Benefit of Switching Dual Antiplatelet Therapy After Acute Coronary Syndrome According to On-Treatment Platelet Reactivity: The TOPIC-VASP Pre-Specified Analysis of the TOPIC Randomized Study

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Received 13 July 2017, Revised 17 August 2017, Accepted 29 August 2017, Available online 18 December 2017.

Abstract

Objectives
This study sought to evaluate the impact of initial platelet reactivity on the benefit of switched strategy.

Background
TOPIC (Timing Of Platelet Inhibition after acute Coronary Syndrome) study suggested that switched dual antiplatelet therapy (DAPT) could improve net clinical benefit after acute coronary syndrome by preventing bleeding.

Methods
Acute coronary syndrome patients, 1 month after coronary stenting and event free, were randomly assigned to aspirin and clopidogrel (switched DAPT) or continuation of drug regimen (unchanged DAPT). All patients underwent platelet function testing at this time and were classified as low on-treatment platelet reactivity (LTPR) (platelet reactivity index vasodilator-stimulated phosphoprotein ≤20%) or non-LTPR (platelet reactivity index vasodilator-stimulated phosphoprotein >20%). The primary endpoint aimed to evaluate the impact of platelet reactivity on clinical outcomes and benefit of switched DAPT strategy.

Results
A total of 645 patients were included, 305 (47%) of whom were classified as LTPR. LTPR patients were less often diabetic ($p = 0.01$), had lower body mass index ($p < 0.01$), and were more often on ticagrelor ($p < 0.01$). Patients defined as LTPR and randomized to unchanged DAPT were at the highest risk of primary endpoint occurrence (31%; $p < 0.01$). Conversely, in the switched arm, LTPR patients had no significant difference in primary outcome incidence compared with non-LTPR patients (hazard ratio [HR]: 0.78; 95% confidence interval [CI]: 0.40 to 1.49; $p = 0.45$). The switched strategy was associated with important

reduction in primary endpoint incidence in LTPR patients (HR: 0.29; 95% CI: 0.17 to 0.51; p < 0.01) and only numerically lower incidence in non-LTPR patients (HR: 0.79; 95% CI: 0.46 to 1.35; p = 0.39).

Conclusions

Switched DAPT was superior regardless of initial platelet reactivity but the benefit was greater in LTPR patients. Indeed, the switched strategy was highly effective in this group, which had impaired prognosis with unchanged DAPT but similar prognosis after switching.

Introduction

After acute coronary syndrome (ACS), adequate platelet inhibition is crucial to minimize the risk of recurrent ischemic events (1). "Newer $P2Y_{12}$ blockers" (i.e., prasugrel and ticagrelor) have a more pronounced inhibitory effect on platelet activation and have proved their superiority over clopidogrel, in association with aspirin (2,3). The clinical benefit provided by these drugs is related to a significant reduction in recurrent ischemic events, despite an increased incidence of bleeding complications (2,3). The TOPIC (Timing Of Platelet Inhibition after acute Coronary syndrome) study recently showed that switching from ticagrelor or prasugrel plus aspirin to fixed dose combination (FDC) of aspirin and clopidogrel, 1 month after ACS, was associated with a reduction in bleeding complications, without increase of ischemic events at 1 year (4).

Platelet function testing has been used for years to assess individual response to antiplatelet agents. Indeed, platelet reactivity has been strongly associated with clinical outcomes after ACS (1,5–7). High on-treatment platelet reactivity (HTPR), defining biological resistance to dual antiplatelet therapy (DAPT) is frequent on clopidogrel and has been associated with an increased risk of cardiovascular events, including stent thrombosis (1,8). In contrast, HTPR is rarely observed with use of newer $P2Y_{12}$ blockers (prasugrel, ticagrelor). Instead, biological hyper-response is frequently noticed and associated with bleeding events on $P2Y_{12}$ blockers (8,9). Low on-treatment platelet reactivity (LTPR) has been proposed to define hyper-response to $P2Y_{12}$ blockers (9). Therefore, the objective of the present analysis was to investigate the impact of LTPR on clinical outcomes after ACS and the relation between initial platelet reactivity and benefit of the switched DAPT strategy tested in the TOPIC study.

Methods

Study design and patients

The design of the TOPIC randomized study has been previously published (4). Briefly, this was an open-label, single-center, controlled trial randomizing patients admitted for ACS and treated with aspirin and a new $P2Y_{12}$ inhibitor. One month after the ACS, eligible patients were then randomly assigned in a 1:1 ratio to receive a FDC of aspirin 75 mg plus clopidogrel 75 mg (switched DAPT) or continuation of aspirin plus the established new $P2Y_{12}$ blocker (unchanged DAPT). Inclusion criteria were admission for ACS requiring early percutaneous coronary intervention (PCI) within 72 h, treatment with aspirin and a newer $P2Y_{12}$ blocker at discharge, no major adverse event 1 month after the ACS, and >18 years of age. Exclusion criteria were history of intracranial bleeding; contraindication to use of aspirin, clopidogrel, prasugrel, or ticagrelor; major adverse event (ischemic or bleeding event) within a month of ACS diagnosis; thrombocytopenia (platelet concentration lower than 50×10^9/l); major bleeding (according to the Bleeding Academic Research Consortium [BARC] criteria) in the

past 12 months; long-term anticoagulation (contraindication for newer $P2Y_{12}$ blockers); and pregnancy. During the randomization visit, patients had to present fasting and biological response to $P2Y_{12}$ blocker was assessed by % platelet reactivity index vasodilator-stimulated phosphoprotein (PRI-VASP). On the basis of PRI-VASP, patients were classified as LTPR (PRI-VASP ≤20%), normal response (20% < PRI-VASP ≤50%), or HTPR (PRI-VASP >50%) (8,9). Due to expected very low rates of HTPR, we decided to pool normal response and HTPR in the non-LTPR cohort (PRI-VASP >20%).

Randomization

All patients received treatment with aspirin and a newer $P2Y_{12}$ inhibitor for 1 month after the ACS. One month after the ACS, eligible patients were then randomly assigned in a 1:1 ratio to receive an FDC of aspirin 75 mg plus clopidogrel 75 mg (switched DAPT) or continuation of aspirin plus continuation of newer $P2Y_{12}$ blocker (unchanged DAPT with same treatment than before randomization). The randomization was performed independently of platelet inhibition status, with the investigators blinded to PRI-VASP results. The randomization sequence was computer generated at Timone Hospital, and patients' allocations were kept in sequentially numbered sealed envelopes. Group allocation was issued by the secretarial staff of the research department at Timone Hospital.

Treatment

During the index admission, a 300-mg loading dose of aspirin was given to patients who were treatment-naive before the study. All patients were pre-treated with a loading dose of ticagrelor 180 mg or prasugrel 60 mg before PCI. Regarding the PCI, the use of second- and third-generation drug-eluting stents was recommended. At the discretion of the attending physician, patients were discharged on ticagrelor 90 mg twice a day or prasugrel 10 mg daily in addition to aspirin. At 1-month patients were randomly assigned to either continue with the standard regimen of 75 mg of aspirin plus newer $P2Y_{12}$ blocker (unchanged DAPT) or receive a single tablet FDC of aspirin 75 mg plus clopidogrel 75 mg (switched DAPT). To reduce the risk of bleeding, use of radial access, proton-pump inhibitors, and access site closure devices (when PCI was undertaken via the femoral artery) were recommended but not mandatory. Other cardiac medications were given according to local guidelines.

Follow-up and endpoint assessments

The primary endpoint of this analysis aimed to evaluate the impact of on-treatment platelet reactivity on clinical outcomes in both groups (unchanged and switched DAPT). The primary endpoint was a composite of cardiovascular death, unplanned hospitalization leading to urgent coronary revascularization, stroke, and bleeding episodes as defined by the BARC classification ≥2 at 1 year after ACS (10). This combination of both ischemic and bleeding events was defined as net clinical benefit. Each of the components was also evaluated independently, as well as the composite of all ischemic events and all BARC bleeding episodes. Factors associated with LTPR status were determined. Unplanned revascularization was defined as any unexpected coronary revascularization procedure (PCI or coronary artery bypass graft surgery) during the follow-up period. Stroke diagnosis was confirmed by a treating neurologist. Computed tomography or magnetic resonance imaging was used to distinguish ischemic from hemorrhagic stroke.

All data were collected prospectively and entered into a central database. Clinical follow-up was planned for 1 year after the index event or until the time of death, whichever came first. After collection, data were analyzed by a physician at our institution dedicated to study follow-up.

Platelet inhibition evaluation

Platelet reactivity was measured using the VASP index. Blood samples for VASP index analysis were drawn by a traumatic venipuncture of the antecubital vein. Blood was taken at least 6 h after ticagrelor intake and 12 h after prasugrel intake. The initial blood drawn was discarded to avoid measuring platelet activation induced by needle puncture; blood was collected into a Vacutainer (Becton Dickinson, New Jersey) containing 3.8% trisodium citrate and filled to capacity. The Vacutainer was inverted 3 to 5 times for gentle mixing and sent immediately to the hemostasis laboratory. VASP index phosphorylation analysis was performed within 24 h of blood collection by an experienced investigator using the CY-QUANT VASP/$P2Y_{12}$ enzyme-linked immunosorbent assay (Biocytex, Marseille, France) (11). Briefly, after a first step of parallel whole blood sample activation with prostaglandin E1 (PGE1) and PGE1+adenosine diphosphate (ADP), platelets from the sample are lysed, allowing released VASP to be captured by an antihuman VASP antibody, which is coated in the microtiter plate. Then, a peroxidase-coupled antihuman VASP-P antibody binds to a phosphorylated serine 239–antigenic determinant of VASP. The bound enzyme peroxidase is then revealed by its activity on tetramethylbenzidine substrate over a pre-determined time. After stopping the reaction, absorbance at 450 nm is directly related to the concentration of VASP-P contained in the sample. The VASP index was calculated using the optical density (OD) (450 nm) of samples incubated with PGE1 or PGE1+ADP according to the formula:

Maximal platelet reactivity was defined as the maximal PRI reached during the study.

Ethics

The ethics committee at our institution approved the study protocol, and we obtained written informed consent for participation in the study. We honored the ethical principles for medical research involving human subjects as set out in the Declaration of Helsinki. The data management and statistical analysis were performed by the research and development section, Cardiology Department, Timone Hospital (Marseille, France).

Statistical analysis

All calculations were performed using the SPSS version 20.00 (IBM Corporation, Armonk, New York) and GraphPad Prism version 7.0 (GraphPad Software, San Diego, California). Baseline characteristics of subjects with and without LTPR were compared. Because randomization was not stratified by LTPR status, baseline characteristics were compared among subjects with and without LTPR by treatment assignment. Continuous variables were reported as mean ± SD or as median (interquartile range) (according to their distribution), and categorical variables were reported as count and percentage. Standard 2-sided tests were used to compare continuous variables (Student *t* or Mann-Whitney *U* tests) or categorical variables (chi-square or Fisher exact tests) between patient groups. Multivariate regression models were used to evaluate the linear association between LTPR status (dependent variable) and clinical characteristics (independent variable) using binary logistic regression. The primary analysis was assessed by a modified intention-to-treat analysis. Percentages of patients with an event

were reported. We analyzed the primary and secondary endpoints by means of a Cox model for survival analysis, with time to first event used for composite endpoints, and results reported as hazard ratio (HR) and 95% confidence interval (CI) for switched DAPT versus unchanged DAPT. Survival analysis methods were used to compare outcomes by treatment assignment (unchanged DAPT vs. switched DAPT) and by presence or absence of LTPR. Hazard ratios (HRs) were adjusted to the factors independently associated with LTPR status. Areas under the receiver-operating characteristic curve were determined using MedCalc Software version 12.3.0 (Ostend, Belgium). According to the receiver-operating characteristic curve, the value of PRI-VASP exhibiting the best accuracy was chosen as the threshold. This study is registered with ClinicalTrials.gov (NCT02099422).

Results

Baseline

Between March 2014 and May 2016, 646 patients were enrolled; 323 patients were randomly assigned to the switched DAPT group, and 323 patients were randomly assigned to the unchanged DAPT group. Follow-up at 1 year was performed for 316 (98.1%) patients in the switched DAPT group and 318 (98.5%) in the unchanged DAPT group (Figure 1). The median follow-up for both groups was 359 days, and the mean follow-up was 355 days in the switched DAPT group versus 356 days in the unchanged DAPT group. The characteristics of the studied cohort are summarized in Table 1. Patients with LTPR had lower body mass index (BMI) and were less often diabetic (Table 1). Platelet reactivity testing was performed for all patients, and results were available for 644 (99.7%) patients.

Table 1. Clinical Characteristics and Treatment at Baseline

	Whole Cohort (N = 646)	**LTPR (n = 306)**	**Non-LTPR (n = 340)**	**p Value**
Male	532 (82)	247 (81)	285 (84)	0.18
Age, yrs	60.1 ± 10.2	60.9 ± 10.3	59.3 ± 10.1	0.05
BMI, kg/m^2	27.2 ± 4.5	26.3 ± 4.0	28.0 ± 4.7	<0.01
Medical history				
Hypertension	313 (49)	148 (48)	165 (49)	0.52
Type II diabetes	177 (27)	68 (22)	109 (32)	<0.01
Dyslipidemia	283 (44)	137 (45)	146 (43)	0.35
Current smoker	286 (44)	126 (41)	160 (47)	0.08
Previous CAD	197 (31)	89 (29)	108 (32)	0.26
Treatment				
Beta-blocker	445 (69)	221 (72)	224 (66)	0.05
RAS inhibitor	486 (75)	224 (73)	262 (77)	0.21
Statin	614 (95)	292 (95)	322 (95)	0.41
PPI	639 (99)	303 (99)	336 (99)	0.81
Antiplatelet agent				<0.01
Ticagrelor	276 (43)	167 (55)	109 (32)	
Prasugrel	370 (57)	139 (45)	231 (68)	

	Whole Cohort (N = 646)	LTPR (n = 306)	Non-LTPR (n = 340)	p Value
Presentation				0.97
STEMI	258 (40)	122 (40)	136 (40)	
UA or NSTEMI	388 (60)	184 (60)	204 (60)	
EF, %	56.4 ± 7.7	55.8 ± 8.4	57.0 ± 6.9	0.04
Biological parameters				
CRP, mg/l	4.6 ± 13.7	5.0 ± 18.7	4.1 ± 6.7	0.43
Platelets, g/l	236.2 ± 68.5	240.0 ± 79.8	233.0 ± 56.4	0.19
Triglycerides, g/l	1.4 ± 1.1	1.3 ± 1.3	1.4 ± 0.9	0.39
Cholesterol, g/l	1.5 ± 0.4	1.5 ± 0.5	1.5 ± 0.4	0.80
HDL, g/l	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	<0.01
LDL, g/l	0.8 ± 0.3	0.8 ± 0.4	0.8 ± 0.3	0.59
Creatinine, µmol/l	91.2 ± 50.9	91.1 ± 34.1	91.4 ± 62.3	0.95
LTPR	305 (47)	151 (47)	154 (48)	
Access site				0.63
Femoral	28 (4)	12 (4)	16 (5)	
Radial	618 (96)	294 (96)	324 (95)	
Number of vessels treated				0.09
1	548 (85)	262 (86)	286 (84)	
2	84 (13)	34 (11)	50 (15)	
3	14 (2)	10 (3)	4 (1)	
Stent type				0.85
DES	585 (91)	277 (91)	308 (91)	
BVS	21 (3)	10 (3)	11 (3)	
BMS	24 (4)	10 (3)	14 (4)	
None	16 (3)	9 (3)	7 (2)	

Values are n (%) or mean ± SD.

BMI = body mass index; BMS = bare-metal stent(s); BVS = bioresorbable vascular scaffold; CAD = coronary artery disease; DES = drug-eluting stent(s); EF = ejection fraction; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LTPR = low on-treatment platelet reactivity; RAS = renin-angiotensin system; PPI = proton pump inhibitors; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; UA = unstable angina.

Platelet inhibition

In the whole cohort, 1 month after ACS, mean PRI-VASP was 26.1 ± 18.6%, corresponding to 27.3 ± 19.4% in the switched arm versus 25.0 ± 17.7% in the unchanged arm (p = 0.12). A total of 305 patients (47%) were classified as LTPR, corresponding to 151 (47%) patients in the switched arm and 154 (48%) patients in the unchanged arm (p = 0.84). Patients on

ticagrelor had a significantly lower platelet reactivity and higher incidence of LTPR than did patients on prasugrel (mean PRI-VASP: 22.2 ± 18.7% vs. 29.1 ± 18.0%; p < 0.01; and 167 [55%] vs. 139 [45%]; p < 0.01, respectively) (Figure 2).

Factors associated with LTPR status

LTPR patients were older (p = 0.05), had lower BMI (p < 0.01), were less often diabetic (p = 0.01), and were more often on ticagrelor (p < 0.01). In multivariate analysis, BMI (p < 0.01), diabetes (p = 0.01), and ticagrelor treatment (p < 0.01) remained associated with LTPR.

Clinical outcomes

Results of the TOPIC study have been previously published and showed a significant reduction in the primary composite endpoint on switched DAPT strategy driven by a reduction in bleeding complications (9.3% vs. 23.5%; p < 0.01) without differences in ischemic endpoints (9.3% vs. 11.5%; p = 0.36).

Effect of LTPR on clinical outcomes in both randomized arms

Unchanged arm

At 1-year follow-up, in the unchanged arm the rate of primary endpoint occurred in 51 (33.1%) patients defined as LTPR and in 34 (20.1%) patients defined as no LTPR (p = 0.01) (Table 2 and Figure 3). Bleeding events defined as BARC ≥2 occurred in 28 (18.2%) LTPR patients and in 20 (11.8%) non-LTPR patients (p = 0.19) (Table 3 and Figure 4), while bleeding events defined as all BARC occurred in 41 (26.6%) LTPR patients and in 35 (20.7%) non-LTPR patients (p = 0.39) (Table 4). Any ischemic endpoint occurred in 23 (14.9%) LTPR patients and in 14 (8.3%) non-LTPR patients (p = 0.04) (Table 5, Figure 5).

Table 2. Primary Endpoint Incidence According to Treatment Arm

	Events	Adjusted HR	95% CI	p Value
Switched LTPR vs. switched non-LTPR	18 (11.9) vs. 25 (14.6)	0.78	0.40–1.49	0.45
Unchanged LTPR vs. unchanged non-LTPR	51 (33.1) vs. 34 (20.1)	1.87	1.16–3.02	0.01
Switched LTPR vs. unchanged LTPR	18 (11.9) vs. 51 (33.1)	0.29	0.17–0.51	<0.01
Switched non-LTPR vs. unchanged non-LTPR	25 (14.6) vs. 34 (20.1)	0.79	0.46–1.35	0.39

Values are n (%) unless otherwise indicated.

CI = confidence interval; HR = hazard ratio; LTPR = low on-treatment platelet reactivity.

Table 3. Bleeding BARC ≥2 Incidence According to Treatment Arm

	Events	Adjusted HR	95% CI	p Value
Switched LTPR vs. switched non-LTPR	8 (5.3) vs. 5 (2.9)	1.90	0.59–6.16	0.29
Unchanged LTPR vs. unchanged non-LTPR	28 (18.2) vs. 20 (11.8)	1.52	0.81–2.83	0.19
Switched LTPR vs. unchanged LTPR	8 (5.3) vs. 28 (18.2)	0.26	0.12–0.57	<0.01
Switched non-LTPR vs. unchanged non-LTPR	5 (2.9) vs. 20 (11.8)	0.26	0.10–0.71	<0.01

Values are n (%) unless otherwise indicated.

BARC = Bleeding Academic Research Consortium; other abbreviations as in Table 2.

Table 4. Bleeding All BARC Incidence According to Treatment Arm

	Events	Adjusted HR	95% CI	p Value
Switched LTPR vs. switched non-LTPR	19 (12.6) vs. 11 (6.4)	2.21	1.01–4.80	0.046
Unchanged LTPR vs. unchanged non-LTPR	41 (26.6) vs. 35 (20.7)	1.23	0.76–2.00	0.39
Switched LTPR vs. unchanged LTPR	19 (12.6) vs. 41 (26.6)	0.42	0.25–0.73	<0.01
Switched non-LTPR vs. unchanged non-LTPR	11 (6.4) vs. 35 (20.7)	0.30	0.15–0.60	<0.01

Values are n (%) unless otherwise indicated.

BARC = Bleeding Academic Research Consortium; other abbreviations as in Table 2.

Table 5. Any Ischemic Endpoint Incidence According to Treatment Arm

	Events	Adjusted HR	95% CI	p Value
Switched LTPR vs. switched non-LTPR	10 (6.6) vs. 20 (11.7)	0.50	0.22–1.15	0.11
Unchanged LTPR vs. unchanged non-LTPR	23 (14.9) vs. 14 (8.3)	2.20	1.04–4.64	0.04
Switched LTPR vs. unchanged LTPR	10 (6.6) vs. 23 (14.9)	0.39	0.18–0.85	0.02

	Events	Adjusted HR	95% CI	p Value
Switched non-LTPR vs. unchanged non-LTPR	20 (11.7) vs. 14 (8.3)	1.67	0.81–3.45	0.17

Values are n (%) unless otherwise indicated.

Abbreviations as in Table 2.

Switched arm

Differently from the unchanged group, at 1-year follow-up, in the switched arm, the rate of primary endpoint was not significantly different and occurred in 18 (11.9%) LTPR patients and in 25 (14.6%) non-LTPR patients (p = 0.45) (Table 2, Figure 3). Bleeding events defined as BARC ≥2 occurred in 8 (5.3%) LTPR patients and in 5 (2.9%) non-LTPR patients (p = 0.29) (Table 3, Figure 4), while bleeding events defined as all BARC occurred in 19 (12.6%) LTPR patients and in 11 (6.4%) non-LTPR patients (p = 0.046) (Table 4). Any ischemic endpoint occurred in 10 (6.6%) LTPR patients and in 20 (11.7%) non-LTPR patients (p = 0.11) (Table 5, Figure 5).

Impact of LTPR on benefit of switching strategy

Patients with LTPR

In LTPR patients, the rate of primary endpoint at 1 year was significantly lower after switching and occurred in 18 (11.9%) patients in the switched arm and in 51 (33.1%) patients in the unchanged arm (p < 0.01) (Table 2, Figure 3). This benefit on primary endpoint was related to lower incidence of both bleeding and ischemic complications. Indeed, the rate of bleeding BARC ≥2 occurred in 8 (5.3%) LTPR patients in the switched arm and in 28 (18.2%) LTPR patients in the unchanged arm (p < 0.01) (Table 3, Figure 4). Also, the rate of all BARC bleeding occurred in 19 (12.6%) patients in the switched arm and in 41 (26.6%) patients in the unchanged arm (p < 0.01) (Table 4). Finally, the rate of any ischemic endpoint occurred in 10 (6.6%) LTPR patients in the switched arm and in 23 (14.9%) LTPR patients in the unchanged arm (adjusted HR: 0.39; 95% CI: 0.18 to 0.85; p = 0.02) (Table 5, Figure 5).

Patients without LTPR

In patients without LTPR the rate of primary endpoint at 1 year was not significantly different but was numerically lower in patients in the switched group compared with the unchanged group: 25 (14.6%) patients versus 34 (20.1%) patients, respectively (p = 0.39) (Table 2, Figure 3). However, the risk of bleeding was, as LTPR patients, significantly lower in the non-LTPR patients after switching. Indeed, the rate of bleeding BARC ≥2 occurred in 5 (2.9%) non-LTPR patients in the switched arm and in 20 (11.8%) non-LTPR patients in the unchanged arm (p < 0.01) (Table 3 and Figure 4) and the rate of all BARC bleedings occurred in 11 (6.4%) patients in the switched arm and in 35 (20.7%) patients in the unchanged arm (p < 0.01) (Table 4). Finally, any ischemic endpoint occurred in 20 (11.7%) patients in the switched arm and in 14 (8.3%) patients in the unchanged arm (adjusted HR: 1.67; 95% CI: 0.81 to 3.45; p = 0.17) (Table 5, Figure 5).

Discussion

The main finding of our study is that the benefit of a switching DAPT strategy on bleeding prevention is observed regardless of a patient's biological response to newer $P2Y_{12}$ blockers. Indeed, the switched strategy allows reduction of bleeding complications without apparent increase in ischemic complications in both the LTPR and the non-LTPR groups. However, benefit of switched DAPT was greater in LTPR patients, who had impaired prognosis with unchanged DAPT but similar rate of adverse events with a switched DAPT strategy.

In patients treated with DAPT, the relationship between platelet reactivity and clinical outcomes has been extensively investigated in clopidogrel-treated patients (8,9). Indeed, resistance to clopidogrel is frequent and defined by an HTPR (7,8,12). Newer $P2Y_{12}$ blockers are characterized by stronger and more predictable platelet inhibition in comparison with clopidogrel (2,3). Both ticagrelor and prasugrel proved, in large randomized trials, their clinical superiority over clopidogrel after ACS (2,3). Although resistance to newer $P2Y_{12}$ blockers is infrequently observed, significant rates of hyper-responders emerged (9). This status, defined as LTPR, has been later associated with increased risk of bleeding events on DAPT (8,9,12,13). Our study confirmed that biological hyper-response to DAPT is frequent on newer $P2Y_{12}$ blockers, with 47% of the patients defined as LTPR, using the definition validated by our group on a large cohort of ACS patients (9). We also confirmed the significant association between LTPR and bleeding complications. Moreover, we observed that patients defined as LTPR on newer $P2Y_{12}$ blockers had worse outcomes if they were maintained on their original "unchanged" DAPT regimen, whereas after switching a similar benefit was observed between LTPR and non-LTPR patients.

Surprisingly, we noticed a trend in favor of the higher incidence of ischemic complications in LTPR patients who remained on unchanged DAPT. In the switched arm, LTPR was associated with nonsignificant reduction in ischemic events, which is in line with stronger platelet inhibition levels. We might hypothesize that hyper-responders maintained on newer $P2Y_{12}$ blockers were exposed to ischemic complications following DAPT change or nonadherence due to side effects such as minor bleedings or ticagrelor-associated dyspnea as well as a play of chance that cannot be excluded.

Despite the strong prognostic value of platelet function testing, strategies aiming to tailor DAPT according to individual platelet inhibition failed to prove significant clinical benefit (14–17). All these studies included mostly patients treated with clopidogrel, or prasugrel last, and aimed to adjust the molecule or the dose according to platelet function. Three of 4 trials aimed to correct poor response to clopidogrel (14–16), whereas only 1 trial did adjust the DAPT regimen according to hyper-response in elderly patients only (>75 years of age) treated with a 5-mg dosage of prasugrel (17). However, it seems that ticagrelor is associated with higher rates of hyper-response than prasugrel is. Consequently, it is possible that platelet function testing may have a role in the management of selected patients treated with ticagrelor after ACS who are at risk of developing hyper-response (i.e., older patients, with low BMI, nondiabetic). Because no large study assessing the benefit of treatment adaptation based on platelet function has been conducted on ticagrelor so far, it is possible that higher rates of hyper-response make relevant the use of platelet function testing in this setting. The next challenge could be to identify which patients will benefit from platelet testing and treatment adaptation in case of hyper-response. However, in our study, benefit of switching DAPT was observed also in non-LTPR patients, which could mitigate the usefulness of platelet testing and reserve it to selected candidates after ACS (such as nondiabetics and lower BMI).

Moreover, despite the fact that the recommended DAPT duration after ACS is 12 months (18), there is evidence that shorter DAPT duration could be safe after ACS in selected patients (19) and therefore benefit of the switched strategy would be less substantial, whereas $P2Y_{12}$ blockers could be stopped after 1 to 3 months. Nevertheless, this strategy of short DAPT after ACS does not apply to all patients but is reserved to very high bleeding risk ACS patients (18). Nevertheless, reduced platelet inhibition potency from 1 to 12 months could maintain ischemic protection while reducing the risk of bleeding as demonstrated in TOPIC study (4).

The effect of switching from a newer $P2Y_{12}$ inhibitor to clopidogrel on platelet inhibition has been assessed in crossover studies (20–23). These studies have shown that switching to clopidogrel is associated with a reduction of platelet inhibition and an increase in rates of HTPR. Therefore, the concern may be that some of the patients switched will have insufficient platelet inhibition on clopidogrel and will be exposed to increased risk of ischemic recurrence. However, the reduced potency of DAPT offered by our switching strategy, 1 month after ACS in patients free of adverse events, was not associated with an increased risk of ischemic events, compared with an unchanged DAPT strategy (4). There is also evidence that 80% of stent thrombosis will occur within the first month after stent implantation (24); it is likely that after this time point the impact of resistance to clopidogrel on stent thrombosis incidence is less critical. Finally, the large ongoing TROPICAL-ACS (Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes) study will provide important additional information about both the concept of evolutive DAPT with switch as well as the value of platelet function testing to guide it (25). This trial will randomize 2,600 ACS patients to standard prasugrel treatment or de-escalation of antiplatelet therapy at 1 week with a switch to clopidogrel. This de-escalation group will undergo platelet testing 2 weeks after switching with a switch back to prasugrel in case of low response (25).

Study limitations

First, it was an open-label study. Nevertheless, all events for which medical attention was sought were adjudicated by a critical events committee unaware of treatment allocation. However, self-reported bleeding episodes and treatment discontinuation, for which patients did not consult a health care professional, were subjective. In case of adverse event reporting or treatment modification, the letters from general practitioners and medical reports were collected and analyzed. Second, this is a post hoc analysis of a randomized trial with inherent bias. Third, we used only the PRI-VASP assay to assess platelet inhibition. However, it is recognized as the most reliable assessment of platelet inhibition, being the only test that specifically measures $P2Y_{12}$ receptor activity (8). Fourth, by protocol we did not reassess platelet inhibition after switching and then could not determine the prognosis and frequency of patients defined as HTPR after switching. Last, initial population calculation was made to compare switched versus unchanged strategy and therefore, the platelet reactivity analysis was underpowered for clinical outcomes and could only be considered as hypothesis generating.

Conclusions

Our data suggest that in patients on aspirin plus ticagrelor or prasugrel without evidence of an adverse event in the first month following an ACS, switching DAPT strategy to aspirin plus clopidogrel is beneficial regardless of biological platelet inhibition status. However, switching DAPT is highly efficient in hyper-responders. Indeed, hyper-response is associated with

worse clinical outcomes with unchanged DAPT, which was corrected by a switched DAPT strategy. Therefore, platelet testing could facilitate tailoring DAPT 1 month after a coronary event, biological hyper-response being 1 more argument to switch DAPT. Further randomized evaluations are necessary to validate antiplatelet regimen adaptation in case of biological hyper-response to $P2Y_{12}$ blockers.

Perspectives

WHAT IS KNOWN? "Newer" $P2Y_{12}$ blockers (i.e., prasugrel and ticagrelor) have a more pronounced inhibitory effect on platelet activation and have proved their superiority over clopidogrel, in association with aspirin. The TOPIC study suggested that switching from ticagrelor or prasugrel plus aspirin to FDC of aspirin and clopidogrel (switched DAPT), 1 month after ACS, was associated with a reduction in bleeding complications, without an increase in ischemic events at 1 year.

WHAT IS NEW? Biological hyper-response to a newer $P2Y_{12}$ blocker is frequent and affects almost one-half of ACS patients. The benefit of a switching DAPT strategy is observed regardless of a patient's biological response to newer $P2Y_{12}$ blockers. However, the benefit of switched DAPT is higher in hyper-responders who have impaired prognosis with unchanged DAPT, whereas switching the DAPT strategy significantly reduces the risk of bleeding and ischemic events at 1 year in this cohort.

WHAT IS NEXT? The next challenge will be to identify which patients will benefit from platelet testing and treatment adaptation in case of hyper-response to a newer $P2Y_{12}$ blocker after ACS.

Acknowledgments

The authors thank their nurse team and technicians in executing this study.

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This work was supported by Assistance-Publique-Hôpitaux-de-Marseille. Dr. Deharo has received personal fees from Sanofi. Dr. Johnson has received personal fees from Abbott Vascular, AstraZeneca, Boston Scientific, Correvio, Daiichi-Sankyo, St. Jude Medical, Terumo, and The Medicines Company. Dr. Cuisset has received personal fees from AstraZeneca, Boston Scientific, Biotronik, Eli Lilly, Medtronic, Sanofi, and Terumo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.