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Poor Responsiveness to Clopidogrel: Drug-Specific or Class-Effect Mechanism?

Evidence From a Clopidogrel-to-Ticlopidine Crossover Study

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Objectives This study was designed to investigate whether poor responders to thienopyridines after clopidogrel remain so even after ticlopidine administration (class effect) or whether a drug-specific effect exists between currently available thienopyridines.

Background Whether clopidogrel poor responders also display inadequate platelet inhibition after ticlopidine administration remains undefined.

Methods Platelet aggregation (PA) was measured in 143 patients, while they were taking aspirin, with light transmission aggregometry using adenosine diphosphate as an agonist at baseline (T_0) and at clopidogrel steady state (T_1). After T_1, clopidogrel was stopped and substituted with ticlopidine. Then PA was assessed at ticlopidine steady state (T_2). Resistance was defined as an absolute difference between T_0 and after-treatment (T_1 or T_2) PA ≤10%.

Results Clopidogrel and ticlopidine responsiveness was normally distributed; PA at T_1 did not differ compared with T_2. Thirty (21%) and 28 (19%) patients were clopidogrel and ticlopidine nonresponders, respectively. Only 5 patients (3.5%) were nonresponders to both clopidogrel and ticlopidine (class effect), whereas 25 patients (83%) who were clopidogrel nonresponders at T_1 were responsive to ticlopidine, reaching a higher level of platelet inhibition at T_2 (PA 69 ± 15 vs. 44 ± 18, $p < 0.01$) (drug-specific response). On the other hand, 23 patients who were responsive to clopidogrel showed resistance to ticlopidine at T_2 (PA 46 ± 15 vs. 70 ± 15, $p < 0.01$) (drug-specific response).

Conclusions Poor responsiveness to either clopidogrel or ticlopidine at steady state was common, whereas nonresponders to both drugs were relatively infrequent (3.5%, 95% confidence interval 1.5% to 7.9%), suggesting that poor response to thienopyridines may frequently be a drug-specific mechanism. (J Am Coll Cardiol 2007;50:1132–7)

Dual antiplatelet treatment based on administration of aspirin plus ticlopidine (first-generation thienopyridine) has been shown to be superior to aspirin alone in the prevention of subacute stent thrombosis (SAT) following percutaneous coronary intervention (PCI). Because of its faster onset of action and improved safety profile (1), clopidogrel (second-generation thienopyridine) has subsequently replaced ticlopidine.

Yet a large interindividual variability in the response to clopidogrel is known to exist. Current available data show that about 4% to 30% of patients do not display adequate antiplatelet response (2–4), being poor responders at higher risk of SAT (5,6) or major adverse cardiac events (MACE) (7–9).

Whether poor responders to clopidogrel display similar inadequate platelet inhibition after ticlopidine administration (class effect) remains undefined. We conducted a prospective crossover study to investigate whether poor responders to thienopyridines after clopidogrel remain so even after ticlopidine administration (class effect) or whether a drug-specific effect exists between currently available thienopyridines.

Methods

Patients. Individuals eligible for enrollment were patients undergoing PCI in our center from November

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2005 to May 2006. Exclusion criteria were glycoprotein IIb/IIIa inhibitors, clopidogrel, or ticlopidine intake in the preceding 30 days; or allergy to aspirin, clopidogrel, or ticlopidine. Subjects were also excluded if they were admitted with non–ST-segment elevation acute coronary syndrome, based on the established role of clopidogrel in preventing recurrences (10). This study was approved by the local ethics committee, and all patients gave written informed consent.

Study design and specimen collection. Figure 1 shows a study flow chart. Venous blood samples were collected at the following time points: visit T_0, baseline, before thienopyridine administration; visit T_1, clopidogrel (300-mg loading dose, followed by 75 mg/day) steady state (5 to 7 days after baseline); and visit T_2, ticlopidine steady state (7 to 10 days after T_1). The timing of T_1 was selected on the basis of previous findings (2,3), suggesting that the maximum inhibitory response to standard clopidogrel regimen occurs within 24 h and appears durable over 5 to 30 days. After T_1, clopidogrel was substituted by ticlopidine (500-mg loading dose, followed by 250 mg twice daily). The timing of T_2 allows clearance from clopidogrel and ticlopidine-induced platelet inhibition at steady state.

Concomitant drugs, PCI, and clinical follow-up. All patients with ST-segment elevation myocardial infarction (STEMI) received aspirin (250 mg intravenously), heparin (50 to 70 U/kg), and glycoprotein IIb/IIIa inhibitors. Patients with stable angina (SA) received aspirin (100 mg once a day) at least 7 days and clopidogrel at least 6 h before procedure. Aspirin (100 mg once a day) was given to all patients indefinitely, whereas thienopyridines were given for 1 or 6 months according to implanted stent. Patients underwent outpatient visits every 4 months. The clinical end points were death, reinfarction, target vessel revascularization, or MACE.

Abbreviations and Acronyms

CI = confidence interval
CYP = cytochrome P450
IPA = inhibition of platelet aggregation
MACE = major adverse cardiac event
PA = platelet aggregation
PCI = percutaneous coronary intervention
SA = stable angina
STEMI = ST-segment elevation myocardial infarction

Platelet function testing. Platelet aggregation (PA) was performed as previously reported (11). Platelets were stimulated with 20 μmol/l of adenosine diphosphate. Platelet aggregation was measured at maximal aggregation (Agg_{max}) and at 5 min (Agg_{late}). Inhibition of PA (%IPA) was defined as the percent decrease in aggregation values (Agg_{max}) obtained at baseline and after treatment: (%PA T_0 − %PA T_1 or T_2)/%PA T_0. Clopidogrel and ticlopidine resistance was defined as: 1) absolute difference between baseline and post-treatment Agg_{max} ≤10% (2,3); or 2) %IPA <20% (12).

Statistical analysis. Continuous data are presented as mean ± SD. Unpaired *t* tests were used for comparison of normally distributed continuous variables between 2 groups. To account for multiple comparisons, we applied 2 linear mixed models (Agg_{max} and Agg_{late}) to estimate the variations of PA values, taking in account the intrasubject

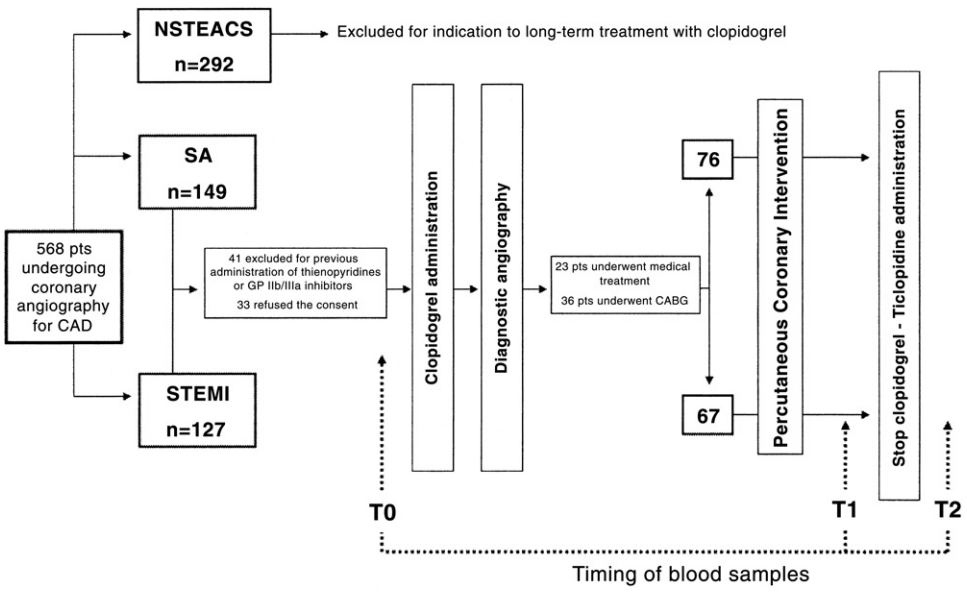

Figure 1 Study Design

CABG = coronary artery bypass graft; CAD = coronary artery disease; GP = glycoprotein; NSTEACS = non–ST-segment elevation acute coronary syndrome; pts = patients; SA = stable angina; STEMI = ST-segment elevation myocardial infarction; T0 = baseline; T1 = clopidogrel steady state; T2 = ticlopidine steady state.

Table 1 Baseline Characteristics of the Patients

Characteristics	Whole Group (n = 143)	SA Group (n = 76)	STEMI Group (n = 67)	p Value*
Age (yrs)	67 ± 10	66 ± 11	68 ± 9	0.3
Men, n (%)	99 (69)	55 (72)	44 (66)	0.2
Body mass index (kg/m^2)	28 ± 7	28 ± 6	28 ± 9	0.5
Diabetes n (%)	32 (27)	21 (27)	11 (16)	0.1
Hypertension, n (%)	104 (73)	63 (84)	41 (61)	<0.01
Smoker, n (%)	31 (22)	13 (17)	18 (26)	0.3
Prior CABG, n (%)	7 (5)	7 (9)	0 (0)	0.01
Prior PCI, n (%)	25 (17)	18 (23)	7 (10)	0.04
Prior MI, n (%)	26 (18)	19 (25)	7 (10)	0.03
Laboratory data				
Platelet count (μ/ml)	260 ± 90	257 ± 87	261 ± 95	0.7
White blood count (μ/ml)	10 ± 5	8 ± 4	13 ± 5	<0.01
Creatinine (mg/dl)	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	0.8
Fibrinogen (mg/dl)	410 ± 140	395 ± 130	420 ± 150	0.3
Pharmacologic treatment†				
Statins, n (%)	132 (92)	68 (90)	64 (95)	0.8
ACE inhibitors, n (%)	125 (87)	65 (85)	60 (90)	0.9
Beta-blockers, n (%)	97 (68)	53 (70)	44 (65)	0.7

*p value for the comparison between SA and STEMI groups; †all patients received aspirin and thienopyridines.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; SA = stable angina; STEMI = ST-segment elevation myocardial infarction.

correlation among the 3 measures. We have adopted as random effect the subject and a compound symmetry as correlation structure. Pearson's correlation coefficients were used to detect any association between variables. A p value >0.2 was used as a threshold to define a normal distribution with the Kolmogorov-Smirnov test. Categorical variables were summarized in terms of number and percentages and were compared using the 2-sided Fisher exact test. Probability was significant at a level of <0.05. Analysis was performed using STATISTICA 7 (Statsoft Inc., Tulsa, Oklahoma) and R-language (R Foundation).

Results

Figure 1 illustrates the disposition of patients in the study. Their clinical characteristics, laboratory data, and medications are shown in Table 1.

Baseline PA. Baseline PA (Agg_{max}: 71 ± 18; Agg_{late}: 63 ± 17) followed a normal distribution and was higher in STEMI compared with SA (Agg_{max}: 77 ± 17 vs. 65 ± 18, p < 0.01; Agg_{late}: 69 ± 15 vs. 57 ± 16, p < 0.01). The presence of diabetes mellitus (r = 0.3, p < 0.01) and current smoking habit (r = 0.2, p < 0.01) were weakly related to PA.

Effect of clopidogrel or ticlopidine. Compared with baseline, PA was significantly reduced after clopidogrel administration (Agg_{max}: 50 ± 17 vs. 71 ± 18, p < 0.01; Agg_{late}: 43 ± 18 vs. 63 ± 17, p < 0.01). Response to clopidogrel followed a normal distribution. After ticlopidine, PA remained normally distributed and was significantly lower than baseline (Agg_{max}: 49 ± 17 vs. 71 ± 18, p < 0.01; Agg_{late}: 43 ± 19 vs. 63 ± 17, p < 0.01), whereas PA did not differ from values observed after clopidogrel (Agg_{max}: 49 ± 17 vs. 50 ± 17, p = 0.5; Agg_{late}: 43 ± 19 vs. 43 ± 18, p = 0.5). Figure 2 illustrates the %IPA from baseline with clopidogrel and ticlopidine.

Clopidogrel or ticlopidine nonresponders. According to definition 1 (Fig. 3), 30 (21%, 95% confidence interval [CI] 14.6% to 28.7%) patients were classified as clopidogrel nonresponders (Table 2). They showed higher baseline PA compared with responders (Table 2). On the basis of definition 1 (Fig. 3), 28 (19%, 95% CI 14.7% to 26.8%) subjects were ticlopidine nonresponders (Table 2); their baseline PA was again higher compared with ticlopidine

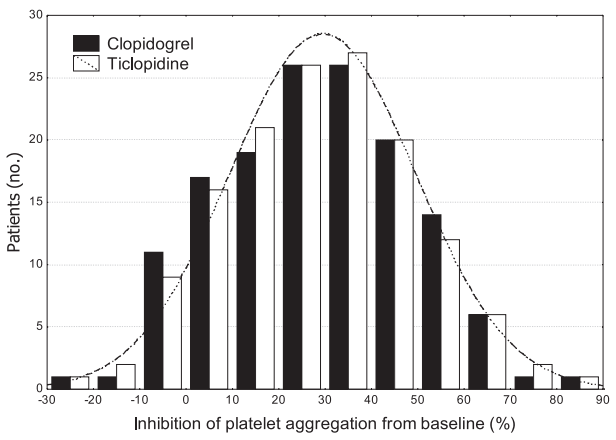

Figure 2 Platelet Inhibition After Thienopyridine Treatment

Distribution of the percent inhibition of platelet aggregation from baseline to after-treatment (clopidogrel steady state = **solid bars**; ticlopidine steady state = **open bars**).

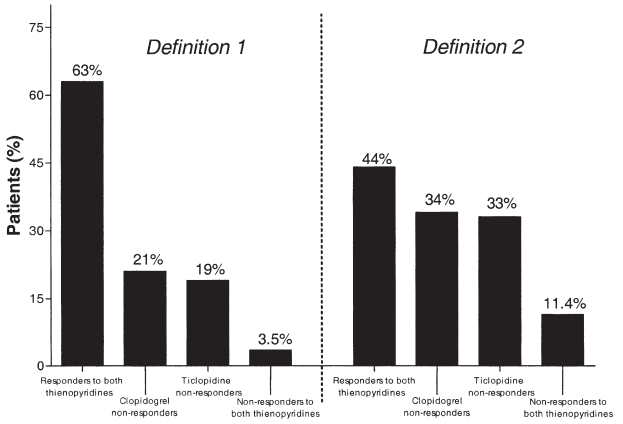

Figure 3 Percentage of Nonresponders

Bars to the left of the dashed line = definition 1, absolute difference between baseline and post-treatment Agg_{max} ≤10%. **Bars to the right of the dashed line** = definition 2, %IPA <20%. IPA = inhibition of platelet aggregation.

responders (Table 2). Of note, diabetes mellitus was more frequent in nonresponders, whereas current smoking was uncommon (Table 2). Twenty-five (83%, 95% CI 66% to 93%) patients who were clopidogrel nonresponders at T_1 were responsive to ticlopidine, reaching a higher level of platelet inhibition at T_2 (Table 3). On the other hand, 23 patients who were responsive to clopidogrel showed resistance to ticlopidine at T_2 (Table 3).

According to definition 2 (Fig. 3), 49 (34%, 95% CI 27 to 42.3) and 47 (33%, 95% CI 25.7 to 41) subjects were clopidogrel and ticlopidine nonresponders, respectively. Baseline PA trended higher (74 ± 13 vs. 69 ± 16, p = 0.09; and 73 ± 16 vs. 70 ± 15, p = 0.1, respectively) and diabetes mellitus tended to be more frequent (28% vs. 19%, p = 0.1; and 28% vs. 20%, p = 0.1, respectively) in the nonresponders. Thirty-three of 49 clopidogrel nonresponders became responsive to ticlopidine, whereas 31 subjects who were clopidogrel responders showed ticlopidine resistance at T_2.

Subjects being nonresponders to both clopidogrel and ticlopidine. According to definition 1, we identified only 5 patients (3.5%, 95% CI 1.5% to 7.9%) who were resistant to both clopidogrel and ticlopidine (Tables 2 and 3). According to definition 2, 16 patients (11.4%, 95% CI 7% to 17.4%) were nonresponders to both thienopyridines.

Clinical outcome. Table 4 shows MACE outcomes (median follow-up 210 ± 45 days). Patients with adverse events had higher PA compared with those without (Agg_{max}: 83 ± 16 vs. 67 ± 17, p < 0.01; Agg_{late}: 75 ± 13 vs. 62 ± 15, p < 0.01).

Discussion

The main findings of this prospective investigation can be summarized as follows:

1. Responsiveness to either ticlopidine (first-generation thienopyridine) or clopidogrel (second-generation thienopyridine) followed a normal distribution, with a percentage of nonresponders of roughly 20%.
2. Patients resistant to clopidogrel are mainly responsive to ticlopidine and vice versa. Only 5 of 143 patients (3.5%, 95% CI 1.5% to 7.9%) were poor responders to both

Table 2 Characteristics of the Patients Stratified According to Thienopyridine Responsiveness

Characteristics	Responders to Both Thienopyridines (n = 90)	Clopidogrel Nonresponders (n = 30)	Ticlopidine Nonresponders (n = 28)	Nonresponders to Both Thienopyridines (n = 5)
Age (yrs)	66 ± 11	69 ± 8	68 ± 7	71 ± 3
Men, n (%)	60 (67)	24 (80)	19 (68)	4 (80)
Diabetes, n (%)	12 (13)	12 (40)*	10 (35)*	2 (40)
Hypertension, n (%)	64 (71)	22 (73)	22 (78)	4 (80)
Current smoker, n (%)	27 (30)	2 (7)*	2 (7)*	0 (0)
Prior CABG, n (%)	4 (4)	2 (7)	1 (4)	0 (0)
Prior PCI, n (%)	15 (17)	7 (23)	4 (15)	1 (20)
Prior MI, n (%)	16 (18)	8 (26)	3 (11)	1 (20)
ST-segment elevation MI, n (%)	47 (52)	17 (56)	14 (50)	2 (40)
Maximal aggregation (Agg_{max}, %)				
Baseline T_0	68 ± 16	76 ± 13‡	77 ± 14‡	80 ± 6§
Clopidogrel steady state T_1	50 ± 17†	70 ± 15	51 ± 18†	76 ± 5
Ticlopidine steady state T_2	49 ± 17†	48 ± 20†	71 ± 13	75 ± 5
Late aggregation (Agg_{late}, %)				
Baseline T_0	63 ± 17	69 ± 14‡	69 ± 15‡	73 ± 6§
Clopidogrel steady state T_1	42 ± 18†	64 ± 15	44 ± 18†	69 ± 5
Ticlopidine steady state T_2	43 ± 19†	41 ± 21†	63 ± 13	70 ± 5

Nonresponders according to definition 1. *p ≤ 0.05 versus responders. †p ≤ 0.01 versus T_0. ‡p = 0.01 versus T_0 of responders to both thienopyridines. §p = 0.05 versus T_0 of responders to both thienopyridines.

Abbreviations as in Table 1.

Table 3 Agg_{max} and Agg_{late} Values in Patients Stratified According to Responsiveness to Clopidogrel and Ticlopidine

	Responders to Both Thienopyridines (n = 90)		Clopidogrel Nonresponders Ticlopidine Responders (n = 25)		Clopidogrel Responders Ticlopidine Nonresponders (n = 23)		Nonresponders to Both Thienopyridines (n = 5)	
	Agg_{max}	Agg_{late}	Agg_{max}	Agg_{late}	Agg_{max}	Agg_{late}	Agg_{max}	Agg_{late}
Baseline (T_0)	68 ± 16	59 ± 16	76 ± 14	68 ± 13	76 ± 16	68 ± 16	80 ± 6	73 ± 5
Clopidogrel steady state (T_1)	45 ± 15*	38 ± 14*	69 ± 15	63 ± 14	46 ± 15*	38 ± 14*	76 ± 5	69 ± 5
Ticlopidine steady state (T_2)	45 ± 13*	38 ± 13*	44 ± 18*†	35 ± 18*†	70 ± 15†	62 ± 13†	75 ± 5	68 ± 5

*$p \leq 0.05$ versus T_0; †$p \leq 0.05$ versus T_1.

drugs according to the most widely used definition of resistance.

Recent data have demonstrated a marked variability in response to standard dosing of clopidogrel, either after acute loading (3,4) or maintenance dosing (13,14). A higher loading dose of clopidogrel demonstrated an improved clopidogrel response in the early hours, but this was not associated with a reduction in the degree of interindividual variability (3,4). Poor responsiveness also occurs during sustained clopidogrel treatment (13–15). Angiolillo et al. (15) have recently reported that doubling the maintenance dose of clopidogrel enhances platelet inhibition. However, response to antiplatelet therapy remained variable, and 60% of patients remained poor responders. This has relevant implications, as recent studies (5–9) indicate that low antiplatelet effect of clopidogrel may be associated with a higher risk of reinfarction or SAT. The American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines (16) recommend the use of a 150-mg daily clopidogrel maintenance dose in class IIa subjects in whom SAT may be catastrophic and in whom an IPA <50% is demonstrated. However, the efficacy of this strategy has never been tested. Aleil et al. (17) reported 3 cases in which clopidogrel was ineffective despite double dosing, whereas adequate response to ticlopidine was obtained. Our present data are in agreement with this observation and confirm that, in patients in whom clopidogrel administration is associated with inadequate response, switching to ticlopidine may lead to an adequate platelet inhibition in 83% of cases (95% CI 66% to 93%). We believe that this finding may carry both pathophysiological and clinical implications.

Clopidogrel is absorbed rapidly from the gastrointestinal tract; ≈85% of the prodrug is hydrolyzed by esterase in the blood to an inactive derivate, and only ≈15% is metabolized by the cytochrome P450 (CYP) system to generate an active metabolite. On the other hand, ticlopidine is known to have a higher oral bioavailability (up to 80%) and, unlike clopidogrel, ticlopidine has nonlinear pharmacokinetics, with its clearance decreasing with repeated dosing. Differences in liver metabolism may be also considered: active metabolites differ after clopidogrel or ticlopidine ingestion, and several isoforms of CYP are involved in the metabolism of ticlopidine and clopidogrel. Production of the active metabolite of clopidogrel strongly depends on isoforms 3A4 and 2C19 (18,19); conversely, metabolic pathways of ticlopidine are not necessarily dependent on these isoforms.

In keeping with previous evidence, diabetes mellitus (14,15) and smoking (8) were found to have a significant, although weak, influence on thienopyridine responsiveness. Smoking seemed to enhance the drug antiplatelet effect. Activation of CYP isoenzymes 3A4 and 1A2 by polycyclic aromatic hydrocarbons could explain our finding.

A third-generation thienopyridine, prasugrel, is currently being tested in randomized controlled trials. Like ticlopidine and clopidogrel, prasugrel is a prodrug and needs liver metabolism. Compared with previous thienopyridine generations, prasugrel is more efficiently transformed into its active metabolite, and it is ≈10 times more potent (12). Our data would encourage assessing response to clopidogrel to identify those patients with low platelet inhibition at steady state who may benefit from alternative compounds such as ticlopidine or prasugrel (20).

Study limitations. All patients first received clopidogrel and then ticlopidine. Although the number of clopidogrel or ticlopidine nonresponders did not differ between STEMI and SA patients, an inflammatory environment in STEMI patients may have influenced platelet reactivity, thus poten-

Table 4 Clinical Outcome in Patients Stratified According to Responsiveness to Clopidogrel and Ticlopidine

	Responders to Both Thienopyridines (n = 90)	Clopidogrel Nonresponders Ticlopidine Responders (n = 25)	Clopidogrel Responders Ticlopidine Nonresponders (n = 23)	Nonresponders to Both Thienopyridines (n = 5)
Death, n (%)	1 (1.1)*	0 (0)	1 (4.3)†	1 (20)*
Reinfarction, n (%)	0 (0)	1 (4)*‡	1 (4.3)*§	1 (20)†
TVR, n (%)	1 (1.1)*	2 (8)*†	3 (13)*†	0
MACE, n (%)	2 (2.2)	3 (12)	5 (22)	2 (40)

*STEMI group; †SA group; ‡attributable to progressional disease in the treated vessel requiring TVR; §reinfarction because of stent thrombosis, which required urgent TVR, during ticlopidine intake. MACE = major adverse cardiac event; TVR = target vessel revascularization; other abbreviations as in Table 1.

tially interfering with responsiveness to thienopyridines. Although response to clopidogrel is known to be durable over time (15,21), and nonresponse early after steady state is maintained in the majority of cases even after longer duration of treatment, it remains theoretically possible that crossover to ticlopidine has unmasked the effect of time in some individuals who were clopidogrel resistant at T_1 and fully responsive to ticlopidine at T_2. A randomized crossover investigation would be desirable to confirm the magnitude of our findings.

Conclusions

Our data, providing critical evidence in favor of drug-specific mechanisms after first- and second-generation thienopyridine resistance, make routine testing for clopidogrel responsiveness an attractive strategy for future clinical trials.

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