misclassification might have occurred in the assessment of TVR and MI. All possible events were initially retrieved from the National Patient Registry by the use of ICD-10 and ICD-10-PCS codes. These events were subsequently crosschecked in hospital files for diagnosis and in the P-base for procedures. Thus, we might have underestimated the event rates, but it seems unlikely that this underreporting should be different among patients receiving and not receiving abciximab. Finally, it would have been a further strength if we had data on bleeding complications, since this is the most important safety issue in abciximab treatment. If we had had such data, it would have been obvious to define a net-MACE endpoint in which both the positive (reduction in MACE) and negative (increase in bleedings) effects of abciximab were included. Unfortunately, we did not have access to data on bleeding complications.

Confounding and biases are more common in observational studies compared to RCTs . Especially in the present studies, where the variable of interest is treatment with abciximab, our results could be confounded by indication. That is, the operator might have assumed the overall clinical situation (lesion complexity, age, comorbidity etc.) to either favor or disfavor treatment with abciximab. Composing the optimal antiplatelet therapy relies on relatively complex considerations and we cannot rule out that this might have been missed in our adjustments. We have addressed this potential confounding issue by performing interaction and multivariable Cox analyses. Due to the large number of patients and endpoints we were able to adjust for all relevant baseline characteristics, but we acknowledge that the risk of residual confounding still exists.

By performing analyses on observational retrospectively collected data, one must keep in mind, that patients from a past era might not necessarily resemble those of a contemporary population. New treatment strategies are continually being tested and some are implemented, and a specific treatment might have been substituted by newer treatments when data from studies are published.

SUMMARY

Introduction: The present thesis ´On the use of abciximab in percutaneous coronary intervention´ is based on 6 papers concerning the glycoprotein IIb/IIIa inhibitor, abciximab. The thesis is divided into 2 sections. One section concerning a randomized trial comparing intracoronary (IC) with intravenous (IV) abciximab in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI), and one section concerning results from 3 registry studies on the effect of abciximab in distinct subgroups of patients with acute coronary syndrome (ACS).

Optimal administration route of abciximab.
A randomized study

Background: The glycoprotein IIb/IIIa inhibitor, abciximab, is used as an adjuvant anti-platelet therapy in PCI-treated patients suffering from ACS. A subgroup of patients with ACS is those with STEMI treated with pPCI. Recommendations on the use of abciximab in this setting are based on trials showing clinical benefit of IV bolus of abciximab compared to placebo. However, it has been speculated, that by administering the initial bolus of abciximab IC, a higher local concentration of the drug could be obtained, and this might confer an even more beneficial effect. Firstly, we searched the literature on the subject and found that no large-scaled randomized trials had been published. Most data were derived from small studies evaluating non-clinical endpoints or were of retrospective design. This overview is published as a review (paper I).

Objectives and methods: In order to investigate if IC administration of bolus abciximab indeed was superior to IV administration, we set up a randomized, open-label, single-center trial. We randomized 355 STEMI patients treated with pPCI between 2006 and 2008 to receive either IC or IV bolus of abciximab. Patients were subsequently contacted for follow-up after 30 days and 1 year, with regards to the endpoints: mortality, need for target vessel revascularization (TVR), and new myocardial infarction (MI).

Results: Of the 355 patients randomized, 185 received IC bolus and 170 IV bolus of abciximab.

The main results are the following:

After 30 days, significantly fewer patients in the IC arm had died or had the need for TVR. We found no difference in the risk of MI. These results are presented in paper II.

After 1 year, significantly fewer patients in the IC arm had died, had the need for TVR, or had experienced a new MI. These results are presented in paper III.

Conclusion: In the setting of pPCI-treated STEMI patients, IC bolus administration of abciximab is superior to IV bolus administration with respect to mortality, TVR and MI.

Differences in the effect of abciximab in 3 subgroups of patients.
Three register studies

Background: Large randomized trials performed from the beginning of the 1990´ies and until now, have overall shown beneficial effects of abciximab in different settings. However, post hoc analyses and dedicated trials have shown that some subgroups of patients might benefit more than others, and that abciximab might even be harmful in yet others. Although data are not consistent, suggestions have been made, that risk factors, such as diabetes, age and complexity of the coronary lesions might influence the efficacy of abciximab.

Objectives and methods: In order to assess the efficacy of abciximab among ACS patients with the above risk factors, we merged data from the 3 registries: 1) P-base, which is the dedicated PCI

database at Gentofte University Hospital, containing baseline and procedural data; 2) The National Person Identification Registry which holds data on vital status; and 3) The Danish National Board of Health´s National Patient Registry which holds data on discharge ICD-10 codes and thus clinical endpoints. By doing so, we were able to evaluate the efficacy in the three following settings:

ACS patients with diabetes (paper IV): 5,003 patients with ACS treated with PCI were stratified by diabetes status and use of abciximab. Follow-up was a maximum of 3 years. The endpoints were: mortality, TVR, MI, and the composite of the three.

Impact of age and abciximab in high risk ACS patients (paper V): 2,068 invasively treated ACS patients with complex lesions were stratified by age and use of abciximab. Follow-up was 1 year. The endpoints were: mortality, TVR, MI, and the composite of the three.

Impact of lesion type and abciximab in STEMI patients (paper VI): 2,935 STEMI patients treated with pPCI were stratified by type of lesions on angiogram (complex versus simple) and use of abciximab. Follow-up was 1 year. The endpoints were: mortality, TVR, MI, and the composite of the three.

Results:

Patients with diabetes who experienced ACS and who were treated with PCI and abciximab had their mortality and need of TVR reduced significantly compared to diabetic patients who did not receive abciximab. Actually, diabetic patients (who have an a priori higher risk of adverse outcome) treated with abciximab had their risk of death or TVR reduced to a level similar to ACS patients without diabetes not treated with abciximab. Paper IV.

Patients with ACS who were older or equal 70 years of age did not seem to have the mortality benefit of abciximab seen in patients younger than 70 years of age. Paper V.

Among STEMI patients treated with pPCI, only those who had a complex lesion assessed by diagnostic coronary angiography had a mortality benefit from abciximab. Paper VI.

Conclusion:

Our results support the use of abciximab in diabetic patients with ACS who undergo PCI.

In patients older or equal 70 years of age, abciximab should be used rarely and with caution, since no benefit on mortality could be detected and because elderly are known to have a higher risk of bleeding complication when treated with abciximab.

Since only STEMI patients with complex lesions benefitted from abciximab, a diagnostic angiogram should be performed in order to characterize the lesion before treatment with abciximab is initiated in STEMI patients and a general and upstream use of abciximab should be avoided.

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