Antiplatelet Therapy in ACS Patients: Comparing Appropriate P2Y12 Inhibition by Clopidogrel to the Use of New P2Y12 Inhibitors

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Aim: In percutaneous coronary intervention (PCI)-treated acute coronary syndrome (ACS) patients on clopidogrel therapy, high on-treatment platelet adenosine diphosphate (ADP) reactivity was observed in numerous studies, with significant increases in non-fatal myocardial infarction, definite/probable stent thrombosis, or cardiovascular mortality. Compared to clopidogrel, prasugrel and ticagrelor provide more potent platelet inhibition. Whether new P2Y12 inhibitors reduce thrombotic events in a similar manner compared to the rate observed with appropriate P2Y12 inhibition by clopidogrel must still be determined. This study sought to compare long-term outcomes between clopidogrel responders (platelet reactivity index [PRI] vasodilator-stimulated phosphoprotein [VASP] < 61%) and patients under prasugrel or ticagrelor therapy following PCI-treated ACS.

Methods: 730 ACS patients undergoing urgent PCI were prospectively enrolled into two groups: clopidogrel responders (n=448) and those under ticagrelor or prasugrel therapy (n=282). The primary endpoint was a composite of cardiovascular death, myocardial infarction, stent thrombosis, and stroke; the secondary endpoint comprised major hemorrhagic events.

Results: The median follow-up was 260 ± 186 days. Clopidogrel patients were older and more likely to present non-ST segment elevation myocardial infarction, cardiovascular risk factors, atrial fibrillation, or prior vascular disease. After propensity score matching, the primary endpoint was met in 7.1% of the clopidogrel group and 4.1% of the prasugrel/ticagrelor group (p = 0.43). Minor bleeding events were significantly reduced in the clopidogrel group (1.1% vs. 3%; p = 0.03). In a multivariate analysis, the antiplatelet treatment strategy was not an independent primary endpoint predictor.

Conclusion: In PCI-treated ACS patients, clopidogrel therapy and PRI VASP < 61% were not associated with increased risks of thrombotic events compared to prasugrel or ticagrelor therapy.

Key words: Myocardial infarction, Thrombosis, Stent, Bleeding

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pidogrel has become generic, the novel P2Y12 inhibitors’ high treatment costs along with the increased risk of bleeding could impede their use. We thus sought to compare long-term clinical outcomes between clopidogrel responders (PRI VASP 61%) and patients under prasugrel or ticagrelor therapy following PCI-treated ACS.

**Methods**

This study prospectively enrolled patients undergoing PCI due to ACS between January 2008 and April 2015 in the Nouvel Hôpital Civil, CHU Strasbourg, France. The trial was performed in accordance with the Declaration of Helsinki, with the protocol approved by the institutional ethics committee and informed written consent obtained from all patients.

**Study Population**

Inclusion criteria: Patients > 18 years old and admitted to the cardiac intensive care unit for PCI with stent implantation due to ACS, with or without ST-segment elevation, or unstable angina. VASP measurement during hospital stay. In general, VASP was realized in high-risk patients more likely to present an enhanced thrombotic risk, in complex PCI, or in clopidogrel has become generic, the novel P2Y12 inhibitors’ high treatment costs along with the increased risk of bleeding could impede their use. We thus sought to compare long-term clinical outcomes between clopidogrel responders (PRI VASP 61%) and patients under prasugrel or ticagrelor therapy following PCI-treated ACS.

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Blood Samples

A blood sample was taken between 6–48 hours after the clopidogrel loading dose (300 or 600 mg). Blood was immediately collected into a vacutainer tube, citrated, and sent to the hemostasis laboratory (EFS-Alsace, France), where a platelet VASP phosphorylation analysis was performed within 48 hours.

Platelet function assays: VASP phosphorylation analysis by flow cytometry

VASP phosphorylation was assessed with standard-
Table 2. Baseline angiographic characteristics

|                          | Clopidogrel (n=448) | Prasugrel/Ticagrelor (n=282) | P  
|--------------------------|----------------------|------------------------------|---
| Mono-vessel disease, n (%) | 170 (38)             | 142 (50.5)                   | 0.001  
| Dual-vessel disease, n (%) | 144 (32)             | 91 (32.4)                    | 0.9  
| Three-vessel disease, n (%) | 135 (30)             | 48 (17.1)                    | 0.0001*  
| LAD, n (%)                | 299 (66.7)           | 173 (61.6)                   | 0.2  
| CX, n (%)                 | 161 (36)             | 85 (30.2)                    | 0.1  
| RCA, n (%)                | 265 (59.2)           | 138 (49.1)                   | 0.009  
| Left main coronary artery, n (%) | 26 (5.8) | 10 (3.6) | 0.2  
| Bifurcation n (%)         | 37 (8.2)             | 5 (1.8)                      | 0.0001  
| Total stent’s length (mm) | 25.9 +/- 15.5 (12-122) | 29.9 +/- 21.7 (12-188) | 0.005  
| Stent’s diameter (mm)     | 3.1 +/- 0.5 (2.5-4.5) | 3.0 +/- 0.5 (3-5) | 0.83  
| DES                       | 236 (52.7)           | 259 (92.5)                   | <0.0001  

Values are n +/- median (range) or n (%)
*Variable used to create propensity score
LAD= left anterior descending artery; CX= circumflex artery; RCA = right coronary artery

Table 3. Biological characteristics

|                          | Clopidogrel (n=448) | Prasugrel/Ticagrelor (n=282) | P  
|--------------------------|----------------------|------------------------------|---
| Glycemia (g/dL)          | 1.43 +/- 0.7 (0.57-4.75) | 1.47 +/- 0.6 (0.68-5.11) | 0.5  
| HbA1c (%)                | 6.3 +/- 1.4 (4.5-16.4) | 6.0 +/- 1.1 (4.7-12.8) | 0.002  
| Creatinine (umol/L)      | 88.4 +/- 45.0 (38.7-565) | 76.6 +/- 24.9 (37-248) | 0.0001  
| Tn admission (ug/L)      | 0.33 [0.008-2.07] | 0.41 [0.07-3.27] | 0.2  
| Tn peak (ug/L)           | 8.24 [0.70-8.24] | 28.60 [3.90-80.90] | 0.0001  
| BNP (ng/l)               | 123 [52-289] | 50 [21-123] | 0.0001  
| CRP (mg/l)               | 4.70 [4-14] | 4 [4-7] | 0.002  
| Leukocytes (10^9/L)      | 9.9 +/- 3.8 (1-29.8) | 11.1 +/- 3.8 (3.9-25.5) | 0.0001  
| Hb (g/dl)                | 13.7 +/- 1.8 (7.8-19.1) | 14.50 +/- 1.6 (5.1-19.1) | 0.0001  
| Platelets (10^9/L)       | 253.8 +/- 85.1 (48-832) | 247.6 +/- 70.5 (85-818) | 0.3  
| Total cholesterol (g/L)  | 1.8 +/- 0.5 (0.8-5.1) | 1.8 +/- 0.4 (0.9-3.2) | 0.4  
| LDLc (g/L)               | 1.1 +/- 0.4 (0.3-2.4) | 1.1 +/- 0.3 (0.3-2.4) | 0.3  
| HDLc (g/L)               | 0.4 +/- 0.1 (0.1-1.8) | 0.4 +/- 0.1 (0.2-1.5) | 0.0001  
| TG (g/L)                 | 1.3 +/- 0.9 (0.3-7.7) | 1.3 +/- 0.9 (0.4-9.5) | 0.01  
| VASP PRI (%)             | 37.3 +/- 16.8 (3-60) | 22.2 +/- 21.2 (3-60) | 0.0001  

Values are n +/- standard deviation (minimum–maximum)
BNP= brain natriuretic peptide; CRP= C-reactive protein; Hb= Hemoglobin; HDLc= High-density lipoprotein; LDLc= Low-density lipoprotein; TG= Triglycerides; Tn= Troponin

ized flow cytometric assay (Platelet VASP; Diagnostica Stago [Biocytex], Asnières, France). A citrated blood sample was incubated with either prostaglandin E1 (PGE1) or PGE1 and ADP for 10 min, fixed with paraformaldehyde, and the platelets were then permeabilized with a non-ionic detergent. The cells were labeled with a primary monoclonal antibody against serine 239-phosphorylated VASP (16C2), followed by a secondary fluorescein isothiocyanate-conjugated polyclonal goat-anti-mouse antibody. Analyses were performed on a Becton Dickinson FACS Calibur flow cytometer as reported. PRI was calculated from median fluorescence intensity (MFI) of samples incubated with PGE1 and ADP according to the formula: PRI VASP = (MFI [PGE1] - MFI [PGE1 + ADP]/MFI [PGE1]) × 100. PRI, expressed as a percentage, is the difference in VASP fluorescence intensity between resting (+ PGE1) and activated (+ ADP) platelets. In unselected patients undergoing PCI, the optimal cutoff value for PRI to predict cardiovascular outcome following PCI was recently found to be 61%
venous aspirin (125–250 mg) and 50–100 IU/Kg of unfractionated heparin to target an ACT >250 s. GP\textsubscript{II}b\textsubscript{III}a inhibitors, mainly Abciximab, were used at the operators’ discretion. Data was extracted from our database. The whole cohort of 730 patients was split into two subgroups: clopidogrel responders and prasugrel/ticagrelor. The clopidogrel responder group included clopidogrel-treated patients with a PRI value \( \geq 61\% \) following a 300–600 mg loading dose. The clopidogrel maintenance dose was 75 mg/day. The prasugrel or ticagrelor group included patients treated with 10

### Study Protocol

The choice of antiplatelet therapy was left to the clinicians’ discretion. Patients were also treated by intra-

<table>
<thead>
<tr>
<th>Variable, n (%)</th>
<th>Clopidogrel ((n=268))</th>
<th>Prasugrel/Ticagrelor ((n=268))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>137 (51.1)</td>
<td>166 (61.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>NSTEMI, n (%)</td>
<td>110 (41)</td>
<td>88 (32.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>20 (7.5)</td>
<td>13 (4.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Symptom, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip (\geq 2)</td>
<td>17 (6.4)</td>
<td>25 (9.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Prior angina</td>
<td>68 (31.3)</td>
<td>94 (35.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Demographic, n (%)</td>
<td>61 +/- 12 (31–89)</td>
<td>58 +/- 11 (31–88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>223 (83.2)</td>
<td>226 (84.3)</td>
<td>0.81</td>
</tr>
<tr>
<td>Female</td>
<td>45 (16.8)</td>
<td>42 (15.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Risk factors/ past medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>135 (50.4)</td>
<td>135 (50.4)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (50.8)</td>
<td>130 (48.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>61 (22.8)</td>
<td>66 (24.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 Kg/m(^2))</td>
<td>27 +/- 4.7 (18.5–44.8)</td>
<td>27 +/- 4.9 (17–54)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>135 (50.4)</td>
<td>121 (45.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Family history of coronary artery disease (CAD)</td>
<td>52 (19.4)</td>
<td>67 (25)</td>
<td>0.15</td>
</tr>
<tr>
<td>Prior STEMI</td>
<td>37 (13.9)</td>
<td>34 (12.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Prior NSTEMI</td>
<td>14 (5.3)</td>
<td>21 (7.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Prior angioplasty</td>
<td>46 (17.2)</td>
<td>40 (14.9)</td>
<td>0.48</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>9 (3.4)</td>
<td>7 (2.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>13 (4.8)</td>
<td>7 (2.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>15 (5.6)</td>
<td>12 (4.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>9 (3.4)</td>
<td>12 (4.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Echographic characteristics, Left Ventricular Ejection Fraction (%)</td>
<td>55 +/- 11.3 (25–76)</td>
<td>55 +/- 10.7 (20–80)</td>
<td>0.30</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>245 (93.9)</td>
<td>247 (92.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Beta–blockers</td>
<td>250 (95.4)</td>
<td>259 (96.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Statins</td>
<td>254 (97)</td>
<td>262 (97.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Oral anticoagulants (VKA antagonists)</td>
<td>32 (12.3)</td>
<td>0 (0.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>GPI\textsubscript{II}b\textsubscript{III}a antagonist</td>
<td>88 (33.7)</td>
<td>83 (31)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Values are n +/- median (range) or n (%)  
ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft surgery; NSTEMI = Non ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction

using a receiver-operating characteristic curve analysis based on the Youden's index maximum value. Patients were considered low clopidogrel responders if their PRI was \( \geq 61\% \), and normal clopidogrel responders if their PRI was <61\%\(^{18}\). In our experience, the 50% threshold did not allow a relevant identification of low clopidogrel responders\(^{18}\).
mg prasugrel daily after a loading dose of 60 mg, or 90 mg ticagrelor twice daily after a loading dose of 180 mg. During hospitalization, patients who switched to prasugrel or ticagrelor were placed into the prasugrel/ticagrelor group, and patients who switched to clopidogrel being excluded.

The study flowchart is illustrated in Fig. 1.

**Study Objectives**

The primary efficacy endpoint was the major adverse cardiac event rate (MACE), defined as the composite of cardiovascular death, both definite and probable stent thrombosis, myocardial infarction (STEMI or NSTEMI), and stroke. ST-segment elevation myocardial infarction (STEMI) was defined as a new ST-segment elevation in two consecutive leads with increased biochemical myocardial necrosis markers, and non-STEMI (NSTEMI) as occurrence of ischemic symptoms associated with ST-segment depression and T-wave abnormalities and increased biochemical myocardial necrosis markers. Post-PCI troponin (Tn) elevations were not considered indicative of recurrent myocardial
in line with the Academic Research Consortium criteria, two ST types were distinguished: 1) definite ST defined as an ACS proved by angiographic or pathologic evidence; 2) probable ST corresponding to unexplained death within 30 days or target vessel infarction without angiographic information. Stroke was defined as a focal loss of neurologic function caused by ischemic events, with residual symptoms lasting >24 hours. Secondary analyses were performed for each primary endpoint component.

The secondary endpoint was the occurrence of major bleeding, with bleeding severity defined using the Bleeding Academic Research Consortium (BARC) criteria. Major bleeding was defined as a BARC score ≥Type 3b, and minor bleeding as a BARC score <Type 3b.

Follow-up information was obtained using a written questionnaire via a telephone interview with the cardiologist, referring physician, or patient. In the absence of response, the patient’s electronic medical file was consulted. Endpoints were adjudicated by two physicians who were blinded to treatment allocation.

**Statistical Analysis**
Continous variables were expressed as median (interquartile range, 25th and 75th percentile) or mean ± SD, and categorical variables as frequencies and percentages. Continuous variables between both groups were compared using Student’s t-test or Mann–Whitney U test, as appropriate. Fisher’s exact test was used to compare categorical variables. Continuous variables were analyzed for normal distribution using the Shapiro-Wilk test. Time to event was defined as the time from PCI to the event date, with patients censored at death, loss to follow-up, or study end on April 30, 2015. Propensity score (PS) matching analysis with 1:1...

### Table 7. Events at 30 days

<table>
<thead>
<tr>
<th>Event</th>
<th>Before PS matching</th>
<th>After PS matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel (n=448)</td>
<td>Prasugrel/Ticagrelor (n=282)</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>15 (3.3)</td>
<td>3 (1.06)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>4 (0.89)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8 (1.78)</td>
<td>3 (1.06)</td>
</tr>
<tr>
<td>Stent thrombosis definite</td>
<td>5 (1.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stent thrombosis probable</td>
<td>4 (0.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.22)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bleeding, n (%)</td>
<td>14 (3.2)</td>
<td>13 (5.1)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (0.4)</td>
<td>1 (0.35)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>2 (0.4)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

Values are n (%)

### Table 8. Events at the end of the follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Before PS matching</th>
<th>After PS matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel (n=448)</td>
<td>Prasugrel/Ticagrelor (n=282)</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>35 (7.8)</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>12 (2.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>19 (4.4)</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Stent thrombosis definite</td>
<td>8 (1.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Stent thrombosis probable</td>
<td>4 (0.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (0.7)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Bleeding, n (%)</td>
<td>14 (3.2)</td>
<td>13 (5.1)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (1.6)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>7 (1.8)</td>
<td>10 (4)</td>
</tr>
</tbody>
</table>

Values are n (%)

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nearest neighbor matching was employed. Variables used in developing PS have been marked by * in Tables 1–3. The main variables were age, gender, clinical presentation, cardiovascular risk factor, peripheral vascular disease, three-vessel disease and chronic kidney disease. These were chosen based on the thrombotic risk's clinical relevance. Following PS analysis, 268 clopidogrel-treated patients were matched with an equal number of prasugrel- or ticagrelor-treated patients.

Kaplan–Meier analysis was employed to establish survival plots without MACE or major bleeding, with the two groups compared using the log-rank test. The Cox model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). A multivariate analysis of MACE was done using Cox models. Variables with $p < 0.05$ in univariate analysis were entered into a stepwise ascending multivariate analysis. The Cox regression results were presented as HRs, 95% CIs, and $p$-values. A $p$ value $< 0.05$ was considered statistically significant.

Statistical analyses were performed using SPSS Version 13.0 software (SPSS Inc., Chicago, Illinois) and the R software (R Development Core Team [2008], Vienna, Austria). The significance level was set at 5%.

**Results**

**Patient Characteristics**

From January 1, 2008 to April 30, 2015, 7009 patients were admitted to our department (NHC, Strasbourg, France) for ACS treated by PCI and stent implantation, with 790 patients under clopidogrel fulfilling the inclusion criteria, 448 patients of which (57%) exhibited a VASP $\leq 61\%$ proving appropriate P2Y$_{12}$ inhibition. These patients were compared to 282 patients under prasugrel ($n=161$, 57%) or ticagrelor ($n=121$, 43%) therapy.

The whole cohort's baseline characteristics were provided in Tables 1–3.

Patients under clopidogrel treatment were generally older, less likely to be male, and more likely to present NSTEMI, multiple comorbidities, and prior atrial fibrillation. The coronary artery disease extent and the bifurcation's lesions were more significant in
the clopidogrel group. PRI value, a marker of P2Y₁₂ inhibition, was significantly lower in the prasugrel/ticagrelor group. Peak Tn was lower in the clopidogrel group, in line with the group’s lower proportion of STEMI, along with higher levels of HbA1c, BNP, and CRP in this group. The timing of VASP testing was longer in the clopidogrel group (clopidogrel 30 +/- 20 h vs 23 +/- 28, \( p < 0.001 \)) probably reflecting the fact that this group presented longer hospital stay (older, multiple comorbidities, etc.).

Characteristics of the patients enrolled in the PS analysis are given in Tables 4–6. Even after PS matching, important differences remained between the two subsets. Of note, clopidogrel patients were older, presented a higher rate of bifurcation lesion and were more frequently implanted with BMS.

**Clinical Outcomes**

Clinical outcomes were available for 684 of 730 patients (93.7%), with a mean follow-up of 260 ± 186 days. Of the 46 patients lost to follow-up (6.3%), 17 (2.3%) were using clopidogrel and 29 (3.9%) prasugrel or ticagrelor. At 30 days, no significant differences in MACE, cardiac death, definite and probable ST, myocardial infarction, stroke and bleedings between groups could be evidenced in the whole cohort and after PS analysis (Table 7).

At the end of the follow-up in the whole cohort, the composite primary endpoint occurred in 7.8% of the clopidogrel patients and 3.9% of those treated with prasugrel/ticagrelor (\( p = 0.034 \)). Myocardial infarction, definite and probable ST, and stroke rates did not significantly differ between groups, while higher cardiac death rates were observed under clopidogrel (Table 8). Kaplan–Meier analyses for MACE-free survival probability did not significantly differ (log-rank test, \( p = 0.108 \)) (Fig. 2).

There were 10 major bleeding events (1.3%) and 17 minor (2.3%) recorded at follow-up, with no significant between-group differences (Table 8). A Kaplan–Meier analysis for major bleeding-free survival probability has been presented in Fig. 3.

At the end of the follow-up, event rates following PS matching were given in Table 8. After matching
ease, total number of implanted stents, high CRP levels, and hemorrhagic events were significant predictors of definite/probable ST. No significant impact of clopidogrel treatment allocation on ST was established (HR 2.23; 95% CI: 0.63– 7.91; \( p = 0.211 \)). Multivariate Cox regression analysis identified hemorrhagic events, elevated CRP levels at admission, and total number of implanted stents as independent predictors of definite/probable ST (Table 10).

### Discussion

Our primary finding was that in PCI-treated ACS patients, appropriate platelet inhibition strategy by clopidogrel, proven by PRI VASP < 61%, did not significantly increase thrombotic event risks compared to prasugrel or ticagrelor therapy. With clopidogrel, there were reduced minor bleeding events with no impact on major bleeding events.

Two large randomized trials primarily enrolling PCI-treated ACS patients have previously demonstrated that prasugrel and ticagrelor substantially reduce thrombotic events compared with clopidogrel^{19, 20}. However, data confirming the new P2Y_{12} inhibitors’ bene-

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**Fig. 4.** Kaplan Meier Analysis of survival without MACE after propensity score matching.
treatment with potent platelet inhibition in the acute phase (where the thrombotic risk prevails) and de-escalation to clopidogrel in the maintenance phase (to limit the bleeding risk) was very recently shown to be safe. In this pioneering work by Sibbing, guided de-escalation of antiplatelet treatment was non-inferior to the standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit.\(^{29}\) Owing to the global economic crisis, cost/effectiveness approaches are widely recommended. In the US, recent analyses have underlined that access to new P2Y12 inhibitors could be limited. In addition to advanced age (\(\geq 75\) years), vascular comorbidities, black ethnicity, and lack of private insurance were key determinants of clopidogrel prescription in ACS patients.\(^{30}\) Besides bleeding and recurrent ischemic event risks, medical drug coverage was recognized as a major determinant of ADP receptor inhibitor selection in contemporary US practice.\(^{31}\) In other countries, health insurers tend to only refund new P2Y12 inhibitors in PCI treatment of high-risk ACS when platelet function assessment confirmed the patients’ non-response to clopidogrel.\(^{32}\)

Several large-scale real-life registries have compared early outcomes of ACS patients treated by either fits over appropriate platelet inhibition by clopidogrel is still lacking. Owing to impaired clopidogrel-induced platelet inhibition in numerous ACS patients,\(^ {25, 26}\) one may speculate that the new P2Y12 inhibitors’ benefits over clopidogrel were mainly accounted for by a drastic reduction in thrombotic risk compared to the risk observed in HPR patients. Conversely, the new P2Y12 inhibitors’ beneficial impact could prove much more limited in patients with appropriate clopidogrel inhibition. In the ACS setting, recent insights suggested that HPR may primarily be an integrate marker of associated comorbidities such as chronic renal disease, ongoing inflammation, and so on, all known to interfere with clopidogrel pharmacodynamics.\(^ {17}\) These comorbidities are unlikely modified by more potent P2Y12 inhibition using either higher clopidogrel doses or new P2Y12 inhibitors. In the ACS setting, another issue to consider is the bleeding risk that is partially determined by the P2Y12 inhibition extent.\(^ {4, 27}\) Several studies have emphasized that high platelet inhibition, similar to that by prasugrel or ticagrelor, does increase bleeding risk.\(^ {4, 27}\) Strategies aiming at an optimal therapeutic window, with the lowest risks of bleeding and ST post-PCI, are highly warranted.\(^ {26, 28}\) Interestingly, a stage-adapted treatment with potent platelet inhibition in the acute phase (where the thrombotic risk prevails) and de-escalation to clopidogrel in the maintenance phase (to limit the bleeding risk) was very recently shown to be safe. In this pioneering work by Sibbing, guided de-escalation of antiplatelet treatment was non-inferior to the standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit.\(^ {29}\) Owing to the global economic crisis, cost/effectiveness approaches are widely recommended. In the US, recent analyses have underlined that access to new P2Y12 inhibitors could be limited. In addition to advanced age (\(\geq 75\) years), vascular comorbidities, black ethnicity, and lack of private insurance were key determinants of clopidogrel prescription in ACS patients.\(^ {30}\) Besides bleeding and recurrent ischemic event risks, medical drug coverage was recognized as a major determinant of ADP receptor inhibitor selection in contemporary US practice.\(^ {31}\) In other countries, health insurers tend to only refund new P2Y12 inhibitors in PCI treatment of high-risk ACS when platelet function assessment confirmed the patients’ non-response to clopidogrel.\(^ {32}\)

Several large-scale real-life registries have compared early outcomes of ACS patients treated by either
clopidogrel or new P2Y12 inhibitors\textsuperscript{30, 33}, yet with conflicting results. It must be emphasized that the platelet inhibition extent was not assessed in these studies. In the studies by Alexopoulos, the switch from clopidogrel to new P2Y12 inhibitors was associated with reduced thrombotic MACE at the price of an increased bleeding rate\textsuperscript{33}. In the TRANSLATE ACS trial, death was more commonly observed in patients who pursued clopidogrel compared to those who switched to prasugrel or ticagrelor, whereas MACE, stroke, and recurrent MI risk did not significantly differ. After adjusting for confounding factors, the mortality rate was however lowered\textsuperscript{30}.

Study data was first analyzed in the whole cohort without adjusting for confounding factors. MACE and cardiac death rates were numerically higher in the clopidogrel responder group, whereas these differences were no longer significant after Cox regression or Kaplan–Meier analyses. Thrombotic events were not significantly increased in patients with appropriate platelet inhibition by clopidogrel. Of note is that causes of fatal events remain difficult to ascertain, and calculation of cardiac mortality must thus be taken with caution. To overcome confounding factors, PS analysis was performed, with patients matched according to certain variables associated with enhanced thrombotic risk. Analysis confirmed that the strategy of appropriate inhibition by clopidogrel did not significantly incr-

\begin{table}[h]
\centering
\caption{Univariate and multivariate analyses to predict MACE}  
\begin{tabular}{lccc}
\textbf{Variable} & \textbf{Univariate Analysis} & \textbf{Multivariate Analysis} \\
 & \textbf{HR [95% CI]} & \textbf{P value} & \textbf{HR [95% CI]} & \textbf{P value} \\
\hline
Age & 1.022 [1.000–1.046] & 0.051 & 1.003 [0.977–1.030] & 0.814 \\
Sex & 1.456 [0.786–2.698] & 0.232 & 2.290 [0.786–2.698] & 0.232 \\
STEMI & 0.542 [0.296–0.995] & 0.048 & 0.959 [0.455–2.023] & 0.913 \\
NSTEMI & 2.011 [1.122–3.604] & 0.019 & 1.742 [0.844–3.592] & 0.133 \\
Unstable angina & 0.813 [0.292–2.269] & 0.693 & 2.290 [0.786–2.698] & 0.232 \\
BMI & 1.012 [0.952–1.075] & 0.710 & 0.229 [0.099–1.008] & 0.180 \\
Smoking & 0.645 [0.351–1.182] & 0.156 & 1.30 [0.351–0.786] & 0.493 \\
Diabetes mellitus & 2.290 [1.278–4.102] & 0.005 & 1.530 [0.846–2.765] & 0.160 \\
Hypertension & 1.536 [0.837–2.818] & 0.166 & 1.09 [0.858–1.387] & 0.280 \\
Dyslipidemia & 1.530 [0.846–2.765] & 0.160 & 1.09 [0.858–1.387] & 0.280 \\
Prior PCI & 0.954 [0.460–1.977] & 0.899 & 1.536 [0.837–2.818] & 0.166 \\
CKD & 3.594 [1.675–7.711] & 0.001 & 1.530 [0.846–2.765] & 0.160 \\
History of stroke & 3.065 [1.298–7.238] & 0.011 & 1.09 [0.858–1.387] & 0.280 \\
Peripheral vascular disease & 2.566 [1.238–5.318] & 0.011 & 1.09 [0.858–1.387] & 0.280 \\
Killip 2 to 4 & 2.295 [1.108–4.757] & 0.025 & 1.530 [0.846–2.765] & 0.160 \\
Creatinine & 1.003 [0.999–1.008] & 0.180 & 2.290 [0.786–2.698] & 0.232 \\
HbA1c & 1.207 [1.025–1.422] & 0.024 & 1.530 [0.846–2.765] & 0.160 \\
BNP at admission & 1.000 [1.000–1.001] & 0.020 & 1.000 [1.000–1.001] & 0.020 \\
CRP at admission & 1.011 [1.005–1.017] & 0.001 & 1.011 [1.004–1.018] & 0.003 \\
Troponin at admission & 1.006 [1.002–1.011] & 0.005 & 1.008 [1.002–1.015] & 0.015 \\
Left ventricular ejection fraction & 0.970 [0.947–0.993] & 0.011 & 1.006 [0.990–1.022] & 0.487 \\
Clopidogrel & 1.741 [0.884–3.429] & 0.109 & 1.006 [0.990–1.022] & 0.487 \\
ACE-inhibitor & 0.320 [0.149–0.686] & 0.003 & 1.006 [0.990–1.022] & 0.487 \\
Statin & 0.274 [0.098–0.765] & 0.013 & 1.006 [0.990–1.022] & 0.487 \\
Stent’s total length & 1.016 [1.005–1.026] & 0.003 & 1.006 [0.990–1.022] & 0.487 \\
Stent’s Diameter & 0.955 [0.608–1.500] & 0.843 & 1.006 [0.990–1.022] & 0.487 \\
DES & 1.865 [0.946–3.678] & 0.072 & 1.006 [0.990–1.022] & 0.487 \\
Three-vessel disease & 1.816 [1.004–3.284] & 0.048 & 1.532 [0.757–3.101] & 0.236 \\
Left main coronary artery & 1.770 [0.635–4.937] & 0.275 & 1.532 [0.757–3.101] & 0.236 \\
Bifurcation & 1.744 [0.689–4.415] & 0.240 & 1.532 [0.757–3.101] & 0.236 \\
Hemorrhagic event & 4.952 [1.938–12.656] & 0.001 & 3.119 [1.020–9.533] & 0.046 \\
\hline
\end{tabular}
\end{table}

HR = Hazard ratio; CI = confidence interval
ACE = angiotensin-converting enzyme; BMI = body mass index; BNP = brain natriuretic peptide; CRP = C-reactive protein; DES = drug eluting stent; NSTEMI = Non ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction
reduction in minor bleedings, without any impact on major bleedings. In the ACS setting, the interplay between bleeding and thrombotic events was emphasized by several studies. As underlined by Aradi et al., patients with a major bleeding event had a 7-fold increased risk of ST32). Additionally, bleeding together with ST was identified as a strong independent 1-year mortality predictor 32). In our study, bleeding was the strongest predictor of MACE and ST. Several hypotheses may be raised to account for the relationship between bleeding and thrombotic events: (i) even minor bleeding may trigger premature antiplatelet agent discontinuation; (ii) greater prevalence of comorbidities in patients suffering from bleeding events; (iii) hemodynamic compromise induced by severe hemorrhages could favor ST; and (iv) transfusion may induce platelet activation17). Lastly, inflammation, either pre-exist-
ing or resulting from blood transfusion, was considered an important mediator of thrombotic process\(^\text{36, 37}\). In line with this, high CRP level was identified in our study as an independent predictor of MACE, including ST. In real world practice, bleeding events appear to be more potent predictors of thrombotic events than the antiplatelet strategy type used. Therefore, the optimal therapeutic window or optimal antiplatelet strategy, enabling us to minimize both bleeding and thrombotic risks, must be further defined.

**Study Limitations**

This study displays several limitations. Firstly, the applied antiplatelet strategy was not randomized. Moreover, group characteristics differed, advanced age and multiple comorbidities being more common in the clopidogrel group. Secondly, clopidogrel response was only assessed at the acute phase, following bolus dose administration, which could have resulted in clopidogrel response overestimation. Thirdly, as the cause of fatal events remains often difficult to ascertain, estimation of cardiac mortality requires caution. Fourthly, an independent committee did not adjudicate cardiovascular events. Due to the relatively low number of events recorded, multivariate analysis should be interpreted with caution with the findings viewed as hypothesis generating. Fifthly, there was no power calculation performed, and we could not exclude that the limited cohort size could have impeded detecting significant differences between the two strategies. Finally, cost/effectiveness analysis was not performed. While these limitations limit to some extent the validity of our comparison, it must be emphasized that registries are mandatory for collecting real-life data on unselected patients.

**Conclusion**

The results of this prospective ACS registry suggest that in clopidogrel-treated patients with appropriate platelet inhibition documented by platelet function test, continuing clopidogrel therapy is not associated with increased risks of thrombotic events compared to prasugrel or ticagrelor therapy.

**Conflicts of Interest**

The authors have no conflicts of interest to declare.

**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>ACT</td>
<td>Activated Clotting Time</td>
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<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
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<tr>
<td>BNP</td>
<td>B-type Natriuretic Peptide</td>
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<tr>
<td>BARC</td>
<td>Bleeding Academic Research Consortium</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>HPR</td>
<td>high on-treatment platelet reactivity</td>
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<td>MACE</td>
<td>major adverse cardiac event</td>
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<tr>
<td>NSTEMI</td>
<td>non-ST-segment elevation myocardial infarction</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>PRI</td>
<td>platelet reactivity index</td>
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<td>Tn</td>
<td>troponin</td>
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<tr>
<td>VASP</td>
<td>vasodilator-stimulated phosphoprotein</td>
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**References**

eluting stents. JAMA. 2005; 293: 2126-2130


