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
receptor inhibition to be detected but also does take into account co-existing patent comorbidities interfering with clopidogrel pharmacodynamics such as chronic renal diseases and advanced age.12-17] These comorbidities per se contribute to adverse outcomes and are unlikely modified by using more potent P2Y12 receptor inhibitors. Optimal P2Y12 inhibition detected by platelet function assays was, however, shown to enable identifying patients at lower ischemic risk.3, 9, 17, 18 Whether the use of new P2Y12 inhibitors could result in reduced thrombotic events compared to those observed in patients with appropriate clopidogrel-induced P2Y12 inhibition has yet to be investigated. Prasugrel and ticagrelor provide more potent platelet inhibition compared to clopidogrel, with a consistent reduction in thrombotic events.19, 20 European and US guidelines have thus advocated the use of prasugrel or ticagrelor instead of clopidogrel in PCI-treated ACS patients21, 22 based on the net benefits observed with new P2Y12 inhibitors over clopidogrel in the PLATO and TRI-TON trials.19, 20 However, no randomized data are available on the long-term efficacy or safety of the use of new P2Y12 inhibitors over the appropriate P2Y12 blockade by clopidogrel. One limitation of using more potent P2Y12 inhibitors is grounded on the greater risk of bleeding19, 20, 23, with an increased risk of short- and long-term morbidity in ACS patients.24 Another issue is the cost/effectiveness of antiplatelet strategy. As 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.

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-treated patients to ascertain platelet responsiveness.

Exclusion criteria: Significant dementia, absent PRI measurement by VASP assay under clopidogrel treatment, PRI >61% under clopidogrel, switch from either prasugrel or ticagrelor to clopidogrel, failed PCI, lack of stent implantation, contraindication to antiplatelet therapy, cardiogenic shock requiring critical care unit admission, and cardiogenic pulmonary edema requiring mechanical ventilation.

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 standardized 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% 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 ≥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

Study Protocol

The choice of antiplatelet therapy was left to the clinicians’ discretion. Patients were also treated by intravenous aspirin (125–250 mg) and 50–100 IU/Kg of unfractionated heparin to target an ACT >250 s.
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 infarction. 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 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 infarction. 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 phy-
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 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 dis-

### Table 1. Baseline demographic and clinical characteristics

| Variable, n (%) | Clopidogrel (n = 448) | Prasugrel/Ticagrelor (n = 282) | p |
|-----------------|-----------------------|--------------------------------|---|
| Clinical presentation, n (%) | | | |
| STEMI, n (%) | 189 (42.2) | 175 (62.1) | 0.0001* |
| NSTEMI, n (%) | 202 (45.1) | 93 (33.0) | 0.001* |
| Unstable angina, n (%) | 54 (12.1) | 13 (4.6) | 0.0005* |
| Symptom, n (%) | | | |
| Killip ≥ 2 | 48 (10.8) | 27 (9.6) | 0.671 |
| Prior angina | 102 (28.1) | 99 (35.1) | 0.06 |
| Demographic, n (%) | | | |
| Age (year) | 66.8 +/- 13.5 (28–93) | 57.8 +/- 11.2 (31–89) | 0.0001* |
| Sex | | | |
| Male | 310 (69.2) | 237 (84.0) | 0.0001* |
| Female | 139 (30.8) | 45 (16.0) | 0.0001* |
| Risk factors/past medical history, n (%) | | | |
| Current smoking | 188 (42) | 142 (50.4) | 0.03* |
| Hypertension | 262 (58.5) | 137 (48.6) | 0.009* |
| Diabetes mellitus | 117 (26) | 67 (23.8) | 0.5 |
| Obesity (BMI > 30 Kg/m²) | 26.6 +/- 4.6 (16–44.7) | 27.7 +/- 4.9 (17–54) | 0.01* |
| Hyperlipidemia | 240 (53.6) | 129 (45.7) | 0.04* |
| Family history of coronary artery disease (CAD) | 69 (15.4) | 70 (24.8) | 0.002* |
| Prior STEMI | 77 (17.2) | 35 (12.5) | 0.09 |
| Prior NSTEMI | 30 (6.7) | 23 (8.2) | 0.47 |
| Prior angioplasty | 91 (20.4) | 42 (14.9) | 0.07 |
| Prior CABG | 28 (6.2) | 8 (2.8) | 0.05 |
| Prior Stroke | 31 (6.9) | 7 (2.5) | 0.009 |
| Peripheral vascular disease | 47 (10.5) | 13 (4.6) | 0.005* |
| Chronic Kidney Disease | 29 (6.5) | 12 (4.3) | 0.25* |
| Echographic characteristics, Left Ventricular Ejection Fraction (%) | 52.6 +/- 12.2 (15–80) | 52.9 +/- 10.6 (20–80) | 0.81 |
| Treatment, n (%) | | | |
| ACE inhibitors | 408 (93) | 259 (92) | 0.6 |
| Beta–blockers | 413 (93.9) | 273 (96.8) | 0.08 |
| Statins | 426 (96.8) | 276 (97.9) | 0.4 |
| Oral anticoagulants (VKA antagonists) | 58 (13.2) | 0 (0.0) | 0.0001 |
| GPIIb/IIIa antagonist | 108 (25.4) | 87 (31) | 0.08 |

Values are n +/- median (range) or n (%)
*Variables used to create propensity score
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

Physicians who were blinded to treatment allocation.

**Statistical Analysis**
Continuous 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 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 dis-
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%.

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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%.

### 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
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

| Variable | Clopidogrel (n=268) | Prasugrel/Ticagrelor (n=268) | p |
|----------|---------------------|-----------------------------|---|
| Clinical presentation, n (%) | | | |
| STEMI, n (%) | 137 (51.1) | 166 (61.9) | 0.01 |
| NSTEMI, n (%) | 110 (41) | 88 (32.8) | 0.06 |
| Unstable angina, n (%) | 20 (7.5) | 13 (4.8) | 0.28 |
| Symptom, n (%) | | | |
| Killip ≥2 | 17 (6.4) | 25 (9.3) | 0.26 |
| Prior angina | 68 (31.3) | 94 (35.1) | 0.44 |
| Demographic, n (%) | | | |
| Age (year) | 61 +/- 12 (31–89) | 58 +/- 11 (31–88) | 0.001 |
| Sex | | | |
| Male | 223 (83.2) | 226 (84.3) | 0.81 |
| Female | 45 (16.8) | 42 (15.7) | 0.81 |
| Risk factors/ past medical history, n (%) | | | |
| Current smoking | 135 (50.4) | 135 (50.4) | 1 |
| Hypertension | 136 (50.8) | 130 (48.5) | 0.67 |
| Diabetes mellitus | 61 (22.8) | 66 (24.6) | 0.33 |
| Obesity (BMI > 30 Kg/m²) | 27 +/- 4.7 (18.5–44.8) | 27 +/- 4.9 (17–54) | 0.74 |
| Hyperlipidemia | 135 (50.4) | 121 (45.1) | 0.26 |
| Family history of coronary artery disease (CAD) | 52 (19.4) | 67 (25) | 0.15 |
| Prior STEMI | 37 (13.9) | 34 (12.7) | 0.70 |
| Prior NSTEMI | 14 (5.3) | 21 (7.9) | 0.29 |
| Prior angioplasty | 46 (17.2) | 40 (14.9) | 0.48 |
| Prior CABG | 9 (3.4) | 7 (2.6) | 0.80 |
| Prior Stroke | 13 (4.8) | 7 (2.6) | 0.25 |
| Peripheral vascular disease | 15 (5.6) | 12 (4.5) | 0.69 |
| Chronic Kidney Disease | 9 (3.4) | 12 (4.5) | 0.66 |
| Echographic characteristics, Left Ventricular Ejection Fraction (%) | 55 +/- 11.3 (25–76) | 55 +/- 10.7 (20–80) | 0.30 |
| Treatment, n (%) | | | |
| ACE inhibitors | 245 (93.9) | 247 (92.2) | 0.50 |
| Beta–blockers | 250 (95.4) | 259 (96.6) | 0.51 |
| Statins | 254 (97) | 262 (97.8) | 0.60 |
| Oral anticoagulants (VKA antagonists) | 32 (12.3) | 0 (0.0) | 0.0001 |
| GPIIb/IIIa antagonist | 88 (33.7) | 83 (31) | 0.52 |

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

**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 <61% proving appropriate P2Y12 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
sented 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

| Table 5. Baseline angiographic characteristics after propensity score matching |
|-----------------------------------------------|
|                                | Clopidogrel (n = 268) | Prasugrel/Ticagrelor (n = 268) | P     |
|-----------------------------------------------|
| Mono-vessel disease, n (%)                  | 131 (48.9)           | 136 (50.8)               | 0.73  |
| Dual-vessel disease, n (%)                  | 81 (30.2)            | 86 (32.1)                | 0.71  |
| Three-vessel disease, n (%)                 | 56 (20.9)            | 46 (17.2)                | 0.32  |
| LAD, n (%)                                   | 160 (59.7)           | 165 (61.6)               | 0.72  |
| CX, n (%)                                    | 83 (31.1)            | 79 (29.5)                | 0.71  |
| RCA, n (%)                                   | 143 (53.4)           | 131 (48.9)               | 0.34  |
| Left main coronary artery, n (%)            | 13 (4.8)             | 10 (3.7)                 | 0.67  |
| Bifurcation n (%)                            | 20 (7.5)             | 4 (1.5)                  | 0.0012|
| Total stent's length (mm)                   | 20 +/- 14.9 (15–122) | 34 +/- 22 (18–188)       | 0.0016|
| Stent's diameter (mm)                       | 3 +/- 0.5 (3–4.5)    | 3.0 +/- 0.8 (2.8–5)      | 0.64  |
| DES                                          | 133 (49.6)           | 247 (92.5)               | 0.0001|

Values are n +/- median (range) or n (%)

LAD=left anterior descending artery; CX=circumflex artery; RCA=right coronary artery

| Table 6. Biological characteristics after propensity score matching |
|-----------------------------------------------|
|                                | Clopidogrel (n = 268) | Prasugrel/Ticagrelor (n = 268) | P     |
|-----------------------------------------------|
| Glycemia (g/dL)                              | 1.2 +/- 0.7 (0.7–4.8) | 1.3 +/- 0.6 (0.7–5.1)          | 0.007 |
| HbA1c (%)                                    | 5.9 +/- 1.4 (4.5–16.4) | 5.7 +/- 1.2 (4.7–12.8)         | 0.001 |
| Creatinine (umol/L)                          | 77.3 +/- 47.7 (38.7–565) | 72.3 +/- 25.4 (37–248.3)       | 0.006 |
| Tn adhesion (ug/L)                           | 0.4 [0.04–480]        | 0.4 [0.04–304]                | 0.90  |
| Tn peak (ug/L)                               | 12.3 [1.4–528]        | 28.9 [4–738]                 | 0.0001|
| BNP (ng/l)                                   | 91 [37–5598]          | 52 [21–2193]                 | 0.0003|
| CRP (mg/l)                                   | 4.4 [4–249]           | 4 [4–193]                    | 0.001 |
| Leukocytes (10^6/μL)                         | 9.3 +/- 3.8 (1.3–29.8) | 10.4 +/- 3.8 (4–25.5)         | 0.002 |
| Hb (g/dl)                                    | 14.2 +/- 1.7 (7.8–19.1) | 14.7 +/- 1.6 (5.1–19.1)       | 0.004 |
| Platelets (10^6/μL)                          | 234 +/- 76.7 (67–584)  | 240 +/- 69.6 (85–818)         | 0.94  |
| Total cholesterol (g/L)                      | 1.8 +/- 0.5 (0.8–5)   | 1.8 +/- 0.4 (0.9–4)           | 0.34  |
| LDLc (g/L)                                   | 1.1 +/- 0.4 (0.4–2.2)  | 1.1 +/- 0.4 (0.3–2.4)         | 0.66  |
| HDLc (g/L)                                   | 0.4 +/- 0.1 (0.1–0.9)  | 0.4 +/- 0.1 (0.2–1.5)         | 0.0034|
| TG (g/L)                                     | 1.1 +/- 1 (0.3–7.2)   | 1.3 +/- 1 (0.4–9.5)           | 0.002 |
| VASP PRI (%)                                 | 41.9 +/- 17 (3–60)    | 15 +/- 21.5 (2–60)            | 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

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.
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

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**Table 7. Events at 30 days**

|                  | Before PS matching | After PS matching | \( p \) | Before PS matching | After PS matching | \( p \) |
|------------------|--------------------|-------------------|--------|--------------------|-------------------|--------|
| MACE, n (%)      | Clopidogrel (\( n=448 \)) | Prasugrel/Ticagrelor (\( n=282 \)) | 0.071  | Clopidogrel (\( n=268 \)) | Prasugrel/Ticagrelor (\( n=268 \)) | 0.20   |
| Cardiac death    | 4 (0.89)           | 0 (0)             | 0.125  | 2 (0.7)            | 0 (0)             | 1      |
| Myocardial infarction | 8 (1.78)       | 3 (1.06)         | 0.503  | 3 (1.1)            | 0 (0)             | 0.74   |
| Stent thrombosis definite | 5 (1.1)      | 0 (0)            | 0.086  | 3 (1.1)            | 0 (0)             | 0.28   |
| Stent thrombosis probable | 4 (0.9)     | 0 (0)            | 0.125  | 3 (1.1)            | 0 (0)             | 0.55   |
| Stroke           | 1 (0.22)           | 0 (0)             | 0.43   | 1 (0.4)            | 0 (0)             | 1      |
| Bleeding, n (%)  | 14 (3.2)           | 13 (5.1)          | 0.214  | 4 (1.5)            | 2 (0.7)           | 0.58   |
| Major bleeding   | 2 (0.4)            | 1 (0.35)          | 0.904  | 3 (1.1)            | 1 (0.4)           | 0.84   |
| Minor bleeding   | 2 (0.4)            | 2 (0.7)           | 0.579  | 1 (0.4)            | 1 (0.4)           | 0.78   |

Values are \( n \) (%)

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

|                  | Before PS matching | After PS matching | \( p \) | Before PS matching | After PS matching | \( p \) |
|------------------|--------------------|-------------------|--------|--------------------|-------------------|--------|
| MACE, n (%)      | Clopidogrel (\( n=448 \)) | Prasugrel/Ticagrelor (\( n=282 \)) | 0.034  | Clopidogrel (\( n=268 \)) | Prasugrel/Ticagrelor (\( n=268 \)) | 0.43   |
| Cardiac death    | 12 (2.8)           | 1 (0.4)           | 0.028  | 7 (2.6)            | 1 (0.4)           | 0.11   |
| Myocardial infarction | 19 (4.4)      | 9 (3.6)           | 0.590  | 12 (4.5)           | 9 (3.4)           | 0.99   |
| Stent thrombosis definite | 8 (1.8)      | 2 (0.8)           | 0.288  | 5 (1.9)            | 2 (0.7)           | 0.44   |
| Stent thrombosis probable | 4 (0.9)     | 1 (0.4)           | 0.454  | 1 (0.4)            | 1 (0.4)           | 0.86   |
| Stroke           | 3 (0.7)            | 1 (0.4)           | 0.621  | 2 (0.7)            | 1 (0.4)           | 0.41   |
| Bleeding, n (%)  | 14 (3.2)           | 13 (5.1)          | 0.214  | 5 (1.9)            | 11 (4.1)          | 0.08   |
| Major bleeding   | 7 (1.6)            | 3 (1.2)           | 0.551  | 2 (0.7)            | 3 (1.1)           | 0.44   |
| Minor bleeding   | 7 (1.8)            | 10 (4)            | 0.091  | 3 (1.1)            | 8 (3)             | 0.03   |

Values are \( n \) (%)

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In univariate Cox analysis, age, clinical presentation, diabetes mellitus, renal dysfunction, medical history, stroke, or vascular diseases, Killip Class 2 to 4, high CRP level, high Tn level at admission, total stent length, three-vessel disease, and hemorrhagic events were significant MACE predictors. No significant impact of clopidogrel treatment allocation on MACE was estab-
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\(^1\), \(^2\). However, data confirming the new P2Y\(_{12}\) inhibitors’ benefits over appropriate platelet inhibition by clopidogrel is still lacking. Owing to impaired clopidogrel-induced platelet inhibition in numerous ACS patients\(^2\), \(^6\), one may speculate that the new P2Y\(_{12}\) 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 P2Y\(_{12}\) 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 integrative marker of associated comorbidities such as chronic renal disease, ongoing inflammation, and so on, all known to inter-

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**Stent Thrombosis Predictors**

In univariate Cox analysis, age, three-vessel disease, 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\(^1\), \(^2\). However, data confirming the new P2Y\(_{12}\) inhibitors’ benefits over appropriate platelet inhibition by clopidogrel is still lacking. Owing to impaired clopidogrel-induced platelet inhibition in numerous ACS patients\(^2\), \(^6\), one may speculate that the new P2Y\(_{12}\) 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 P2Y\(_{12}\) 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 integrative marker of associated comorbidities such as chronic renal disease, ongoing inflammation, and so on, all known to inter-
In addition to advanced age (>75 years), vascular comorbidities, black ethnicity, and lack of private insurance were key determinants of clopidogrel prescription in ACS patients. 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. 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.

Several large-scale real-life registries have compared early outcomes of ACS patients treated by either clopidogrel or new P2Y12 inhibitors, 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. 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. 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 increase the thrombotic risk. On the other hand, such strategy was found ineffective in reducing major bleeding events, in line with a large multicenter Swiss cohort. Our data extends recent findings by Aradi et al. In their study, thrombotic and hemorrhagic events rate were similar in HPR patients switched to prasugrel and in clopidogrel responders. This suggests that in ACS patients under clopidogrel, drug administration may be continued for managing thrombotic risks provided that appropriate platelet inhibition has been documented.

Safety concerns and the assessment of bleeding events are key when assessing any antiplatelet strategy’s net beneficial effects. When considering the whole cohort, no significant reduction in bleeding events was observed in the clopidogrel group. Following PS matching, the clopidogrel strategy resulted in a significant 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 ST. Additionally, bleeding together with ST was identified as a strong independent 1-year mortality predictor. 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 dis-

Fig. 4. Kaplan Meier Analysis of survival without MACE after propensity score matching.
continuation; (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 activation\(^\text{17}\). Lastly, inflammation, either pre-existing 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 com-
Table 9. Univariate and multivariate analyses to predict MACE

| Variable                        | Univariate Analysis | Multivariate Analysis |
|---------------------------------|---------------------|-----------------------|
|                                 | HR [95% CI]         | P value               |
|                                 |                     | HR [95% CI]           | P value               |
| 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                 |                       |                       |
| STEMI                           | 0.542 [0.296–0.995] | 0.048                 |                       |                       |
| 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                 |                       |                       |
| BMI                             | 1.012 [0.952–1.075] | 0.710                 |                       |                       |
| Smoking                         | 0.645 [0.351–1.182] | 0.156                 |                       |                       |
| Diabetes mellitus               | 2.290 [1.278–4.102] | 0.005                 | 0.959 [0.455–2.023]  | 0.913                 |
| Hypertension                    | 1.536 [0.837–2.818] | 0.166                 |                       |                       |
| Dyslipidemia                    | 1.530 [0.846–2.765] | 0.160                 |                       |                       |
| Prior PCI                       | 0.954 [0.460–1.977] | 0.899                 |                       |                       |
| CKD                             | 3.594 [1.675–7.711] | 0.001                 | 1.726 [0.641–4.645]  | 0.280                 |
| History of stroke               | 3.065 [1.298–7.238] | 0.011                 | 1.447 [0.503–4.162]  | 0.493                 |
| Peripheral vascular disease     | 2.566 [1.238–5.318] | 0.011                 | 1.865 [0.807–4.311]  | 0.145                 |
| Killip 2 to 4                   | 2.295 [1.108–4.757] | 0.025                 | 1.940 [0.368–2.400]  | 0.897                 |
| Creatinine                      | 1.003 [0.999–1.008] | 0.180                 |                       |                       |
| HbA1c                           | 1.207 [1.025–1.422] | 0.024                 |                       |                       |
| BNP at admission                | 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                |                       |                       |
| Clopidogrel                     | 1.741 [0.884–3.429] | 0.109                 |                       |                       |
| ACE-inhibitor                   | 0.320 [0.149–0.686] | 0.003                 |                       |                       |
| Statin                          | 0.274 [0.098–0.765] | 0.013                 |                       |                       |
| 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                 |                       |                       |
| DES                              | 1.865 [0.946–3.678] | 0.072                 |                       |                       |
| 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                 |                       |                       |
| Bifurcation                     | 1.744 [0.689–4.415] | 0.240                 |                       |                       |
| Hemorrhagic event               | 4.952 [1.938–12.656] | 0.001               | 3.119 [1.020–9.533]  | 0.046                 |

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

pared to prasugrel or ticagrelor therapy.

Conflicts of Interest
The authors have no conflicts of interest to declare.

List of Abbreviations

ACS: acute coronary syndrome
ACT: Activated Clotting Time
ADP: adenosine diphosphate
BARC: Bleeding Academic Research Consortium
BNP: B-type Natriuretic Peptide
HPR: high on-treatment platelet reactivity

MACE: major adverse cardiac event
NSTEMI: non ST-segment elevation myocardial infarction
PCI: percutaneous coronary intervention
PRI: platelet reactivity index
Tn: Troponin
VASP: vasodilator-stimulated phosphoprotein

References
1) Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, Gick M, Caputo A, Büttner HJ, Neumann FJ. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early
Table 10. Univariate and Multivariate analyses to predict Stent Thrombosis

| Variable                                      | Univariate Analysis | Multivariate Analysis |
|-----------------------------------------------|---------------------|-----------------------|
|                                               | HR 95% CI           | p                     | HR 95% CI           | p                     |
| Age                                           | 1.04 [0.99–1.08]    | 0.05                  | 1.015 [0.974–1.058] | 0.471                |
| Sex                                           | 0.75 [0.21–2.66]    | 0.66                  |                       |                       |
| STEMI                                         | 1.17 [0.43–3.23]    | 0.76                  |                       |                       |
| NSTEMI                                        | 1.33 [0.48–3.66]    | 0.59                  |                       |                       |
| Smoking                                       | 0.61 [0.21–1.78]    | 0.36                  |                       |                       |
| Diabetes                                      | 1.99 [0.71–5.60]    | 0.19                  |                       |                       |
| Hypertension                                  | 0.94 [0.34–2.58]    | 0.89                  |                       |                       |
| Family history of coronary artery disease     | 2.21 [0.75–6.46]    | 0.15                  |                       |                       |
| Dyslipidemia                                  | 1.10 [0.40–3.04]    | 0.85                  |                       |                       |
| BMI >30                                       | 1.17 [0.37–3.68]    | 0.79                  |                       |                       |
| Prior STEMI                                   | 0.37 [0.05–2.79]    | 0.33                  |                       |                       |
| Prior NSTEMI                                   | 0.89 [0.12–6.74]    | 0.91                  |                       |                       |
| Prior PCI                                     | 0.62 [0.14–2.74]    | 0.53                  |                       |                       |
| Prior CABG                                     | 1.33 [0.17–10.09]   | 0.79                  |                       |                       |
| History of stroke                             | 1.41 [0.19–10.76]   | 0.74                  |                       |                       |
| Peripheral vascular disease                   | 1.60 [0.36–7.11]    | 0.53                  |                       |                       |
| CKD                                           | 1.17 [0.15–8.92]    | 0.88                  |                       |                       |
| Killip 2 to 4                                  | 2.28 [0.64–8.07]    | 0.20                  |                       |                       |
| Left ventricular ejection fraction            | 0.97 [0.93–1.01]    | 0.19                  |                       |                       |
| Clopidogrel                                    | 2.23 [0.63–7.91]    | 0.211                 |                       |                       |
| ACE-inhibitor                                  | 0.28 [0.08–1.004]   | 0.05                  |                       |                       |
| Statin                                         | 0.075 [0.024–0.24]  | 0.0001                |                       |                       |
| HbA1c                                         | 1.27 [0.99–1.63]    | 0.06                  |                       |                       |
| Troponin at admission                          | 1.006 [0.99–1.01]   | 0.10                  |                       |                       |
| CRP at admission                               | 1.013 [1.004–1.022] | 0.005                 | 1.013 [1.004–1.023]  | 0.005                |
| Three vessel                                   | 3.26 [1.18–9.00]    | 0.02                  | 1.733 [0.538–5.581]  | 0.357                |
| Stent number                                   | 1.74 [1.25–2.43]    | 0.001                 | 1.661 [1.097–2.514]  | 0.016                |
| Hemorrhagic events                             | 5.44 [1.21–24.46]   | 0.03                  | 6.429 [1.349–30.633] | 0.019                |

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

clinical outcome of elective coronary stent placement. Journal of the American College of Cardiology. 2006; 48: 1742-1750
2) Geisler T, Zurn C, Simonenko R, Rapin M, Kraibooj H, Kilias A, Bigalke B, Stellos K, Schwab M, May AE, Herdeg C, Gawaz M. Early but not late stent thrombosis is influenced by residual platelet aggregation in patients undergoing coronary interventions. European heart journal. 2010; 31: 59-66
3) Morel O, El Ghannudi S, Jesel L, Radulescu B, Meyer N, Wiesel ML, Caillard S, Campia U, Moulin B, Gachet C, Ohlmann P. Cardiovascular mortality in chronic kidney disease patients undergoing percutaneous coronary intervention is mainly related to impaired P2Y12 inhibition by clopidogrel. Journal of the American College of Cardiology. 2011; 57: 399-408
4) Cuisset T, Frere C, Quilici J, Morange PE, Camoin L, Bali L, Lambert M, Juhan-Vague I, Alessi MC, Bonnet JL. Relationship between aspirin and clopidogrel responses in acute coronary syndrome and clinical predictors of non response. Thromb Res. 2009; 123: 597-603
5) Frere C, Cuisset T, Quilici J, Camoin L, Carvajal J, Morange PE, Lambert M, Juhan-Vague I, Bonnet JL, Alessi MC. ADP-induced platelet aggregation and platelet reactivity index VASP are good predictive markers for clinical outcomes in non-ST elevation acute coronary syndrome. Thrombosis and haemostasis. 2007; 98: 838-843
6) Range G, Yayehd K, Belle L, Thuaire C, Richard P, Cazaux P, Barbou F, König R, Chassaing S, Teiger E, Berthier R, Decomis MP, Claudel JP, Delarche N, Brunel P, De Poli F, Dupouy P, Beygui F, Albert F, Collet JP, Montalescot G. Thrombotic and bleeding events after coronary stenting according to clopidogrel and aspirin platelet reactivity: VerifyNow French Registry (VERIFRENCHY). Arch Cardiovasc Dis. 2014; 107: 225-235
7) Cuisset T, Cayla G, Silvain J. Clopidogrel resistance: what’s new? Arch Cardiovasc Dis. 2010; 103: 349–353
8) Iakovou I, Schmidt T, Bonizzi E, Ge L, Sangiorgi GM,
Stankovic G, Airolidi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA. 2005; 293: 2126-2130

9) Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA. 2011; 305: 1097-1105

10) Tenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Muller U, Richardt G, Jakubowski JA, Neumann FJ. A Randomized Trial of Prasugrel Versus Clopidogrel in Patients With High Platelet Reactivity on Clopidogrel After Elective Percutaneous Coronary Intervention With Implantation of Drug-Eluting Stents: Results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) Study. Journal of the American College of Cardiology. 2012; 59: 2159-2164

11) Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Poulilott C, Henry P, Motreff P, Carré D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monséguy J, Sabouret P, O’Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthélémy O, Beygui F, Silvain J, Vicaut E, Montalescot G. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med. 2012; 367: 2100-2109

12) Angiolillo DJ, Bernardo E, Capodanno D, Vivas D, Sabate M, Ferreiro JL, Ueno M, Jimenez-Quevedo P, Alfonso F, Bass TA, Macaya C, Fernandez-Ortiz A. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. Journal of the American College of Cardiology. 2010; 55: 1139-1146

13) El Ghannudi S, Ohlmann P, Jesel L, Radulescu B, El Adraa E, Crimizade U, Wiesel ML, Gachet C, Morel O. Impaired inhibition of P2Y(12) by clopidogrel is a major determinant of cardiac death in diabetes mellitus patients treated by percutaneous coronary intervention. Atherosclerosis. 2011; 217: 465-472

14) Muller C, Caillard S, Jesel L, El Ghannudi S, Ohlmann P, Sauleau E, Hannedouche T, Gachet C, Moulin B, Morel O. Association of estimated GFR with platelet inhibition in patients treated with clopidogrel. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2012; 59: 777-785

15) Morel O, El Ghannudi S, Hess S, Reydel A, Crimizade U, Jesel L, Radulescu B, Wiesel ML, Gachet C, Ohlmann P. The extent of P2Y12 inhibition by clopidogrel in diabetes mellitus patients with acute coronary syndrome is not related to glycaemic control: roles of white blood cell count and body weight. Thrombosis and haemostasis. 2012; 108: 338-348

16) Geisler T, Mueller K, Aichele S, Bigalke B, Stellos K, Htun P, Ninci E, Fateh-Moghadam S, May AE, Gawaz M. Impact of inflammatory state and metabolic control on responsiveness to dual antiplatelet therapy in type 2 diabetics after PCI: prognostic relevance of residual platelet aggregability in diabetics undergoing coronary interventions. Clin Res Cardiol. 2010; 99: 743-752

17) Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, Stone GW, Curzen N, Geisler T, Ten Berg J, Kirtane A, Siller-Matula J, Mahla E, Becker RC, Bhatt DL, Waksman R, Rao SV, Alexopoulos D, Marcucci R, Reny JL, Tenk D, Sibbing D, Gurcel BA. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. Journal of the American College of Cardiology. 2013; 62: 2261-2273

18) El Ghannudi S, Ohlmann P, Meyer N, Wiesel ML, Radulescu B, Chauvin M, Bareiss P, Gachet C, Morel O. Impact of P2Y12 inhibition by clopidogrel on cardiovascular mortality in unselected patients treated by percutaneous coronary angioplasty: a prospective registry. JACC Cardiovascular interventions. 2010; 3: 648-656

19) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357: 2001-2015

20) Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361: 1045-1057

21) Authors/Task Force m, Windecker S, Kolk P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jünip S, Kappetein AP, Kastrati A, Knutui J, Landmesser U, Laufar G, Neumann FJ, Richter DJ, Schaute R, Sousa Uva M, Stefanini GG, Taggaret DR, Torracce L, Valgimigli M, Wijns W, Witowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European heart journal. 2014; 35: 2541-2619

22) Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O’Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2016

23) Hochholzer W, Wiviott SD, Antman EM, Contant CF, Guo J, Giugliano RP, Dalby AJ, Montalescot G, Braunwald E. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel--Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). Circulation. 2011; 123: 2681-2689

24) Chhatriwalla AK, Amin AP, Kennedy KP, House JA,
Cohen DJ, Rao SV, Messenger JC, Marso SP. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. JAMA. 2013; 309: 1022-1029

25) Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, Bhatt DL, Cattaneo M, Collet JP, Cuisset T, Gachet C, Montalescot G, Jennings LK, Kereiakes D, Sibbing D, Trenk D, Van Werkum JW, Paganelli F, Price MJ, Waksman R, Gurbel PA. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. Journal of the American College of Cardiology. 2010; 56: 919-933

26) Aradi D, Storey RF, Komocsi A, Trenk D, Gulba D, Kiss RG, Husted S, Bonello L, Sibbing D, Collet JP, Huber K. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. European heart journal. 2014; 35: 209-215

27) Parodi G, Bellandi B, Venditti F, Carrabba N, Valenti R, Migliorini A, Grassellini S, Ramazzotti E, Antonucci D. Residual platelet reactivity, bleedings, and adherence to treatment in patients having coronary stent implantation treated with prasugrel. Am J Cardiol. 2012; 109: 214-218

28) Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, ten Berg J, Janssen P Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. European heart journal. 2015; 36: 1762-1771

29) Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komocsi A, Dezsi CA, Holdt L, Felix SB, Parma R, Klopotowski M, Schwinger RHG, Rieber L, Huber K, Neumann FJ, Koltofisk L, Mehillij J, Huczek Z, Massberg S. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet. 2017

30) Bagai A, Peterson ED, Honeycutt E, Efron MB, Cohen DJ, Goodman SG, Anstrom KJ, Gupta A, Messenger JC, Wang TY. In-hospital switching between adenosine diphosphate receptor inhibitors in patients with acute myocardial infarction treated with percutaneous coronary intervention: Insights into contemporary practice from the TRANSLATE-ACS study. Eur Heart J Acute Cardiovasc Care. 2015; 4: 499-508

31) Bagai A, Wang Y, Wang TY, Curtis JP, Gurm HS, Shah B, Cheema AN, Peterson ED, Sauedo JF, Granger CB, Roe MT, Bhatt DL, McNamara RL, Alexander KP. In-hospital switching between clopidogrel and prasugrel among patients with acute myocardial infarction treated with percutaneous coronary intervention: insights into contemporary practice from the national cardiovascular data registry. Circulation Cardiovascular interventions. 2014; 7: 585-593

32) Aradi D, Tornynos A, Pinter T, Vorobcsuk A, Konyi A, Falukozy J, Veress G, Magyari B, Horvath IG, Komócsi A. Optimizing P2Y12 receptor inhibition in patients with acute coronary syndrome on the basis of platelet function testing: impact of prasugrel and high-dose clopidogrel. Journal of the American College of Cardiology. 2014; 63: 1061-1070

33) Alexopoulos D, Xanthopoulou I, Deftereos S, Sitafidis G, Kanakakis I, Hamilos M, Angelidis C, Petousis S, Stakos D, Parissis H, Vavouranakis M, Davlouros P, Goudevenos J, Stefanadis C. In-hospital switching of oral P2Y12 inhibitor treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention: prevalence, predictors and short-term outcome. American heart journal. 2014; 167: 68-76 e2

34) Klingenberg R, Heg D, Raber L, Carballo D, Nanchen D, Gencer B, Auier R, Jaguszewski M, Stähli BE, Jakob P, Templin C, Stefanini GG, Meier B, Vogt P, Roiff M, Maier W, Landmesser U, Rodondi N, Mach F, Windecker S, Jüni P, Lüscher TF, Matters CM. Safety profile of prasugrel and clopidogrel in patients with acute coronary syndromes in Switzerland. Heart. 2015; 101: 854-863

35) Bacquier B, Oger E, Filippi E, Hacot JP, Auffret V, Le Guellec I, Castellani P, Moquet B, Druelles P, Rialan A, Rouault G, Boulangier B, Treuil J, Leurent G, Bedossa M, Boulmier D, Avez B, Gilard M, Le Breton H. Safety of prasugrel in real-world patients with ST-segment elevation myocardial infarction: 1-year results from a prospective observational study (Bleeding and Myocardial Infarction Study). Arch Cardiovasc Dis. 2016; 109: 31-38

36) Palmerini T, Genereux P, Mehran R, Dangas G, Caixeta A, Riva DD, Mariani A, Xu K, Stone GW. Association among leukocyte count, mortality, and bleeding in patients with non-ST-segment elevation acute coronary syndromes (from the Acute Catheterization and Urgent Intervention Triage StrategY [ACUITY] trial). Am J Cardiol. 2013; 111: 1237-1245

37) Inoue T, Croce K, Morooka T, Sakuma M, Node K, Simon DI. Vascular inflammation and repair: implications for re-endothelialization, restenosis, and stent thrombosis. JACC Cardiovascular interventions. 2011; 4: 1057-1066