Early but not late stent thrombosis is influenced by residual platelet aggregation in patients undergoing coronary interventions

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Aims
Recent studies suggest a relevant association of post-interventional residual platelet aggregation (RPA) under therapy with oral platelet inhibitors and the occurrence of atherothrombotic events. The influence of post-interventional RPA on the incidence of stent thrombosis (ST) has not been sufficiently evaluated in consecutive unselected cohorts of percutaneous coronary intervention (PCI) patients. The aim of this observational study was to investigate the impact of RPA on the incidence of ST within 3 months in patients treated with dual antiplatelet therapy.

Methods and results
The study population included a consecutive cohort of 1019 patients treated with PCI (n = 741 bare-metal stent (BMS) and n = 278 drug-eluting stent (DES)) due to symptomatic coronary artery disease. Residual platelet activity was assessed by adenosine disphosphate (20 μmol/L)-induced PA after 600 mg clopidogrel loading dose. Maximum RPA was measured as peak of aggregation, final RPA was measured 5 min after addition of agonist. The primary endpoint was the occurrence of ST within 3 months defined according to academic research consortium (ARC) criteria. Final and maximum RPA were independent predictors of ST after 3 months. In secondary analysis, the observed effects were independently associated with early ST (HR 1.05, 95% CI 1.01–1.08 and HR 1.05, 95% CI 1.01–1.09, P < 0.01, respectively). However, incidence of 3-month late stent thrombosis (LAT) was not influenced by post-interventional RPA in multivariable analysis.

Conclusion
Post-interventional RPA is associated with the occurrence of early ST in patients treated with either BMS or DES; however, there is no predictive value of RPA for the incidence of 3-month LAT, suggesting the involvement of other possible mechanisms like discontinuation of antiplatelet therapy.

Keywords
Stent thrombosis • Clopidogrel • Antiplatelet drug resistance • Aggregation • Percutaneous coronary intervention

Introduction
Recently, several studies demonstrated that residual platelet aggregation (RPA) influences cardiovascular outcome in patients treated with dual antiplatelet therapy after percutaneous coronary intervention (PCI).1–4 The incidence of early and late stent thrombosis (LAT) has been reported with a rate of 0.5–2.8% depending on stent-type and different definitions applied.5,6 Stent thrombosis (ST) is a very serious complication with mortality rates of ~50%.7–9 Its causes are manifold and range from non-adherence to antiplatelet therapy to procedure-related factors like bifurcational stenting to clinical conditions like diabetes mellitus.10 Several case–control trials suggested an association of measured platelet aggregation and ST.11,12 In a recent published article, Buonamici et al.13 investigated the relationship between residual platelet reactivity and the incidence of 6 months ST in drug-eluting
stent (DES)-treated patients. In this study, low responsiveness to clopidogrel was a strong predictor for the incidence of the composite of ST (early ST and LAT). In addition, different platelet functional parameters have been used to define residual platelet reactivity in the previous studies. The aim of the present study was to evaluate the association of post-interventional platelet aggregation with the incidence of ST (early ST and 3-month LAT) in a consecutive, heterogeneous setting of patients with either bare-metal stent (BMS) or DES implantation.

Methods
This study was a monocentre observational study conducted at the University Hospital, Tübingen, Germany. Patients admitted to the clinic due to coronary intervention for symptomatic coronary artery disease are consecutively investigated by platelet function analysis and registered in a database. The study design was approved by the local Ethics Committee and signed informed consent was obtained from all subjects. The primary endpoint of the study was the combined incidence of early ST (<30 days) and LAT within 3 months. Stent thrombosis was defined according to the academic research consortium (ARC) as previously described.14

Subjects
A total of 1479 patients were eligible and screened for this study. Of these, 1286 patients gave their willing consent and were enrolled in the platelet aggregation study. Of the investigated patients, 1019 were followed up for the incidence of ST; flowchart, Figure 1. The followed-up cohort consisted of consecutive, unselected patients who underwent coronary stenting for symptomatic coronary artery disease. Seven hundred and forty-one patients received BMS and 278 patients DES. Acute coronary syndrome (ACS) was diagnosed if one of the following criteria was fulfilled: unstable angina (clinical symptoms and new ECG changes, but no markers of myocardial necrosis), acute myocardial infarction with markers of myocardial necrosis (troponin or CK-MB) including ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). Inclusion criteria were an age older than 18 years and willing consent. Patients with known platelet function disorders were excluded from the study. A loading dose of 600 mg clopidogrel was given to all patients prior to PCI followed by ASA 100 mg per day. The majority of patients received 500 mg of acetylsalicylic acid (ASA) intravenously before PCI followed by ASA 100 mg per day. The majority of patients (~90%) were already pre-treated with a chronic aspirin therapy (100 mg per day). Unfractionated heparin was peri-procedurally administered to all patients at a dosage of 70 U/kg body weight.

Blood sampling and platelet aggregation
Patient blood was collected earliest at 6 h after first administration of 600 mg clopidogrel, when maximum platelet inhibition is achieved according to the previous observations.15,16 In a minority of patients who were on chronic clopidogrel treatment (75 mg/day) and received an additional loading dose of 300 mg platelet function was assessed earliest at 24 h (15.4% of total patients). Venous blood was collected in 3.8% citrate plasma. Samples were centrifuged at 150 g for 10 min to obtain platelet-rich plasma (PRP) and additionally 10 min at 2000 g to recover platelet-poor plasma (PPP). Platelet concentration of PRP was adjusted to 2 × 10^8/μL by adding homologous PPP. Percent platelet aggregation after stimulation with 20 μmol/L adenosine diphosphate (ADP) was assessed with the turbidimetric method using a Chronolog Lumi aggregometer with Aggro-Link Software.17,18 Residual platelet aggregation was measured as maximum aggregation and final aggregation. The latter was assessed 5 min after addition of the agonist. Low responders were defined by a final aggregation in the upper tertile of the collective.

Follow-up
At 3 months, the incidence of ST was assessed by review of patient’ charts on hospital re-admission and review of angiograms in case of interventional treatment of ST. Early ST was defined in a time window of 30 days and LAT if occurring >30 days after index PCI. Persons involved in review of patient’s records and interpretation of angiograms were blinded on behalf of results of platelet aggregation.

Statistical analysis
The primary endpoint of the study was the incidence of ST within 3-month follow-up. The primary objective was to investigate the difference between post-interventional platelet aggregation in patients with subsequent ST compared with patients without ST. Sample size estimation to calculate minimum patient number for follow-up was performed after initiation of patient’s recruitment, but before follow-up was completed and final data analysis concerning the primary endpoint was possible. On the basis of an assumed rate of early ST and LAT of each 1.5% within 30 days and 30 days to 3 months, respectively, and a statistical power of 95% at one-sided 5.0% significance level, we estimate a sample size of 1005 patients to detect a minimal increase of PA of 13% in patients with 3-month events. Secondary objective was to compare association of RPA with events between patients with early and 3-month LAT. Continuous data are expressed as mean ± standard deviation, not normally distributed data are presented as median and interquartile range. Dichotomous variables are shown as number (%) and the equality of distribution between subgroups was analysed by χ² test. Cox proportional hazards survival regression was used to investigate predictors of ST with inclusion of relevant clinical factors, in detail left ventricular (LV) dysfunction, age, gender, ACSs, diabetes mellitus, smoking, renal function assessed by MDRD formula, stent type, and either maximum or final platelet aggregation as continuous variable. Variables were selected by the enter method. Time to first event analysis was calculated by the Kaplan–Meier method, and survival
across different groups of tertiles of final RPA was compared with the log-rank test. The proportional hazard assumption was assessed by a plot of log(−log(survival function)) vs. time. All tests were two-sided, and a level of 5% was considered to indicate statistical significance. Statistical analysis was performed with SPSS, Version 15 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

A consecutive cohort of 1019 patients could be followed up for the occurrence of ST. Baseline characteristics for patients stratified to those developing ST and those who stayed free from ST within follow-up are shown in Table 1. Around one-third of total patients suffered from type II diabetes. Five hundred and five patients (49.6%) of total patients were initially admitted with ACSs, 514 patients with stable angina (50.4%) underwent elective coronary intervention; and 72.7% of included patients underwent coronary stenting deploying BMS and 27.3% DES. All patients were prescribed clopidogrel (75 mg/day) and aspirin (100 mg/day) treatment for at least 3 months after index PCI. A minority of patients (<10%) received peri-procedural GPlib–IIa inhibitor treatment (abciximab). In these patients, platelet function testing was performed 5 days after coronary intervention/clopidogrel loading dose. Tertiles of final RPA were divided by equal distribution of cases. Thus, the border of the upper tertile was defined by a value >42.5%. There was an overall incidence of 29 cases of ST (2.8% of total). Fifteen patients (1.5% of total) suffered from acute and sub-acute (= early) ST. Of these patients, five had angiographic confirmation of ST, in 10 patients ST was probable according to ARC criteria. Fourteen patients (1.4%) suffered from LAT (six definite, four probable, four possible). Median time of occurrence was 12 days for early ST and 57 days for LAT. Patients with ST had a significantly higher RPA than patients without ST (Figure 2). When analysing the results separately for

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients without ST</th>
<th>Patients with early ST</th>
<th>Patients with 3 months LAT</th>
<th>P-value (early ST/LAT vs. no ST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, m/f (%)</td>
<td>733/257 (74.0/26.0)</td>
<td>13/2 (86.7/13.3)</td>
<td>10/4 (71.4/28.6)</td>
<td>0.27/0.83</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.7 ± 10.5</td>
<td>71.7 ± 11.0</td>
<td>72.6 ± 9.0</td>
<td>0.14/0.08</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.6 ± 4.8</td>
<td>27.5 ± 5.0</td>
<td>26.4 ± 3.2</td>
<td>0.99/0.46</td>
</tr>
<tr>
<td>Acute coronary syndrome (%)</td>
<td>487 (49.2)</td>
<td>9 (60.0)</td>
<td>9 (64.3)</td>
<td>0.41/0.26</td>
</tr>
<tr>
<td>Left ventricular function (%)</td>
<td>218 (22.1)</td>
<td>1 (7.1)</td>
<td>3 (21.4)</td>
<td>&lt;0.001/0.09</td>
</tr>
<tr>
<td>EF 45–55</td>
<td>160 (16.2)</td>
<td>1 (7.1)</td>
<td>5 (35.7)</td>
<td>0.3/0.45</td>
</tr>
<tr>
<td>&lt;35</td>
<td>90 (9.1)</td>
<td>8 (57.1)</td>
<td>3 (21.4)</td>
<td>0.005/0.17</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>802 (81.2)</td>
<td>7 (50.0)</td>
<td>10 (71.4)</td>
<td>0.003/0.36</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>593 (60.0)</td>
<td>7 (46.7)</td>
<td>7 (50.0)</td>
<td>0.3/0.45</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>320 (32.4)</td>
<td>10 (66.7)</td>
<td>7 (50.0)</td>
<td>0.005/0.17</td>
</tr>
<tr>
<td>Insulin dependent (%)</td>
<td>116 (15.3)</td>
<td>6 (60.0)</td>
<td>2 (18.2)</td>
<td>&lt;0.001/0.9</td>
</tr>
<tr>
<td>Smoking history</td>
<td>377 (38.1)</td>
<td>5 (35.7)</td>
<td>4 (28.6)</td>
<td>0.85/0.47</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>752 (76.1)</td>
<td>11 (73.3)</td>
<td>12 (85.7)</td>
<td>0.8/0.4</td>
</tr>
<tr>
<td>Glomerular filtration rate (MDRD; mL/min/1.73 m²)</td>
<td>59.6 ± 20.1</td>
<td>36.6 ± 22.8</td>
<td>53.8 ± 27.0</td>
<td>&lt;0.001/0.44</td>
</tr>
<tr>
<td>Renal failure (MDRD &lt; 40 mL/min/1.73 m²)</td>
<td>144 (15.8)</td>
<td>11 (73.3)</td>
<td>5 (35.7)</td>
<td>&lt;0.001/0.04</td>
</tr>
<tr>
<td>Medication</td>
<td>868 (87.9)</td>
<td>9 (60.0)</td>
<td>8 (57.1)</td>
<td>&lt;0.01/0.01</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>799 (81.5)</td>
<td>7 (53.8)</td>
<td>11 (78.6)</td>
<td>0.01/0.78</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>128 (13.1)</td>
<td>2 (15.4)</td>
<td>0 (0)</td>
<td>0.34/0.15</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>910 (93.0)</td>
<td>8 (61.5)</td>
<td>10 (71.4)</td>
<td>&lt;0.001/0.01</td>
</tr>
<tr>
<td>BMS/DES/both (%)</td>
<td>716 (72.3/274 (27.7)</td>
<td>13 (86.7)/2 (13.3)</td>
<td>12 (85.7)/2 (14.3)</td>
<td>0.22/0.26</td>
</tr>
<tr>
<td>No. of stents</td>
<td>1.47 ± 0.79</td>
<td>1.4 ± 0.51</td>
<td>1.5 ± 0.94</td>
<td>0.72/0.9</td>
</tr>
<tr>
<td>Drug coating (%)</td>
<td>39 (14.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.92/0.6</td>
</tr>
<tr>
<td>Sirolimus (%)</td>
<td>92 (33.7)</td>
<td>1 (50.0)</td>
<td>0 (0)</td>
<td>0.01/0.78</td>
</tr>
<tr>
<td>Zotarolimus (%)</td>
<td>142 (52.0)</td>
<td>1 (50.0)</td>
<td>2 (100)</td>
<td>0.92/0.6</td>
</tr>
</tbody>
</table>

LD, loading dose; EF, ejection fraction; BMS, bare-metal stents; DES, drug-eluting stents.

*Mean ± standard deviation.

**Median (interquartile range).
patients with early ST and LAT, this difference was rather based on the higher degree of platelet aggregation in patients with early ST (median of final aggregation compared with patients without ST 51.9% vs. 31.9%; \( P = 0.007 \) and for maximum platelet aggregation 53 vs. 40.6%; \( P = 0.009 \)). In contrast, no significant difference was observed between patients with LAT compared with patients without ST (final PA 26.9% vs. 31.9%; \( P = 0.71 \) and maximum PA 46.6% vs. 40.6%; \( P = 0.47 \)). Low responders as defined by final RPA in the upper tertile were found more frequently in patients with subsequent early ST compared with event-free patients (60.0% vs. 40.0%; \( P = 0.02 \)).

Univariate influence of baseline characteristics

Patients who developed early ST, had more frequently diabetes (\( P = 0.01 \)) and renal failure (\( P < 0.001 \)), had less frequently arterial hypertension (\( P < 0.01 \)), were less often treated with ACE-inhibitors (\( P = 0.01 \)), beta-blockers (\( P < 0.001 \)), and cholesterol-synthesis enzyme-inhibitors (statins) (\( P < 0.01 \)), and showed a poorer LV function (\( P < 0.001 \)) compared with patients without ST. Neither deployment of different type of stents (BMS/DES) nor total number of implanted stents nor subgroups of various drug coating did show a relevant different distribution in patients with ST compared with patients without (Table 1).

Results of initial coronary quantitative angiography and procedural data of patients with subsequent ST are specified in Table 2.

Incidence of cardiovascular events

Within 3-month follow-up, a total of 60 cardiovascular events (5.9%) including cardiovascular death, myocardial infarction, and ischaemic stroke occurred in the study population. Patients defined as low-responders to clopidogrel showed a higher incidence of combined cardiovascular events and 3-month ST compared with patients with adequate response (Table 3).

Multivariate and survival analysis

After inclusion of relevant prognostic variables in Cox proportional hazard survival regression, platelet aggregation (final and maximum aggregation) was associated with the incidence of 3-month ST [final PA hazard ratio (HR) 1.0, 95% confidence interval (CI) 1.0–1.04, maximum PA 1.03, 95% CI 1.0–1.05].
In sub-analysis, this association was mainly based on the significant influence of platelet aggregation on the incidence of early ST (HR 1.05, 95% CI 1.01–1.08; \( P = 0.006 \) and HR 1.05, 95% CI 1.02–1.09, \( P = 0.005 \), respectively) besides severe LV dysfunction (EF \( < 35 \)), diabetes mellitus, and renal failure. Late stent thrombosis was not influenced by post-interventional platelet aggregation in multivariable regression (Table 3). Thus, RPA was identified as an independent predictor for early ST and the hazard exponentially correlated with increasing absolute aggregation values (Figure 3). In Kaplan–Meier analysis, patients with a final aggregation in the upper tertile (e.g. low responders) showed a significant decreased event-free cumulative survival from 3-month ST compared with patients with values of lower tertiles (log-rank 0.03; Figure 4A). There was a significant relationship between tertiles of RPA with the incidence of early ST (log-rank 0.02; Figure 4B) but not with the incidence of 3-month LAT (Figure 4C and Table 4).

### Discussion

In the past, different clinical entities including those identified in the present study were considered to be associated with the development of thrombotic occlusions of BMS and DES under dual antiplatelet therapy with aspirin and thienopyridines. Among those influencing factors premature thienopyridine discontinuation was one of the strongest predictors of ST. Thus, it is suggesting that effective platelet inhibition plays a pivotal role for developing ST. Recently, a high variability of response to thienopyridine treatment has been described in a number of reports.

In an initial study investigating the role of measured platelet aggregation in clopidogrel and ASA-treated stent patients, early ST exclusively occurred in the group presenting a very low platelet inhibition (e.g. non-responders to clopidogrel). Further case–control studies demonstrated higher platelet reactivity in patients with experienced ST.

In the current registry study, a total rate of ST of 2.8% was observed which is in agreement with previous observational studies which applied the ARC criteria and in which a similar risk collective including patients with ACS was described. Furthermore, the rate of 1.07% of definite ST was low when compared with recent sub-analysis of the TRITON-TIMI-38 trial in which a rate of 2.03% was observed in the clopidogrel arm. As primary results, patients with 3-month ST showed a significantly higher post-interventional platelet aggregation measured by final and maximum aggregation and low responders classified by final RPA in the upper tertile of the collective were more often found in patients with subsequent ST.

As further result, the occurrence of early ST (\( \leq 30 \) days) but not LAT (30–90 days after PCI) was associated with post-interventional platelet aggregation in this study. Although the sample size was not initially calculated for the analysis of subgroups of patients with early ST and LAT, the results still suggest that post-interventional platelet aggregation might not be associated with later onset of ST and that other mechanisms might play a major role for development of LAT.

Buonamici et al. reported a significant association between an increased post-treatment platelet aggregation (\( \geq 70\% \) ADP-induced aggregation) and the incidence of LAT within 6 months, but not with the incidence of early ST in 804 patients undergoing
DES implantation. However, the setting in the present study was different. First, we investigated a heterogeneous cohort of patients receiving BMS or DES. Second, platelet aggregation was studied as a continuous variable not used as cut-off value to define low responders as in the Re-Close trial. On the basis of the current data, we are convinced that post-interventional measured platelet function rather marks the short-term atherothrombotic burden than the long-term risk for developing thrombotic stent occlusion. Response to antiplatelet therapy especially clopidogrel is a highly variable phenomenon and measured platelet aggregation under dual antiplatelet therapy can significantly vary over the course of time. Thus, Gurbel et al.\textsuperscript{22} initially found that response rates to clopidogrel increased when platelet function measurement was performed at later time points up to 30 days after first administration of clopidogrel loading dose. This time-dependent relationship could be confirmed by a meta-analysis of platelet function studies in clopidogrel-treated PCI patients.\textsuperscript{25} Therefore, it is hard to determine whether one single peri-interventional platelet function value can influence the incidence of LAT, as it cannot reflect the real platelet activity degree at later time points. In previous studies, like in the current study, patients were not re-admitted for repeated platelet function testing after 30 days. Such a regimen would be necessary to correlate platelet aggregation under chronic clopidogrel therapy with the incidence of LAT.

We are aware that the present study bares some limitations due to its design. First, this is a non-randomized, single-centre study and the effects might have been over-estimated due to low event rate of ST. Secondly, the follow-up rate of patients initially enrolled for platelet function analysis was relatively low. Additionally, we did only assess one single platelet function parameter and we did not measure the active metabolite of clopidogrel in the studied patients. Finally, other mechanisms which were not considered in this analysis might have played a role for the incidence of ST. Adherence to antiplatelet might represent an important factor, however, we did not systematically screen for drug compliance in our study.

**Figure 4** Kaplan–Meier curves showing the cumulative event-free survival from composite of 3-month stent thrombosis (A), early (B) and late stent thrombosis (C) stratified according to tertiles of post-interventional platelet aggregation (final aggregation).
clinical predictors for ST, platelet hyper-reactivity might play a key role as mediator between classical atherothrombotic risk factors and the risk of ST. Besides these non-genetic factors, genetic polymorphic variants that are known to affect efficacy of antiplatelet therapy might also play a considerable role for the risk to develop ST. Hence, a number of recent studies demonstrate an association of the CYP450 2C19*2 haplotype, platelet reactivity under clopidogrel treatment and increased rate of ST.\textsuperscript{29–31} The clinical relevance of platelet pharmacogenomics for the risk of ST remains to be further elucidated.

Conclusions

In conclusion, post-interventional platelet aggregation after 600 mg clopidogrel loading dose correlates with the incidence 3-month ST, especially early ST (≤30 days after PCI). However, on the basis of the current results, it does not represent a reliable marker for prediction of LAT. Further studies are needed to evaluate the influence of ‘on-chronic-treatment’ platelet function for the development of LAT. Additionally, optimization of post-interventional platelet inhibition should be achieved in patients presenting with a high RPA to reduce the incidence of early ST.

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