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

Aim

In acute coronary syndrome (ACS) patients treated with percutaneous coronary intervention (PCI) and antiplatelet therapy including clopidogrel therapy, high on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) was shown to be associated with a significant increase in non-fatal myocardial infarction, definite/probable stent thrombosis (ST), or cardiovascular mortality[1-7]. Among the well-described factors associated with ST[8], HPR to ADP likely accounted for up to 60% of early ST events. Yet, to date, large randomized trials concerning personalized antiplatelet therapies failed to confirm the benefits of platelet function assessment in improving survival. Disappointments in personalized antiplatelet therapies[9-11] could be explained by the observation that HPR on clopidogrel treatment allows not only for ineffective P2Y12

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[3, 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 patients[21, 22] based on the net benefits observed with new P2Y12 inhibitors over clopidogrel in the PLATO and TRITON 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 bleeding[19, 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: $PRI\ VASP = (MFI_{[PGE1]} - MFI_{[PGE1+ADP]}/MFI_{[PGE1]}) \times 100$. 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.
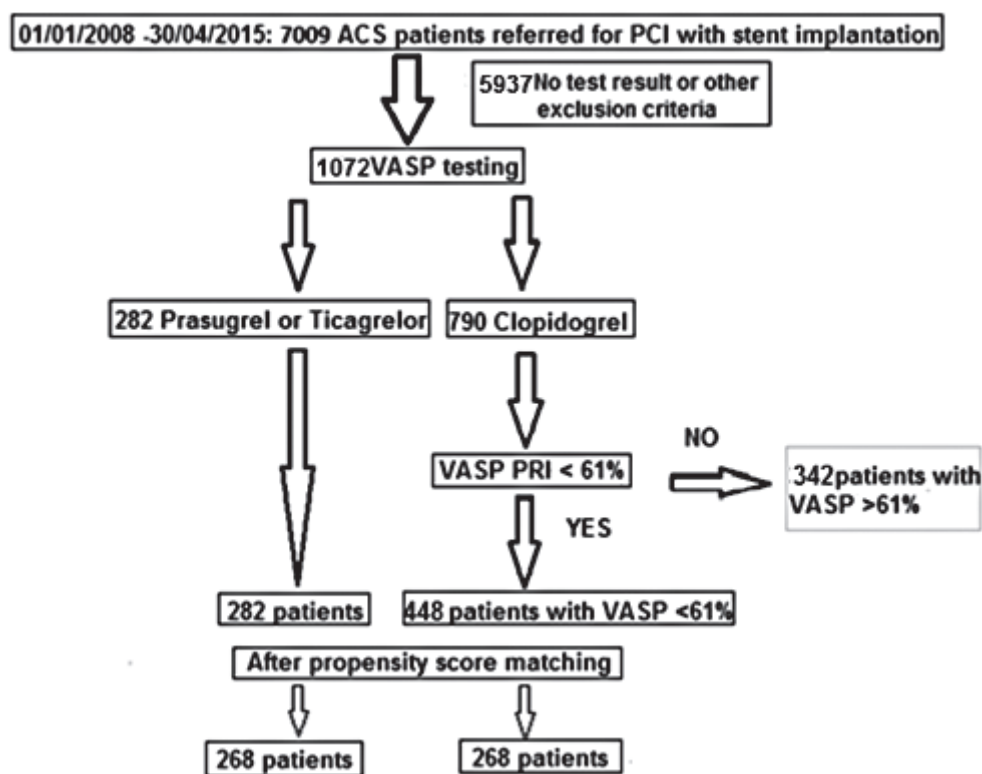
Fig. 1. Flow chart.

GPⅡbⅢa 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 <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 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 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-

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
GPⅡbⅢa 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

sicians 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-

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

ease. 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%.

Table 4. Baseline demographic and clinical characteristics after propensity score matching

Variable, n (%)	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
GP ⅡbⅢa 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibition, was significantly lower in the prasugrel/ticagrelor group. Peak Tn was lower in the clopidogrel

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 admission (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 (10^9/L)	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 (10^9/L)	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, pre-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%) prasug-rel or ticagrelor. At 30 days, no significant differences in MACE, cardiac death, definite and probable ST, myocardial infarction, stroke and bleedings between

Table 7. Events at 30 days

	Before PS matching			After PS matching		
	Clopidogrel (n=448)	Prasugrel/Ticagrelor (n=282)	p	Clopidogrel (n=268)	Prasugrel/Ticagrelor (n=268)	p
MACE, n (%)	15 (3.3)	3 (1.06)	0.071	9 (3.4)	0 (0)	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		
	Clopidogrel (n=448)	Prasugrel/Ticagrelor (n=282)	p	Clopidogrel (n=268)	Prasugrel/Ticagrelor (n=268)	p
MACE, n (%)	35 (7.8)	11 (3.9)	0.034	19 (7.1)	11 (4.1)	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 (%)

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 the two groups for recognized confounding cofactors, there was no significant increase in thrombotic events and major bleeding observed in patients under appropriate clopidogrel inhibition (**Table 8**), along with reduced minor bleeding events (**Table 8**).

A Kaplan−Meier analysis for the probability of MACE-free survival, major bleeding-free survival after PS is given in **Figs. 4** and **5**.

MACE Predictors

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-
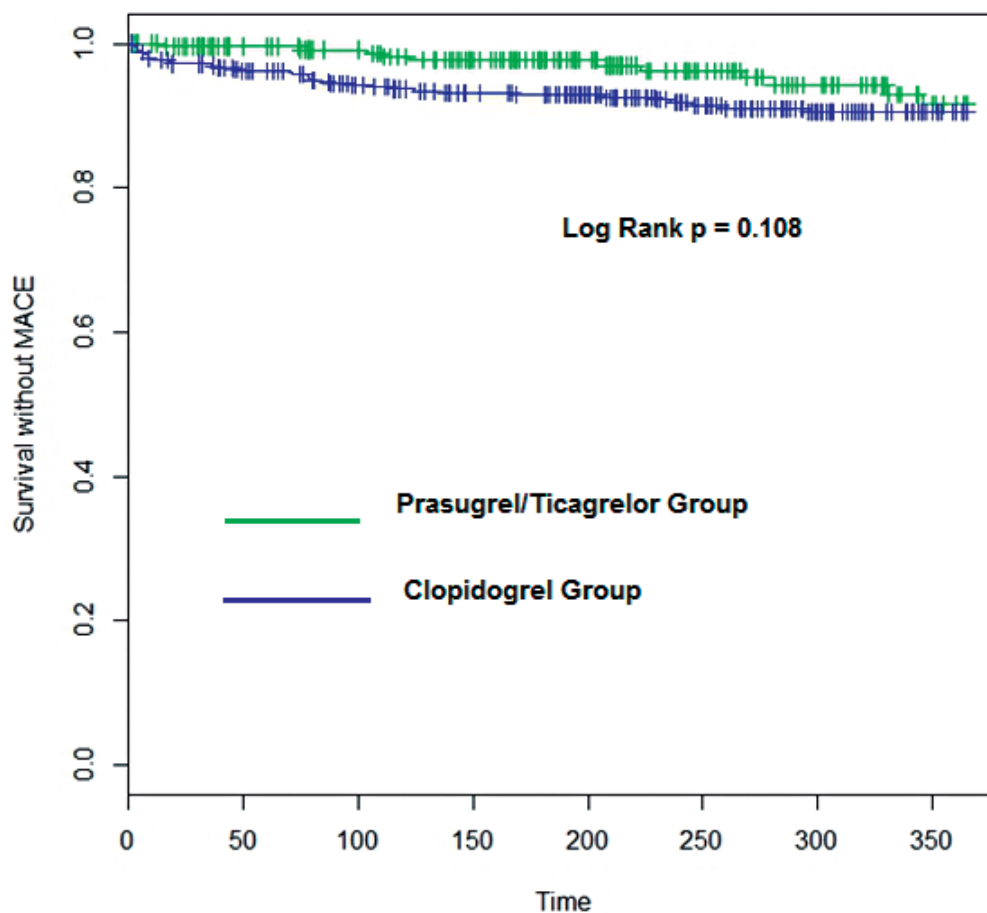
Fig. 2. Kaplan Meier Analysis of survival without MACE in the whole cohort.

lished (HR 1.741; 95% CI: 0.884−3.429); $p=0.109$). Multivariate Cox regression analysis identified hemorrhagic events and high CRP and troponin levels at admission as independent MACE predictors (**Table 9**).

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 sig-

nificantly 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' benefits 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 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 integrate marker of associated comorbidities such as chronic renal disease, ongoing inflammation, and so on, all known to inter-
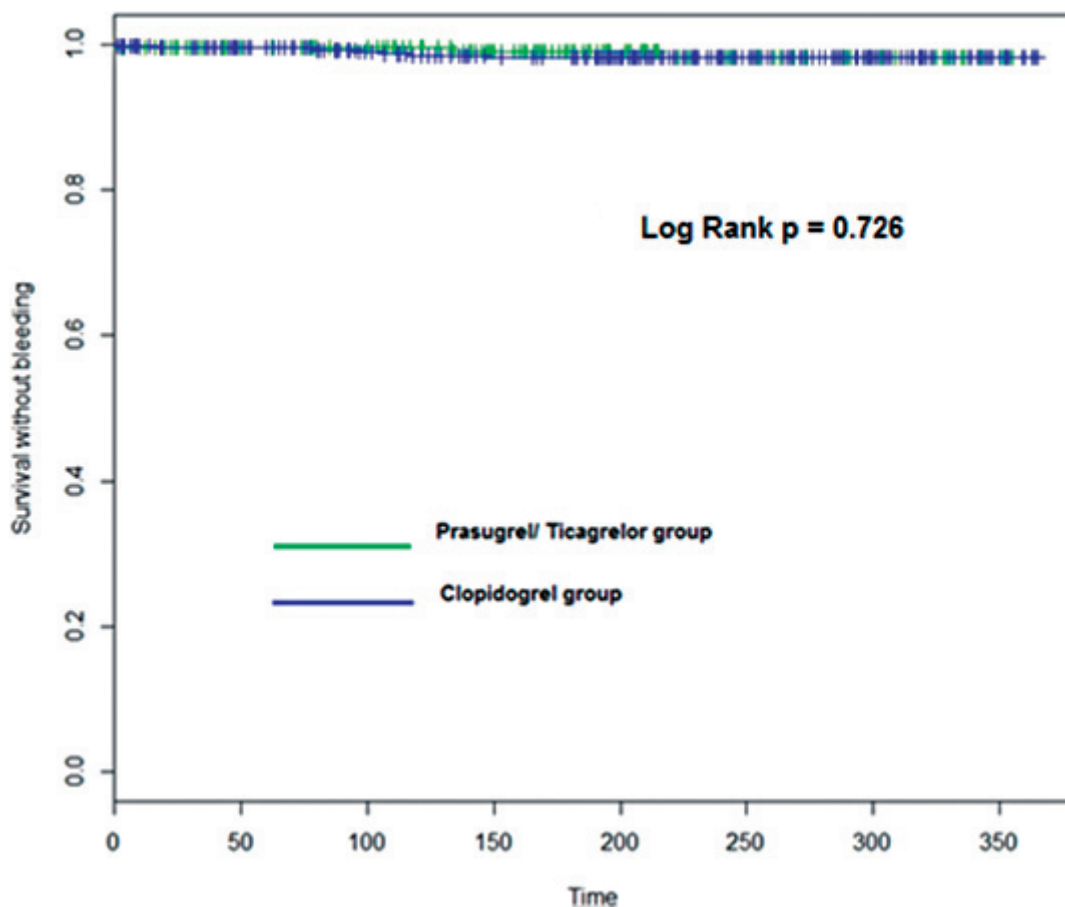
Fig. 3. Kaplan-Meier Analysis of survival without major bleeding in the whole cohort.

fere with clopidogrel pharmacodynamics[17]. These comorbidities are unlikely modified by more potent $P2Y_{12}$ inhibition using either higher clopidogrel doses or new $P2Y_{12}$ inhibitors. In the ACS setting, another issue to consider is the bleeding risk that is partially determined by the $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors could be lim-ited. 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[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 $P2Y_{12}$ 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[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[33]. In the TRANSLATE ACS trial, death was more commonly observed in patients who pursued clopidogrel compared to those who switched
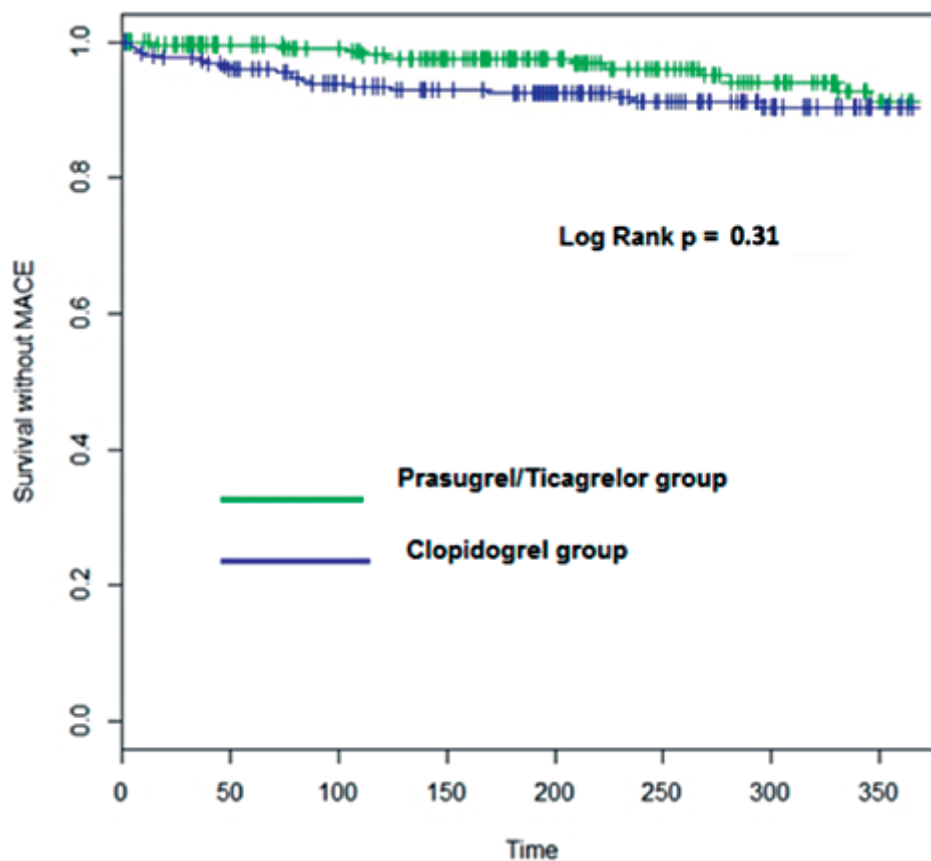
Fig. 4. Kaplan Meier Analysis of survival without MACE after propensity score matching.

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[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 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[34]. Our data extends recent findings by Aradi *et al.*[32]. In their study, thrombotic and hemorrhagic events

rate were similar in HPR patients switched to prasugrel and in clopidogrel responders[32]. 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[35]. 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[32]. 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 dis-
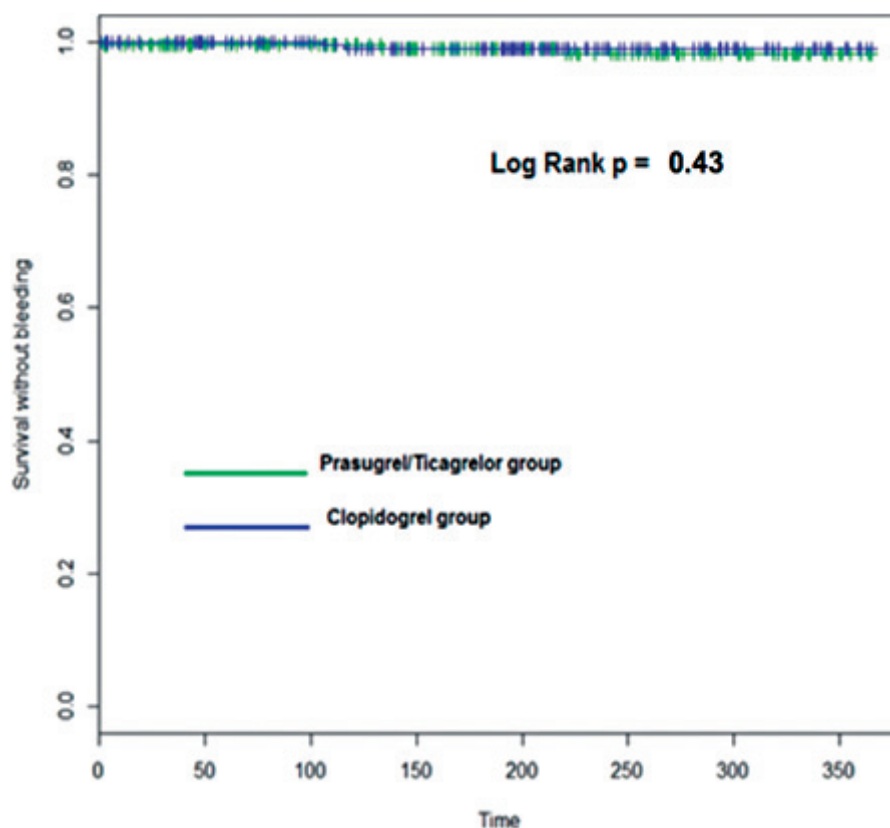
Fig. 5. Kaplan-Meier Analysis of survival without major bleeding after propensity score matching.

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[17]. Lastly, inflammation, either pre-existing or resulting from blood transfusion, was considered an important mediator of thrombotic process[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 clopido-grel 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

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Table 10. Univariate and Multivariate analyses to predict Stent Thrombosis

Variable	Unvariate 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

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