Clopidogrel response status assessed with Multiplate point-of-care analysis and the incidence and timing of stent thrombosis over six months following coronary stenting

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Summary
Clopidogrel low-responsiveness assessed with multiple electrode platelet aggregometry (MEA) has been shown to be a strong and independent predictor of early stent thrombosis (ST) after coronary stenting. The relation of clopidogrel response status, as assessed with MEA, with incidence and timing of ST during an extended follow-up period has never been reported. Here, we report the six-month follow-up results of a prospective trial assessing clopidogrel responsiveness with MEA in patients undergoing percutaneous coronary intervention (PCI). A total of 1,608 consecutive patients with planned drug-eluting stent placement were enrolled in this study. Before PCI patients uniformly received 600 mg clopidogrel and blood was taken directly before PCI to measure ADP-induced platelet aggregation with MEA. The upper quintile (20%) of patients according to MEA measurements (n=323) was defined as clopidogrel low responders. Compared with normal responders (n=1,285), the cumulative incidence of definite ST within six months was significantly higher in low responders [2.5% vs. 0.4%; OR 6.5; 95% CI, 2.4–17.0; P<0.001]. The combined incidence of definite or probable ST was higher as well in low vs. normal responders [4.1% vs. 0.7%; OR 5.8; 95% CI, 2.8–12.3; P<0.0001]. A significant inverse correlation of MEA values and the timing of definite or probable ST (in days) was observed (Spearman coefficient = –0.45; P=0.04) with events occurring earlier in the low-responder group. MEA measurements are highly predictive for the occurrence of ST during the first six months following coronary stenting. In the majority of clopidogrel low responders suffering ST, the ischaemic event occurs early in the course after the procedure.

Keywords
Clopidogrel, stent thrombosis, platelet aggregation, whole blood aggregometry

Introduction
For patients undergoing coronary stent placement, oral antplatelet treatment with the cyclooxygenase inhibitor aspirin and the thienopyridine clopidogrel is the mainstay treatment to prevent thrombotic events after percutaneous coronary interventions (PCI) (1). Large-scale clinical trials (2–4), however, have demonstrated that despite optimal oral antplatelet treatment and regardless of the intravascular anticoagulant used, ischaemic events including stent thrombosis (ST) still occur in PCI-treated patients initially presenting with stable angina or an acute coronary syndrome (ACS).

In recent years, response variability to clopidogrel treatment and the phenomenon of low- or non-responsiveness to clopidogrel has been explored (5–7) and a number of prospective and retrospective studies have clearly established a link between an attenuated response to clopidogrel treatment and an increased risk of ischaemic events following PCI including the occurrence of ST (8–15). Studies investigating this issue have implemented different methods of platelet function testing including light transmission aggregometry (LTA) (8–10) as the most widely used technique, the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA) enabling point-of-care platelet function testing (12,13) and the flow cytometry based VASP (vasodilator-stimulated phosphoprotein) assay (PLT VASP/P2Y12, Biocytex) being specific for P2Y12 receptor inhibition (14). The different currently available assays indicate the lack of standardisation that exists in the field of platelet function testing (16). At present, a number of different assays are under laboratory and clinical evaluation (17, 18).

Recently, a new point-of-care assay named multiple electrode
platelet aggregometry (MEA) using a device called Multiplate analyzer (Dynabyte, Munich, Germany) has become available for rapid and standardised assessment of platelet function parameters in various clinical settings (11, 18–23). MEA is highly capable of detecting the effect of clopidogrel treatment and the results of MEA correlate well with LTA (17, 19, 24). Using MEA, we were able to demonstrate in a large prospective trial (11) including 1,608 clopidogrel-treated patients undergoing PCI, that clopidogrel low responsiveness is a strong and independent predictor for the occurrence of early ST during a 30-day follow-up period. The relation of clopidogrel response status, as determined with the MEA technique, with the incidence and timing of ST during an extended follow-up period has never been reported. Here, we report the results of a prospective trial assessing platelet response to clopidogrel with MEA and its relation with the incidence and timing of ST over six months following coronary stent placement.

Materials and methods

Study population

The design of the trial has been described in detail previously (11). In brief, between February 2007 and April 2008 patients with planned drug-eluting stent (DES) implantation in the two participating centers (Deutsches Herzzentrum München and I. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Germany) were enrolled in this study. All patients were uniformly pretreated with a loading dose of 600 mg clopidogrel, which was recommended to be given at least 2 hours before the procedure. Coronary interventions were performed according to current standard guidelines (1). A small subset of the patients (<5%) received intravenous antiplatelet therapy with the GP IIb/IIIa inhibitor abciximab (0.25 mg/kg of body weight bolus, followed by a 0.125 μg/kg/minute infusion for 12 hours) in addition to a reduced dose of heparin. After PCI, patients were treated with 150 mg/day clopidogrel in hospital for three days plus 100 mg aspirin (bid) and patients were discharged on a dual antiplatelet regimen of 75 mg/day clopidogrel and 100 mg aspirin (bid), which was recommended to be given for at least six months following coronary stent placement. For this study, patients were considered eligible irrespective of the clinical presentation (stable angina, unstable angina, ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI]) at the time point of the procedure. The procedures for patients presenting with an STEMI were emergent procedures and the patients did not receive thrombolytic therapy. Exclusion criteria were contraindications to aspirin or clopidogrel treatment and prior treatment with GP IIb/IIIa inhibitors during the 10 days before the PCI. The study complies with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients gave written informed consent prior to entering the study.

Point-of-care platelet function testing

For platelet function testing with MEA, whole blood was obtained from the arterial sheath of all patients directly before PCI. The blood obtained was placed in 4.5 ml plastic tubes containing the anticoagulant lepirudin (25 μg/ml, Refludan, Hirudin blood collection tubes, Dynabyte). ADP (6.4 μM)-induced platelet aggregation in whole blood was assessed with MEA using a Multiplate analyzer (Dynabyte) (19, 25). Details of this method have been reported previously (19, 23, 26). Aggregation measured with MEA is quantified as aggregation units (AU) and area under the curve (AUC) of arbitrary units (AU•min). All material used for platelet function testing was obtained from the manufacturer (Dynabyte).

Follow-up and endpoints

For the present study, we prospectively defined clopidogrel low responsiveness by setting a cut-off point at the upper quintile (20%) of MEA measurements, which was also the basis for the primary sample size calculation (11). For the six-month follow-up period, we focused on the incidence of stent thrombosis using the different categories of ST established by the Academic Research Consortium (ARC) (27). According to ARC criteria, definite ST was defined as the occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of stent thrombosis. Probable ST was defined as any unexplained death within 30 days or as target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion. Possible stent thrombosis was defined as any unexplained death after 30 days following the procedure. We further assessed the incidence of death from any cause, the combined incidence of death or definite ST, cardiac death (27), ischaemic stroke and MI. The diagnosis of MI was made according to TIMI criteria (28) and based on new abnormal Q-wave appearance in the electrocardiogram and/or an increase of the CK-MB value to three or more times the upper limit of normal. All adverse events occurring in this study were adjudicated by an event adjudication committee blinded to the platelet function status of patients and not involved in the follow-up process. For the follow-up process, patients were interviewed by telephone call after 30 days (± 7 days) and six months. Patients reporting cardiac symptoms were seen in the outpatient clinic for complete clinical, electrocardiographic and laboratory check-up. In addition, all possible information from referring physicians, relatives and from hospital readmissions was collected as well.

Statistical analysis

Variables are presented as mean ± standard deviation (SD), counts (percentages) or median with interquartile range [IQR]. Categorical variables were compared using Chi²-test. Kolmogorov-Smirnov test was used to test for normal distribution of continuous
data. Normally distributed continuous variables were compared with two-sided unpaired t-test and not normally distributed data were compared with Wilcoxon test. As platelet function measurements obtained with MEA were not normally distributed, the Spearman rank correlation coefficient was calculated to test for the correlation of MEA values and timing (in days after study enrollment) of ST. A receiver-operating characteristic (ROC) curve analysis was calculated to determine the ability of MEA to distinguish between patients with and without definite or probable ST in the six months after the procedure. The optimal cut-off value was calculated by determining the value for platelet aggregation (in AU*min) that provided the greatest sum of sensitivity and specificity. Survival analyses were generated using the Kaplan-Meier method. Differences between groups were assessed by log-rank test with calculation of odds ratios (ORs) (95% confidence intervals [CIs]) associated with the six-month incidence of the endpoints of interest. A Cox proportional hazards model was used to test for an independent association of MEA measurements and the incidence of stent thrombosis (definite or probable). The occurrence of definite or probable ST was therefore defined as the dependent variable. Independent variables were clopidogrel low responsiveness (defined as the upper quintile of patients) and all variables shown in Table 1 with significant differences (P<0.05) between normal and low responders. The hazard ratios (HR) and the corresponding 95% CIs were calculated. A p-value <0.05 was considered significant and analyses were performed using the software package S-PLUS version 4.5 (Insightful Corp, Seattle, WA, USA).

Results

A total of 1,608 CAD patients with coronary stent placement were enrolled in this study. The distribution of MEA measurements is demonstrated in Figure 1. Measurements for ADP-induced platelet aggregation (in AU*min) values in the entire study population (n=1,608) is shown. ADP, adenosine diphosphate; AU, aggregation units.

Table 1: Baseline characteristics of the study population. Data presented are means ± SD or numbers of patients (percentages). Time from clopidogrel loading (hours) to blood sampling is expressed as median [interquartile range, IQR]. CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment myocardial infarction.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal responders (n=1,285)</th>
<th>Low responders (n=323)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years)</td>
<td>67.7 ± 10.4</td>
<td>66.7 ± 10.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Woman, n (%)</td>
<td>287 (22.3)</td>
<td>87 (26.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.3 ± 4.2</td>
<td>28.3 ± 4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, (%)</td>
<td>54.9 ± 10.9</td>
<td>53.2 ± 12.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>352 (27.4)</td>
<td>110 (34.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>156 (12.1)</td>
<td>60 (18.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1182 (92.0)</td>
<td>291 (90.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>895 (70.0)</td>
<td>227 (70.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>396 (30.8)</td>
<td>111 (34.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>1088 (85.0)</td>
<td>281 (87.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>CAD presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina, n (%)</td>
<td>881 (68.6)</td>
<td>194 (60.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>291 (22.6)</td>
<td>66 (20.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>NSTEMI, n (%)</td>
<td>93 (7.2)</td>
<td>43 (13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>20 (1.6)</td>
<td>20 (6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count, x10³/µl</td>
<td>213 ± 62</td>
<td>236 ± 64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from loading, (h)</td>
<td>4.0 [2.0–15.5]</td>
<td>3.0 [2.0–7.0]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
tributed (one sample Kolmogorov-Smirnov Test; P<0.001) with a median [interquartile range] value of 225 AU*min [141–369]. The cut-off value for MEA measurements defining the upper quintile (20%) of patients was 416 AU*min and 323 patients were therefore defined as clopidogrel low responders. A total of 1,285 patients were defined as clopidogrel normal responders. The baseline clinical characteristics of the study population are shown in Table 1. Angiographic and procedural characteristics of the study population have been reported previously (11).

**Stent thrombosis and MEA**

The six-month follow-up was completed in all but 27 (1.7%) patients, who were lost to follow-up. Compared with normal responders (n=1,285), the cumulative incidence of definite ST within six months was significantly higher in the low responder group (n=323) [2.5% vs. 0.4%; OR 6.5; 95% CI, 2.4–17.0; P<0.001], as was the incidence of probable ST [1.6% vs. 0.3%; OR 5.0; 95% CI, 1.5–16.3; P=0.008]. The combined incidence of definite or probable ST was significantly higher in low vs. normal responders [4.1% vs. 0.7%; OR 5.8; 95% CI, 2.8–12.3; P<0.0001]. A landmark analysis starting at 30 days after the procedure showed that the combined incidence of definite or probable ST after this time point was higher in low vs. normal responders [1.2% vs. 0.3%; OR 4.1; 95% CI, 1.1–14.7; P=0.03]. Figure 2 shows the cumulative incidence of definite ST and Figure 3 shows the cumulative incidence of definite or probable ST during the six-month follow-up period in clopidogrel low vs. normal responders. The combined incidence of death or definite ST was significantly higher in low vs. normal responders [5.0% vs. 2.3%; OR 2.2; 95% CI, 1.2–4.1; P=0.008]. Table 2 shows the entire clinical outcome data for ischaemic events in low vs. normal responders over six months.

A Cox proportional hazards model was used to test for an independent association of MEA measurements and definite or probable ST over six months after the procedure. The Cox model included clopidogrel low-responsiveness (defined as a platelet aggregation value [in AU*min] in the upper quintile of patients) as well as possible confounding variables (see Table 1) of patients’ baseline characteristics, which were diabetes mellitus, active smoking, body mass index, ejection fraction, platelet count, time from clopidogrel loading to blood sampling and the presence of an acute coronary syndrome (in the form of a STEMI or NSTEMI). Results of this Cox model demonstrated that clopidogrel low-responsiveness, as determined with MEA, was the strongest and independent predictor of ST [HR 5.3, 95% CI 2.0–13.7; P=0.0006]. In this study population, other independent predictors of ST were diabetes mellitus [HR 4.4, 95% CI 1.8–11.2; P=0.002], presence of an ACS [HR 3.8, 95% CI 1.4–10.3; P=0.007] and platelet count (calculated for an increase of 100 x10³/μl in platelet count) [HR 1.7, 95% CI 1.2–2.5; P=0.002]. The remaining variables included in the model were not found to be independent predictors of ST (P≥0.13).

**Timing of stent thrombosis and clopidogrel response status**

The cumulative incidence of six-month definite or probable ST was 1.4% (22 events: 13 definite ST, 9 probable ST). In none of these patients non-compliance to dual antiplatelet treatment was reported in the time period before the event occurred. The median [IQR] time (in days) from study inclusion to the occurrence of definite or probable ST was 14 [2–83] days. The large majority of stents implanted during the PCI procedure were drug-eluting stents (98.0% in normal-responders vs. 98.2% in low-responders; P=0.93). Among the 22 definite or probable STs observed, 21 oc-
curred following drug-eluting stent placement and one event occurred following bare-metal stenting.

From the 13 definite ST observed over six months in the present study population, 10 (77%) early ST (in the first 30 days) occurred after the procedure and only 3 (23%) late ST (after 30 days) were observed. From the eight definite ST observed in the low-responder group, 7 (88%) were classified as an early ST and only one event occurred after 30 days.

For the combined endpoint of definite or probable ST, the majority of events (n=17, 77%) occurred during the first three months after study inclusion. The time from study inclusion to the occurrence of definite or probable ST was shorter in low vs. normal responders (7 [2–72] days in low vs. 18 [8–134] days in normal responders; P=0.15). From the 13 definite or probable ST observed in the low responder group, 12 events (92%) occurred during the first three months after study inclusion. The correlations of MEA values from ST patients (n=22) with the timing of definite or probable ST (in days) during the six-month follow-up period are demonstrated in Figure 4. A significant inverse correlation of MEA values and the timing of ST (in days) was observed (Spearman rank correlation coefficient = –0.45; P=0.04).

Receiver-operating characteristic (ROC) curve analysis

The ROC curve of MEA measurements for the prediction of definite or probable ST at six months following coronary stent placement is shown in Figure 5. The optimal cut-off value according to ROC analysis to predict the occurrence of definite or probable ST at six months was 425 AU*min. With this cut-off value, MEA had 59% sensitivity and 81% specificity. The area under the ROC

Table 2: Ischaemic events during a six-month follow-up period. CI, confidence interval; ST, stent thrombosis.

<table>
<thead>
<tr>
<th>Ischaemic events, n (%)</th>
<th>Normal responders (n=1,285)</th>
<th>Low responders (n=323)</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis (ST)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite ST</td>
<td>5 (0.4)</td>
<td>8 (2.5)</td>
<td>6.5 (2.4–17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probable ST</td>
<td>4 (0.3)</td>
<td>5 (1.6)</td>
<td>5.0 (1.5–16.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Possible ST</td>
<td>5 (0.4)</td>
<td>0 (0.0)</td>
<td>-</td>
<td>0.26</td>
</tr>
<tr>
<td>Combined probable/definite ST</td>
<td>9 (0.7)</td>
<td>13 (4.1)</td>
<td>5.8 (2.8–12.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death (all cause)</td>
<td>25 (2.0)</td>
<td>10 (3.2)</td>
<td>1.6 (0.8–3.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Combined death/definite ST</td>
<td>29 (2.3)</td>
<td>16 (5.0)</td>
<td>2.2 (1.2–4.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>13 (1.0)</td>
<td>8 (2.5)</td>
<td>2.5 (1.1–5.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>Combined cardiac death/definite ST</td>
<td>17 (1.3)</td>
<td>14 (4.4)</td>
<td>3.3 (1.7–6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>49 (3.8)</td>
<td>17 (5.2)</td>
<td>1.4 (0.8–2.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3 (0.2)</td>
<td>3 (0.9)</td>
<td>4.0 (0.9–17.6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
curve was 0.74 (95% CI 0.62–0.86, P<0.0001). When applying this cut-off value, 311 patients (19.3 %) of the study population had MEA values above this cut-off.

Diabetes, overweight, high fibrinogen and platelet aggregation

A total of 462 patients of the study population were diabetic patients. Absolute platelet aggregation values were significantly higher in diabetic vs. non-diabetic patients (246 [164–403] AU*min vs. 216 [135–346] AU*min; P=0.0003). A total of 1,149 patients of the study population were overweight patients with a body mass index ≥25. Absolute platelet aggregation values were significantly higher in overweight vs. non-overweight patients (231 [143–388] AU*min vs. 215 [136–328] AU*min; P=0.03). Fibrinogen levels at the time point of the procedure were available in 1,298 patients. Absolute platelet aggregation values were significantly higher in patients (n=750) with a high fibrinogen level (≥3.75g/l) vs. patients (n=548) with a normal fibrinogen level (245 [152–405] AU*min vs. 208 [131–312] AU*min; P<0.0001).

Discussion

Here, we report the six-month follow-up results of a prospective study investigating the interrelationship of platelet response to clopidogrel, as assessed with MEA, and the incidence and timing of ST following coronary stent placement. Major findings of our study are that (i) low-responsiveness to clopidogrel treatment determined with MEA is significantly associated with the occurrence of ST in the first six months following coronary stent placement, that (ii) in the majority of clopidogrel low responders suffering ST, the ischaemic event occurs early in the course after the procedure and that (iii) a significant correlation exists between MEA values measured at the time point of stent placement and the timing of ST following the procedure with stent thrombosis occurring earlier in low as compared to normal responders.

At present, a number of different assays for platelet function testing in clopidogrel-treated patients are under laboratory and clinical evaluation (8, 10, 12–14, 29). A relatively low positive predictive value for the occurrence of ischaemic events has been observed for these different assays (8, 12), as it is also the case for the Multiplate device, which shows a positive predictive value of 4% but a high negative predictive value of 99.3% for the occurrence of definite or probable ST. Among these assays, LTA and the VerifyNow assay are besides MEA the most commonly used methods for assessment of ADP-induced platelet aggregation. The predictive power for LTA and the point-of-care VerifyNow P2Y12 assay has been established in different clinical studies applying short (10) as well as extended follow-up periods (8–10, 12, 13). Whereas for MEA only short-term follow-up results were available up to now (11), we now present data for an extended follow-up period of six months. Based on the results reported here, the predictive power of MEA measurements for the occurrence of ST after PCI,
which has already been demonstrated in the short term (11), was maintained during a six-month follow-up period. For the present analysis we focused on stent thrombosis and the different ST categories according to ARC criteria (27). Applying the ARC criteria for definite or probable ST, we observed an approximately six-fold increase in the incidence of this combined end point in low vs. normal responders. Multivariate analysis revealed that low response to clopidogrel assessed with MEA is an independent predictor for the occurrence of definite or probable ST in the first six months following PCI. Of all variables included in the Cox model, clopidogrel low-responsiveness determined with MEA was found to be the strongest predictor of six-month ST. The observed associations of diabetes mellitus, presence of an acute coronary syndrome and a higher platelet count with ST are consistent with previous reports (30–32) investigating predictors of ST and do therefore strengthen the validity of the multivariable Cox model we applied.

Applying a ROC analysis to our data for the combined end point of definite or probable ST, we found an area under the ROC curve of 0.74. The results of this ROC analysis with an AUC of 0.74 for the Multiplate device are similar to the results of ROC analyses using the VerifyNow P2Y12 assay in previous studies, were an area under the ROC curve of 0.66 or 0.71 was reported (12, 13). Using ROC analysis, the observed cut-off value of 425 AU* min for the occurrence of definite or probable ST was found to be very close to the prospectively defined cut-off value defining the upper quintile (20%) of patients as clopidogrel low responders (416 AU* min) and also close to the cut-off value observed to predict 30-day definite ST (468 AU* min) (11). The different endpoints chosen (definite ST vs. combined definite or probable ST) and the different time interval that was analysed (30 days vs. six months) may account for the slightly different values observed according to ROC analysis. With the establishment of these cut-off values for the Multiplate device during both a short and an extended follow-up period, we are now able to define a selected at-risk population, in which thrombotic event rates are found to be substantially increased. As the ROC cut-off value for six-months definite or probable ST is based on a larger number of clinical events than the 30-day cut-off value for definite ST, it may be better suited in a clinical setting. It has to be emphasised, however, that the usefulness of the cut-off values provided has to be tested in separate studies, where patients with a platelet aggregation value above a certain cut-off are randomised to an intensified antiplatelet treatment regimen.

The relationship of ADP-induced platelet aggregation values measured at the time point of the coronary intervention in clopidogrel treated patients with the timing of adverse events such as stent thrombosis has never been discussed separately in previous trials. The recording of the incidence of ST during an extended follow-up period allowed us to explore the timing of events in relation to clopidogrel response status. The observation that the large majority of events occurs early in the time period after coronary stent placement is in line with previous reports (32). Here, we report a significant inverse correlation of ADP-induced platelet aggregation values and the timing of ST following coronary stent placement. It has to be emphasised, however, that the correlation observed was borderline significant (P=0.04), and further studies are needed to corroborate present results. High ADP-induced platelet aggregation values (in AU* min) measured at the time point of stent placement, are commonly found in ST patients with an earlier occurrence of the event following PCI, whereas lower ADP-induced platelet aggregation values are more commonly found in ST patients with events occurring later in the course after PCI. Late events, in consequence, seem to be unrelated to clopidogrel response status and other factors may account for it. This observation seems self-evident in the context of clopidogrel low-responsiveness. In clopidogrel low responders with recent coronary stent placement, circulating platelets are not sufficiently inhibited by dual antiplatelet treatment and therefore the hazard of stent thrombosis is omnipresent from the very first time after the procedure. In this context, however, it has to be stated as a limitation of the present study, that platelet response to clopidogrel was only assessed at one single time point. It can therefore not be excluded that changes in life-style, changes in co-medications or a worse control of cardiovascular risk factors have altered the platelet response to clopidogrel in some of the patients shifting a prior normal responder to a low responder (or vice versa). In the future, specifically designed studies with serial assessments of platelet function parameters, should determine the stability of the low-responder phenotype over the course of time.

The association of a low response to clopidogrel and the occurrence of stent thrombosis was found to be weaker in a landmark analysis starting at 30 days after the procedure as compared to the early period (=30 days) (11) after coronary stenting. Taking into account the results observed for the timing of events in relation to clopidogrel response status and also the findings from the landmark analysis, the role of platelet function testing in clinical practice is sup-

What is known about this topic?
- Clopidogrel low-responsiveness assessed with multiple electrode platelet aggregometry (MEA) has been shown to be a strong and independent predictor of early stent thrombosis (ST) during a 30-day follow-up period after coronary stenting.
- Prospective and retrospective studies have clearly established a link between an attenuated response to clopidogrel treatment and an increased risk of ischaemic events following coronary stenting including the occurrence of stent thrombosis.

What does this paper add?
- A low-responsiveness to clopidogrel treatment determined with MEA is significantly associated with the occurrence of ST in the first six months following coronary stenting.
- In the majority of clopidogrel low responders suffering ST, the ischaemic event occurs early in the course after the procedure.
- A significant correlation exists between MEA values measured at the time point of stent placement and the timing of ST following the procedure with stent thrombosis occurring earlier in low as compared to normal responders.
posed to be much more relevant for predicting ischaemic events that occur early after the procedure than for predicting late ischaemic events. In view of the results of the present trial and other prospective studies (8–10, 12–14) having sufficiently linked clopidogrel low-responsiveness with the occurrence of ischaemic events including stent thrombosis, it is quite obvious that platelet function testing in PCI-treated patients is clinically relevant. It has not been well established yet, however, that guidance of antiplatelet treatment with selective intensification of treatment regimens based on platelet function testing is safe and effective in reducing ischaemic events after DES implantation. First pilot studies in smaller subsets of patients using the VASP assay provided promising results (33, 34) and opened the field for randomised large-scale clinical trials that are now needed to address this issue specifically. The Gauging Responsiveness With A VerifyNow Assay-impact On Thrombosis And Safety (GRAVITAS) trial (ClinicalTrials.gov Identifier: NCT00645918) using the VerifyNow P2Y12 assay is currently on the way to address this issue with a planned enrollment of 2,800 patients and platelet function guided adjustment of clopidogrel therapy (35). Results of our study show great promise for the Multiplate device as a tool for tailoring antiplatelet treatment to the needs of individual patients. The assay is highly standardised, detects a status of platelet hyper-reactivity as it is the case in diabetic (36) or overweight patients (37) or in patients with high fibrinogen levels (38), enables near-patient platelet function testing and is predictive for the occurrence of thrombotic events following PCI. Its usefulness, however, for guidance of tailored antiplatelet treatment has to be tested separately in large-prospective clinical trials, where patients defined as low-responders are randomized to an intensified antiplatelet treatment.

Limitations

Results of this trial are only based on measurements with MEA and were not compared with LTA or the VerifyNow assay in the present study population. The comparison of different methods in terms of predicting the clinical outcome of patients in one and the same study population would provide important data and would allow comparing the different assays better as it can be done at present across different studies with different study populations and different definitions of clopidogrel low-responsiveness.

Conclusion

MEA measurements are highly predictive for the occurrence of ST during the first six months following coronary stent placement. In the majority of clopidogrel low responders suffering ST, the ischaemic event occurs early in the course after the procedure.

References


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