A comparative cohort study on personalised antiplatelet therapy in PCI-treated patients with high on-clopidogrel platelet reactivity

Results of the ISAR-HPR registry

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Summary

In clopidogrel-treated patients undergoing percutaneous coronary intervention (PCI), high platelet reactivity (HPR) is associated with a higher risk for thrombotic events including stent thrombosis (ST). A personalised therapy with selective intensification of treatment may improve HPR patients´ outcome in this setting although recent randomised trials are against this hypothesis. The aim of the ISAR-HPR registry was to assess whether clopidogrel-treated HPR patients benefit from selective intensification of P2Y12 receptor inhibition. For the registry, outcomes were compared between two cohorts. We identified 428 clopidogrel treated HPR patients (AU x min ≥468 on the Multiplate analyser) between 2007–2008 (historical control cohort) without a change of treatment based on platelet function (PF) testing results. Between 2009–2011, we identified 571 HPR patients (guided therapy cohort) and used this information for guidance and selective intensification of P2Y12 receptor directed treatment (reloading with clopidogrel, switch to prasugrel, re-testing) in a setting of routine PF testing. The primary outcome was the composite of death from any cause or ST after 30 days. Major bleeding according to TIMI criteria was also monitored. The incidence of the primary outcome was significantly lower in the guided vs the control cohort (7 [1.2%] vs 16 [3.7%] events; HR 0.32, 95% CI 0.13–0.79; p=0.009). The incidence of major bleeding was numerically but not statistically higher in the guided vs the control cohort (1.9 vs 0.7%; p=0.10). In conclusion, present findings are in support for a PF testing guided antiplatelet therapy with selective intensification of P2Y12 receptor inhibition. The issue of personalised antiplatelet treatment warrants further investigation in randomized and well-controlled clinical trials.

Keywords

High platelet reactivity, clopidogrel, prasugrel, stent thrombosis

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Introduction

Monitoring the individual level of platelet inhibition by platelet function (PF) testing and using these results for guidance of tailored treatment may prove useful for improving patients´ outcome. Current guidelines have included PF testing as a means to guide treatment in selected cases (1). However, the assets and drawbacks of such a personalised treatment approach remain to be elucidated (2–7). Prior randomised trials using the point-of-care VerifyNow assay were not supportive for an individualised treatment approach (5–7). Importantly, these studies are characterised by little utilisation of potent antiplatelet agents such as prasugrel or ticagrelor and included mainly stable PCI patients; a cohort of patients where routine PF testing with adaption of treatment may be of limited value as compared to high-risk patients undergoing coronary stenting (8). Interestingly, smaller studies using the VASP or the Multiplate assay provided promising results for a tailored antiplatelet treatment approach based on PF testing with these devices (4, 9, 10). While such studies cannot substitute for randomised trials, it was suggested just recently that specifically the Multiplate analyser should be used for future studies investigating the value of PF monitoring (2). At present, limited data is available with this assay and the value of testing in a real-life setting and in high-risk patients is unknown. Thus, the aim of the ISAR-HPR registry was to assess whether clopidogrel HPR patients may benefit from selective intensification of P2Y12 receptor inhibition.

Materials and methods

Study populations

For the ISAR-HPR registry, patients undergoing PCI in two participating centres (Deutsches Herzzentrum München and I. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität

München, Munich, Germany) were investigated. Data from all patients being part of this analysis was prospectively collected. Between the years 2007–2011, consecutive HPR patients were analysed with regard to platelet aggregation data and their clinical outcome (ischaemic and bleeding events). HPR patients undergoing PCI from two different cohorts (historical control cohort without treatment adjustment vs registry of patients with guided treatment) were compared in this analysis. The key prerequisite for all patients being part of this analysis was the availability of a platelet function assessment (post clopidogrel loading) obtained at the time point of the PCI.

Study cohort without treatment adjustment (control cohort)

The control cohort (n=428 consecutive patients) is a historical cohort *without* any treatment adjustment based on obtained PF testing results. This cohort stems from a study of 2,533 patients that we conducted between 2007 and 2008. Details of this study including inclusion and exclusion criteria have been reported previously (11). In brief, for the present analysis we used all patients (n=428) showing HPR (defined per consensus definition [12]) from the entire cohort. For this study, patients were enrolled regardless of their clinical presentation. All patients were uniformly pretreated with a loading dose (LD) of 600 mg clopidogrel, which was recommended to be given at least 2 hours before the procedure. Post-interventional antiplatelet treatment consisted of clopidogrel 75 mg twice daily for the remainder of the hospitalisation up to three days, followed by 75 mg/day. All patients were discharged on a maintenance dose (MD) of 75 mg/day clopidogrel. Aspirin 100 mg/bid was recommended indefinitely in this control cohort as well as in the guided cohort of patients.

Study cohort with treatment adjustment (guided therapy cohort)

Since 2009, obtained on-clopidogrel treatment platelet aggregation values have been used for guidance of tailored P2Y12 receptor directed antiplatelet treatment. Of note, clinical and procedural variables, comorbidities, the complexity of the performed PCI procedure as well as the measured ADP-induced platelet aggregation values of patients were considered for the decision if, when and how to intensify the antiplatelet treatment. Therefore platelet function testing was only one parameter among others that were used for guidance of treatment. Intensified treatment was only initiated selectively after weighting the risk for thrombotic and bleeding events in the individual patient. There was no prescribed protocol of treatment adjustment. All these data represent the daily clinical practice of decision making.

From 2009 to August 2011 we identified a total of 571 consecutive HPR patients, who now constitute a registry of patients with selective intensification of antiplatelet treatment. All 571 patients received a 600 mg clopidogrel LD (LD_1) in preparation for the PCI procedure (identical regimen as compared to the control cohort) and had an initial PF assessment available at the time point of the PCI. This index PF testing was performed post clopidogrel LD, after diagnostic angiography and directly before the PCI procedure, which is identical to the time point of single testing in the control cohort. However, the majority of patients in the guided cohort received serial PF tests and the results of all tests were taken into consideration for a change of antiplatelet treatment. Based on the obtained individual testing results patients were (i) switched over to prasugrel treatment, (ii) patients received additional loading doses of clopidogrel or (iii) the antiplatelet treatment was not changed at all after re-testing or after considering the individual risk for ischaemic or bleeding complications.

Prasugrel

Once the decision was made to switch to prasugrel, a prasugrel LD was administered and testing was repeated again with a sufficient time lag post prasugrel LD treatment. All patients in this cohort who were switched over to prasugrel were discharged on prasugrel MD treatment.

Clopidogrel (re-)loading

While all patients in this study received at least one 600 mg clopidogrel LD (LD_1), part of the patients from the guided cohort received additional (up to three) LDs (LD_{2-4}). Following the clopidogrel LDs, PF testing was repeated again with a sufficient time lag post clopidogrel LD treatment. All patients in this cohort were discharged on clopidogrel MD treatment.

Monitoring without change of treatment

Following re-testing or after considering the risk for thrombotic and bleeding events, part of the HPR patients in the guided cohort were kept on standard clopidogrel treatment (no re-loading or switch to prasugrel). Importantly, a re-assessment of platelet function was done in most cases with a time delay to the initial testing to confirm or to refute a status of HPR.

Blood sampling and platelet function testing

For both cohorts, whole blood for platelet function testing was collected into 4.5 ml plastic tubes containing the anticoagulant lepirudin (25 µg/ml, Refludan, Dynabyte, Munich, Germany) and the ADP (6.4 µM)-induced platelet aggregation (in aggregation units [AU] x minute [min]) was assessed using multiple electrode platelet aggregometry (MEA) on the Multiplate analyser (Verum Diagnostica, Munich, Germany) as described previously (13). Ten aggregation units [AU] x min equal one unit [U]. Along with the index PCI, blood samples for PF testing were obtained in the laboratory from the arterial sheath of patients during the PCI. For all other PF tests (serial on-clopidogrel or on-prasugrel treatment measurements in the guided cohort), blood samples were taken from patients post PCI in a steady state condition with a loose tourniquet through a short venous catheter from an antecubital vein.

Study endpoints, definitions and follow-up

For platelet function measurements, the definition of high platelet reactivity (HPR, ≥468 AU x min) was based on prior studies (11,

Table 1: Baseline characteristics of the patients.

Characteristic	Guided cohort (n=571)	Control cohort (n=428)	P value
Age – years	69.1 ± 11.2	67.0 ± 10.9	0.004
Female sex – no. (%)	148 (25.9)	113 (26.4)	0.86
Body Mass Index – kg/m2	28.1 ± 4.9	28.2 ± 4.7	0.74
Diabetes mellitus – no. (%)	184 (32.2)	137 (32)	0.94
Arterial hypertension – no. (%)	503 (88.1)	371 (86.7)	0.51
Hypercholesterolemia – no. (%)	418 (73.2)	296 (69.2)	0.16
Familial disposition – no. (%)	200 (35)	177 (41.4)	0.04
Active smoker – no. (%)	98 (17.2)	72 (16.8)	0.89
Previous MI – no. (%)	119 (20.8)	134 (31.3)	<0.001
Previous bypass surgery – no. (%)	70 (12.3)	53 (12.4)	0.95
CPR at admission – no. (%)	30 (5.3)	7 (1.6)	0.003
CAD presentation – no. (%)			<0.001
STEMI	115 (20.1)	39 (9.1)	
NSTEMI	113 (19.8)	60 (14)	
Unstable angina	89 (15.6)	87 (20.3)	
Stable angina	254 (44.5)	242 (56.5)	
Left ventricular EF – (%)	52 ± 12	52.2 ± 12.7	0.87

Data presented are means SD or numbers of patients (percentages). CAD, coronary artery disease; CPR, cardiopulmonary reanimation; EF, ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

13) and the consensus document (12) of the Working Group on High On-Treatment Platelet Reactivity. All ischaemic endpoints were assessed during a 30-day follow-up period. The primary ischaemic outcome measure was the composite of death from any cause or stent thrombosis (definite or probable). Definite and probable ST was defined according to the Academic Research Consortium (ARC) criteria (14). We also assessed the incidence of the single components of the primary outcome measure and myocardial infarction (MI, defined as described previously [13]). With regard to bleeding, we assessed the incidence of major in-hospital bleeding events defined according to the TIMI criteria. Patients were planned to stay in hospital for at least two days after the PCI. Discharged patients were interviewed by telephone call after 30 days (± 7 days). Those patients with cardiac symptoms were seen in the outpatient clinic for complete clinical, electrocardiographic and laboratory check-up. Data of patients were collected and prospectively entered into a computer database by specialised personnel from the ISAR study centre. All possible information from referring physicians, relatives and from hospital readmissions were entered as well. Source documentations were checked to ensure high-quality data.

Statistical methods

Variables are presented as mean ± standard deviation (SD), counts (percentages) and median with interquartile range (IQR). Kolmogorov-Smirnov test was used to test for normal distribution of continuous data. PF data were non-normally distributed and dependent data were compared with two-sided Wilcoxon-test. Normally distributed variables were compared using the two-sided t-test.

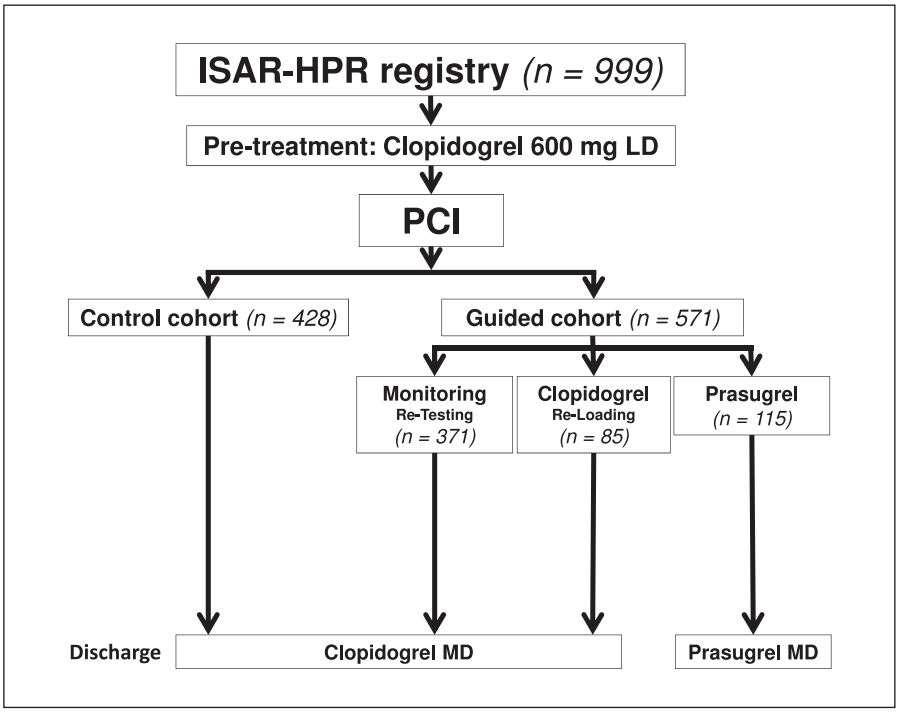

Figure 1: Flow chart of the two study cohorts in the ISAR-HPR registry. The figure shows a flow chart of the two cohorts of patients included in our registry. All patients (n=999) in this registry received a loading dose (LD) of 600 mg clopidogrel in preparation for the PCI procedure. Blood for initial platelet function testing was drawn in all patients after the diagnostic angiography and immediately before PCI. For the historical control cohort HPR patients without change of treatment based on platelet function data were identified between 2007 and 2008. In the guided cohort (2009–2011), platelet function data was used for guidance and selective intensification of antiplatelet treatment (re-testing, clopidogrel re-loading or switch to prasugrel). LD, loading dose; MD, maintenance dose.

Table 2: Angiographic and procedural characteristics.

Characteristic	Guided cohort (n=571)	Control cohort (n=428)	P value
Target vessel – no. (%)			0.03
Left main coronary artery	19 (3.3)	32 (7.5)	
Left anterior descending coronary artery	234 (41)	153 (35.7)	
Left circumflex coronary artery	133 (23.3)	108 (25.2)	
Right coronary artery	168 (29.4)	121 (28.3)	
Venous bypass graft	17 (3)	14 (3.3)	
Multivessel disease – no. (%)	486 (85.1)	368 (86.0)	0.70
Complex (type B2 or C) lesions – no. (%)	438 (76.7)	321 (75.0)	0.53
Bifurcational lesions – no. (%)	130 (22.8)	106 (24.8)	0.46
TIMI flow grade before intervention – no. (%)			0.04
0	80 (14.0)	47 (11)	
1	25 (4.4)	18 (4.2)	
2	84 (14.7)	43 (10.0)	
3	382 (66.9)	320 (74.8)	
Type of intervention – no. (%)			0.98
Placement of drug-eluting stent	526 (92.1)	393 (91.8)	
Cypher	7 (1.3)	39 (9.9)	
Dual drug-eluting stent*	61 (11.6)	139 (35.4)	
Endeavor	1 (0.2)	6 (1.5)	
Endeavor Resolute	48 (9.1)	71 (18.1)	
Nobori	73 (13.9)	0 (0.0)	
Taxus	15 (2.9)	17 (4.3)	
Xience	199 (37.8)	85 (21.6)	
Yukon Choice PC	122 (23.2)	36 (9.2)	
Placement of bare-metal stent	10 (1.8)	8 (1.9)	
Balloon angioplasty	35 (6.1)	27 (6.3)	
TIMI flow grade after intervention – no. (%)			0.27
0	3 (0.6)	7 (1.6)	
1	3 (0.5)	3 (0.7)	
2	15 (2.6)	15 (3.5)	
3	550 (96.3)	403 (94.2)	

Data presented are means ± SD or numbers of patients (percentages). SD, standard deviation; TIMI, Thrombolysis in Myocardial Infarction. * Probucol plus sirolimus eluting stent.

Table 3: Comedication at admission of the study population.

Medication (at admission) – no. (%)	Guided cohort (n=571)	Control cohort (n=428)	P value
Aspirin	353 (65.3)	296 (69.2)	0.016
Thienopyridines	79 (14.6)	93 (21.7)	0.001
Insulin treatment	51 (8.9)	48 (11.2)	0.23
Beta-blockers	326 (57.1)	295 (68.9)	<0.001
Statin	317 (55.5)	258 (60.3)	0.13
Calcium channel blocker	124 (21.7)	61 (14.3)	0.003
Coumarin derivatives	60 (10.5)	58 (13.6)	0.14
AT1 receptor blockers	98 (17.2)	72 (16.9)	0.89
Nitrates	45 (7.9)	42 (9.8)	0.28
Diuretics	240 (42.3)	160 (37.4)	0.14
Proton pump inhibitors			0.03
No PPI	432 (75.7)	335 (78.3)	
Esomeprazole	10 (1.8)	19 (4.4)	
Omeprazole	45 (7.9)	23 (5.4)	
Pantoprazole	82 (14.4)	51 (11.9)	
Rabeprazole	2 (0.4)	0 (0.0)	

Data presented are numbers of patients (percentages). PPI, proton pump inhibitor.

Categorical variables were compared using Chi^2-test or Fisher´s exact test as appropriate. Survival analyses were generated using the Kaplan-Meier method. A Cox proportional hazards model was used to calculate hazard ratios (HR) with the corresponding 95% confidence intervals (CIs) for the outcomes of interest (monovariate) and to test (multivariate) whether treatment adjustment is an independent predictor of the primary outcome measure (incidence of death from any cause or ST after 30 days). The primary outcome was set as the dependent variable and treatment adjustment (= guided cohort) was included into the model as an independent variable. We also adjusted for age as well as for clinical variables (previous myocardial infarction [MI], clinical presentation [NSTEMI/STEMI], cardiopulmonary reanimation at admission) that differed ($p<0.01$) between the two cohorts (see ►Table 1). Interaction was tested for significance in this Cox proportional hazard model by adding the respective interaction term to the multivariate model. The HRs and the corresponding 95% CIs were calculated for each variable included in the multivariate model. A multivariate logistic regression model was used to test whether treatment adjustment is an independent predictor of major bleeding events. Major bleeding was set as the dependent variable and treatment adjustment (= guided cohort) was included into the model as an independent variable. We adjusted for the same variables where adjustment was made for in the Cox model (see above). For all statistical analyses a p-value <0.05 was considered significant. Analyses were performed using the software package S-PLUS (TIBCO software Inc, Palo Alto, CA, USA).

Results

Study cohorts

Baseline characteristics of the two study cohorts of the ISAR-HPR registry are shown in ►Table 1. ►Figure 1 shows a flow chart of the two study cohorts of our registry. The two cohorts differed with regard to some baseline characteristics. In detail, patients were older and the proportion of patients with prior cardiopulmonary reanimation (CPR) or a biomarker-positive acute coronary syndrome (ACS) at presentation (STEMI and NSTEMI) was higher in the guided cohort, whereas the incidence of a prior myocardial infarction was higher in the control cohort. Detailed information on angiographic and procedural characteristics of both

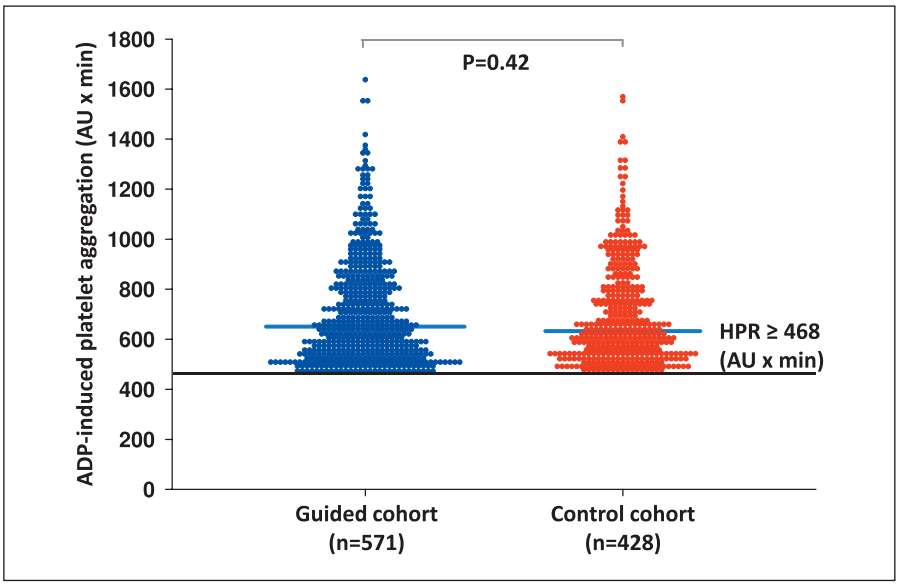

Figure 2: Baseline on-clopidogrel treatment aggregation values in the two study cohorts. The figure shows the baseline ADP-induced platelet aggregation values after first clopidogrel LD_1 treatment of the guided vs the control cohort. The blue lines represent median values. Blue dots represent individual platelet aggregation values for the clopidogrel LD measurement (LD_1) in the guided cohort. Red dots represent individual platelet aggregation values after clopidogrel LD measurement (LD_1) in the control cohort. The black line illustrates the cut-off value for HPR (≥468 AU x min per consensus definition). ADP, adenosine diphosphate; AU, aggregation units; LD, loading dose.

study cohorts are shown in ▶Table 2. The comedication at admission differed in part between the two cohorts and detailed information is outlined in ▶Table 3.

On-clopidogrel treatment platelet function data

Per study protocol, the ADP-induced platelet aggregation of patients in the control cohort was ≥468 AU x min for all 428 patients and the median [IQR] value was 633 [544–803] AU x min (range of values from 468 – 1569 AU x min). The median [IQR] aggregation value of patients in the guided cohort (post clopidogrel LD_1) was 651 [544–825] AU x min (range of values from 468 – 1637 AU x min). ▶Figure 2 illustrates the ADP-induced aggregation values that did not differ significantly between the two cohorts (p=0.42).

The P2Y12 receptor directed antiplatelet treatment was modified in selected cases of patients within the guided cohort (n=571). A total of 115 patients (20.1%) were switched to prasugrel treatment (see below), whereas 85 patients (14.9%) received an additional clopidogrel LD treatment. In a total of 371 (65%) no intensification of antiplatelet treatment was performed.

Clopidogrel re-loading

In 85 patients, adaption of treatment was done by the administration of additional clopidogrel LDs (LD_{2-4}). All 85 patients received at least one additional clopidogrel LD (clopidogrel LD_2). Two patients received a 3rd LD (clopidogrel LD_3) and one patient a fourth LD (clopidogrel LD_4). This intensification of therapy resulted in a significant reduction of the ADP-induced platelet ag-

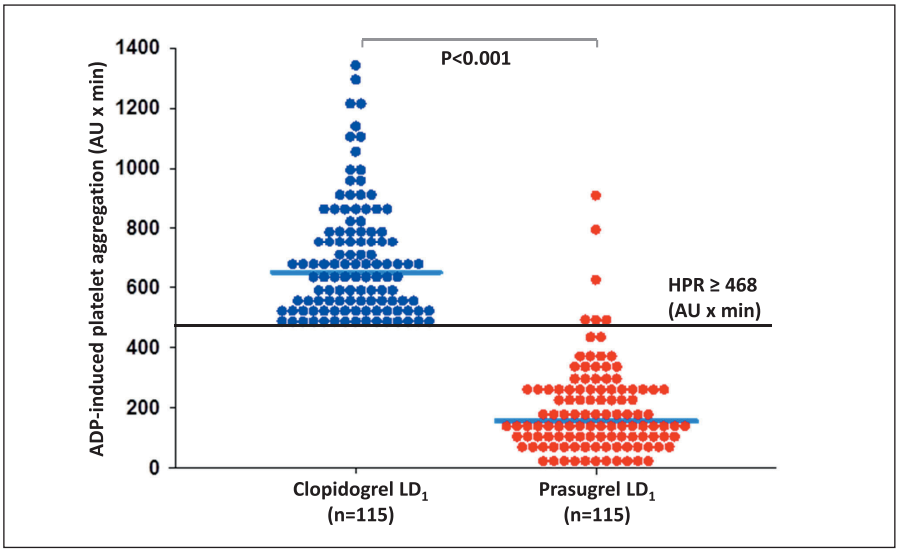

Figure 3: Platelet aggregation on-clopidogrel treatment and after switch to prasugrel. The figure shows the ADP-induced platelet aggregation values after the initial clopidogrel LD treatment and after switch over to prasugrel treatment. The blue lines represent median values. Blue dots represent individual on-clopidogrel treatment platelet aggregation values. Red dots represent individual platelet aggregation after switch over to prasugrel. The black line illustrates the cut-off value for HPR (≥468 AU x min per consensus definition). ADP, adenosine diphosphate; AU, aggregation units; LD, loading dose.

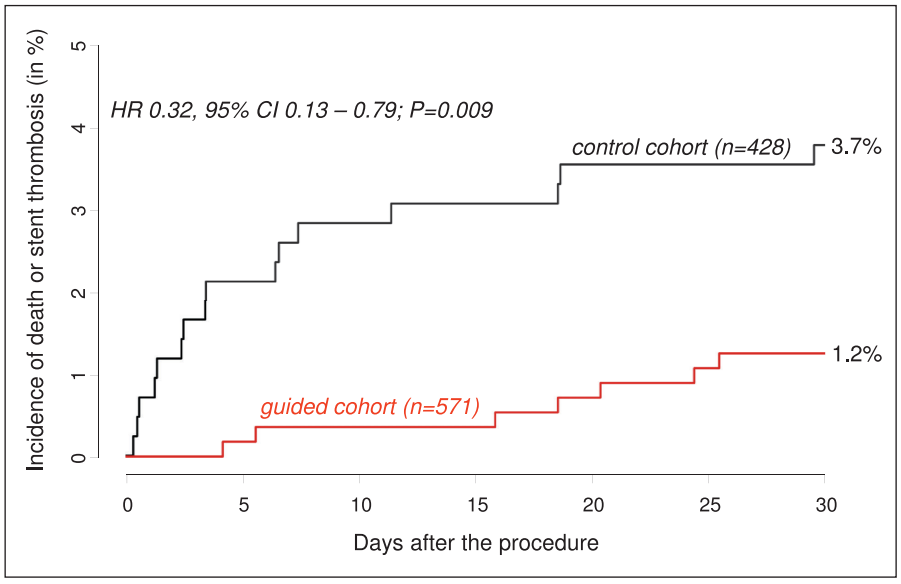

Figure 4: Incidence of death or stent thrombosis. The figure shows the incidence of the primary end point (death or stent thrombosis) during the 30-day follow-up period in the guided cohort (red line) vs the control cohort (black line). CI, confidence interval; HR, hazard ratio.

gregation values (794 [643–1017] AU x min after LD_1 vs 172 [116–238] AU x min after LD_{2-4}; p=<0.001). None of the patients remained with a status of HPR following additional clopidogrel LDs (range of values from 24 – 443 AU x min after LD_{2-4}).

Monitoring without change of treatment

The median [IQR] aggregation value after clopidogrel LD_1 in the 371 patients without intensified treatment was 632 [539–812] AU x min (range of values from 468 – 1637 AU x min). Instead of changing treatment based on this initial assessment, the majority of patients within this subgroup (n=334 patients, 90%) were scheduled for a 2nd assessment of drug response with a sufficient time lag. This is also why the response to a single high loading dose of clopidogrel is not immediate in all patients (15) and a reassessment was preferred over an intensification of treatment (weighting bleeding and thrombotic risk on an individual basis). Among the 334 patients, 327 patients (98%) showed an aggregation value <468 AU x min (median [IQR] platelet aggregation of 202 [130–299] AU x min) and only seven patients remained with a status of HPR after a 2nd assessment. All 371 patients were discharged on-clopidogrel MD treatment without any further therapy intensification.

On-prasugrel treatment platelet function data in the guided cohort

A total of 115 patients within the guided study cohort were switched over to prasugrel treatment. Switching was either done directly (in 35 patients) after the initial clopidogrel loading (LD_1) or after one (LD_2

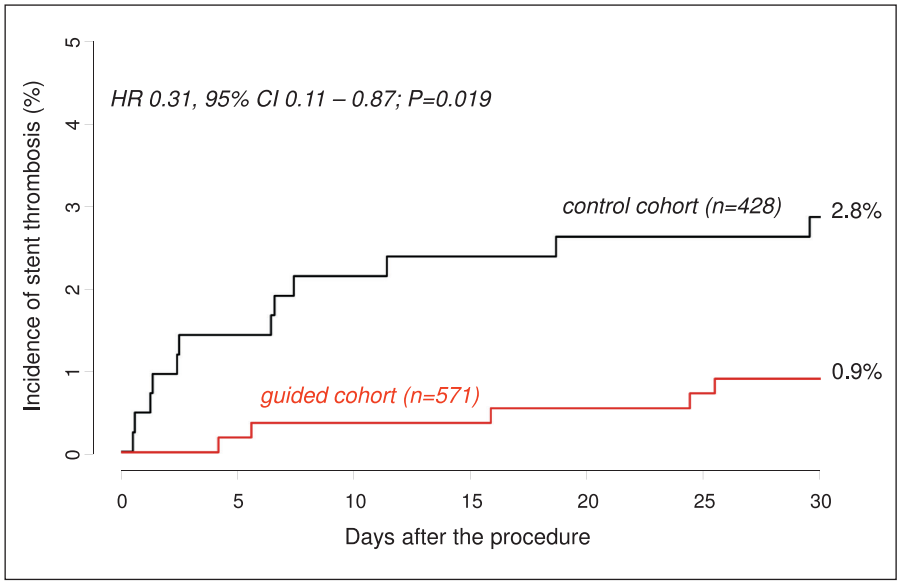

Figure 5: Incidence of definite or probable stent thrombosis. The figure shows the incidence of stent thrombosis (probable or definite) during the 30-day follow-up period in the guided cohort (red line) vs the control cohort (black line). CI, confidence interval; HR, hazard ratio.

Ischaemic events, n (%)	Guided cohort (n=571)	Control cohort (n=428)	Unadjusted HR [95% CI]	P value
Combined probable and definite ST	5 (0.9)	12 (2.8)	0.31 [0.11–0.87]	0.019
Definite ST	3 (0.5)	9 (2.1)	0.25 [0.07–0.91]	0.023
Probable ST	2 (0.4)	3 (0.7)	0.50 [0.08–2.97]	0.438
Death	4 (0.7)	8 (1.9)	0.37 [0.11–1.24]	0.095
Combined death/ST	7 (1.2)	16 (3.7)	0.32 [0.13–0.79]	0.009
Myocardial infarction	18 (3.2)	16 (3.7)	0.84 [0.43–1.65]	0.621
Combined death/ST/MI	21 (3.7)	22 (5.1)	0.71 [0.39–1.30]	0.270

Data presented are numbers of patients (percentages). CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; ST, stent thrombosis.

Table 4: Ischaemic clinical outcome data in the guided cohort vs the control cohort at 30 days.

in 73 patients) or two (LD_3 in 7 patients) additional clopidogrel LDs since this reloading treatment did not substantially lower the ADP-induced aggregation values (651 [543–780] AU x min after LD_1, 552 [472-693] AU x min after LD_2, 636 [481–918] AU x min after LD_3). ►Figure 3 shows the individual ADP-induced platelet aggregation values on-clopidogrel (post clopidogrel LD_1) and on-prasugrel treatment (post prasugrel LD_1). Prasugrel LD administration on top of clopidogrel LD treatment significantly lowered the ADP-induced platelet aggregation values (651 [543–780] vs 156 [88–261] AU x min; p<0.001). Only six (5.2%) patients continued to show a high on-treatment platelet reactivity (≥468 AU x min) following prasugrel treatment. These patients as well as two patients with high platelet reactivity levels just below the HPR cut-off value received an additional prasugrel LD (LD_2) resulting in a reduction of their ADP-induced PA values to a range of 71–440 AU x min. All 115 patients switched over to prasugrel treatment were also discharged on a prasugrel MD treatment (low 5 mg MD dosing in 20 patients, 17.4%).

Clinical outcome for ischaemic events

The 30-day follow-up was complete (100%) for all patients in both study cohorts. The incidence of the primary outcome (incidence of 30-day death or stent thrombosis) was significantly lower in the guided cohort vs the control cohort (7 [1.2%] vs 16 [3.7%] events; HR 0.32, 95% CI 0.13-0.79; p=0.009). ►Figure 4 shows the cumulative incidence of the primary outcome during the 30-day follow-up period in the control vs the guided cohort. The risk for 30-day ST (definite or probable) was significantly lower in the guided vs the control cohort of patients (5 STs [0.9%] vs 12 STs [2.8%]; HR 0.31, 95% CI 0.11-0.87; p=0.019; see ►Figure 5). ►Table 4 shows the entire clinical outcome data for the guided vs the control cohort of patients. ►Table 5 shows the results for the number of events of the primary ischaemic outcome measure (death or stent thrombosis) for the control cohort and all subgroups of the guided cohort of patients. For the guided cohort of patients we also analysed clinical characteristics and outcome data for patients with modification (prasugrel and re-loading subgroup) vs patients without (monitoring subgroup) modification of treatment. Results of this subgroup comparison are shown in Suppl. Tables 1-4 (available online at www.thrombosis-online.com).

Clinical outcome for bleeding events

The incidence of major bleeding events was numerically but not statistically higher in the guided cohort of patients vs the control cohort (11 bleeding events [1.9%] in the guided cohort vs 3 bleeding events [0.7%] in the control cohort; p=0.10). ►Table 5 shows the results for the number of major bleeding events for the control cohort and all subgroups of the guided cohort of patients. The bleeding risk was significantly different across the subgroups and was highest (8.7%) in the subgroup of patients that received prasugrel in the guided cohort of patients. Of note, eight (57%) of the 14 major bleedings events occurred in patients (n=37) that required cardiopulmonary reanimation (CPR) directly preceding the hospital visit or with their hospital admission, whereas the remaining 6 events occurred in the 962 patients without CPR (p<0.0001 for

	Control cohort (n=428)	Monitoring (n=371)	Clopidogrel Re-loading (n=85)	Prasugrel (n=115)	p-value
Combined death/ST	16 (3.7)	5 (1.3)	0 (0.0)	2 (1.7)	0.06
TIMI major bleeding	3 (0.7)	1 (0.3)	0 (0.0)	10 (8.7)	<0.001

Data presented are numbers of patients (percentages). ST, stent thrombosis.

Table 5: Subgroup analysis of clinical outcome data. The table shows the primary endpoint (composite of death from any cause or ST) and incidence of bleeding (TIMI major in-hospital) in the different subgroups of our registry at 30 days (control cohort vs the 3 subgroups of the guided cohort).

comparing the bleeding risk in CPR vs no-CPR patients). In 26 patients (87%) of the 30 patients with CPR in the guided cohort treatment was switched from clopidogrel to prasugrel.

Multivariate analyses

In a Cox proportional hazards model with the primary outcome as the dependent variable and treatment adjustment as well as other variables (age, previous MI, coronary artery disease presentation, cardiopulmonary reanimation at admission) as independent variables, treatment adjustment was found to be an independent predictor of the primary outcome (HR_{adj} 0.18, 95% CI 0.07–0.50; p=0.0008) along with CPR being associated with a higher risk for the outcome measure (p=0.003 for CPR). No significant interaction was observed between the patient groups (guided vs control cohort) and the presence of diabetes ($p_{(interaction)}$=0.24), the presence of an ACS (STEMI, NSTEMI, unstable angina) at admission ($p_{(interaction)}$=0.60) or the type of stent (first generation stents vs newer generation stents) that was used during PCI ($p_{(interaction)}$=0.92) regarding the primary endpoint (death or ST) of the study. Thus, diabetics and non-diabetics, ACS and non-ACS patients as well as patients with old (e.g. Cypher, Taxus) and newer generation stents (e.g. Xience, Endeavour) benefited equally from a guided treatment approach.

In a multivariate logistic regression model with major bleeding as the dependent variable, treatment adjustment was not independently associated with a higher bleeding risk (p=0.46). Need for CPR was the only variable that was independently associated with a higher bleeding risk (p=0.0001).

Discussion

The key findings of this study are that (i) a *selective* adaption and intensification of P2Y12 receptor directed antiplatelet treatment significantly lowered the risk for death or stent thrombosis, that (ii) guidance of treatment was found to be an independent predictor for a lower risk of ischaemic events and that (iii) a switch over from clopidogrel to prasugrel resulted in a very low rate of high on-prasugrel treatment platelet reactivity patients.

Of note, the majority of major bleeding events observed in the guided cohort of patients accumulated in the subgroups of prasugrel-treated patients and also in patients that required CPR. For prasugrel, this finding is in line with the higher bleeding risk observed for prasugrel-treated patients in the TRITON-TIMI 38 trial (16). For CPR patients little is known about the bleeding risk for prasugrel when used in this cohort since such patients were excluded in the pivotal randomised trials (16). However, the high bleeding risk observed in this subcohort here raises caution towards a regular use of prasugrel for CPR patients and warrants further investigation in larger populations. Of note, part of the prasugrel-treated patients were switched to prasugrel only after reloading doses of clopidogrel. This mode of action may contribute to the higher bleeding risk observed within the prasugrel-treated subgroup of patients. The decision to switch patients from clopidogrel to prasugrel has to be carefully made and, since present results are observational, further studies are urgently needed to better characterise the group of patients that would benefit from treatment with potent novel P2Y12 inhibitors without an increased risk of bleeding. Using PF testing for guidance of antiplatelet treatment resulted in a very selective use of prasugrel in our study cohort. This implies a chance for reducing the overall bleeding risk, but the role of testing in this regard warrants further investigation in larger and randomised cohorts.

Present findings encourage a *selective use* of potent P2Y12 receptor inhibitors like prasugrel in PCI-treated patients showing a status of HPR. With regard to this it must be emphasised that only a part of all HPR patients in the guided cohort were switched over to prasugrel or received additional clopidogrel LDs. Within the guided study cohort the assessment of platelet function must be understood as an important element among a number of other clinical, laboratory and procedural variables that act in concert on the clinical decision making with regard to the choice whether to intensify the antiplatelet treatment in a specific patient or not. In ACS patients, in patients with CPR at admission, in patients with a low ejection fraction and in patients with a lower TIMI flow grade before PCI, physicians opted significantly more often for a modification of treatment. Vice versa, in stable patients, a "watch and wait" approach was predominantly preferred (see Suppl. Tables 1–4, available online at www.thrombosis-online.com). Such considerations if and when to use a status of HPR to alter the antiplatelet treatment are necessary as the newly developed and potent P2Y12 receptor inhibitors prasugrel and ticagrelor have been found to be associated with higher bleeding risk (16, 17). The decision on the exact mode and dose of antiplatelet treatment was an individual one for each patient within the guided cohort of our registry and did not follow a predefined protocol. Indeed, such a course of action with *selective intensification* is in agreement with current guidelines for ACS and non-ACS patients that have included a class IIb indication for PF testing (1). However, there is no recommendation that testing results *must* alter treatment regimens.

In line with prior studies (15), present results also provide evidence that the antiplatelet effect of clopidogrel is delayed in some patients. A subgroup of patients with a status of HPR, which is based on a single initial testing, must be considered as "delayed responders" since a time-delayed re-assessment of clopidogrel response in these patients changed their phenotype. This finding is important since premature intensification of antiplatelet treatment may not be needed in these patients and a 2nd testing would be able to confirm an adequate (albeit delayed) response to clopidogrel. Another important aspect is the reproducibility of PF measurements in a stable setting vs an acute emergency setting of an ACS, which was the case in the majority of patients included in the guided cohort of this registry. While PF testing in stable patients provides stable and reproducible results (18), this can only be applied with restrictions to ACS patients and especially to patients who are in need for CPR. Reasons attributed to this include the transient high-levels of platelet activation in the initial phase of ACS and a significantly delayed drug absorption and metabolisation in cardiogenic shock patients. This underscores the need for

a further re-assessment of platelet function in these patients, as it was performed in our guided therapy cohort.

Results of the present study are in contrast to previous reports of randomised trial. Different reasons may account for this observation: First, studies like GRAVITAS (6), TRIGGER-PCI (5) and ARCTIC (7) mainly enrolled stable patients undergoing elective PCI. Therefore, data from these negative trials as well as data from the large Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) registry (8) suggest that the existence of HPR and switching patients to intensified antiplatelet treatment regimens may play a more prominent role in ACS and high-risk patients undergoing urgent PCI procedures. Indeed, the risk profile of the ISAR-HPR registry is different from the risk profile of patients enrolled in GRAVITAS, TRIGGER-PCI or ARCTIC (5–7). Especially for the guided cohort of patients of this registry we observed a very high rate of ACS patients (STEMI or NSTEMI) as well as a high proportion of patients with CPR at admission. Present results obtained in such a high-risk cohort of patients are an important addition to the data from published randomised trials having investigated low-to-intermediate risk cohorts of patients. Second, the proportion of patients that end up as at being an HPR patient on clopidogrel depends on the device and HPR cut-off value that is used for testing and subsequent stratification of patients (12). All major randomised studies (5–7) used the VerifyNow P2Y12 assay for testing and implemented cut-off values that led to a comparatively high proportion of up to 30–40% of patients with a status of HPR. The situation is different for the present registry as the HPR cut-off value (12) for the Multiplate analyser is associated with a rate of HPR patients below 20%. Third, properties of the trial design of GRAVITAS, ARCTIC and TRIGGER-PCI may also account for the above mentioned discrepancies. With regard to this it is worth mentioning that GRAVITAS (6) only used high-dose clopidogrel dosing regimens and lacked the use of prasugrel or ticagrelor, while ARCTIC (7) only had little utilisation of these newer agents. Another aspect here is the inclusion of periprocedural MI as a major component of the primary endpoint in the ARCTIC trial (7, 19) as this endpoint in contrast to stent thrombosis is not necessarily related to the response to antiplatelet treatment (8, 13, 19).

With regard to PF data, our study results provide insights into the antiplatelet action of prasugrel in a high-risk cohort of patients that failed to show an adequate response to clopidogrel treatment. Indeed, the majority of patients in the guided cohort showed an adequate response to prasugrel treatment while only a small proportion of patients (~5%) continued to show a status of HPR on prasugrel. In concert with other studies, our study adds to existing evidence that HPR is not only an issue in association with clopidogrel therapy (12, 13, 20) but can also occur on prasugrel treatment (21–23), although to a much lesser extent.

Our registry provides real-life and comparative data from two cohorts of patients with and without adjustment of treatment based on obtained PF testing values. With the arrival of the new potent P2Y12 inhibitors prasugrel and ticagrelor more potent drugs than clopidogrel are available which has clinical implications especially for ACS patients according to current guidelines (1, 24). Both new potent P2Y12 inhibitors lead to greater platelet inhibition than clopidogrel but at the expense of an increased risk for bleeding events. This is also why these agents are currently underutilised in clinical practice (25). An idea that reflects both bleeding and thrombotic risk is the concept of a therapeutic window of platelet inhibition (26). Such a concept sounds attractive with regard to improving patients´ outcome but further studies are surely needed here. Besides the negative results reported in GRAVITAS (6), TRIGGER-PCI (5) and ARCTIC (7), other studies (10) and a recently published meta-analysis (4) on the value of personalised antiplatelet treatment provided results in support for an individualised treatment approach. In line with our results provided here and with a focus on ST risk, the randomised MADONNA (Multiple electrode Aggregometry in patients receiving Dual antiplatelet therapy to guide treatment with Novel platelet Antagonists) study (9) and a just recently published well-characterised registry (27) showed a lower ST risk for patients in the guided group vs the non-guided group.

Limitations

Our study lacks a parallel control group but uses a historical control cohort instead. This is the case as we had been concerned about the outcome and especially the high ST risk of HPR patients observed in our historical cohort of patients and in consequence we did not want to repeat this scenario with a 2nd (parallel) control cohort. Of note, while both groups differ with regard to some baseline and procedural characteristics, the proportion of patients with CPR at admission and STEMI or NSTEMI patients was even higher in the guided cohort, expressing the high-risk profile of the guided vs the control cohort. A further limitation of the study is

What is known about this topic?

- Personalised antiplatelet treatment regimens with selective intensification of treatment may improve the outcome of high platelet reactivity (HPR) patients undergoing percutaneous coronary intervention (PCI).
- Data in support of this hypothesis is limited as well as real-life data from a background of routine platelet function testing has mainly been shown in stable patients undergoing elective PCI.

What does this paper add?

- This study shows that in a group of HPR patients undergoing PCI the incidence of the primary outcome (death or stent thrombosis) as well as the incidence of definite or probable stent thrombosis is significantly lower in the cohort with selective intensification of antiplatelet treatment (guided cohort) vs the control cohort.
- Our data suggest that the existence of HPR and switching patients to intensified antiplatelet treatment regimens may play a more prominent role in acute coronary syndrome and high-risk patients undergoing urgent PCI procedures and may only play a minor role in stable patients undergoing elective PCI.

related to the low number of ST events. This reflects the increased safety associated with current PCI but also underscores the need for larger studies to corroborate present results. Especially for the endpoint of death, numbers reported here in both cohorts are small and the difference is not significant per se. Whether an individualised antiplatelet treatment may reduce mortality risk is unclear at present and warrants further investigation in significantly larger cohorts. Here, we only used one device (Multiplate analyser) for platelet function testing and it is unknown in how far our findings can be extrapolated to other platelet function assays and clinical scenarios. Treatment modification in the guided cohort of patients included in this analysis did not follow a strict predefined protocol, as these data present daily clinical practice of decision making up to the discretion of the treating physician. In addition, the stent types used differed between the two cohorts and it cannot be excluded that this circumstance may have influenced outcome results. Finally, we used prasugrel for intensification of treatment as ticagrelor and clinical experience with the drug was not available during most of the study period. Analyses with a similar approach and implementing ticagrelor are urgently needed.

Conclusion

Present findings are in support for a guidance of antiplatelet treatment with selective intensification of P2Y12 receptor inhibition. Although present data is observational with all its inherent limitations and outcome data were compared to a historical control cohort, the issue of personalised antiplatelet treatment warrants further investigation in randomised and well-controlled clinical trials.

Conflicts of interest

Dr Sibbing reports receiving speaker fees from Daiichi Sankyo and Roche and fees for advisory board activities from Verum Diagnostica and Eli Lilly. Prof. Schunkert reports receiving speaker fees from Sanofi-Aventis and Daiichi Sankyo and grants from Bristol-Myers Squibb. Prof. Hausleiter reports receiving grants from Siemens Medical Solutions and speaker fees from Abbott Vascular. Prof. Kastrati reports receiving lecture fees from Daiichi-Sankyo and lecture fees and fees for advisory board activities from AstraZeneca. No conflict of interest for the other authors.

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