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CLINICAL RESEARCH

Effect of upstream clopidogrel treatment in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Aims Immediate treatment with a loading dose of clopidogrel at diagnosis of ST-segment elevation myocardial infarction (STEMI) is recommended by ESC/AHA/ACC guidelines in patients eligible for primary percutaneous coronary intervention (PCI). However, the evidence for this practice is scarce.

Methods and results All patients who underwent PCI for STEMI in Sweden between 2003 and 2008 were identified from the national Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Patients with concomitant warfarin treatment and patients not having received aspirin upstream were excluded, leaving 13 847 patients for the analysis. Groups were compared for death and myocardial infarction (MI) during 1-year of follow-up using Cox regression models with adjustment for differences in baseline characteristics by propensity score methods. The combined primary endpoint of death or MI during 1-year follow-up occurred in 1325 of 9813 patients with upstream clopidogrel and in 364 out of 4034 patients without upstream treatment. After propensity score adjustment, a significant relative risk reduction (HR 0.82, 95% CI 0.73–0.93) in death/MI at 1 year was observed. The secondary endpoint of total 1-year death was significantly reduced (HR 0.76, 95% CI: 0.64–0.90), while the incidence of 1-year MI did not show any significant reduction (HR 0.90, 95% CI 0.77–1.06). Similar results were observed in multivariate analysis on top of propensity scoring and in sensitivity analyses excluding patients without clopidogrel and aspirin at discharge.

Conclusion This large observational study suggests that upstream clopidogrel treatment prior to arrival at the catheterization lab is associated with a reduction in the combined risk of death or MI as well as death alone in patients with STEMI treated with primary PCI.

Keywords Clopidogrel • Myocardial infarction • STEMI • Primary PCI

Introduction

Clopidogrel treatment constitutes a cornerstone therapy for acute coronary syndromes. As shown in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial the treatment benefit extends to both conservatively as well as percutaneous coronary intervention (PCI)-treated patients with non-ST-elevation myocardial infarction (NSTEMI).[1] The role of clopidogrel in myocardial infarction with ST-segment elevation (STEMI) was early addressed in the COMMIT trial with an observed beneficiary effect. However, the primary method of reperfusion therapy was thrombolysis and only 54% of the patients underwent active revascularization.[2] Other published trials further support the role of clopidogrel in STEMI patients undergoing fibrinolytic therapy.[3,4] The role of clopidogrel in STEMI patients undergoing primary PCI and especially the effects of upstream clopidogrel treatment (prior to

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arrival at the catheter lab either pre-hospital, in referring hospital or in-hospital) have not been studied in any published prospective randomized trial (the CIPAMI trial, currently submitted for publication, is the first prospective randomized study). Although several register studies have been published, they have been non-conclusive concerning mortality due to small sample sizes.[5,6]

The current ESC guidelines recommend an immediate loading dose of clopidogrel at diagnosis of STEMI with a class I recommendation, however with a level of evidence C (consensus of expert opinion and/or small studies, retrospective studies).[7] A similar level of evidence has been given by the updated AHA/ACC guidelines, both evidence levels highlighting the need for further studies in this matter.[8]

The aim of our study was to evaluate long-term clinical outcomes of upstream clopidogrel treatment in patients undergoing primary PCI for STEMI during the years 2003–08 in the national Swedish Coronary Angiography and Angioplasty Registry (SCAAR).

Methods

Study sample

Using the national Swedish SCAAR registry, patients undergoing PCI between the years 2003 and 2008 with a first presentation of a STEMI during this time period were screened. Patients on concomitant warfarin medication (483 patients) as well as patients not having received aspirin upstream (4274 patients) were excluded leaving 13 853 patients for the analysis. Out of these, missing values pertaining to upstream clopidogrel treatment were recorded for 6 patients leaving a total of 13 847 patients for final inclusion.

National registers

SCAAR includes data from all 29 centres that perform coronary angiography or PCI in Sweden. All consecutive patients undergoing coronary angiography and/or PCI are included. Based on the unique 10-digit personal identification number of each Swedish citizen, the SCAAR register is merged with other national registries. Data on death were obtained from the national population register through 31 December 2008. Data regarding previous medical history and patient follow-up including myocardial infarctions (MIs) were obtained from the Swedish Hospital Discharge Register through 31 December 2008. Data regarding discharge medications were obtained from The Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA). Data regarding collected medications from pharmacies were obtained from the Swedish Pharmaceutical registry (data only available from the latter half of 2005).

Endpoints

The primary endpoint was a composite of 1-year total mortality and MI. Secondary endpoints were mortality, MI, and stent thrombosis defined as a thrombotic stent occlusion with an acute clinical presentation in the SCAAR registry.

Statistical analysis

Groups were compared for each endpoint using Cox proportional hazards models with propensity scoring methods. Propensity scoring was performed for age, gender, diabetes, hypertension, smoking status, heparin upstream treatment, glycoprotein IIb/IIIa upstream treatment, low molecular weight heparin (LMWH) upstream treatment, previous MI, previous dementia, previous cancer, previous heart failure, previous kidney failure, hospital of procedure, and year of procedure. In a separate model cardiogenic shock was also included in the propensity score.

In a secondary analysis, additional direct adjustments were performed on top of propensity scoring for glycoprotein IIb/IIIa treatment during PCI procedure, LMWH treatment during procedure, heparin treatment during procedure, discharge rates of statins, discharge rates of ACE-inhibitors, discharge rates of beta-blockers, symptom-to-PCI time, stenting vs. only PCI and DES vs. BMS.

All tests were two-sided with a *P*-value for significance <0.05. Survival was estimated using the Kaplan–Meier estimator. All analyses were performed in SPSS (SPSS version 16, SPSS, Inc., Chicago).

Results

Of the study sample of 13 847 patients, 9813 patients (71%) received upstream clopidogrel (prior to arrival at the catheter lab), and 4034 patients (29%) did not. Baseline characteristics are presented in *Table 1*. The patients were relatively well balanced in several baseline parameters; however, differences were also noted, in particular concerning the use of upstream heparin as well as LMWH.

Composite endpoint (death/myocardial infarction)

Propensity-adjusted incidence curves for the composite endpoint of death or MI are shown in *Figure 1A*. The combined primary endpoint occurred in 1325 patients in the upstream clopidogrel group (14.3%) and in 712 patients (17.9%) in the non-upstream group at 1 year (*Table 2*, percentages expressed as Kaplan–Meier event rates). Using propensity score methods, there was a significant risk reduction at 30 days (HR 0.83, 95% CI 0.71–0.97) as well as at 1 year (HR 0.82, 95% CI 0.73–0.93) (*Table 2*). Both results remained significant after additional multivariate analysis on top of propensity scoring.

Survival

Propensity adjusted 1-year mortality curves are illustrated in *Figure 1B*. A total of 376 (9.4%) and 665 deaths (7.2%) occurred in the non-upstream and upstream groups, respectively, at 1 year (*Table 2*, percentages expressed as Kaplan–Meier event rates). Using propensity score methods the adjusted mortality reduction was significant both at 30 days (HR 0.70, 95% CI 0.57–0.85) as well as at 1 year (HR 0.76, 95% CI 0.64–0.90) (*Table 2*). The results remained significant after additional multivariate analysis on top of propensity scoring.

Myocardial infarction

Propensity-adjusted incidence curves for MI are shown in *Figure 1C*. A total of 369 (9.9%) and 719 (8.2%) MIs occurred in the non-upstream and upstream groups, respectively. After adjustment with propensity score methods the groups did not differ either at 30 days (HR 1.00, 95% CI 0.79–1.26) or at 1 year (HR 0.90, 95% CI 0.77–1.06) (*Table 2*). The results were similar after additional multivariate analysis on top of propensity scoring.

Table 1 Baseline characteristics

	Total	Upstream clopidogrel treatment (%)	No upstream clopidogrel treatment	*P*-value
Age	13 847	65.8 years	67.0 years	0.11
Male sex	13 847	6957 (70.9)	2760 (68.4)	<0.01
Hypertension	13 297	1211 (12.3)	526 (13.0)	0.26
Smoking status	12 264			<0.01
Never smoked		3517 (40.1)	1488 (42.6)	
Previous smoker		2276 (25.9)	889 (25.5)	
Current smoker		2980 (34.0)	1114 (31.9)	
Anti-thrombotic treatment				
Upstream heparin treatment	13 846	2430 (24.8)	709 (17.6)	<0.01
Heparin treatment during procedure	13 844	5846 (59.6)	2723 (67.5)	<0.01
Upstream GpIIb/IIIa-inhibitor	13 847	1235 (12.6)	587 (14.6)	<0.01
GpIIb/IIIA-inhibitor during procedure	13 845	6701 (68.3)	2733 (67.8)	0.55
Upstream LMWH	13 847	2095 (21.3)	434 (10.8)	<0.01
LMWH during procedure	13 847	419 (4.3)	420 (10.4)	<0.01
Previous medication				
Statin	13 648	1042 (10.8)	558 (14.1)	<0.01
ACE-inhibitor	13 636	912 (9.4)	433 (10.9)	0.02
Beta-blocker	13 618	2012 (20.8)	1003 (25.4)	<0.01
Medications at discharge				
Statin	13 738	8762 (89.9)	3392 (85.1)	<0.01
ACE-inhibitor	13 730	6324 (64.9)	2313 (58.0)	<0.01
Beta-blocker	13 742	8701 (89.2)	3536 (88.6)	0.51
Aspirin	13 751	9318 (95.5)	3720 (93.2)	<0.01
Clopidogrel	13 750	9149 (93.8)	3563 (89.2)	<0.01
Prior diseases				
Kidney failure	13 847	88 (0.9)	47 (1.2)	0.14
Chronic obstructive pulmonary disease	13 847	549 (5.6)	213 (5.3)	0.46
Dementia	13 847	24 (0.2)	6 (0.1)	0.27
Heart failure	13 847	215 (2.2)	134 (3.3)	<0.01
Myocardial infarction	13 847	428 (4.4)	310 (7.7)	<0.01
Diabetes	13 847	1417 (14.4)	615 (15.2)	0.22
Cancer	13 847	250 (2.5)	123 (3.0)	0.10
Cardiogenic shock	13 180	530 (5.4)	349 (8.7)	<0.01
Treated vessel	13 824			0.15
Right coronary artery		3944 (40.2)	1673 (41.7)	
Left anterior descending artery		4362 (44.5)	1778 (44.3)	
Left circumflex artery		1407 (14.3)	518 (12.9)	
Left main stem		96 (1.0)	45 (1.1)	
Procedure with stent	13 847	9324 (95.0)	3699 (91.7)	<0.01
Drug eluting stent	13 847	1757 (17.9)	773 (19.2)	<0.01

Stent thrombosis

The incidence of angiographically verified stent thrombosis at 1 year occurred in 29 cases (0.79%) in the non-upstream group and in 88 cases (1.05%) in the upstream group. There were no differences at 1 year between the groups after propensity score adjustment (HR 0.94, 95% CI 0.56–1.59) or after multivariate analysis on top of propensity score adjustment.

Adjusting for platelet medications at discharge

Data regarding aspirin and clopidogrel at discharge were available in 13 750 patients for aspirin and in 13 751 patients for clopidogrel. In the non-upstream group, 3570 patients out of a total of 3994 patients (89.2%) were prescribed clopidogrel at discharge from hospital. In the upstream clopidogrel group, 9183 patients out of

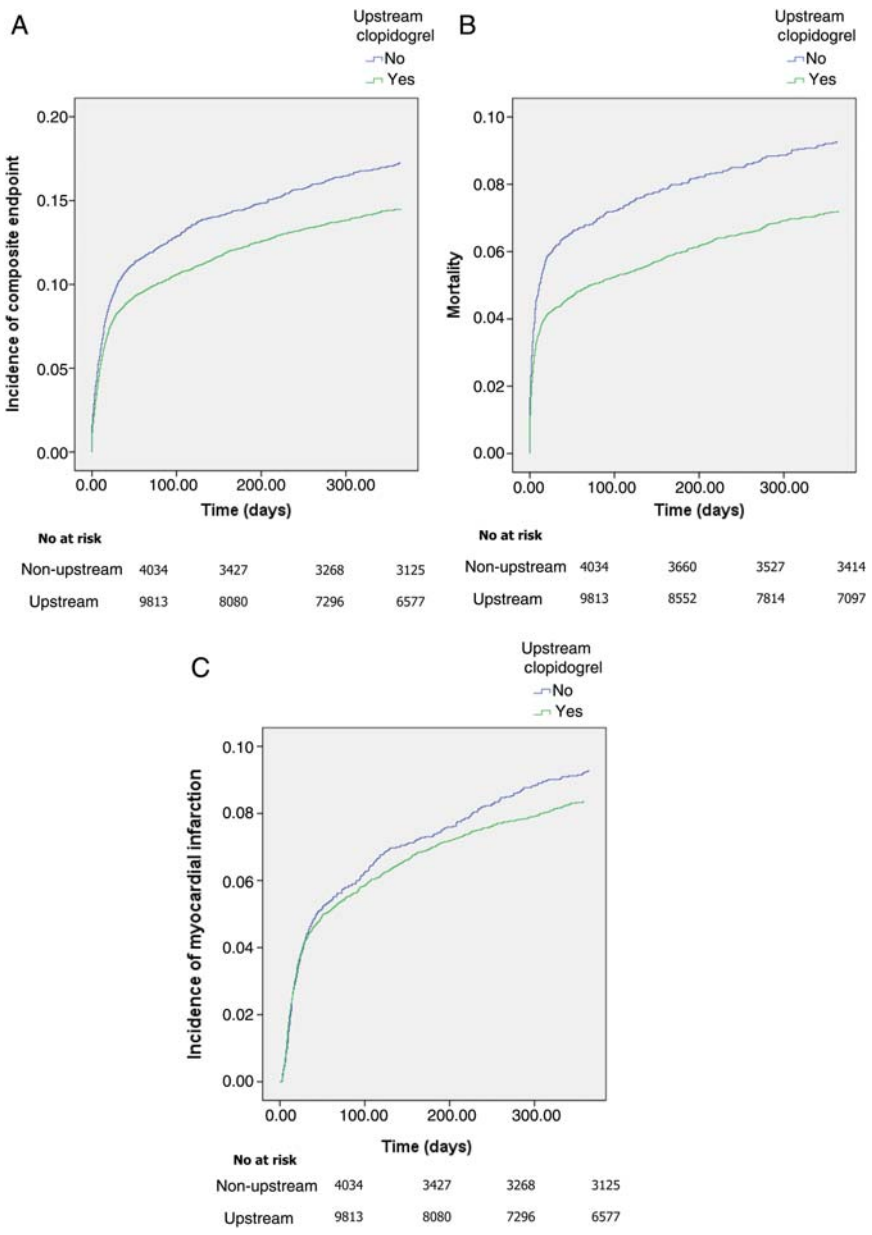

Figure 1 Propensity score-adjusted incidence of (*A*) composite endpoint of death/myocardial infarction (*B*) mortality, and (*C*) myocardial infarction at 1 year.

9757 patients (93.8%) were prescribed clopidogrel at discharge. The rates of aspirin at discharge were 93.1 and 95.4% in the non-upstream and upstream groups, respectively. To assess the impact of these differences, a Cox regression model excluding patients not on dual anti-platelet therapy at discharge was fitted. Results showed a continued significant 1-year relative risk reduction in the combined composite endpoint of death/MI (HR 0.86, 95% CI 0.75–0.99) as well as total mortality (HR 0.76, 95% CI 0.61–0.95) for the clopidogrel upstream group. No significant relative risk reduction for MI was shown (HR 0.93, 95% CI 0.78–1.11). Results remained unchanged after additional multivariate analysis on top of propensity scoring.

Data regarding medicines dispensed were obtained from the Swedish Pharmaceutical registry, but only information from the latter half of 2005 through 2008 were available. However, when analysing available data, out of all patients being discharged from hospital with clopidogrel, 4.4% of patients in the non-upstream group, and 2.8% of patients in the upstream group did not collect any clopidogrel from any pharmacy. All other patients had at least one expedition of clopidogrel and since the smallest available package in Sweden consists of 28 tablets, the above-mentioned percentages represent a crude 1-month discontinuation rate. The continued discontinuation rate is difficult to ascertain despite knowing amount of expeditions of clopidogrel, since

Table 2 Kaplan–Meier event rates and risk estimates at 30 days and 1 year

	Death/MI	Death	MI	Stent thrombosis
Events at 30 days				
Non-upstream group ($n = 4034$)	420 (10.4%)	252 (6.3%)	176 (4.6%)	18 (0.47%)
Upstream group ($n = 9813$)	797 (8.2%)	419 (4.3%)	385 (4.1%)	52 (0.55%)
Unadjusted hazard ratio (95% CI)	0.78 (0.69–0.87)	0.68 (0.58–0.80)	0.89 (0.75–1.07)	1.86 (1.09–3.18)
Propensity-adjusted hazard ratio (95% CI)	0.83 (0.71–0.97)	0.70 (0.57–0.85)	1.00 (0.79–1.26)	1.55 (0.80–3.00)
Events at 1 year				
Non-upstream group ($n = 4034$)	712 (17.9%)	376 (9.4%)	369 (9.9%)	29 (0.79%)
Upstream group ($n = 9813$)	1325 (14.3%)	665 (7.2%)	719 (8.2%)	88 (1.05%)
Unadjusted hazard ratio (95% CI)	0.78 (0.71–0.86)	0.74 (0.66–0.84)	0.82 (0.72–0.93)	1.32 (0.87–2.01)
Propensity-adjusted hazard ratio (95% CI)	0.82 (0.73–0.93)	0.76 (0.64–0.90)	0.90 (0.77–1.06)	0.94 (0.56–1.59)

the amount of tablets expedited on each occasion is not known; however, the groups showed relatively similar rates of expeditions.

Cardiogenic shock

When including cardiogenic shock in the propensity score model, there was a significant reduction in the primary composite endpoint (HR 0.89, 95% CI 0.79–1.00, $P = 0.048$). Tendencies towards reduced 1-year mortality (HR 0.88, 95% CI 0.74–1.03) as well as reduced 1-year incidence of MI (HR 0.91, 95% CI 0.77–1.07) in the clopidogrel upstream group were observed, although not achieving significance.

When performing additional multivariate analysis on top of propensity scoring both the composite endpoint (HR 0.85, 95% CI 0.74–0.97) and mortality alone (HR 0.82, 95% CI 0.67–0.99) were significantly reduced in the clopidogrel upstream arm at 1 year. Mortality alone was also significantly reduced at 30 days (0.73, 95% CI 0.57–0.93) in the upstream arm. If cardiogenic shock patients were excluded all together from the analysis there was a borderline significant risk reduction in the 1-year composite endpoint of death/MI (HR 0.87, 95% CI 0.75–1.00, $P = 0.055$) in favour of the upstream clopidogrel group after propensity and multivariate analysis.

Bleeding

Bleeding data regarding in-hospital bleedings were available in 12 548 patients. Major bleedings defined by fatal bleeding, intracranial bleeding or bleeding requiring surgery or blood transfusion occurred in 2.5% of patients in the non-upstream arm and in 1.8% in the upstream arm. The adjusted difference was not significant. Furthermore no differences were noted concerning fatal bleedings or intracranial bleedings alone, between the groups.

Additional subgroup analyses

Time trends showed increased use of upstream clopidogrel over time (*Figure 2*). In 2003, 35.8% of STEMI patients undergoing primary PCI received clopidogrel upstream, with increasing numbers for each consecutive year and reaching a maximum in 2008 with 87.3% of patients receiving upstream treatment. The unadjusted 1-year risk reduction in mortality was consistent across 2003–08 with lower mortality in the group receiving upstream clopidogrel (*Figure 2*).

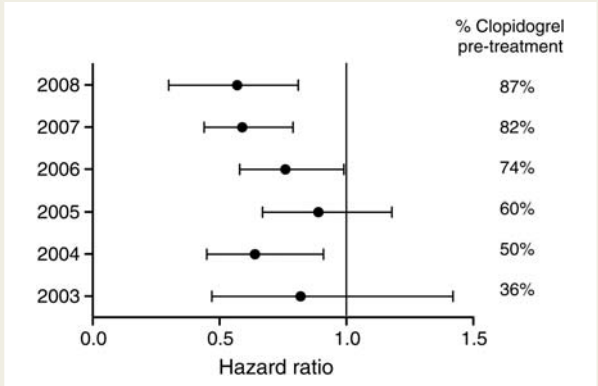

Figure 2 Subgroup analysis of 1-year mortality over time with percentage of total population receiving upstream clopidogrel visualized in the right column.

The seven highest volume centres (the majority being major Swedish University Hospitals) showed identical rates of upstream clopidogrel compared with the entire cohort (67% compared with 71%).

A tendency towards greater beneficial effects in males vs. females as well as in patients weighing >60 vs. <60 kg was noted (*Figure 3*). A tendency towards a greater effect in patients not receiving GpIIb/IIIa-blockers upstream was also noted. None of these subgroups showed a *P*-value for interaction <0.05.

Data regarding onset-of-symptoms-to-PCI were available in 11 937 patients. The median time delay from onset of symptoms to balloon dilatation was 3 h and 30 min in the upstream clopidogrel group and 3 h and 13 min in the non-upstream group.

Information regarding patients on prior chronic clopidogrel was only available from middle of 2005 and onwards. In this group, a total of 78 patients were identified with prior chronic clopidogrel within 6 months of their presentation of STEMI.

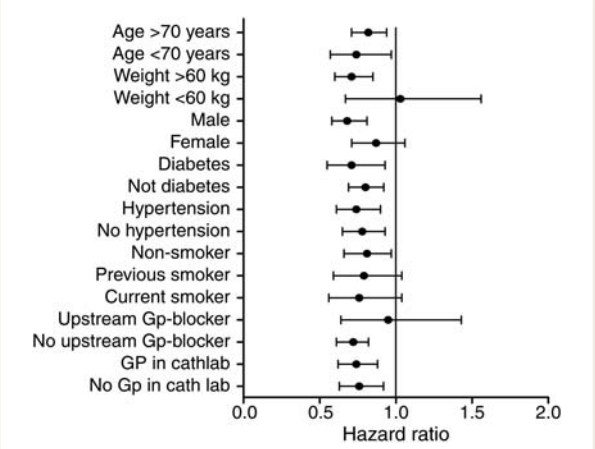

Figure 3 Forrest plot showing effect of upstream clopidogrel on various subgroups (mortality).

Propensity scoring

The *C*-statistic for the propensity score was 0.88, both for propensity scoring with and without cardiogenic shock in the model.

Discussion

Upstream administration of clopidogrel as early as possible is common practice in many countries for STEMI patients undergoing primary PCI, and is currently recommended in ESC and AHA/ACC guidelines.[6,7] There is, however, no definitive evidence for this early treatment regimen. The results from our large observational study, which to our knowledge constitutes the largest trial to date addressing this issue, indicate a potential beneficial effect of early administered clopidogrel in this patient group. The composite endpoint of death/MI as well as death alone was decreased in patients administered clopidogrel upstream compared with peri-procedural administration. The benefits were shown both at 30 days as well as 1 year for both endpoints. The incidence of stent thrombosis did not vary among the groups. Our study, however, only had information regarding angiographically verified stent thrombosis and did not include possible or probable stent thrombosis according to the Academic Research Consortium criteria, which might have yielded a different outcome.

The effects on MIs alone did not yield any statistically significant benefits. In order to minimize confounding factors, all patients were required to have received aspirin upstream and no concomitant warfarin medication was allowed. Several differences were noted in baseline characteristics, especially concerning upstream heparin and LMWH treatment with increased use of both drugs in the clopidogrel upstream arm. Propensity scoring methods were used to indicate the likelihood of a patient receiving upstream clopidogrel or not based on background characteristics outlined previously. In a secondary analysis, multivariate analysis was then performed on top of propensity scoring.

Subgroups analysis

A high degree of patients were discharged with clopidogrel irrespective of their upstream status, however, with a slight bias towards increased clopidogrel discharge rate in the upstream clopidogrel group. All patients in the study had received aspirin upstream and the groups were relatively well matched in the aspirin discharge rate. However, a further more rigid Cox analysis was performed with all patients not on dual anti-platelet therapy at discharge excluded from the analysis. Results showed similar levels of treatment benefits in both the composite endpoint of 1-year death/MI as well as death alone.

Cardiogenic shock represents a special case of cause or effect. It could be argued that differences in the rate of cardiogenic shock are a result of early clopidogrel administration with better post-procedural TIMI-flow, long-term stent patency, etc. However, cardiogenic shock could also be interpreted as a treatment confounder where patients with cardiogenic shock might to a lesser degree get early clopidogrel treatment. Our primary results are presented without taking cardiogenic shock into account in the propensity score. If accounting for cardiogenic shock in the propensity score, results still showed a significant reduction in the primary composite endpoint (both before and after multivariate analysis) and tendencies for reduction in all-cause mortality as well. However, with additional multivariate analysis on top of propensity scoring, results showed significant reduction even in mortality both at 30-days as well as 1 year. Even when all patients with cardiogenic shock were removed from the analysis a borderline statistical significance in favour of early clopidogrel administration was noted for the primary composite endpoint. The collected data thus highlight the effect of early clopidogrel administration even when accounting for or in the absence of cardiogenic shock altogether.

Increased use of early upstream treatment with clopidogrel coincided with increased use of PCI as primary reperfusion modality and thus our results could reflect improved skill of PCI operators rather than effect of upstream treatment. However, graphs over time trends showed persistent treatment benefits of clopidogrel throughout 2003–08 (*Figure 1*). Furthermore, adjustment for year of procedure was taken into account in the propensity scoring model.

There seemed to be a tendency for greater clinical benefit of upstream clopidogrel in patients weighing >60 kg. This could be due to increased bleeding in the underweight patient population but this could not be confirmed in our study. However, the results are in accordance with the TRITON trial where underweight patients were neutral in net clinical benefit.[9]

A tendency towards neutral effect was noted for patients having received a GpIIb/IIIa-inhibitor upstream. This is in contrast to GpIIb/IIIa-inhibitor-naïve patients who showed a good effect of early loading of clopidogrel. This is probably explained by complete blocking of platelet function by GpIIb/IIIa-blockers and that early vs. later administration of clopidogrel thus does not impact outcome. The reverse scenario, i.e. addition of GpIIb/IIIa-inhibitors or not on top of upstream loading dose of clopidogrel, has been addressed in different studies with conflicting results. Whereas the BRAVE-3 trial showed no significant improvement in infarct size with the addition of upstream abciximab to upstream 600 mg clopidogrel, the 1-year data from the On-TIME 2 trial demonstrated strong trends, with borderline significance, towards decreased mortality in patients given upstream tirofiban in addition to upstream

clopidogrel.[10,11] Subgroup studies on bivalirudin were not performed in our study due to small sample numbers.

Consistent treatment results were observed in other subgroups like smokers vs. non-smokers and hypertensives vs. normotensives. Diabetics could be argued, due to potentially decreased intestinal motility, might have a greater benefit of as early clopidogrel administration to compensate for possible slower absorption. However, diabetes is also associated with higher degree of poor clopidogrel responsiveness, thus potentially obviating any effects of pretreatment.[12] In our trial, diabetic patients seemed to enjoy similar levels of treatment benefits as non-diabetics.

To compensate for regional differences, each centre was accounted for in our propensity model. Furthermore the highest volume centres showed similar rates of upstream clopidogrel treatment as the study population as a whole, suggesting that the observed benefit of upstream clopidogrel is not an effect of skewed upstream distribution in favour of high volume centres.

Previous data

Our results are consistent with a meta-analysis by Vlaar *et al.*,[13] where upstream treatment with clopidogrel resulted in decreased mortality as well as mortality/MI. However, this meta-analysis has several shortcomings, as the analysis included trials with vastly different trial designs, PCI strategies and pharmacological therapies during and after PCI. Two register trials by Fefer *et al.*[5] and Lev *et al.*[6] showed that clopidogrel upstream treatment reduced a composite endpoint of recurrent acute coronary syndrome, stent thrombosis, congestive heart failure, and death at 30 days[5] as well as improved TIMI-flow and less MI.[6] None of these trials could demonstrate a mortality benefit alone; however, both trials had few patients included ($n = 383$ and $n = 292$) and therefore underpowered for mortality. In a pooled analysis of the PCI-CURE, CREDO, and PCI-CLARITY trials, a reduction in the composite of cardiovascular death, MI, or stroke was shown for patients pre-treated with clopidogrel, results in accordance with ours. However, only the PCI-CLARITY trial included STEMI patients, and none of these underwent primary PCI (instead thrombolysis). However, the results still point towards a general benefit of clopidogrel pre-treatment.[14] In another register trial, Larsson *et al.* studied the effect of early vs. late upstream treatment of clopidogrel in STEMI patients undergoing PCI. Although a total of 2014 patients were included, the trial had confounding geographic factors, where patients receiving early upstream treatment to a higher degree had longer transportation times to a catheterization lab. The trial did, despite this fact, show a reduction in MI/ischaemia as well as stent thrombosis/target vessel revascularization in the early upstream group. No difference in mortality was seen.[15] In a pre-specified analysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial ($n = 3311$), a 600 vs. 300 mg loading dose of clopidogrel in STEMI patients undergoing primary PCI was, after adjustment with either multivariate analysis or propensity scoring, associated with a reduced rate of major adverse cardiovascular events. Unadjusted lower mortality or re-infarction was observed in the 600 mg group; however, adjusted data regarding mortality or re-infarction alone were not significant but showed 'association' towards improvement in the upstream group.[16] In comparison the large randomized CURRENT-OASIS 7 trial, comparing a 600 mg loading dose clopidogrel followed by 150 mg daily dose for 6 days and 75 mg daily thereafter vs. a 300 mg loading dose, followed by 75 mg daily was not associated with improved outcome in patients with acute coronary syndromes.[17] It is of importance to note that both Dangas *et al.*[16] and the CURRENT-OASIS 7 trial are similar to our trial in respect to the effects of early clopidogrel administration, but also differ from our study, since the mentioned trials have studied higher vs. lower bolus doses of clopidogrel, given at similar time points. In our study, clopidogrel is administered at different time points (either upstream or peri-procedural). Other randomized pre-treatment trials like PRAGUE-8 and ARMYDA-5 have been negative; however, none of these trials has included patients with STEMI undergoing primary PCI.[18,19] We believe that STEMI patients represent a special high-risk group different from other coronary patients pertaining to effects of early platelet inhibition.[20] The only randomized clinical trial of pre-hospital administration of clopidogrel before primary PCI is the CIPAMI trial, (Zeymer *et al.*, submitted for publication). A pre-hospital loading dose of 600 mg of clopidogrel compared with clopidogrel after angiography did not reduce pre-PCI patency of the infarct vessel, but despite being underpowered for hard clinical events, the trial showed a reduced combined endpoint of death, re-infarction, and urgent target revascularization from 7.5 to 2.5% with a borderline significance ($P = 0.06$, $n = 337$). No increase in bleeding complications was noted.

Lack of effect on myocardial infarction

Our trial showed an unadjusted significant reduction in MI in the upstream group (*Table 2*); however, the difference was not significant after propensity scoring or multivariate analysis on top of propensity scoring although a tendency towards reduction was noted in the clopidogrel upstream arm. Although this finding might seem unexpected, it could be argued that as long as patients are discharged from hospital with similar anti-platelet agents in similar doses and for similar durations, the effects on MI might be modest. Data from previous trials have been conflicting pertaining to effects on MI. Fefer *et al.*[5] showed no tendency towards reduction in MI, whereas Lev *et al.*[6] showed significant reduction in MI. None of the trials had reported discharge rates of clopidogrel. The CLARITY-TIMI 28 trial, although dealing with fibrinolysis and not primary PCI did not show a statistically significant reduction in MI alone in patients treated with clopidogrel compared with placebo although a tendency towards reduction in the clopidogrel group was noted, data similar to ours.[3] Dangas *et al.* showed unadjusted significant risk reduction in MI for STEMI patients undergoing primary PCI stratified accordingly to 600 vs. 300 mg bolus dose clopidogrel. However, the results were not significant after statistical adjustment, results in accordance with ours.[16] Pooled data from Vlaar *et al.*[13] and Sabatine *et al.*[14] showed a decrease in MI with clopidogrel pre-treatment. However, both trials have limitations discussed above and comparisons between the pooled study populations and ours cannot be readily made due to different study designs and patient selection/treatment. In summary the general tendency in nearly all trials (including our study) has been a reduction in MI with pre-

treatment of clopidogrel; however, achieving a statistically significant reduction has been more difficult to ascertain and differs from various trials.

Limitations

Like all observational studies, our trial has to be interpreted with a certain degree of caution and being a register study cannot provide definite evidence of causality. We observed several differences between the groups. Although propensity score methods and secondary multivariate analysis on top of propensity scoring were used, a role of unmeasured confounding factors cannot be ruled out. Furthermore, the exact upstream loading dose (300 vs. 600 mg) was not known. Owing to considerably more potent reduction in mortality compared with MI, information regarding post-PCI TIMI flow, or final infarct size would have been of great value, since the observed beneficial effect of upstream clopidogrel could possibly be explained by better effects of primary PCI, including reduction better TIMI flow, reduction in infarct size, or microvascular obstruction. However, we do not have sufficiently adequate data regarding post-PCI TIMI flow or final infarct size. Although we included year of procedure in our propensity scoring and subsequent subgroups analysis showed consistent treatment benefits across 2003–08, there could be confounding effects due to long-time period of inclusion that we have not accounted for. Information regarding patients on prior chronic clopidogrel was only available from middle of 2005 and onwards and in this group a total of 78 patients were identified with prior chronic clopidogrel treatment within 6 months of their presentation of STEMI. Since so few cases were identified any analysis in outcomes between this patient group and the group as a whole was not possible.

Conclusions

In the presented register data of 13 847 patients, which to our knowledge constitutes the largest study published so far regarding upstream clopidogrel treatment in STEMI patients undergoing primary PCI, upstream clopidogrel treatment was associated with reductions in cardiovascular clinical endpoints, including total mortality. These findings reinforce current guideline recommendations for as early as possible clopidogrel administration in the setting of STEMI.

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