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Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation

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Aims The aim of this study was to determine whether platelet reactivity on clopidogrel therapy, as measured by a point-of-care platelet function assay, is associated with thrombotic events after percutaneous coronary intervention (PCI) with drug-eluting stents (DESs).

Methods and results Platelet reactivity on clopidogrel (post-treatment reactivity) was measured with the VerifyNow P2Y12 assay (Accumetrics Inc., San Diego, CA, USA) in 380 patients undergoing PCI with sirolimus-eluting stents. Receiver-operating characteristic curve analysis was used to derive the optimal cut-off value for post-treatment reactivity in predicting 6 month out-of-hospital cardiovascular (CV) death, non-fatal MI, or stent thrombosis. The mean post-treatment reactivity was 184 $\pm$ 85 PRU (P2Y12 reaction units). The optimal cut-off for the combined endpoint was a post-treatment reactivity $\geq$235 PRU [area under the curve 0.711 (95% confidence interval 0.529–0.893), $P = 0.03$], which was similar to the threshold of the upper tertile (231 PRU). Patients with post-treatment reactivity greater than the cut-off value had significantly higher rates of CV death (2.8 vs. 0%, $P = 0.04$), stent thrombosis (4.6 vs. 0%, $P = 0.004$), and the combined endpoint (6.5 vs. 1.0%, $P = 0.008$).

Conclusion High post-treatment platelet reactivity measured with a point-of-care platelet function assay is associated with post-discharge events after PCI with DES, including stent thrombosis. Investigation of alternative clopidogrel dosing regimens to reduce ischaemic events in high-risk patients identified by this assay is warranted.

Keywords Platelets • Thienopyridine • Stent • Clopidogrel • Thrombosis

The inhibitory response to clopidogrel varies considerably among individuals.[1–7] An impaired response to therapy measured by ADP-induced platelet reactivity on light transmittance aggregometry (LTA) has been associated with adverse outcomes after percutaneous coronary intervention (PCI).[8–14] Case–control studies have demonstrated that despite clopidogrel therapy, patients with stent thrombosis have increased ADP-induced platelet reactivity on LTA and incomplete P2Y12 receptor inhibition by vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay when measured after the thrombotic event.[15,16] However, it has been proposed that the elevated platelet reactivity observed in these case–control studies may not be an aetiological factor underlying stent thrombosis, but may instead be a manifestation of the acute presentation of the thrombotic event itself.[17] Evidence for a mechanistic relationship between an impaired clopidogrel response and stent thrombosis requires

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the prospective measurement of platelet reactivity prior to the thrombotic event.

LTA and the VASP phosphorylation assay are labour intensive, require special training to perform, and are not routinely available. They are thus not a practical approach to risk-stratifying most patients undergoing PCI. The effect of clopidogrel on platelet reactivity can be assessed at the point-of-care with the VerifyNow P2Y12 assay (Accumetrics Inc.).[4,18–21] The results of this assay have been shown to be well correlated with ADP-induced platelet aggregation by LTA.[19,22,23] However, little data exist regarding the distribution of post-clopidogrel platelet reactivity with this point-of-care assay in patients undergoing PCI, nor are there data regarding the relationship between the results of this assay and post-discharge events. The objective of this study was to determine whether platelet reactivity on clopidogrel therapy as assessed by the VerifyNow P2Y12 assay is associated with post-discharge outcomes, including stent thrombosis, after drug-eluting stent (DES) implantation.

Methods

This study complied with the Declaration of Helsinki and was approved by the Scripps Clinic institutional review board. Informed consent was obtained from all patients prior to the index procedure.

Patient eligibility

Patients were eligible for enrolment if they had at least one lesion $\geq$50% diameter stenosis requiring PCI and had no known allergy to aspirin, clopidogrel, or a sirolimus-eluting stent (SES). Patients on clopidogrel therapy or who were clopidogrel naïve were eligible for inclusion. However, to ensure that those patients on clopidogrel therapy prior to the procedure were optimally and consistently treated at the time of platelet function assessment, only those patients who had received a loading dose of 600 mg at least 12 h prior to the procedure or were on a maintenance dose of clopidogrel 75 mg/day for more than 5 days were included. Patients receiving peri-procedural glycoprotein inhibitors were not enrolled due to interference with the P2Y12 assay. Screened patients were part of a prospective 'real-world' registry of the on- and off-label use of SESs made possible through an investigational device exemption obtained from the Federal Drug Administration.

Timing of blood sampling

Whole blood was obtained at the time of catheterization from the side-port of the arterial sheath prior to anticoagulant therapy in patients on previous clopidogrel therapy and by phlebotomy 12 h after PCI and a 600 mg clopidogrel loading dose in patients who were clopidogrel naïve. Blood was placed into 1.8 mL-draw plastic Vacuette® tubes (Greiner, Monroe, NC, USA) containing 3.2% sodium citrate. All tubes containing any anticoagulant other than sodium citrate (e.g. EDTA for platelet counts) were drawn subsequent to the tubes containing sodium citrate in order to avoid cross-contamination of samples by an anticoagulant.

Point-of-care platelet reactivity assays

The inhibitory effect of clopidogrel was measured using the VerifyNow P2Y12 assay (Accumetrics Inc.).[20] VerifyNow P2Y12 is a rapid platelet-function cartridge-based assay designed to measure directly the effects of drugs on the P2Y12 receptor. The assay contains 20 μmol ADP and 22 nmol prostaglandin E1 to reduce the activation contribution from ADP binding to P2Y1 receptors. Fibrinogen-coated microparticles are used in the VerifyNow P2Y12 cartridge to bind to available platelet receptors. The VerifyNow instrument measures platelet-induced aggregation as an increase in light transmittance and utilizes a proprietary algorithm to report values in P2Y12 reaction units (PRU). With this assay, a higher PRU reflects greater ADP-mediated platelet reactivity. The mean coefficient of variation of test precision has been reported to be 3.2% in patients with coronary artery disease.[23]

Stent procedure and pharmacological approach

Interventional strategy was at the discretion of the operator. Either intra-procedural unfractionated heparin (with a goal-activated clotting time $>$250 s) or bivalirudin was used during the procedure. All patients received SES, and they received aspirin 325 mg on the day of the procedure regardless of previous aspirin use. Patients not previously on clopidogrel received a 600 mg loading dose at the conclusion of the procedure before leaving the catheterization laboratory. Patients already receiving clopidogrel therapy (as noted in the inclusion/exclusion criteria earlier) did not receive an additional loading dose. Patients were instructed to take aspirin 325 mg indefinitely and clopidogrel 75 mg daily for a minimum of 3 months post-procedure.

Data collection and follow-up

All data were prospectively collected and entered into a central database. Clinical follow-up information, including clopidogrel status, was obtained by contacting all patients at 30 days and 6 months post-procedure, and source documents of potential events were obtained. If clopidogrel had been discontinued, the date of discontinuation was captured.

Definitions and endpoints

Post-treatment platelet reactivity was defined as the PRU on clopidogrel (12 h after PCI and a 600 mg loading dose in patients not previously on clopidogrel, or at the time of catheterization prior to PCI in patients already on clopidogrel). Technical success was defined as a final diameter stenosis $\leq$30% and thrombolysis in myocardial infarction (TIMI) flow grade 3. Clinical endpoints measured were cardiovascular (CV) death, non-fatal myocardial infarction (MI), and stent thrombosis. MI over follow-up was defined as any typical rise and fall of cardiac biomarkers in the setting of clinical signs or symptoms consistent with cardiac ischaemia, following the American College of Cardiology definition.[24] The Academic Research Consortium definitions were used for stent thrombosis (definite, probable, possible).[25] Subacute stent thrombosis was defined as stent thrombosis occurring after discharge to 30 day follow-up, and late-stent thrombosis was defined as stent thrombosis occurring between 30 day and 6 month follow-ups. An independent clinical events committee that was unaware of the results of the platelet function assays adjudicated all clinical endpoints using source documentation.

Statistical methods

The computer-based analysis program SPSS (Statistical Package for the Social Sciences, 12.0 for PC, SPSS Inc., Chicago, IL, USA) was used for statistical calculations. Randomized studies of stent implantation with and without thienopyridine therapy[26–30] have demonstrated a 75–85% relative reduction in cardiac events in patients treated with dual antiplatelet therapy compared with aspirin alone. We estimated a sample size of 380 patients would provide 70% power to detect an 80% relative difference in the rate of events using a one-sided

Fisher's exact test, assuming an event rate of 1.0% in responders and a clopidogrel non-responsiveness rate of one-third.[10] Comparison of continuous variables was performed using Student's *t*-test. The χ^2 test was used to detect differences in categorical variables, and a Fisher's exact test was used when any expected cell count was <5 for a 2 by 2 table. The Kolmogorov–Smirnov test was used to test for normality. A receiver-operating characteristic (ROC) curve analysis was used to determine the ability of the VerifyNow P2Y12 assay to distinguish between patients with and without post-discharge events after PCI. The optimal cut-off point was calculated by determining the post-treatment PRU that provided the greatest sum of sensitivity and specificity. Bootstrap validation was performed using R software. Survival curves were generated using the Kaplan–Meier method, and the difference between curves was assessed by log-rank test. A *P*-value <0.05 was considered significant.

Results

Between July 2005 and August 2006, a total of 380 patients were enrolled in this study (*Figure 1*). Baseline clinical, lesion, and procedural characteristics are shown in *Tables 1* and *2*. Overall, the average age was 68 $\pm$ 11 years, 76.8% were male, 14.2% had renal insufficiency, 28.9% were diabetic, and 44.5% were on clopidogrel therapy at the time of PCI. The procedural indication was stable angina or ischaemia in most patients (93.9%). An average of 1.7 $\pm$ 0.8 lesions per patient were treated. The mean lesion length was 20.0 $\pm$ 13.1 mm, and a mean of 1.4 $\pm$ 0.7 SESs were implanted per lesion. Technical success was achieved in all patients.

Platelet reactivity

Post-treatment PRU was normally distributed (one sample Kolmogorov–Smirnov test, $P = 0.2$). The mean post-treatment reactivity was 184 $\pm$ 85 PRU. There was no difference in post-treatment reactivity between patients on previous clopidogrel therapy and clopidogrel-naïve patients receiving a loading dose (186 $\pm$ 73 vs. 183 $\pm$ 94 PRU, $P = 0.7$), nor was there a difference in reactivity between patients receiving intra-procedural heparin or bivalirudin (184 $\pm$ 86 vs. 184 $\pm$ 84 PRU, $P = 1.0$).

Out-of-hospital clinical outcomes at 6 months

Clinical follow-up at 6 months was complete in 98.9% of patients. After discharge, there were three CV deaths (0.8%), two of which were sudden (84 and 186 days post-procedure). There was one non-CV death (due to sepsis) 32 days post-procedure. Non-fatal MI occurred in five patients (1.3%). There were six episodes of stent thrombosis (1.6%): three were definite subacute, one was

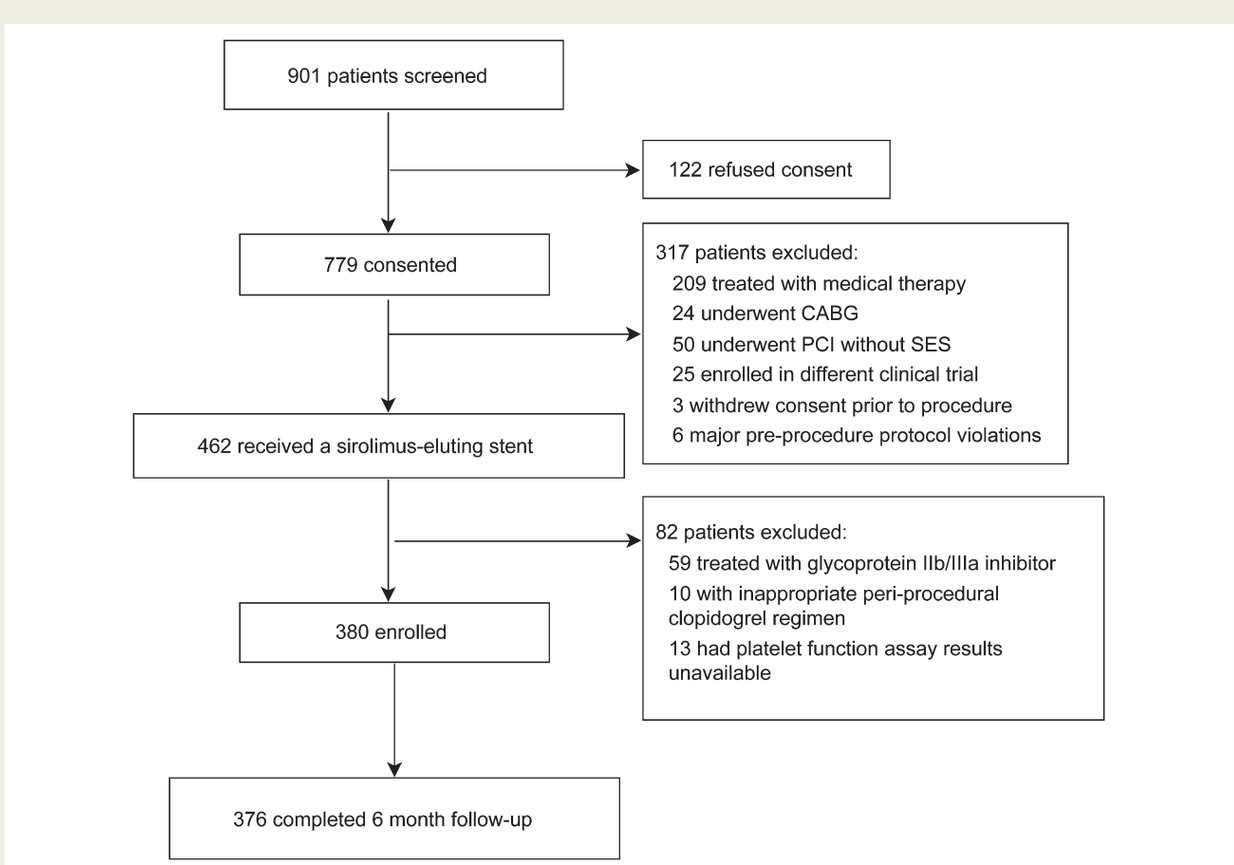

Figure 1 Study flow diagram. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SES, sirolimus-eluting stent; gpIIbIIIa, glycoprotein IIb/IIIa inhibitor.

Table 1 Baseline clinical characteristics of the study population

Characteristic	Overall group (n = 380)	Lower reactivity[a] (n = 258)	High reactivity[a] (n = 122)	P-value
Age, years	68 ± 11	67 ± 11	70 ± 10	0.01
Male gender, n (%)	292 (76.8)	201 (77.9)	91 (74.6)	0.5
Diabetes mellitus, n (%)	110 (28.9)	59 (22.9)	51 (41.8)	<0.001
Previous MI, n (%)	120 (31.6)	77 (29.8)	43 (35.2)	0.3
History of hypertension, n (%)	335 (88.2)	225 (87.2)	110 (90.2)	0.4
History of congestive heart failure, n (%)	36 (9.5)	21 (8.3)	15 (12.0)	0.2
LVEF < 40%, n (%)	34 (9.5)	22 (9.2)	14 (10.3)	0.7
Renal insufficiency (creatinine > 1.5), n (%)	54 (14.2)	31 (12.0)	23 (18.9)	0.08
Current smoker, n (%)	34 (8.9)	25 (9.7)	9 (7.4)	0.5
Body mass index, kg/m^2	29.6 ± 6.9	29.3 ± 6.6	30.2 ± 7.6	0.2
Concomitant medications, n (%)				
ACE-inhibitor	140 (36.8)	91 (35.3)	49 (40.2)	0.4
Beta-blocker	241 (63.4)	151 (58.5)	90 (73.8)	0.004
Atorvastatin	135 (35.5)	95 (36.8)	40 (32.8)	0.4
Aspirin	328 (86.3)	223 (86.4)	105 (86.1)	1.0
Stable angina/ischaemia	356 (93.7)	242 (93.8)	114 (93.4)	1.0

[a]High reactivity defined as post-treatment reactivity above the optimal cut-off point by ROC curve analysis (PRU ≥ 235) and lower reactivity below this threshold.

Table 2 Lesion and procedural characteristics

Characteristic	Overall group (n = 380)	Lower reactivity (n = 258)	Higher reactivity (n = 122)	P-value
Number of lesions per patient	1.7 ± 0.8	1.7 ± 0.8	1.5 ± 0.7	0.01
Number of vessels per patient	1.4 ± 0.5	1.4 ± 0.6	1.3 ± 0.5	0.1
Lesion type, n (%)				
AHA/ACC type B2/C	299 (78.7)	205 (79.2)	94 (77.7)	0.7
Bifurcation	92 (24.2)	62 (24.0)	30 (24.8)	0.9
Saphenous vein graft	31 (8.2)	18 (7.0)	13 (10.7)	0.2
Chronic total occlusion	26 (6.8)	16 (6.2)	10 (8.2)	0.5
Thrombus-containing lesion	4 (1.1)	3 (1.2)	1 (0.8)	1.0
Number of stents per lesion	1.4 ± 0.7	1.4 ± 0.8	1.4 ± 0.7	0.3
Stent diameter, mm	2.86 ± 0.36	2.84 ± 0.35	2.91 ± 0.38	0.004
Stent length per lesion, mm	30.3 ± 20.2	30.6 ± 20.9	29.6 ± 18.5	0.5
Maximum balloon inflation, atm	16.6 ± 2.2	16.5 ± 2.3	16.7 ± 2.0	0.3
IVUS performed, n (%)	150 (39.5)	105 (40.5)	45 (37.2)	0.5
Bivalirudin used, n (%)	152 (40.0)	108 (41.9)	44 (36.1)	0.3

definite late, and two were possible late-stent thromboses. The combined endpoint of CV death, non-fatal MI, or stent thrombosis occurred in 10 patients (2.6%). None of these patients had suboptimal angiographic results or angiographic evidence of residual dissection during the index procedure. One patient who suffered a subacute stent thrombosis 8 days post-PCI did not take clopidogrel after discharge (i.e. no clopidogrel beyond 24 h following the procedure). All other events occurred while patients were taking dual-antiplatelet therapy. The post-treatment reactivity of the patients who had stent thrombosis while taking antiplatelet therapy were 283, 292, 236, 244, and 271 PRU.

A total of 373 patients (98.2%) were on maintenance clopidogrel therapy at 3 months post-procedure, and 317 patients (83.4%) were on maintenance therapy at 6 months follow-up. *Table 3* demonstrates the event rates in patients who were receiving clopidogrel therapy through 6 month follow-up, and *Table 4* demonstrates the 6 month event rates in patients completing a minimum 3 month course of clopidogrel therapy. Patients with adverse events had significantly higher platelet reactivity than those who did not (242 vs. 186 PRU, one-tailed t-test $P = 0.03$).

Table 3 Six month out-of-hospital outcomes in patients on clopidogrel therapy through 6 month follow-up

	Overall (n = 317)	Lower reactivity (n = 209)	High reactivity (n = 108)	P-value[a]
CV death, n (%)	3 (0.9)	0	3 (2.8)	0.04
Non-fatal MI, n (%)	4 (1.3)	2 (1.0)	2 (1.9)	0.6
Stent thrombosis, n (%)	5 (1.6)	0	5 (4.6)	0.004
CV death, non-fatal MI, stent thrombosis, n (%)	9 (2.8)	2 (1.0)	7 (6.5)	0.008

[a]Comparison between groups with high and lower reactivity (*Table 1*).

Table 4 Six month out-of-hospital outcomes in patients on clopidogrel therapy for a minimum of 3 months post-procedure

	Overall (n = 373)	Lower reactivity (n = 252)	High reactivity (n = 121)	P-value[a]
CV death, n (%)	3 (0.8)	0	3 (2.5)	0.03
Non-fatal MI, n (%)	4 (1.1)	2 (0.8)	2 (1.7)	0.6
Stent thrombosis, n (%)	5 (1.3)	0	5 (4.1)	0.003
CV death, non-fatal MI, stent thrombosis, n (%)	9 (2.4)	2 (0.8)	7 (5.8)	0.006

[a]Comparison between groups with high and lower reactivity (*Table 1*).

Receiver-operating characteristic curve analysis

ROC curve analysis of post-treatment platelet reactivity in the patients who maintained clopidogrel therapy through 6 month follow-up demonstrated that post-treatment PRU was able to distinguish between patients with and without subsequent events [area under the curve 0.711 [95% confidence interval 0.529–0.893), $P = 0.03$] (*Figure 2*). A PRU $\geq$ 235 was identified as the optimal cut-off value to predict post-discharge 6 month outcomes, providing a sensitivity of 78% (95% CI 46–94), specificity of 68% (95% CI 67–69), and a negative predictive value of 99% (95% CI 98–100). By bootstrap analysis using 10 000 replicates, the bounds for the 95% confidence interval of the optimal cut-off was 174–291 PRU. The optimal cut-off was 235 PRU (95% CI by bootstrapping 174–291 PRU) in the cohort of patients who completed at least 3 months of clopidogrel [area under the curve 0.720 (95% confidence interval 0.540–0.900), $P = 0.02$; sensitivity 78% (95% CI 46–94), specificity 70% (95% CI 69–70)]. This cut-off was similar to the boundary of the upper tertile of post-treatment reactivity (>231 PRU). Patients with post-treatment reactivity above the optimal cut-off value were considered to have 'high' post-treatment reactivity. Patients with high post-treatment reactivity were significantly older, more likely to be diabetic, tended to have renal insufficiency, and were more likely to be taking a beta-blocker than patients with lower post-treatment reactivity (*Table 1*). Patients with high post-treatment reactivity also had fewer lesions per patient and had on average a larger diameter stent implanted (*Table 2*).

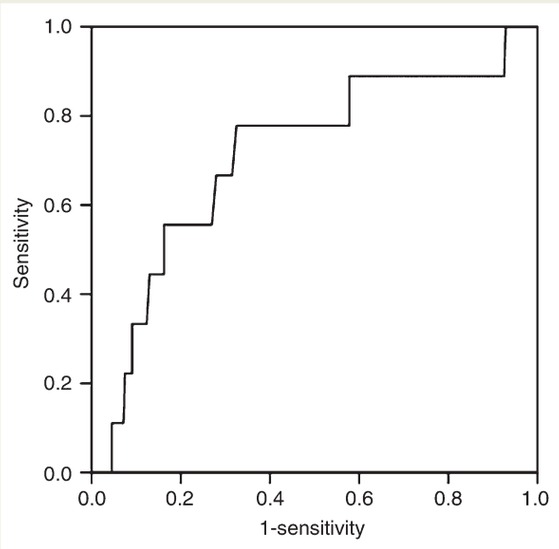

Figure 2 Receiver-operating characteristic curve for the VerifyNow P2Y12 assay. An area under the curve of 0.711 was observed ($P = 0.03$).

Six month outcomes in patients stratified by post-treatment reactivity

Patients with high post-treatment reactivity had significantly greater rates of CV mortality (2.8 vs. 0%, $P = 0.04$), any stent thrombosis (4.6 vs. 0%, $P = 0.004$), definite or probable stent

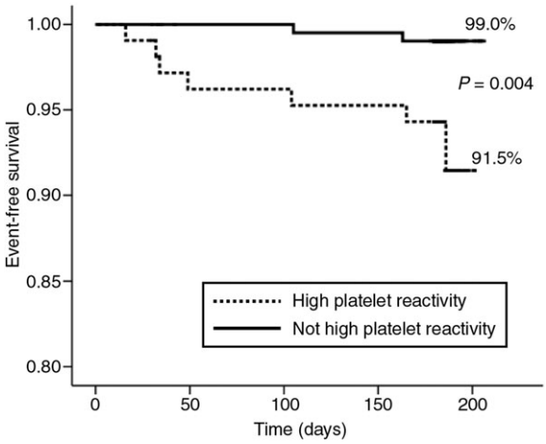

Figure 3 Survival free of out-of-hospital cardiovascular death, non-fatal myocardial infarction, and stent thrombosis in patients with and without high post-treatment reactivity.

thrombosis (2.8 vs. 0%, $P = 0.04$), and the combined endpoint of CV death, non-fatal MI, or stent thrombosis (6.5 vs. 1.0%, $P = 0.008$) (*Tables 3* and *4*). The difference in outcomes was still significant when considering all-cause death, non-fatal MI, or stent thrombosis (6.5 vs. 1.4%, $P = 0.035$). The event-free survival curves are shown in *Figure 3*. The survival rate free from the combined endpoint of CV death, non-fatal MI, or stent thrombosis was 91.4% in patients with high post-treatment reactivity and 99.0% in patients without high post-treatment reactivity ($P = 0.004$).

Discussion

The major finding of this study is that platelet reactivity on clopidogrel therapy as measured with a point-of-care assay during the index hospitalization appears to be predictive of out-of-hospital outcomes after DES implantation, including stent thrombosis.

The wide inter-individual variability in the inhibitory effect of clopidogrel has been well described.[1,4,31] We performed an ROC analysis on a cohort of patients undergoing PCI with DES to (i) determine the ability of this point-of-care assay to distinguish between patients with and without subsequent post-discharge events, and to (ii) identify a clinically based threshold to determine the relative rates of events among patients with high and lower reactivity. We observed that this point-of-care assay had a modestly strong predictive value with an area under the curve of 0.711. The optimal cut-off for the identification of high-risk patients was a PRU of $\geq$235; all CV deaths and stent thromboses occurred in patients with reactivity above this threshold. The definitions of clopidogrel non-responsiveness have been relatively arbitrary in previous studies using LTA to examine the association between clopidogrel response variability and ischaemic outcome. Many investigators have used a population-based threshold (e.g. upper quartile of reactivity[14,32]), and others an absolute threshold (e.g. ADP-induced aggregation $>$50%[33] or $>$70%[12,13,34]). We used ROC analysis to define the level of post-treatment reactivity that provided the optimal cut-off for a clinically driven threshold of non-responsiveness. This cut-off point was similar to the boundary of the upper tertile of PRU in the population studied, consistent with previous observations that high post-clopidogrel reactivity is associated with subsequent CV events. The bootstrap estimation of the 95% confidence interval around the optimal cut-off was fairly wide, likely due to the low number of events that occurred in this study. Notably, however, the low range of the 95% confidence interval was still above the mean PRU in the population, which is consistent with previous findings that patients with residual platelet reactivity above the median around the time of PCI are at higher risk for subsequent events.[9] Our threshold for non-responsiveness using ROC curve analysis must be validated in a large, prospective population.

We demonstrate in this observational study a significant relationship between stent thrombosis and the presence of high post-clopidogrel platelet reactivity prior to the thrombotic event. The overall rate of subacute (0.8%) and late-stent thrombosis (0.8%) in our study is consistent with previous reports.[35–37] This is the largest study to date using a point-of-care assay to examine the relationship between the inter-individual variability in the inhibitory response to clopidogrel and out-of-hospital clinical outcomes after DES implantation. Previous case–control studies using VASP[15,16] and LTA[15] that measured platelet activity after the event found that patients with stent thrombosis have incomplete P2Y12 receptor inhibition and higher post-treatment platelet reactivity. However, it is not known whether the high platelet reactivity found in these patients is simply a result of their presentation rather than the aetiology of the stent thrombosis.[17] In our study, platelet function assessment was performed prior to the thrombotic events, and therefore our data support the hypothesis that high post-clopidogrel reactivity is not an innocent bystander but is itself an aetiological factor in stent thrombosis.

Although this study is the largest to date to investigate the relationship between a point-of-care assessment of clopidogrel response and stent thrombosis, the relatively small number of patients and events precluded the identification of other factors which may contribute to thrombotic events after PCI with DES. Large registries that did not examine the role of clopidogrel responsiveness have elucidated the multifactorial aetiology of DES thrombosis.[38,39] The contribution of mechanical factors (e.g. stent underexpansion) to the thrombotic events we observed cannot be excluded, as intravascular ultrasound (IVUS) was not routinely performed at the time of the ischaemic event. However, given our frequent use of IVUS and high-pressure balloon inflations during the index procedure (*Table 2*), our findings emphasize the importance of high post-treatment platelet reactivity on outcomes even in the setting of an aggressive technical approach to complex PCI. Our findings are also consistent with those of Buonomici *et al.*,[40] who studied the association between high post-treatment reactivity by LTA and ischaemic events after PCI. In that larger study, the presence of diabetes mellitus was also significantly associated with high post-treatment reactivity, and high post-treatment reactivity was a strong, independent predictor of CV death and stent thrombosis at 6 months post-DES implantation.

Our findings suggest that it may be possible to stratify patients at risk for out-of-hospital ischaemic events, and in particular, stent thrombosis, using a point-of-care platelet function assessment performed during the index hospitalization. Increased maintenance dosing regimens of clopidogrel can improve platelet inhibition in unselected patients[21] and in diabetic patients at high risk for an impaired response.[33] The third-generation theinopyridine prasugrel and other novel P2Y12 inhibitors can provide more potent and uniform PY12 inhibition.[41–43] However, there is currently no data supporting the clinical use of point-of-care platelet function assays in the management of patients undergoing PCI. Before platelet function testing can be widely adopted to risk-stratify patients post-PCI, prospective studies must determine: (i) whether the use of increased clopidogrel maintenance dosing or alternative antiplatelet agents can improve platelet inhibition in patients with high post-treatment reactivity on a standard maintenance dose; (ii) whether such an approach is effective in reducing stent thrombosis and other ischaemic events, and (iii) whether aggressive antiplatelet therapy in non-responders is safe and not associated with significantly increased bleeding. Stent thrombosis is a rare event, and clopidogrel non-responsiveness is not uncommon, and therefore many patients with high post-clopidogrel reactivity do not experience an adverse event. A large randomized clinical trial must evaluate whether the benefits of an aggressive antiplatelet therapy in non-responders outweigh any potential risk of increased bleeding.

Limitations

This is an observational study, but ROC curve analysis demonstrated that the VerifyNow P2Y12 assay was able to discriminate between patients with and without subsequent events. Our findings must be considered to be hypothesis-generating given the exploratory nature of our analysis and must be confirmed in larger, prospective studies. Given the 'real-world' nature of our registry, clopidogrel status was heterogeneous at the time of PCI, as some patients were already on clopidogrel therapy while others received a loading dose at the time of intervention; the timing of the measurement of platelet reactivity around the time of the procedure also differed between these two groups. This could have potentially led to differences in platelet reactivity between these groups. However, the study was carefully designed to measure platelet reactivity when the clopidogrel effect was therapeutic in all patients; this is supported by the finding that there was no significant difference in the post-clopidogrel PRU between patients with and without prior clopidogrel therapy. The use of different intra-procedural anticoagulants (heparin and bivalirudin) may have potentially impacted platelet reactivity. However, heparin does not appear to increase ADP-induced platelet reactivity at the agonist concentration used in the VerifyNow assay,[44] and there was no difference in the PRU in patients receiving either antithrombin agent. In addition, we focused our analysis on post-discharge events at 6 month follow-up, which would likely be less impacted by the heterogeneity in anticoagulant strategy or the status of clopidogrel therapy at the time of PCI. Patients who reported taking clopidogrel at follow-up may not have been compliant with the medication; however, self-reported adherence is a commonly used measure of compliance.[45]

Conclusions

Following PCI with DES, high platelet reactivity in patients on clopidogrel measured with a point-of-care assay is associated with post-discharge events, including stent thrombosis. Investigation of alternative clopidogrel dosing regimens that may reduce stent thrombosis and other ischaemic events in high-risk patients identified by this assay is warranted.

Conflict of interest: M.J.P. has received honoraria, consulting fees, and research support from Accumetrics, Inc., honoraria from Cordis Corporation, and honoraria from Boston Scientific. P.S.T. has received research grants, royalty fees, and honoraria from Cordis Corporation and Boston Scientific.

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