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Long-Term Clinical Outcome Based on Aspirin and Clopidogrel Responsiveness Status After Elective Percutaneous Coronary Intervention

A 3T/2R (Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel) Trial Substudy

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Objectives The purpose of this study was to investigate the long-term outcome after elective percutaneous coronary intervention in low-risk patients screened for aspirin and/or clopidogrel responsiveness in the 3T/2R (Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel) trial.

Background The impact of aspirin and/or clopidogrel poor response on long-term outcome is debated.

Methods Aspirin and clopidogrel response was measured with the VerifyNow system aspirin and P2Y12 assays. After percutaneous coronary intervention (PCI), death, stroke, and myocardial infarction were assessed up to 1 year.

Results Overall, 1,277 patients were screened, and 826 (65%) were treated with PCI. In all, 124 patients were found to be aspirin poor responders, and there were 179 clopidogrel poor responders (totally, 278 poor responders). The 1-year end point was significantly higher in poor responders as compared to full responders (15.8% vs. 8.6%, $p = 0.002$), which is principally due to more myocardial infarction occurrence. At multivariable analysis, clopidogrel poor response emerged as an independent predictor (hazard ratio: 1.15, 95% confidence interval: 1.03 to 1.28). Receiver-operator characteristic analysis identifies ≤23 of percentage of platelet inhibition and ≥208 of $P2Y_{12}$ reactivity units as optimal cut offs to predict 1-year end point. Excluding periprocedural events, also peri-PCI myocardial infarction, which is strongly related to aspirin/clopidogrel poor response, was an independent predictor (hazard ratio: 1.25, 95% confidence interval: 1.14 to 1.37). Glycoprotein IIb/IIIa inhibitor administration reduces this risk in poor responders (21.2% vs. 34.7%, $p = 0.02$), but not in full responders (6.3% vs. 6.5%, $p = 0.8$).

Conclusions Poor response to clopidogrel is an independent predictor of periprocedural myocardial infarction and worse 1-year outcome in low-risk patients undergoing PCI, whereas poor response to aspirin failed to predict a worse outcome. Contrary to what was observed in poor responders, glycoprotein IIb/IIa inhibitor therapy failed to provide a benefit in aspirin and/or clopidogrel full responders. (J Am Coll Cardiol 2010;56:1447–55) © 2010 by the American College of Cardiology Foundation

Dual-antiplatelet therapy with aspirin and clopidogrel significantly improves long-term clinical outcomes in patients who undergo percutaneous coronary intervention (PCI) (1). However, despite dual-antiplatelet therapy, some patients still have recurrent cardiovascular events, including stent thrombosis (ST). Antiplatelet response to aspirin and clopidogrel, as assessed by platelet function tests, varies widely among patients (2,3). Differences in assays, agonist concentrations, and cut-off values have contributed to the variability in the reported prevalence of low response, which ranges from 1% to 45% for the 2 drugs (2,3).

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Abbreviations and Acronyms

ARU = aspirin reactivity unit
AUC = area under the curve
COX = cyclooxygenase
GP = glycoprotein
MI = myocardial infarction
PCI = percutaneous coronary intervention
%PI = percentage of platelet inhibition
PRU = $P2Y_{12}$ reactivity unit
ST = stent thrombosis

Previous studies largely focusing on patients with intermediate- to high-risk clinical features have shown that poor responders to aspirin and/or clopidogrel undergoing PCI are at greater risk for death, myocardial infarction (MI), and ST (4–6). Contrarily, the prognostic implications of aspirin and/or clopidogrel poor responsiveness in low-risk patients undergoing elective PCI is still elusive. Moreover, while light transmittance aggregometry still to date remains the gold standard, it is time consuming, technically demanding, and not available in most centers, limiting its broad-scale application in the clinical setting.

As part of a pre-specified substudy of the 3T/2R (Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel) trial (7), we sought to investigate the long-term clinical outcomes of aspirin, clopidogrel, or dual poor responders undergoing elective PCI through a commercially available point of care.

Methods

Patients. This is a pre-specified substudy of the 3T/2R trial (7,8). Accordingly, inclusion and exclusion criteria have been previously reported (7,8). Briefly, in the 3T/2R main study, 263 low-risk patients (with stable coronary artery disease and negative cardiac markers) undergoing PCI who were poor responders to aspirin and/or clopidogrel were enrolled and randomly assigned to placebo or tirofiban. We found a significant reduction of the primary end point (periprocedural MI) and of adverse events at 30 days in the arm receiving tirofiban. Contrarily, this study reports the long-term clinical outcome (1 year) of all patients screened for aspirin and/or clopidogrel response (both full and poor responders) who are treated after coronary artery angiography with PCI. Figure 1 illustrates the study profile and outlines the different study groups.

Screening procedure to evaluate aspirin and clopidogrel poor/full response. A screening procedure to assess aspirin responsiveness was performed in patients at steady-state for

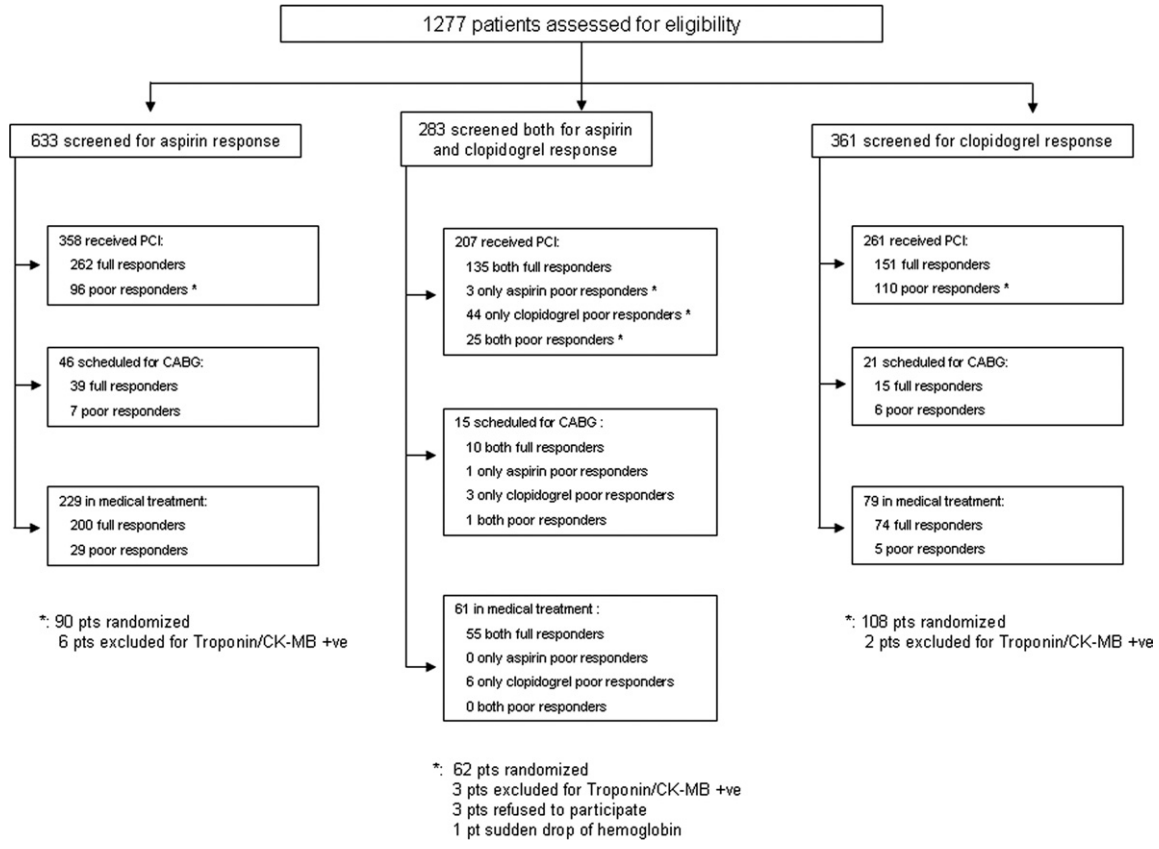

Figure 1 Study Profile

CABG = coronary artery bypass graft surgery; CK-MB = creatine kinase-myocardial band; PCI = percutaneous coronary intervention; pts = patients; +ve = positive.

aspirin (≥80 mg/day for at least 5 days) (7,8). Clopidogrel responsiveness was measured in patients at steady-state for both aspirin and clopidogrel, the latter being defined as 600 mg at least 2 h before or 300 mg at least 6 h before or 75 mg/day for at least 7 days (7,8). Blood sample for screening was always collected before coronary artery angiography and PCI procedures.

Platelet function testing. To perform the screening procedure, the VerifyNow system (Accumetrics, San Diego, California) was employed (7,8). Specific assays to test aspirin (VerifyNow Aspirin) and clopidogrel (VerifyNow P2Y12) are available. In the VerifyNow Aspirin assay, the result is expressed as aspirin reaction unit (ARU). The VerifyNow P2Y12 assay was used to evaluate the clopidogrel effect on the $P2Y_{12}$ receptor. The results are expressed in $P2Y_{12}$ reaction units (PRU). The P2Y12 assay gives also a baseline PRU value, and using PRU and baseline PRU values determines the percentage of platelet inhibition (%PI) by clopidogrel.

Definitions, study medications, and interventions. An ARU ≤550 identifies aspirin full responders, whereas an ARU >550 indicates aspirin poor responders (7,8). Full response to clopidogrel is indicated by %PI ≥40%, whereas %PI <40% identifies poor responders (7,8). Of note, we defined patients as "full or poor responder to both" if they were screened for both aspirin and clopidogrel response; whereas the nonspecific term "full or poor responders" (or the term full/poor responders to either) identified patients evaluated for aspirin and/or clopidogrel response (Table 1). Aspirin (100 mg/day) was given to all patients indefinitely. Clopidogrel (75 mg/day) was given for at least 1 month to patients with stable disease as an indication for PCI and receiving bare metal stent implantation, whereas it was given for at least 1 year to patients with unstable angina and/or who were receiving drug-eluting stent implantation. In poor responders, which were included in the 3T/2R main study, the use of tirofiban was randomized as previously reported (7,8). Conversely, in other patients, the use and type of glycoprotein (GP) IIb/IIIa inhibitors were according to the operator's choice.

Clinical end points and follow-up. In the 3T/2R main study, we reported the periprocedural MI occurrence (pri-

Table 1 Baseline Characteristics of the Patients According to Aspirin and Clopidogrel Response

	Full Responders				Poor Responders			
	Either (n = 548)	Both (n = 135)	Aspirin (n = 441)	Clopidogrel (n = 289)	Either (n = 278)	Both (n = 25)	Aspirin (n = 124)	Clopidogrel (n = 179)
Age, yrs	68 ± 12	67 ± 13	68 ± 13	67 ± 11	68 ± 10	74 ± 14*	69 ± 10	67 ± 10
Male sex	418 (76)	102 (76)	331 (75)	219 (76)	200 (72)	14 (56)	84 (68)	130 (73)
Diabetes mellitus	123 (23)	31 (25)	111 (25)	61 (21)	75 (27)	6 (24)	31 (25)	50 (28)
OH treatment	97 (18)	24 (18)	84 (19)	49 (17)	57 (20)	6 (24)	25 (20)	38 (21)
Insulin treatment	27 (5)	9 (7)	27 (6)	17 (6)	25 (9)	1 (4)	9 (7)	17 (9)
Hypertension	399 (73)	98 (72)	320 (71)	210 (72)	198 (71)	22 (88)	84 (68)	136 (76)
Hyperlipidemia	323 (59)	84 (62)	262 (59)	169 (58)	148 (53)	17 (68)	66 (56)	99 (55)
Current cigarette use	164 (30)	48 (35)	128 (30)	94 (32)	46 (16)†	5 (20)	25 (20)	26 (14)‡
Prior MI	202 (37)	48 (35)	150 (35)	121 (41)	117 (42)	4 (16)	46 (37)	75 (42)
Prior PCI	183 (33)	49 (36)	136 (31)	116 (40)	107 (38)	6 (24)	34 (27)	79 (44)
Prior CABG	50 (9)	15 (10)	35 (8)	32 (11)	19 (7)	0 (0)	7 (6)	12 (7)
LVEF, %	54 ± 10	54 ± 10	55 ± 10	55 ± 10	55 ± 10	54 ± 9	55 ± 9	56 ± 9
Clinical presentation								
Silent ischemia	151 (27)	34 (25)	110 (24)	91 (31)	68 (24)	5 (20)	26 (21)	47 (26)
Stable angina	196 (36)	55 (40)	178 (40)	92 (32)	117 (42)	12 (48)	69 (56)‡	60 (33)
Low-risk UA	201 (37)	46 (35)	156 (36)	106 (37)	93 (33)	8 (32)	29 (23)‡	72 (40)
Angiographic features								
Multivessel	341 (62)	88 (64)	282 (64)	177 (61)	201 (78)	18 (72)	95 (77)	124 (69)
Multivessel PCI	159 (30)	42 (31)	140 (32)	78 (27)	95 (34)	3 (12)	40 (32)	58 (32)
Number of stents	1.2 ± 0.4	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.5	1.3 ± 0.5
Drug-eluting stent	377 (68)	101 (75)	293 (66)	229 (79)	183 (66)	20 (80)	70 (56)	133 (74)
Medical therapy								
GP IIb/IIIa inhibitors	116 (21)	27 (20)	98 (22)	56 (19)	146 (52)†	12 (48)*	68 (55)§	90 (50)‡
Aspirin at 1 yr	537 (95)	130 (96)	431 (98)	284 (98)	269 (97)	24 (96)	119 (96)	174 (97)
Clopidogrel at 1 yr	444 (81)	108 (80)	353 (80)	243 (84)	233 (84)	22 (88)	102 (82)	153 (85)
ACE inhibitors	318 (58)	81 (60)	256 (58)	168 (58)	161 (58)	15 (60)	72 (58)	104 (58)
Beta-blockers	340 (62)	85 (63)	273 (62)	179 (62)	202 (73)	16 (64)	78 (63)	140 (63)
Statins	351 (64)	87 (65)	282 (64)	185 (64)	181 (65)	16 (64)	81 (65)	116 (65)

Values are mean ± SD or n (%). *$p < 0.05$ versus full responders to both. †$p < 0.05$ versus full responders to either. ‡$p < 0.05$ versus full responders to clopidogrel. §$p < 0.05$ versus full responders to aspirin.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; GP = glycoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OH = oral hypoglycemic; PCI = percutaneous coronary intervention; UA = unstable angina.

mary end point) and 30-day incidence of death, MI, and urgent target vessel revascularization only in poor responder patients who were randomly allocated to placebo or tirofiban (8). The current analysis reports the 1-year follow-up data of all screened patients receiving PCI. Thus, the primary objective of this substudy was the 1-year occurrence of death, MI, and stroke. Myocardial infarction is defined as an elevation of creatine kinase-myocardial band (CK-MB) ≥3 times the upper limit of normal (ULN). According to the recent universal definition of MI and the 3T/2R main study (8,9), periprocedural MI is also reported as elevation of troponin I/T ratio ≥3 times ULN within 48 h after completion of PCI. To better evaluate and describe periprocedural and late adverse events, we performed landmark analysis, with landmark set at 3 days. Finally, definite and probable ST occurrence according to the Academic Research Consortium classification and bleedings according to the criteria of the TIMI (Thrombolysis In Myocardial Infarction) trial were assessed.

Statistical analysis. Continuous data are presented as mean ± SD. They were tested for normal distribution with the Kolmogorov-Smirnov test and with the significance of differences judged by *t* test. Categorical variables were summarized in terms of number and percentages and were compared using 2-sided Fisher exact test. Spearman's correlation coefficients were used to detect any association between variables. Survival curves were constructed by the Kaplan-Meier method, and survival among groups was compared using the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Multivariable analysis, considering all clinical or angiographic variables differently distributed (using a p value <0.20 as a threshold) and also GP IIb/IIIa inhibitor therapy, was performed to identify independent predictors for adverse events. Ability to discriminate between patients with and without adverse events was evaluated by receiver-operating characteristic (ROC) curve analysis. The best prognostic cut off for freedom from composite end point was defined as the 1 that maximized both sensitivity and specificity. A 2-sided value of $p < 0.05$ was considered significant. All analyses were performed with STATISTICA version 8 (StatSoft, Tulsa, Oklahoma) and STATA version 9.2 (StataCorp LP, College Station, Texas).

Results

In all, 1,277 patients were screened for responsiveness to aspirin, clopidogrel or both, of whom 826 (64.7%) underwent PCI and represent our study population (Fig. 1). Of the total group, 358 patients were screened for aspirin responsiveness only, of whom 96 (26.8%) were aspirin poor responders; of 261 patients who underwent assessment for clopidogrel responsiveness only, 110 (42.1%) satisfied drug poor responsiveness criteria, whereas 207 underwent screening for both oral antiplatelet agents. In the latter group, 44 (21.9%) were only clopidogrel poor responders, 3 (1.5%) were only aspirin poor responders, and 25 (12.1%) were poor responders to both. Thus, the prevalence of aspirin poor responsiveness among patients who underwent the dual screening process was markedly lower (13.5%) than among patients, who, being at steady state for aspirin but not clopidogrel, were only screened for the former drug (26.8%, $p = 0.003$). Hence, the final patient population consisted of 548 aspirin and/or clopidogrel full responders, of whom 116 received GP IIb/IIIa inhibitors at the time of PCI per physician preference; 278 aspirin and/or clopidogrel poor responders, of whom 132 received treatment with GP IIb/IIIa inhibitor at the time of PCI as per randomization scheme; and 14 patients who failed to satisfy all inclusion/exclusion study criteria and were given GP IIb/IIIa inhibitor per physician preference (Table 1).

Baseline characteristics. Table 1 resumes baseline characteristics of study population. The ARU values were not normally distributed, and we observed the first peak around 375 (responders) and a second peak around 570 (poor responders) (Fig. 2A). Contrarily, as already seen, %PI (mean 48.3, median 49, lower quartile 24.8, upper quartile 68) and PRU (mean 142.1, median 139, lower quartile 96, upper quartile 196) values were both normally distributed and were highly correlated ($r = -86$) (Fig. 2B). The pre-specified threshold of %PI ≥40% corresponded to PRU value in the range of 165 in regression analysis (Fig. 2B).

Clinical outcomes. At 1 year, there were 18 (2.2%) deaths, 80 (9.7%) MIs, and 2 (0.2) strokes. The 1-year composite end point of overall mortality, MI, and stroke was higher for aspirin or clopidogrel poor responders (15.8%) as well as for dual poor responders (20%), compared with responders (8.6%; $p = 0.002$ and $p = 0.07$, respectively), largely driven by a higher rate of MI (Table 2). Definite ST was twice as frequent among poor responders (1.8%) as compared with full aspirin and/or clopidogrel responders (0.9%, $p = 0.2$) (Table 2). At multivariable analysis, clopidogrel and not aspirin poor response emerged as an independent predictor of worse outcomes (Table 3). A %PI ≤23% (AUC: 0.67, 95% CI: 0.52 to 0.81; sensitivity 66% and specificity 71%) and a PRU value ≥208 (AUC: 0.7, 95% CI: 0.58 to 0.8; sensitivity 69% and specificity 76%) were identified as optimal cut offs to predict 1-year composite end point. At sensitivity analysis focused on patients who did not receive GP IIb/IIIa inhibitors, the cut offs remained largely unchanged. In addition, no significant difference was observed for the incidence of major and minor bleeding (Table 2).

Landmarks analyses. 0 TO 3 DAYS. Within day 3, there were 55 (6.6%) MIs, of which 54 were index PCI-related, and 1 event occurred after staged PCI that was performed at day 2. Poor responders showed a significantly higher MI rate (10.1% vs. 4.9%, $p = 0.008$) (Table 2). Clopidogrel and not aspirin poor response emerged as an independent predictor after adjustment for potential confounders (Table 3). Interestingly, periprocedural GP IIb/IIIa administration tended to reduce index PCI-related ischemic events in poor responders (7.1% vs. 13.2%, $p = 0.08$) but not in full

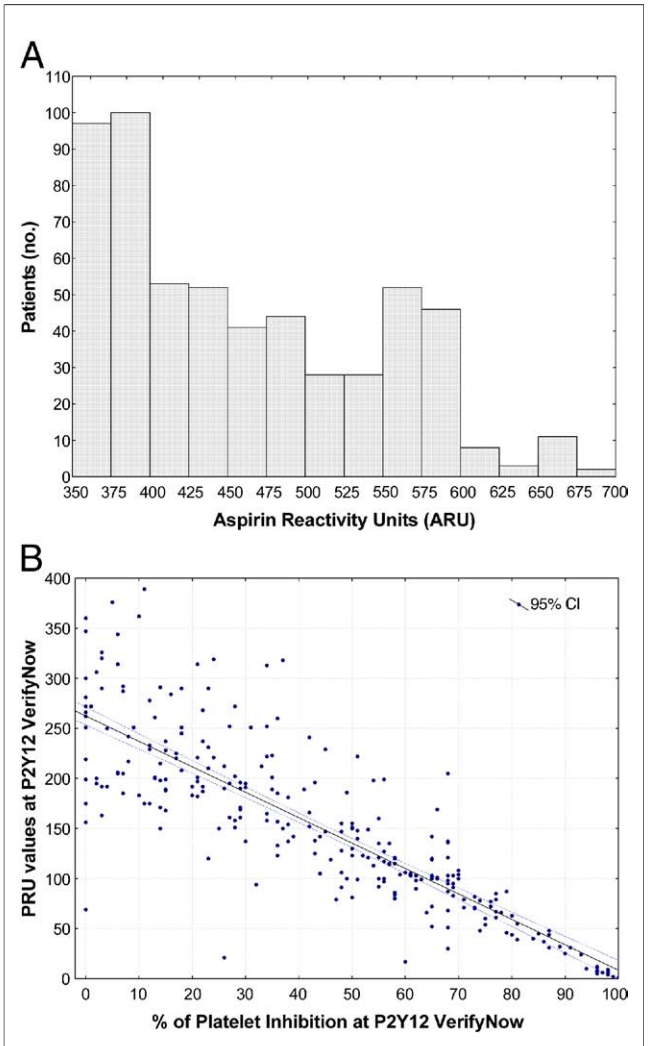

Figure 2 ARU and PRU

(A) Aspirin reactivity units (ARU) and **(B)** $P2Y_{12}$ reactivity units (PRU) values distribution in our study population. CI = confidence interval.

responders (4.7% vs. 5%, p = 0.6). Based on the prespecified periprocedural MI definition consisting of ≥3× ULN troponin I/T elevation, overall, there were 114 (13.8%) periprocedural MIs, which were again more frequent among poor responders (28.4% vs. 6.4%, p < 0.01). At multivariable analysis, both aspirin and clopidogrel poor responsiveness along with multivessel PCI were identified as independent predictors (Table 3). GP IIb/IIIa inhibition significantly reduced PCI-related MIs among poor responders (21.2% vs. 34.7%, p = 0.02) but failed to do so among full responders (6.3% vs. 6.5%, p = 0.8) (Fig. 3). At ROC analysis, %PI values ≤20 (AUC: 0.76, 95% CI: 0.69 to 0.82; sensitivity 78% and specificity 68%) and PRU values ≥210 (AUC: 0.8, 95% CI: 0.73 to 0.88; sensitivity 75% and specificity 78%) were identified as optimal cut offs. At sensitivity analysis focused on patients who did not receive GP IIb/IIIa inhibitors, the cut offs remained largely unchanged.

3 TO 360 DAYS. Overall, 18 (2.2%) deaths, 32 (3.9%) MIs, and 2 (0.2%) strokes were observed after day 3 up to 1 year. The composite end point was 9.3% in poor responders versus 4.4% in responders (p = 0.007) (Table 2). This finding is principally due to worse outcome of clopidogrel poor responders as compared with full responders (Fig. 4). At multivariable analysis, clopidogrel poor response and periprocedural MI were both independent predictors of adverse events (Table 3). Periprocedural MI still remained independently associated with a worse 1-year outcome based on both CK-MB ≥3× ULN definition (HR: 1.25, 95% CI: 1.14 to 1.37) and troponin ≥3× ULN definition (HR: 1.2, 95% CI: 1.1 to 1.28). As for the periprocedural events, GP IIb/IIIa inhibitor administration did not influence long-term outcome in full responders (3.6% vs. 3.7%, p = 0.9 at log-rank) (Fig. 5, blue lines). Contrarily, we tended to observe fewer adverse events in poor responders receiving GP IIb/IIIa as compared with patients not receiving it, without reaching statistical significance (9.5% vs. 11.9%, p = 0.3 log-rank) (Fig. 5, red lines).

Table 2 Recurrence of Adverse Events in Study Population

	Overall Study Population			Screened for Aspirin			Screened for Clopidogrel		
Adverse Events	FR (n = 548)	PR (n = 278)	p Value	FR (n = 441)	PR (n = 124)	p Value	FR (n = 289)	PR (n = 179)	p Value
Death	10 (1.8)	8 (2.9)	0.4	7 (1.3)	5 (4)	0.3	5 (1.7)	4 (2.2)	0.4
Stroke	0 (0)	2 (0.2)	0.2	1 (0.2)	0 (0)	0.5	0 (0)	2 (1.1)	0.2
Myocardial infarction	40 (7.3)	40 (14.3)	0.001	37 (8.4)	14 (11.3)	0.4	13 (4.5)	29 (16.2)	0.001
Composite primary end point	47 (8.6)	44 (15.8)	0.002	44 (10)	16 (13)	0.4	17 (5.9)	31 (17.3)	0.001
0 to 3 days	27 (4.9)	28 (10.1)	0.008	26 (5.9)	10 (8.1)	0.4	8 (2.8)	20 (11.1)	0.004
3 to 365 days	24 (4.4)	26 (9.3)	0.007	20 (4.5)	11 (8.3)	0.3	11 (3.8)	17 (9.5)	0.02
Definite ST	5 (0.9)	5 (1.8)	0.2	4 (0.9)	3 (2.5)	0.1	2 (0.6)	3 (1.7)	0.3
Definite/probable ST	7 (1.3)	8 (2.9)	0.1	5 (1.1)	4 (3.2)	0.1	3 (1)	5 (2.8)	0.1
TIMI major bleeding	4 (0.7)	1 (0.3)	0.5	2 (0.4)	0 (0)	0.6	2 (0.6)	1 (0.5)	0.8
TIMI minor bleeding	20 (3.6)	7 (2.5)	0.4	14 (3.1)	3 (2.5)	0.5	9 (3.1)	4 (2.2)	0.4

Values are n (%).
FR = full responder; PR = poor responder; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction.

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Table 3 Predictors of Primary Composite End Point

	HR	95% CI	p Value
1-year primary end point			
(18 deaths, 80 MIs, 2 strokes; 12.1%)			
Univariate analysis			
Prior MI	1.13	1.06–1.20	<0.01
Clopidogrel poor response	1.20	1.10–1.30	<0.01
Multivessel PCI	1.09	1.03–1.16	<0.01
Multivariable analysis			
Clopidogrel poor response	1.30	1.07–1.56	0.01
Primary end point 0 to 3 days			
(55 MIs; 6.6% using ≥3× ULN of CK-MB definition)			
Univariate analysis			
Clopidogrel poor response	1.19	1.09–1.28	<0.01
Multivessel PCI	1.11	1.04–1.18	<0.01
Multivariable analysis			
Clopidogrel poor response	1.15	1.05–1.35	0.01
Multivessel PCI	1.10	1.01–1.32	0.04
(114 MIs; 13.8% using ≥3× ULN of troponin I/T definition)			
Univariate analysis			
Aspirin poor response	1.27	1.17–1.37	<0.01
Clopidogrel poor response	1.39	1.28–1.50	<0.01
Multivessel PCI	1.32	1.24–1.40	<0.01
Multivariable analysis			
Aspirin poor response	1.18	1.01–1.35	0.04
Clopidogrel poor response	1.30	1.07–1.56	0.01
Multivessel PCI	1.26	1.05–1.51	0.01
Primary end point 3 to 365 days			
(18 deaths, 32 MIs, 2 strokes; 5.1%)			
Univariate analysis			
Clopidogrel poor response	1.15	1.05–1.29	0.01
Prior MI	1.10	1.03–1.18	0.02
Prior CABG	1.09	1.02–1.16	0.01
Diabetes mellitus	1.08	1.02–1.15	0.02
Peri-PCI MI (CK-MB 3×)	1.24	1.17–1.32	<0.01
Multivariable analysis			
Clopidogrel poor response	1.12	1.06–1.25	0.03
Peri-PCI MI (CK-MB 3×)	1.25	1.14–1.37	<0.01

CI = confidence interval; CK-MB = creatine kinase-myocardial band; HR = hazard ratio; ULN = upper limit of normal; other abbreviations as in Table 1.

Discussion

In this prospective study of a large number of low-risk patients undergoing PCI with dual antiplatelet therapy treatment, we found that clopidogrel poor response, as measured by a point-of-care assay, is an independent predictor of 1-year adverse events. Poor response to clopidogrel similarly impacted on both periprocedural and nonprocedural major cardiovascular events with an identified cut-off value in the range of 210 for PRU and 20% for %PI for both. Contrarily, aspirin poor response is associated with higher risk of periprocedural MI, but it failed to remain associated with worse outcomes at long-term follow-up.

Current data complement and extend the findings from previous studies. As compared to previously, we enrolled a very low-risk patient population (patients with stable coronary artery disease and negative cardiac markers) (4), we evaluated both aspirin and clopidogrel response (4,5,10,11), we used a rapid point-of-care (VerifyNow System) assay (5,6), and the occurrence of both periprocedural MI and long-term clinical outcomes was investigated (4–6,10–12).

Despite a remarkable body of literature focusing on "aspirin resistance," its definition, diagnosis, prevalence, causes, and clinical consequences are still uncertain (13). Direct comparison of different laboratory methods to detect aspirin resistance showed relatively weak or even no correlation, indicating that they are sensitive to different parameters. In addition, studies that measured serum thromboxane B2 levels in aspirin-treated patients reported a prevalence of "aspirin resistance" that ranged between 1% and 1.7% (14). Therefore, aspirin resistance, when tested appropriately with cyclooxygenase (COX)-1 specific assays, appears to be extremely rare, and in most instances, due to underdosing or noncompliance issues.

Our current analysis provides 2 interesting findings: 1) aspirin poor response, as evaluated by VerifyNow, predicts periprocedural MI but not 1-year clinical outcome;

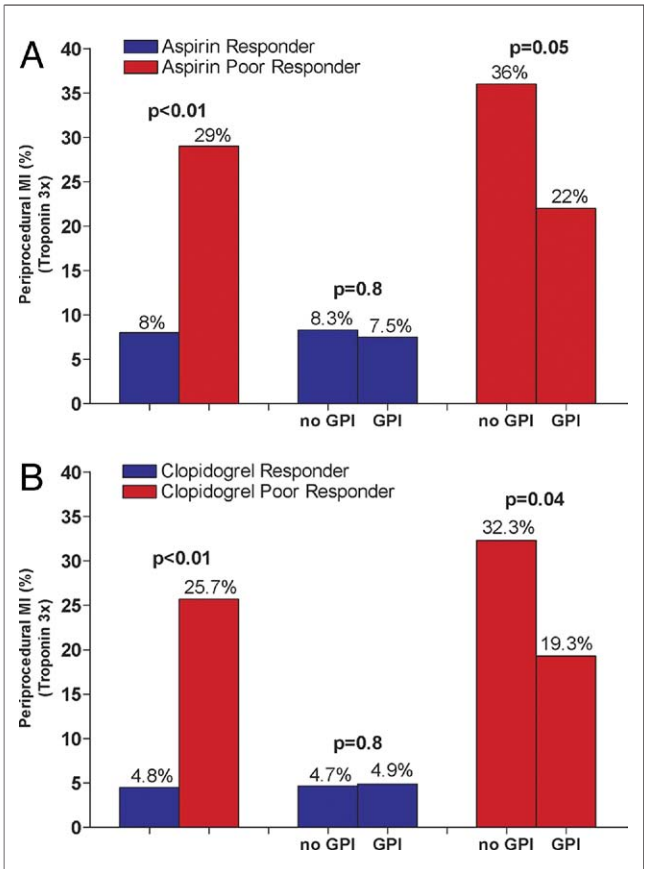

Figure 3 Rate of Periprocedural MI

(A) Periprocedural myocardial infarction (MI) in patients stratified according to aspirin response and glycoprotein IIb/IIIa inhibitors (GPI) administration. **(B)** Periprocedural MI in patients stratified according to clopidogrel response and GPI administration. **Blue bars** = full responders; **red bars** = poor responders.

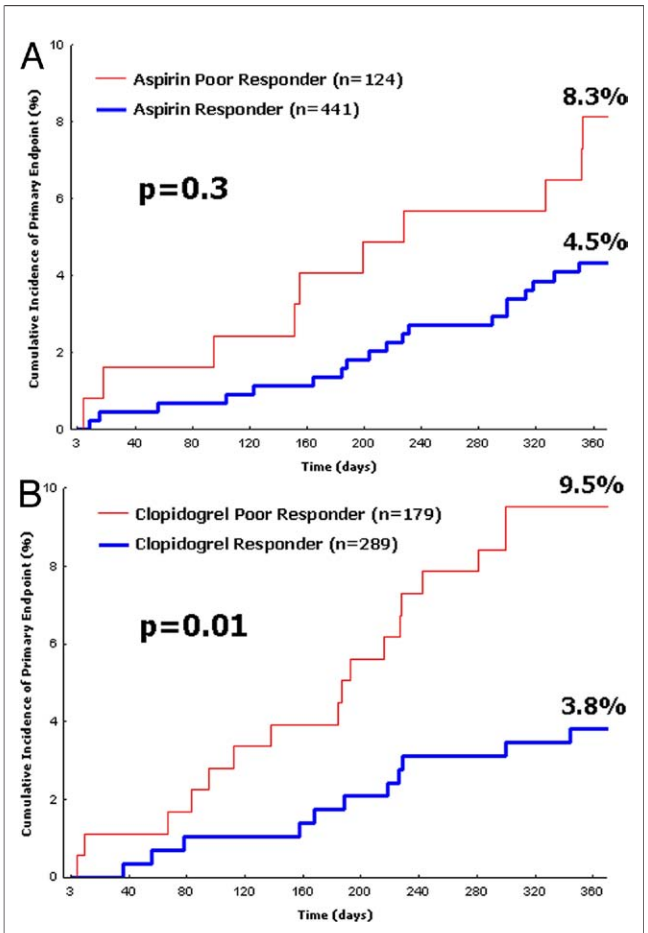

Figure 4 **Cumulative Incidence of 1-Year Primary End Point for Aspirin and Clopidogrel**

Cumulative incidence of 1-year primary end point, excluding periprocedural events. **(A)** Full responders to aspirin **(blue line)** versus poor responders to aspirin **(red line)**. **(B)** Full responders to clopidogrel **(blue line)** versus poor responders to clopidogrel **(red line)**.

and 2) in patients who underwent screening for both aspirin and clopidogrel, poor response to aspirin only was uncommon (1.5%), similar to the previously reported incidence of aspirin resistance based on serum thromboxane B2 levels (14), and much lower than the prevalence observed among patients who underwent screening for aspirin only (27%). Therefore, it is plausible to speculate that the VerifyNow system may not be a suitable assay to test aspirin COX-1 mediated response. In particular, aspirin poor response, as detected with the VerifyNow system, may simply identify high pre- and on-treatment platelet reactivity more than a real failure of aspirin to "hit the target," namely, to inhibit COX-1 activity. Thus, the previously reported capability of aspirin resistance, as detected with this assay, to predict worse cardiovascular outcomes (11) may reflect clopidogrel poor responsiveness or high residual on-treatment platelet reactivity. Thus, altogether our data, in keeping with emerging evidence based on more sophisticated and more COX-1 specific platelet assays (15–19), questions the value of a pure aspirin resistance phenomenon, and provides a possible explanation for the contrasting evidence available in the literature (10,11,15–19).

Clopidogrel is a prodrug that must be metabolized in the liver by several cytochrome P (CYP) proteins, including CYP3A and CYP2C19, to become active and to inhibit adenosine diphosphate-induced platelet aggregation (2). There is growing evidence that the response to clopidogrel may be influenced by pharmacokinetic variables such as intestinal absorption and metabolic activation in the liver, both of which are affected by genetic polymorphisms (2). Our data confirm that clopidogrel poor responder patients were at increased risk during PCI of periprocedural MI and then, during the follow-up, of death, stroke, and MI. Interestingly, our ROC analysis identified cut offs of %PI and PRU values slightly lower as compared with those previously reported (4,12,20). Nevertheless, our cut offs, while slightly lower, still coincide with the upper quartile value of our study population, as it was in all previous studies (12). Probably, this finding is due to the low-risk profile of our patients (stable coronary disease and negative cardiac markers vs. moderate- to high-risk acute coronary syndromes) (21). In keeping with this hypothesis, it has been well documented that platelet reactivity, as well as drug responsiveness, is influenced by clinical presentation, it being higher in patients with MI as compared with patients who have stable angina or silent ischemia (21,22). A potential important consequence of this observation is that the best cut-off value for platelet hyper-reactivity to predict worse cardiovascular outcomes during treatment may be disease specific.

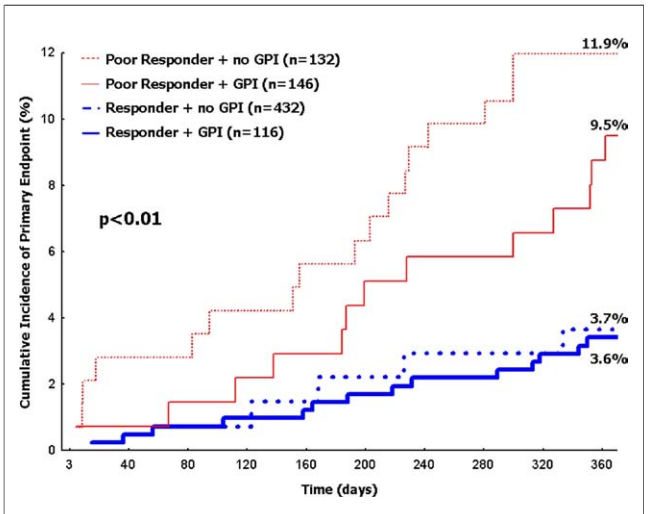

Figure 5 **Cumulative Incidence of 1-Year Primary End Point for Aspirin/Clopidogrel Response and GP Inhibitors Use**

Cumulative incidence of 1-year primary end point, excluding periprocedural events. **Blue lines** = full responders; **red lines** = poor responder. **Solid lines** = glycoprotein (GP) IIb/IIIa inhibitor administration during percutaneous coronary intervention (PCI). **Dotted lines** = no GP IIb/IIIa administration during PCI.

In the 3T/2R main study, we found that GP IIb/IIIa inhibitor administration significantly reduces periprocedural MI in poor responder patients (8). In this analysis, we clearly showed that the protective effect of GP IIb/IIIa inhibitor is restricted to poor responders, whereas no benefit was observed in full responders to aspirin and/or clopidogrel, confirming that a tailored intensification of antiplatelet activity is the best strategy to further improve the clinical outcome of low-risk patients undergoing PCI. Previously, periprocedural MI has been associated with worse clinical outcome (23,24). In our study, periprocedural MI is an independent predictor of composite end point, underlining the need for carefully tailoring intensity of antithrombotic treatment at the time of coronary intervention. We believe that GP IIb/IIIa inhibitor therapy still remains a very attractive option to reduce the periprocedural ischemic burden of poor responsiveness (8), especially in clinical settings where delaying the procedure to allow more complete platelet inhibition by clopidogrel is questionable and not cost effective (25). While prasugrel or ticagrelor may also be attractive strategies to overcome clopidogrel poor responsiveness, there are currently no data to support their use in stable patients undergoing elective PCI. Finally, GP IIb/IIIa therapy is an optimal strategy to reduce periprocedural events and to improve short-term outcome. Although this may have a positive effect, different strategies for maintenance therapy (e.g., higher doses or switch to other drugs) should be tested to optimize the long-term outcome of poor responder patients.

Study limitations. This is a complementary study of the 3T/2R trial, so several limitations are present. First, there is no formal sample size calculation; thus, our data should be regarded as hypothesis-generating. Second, the use of GP IIb/IIIa inhibitors was randomized only for poor responder patients; therefore, the data of full responder patients should be considered exploratory. Third, for patients receiving 600 mg clopidogrel, 2 h may be not sufficient to obtain a steady-state effect. However, our time between loading dose and PCI was longer (4.1 ± 2.1 h). Finally, not all the study population was screened for both tests. Nevertheless, all analyses comparing screened patients and patients not screened for aspirin or clopidogrel excluded any influence on short- and long-term clinical outcome results.

Conclusions

Poor response to clopidogrel is an independent predictor of periprocedural MI and a worsening of a 1-year clinical outcome in low-risk patients with stable coronary artery disease who are undergoing PCI, even after excluding periprocedural events from the analysis. Contrarily, poor response to aspirin failed to consistently and independently predict a worse outcome. In keeping with recent data (19), this result suggests that aspirin resistance should remain under scrutiny. Finally, contrary to what was previously reported for poor responder patients (8), GP IIb/IIIa inhibitors failed to provide a benefit for aspirin and/or clopidogrel full responders.

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Key Words: aspirin ■ clopidogrel ■ glycoprotein IIb/IIIa inhibitor ■ percutaneous coronary intervention ■ poor response ■ 1-year outcome.