A comparison between upfront high-dose tirofiban versus provisional use in the real-world of non-selected STEMI patients undergoing primary PCI

Insights from the Zwolle acute myocardial infarction registry

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Background. Despite the proven benefit of glycoprotein IIb/IIIa blockers in patients with acute ST-segment elevation myocardial infarction (STEMI), there is still debate on the timing of administration of these drugs and whether all or only a selection of patients should be treated. We evaluated the effect of routine upfront versus provisional use of high-dose tirofiban (HDT) in a large real-world population of non-selected STEMI patients.

Methods. Consecutive STEMI patients were registered in a single-centre dedicated database.

Patients with upfront HDT therapy before first balloon inflation were compared with patients who received the drug on a provisional basis, after first balloon inflation. Initial TIMI flow of the infarct-related vessel and enzymatic infarct size and 30-day clinical outcome were assessed.

Results. Out of 2679 primary PCI patients HDT was given upfront in 885 (33.0%) and provisionally in 812 (45.3%). Upfront as compared with provisional HDT showed higher initial patency (22.3 vs. 17.9%, $p=0.006$), smaller infarct size (1401 IU/l (IQR 609 to 2948) vs. 1620 (753 to 3132), $p=0.03$) and a lower incidence of death or recurrent MI at 30 days (3.3 vs. 5.1%, $p=0.04$) without an increase in TIMI bleeding ($p=0.24$). Upfront HDT independently predicted initial patency (odds ratio (OR) 1.47, 95% confidence interval (CI) 1.15 to 1.88, $p=0.02$), enzymatic infarct size (OR 0.70, 95% CI 0.56 to 0.86, $p=0.001$) and 30-day death or recurrent MI (OR 0.59, 95% CI 0.37 to 0.95, $p=0.03$).

Conclusion. Our findings support the use of upfront potent antiplatelet and antithrombotic therapy in STEMI patients and encourage further clinical investigations in this field. (Neth Heart J 2010;18:592-7.)

Keywords: Tirofiban, Myocardial Infarction, Angioplasty, Timing of Drug Administration

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Despite the proven benefit of glycoprotein IIb/IIIa blockers in patients with acute ST-segment elevation myocardial infarction (STEMI), there is still debate whether these drugs should be given to all patients before primary percutaneous coronary intervention (PCI) or only to a selected group with

complications during PCI as bail-out therapy.^{1,2} In addition, the timing of administration of these drugs might be debated. The Zwolle Acute Myocardial Infarction (AMI) registry provides a unique opportunity to evaluate upfront versus provisional use of high-dose tirofiban (HDT) in a large real-world population of non-selected STEMI patients.

Methods

The Zwolle AMI registry is a dedicated database, which registers all consecutive STEMI patients presented for primary PCI at our institution. The institutional review board approved our registry, and all patients gave informed consent.

Procedural details and adjunctive medical therapy

According to protocol all patients received 500 mg of aspirin (Aspegic®), 5000 IU unfractionated heparin intravenously and a loading dose of clopidogrel. HDT therapy consisting of tirofiban (25 µg/kg bolus and 0.15 µg/kg/min maintenance infusion for 12 hours). According to institutional guidelines additional unfractionated heparin was administered only in cases where the activated clotting time was less than 200 seconds. Primary PCI was performed by standard techniques using the femoral approach in most cases. Detailed data of adjunctive medical therapy and procedural details were collected.

Clinical and angiographic variables

Baseline clinical characteristics and outcome data were collected in a case record form. Detailed data on angiographic characteristics and procedural details of the primary PCI were collected. Initial as well as final TIMI flow of the infarct-related vessel were assessed using the Thrombolysis in Myocardial Infarction (TIMI) criteria by the performing operator and all data including the procedural characteristics were entered into a dedicated database.

Follow-up and determination of myocardial infarct size

Enzymatic myocardial infarction size was estimated by peak creatinine kinase (CK) and CK-MB in IU/l in the first 48 hours after the acute event, as previously described.³ Clinical outcome was assessed at 30-day follow-up. Criteria for recurrent myocardial infarction (MI) consisted of a new episode of chest pain with ischaemic electrocardiographic changes and increase of cardiac biomarkers. Bleeding was defined according to the TIMI criteria.⁴ Death was defined as all-cause mortality.

Statistical analysis

Patients who were treated with routine upfront HDT were compared with patients who received the drug on a provisional basis. The use of HDT was classified into upfront or provisional according

to the timing of administration of the HDT bolus relative to the time of balloon inflation (upfront: HDT bolus before balloon inflation and provisional: no HDT or HDT bolus after balloon inflation).

Categorical variables were compared using the χ^2 test or Fisher's exact test or the χ^2 for trend for ordinal variables, and the Mann-Whitney U test was used for continuous variables. Multivariate analyses of predictors for initial patency, enzymatic infarct size and the combined incidence of recurrent myocardial infarction and mortality were done using logistic regression models. All p values were two-sided with a significance level of $p < 0.05$. All statistical analyses were performed with SPSS for Windows (Rel. 16.0.1.1. 2007. Chicago: SPSS Inc.).

Results

From January 2004 to January 2009, 3943 consecutive STEMI patients were presented at our centre. Patients included in the Ongoing Tirofiban in Myocardial infarction Evaluation (On-TIME) 2 trial ($n = 732$) and patients who did not receive primary PCI ($n = 510$) were excluded from this analysis (figure 1).⁵ Of the 2701 STEMI patients who were treated with primary PCI the timing of administration of HDT in relation to first balloon inflation was known in 2679 patients (99.2%) and these patients form the basis of this report. In total, 885 patients (33.0%) were routinely treated upfront with HDT. In the other 1794 patients HDT was given in 812 patients (45.3%) mostly as bailout therapy. Baseline characteristics of the patients are described in table 1. Patients who received upfront HDT treatment were of younger age, more often had undergone prior revascularisation or had suffered from a prior MI. Of interest is that patients with upfront HDT treatment were more often diagnosed in a referring centre and that symptom onset to arrival at our PCI centre, door to balloon

Figure 1. Patient flow Zwolle AMI registry.

Table 1. Baseline characteristics.

Variable	Upfront HDT* (n=885)	Provisional HDT† (n=1794)	p value
Age, mean ± SD	62.51 ± 12.34	63.38 ± 12.54	0.09
Female gender, n (%)	236 (26.7)	506 (28.3)	0.38
Hypertension, n (%)	328 (37.1)	625 (35.1)	0.30
Smoking, n (%)	383 (44.1)	762 (43.6)	0.82
Hypercholesterolaemia, n (%)	210 (24.0)	352 (19.9)	0.02
Family history of CAD, n (%)	342 (39.9)	693 (41.0)	0.59
Previous PCI, n (%)	101 (11.4)	146 (8.2)	0.006
Previous CABG, n (%)	41 (4.6)	42 (2.3)	0.001
Previous MI, n (%)	103 (11.7)	163 (9.1)	0.04
Previous stroke, n (%)	26 (2.9)	52 (2.9)	0.96
Diabetes mellitus, n (%)	107 (12.1)	199 (11.1)	0.46
TIMI risk score >3, n (%)	304 (35.8)	591 (37.1)	0.53
Infarct-related artery, n (%)			
- RCA	332 (37.6)	731 (40.9)	0.10
- LAD	384 (43.5)	771 (43.2)	0.88
- CX	141 (16.0)	259 (14.5)	0.32
- Left main	2 (0.2)	12 (0.7)	0.16
Single-vessel disease, n (%)	465 (52.8)	932 (52.4)	0.82
Three-vessel disease, n (%)	148 (16.8)	326 (18.3)	0.34
Symptom-onset to diagnosis, min (IQR)	116 (57-255.5)	100 (56-193)	0.04
Time from symptom-onset to arrival PCI centre, min (IQR)	180 (112-326)	165 (110-262.5)	0.02
Total ischaemic time, min (IQR)	248.5 (166-431.25)	215 (160-328)	< 0.001
Door to balloon time, min (IQR)	51 (32-85)	45 (29-71)	< 0.001
Ischaemic time <180 min, n (%)	248 (28.6)	608 (34.9%)	0.001
Door to balloon time <45 min, n (%)	363 (41.8)	850 (49.1%)	< 0.001
Diagnosis in ambulance, n (%)	369 (41.7)	931 (51.9%)	< 0.001
Diagnosis in referring centre, n (%)	469 (53.1)	781 (43.6%)	< 0.001
Diagnosis in PCI centre, n (%)	46 (5.2)	81 (4.5%)	0.43

HDT=high-dose tirofiban, CAD=coronary artery disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, MI=myocardial infarction, TIMI=thrombolysis in myocardial infarction, RCA=right coronary artery, LAD=left anterior descending coronary artery, RCX=ramus circumflex coronary artery. *Upfront HDT=HDT bolus before balloon inflation. †Provisional HDT=no HDT or HDT bolus after balloon inflation.

time and total ischaemic time were significantly longer as compared with patients who received HDT therapy on a provisional basis.

Timing of administering of high-dose tirofiban

The median pretreatment time before balloon inflation in patients with upfront HDT treatment was 94 (IQR: 63 to 130) minutes. In the 812 patients who were treated with HDT in the provisional HDT group the median time of administering HDT was 37 (IQR: 17 to 62) minutes after balloon inflation.

Effect on initial patency, enzymatic infarct size and outcome

The effect of upfront HDT therapy on initial patency, enzymatic infarct size and outcome is shown in table 2. Initial patency (TIMI 3 flow) of the infarct-

related vessel was significantly higher in patients with upfront HDT therapy as compared with those who received HDT on a provisional basis (22.3 vs. 17.9%, $p=0.006$). Data on enzymatic infarct size were available in 97% of patients. Median enzymatic infarct size was 1550 IU/l (700-3066) overall and was significantly smaller in patients routinely treated with upfront HDT therapy. We found no significant difference in stroke as shown in table 2. The rate of TIMI bleeding was similar to routine upfront HDT therapy as compared with provisional use (TIMI major bleeding 2.9 vs. 3.4%, $p=0.50$ and TIMI major or minor bleeding 6.2 vs. 7.5%, $p=0.24$). The combined incidence of 30-day death or recurrent MI occurred less often in patients with upfront HDT as compared with patients with provisional HDT use (3.3 vs. 5.1%, $p=0.04$). Survival free of death or recurrent MI at one year is shown in figure 2.

Table 2. Angiographic outcome, infarct size and clinical outcome at 30 days.

Variables	Upfront HDT* (n=885)	Provisional HDT† (n=1794)	P value
TIMI 3 flow IRV before PCI, n (%)	197 (22.3)	320 (17.9)	0.006
TIMI 3 flow IRV after PCI, n (%)	817 (92.5)	1660 (92.7)	0.88
CK max IU/l, (IQR)	1401 (609-2948)	1620 (753-3132)	0.03
Death, n (%)	20 (2.3)	60 (3.5)	0.12
Recurrent MI, n (%)	10 (1.2)	30 (1.7)	0.27
Death or recurrent MI, n (%)	28 (3.3)	88 (5.1)	0.04
Stroke, n (%)	0 (0.0)	5 (0.3)	0.18
TIMI major or minor bleeding, n (%)	53 (6.2)	129 (7.5)	0.24
TIMI major bleeding, n (%)	25 (2.9)	59 (3.4)	0.50

HDT=high-dose tirofiban, TIMI=thrombolysis in myocardial infarction, IRV=infarct related vessel, PCI=percutaneous coronary intervention, CK=creatinine kinase, MI=myocardial infarction. *Upfront HDT=HDT bolus before balloon inflation. †Provisional HDT=no HDT or HDT bolus after balloon inflation.

Figure 2. Kaplan Meier survival free of death or recurrent myocardial infarction at one year.

Multivariate analysis of predictors for initial patency, enzymatic infarct size and outcome

Independent predictors for initial patency (TIMI 3 flow) of the infarct-related artery (IRA) were upfront HDT therapy (odds ratio (OR) 1.33, 95% confidence interval (CI) 1.06 to 1.67, $p=0.02$), single-vessel disease (OR 1.37, 95% CI 1.1 to 1.70, $p=0.01$), TIMI risk score >3 (OR 0.76, 95% CI 0.60 to 0.97, $p=0.03$) and male gender (OR 0.67, 95% CI 0.53 to 0.84, $p=0.001$).

The independent predictors of a larger median enzymatic infarct size (CK max >1550 IU/l) were a TIMI risk score >3 (OR 1.66, 95% CI 1.26 to 2.19, $p<0.0001$), male gender (OR 0.72, 95% CI 0.56 to 0.93, $p=0.01$), upfront HDT therapy (OR 0.70, 95% CI 0.56 to 0.86, $p=0.001$) and previous CABG (OR 0.47, 95% CI 0.25 to 0.88, $p=0.02$).

For the combined incidence of death or recurrent MI at 30 days independent predictors after multivariate analyses were TIMI risk score >3 (OR 3.0, 95% CI 1.76 to 5.28, $p<0.0001$) and upfront HDT (OR 0.59, 95% CI 0.37 to 0.95, $p=0.03$).

Figure 3. Efficacy of high-dose tirofiban in relation to time from symptom onset to STEMI diagnosis.

Efficacy of high-dose tirofiban in relation to time from symptom onset to STEMI diagnosis

The median (IQR) time of symptom onset to the time of STEMI diagnosis was 103 minutes. The effect of upfront HDT on initial patency, enzymatic infarct size and outcome was related to the time from symptom onset to first diagnosis as shown in figure 3. In patients with early diagnosis (less than the median time from symptom onset to diagnosis) upfront HDT therapy reduced enzymatic infarct

size (CK max 1300 IU/l (IQR 449 to 2860) vs. 1571 (751 to 3129), $p=0.04$), 30-day mortality (1.7 vs. 3.8%, $p=0.05$) and reduced the combined incidence of 30-day death or recurrent MI (2.5 vs. 5.1%, $p=0.04$) as compared with provisional use. However, in patients with a longer delay to diagnosis (symptom onset to diagnosis more than 103 minutes) no effect on enzymatic infarct size (CK max 1548 (726 to 2980) vs. 1730 (806 to 3197), $p=0.14$), 30-day mortality (3.2 vs. 2.7%, $p=0.61$) or the combined incidence of death or recurrent MI (4.2 vs. 4.1%, $p=0.89$) was found.

Discussion

In this registry of non-selected primary PCI patients, upfront high-dose tirofiban (HDT) improved initial patency of the infarct-related vessel, reduced myocardial infarct size and improved clinical outcome as compared with a strategy of provisional use after PCI. Importantly, we found no differences in major bleeding complications between upfront versus provisional use of HDT.

ESC guidelines recommend the administration of glycoprotein IIb/IIIa blockers in STEMI because of the reported reduction of 30-day mortality of up to 32% without affecting the risk of haemorrhagic stroke or TIMI major bleeding.^{2,6} However, large registry studies show that in real-world practice, glycoprotein IIb/IIIa blockers are given to only 30 to 50% of patients with STEMI, often for bail-out situations.^{7,8} In our registry, 63% of patients were treated with a glycoprotein IIb/IIIa blocker (885 patients upfront before PCI and 815 patients on a provisional basis during or after PCI) reflecting real-world practice. It also shows that in routine daily practice, delays to reperfusion are longer and consequently pretreatment times with potent antithrombotic and antiplatelet drugs when given upfront are longer. The 94 minutes of pretreatment time is much longer than the 55 minutes of pretreatment time seen in the On-TIME 2 trial.⁵

The results of this analysis confirm the results of the On-TIME 2 trial which demonstrated improved ST-segment resolution and clinical outcome with prehospital initiated HDT therapy on top of dual antiplatelet therapy (aspirin/clopidogrel) as compared with provisional IIb/IIIa therapy.^{5,9} These results may not be compared with studies investigating routine early versus routine late IIb/IIIa therapy. Results from these studies show conflicting results. The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial failed to demonstrate benefit from upfront IIb/IIIa blocker administration as compared with the routine administration in the cath lab.¹⁰ However, a recent meta-analysis showed improved initial patency and ST resolution in patients with upfront IIb/IIIa blockers.¹¹ Recently other studies have found a beneficial effect of early

initiation of a glycoprotein IIb/IIIa blocker as well. Ortolani and co-workers found that pretreatment with a IIb/IIIa blocker in patients referred to a PCI centre was associated with a better clinical outcome.¹² The same was found by Hassan et al.,¹³ where the early administration of abciximab was associated with a 26% incidence of aborted myocardial infarction. Upstream administration before primary PCI, however, is not supported by the current ESC guidelines. From the above-mentioned studies, one may conclude that in STEMI patients, routine administration is superior to provisional administration and that earlier administration might have some advantages as well; however, this needs to be confirmed in larger trials.

Our analysis was not a randomised comparison of routine versus provisional use of HDT in STEMI patients. Upfront HDT treatment occurred less often in the ambulance and patient delay, door to balloon time and total ischaemic time were significantly longer as compared with patients who received HDT therapy on a provisional basis. All these parameters are related to worse outcome and therefore, the effect of upfront HDT became more pronounced after correction for these differences. The reported reduced incidence of acute stent thrombosis with prehospital initiation of HDT,¹⁴ although not an endpoint in this analysis, might contribute to a reduced incidence of recurrent MI partly explaining the beneficial effect of upfront HDT on clinical outcome in our registry.

In the present analysis upfront HDT therapy was especially effective in the early hours after symptom onset. This finding of higher efficacy in the early hours of acute myocardial infarction is consistent with the findings of (prehospital) thrombolytic therapy, where highest efficacy was found in patients who received lytic therapy within the so called 'golden hour'.¹⁵

Our findings emphasise that potent antiplatelet and antithrombotic treatment should be given routinely in all STEMI patients scheduled for primary PCI and not only in patients with complications.

In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial routine IIb/IIIa therapy was compared with the direct thrombin inhibitor, bivalirudin.¹⁶ This trial showed a significant reduction in major bleeding with bivalirudin and was associated with a reduced 30-day mortality. However, acute stent thrombosis occurred more frequently. In HORIZONS-AMI, a relatively high rate of major bleeding in the glycoprotein IIb/IIIa group was found and this might partly be due to a less strict heparin protocol with target-activated clotting time around 250 seconds. In addition, IIb/IIIa therapy was given relatively late thereby losing the opportunity to have a significant effect on initial patency, infarct size and outcome. In con-

trast to the findings in the HORIZONS-AMI trial, a recent meta-analysis did not report an increase in TIMI major bleeding with routine administration of IIB/IIIa therapy.¹⁷

Limitations

There are several aspects of this analysis that merit careful consideration. First, the timing of and dosage of clopidogrel has changed over the years from in a low dose in the cath lab to a high dose in the ambulance. Bioavailability of clopidogrel is known to be significantly impaired in STEMI patients and the magnitude of clopidogrel-induced platelet inhibition is lower and delayed in this clinical setting.¹⁸ These differences in timing and dosage of clopidogrel are probably of minor impact in relation to the impact that upfront versus provisional HDT therapy has. Secondly, this is a post-hoc analysis of a registry of non-randomised patients, introducing potential bias.

Conclusion

In this registry of non-selected primary PCI patients, upfront high-dose tirofiban improved initial patency of the infarct-related vessel, reduced myocardial infarct size and improved clinical outcome as compared with a strategy of provisional use after PCI. Importantly, we found no increased bleeding rate with routine upfront therapy. Our findings support further clinical investigations for the use of upfront potent antiplatelet and antithrombotic therapy in STEMI patients, preferably in the ambulance. ■

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