

Clinical Implications of “Tailored” Antiplatelet Therapy in Patients With Chronic Total Occlusion

Maria Grazia De Gregorio, MD; Rossella Marcucci, MD, PhD; Angela Migliorini, MD; Anna Maria Gori, BS; Betti Giusti, BS; Ruben Vergara, MD; Rita Panizza, BS; Nazario Carrabba, MD; Niccolò Marchionni, MD, PhD; Renato Valenti, MD

Background—Clopidogrel nonresponsiveness is a prognostic marker after percutaneous coronary intervention. Prasugrel and ticagrelor provide a better platelet inhibition and represent the first-line antiplatelet treatment in acute coronary syndrome. We sought to assess the prognostic impact of high platelet reactivity (HPR) and the potential clinical benefit of a “tailored” escalated or changed antiplatelet therapy in patients with chronic total occlusion.

Methods and Results—From Florence CTO-PCI (chronic total occlusion-percutaneous coronary intervention) registry, platelet function assessed by light transmission aggregometry, was available for 1101 patients. HPR was defined by adenosine diphosphate test $\geq 70\%$ and optimal platelet reactivity by adenosine diphosphate test $< 70\%$. The endpoint of the study was long-term cardiac survival. Patients were stratified according to light transmission aggregometry results: optimal platelet reactivity (82%) and HPR (18%). Means for the adenosine diphosphate test were $44 \pm 16\%$ versus $77 \pm 6\%$, respectively. Three-year survival was significantly higher in the optimal platelet reactivity group compared with HPR patients ($95.3 \pm 0.8\%$ versus $86.2 \pm 2.8\%$; $P < 0.001$). With the availability of new P2Y₁₂ inhibitors, a deeper platelet inhibition ($46 \pm 17\%$) and similar survival to the optimal platelet reactivity group were achieved in patients with HPR on clopidogrel therapy after escalation. Conversely, HPR on clopidogrel therapy “not switched” was associated with cardiac mortality (hazard ratio 2.37; $P = 0.003$) after multivariable adjustment.

Conclusions—HPR on treatment could be a modifiable prognostic marker by new antiaggregants providing a deeper platelet inhibition associated with clinical outcome improvement in complex chronic total occlusion patients. A “tailored” antiplatelet therapy, also driven by the entity of platelet inhibition, could be useful in these high risk setting patients. (*J Am Heart Assoc.* 2020;9:e014676. DOI: 10.1161/JAHA.119.014676.)

Key Words: antiplatelet therapy • chronic total occlusion • platelet reactivity

Chronic total occlusion (CTO) is a severe expression of advanced coronary artery disease.^{1–4} Generally patients affected are older and present with several morbidities. Patients who undergo percutaneous coronary intervention (PCI) for CTO are at high risk of thrombotic events.^{5,6} Antiplatelet therapy could play a leading role in reducing clinical event rates. Clopidogrel nonresponsiveness is a well-

known marker of cardiac death and risk of stent thrombosis after PCI.^{7–18} The majority of evidence has been obtained in the clinical setting of acute coronary syndrome (ACS). New P2Y₁₂ antagonists prasugrel and ticagrelor have demonstrated in the past decade a more reliable pharmacodynamic effect and a deeper platelet inhibition.^{19–22} For these reasons, guidelines indicate them as first-line antiplatelet drugs in ACS patients. Notwithstanding, some randomized controlled trials have been unable to show the clinical superiority of a strategy of platelet function monitoring to adjust therapy in patients undergoing PCI either in the stable coronary artery disease or ACS setting.^{23–27} On the other hand, the TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial demonstrated the efficacy and safety of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing.²⁷ Currently, the availability of more P2Y₁₂ receptor antagonists with their own pharmacodynamic and pharmacokinetic profiles can enable clinicians to individualize antiplatelet therapy, balancing clinical circumstances and personal bleeding/thrombotic risk for each

From the Cardiovascular Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy (M.G.D.G., R.M., A.M., R. Vergara, N.C., N.M., R. Valenti); Experimental and Clinical Medicine Department, University of Florence, Italy (M.G.D.G., R.M., A.M.G., B.G., R.P., N.M.).

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Correspondence to: Renato Valenti, MD, Cardiovascular Department, AOU Careggi, Florence, Italy, Largo Brambilla 3, I-50134, Florence, Italy. E-mail: renato.valenti2@tin.it

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Clinical Perspective

What Is New?

- In the “individualized” medicine era, the availability of more P2Y₁₂ receptor inhibitors could ideally allow clinicians to escalate/de-escalate and change antiplatelet therapy.
- Indeed, current guidelines contemplate the possibility of switching therapy according to specific clinical scenarios, but data supporting long-term benefit are missing.
- Data from our study suggest that a therapeutic approach, “tailored” either on platelet reactivity assessment or global view of atherothrombotic risk, could be helpful in the “real-world” subset of patients with chronic total occlusions.

What Are the Clinical Implications?

- The clinical decision-making of a “tailored” antiplatelet therapy in patients with high atherothrombotic risk, by switching and/or escalating drugs, based on platelet test results and clinical aspects could lead to a survival benefit.
- In this setting, the achievement of more effective platelet inhibition after the guided escalation (as confirmed by platelet reactivity test) and the decision of a prolonged dual antiplatelet therapy, in patients with extensive coronary artery disease treated by a complex percutaneous revascularization, could be the links for survival improvement.

subject.^{28,29} No data are available on the long-term impact of a “tailored” antiplatelet therapy, based on platelet function assessment, in patients undergoing CTO-PCI on clopidogrel and new antiplatelet therapy. The objective of the study was to assess the prognostic implication of platelet hyperreactivity in CTO patients, either before or after the introduction of new P2Y₁₂ inhibitors that allowed escalation or change in antiplatelet therapy in nonresponder patients.

Methods

Data Sharing

Our study data cannot be made available because of institutional review board restrictions. However, study materials supporting the findings of this study and the methods used in the analyses will be provided by the corresponding author upon reasonable request.

Study Design and Population

From the Florence CTO-PCI (chronic total occlusion-percutaneous coronary intervention) registry, we retrospectively identified consecutive patients who underwent CTO-PCI between 2004 and 2017. Details of the Florence CTO-PCI registry have been previously published.^{5,30} CTO was defined

as a coronary obstruction with Thrombolysis in Myocardial Infarction flow grade 0 with an estimated duration >3 months. The indication for CTO-PCI was supported by demonstration of viable myocardium in the territory of the occluded vessel by echographic or scintigraphic provocative tests when needed. Complete revascularization was based on post-PCI angiographic evaluation.^{5,30} Inclusion criteria of the study were the following: (1) patients undergoing CTO-PCI attempt; and (2) the availability of platelet function assessment. The only exclusion criterion was concomitant anticoagulant therapy (Figure 1).

Treatment

Platelet function was assessed by light transmission aggregometry (LTA) (APACT4, Helena Laboratories, Milan, Italy), performed on platelet-rich plasma using arachidonic acid and adenosine diphosphate (ADP) as agonists of platelet aggregation. Blood samples anticoagulated with 0.109 M sodium citrate (ratio 9:1) were obtained 12 to 18 hours after clopidogrel (600 mg) or prasugrel (60 mg) or ticagrelor (180 mg) loading dose and before CTO-PCI. Platelet-rich plasma, obtained by centrifuging whole blood for 10 minutes at 200g, was then stimulated with 10 μmol/L ADP. Patients with platelet aggregation by 10 μmol ADP ≥90th percentile of controls were considered abnormal. HPR was defined as residual platelet aggregation by ADP ≥70%.^{10,13–17} Optimal platelet reactivity (OPR) was defined when LTA <70%. From 2011, therapy of nonresponders on clopidogrel (preprocedural LTA ≥70%) was escalated to prasugrel or ticagrelor, while a change between prasugrel and ticagrelor was made if HPR with the same LTA threshold (≥70%) was found in patients on new P2Y₁₂ receptor antagonist treatment. A second platelet inhibition test was then performed within the following 7 to 30 days. All patients were treated for at least 12 months with aspirin (100 mg daily indefinitely) and clopidogrel (75 mg daily) and from 2011 with prasugrel (5 or 10 mg daily as appropriate) or ticagrelor (90 mg bid) in those with ACS and concurrent CTO and/or high anatomic coronary complexity. A prolonged dual antiplatelet therapy (DAPT) beyond 12 months was allowed after the assessment at 1 year of the ischemic/bleeding risk in patients with complex and extended coronary disease who received complex PCI procedures according to institutional protocol. Other drugs such as β-blockers, angiotensin-converting enzyme inhibitors, and statins were used in accordance with standard and recommended practice. All patients had clinical examination at 6 to 12 months and yearly thereafter. All other possible information derived from hospital re-admission or by the referring physician, relatives, or municipality live registries were entered into the prospective database. The study conformed to the principles of the Helsinki Declaration and all subjects gave written consent to participate.

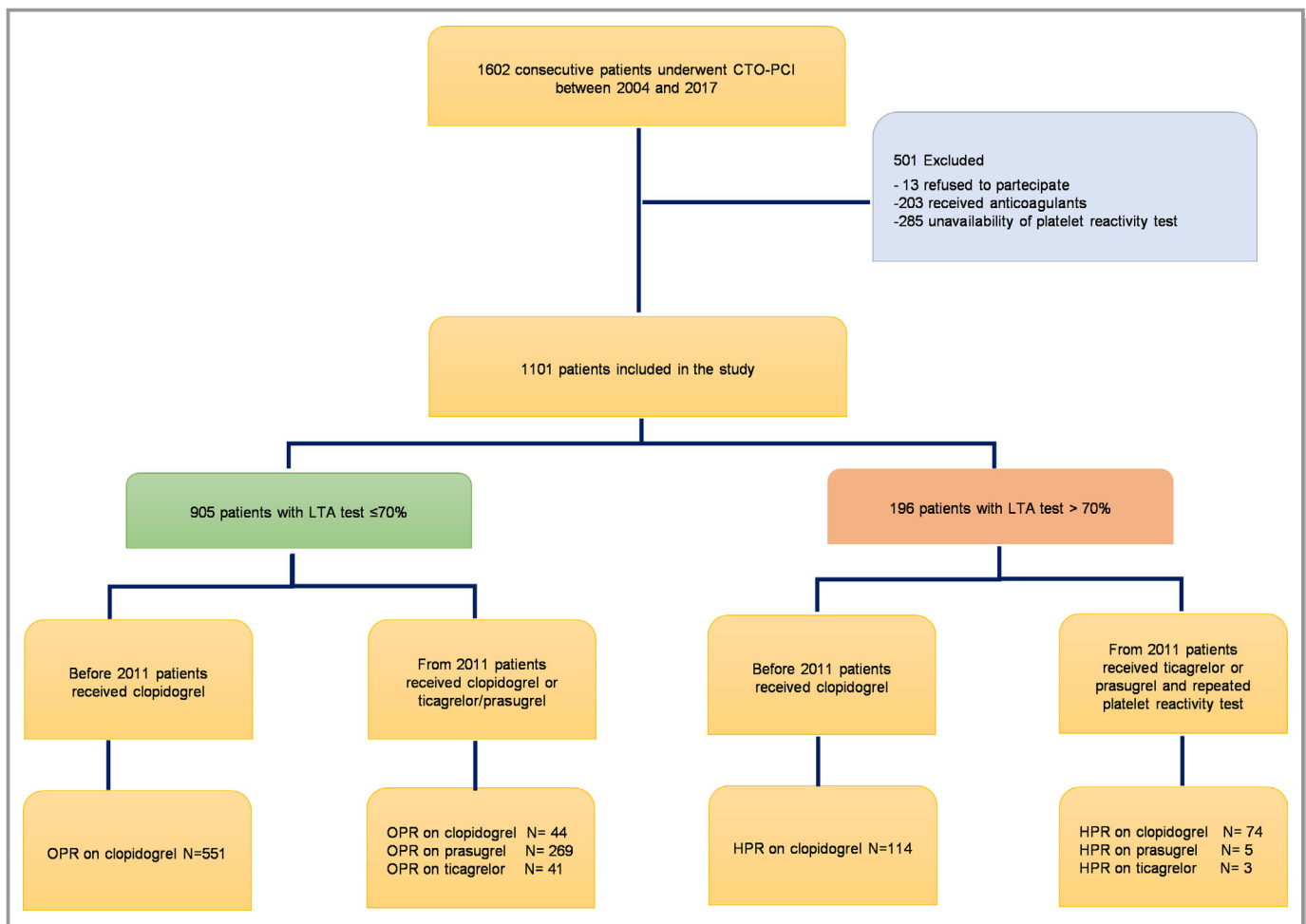


Figure 1. Flow-chart of the study. CTO indicates chronic total occlusion; HPR, high platelet reactivity; LTA, light transmission aggregometry; OPR, optimal platelet reactivity; PCI, percutaneous coronary intervention.

End Point

The primary end point of the study was long-term cardiac survival: all deaths were considered cardiac unless otherwise documented.³¹ All other outcome end points were explorative.

Statistical Analysis

Patients were divided mainly in 2 groups according to the platelet reactivity results. Discrete data are summarized as frequencies, while continuous as mean±SD or median and interquartile range. The χ^2 test or Fisher exact test when appropriate were used for comparison of categorical variables, while the unpaired 2-tailed Student *t* test or Mann-Whitney rank-sum test were used to test differences among continuous variables. A paired *t* test was used to test the difference between paired data. Survival curves were generated using the Kaplan-Meier method, and the difference between groups was assessed by a log-rank test. The

univariable and multivariable analyses to evaluate the independent contribution of clinical and angiographic variables to the primary end point were performed by the Cox proportional hazards model. The variables that reached the highest significance at the univariable analysis were considered in the final multivariable model in order to avoid overfitting. Hazard ratios (HR) and their 95% CI were calculated. All tests were 2-tailed. In order to minimize the bias because of the nonrandomized nature of the study and the possibility of overfitting, a propensity score analysis was performed using a logistic regression model from which the probability for HPR was calculated for each patient; variables introduced into the propensity score model were age (years), male sex, diabetes mellitus, previous coronary artery bypass graft, previous myocardial infarction (MI), chronic kidney disease, left ventricular ejection fraction <0.40, ACS, left anterior descending artery CTO, and 3-vessel disease. Model discrimination was assessed with the C-statistic and goodness-of-fit with Hosmer and Lemeshow test. Thereafter, a Cox multivariable analysis was performed using the propensity score as a

continuous covariate. A $P<0.05$ was considered significant. Analyses were performed using the software packages SPSS 19 (SPSS Inc., Chicago, IL).

Results

Study Population

Between 2004 and 2017, 1602 consecutive patients underwent a CTO-PCI attempt in our institution. Out of these, 488 (30%) were excluded from the study analysis because of concomitant anticoagulant therapy or the absence of data concerning platelet inhibition assessment. Inclusion criteria were met for 1101 patients (Figure 1). HPR by ADP was found in 196 patients (18%) (Table S1) while LTA revealed OPR in 905 subjects (82%). Table 1 summarizes baseline, clinical, and angiographic characteristics of the overall population, OPR, and HPR groups by ADP LTA test. Overall, 32% of patients were older than 75 years, 27% had diabetes mellitus, half of the patients had a history of MI, almost one fourth presented with ACS, and more than one third had a moderate/severe left ventricular dysfunction with left ventricular ejection fraction <0.40 . Chronic kidney disease, defined as estimated glomerular filtration rate <60 mL/min per 1.73 m² calculated by Cockcroft-Gault equation, was found in 9% of patients. The large majority of subjects had multivessel disease and 3-vessel disease was revealed in more than half of the study cohort. Successful CTO-PCI and completeness of revascularization were achieved in 81% and 70% of cases, respectively. There were no significant differences in baseline clinical characteristics between OPR and HPR groups except older age and diabetes mellitus, which were more frequent in patients with HPR, while more subjects in the OPR group achieved a complete revascularization. At discharge, 318 patients (29%) received new P2Y₁₂ antiplatelet therapy (86% prasugrel, 14% ticagrelor). In this group the prevalence of diabetes mellitus (34% versus 24%; $P<0.001$), previous PCI (52% versus 42%; $P=0.002$), second-generation drug-eluting stents (90% versus 41%; $P<0.001$), successful CTO-PCI (88% versus 78%; $P<0.001$), and completeness of revascularization (75% versus 68%; $P<0.001$) was higher.

Platelet Reactivity

Results of platelet reactivity stimulated by ADP and measured by LTA are listed in Table 1. Among 196 patients who were clopidogrel nonresponders, antiplatelet therapy for 82 patients (42%) belonging to new DAPT era was escalated to prasugrel and ticagrelor; thereafter they underwent a second platelet function assessment (Table 1). Data of the latter platelet inhibition test were available for 75 subjects (90%); HPR was found in only 6 patients (8%) of this subgroup on

prasugrel treatment, promptly changed to ticagrelor. A significant difference was found between paired data of LTA tests of the HPR group before and after escalation to new P2Y₁₂ inhibitors ($P<0.001$). No significant baseline, clinical, or angiographic differences resulted among patients previously on treatment with clopidogrel and subsequently escalated to new P2Y₁₂ inhibitors and those who received prasugrel or ticagrelor from the beginning. A prolonged DAPT beyond 12 months was adopted in most of the patients (72%) with a median time of 28 months. After 2 years, 67% of the patients were on DAPT (86% in the HPR group).

One-Year Outcome

In Table 2 are summarized clinical outcomes. Clinical follow-up rate at 1 year was 100%. Overall 1-year cardiac mortality was 3% and the MI rate was 1.5%. No significant differences were found in the definite/probable stent thrombosis rate according to the Academic Research Consortium definition³¹ and 1-year all-cause death; furthermore, 1-year cardiac death rate was numerically higher in the HPR group. The composite end point of 1-year coronary events (cardiac death, nonfatal MI and definite/probable stent thrombosis) was significantly lower in the OPR cohort (4.6% versus 8.1%; $P=0.045$). Conversely, in the HPR subgroup of patients “not switched,” 1-year cardiac mortality was significantly increased compared with the OPR group (7.0% versus 2.7%; $P=0.010$).

Thrombolysis in Myocardial Infarction major bleedings were numerically higher in patients receiving new P2Y₁₂ inhibitors (prasugrel and ticagrelor) when compared with patients treated with clopidogrel, but this difference was not significant (2.6% versus 1.9% respectively; $P=0.528$).

Long-Term Outcome

The 3-year cardiac survival (median follow-up 3 years [interquartile range 2.0–4.0]) was significantly higher in the OPR group as compared with the HPR group ($95.3\pm0.8\%$ versus $86.2\pm2.8\%$; $P<0.001$) (Table 2). Survival was numerically higher in the OPR group with a statistical trend difference, also excluding patients with incomplete coronary revascularization ($97.4\pm0.7\%$ OPR versus $94.1\pm0.2\%$ HPR; $P=0.097$). When the 3-year cardiac survival was analyzed according to platelet reactivity in patients on clopidogrel therapy “not switched,” patients with OPR showed a significant increase in survival as compared with the HPR group ($95.3\pm0.8\%$ versus $83.2\pm3.8\%$; $P<0.001$) (Figure 2). Conversely, cardiac survival was similar in patients with OPR as compared with those with HPR whose therapy had been escalated to new antiplatelet therapy ($95.3\pm0.8\%$ versus $90.7\pm3.9\%$; $P=0.172$) (Figure 2). In a further analysis, after the inclusion of discontinuation time of DAPT as censoring event together with death and loss

Table 1. Baseline Characteristics

	All patients (n=1101)	OPR (n=905)	HPR (n=196)	P Value
Age, y	68.8±10.4	68.4±10.3	70.5±10.1	0.010
≥75 y	351 (32)	274 (30)	77 (39)	0.014
Male sex, (%)	940 (85)	780 (86)	160 (82)	0.102
Hypertension, (%)	695 (63)	564 (62)	131 (67)	0.235
Hypercholesterolemia, (%)	684 (62)	557 (61)	127 (65)	0.395
Diabetes mellitus, (%)	296 (27)	230 (25)	66 (34)	0.018
CKD, (%)	100 (9)	76 (12)	24 (17)	0.126
Previous MI, (%)	554 (50)	451 (50)	103 (53)	0.490
Previous PCI, (%)	492 (45)	413 (46)	79 (40)	0.174
Previous CABG, (%)	154 (14)	119 (13)	35 (18)	0.085
ACS, (%)	256 (23)	207 (23)	49 (25)	0.523
LVEF (%)	45.3±12.6	45.2±12.9	45.4±12.6	0.858
LVEF <0.40, (%)	372 (34)	305 (34)	67 (34)	0.905
Multivessel disease, (%)	936 (85)	762 (84)	174 (89)	0.104
Three-vessel disease, (%)	585 (53)	479 (53)	106 (54)	0.769
CTO vessel				0.440
LAD, (%)	330 (30)	271 (30)	59 (30)	
RCA, (%)	468 (42)	379 (42)	89 (45)	
Second generation DES, (%)	508 (56)	417 (56)	91 (60)	0.358
Successful CTO PCI, (%)	889 (81)	738 (81)	151 (77)	0.147
Complete revascularization, (%)	772 (70)	651 (72)	121 (62)	0.005
Platelet Reactivity: ADP Test Results by LTA				
Overall population				
P2Y ₁₂ antagonist responders		n=905		
Mean, (%)		44±16		
Median, (%)		51 [15–68]		
HPR on clopidogrel therapy		n=196		
Mean, (%)		77±6		
Median, (%)		77 [71–90]		
HPR group on clopidogrel				
“not switched”		n=114		
Mean, (%)		78±6		
Median, (%)		76 [71–92]		
“switched”		n=82		
Mean, (%)		46±17		
Median, (%)		49 [19–74]		

Values are mean±SD, number of patients (%) and median (%) [25th–75th percentiles]. ACS indicates acute coronary syndrome; ADP, adenosine diphosphate; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CTO, chronic total occlusion; DES, drug-eluting stent; HPR, high platelet reactivity; LAD, left anterior descending artery; LTA, light transmission aggregometry; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPR, optimal platelet reactivity; PCI, percutaneous coronary intervention; RCA, right coronary artery.

to follow-up, the between-group survival difference in OPR and HPR “not switched” groups was similar ($95.2\pm0.8\%$ versus $83.0\pm4.4\%$, respectively; $P<0.001$); notably, survival curves of patients in OPR and HPR “switched” groups were found to be

very close ($95.2\pm0.8\%$ versus $92.4\pm3.5\%$, respectively; $P=0.410$), probably supporting the potential effect of a “tailored” DAPT in reducing the prognostic differences between these subsets of patients (Figure 2B).

Table 2. Clinical Outcomes

	OPR (n=905)	HPR (n=196)	P Value
One-year outcome			
All-cause death	37 (4.1)	12 (6.1)	0.211
Cardiac death	24 (2.7)	10 (5.1)	0.072
Nonfatal myocardial infarction	13 (1.4)	4 (2.1)	0.529
Stroke	4 (0.5)	0 (0)	0.355
CTO-vessel repeated PCI	95 (10.5)	21 (10.8)	0.918
CABG	10 (1.1)	1 (0.5)	0.448
MACCE	146 (16)	36 (18)	0.445
Definite/probable stent thrombosis	5 (1.0)	2 (2.2)	0.366
Composite of coronary events*	42 (4.6)	16 (8.1)	0.045
Long-term survival			
Cardiac survival			<0.001
1 y	97.6±0.5	94.9±1.6	
3 y	95.3±0.8	86.2±2.8	
All-cause death			
3 y	86±1.5	75±3.7	0.001

Values are number of events (%) or mean±SE for survival analyses. CABG indicates coronary artery bypass grafting; CTO, chronic total occlusion; HPR, high platelet reactivity; MACCE, major acute cardiovascular and cerebrovascular events; OPR, optimal platelet reactivity; PCI, percutaneous coronary intervention.

*Composite of cardiac death, nonfatal myocardial infarction, and stent thrombosis.

Up to 3 years, refractory congestive heart failure represented the most frequent cause of death (51% of patients in OPR group versus 35% in HPR cohort); fatal MI occurred in 13% in the OPR group versus 22% in the HPR cohort and possible stent thrombosis in 19% of OPR patients versus 26% of the HPR group, respectively. Other indeterminable deaths were derived from municipality live registries and were classified as cardiac death per protocol definition. Overall fatal MI and stent thrombosis occurred numerically higher in the HPR than in the OPR group (5.6% versus 1.3%).

Table 3 reports univariable and multivariable analyses. At univariable analysis, HPR on clopidogrel therapy “not switched” to new P2Y₁₂ inhibitors was independently related to long-term cardiac mortality (hazard ratio 3.46; $P<0.001$) and remained significantly associated (hazard ratio 2.37; $P=0.003$) after multivariable adjustment (Table 3). Conversely, HPR was not significantly associated with long-term cardiac mortality after escalation of therapy to new P2Y₁₂ inhibitors ($P=0.436$). HPR in patients whose therapy was “not switched” remained significantly associated with the primary end point after propensity score adjustment (hazard ratio 3.01, 95% CI 1.69–5.36; $P<0.001$) (C-statistic 0.64; $P=0.327$ for Hosmer-Lemeshow test).

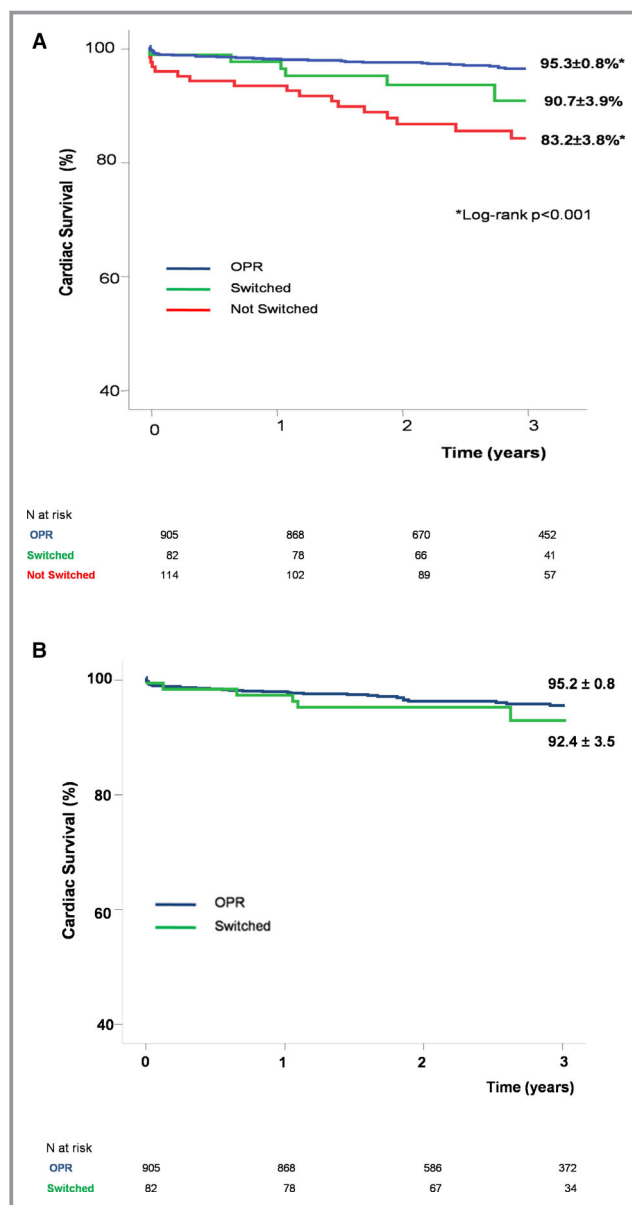


Figure 2. Survival analysis according to platelet reactivity. **A**, Cardiac survival curves demonstrated a long-term benefit in the OPR group compared with the HPR subgroup in which antiplatelet therapy was “not switched.” Conversely, after a “tailored” antiplatelet therapy by escalation and/or change, no more significant differences in survival curves were detected between the HPR “switched” subgroup and the OPR group. **B**, Survival analysis including discontinuation time of DAPT as censoring event together with death and loss to follow-up in OPR and HPR “switched” groups. DAPT indicates dual antiplatelet therapy; HPR, high platelet reactivity; OPR, optimal platelet reactivity.

Discussion

The main findings of the study can be summarized as follows: (1) HPR to ADP in patients undergoing CTO-PCI was associated with long-term cardiac mortality; (2) HPR on clopidogrel treatment could be successfully overcome by

Table 3. Unadjusted and Adjusted Predictors Associated with Long-Term Cardiac Mortality

	Unadjusted Hazard Ratio (95% CI)	P Value	Multivariable Adjusted Hazard Ratio (95% CI)	P Value
Age (per y)	1.08 (1.05–1.11)	<0.001	1.07 (1.04–1.10)	<0.001
Male sex	0.42 (0.24–0.74)	0.003		
Diabetes mellitus	3.39 (2.04–5.64)	<0.001	2.86 (1.70–4.80)	<0.001
Previous MI	1.68 (0.99–2.85)	0.051		
Previous CABG	2.54 (1.46–4.41)	0.001		
Chronic kidney disease	4.51 (2.57–7.92)	<0.001		
ACS	1.70 (0.99–2.90)	0.053		
LVEF <0.40	7.06 (3.88–12.85)	<0.001	5.27 (2.87–9.65)	<0.001
Left anterior descending artery CTO	1.81 (1.09–3.02)	0.022		
Three-vessel disease	1.67 (0.98–2.84)	0.058		
Successful CTO-PCI	0.33 (0.20–0.56)	<0.001		
Complete Revascularization	0.20 (0.12–0.34)	<0.001	0.31 (0.18–0.54)	<0.001
HPR on clopidogrel not “switched”	3.46 (1.97–6.07)	<0.001	2.37 (1.33–4.20)	0.003
HPR on clopidogrel “switched”	1.39 (0.60–3.25)	0.436		
New P2Y ₁₂ antagonist therapy	0.84 (0.46–1.52)	0.578		
Year index	0.99 (0.85–1.16)	0.980		
Second generation DES	0.90 (0.56–1.46)	0.697		

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CTO, chronic total occlusion; DES, drug-eluting stent; HPR, high platelet reactivity; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

switching to new P2Y₁₂ receptor inhibitors as shown by platelet function laboratory tests; (3) HPR of nonresponders, whose therapy had been effectively escalated to prasugrel and ticagrelor or changed between these drugs, was no longer significantly related to long-term cardiac mortality.

To our knowledge, this was the first study to assess the long-term prognosis of patients undergoing CTO-PCI and managed with a “tailored” antiplatelet therapy based on platelet function testing in the new antiplatelet era. Several observational studies and randomized controlled trials have explored the impact of platelet hyperreactivity on cardiovascular event rates in different clinical settings, often with conflicting results.^{12,22–27} In particular, results of previous randomized controlled trials that did not establish clinical improvements after treatment adjustments based on platelet function testing had a strong impact driving clinical practice guidelines that do not currently recommend routine assessment of platelet reactivity. The GRAVITAS (Gauging Responsiveness with a VerifyNow P2Y₁₂ Assay: Impact on Thrombosis and Safety) study showed the inability of a double dose of clopidogrel to completely overcome HPR and improve outcomes; furthermore, the population was underpowered and the follow-up time was short (6 months). TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study failed to demonstrate a 6-month survival

benefit in patients with HPR switched to prasugrel for a very low observed ischemic event rate in a low-risk population that was even underpowered. The ARCTIC (Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy) trial extended the follow-up time to 12 months and included 27% of ACS but only 9.3% of patients were discharged home on prasugrel in the monitoring group. In the ANTARCTIC (Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel) trial, patients included were older >75 years and all presented with ACS: in this high-risk population, platelet function monitoring did not improve 1-year ischemic or safety outcomes. More recently, in TROPICAL-ACS, guided de-escalation of antiplatelet treatment was noninferior to standard treatment with prasugrel after PCI in terms of net clinical benefit at 1 year. All these randomized controlled trials have been conducted with different platelet function assays and thresholds; hypothetically, the results obtained with 1 of these tests could not be transferred to the others.

In our study, platelet aggregation was assessed by LTA, a laboratory assay considered as a gold standard past years but currently replaced by other tests (VerifyNow, VASP, and Multiplate) because of the lack of standardization between institutions.³² HPR to ADP was found in 18% of the study population, mainly older and diabetic patients, consistently

with previous data.^{11,17,18} The clinical benefit demonstrated by prasugrel in diabetic patients²¹, the earlier availability of this agent, and the better compliance of patients explain the prevalence of this prescription; ticagrelor was mainly prescribed in case of contraindications to prasugrel therapy. In the HPR cohort of our study, 82 patients (42%) belonging to the new DAPT era received a “tailored” antiplatelet therapy with drugs whose major effectiveness had been proved. This latter era was also characterized by the predominant use of second-generation drug-eluting stents (mainly everolimus eluting stents) whose superior safety and effectiveness have been widely confirmed; however, no significant statistical associations were found between long-term cardiac mortality and first/second generation drug-eluting stents or year of the index procedure (Table 3). The high anatomical complexity and the extended coronary multivessel disease, together with a more pronounced atherothrombotic risk in the large majority of patients, led to the preferred prolongation of DAPT beyond 12 months, in agreement with the results of contextual studies that showed a benefit in this subset of patients.^{33–36} Patients presented with ACS, history of prior MI, prior percutaneous or surgical revascularization, diabetes mellitus, lack of optimal risk factors control, residual cardiovascular risk, multivessel coronary disease, complex PCI procedures, and any other condition at increased ischemic risk were the preferred candidates for a prolonged DAPT strategy. The indication was then confirmed at 1 year re-evaluation in the absence of major bleeding complications. The duration of DAPT was prescribed at the physician’s discretion as an integral part of a clinical decision-making process, consistent with a “tailored” therapy approach.

Our study cohort was very representative of a “real world” population presenting with advanced coronary artery disease: 50% had a history of MI, mean left ventricular ejection fraction was $45.3 \pm 12.6\%$, 85% had multivessel disease, and 53% had 3-vessel disease. Notwithstanding, completeness of revascularization was achieved in 70% of patients. Of course, complete coronary revascularization was a strong point in our population: its prognostic impact has been widely acknowledged.^{30,37,38}

The lack of 1-year cardiac survival benefit, according to platelet reactivity between OPR and HPR groups (Table 2), could be explained by the inclusion of an “escalated therapy” cohort in HPR group; of note, in support of this hypothesis, 1-year cardiac mortality of the HPR patients with “not switched” therapy was significantly higher when compared with the OPR group. The achievement of more effective platelet inhibition after the guided escalation, as confirmed by the platelet reactivity test, could be the main drive and the link with an associated improvement in terms of survival. Indeed, no significant prognostic association was detected between the HPR group after escalation or change of antiplatelet therapy and OPR group. Probably, the “tailored” antiplatelet therapy of these patients, through the reversal of nonresponsiveness,

allowed achievement of a clinical outcome comparable to that of OPR patients.

Study Limitations

The study had several limitations; first, data were derived from a single-center registry and was a retrospective analysis. Despite the use of multivariable analysis, it remains unknown whether residual confounders may have affected the outcome in the present analyses. Another limitation was the number of “switched” patients, which made type II errors possible. Furthermore, a prolonged DAPT beyond 12 months was adopted in most patients at the clinician’s discretion; different decisions could have affected the results, although the “clinical decision-making” process is part of a “tailored” therapy approach. It must be acknowledged that this study did not show a cause-and-effect relationship, but only an association. Thus, the results of this study should be considered only as hypothesis generating. Furthermore, platelet inhibition tests were not available during follow-up. The use of LTA to assess platelet reactivity could be currently considered out of date.

Conclusions

In conclusion, data of our “real world” registry, in this setting of increased atherothrombotic risk patients, suggest a potential clinical benefit of a “tailored” antiplatelet therapy also based on platelet function assays. In an era of individualized medicine, further clinical investigations are needed to assess and balance the thrombotic and bleeding risk with a “tailored” antiplatelet therapy.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics.

	HPR patients	Clopidogrel	Ticagrelor/Prasugrel	p value
	n=196	n=114	n=82	
Age (years)	70.5±10.1	69.9±11.2	71.4±10.0	0.322
≥75 years	77 (39)	44 (39)	33 (40)	0.466
Male sex, (%)	160 (82)	91(80)	69 (84)	0.281
Hypertension, (%)	131 (67)	68 (60)	63 (77)	0.008
Hypercholesterolemia, (%)	127 (65)	73 (64)	54 (66)	0.457
Diabetes, (%)	66 (34)	38 (33)	28 (34)	0.513
CKD, (%)	24 (12)	16 (14)	8 (10)	0.250
Previous MI, (%)	103 (53)	64 (56)	39 (48)	0.149
Previous PCI, (%)	79 (40)	42 (37)	37 (45)	0.154
Previous CABG, (%)	35 (18)	21 (18)	14 (17)	0.481
ACS, (%)	49 (25)	29 (25)	20 (24)	0.867
LVEF < 0.40, (%)	67 (34)	45 (39)	22 (27)	0.045
Multivessel disease, (%)	174 (89)	99 (87)	75 (91)	0.219
Three-vessel disease, (%)	106 (54)	58 (51)	48 (58)	0.180
LAD CTO (%)	59 (30)	29 (25)	30 (37)	0.065

Values are mean ± SD and number of patients (%).

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; CTO = chronic total occlusion; DES = drug-eluting stent; HPR= high platelet reactivity; LAD = left anterior descending artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.