High Residual Platelet Reactivity After Clopidogrel Loading and Long-Term Clinical Outcome After Drug-Eluting Stenting for Unprotected Left Main Coronary Disease

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Background—No data exist about the impact of high residual platelet reactivity (HRPR) after clopidogrel loading on long-term clinical outcome in patients undergoing drug-eluting stent (DES) implantation for unprotected left main disease (ULMD).

Methods and Results—Consecutive patients who underwent percutaneous coronary intervention for ULMD had prospective platelet reactivity assessment by light transmittance aggregometry after a loading dose of 600 mg of clopidogrel. The primary end point of the study was cardiac mortality, and the secondary end point was stent thrombosis. From January 2005 to September 2008, 215 consecutive patients were treated with DES for ULMD. The incidence of HRPR after clopidogrel loading was 18.6%. The median follow-up was 19.3 months. The overall estimated 1-, 2-, and 3-year cardiac mortality rate was 3.9\% , 7.5\%, and 12.2\%, respectively. The 3-year cardiac mortality rate was 8.0\% ± 3.1\% in the low residual platelet reactivity (LRPR) group and 28.3\% ± 10.4\% in the HRPR group (P=0.005). The 3-year stent thrombosis rate was 4.2\% ± 1.8\% in the low residual platelet reactivity group and 16.0\% ± 7.3\% in the HRPR group (P=0.021). By forward stepwise regression analysis, HRPR after clopidogrel loading was the only independent predictor of cardiac death (hazard ratio, 3.82; 95% confidence interval, 1.38 to 10.54; P=0.010) and stent thrombosis (hazard ratio, 3.69; 95% confidence interval, 1.12 to 12.09; P=0.031).

Conclusions—HRPR after 600-mg clopidogrel loading is a strong marker of increased risk of cardiac death and DES thrombosis in patients receiving DES stenting for ULMD. Routine assessment of in vitro residual platelet reactivity after clopidogrel loading in patients with ULMD potentially suitable for DES-supported percutaneous coronary intervention should be considered to guide patient care decisions. (Circulation. 2009;120:2214-2221.)

Key Words: platelets ▪ stents ▪ thrombosis

There is growing evidence that in vitro high residual platelet reactivity (HRPR) after a loading dose of clopidogrel is a strong marker of high risk of stent thrombosis in patients undergoing drug-eluting stent (DES)–supported percutaneous coronary intervention (PCI).1-4 No data exist about the impact of HRPR after clopidogrel loading on clinical outcome in the subset of patients undergoing DES implantation for unprotected left main disease (ULMD). This subset of patients is highly important and relevant when one considers that a thrombotic event is likely to be fatal in most cases and that data from registries show a quick increase in the use of PCI for ULMD,5-9 whereas a concluded randomized trial comparing PCI with coronary surgery shows that the 2 strategies are equivalent in terms of mortality.10 The aim of this study was to assess the impact of HRPR after clopidogrel loading on cardiac mortality and DES thrombosis in patients undergoing PCI for ULMD.

Clinical Perspective on p 2221

Methods

Patients

This study includes all consecutive patients who underwent PCI for ULMD and who had platelet reactivity assessment by light transmittance aggregometry after a loading dose of 600 mg of clopidogrel. ULMD was defined as a de novo >50% stenosis in the left main stem. Patients with stable coronary artery disease as well as acute coronary syndromes and non-ST-segment elevation acute myocardial infarction were included irrespective of the coronary anatomy. Patients underwent PCI instead of coronary surgery because of either the patient’s preference or the high risk associated with surgery. High surgical risk was defined as a logistic EuroSCORE ≈6.11 The
exclusion criteria for the study were (1) ST-segment elevation acute myocardial infarction and (2) anticipated noncompliance to dual antiplatelet treatment for at least 12 months. The study was approved by the institutional review committee, and all patients gave informed written consent to intervention and study.

**Residual Platelet Reactivity After Clopidogrel Loading**

Platelet reactivity testing responsiveness to clopidogrel and aspirin was assessed by light transmittance aggregometry (APACT4, Helena Laboratories, Milan, Italy) with the use of ADP and arachidonic acid as agonists. Blood samples anticoagulated with 0.129 mol/L sodium citrate (ratio 9:1) were obtained 12 to 18 hours after 600-mg clopidogrel loading and before PCI, and no patient received glycoprotein IIb/IIIa inhibitors before the intervention. Platelet-rich plasma, obtained by centrifuging whole blood for 10 minutes at 200g, was stimulated with 10 μmol/L of ADP and with 1 mmol/L of arachidonic acid. The 100% line was set with the use of platelet-poor plasma, and the 0 baseline was established with platelet-poor plasma (adjusted from 18×10^9/L to 30×10^9/L). Platelet aggregation (according to the Born method) was evaluated with consideration of the maximal percentage of platelet aggregation in response to stimulus. The coefficient of variation of ADP and arachidonic acid platelet aggregation was 6.8% and 5.8%, respectively. Control samples from 100 healthy volunteers were run to determine the normal reference laboratory aggregation value, which was 68% (range, 55% to 99%). Patients with platelet aggregation by 10 μmol ADP ≥90th percentile of controls and platelet aggregation by arachidonic acid ≥20% were considered abnormal.1,12 HRPR was defined as platelet aggregation by ADP ≥70%.

**Percutaneous Coronary Intervention**

All patients were pretreated with aspirin (325 mg daily) and clopidogrel (loading dose 600 mg) at least 12 hours before PCI. Standard techniques were used to treat ULMD and the other lesions in patients with multivessel disease. Multivessel disease was defined as stenosis >70% of 1, 2, or 3 major coronary arteries on visual assessment at baseline angiography besides the left main lesion. Disease of the left anterior descending artery and of the circumflex artery included lesions >10 mm from the ostia. For distal left main disease, a single stent technique was preferred in patients with a normal- or diminutive-appearing side branch, whereas a double stent technique was considered in patients with disease of both ostia and proximal segments of the left anterior descending artery and circumflex artery. Whatever the stenting technique used, routine final “kissing balloon” technique after dilation with poorly compliant balloons had to be performed in all cases. The use of glycoprotein IIb/IIIa inhibitors, rotational atherectomy, intra-aortic balloon counterpulsation, and intravascular ultrasound was at the operator’s discretion.

Procedural success was defined as a final diameter stenosis <30% with a Thrombolysis in Myocardial Infarction grade 3 of all the treated vessels on visual assessment, without death, acute coronary occlusion, or emergency coronary surgery. The diagnosis of non–Q-wave myocardial infarction was based on an increase of creatine kinase myocardial band isoenzyme or troponin I > 3 times the upper limit of normal or, for patients with elevated values on admission, a re-elevation of creatine kinase–MB or troponin I values. A Q-wave myocardial infarction was defined as the development of new Q waves in ≥2 ECG leads in addition to creatine kinase–MB or troponin I elevation. Creatine kinase–MB fraction and troponin I were routinely assessed 12 hours after PCI in all patients and at least 3 times every 6 hours in patients with recurrent chest pain. Complete revascularization was defined as a restoration of Thrombolysis in Myocardial Infarction grade 3 flow with residual stenosis <30% on visual assessment in the 3 coronary arteries and their major branches (branch diameter ≥2 mm).

**Long-Term Dual Antiplatelet Treatment**

All patients were prescribed aspirin (325 mg daily) indefinitely and clopidogrel (75 mg daily) for at least 12 months. Patients who were nonresponders to a 600-mg loading dose of clopidogrel were prescribed 150 mg daily of the drug or were shifted to ticlopidine (500 mg daily). After 12 months, indefinite clopidogrel treatment was recommended.

**Follow-Up**

All patients had scheduled examinations at 1, 3, 6, and 12 months and then annually thereafter. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries was entered into the prospective data-
Base. All eligible patients were scheduled for angiographic follow-up at 6 to 9 months. Unscheduled angiography was allowed on the basis of clinical indications.

End Points
The primary end point of the study was cardiac mortality. All deaths were considered cardiac unless an unequivocal noncardiac cause could be documented. The secondary end point was stent thrombosis. Stent thrombosis was defined according to the Academic Research Consortium definition as definite, probable, or possible stent thrombosis.\textsuperscript{13} Definite stent thrombosis was defined as acute coronary syndrome and either angiographic or pathological confirmation of thrombosis. Probable stent thrombosis was defined as sudden or otherwise explained death within 30 days or nonfatal myocardial infarction in the territory supplied by a stented vessel without angiographic confirmation irrespective of the time from the index procedure. Possible stent thrombosis was defined as unexplained death after 30 days from the procedure. Event time was categorized as early (within 30 days from stent implantation), late (31 days to 365 days), and very late (>365 days). All events were adjudicated by 3 observers (G.C., N.C., R.A.) who were blinded to patient responsiveness to clopidogrel and not involved in the follow-up process.

Statistical Analysis
Discrete data are summarized as frequencies, and continuous data are expressed as mean \(\pm\) SD or median and interquartile range as appropriate. The \(\chi^2\) test was used for comparison of categorical variables, and the unpaired 2-tailed Student \(t\) test or Mann–Whitney rank sum test was used to test differences among continuous variables. Survival curves were generated with the use of the Kaplan–Meier method, and the difference between groups was assessed by log-rank test. The multivariable analysis to evaluate the independent contribution of clinical, angiographic, procedural, and platelet reactivity variables to the primary and secondary end points was performed by the forward stepwise Cox proportional hazards model. Dichotomous platelet reactivity variables according to high platelet reactivity criteria were used (ADP test \(>70\%\), arachidonic acid test \(>20\%\), and the interaction term of both abnormal tests). The other variables entered into the model were as follows: age (years), male sex, diabetes mellitus, serum creatinine \(>150 \text{ mmol/L}\), history of myocardial infarction, left ventricular ejection fraction (\%), 3-vessel coronary disease, right coronary artery chronic total occlusion, EuroSCORE \(>6\), left main bifurcation lesion, left main stenting of both branches, total left main stent length, total stent length, completeness of coronary revascularization, abciximab use, intra-aortic balloon counterpulsation, and major bleeding (Thrombolysis in Myocardial Infarction criteria).\textsuperscript{14} A propensity score analysis was performed with the use of a logistic regression model from which the probability for HRPR to the ADP test was calculated for each patient. The variables included in the logistic model were as follows: age (years), male sex, diabetes mellitus, serum creatinine \(>150 \text{ mmol/L}\), history of myocardial infarction, left ventricular ejection fraction \(<40\%\), peripheral vascular disease, multivessel coronary disease, and acute coronary syndrome. Model discrimination was assessed with the \(c\) statistic and goodness of fit with the Hosmer-Lemeshow test. Thereafter, a Cox multivariate analysis was performed to adjust HRPR for propensity score used as continuous covariate. A \(P\) value \(<0.05\) was considered significant. Analyses

| Table 1. Baseline Clinical and Angiographic Characteristics According to Responsiveness to Clopidogrel |
|---------------------------------|-----------|-----------|-----------|-----------|
|                                | Overall (n=215) | LRPR (n=175) | HRPR (n=40) | \(P\)     |
| Age, y                         | 71±10      | 71±10      | 72±10      | 0.729     |
| Male sex, n (%)                | 166 (77)   | 141 (81)   | 25 (63)    | 0.014     |
| Current smokers, n (%)         | 40 (19)    | 34 (19)    | 6 (15)     | 0.516     |
| Arterial hypertension, n (%)   | 168 (78)   | 134 (77)   | 34 (85)    | 0.245     |
| Diabetes mellitus, n (%)       | 59 (27)    | 41 (23)    | 18 (45)    | 0.006     |
| Hypercholesterolemia, n (%)    | 147 (68)   | 117 (67)   | 30 (75)    | 0.318     |
| Peripheral vascular disease, n (%) | 68 (32) | 54 (31)   | 14 (35)    | 0.611     |
| Previous myocardial infarction, n (%) | 50 (23) | 39 (22)   | 11 (28)    | 0.481     |
| Previous PCI, n (%)            | 70 (33)    | 58 (33)    | 12 (30)    | 0.702     |
| Stable angina, n (%)           | 43 (20)    | 36 (21)    | 7 (18)     | 0.661     |
| Unstable angina, n (%)         | 122 (57)   | 97 (55)    | 25 (63)    | 0.415     |
| NSTEMI, n (%)                  | 41 (19)    | 34 (19)    | 7 (18)     | 0.779     |
| Acute coronary syndrome, n (%) | 163 (76)   | 131 (75)   | 32 (80)    | 0.493     |
| Creatinine >150 \text{ mmol/L}, n (%) | 37 (17) | 29 (17)   | 8 (20)     | 0.604     |
| LVEF, %                        | 46.2±13.1  | 46.8±12.8  | 43.7±13.8  | 0.178     |
| LVEF <40%, n (%)               | 74 (34)    | 58 (33)    | 16 (40)    | 0.410     |
| EuroSCORE, median (IQR)        | 6.53 (3.3–18.4) | 6.12 (3.0–16.6) | 12.80 (3.7–18.9) | 0.053 |
| EuroSCORE ≥6, n (%)            | 116 (54)   | 89 (51)    | 27 (68)    | 0.057     |
| EuroSCORE ≥13, n (%)           | 75 (35)    | 55 (31)    | 20 (50)    | 0.026     |
| LM plus 2-vessel disease, n (%) | 78 (36)   | 63 (36)    | 15 (37)    | 0.859     |
| LM plus 3-vessel disease, n (%) | 53 (25)   | 43 (25)    | 10 (25)    | 0.954     |
| RCA disease, n (%)             | 130 (60)   | 107 (61)   | 23 (57)    | 0.671     |
| RCA chronic total occlusion, n (%) | 50 (23) | 40 (23)   | 10 (25)    | 0.772     |
| Distal LM location, n (%)      | 180 (84)   | 148 (85)   | 32 (80)    | 0.480     |

NSTEMI indicates non–ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; IQR, interquartile range; LM, left main; and RCA, right coronary artery.
were performed with the use of the software package SPSS 11.5 (SPSS Inc, Chicago, Ill).

### Results

From January 2005 to September 2008, 300 consecutive patients were treated with DES for ULMD. Of the 300 patients, 85 were treated on an emergent basis, whereas 215 had in vitro platelet reactivity assessment after a 600-mg loading dose of clopidogrel and before PCI (Figure 1). The incidence of HRPR after clopidogrel loading was 18.6%, and that of an abnormal arachidonic acid test was 25%; both abnormal tests were revealed in 9.8% of patients. Baseline patient characteristics are presented in Table 1. Overall, the mean age of patients was 71 years, and an acute coronary syndrome on admission was present in the large majority of patients. More than half of the patients were at high surgical risk (EuroSCORE ≥6). Most patients had distal ULMD (84%). ULMD was associated with disease of other coronary vessels in the large majority of cases (93%), and nearly one fourth of the patients had chronic total occlusion of the right coronary artery. Patients with HRPR were more likely to be women, to be diabetics, and to have a higher EuroSCORE compared with patients with low residual platelet reactivity (LRPR), whereas there were no differences in the other baseline characteristics between groups.

### Procedural Characteristics

Procedural characteristics are summarized in Table 2. Left main disease was treated with a single stent in the majority of patients, whereas 61 patients, all with distal ULMD, had stenting of both branches. In the left main procedure, a multivessel PCI was performed in 60% of the patients, and a second procedure with the goal of complete revascularization was performed within 1 month in 28 patients. Overall, complete coronary revascularization was achieved in 80% of the patients. The median total stent length was 60 mm (interquartile range, 34 to 96 mm), and the number of stents per patient was 3.8 ± 2.0. The 2 patient groups were similar in all procedural characteristics. Five patients developed periprocedural non–Q-wave myocardial infarction. No procedural death, Q-wave myocardial infarction, or stroke occurred.

### Repeat In Vitro Assessment of Platelet Reactivity in HRPR Patients

All but 1 patient with HRPR after 600-mg clopidogrel loading underwent repeat measurement of platelet reactivity after therapeutic adjustments. A platelet aggregation by ADP 70% was revealed in 14 patients (36%).

### Clinical Outcome

#### Cardiac Mortality and Stent Thrombosis

The clinical outcome is summarized in Table 3. All patients had a clinical follow-up of at least 6 months. The median follow-up was 19.3 months (interquartile range, 9.4 to 34.3 months), and the follow-up rate was 100%. All but 10 patients were on clopidogrel therapy at the time of the last contact (1 in the HRPR group and 9 in the LRPR group).

There were 15 cardiac deaths (7.0%): 8 in the LRPR group (4.6%) and 7 (17.5%) in the HRPR group. Sudden unexplained death occurred in 3 patients in the LRPR group (1 at 60 days, 1 at 218 days, and 1 at 573 days) and in 2 patients...
in the HRPR group (1 at 15 days and 1 at 94 days). Death was due to acute myocardial infarction in 2 LRPR patients (1 at 42 days and 1 at 86 days) who discontinued clopidogrel for elective noncardiac surgery and in 2 HRPR patients (1 at 13 days and 1 at 732 days). The remaining 6 cardiac deaths were due to chronic heart congestive failure without evidence of acute myocardial infarction (3 patients with LRPR and 3 with HRPR). Congestive heart failure preexisted before PCI in 4 patients, whereas it developed after successful emergent PCI for definite early left main stent thrombosis and acute myocardial infarction in 2 (1 with LRPR and 1 with HRPR). All but 2 deaths occurred while patients were on dual antiplatelet treatment. The mortality rate at 6 months was 2.3% for the LRPR group and 7.5% for the HRPR group, respectively (P=0.094). Figure 2 shows the survival curves of the 2 patient groups. The overall estimated 1-, 2-, and 3-year cardiac mortality rate was 3.9±1.3%, 7.5±2.2%, and 12.2±3.4%, respectively. The 3-year cardiac mortality rate was 8.0±3.1% in the LRPR group and 28.3±10.4% in the HRPR group (P=0.005).

Definite stent thrombosis occurred in 3 patients (1 with LRPR and 2 with HRPR), and all were early stent thromboses. Probable stent thrombosis occurred in 2 patients of the LRPR group and 2 patients of the HRPR group (1 acute myocardial infarction at 732 days and 1 sudden death at 15 days). Possible stent thrombosis was revealed in 3 patients of the LRPR group and in 1 patient of the HRPR group. The 3-year definite, probable, or possible stent thrombosis rate was 4.2±1.8% in the LRPR group and 16.0±7.3% in the HRPR group (P=0.021). Figure 3 depicts the DES thrombosis–free survival curves of the 2 groups.

### Restenosis and Target Vessel Revascularization

The 6- to 9-month angiographic follow-up rate was 93% (194/208). The binary restenosis rate at the scheduled or unscheduled angiographic follow-up was 15%. All patients with restenosis underwent repeat PCI.

### Other Adverse Events

Overall, 10 patients died of a noncardiac cause: 6 patients died of cancer, 1 of chronic renal insufficiency, 2 of sepsis, and 1 of hemorrhagic stroke. Major bleeding rate (Thrombolysis in Myocardial Infarction criteria) was 2.3% in the LRPR group and 7.5% in the HRPR group (P=0.094).

### Predictor of Cardiac Death and Stent Thrombosis

By forward stepwise regression analysis, HRPR after clopidogrel loading was the only independent predictor of cardiac death (hazard ratio [HR], 3.82; 95% confidence interval [CI], 1.38 to 10.54; P=0.010) and stent thrombosis (HR, 3.69; 95% CI, 1.12 to 12.09; P=0.031). Multivariable analysis was also performed with the propensity score and HRPR after clopidogrel loading as covariate. A balance between the 2 groups was achieved by propensity score. The c statistic of the regression model of the propensity score was 0.70 (P=0.543, Hosmer-Lemeshow goodness-of-fit test). After adjustment for propensity
score, HRPR remained significantly related to cardiac mortality (HR, 3.29; 95% CI, 1.16 to 9.37; \( P = 0.025 \)) and to DES thrombosis (HR, 3.44; 95% CI, 1.01 to 11.80; \( P = 0.049 \)). If the variable HRPR was not entered into the model, the EuroSCORE became an independent risk factor of cardiac death (HR, 1.03; 95% CI, 1.01 to 1.05; \( P = 0.007 \)).

**Discussion**

This is the first study that assessed the impact of HRPR after clopidogrel loading on clinical outcome in patients undergoing PCI for ULMD. The study, based on 215 consecutive patients who underwent DES-supported PCI for ULMD disease and had prospective platelet reactivity assessment...
after a 600-mg loading dose of clopidogrel, shows that HRPR is the only independent predictor of both stent thrombosis and cardiac death at long-term follow-up. Patients with HRPR had a nearly 4-fold increase in the risk of stent thrombosis and cardiac death compared with patients with LRPR.

Previous studies have shown that patients with ULMD are at high risk of death and other major adverse events either with surgical revascularization or DES-supported PCI. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial, which included 705 patients treated with paclitaxel-eluting stents or coronary surgery with a low surgical risk (EuroSCORE\textsubscript{1} = 3.9 ± 2.8), showed that death, stroke, or myocardial infarction rate at 1 year follow-up was 7.0% in patients treated with PCI and 9.1% in patients treated with coronary surgery.\textsuperscript{10} The Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) registry, which included 2240 patients who underwent coronary surgery or PCI with bare-metal stents or DES, reports a 3-year cardiovascular mortality rate of 5.7%.\textsuperscript{3} In other studies of DES-supported PCI for ULMD, the cardiac mortality rate at 1- to 3-year follow-up ranged from 5.5% to >10%; differences in patient characteristics and duration of follow-up account for this variability.\textsuperscript{5–8} In most studies, the calculated surgical risk is highly predictive of death and other major adverse events after PCI, and patients at high surgical risk carry a cardiac mortality rate that can be >20%.\textsuperscript{15} In contrast to these studies, in our series of patients the surgical risk as assessed by the EuroSCORE was not predictive of cardiac death. This discrepancy may be explained mainly by the effect on the logistic regression analysis of HRPR after clopidogrel loading. Another feature that presumably decreases the predictive value of surgical risk is the very high risk profile of the entire cohort of patients with a median EuroSCORE of 6.53 for the entire population and of 12.80 for the HRPR group. Consistent with other reports, no angiographic or procedural characteristic had a significant impact on cardiac death.

Several studies have shown that HRPR after clopidogrel loading as assessed by in vitro tests prospectively is a marker of increased risk of thrombotic events in patients undergoing DES implantation.\textsuperscript{1–4} The clinical impact of this variable is maximized in the subset of patients treated for ULMD because in most cases the thrombotic event will result in sudden death or, in the few patients who survive after emergency PCI, in large infarcts with a subsequent high mortality rate. Interestingly, the cardiac mortality rate in the HRPR group continues to increase during long-term follow-up. The cardiac mortality rate at 2 years is nearly 3-fold that observed at 1 year, whereas the survival curve of the LRPR group shows a nearly flat pattern 6 months after PCI. This finding suggests a persistent increased risk of thrombotic events despite the fact that most of these patients received a long-term double dose of clopidogrel or shifted to ticlopidine with a decrease in residual platelet reactivity in more than one third of cases. The finding that HRPR patients remain at high risk despite some in vitro effects of a long-term double dose of clopidogrel or ticlopidine should be considered with caution because of the small number of patients, and the possibility of effectively tailoring the antiplatelet therapy for each patient under the guidance of in vitro tests is not yet proven. Moreover, it is still unknown whether more potent antiplatelet agents, such as prasugrel, which provides more predictable in vitro platelet aggregation inhibition,\textsuperscript{16} will replace clopidogrel in all patients receiving DES or whether HRPR after 600-mg clopidogrel loading will remain a marker of increased risk of DES thrombosis and more generally of thrombotic events also using new antiplatelet agents. Meanwhile, routine assessment of in vitro responsiveness to a 600-mg loading dose of clopidogrel in patients with ULMD potentially suitable for DES-supported PCI should be considered to guide patient care decisions.

**Study Limitations**

There was a trend toward an increased major bleeding rate in HRPR patients that could be explained by the increased dose of clopidogrel in most of these patients. Patients with HRPR were treated differently from those with LRPR, and one can therefore not rule out whether the higher risk was due to the abnormal response to clopidogrel or to the higher doses of clopidogrel. However, this hypothesis seems unlikely because bleeding as a variable was entered into the Cox model and was not related to mortality.

**Conclusions**

HRPR after 600-mg clopidogrel loading is a strong marker of increased risk of cardiac death and DES thrombosis in patients receiving DES stenting for ULMD. Routine assessment of in vitro responsiveness to clopidogrel in patients with ULMD potentially suitable for DES-supported PCI should be considered to guide patient care decisions.

**Disclosures**

None.

**References**

There is growing evidence that in vitro high residual platelet reactivity after a loading dose of clopidogrel is a strong marker of the risk of stent thrombosis. This study assessed the impact of high residual platelet reactivity after a clopidogrel loading on clinical outcome in 215 patients undergoing drug-eluting stent implantation for unprotected left main disease. The study shows that high residual platelet reactivity is the only independent predictor of stent thrombosis and cardiac death at long-term follow-up, whereas other variables such as left main bifurcation, number of stents, completeness of revascularization, and surgical risk are not related to stent thrombosis and cardiac death. Patients with high residual platelet reactivity had a nearly 4-fold increase in the risk of stent thrombosis and cardiac death compared with patients with low residual platelet reactivity. The cardiac mortality rate in patients with high residual platelet reactivity continues to increase during long-term follow-up, and this finding suggests a persistent increased risk of thrombotic events despite most of these patients receiving a long-term double dose of clopidogrel or shifting to ticlopidine. It is unknown whether high residual platelet reactivity after clopidogrel loading will remain a marker of increased risk of drug-eluting stent thrombosis and more generally of thrombotic events also using new potent antiplatelet agents. Meanwhile, routine assessment of in vitro residual platelet reactivity to a 600-mg loading dose of clopidogrel in patients with unprotected left main disease potentially suitable for drug-eluting stenting should be considered to guide patient care decisions.

**CLINICAL PERSPECTIVE**
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