

# A Randomized Trial of Prasugrel Versus Clopidogrel in Patients With High Platelet Reactivity on Clopidogrel After Elective Percutaneous Coronary Intervention With Implantation of Drug-Eluting Stents

Results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) Study

Dietmar Trenk, PhD,\* Gregg W. Stone, MD,† Meinrad Gawaz, MD,‡ Adnan Kastrati, MD,§ Dominick J. Angiolillo, MD, PhD,|| Ulrike Müller, MD,¶ Gert Richardt, MD,# Joseph A. Jakubowski, PhD,\*\* Franz-Josef Neumann, MD\*

*Bad Krozingen, Tuebingen, Muenchen, Leipzig, and Bad Segeberg, Germany; New York, New York; Jacksonville, Florida; and Indianapolis, Indiana*

<b>Objectives</b>	This study sought to investigate the efficacy, safety, and antiplatelet effect of prasugrel as compared with clopidogrel in patients with high on-treatment platelet reactivity (HTPR) after elective percutaneous coronary intervention (PCI).
<b>Background</b>	The extent to which prasugrel can correct HTPR and improve clinical outcomes in patients undergoing elective PCI is unknown.
<b>Methods</b>	Stable coronary artery disease (CAD) patients with HTPR (>208 P2Y <sub>12</sub> reaction units [PRU] by the VerifyNow test) after elective PCI with at least 1 drug-eluting stent (DES) were randomly assigned to either prasugrel 10 mg daily or clopidogrel 75 mg daily. Platelet reactivity of the patients on the study drug was reassessed at 3 and 6 months. The study was stopped prematurely for futility because of a lower than expected incidence of the primary endpoint.
<b>Results</b>	In 212 patients assigned to prasugrel, PRU decreased from 245 (225 to 273) (median [interquartile range]) at baseline to 80 (42 to 124) at 3 months, whereas in 211 patients assigned to clopidogrel, PRU decreased from 249 (225 to 277) to 241 (194 to 275) ( $p < 0.001$ vs. prasugrel). The primary efficacy endpoint of cardiac death or myocardial infarction at 6 months occurred in no patient on prasugrel versus 1 on clopidogrel. The primary safety endpoint of non-coronary artery bypass graft Thrombolysis In Myocardial Infarction major bleeding at 6 months occurred in 3 patients (1.4%) on prasugrel versus 1 (0.5%) on clopidogrel.
<b>Conclusions</b>	Switching from clopidogrel to prasugrel in patients with HTPR afforded effective platelet inhibition. However, given the low rate of adverse ischemic events after PCI with contemporary DES in stable CAD, the clinical utility of this strategy could not be demonstrated. (Testing platelet Reactivity In patients underGOing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel [TRIGGER-PCI]; NCT00910299) (J Am Coll Cardiol 2012;59:2159-64) © 2012 by the American College of Cardiology Foundation

The TRIGGER-PCI (Testing platelet Reactivity In patients underGOing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel) trial investigated the ef-

fectiveness of prasugrel versus clopidogrel in patients with high on-treatment platelet reactivity (HTPR) on clopidogrel after elective percutaneous coronary intervention (PCI) with drug-

From the \*Universitaets-Herzzentrum Freiburg-Bad Krozingen, Klinik fuer Kardiologie und Angiologie, Bad Krozingen, Germany; †Columbia University Medical Center, New York, New York; ‡Universitaetsklinikum der Eberhard-Karls-Universitaet Tuebingen, Medizinische Klinik III, Tuebingen, Germany; §Deutsches Herzzentrum, Muenchen, Germany; ||University of Florida College of Medicine, Jacksonville, Florida; ¶Herzzentrum Leipzig, Leipzig, Germany; #Segeberger Kliniken, Bad Segeberg, Germany; and the \*\*Lilly Research Laboratories, Indianapolis,

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**Abbreviations  
and Acronyms**

<b>CAD</b>	= coronary artery disease
<b>DES</b>	= drug-eluting stent(s)
<b>HTPR</b>	= high on-treatment platelet reactivity
<b>LD</b>	= loading dose
<b>MD</b>	= maintenance dose
<b>MI</b>	= myocardial infarction
<b>PCI</b>	= percutaneous coronary intervention
<b>PRU</b>	= P2Y <sub>12</sub> reaction unit(s)
<b>TIMI</b>	= Thrombolysis In Myocardial Infarction

eluting stents (DES). Specifically, we intended to address the extent to which prasugrel can correct HTPR and the clinical benefit-to-risk ratio of prasugrel in this setting.

**Methods**

**Patient selection and interventions.** The study protocol of TRIGGER-PCI was approved by the institutional ethics committee of each study site. Written informed consent was obtained from all patients.

For recruitment to the study, we screened consecutive patients with stable coronary artery disease (CAD) and clinical indication for PCI, who had undergone successful, elective coronary implantation of at least 1 DES without major peri-interventional complications. To be eligible for screening, patients age 18 to 80 years had to be pre-treated with a loading dose (LD) of clopidogrel 600 mg along with aspirin, at least 250 mg (intravenous or oral), between 24 h before and at the time of PCI. Exclusion criteria were: non-ST-segment elevation or ST-segment elevation myocardial infarction within 14 days prior to randomization; body weight <60 kg; glycoprotein IIb/IIIa inhibitors eptifibatid or tirofiban within 24 h before or during PCI or abciximab within 10 days before or during PCI; daily treatment with nonsteroidal anti-inflammatory drugs; and contraindication to aspirin or any of the study drugs.

**Study procedures.** A citrated blood sample was drawn between 2 to 7 h after the first clopidogrel 75-mg maintenance dose (MD) the morning after PCI. Platelet function was assessed with the VerifyNow P2Y12 system (Accumetrics, San Diego, California) (1). HTPR was defined using a pre-specified cut-point of >208 PRU, which corresponded to the cut-point validated in an earlier study (2).

Randomization to prasugrel or clopidogrel was performed in a 1:1 ratio. Thereafter, treatment with the study drugs was initiated by administration of a LD within 9 h after administration of the non-study-related MD of clopidogrel 75 mg. The LD of the study drug consisted of either 60-mg prasugrel or placebo. The MD treatment of the study drug was commenced with either prasugrel 10 mg daily or clopidogrel 75 mg daily plus corresponding placebo the day after the LD of the study drug. Subjects returned for clinical visits to the study sites at day 90 and day 180, at which time blinded assessments of platelet reactivity were performed. The trial algorithm is shown in Figure 1.

**Study objectives.** The primary objective of the TRIGGER-PCI study was to test the hypothesis that the outcome of patients with HTPR on clopidogrel after elective PCI with DES can be improved by switching to prasugrel. The primary efficacy measure was the composite of cardiovascular death or myocardial infarction (MI) through 6 months follow-up. MI was defined according to published guidelines (3). All endpoints were adjudicated by a clinical endpoints committee blinded to treatment assignment.

The primary safety endpoint was non-coronary artery bypass graft-related major bleeding classified by the Thrombolysis In Myocardial Infarction (TIMI) hemorrhage classification scheme (4). Main pharmacodynamic outcome measure was PRU on the study drug at 3 months.

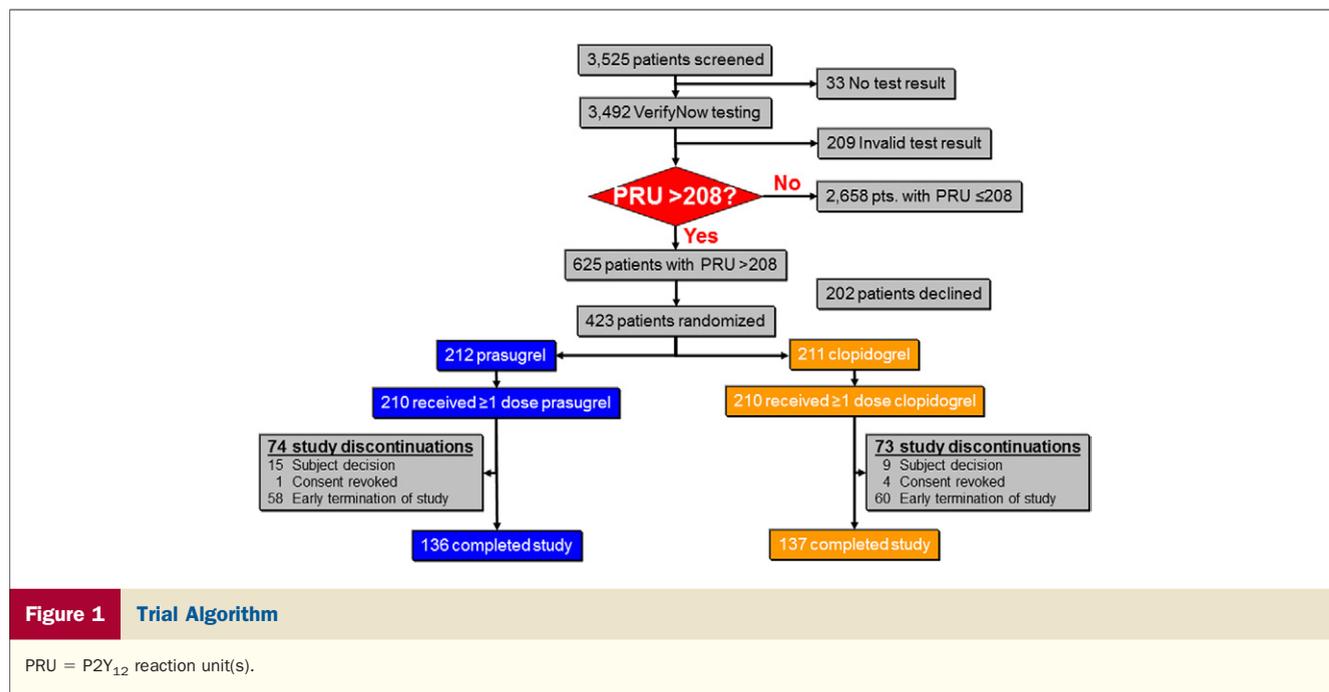
**Statistical analysis.** Sample size calculations were based on 3 assumptions: 1) according to published data (5–7), the incidence of the primary endpoint was estimated as 4.7% in the entire clopidogrel-treated population; 2) patients with a PRU >208 represent the upper tertile of the entire population with respect to on-clopidogrel platelet reactivity (2); and 3) the incidence of the primary endpoint in patients on clopidogrel with PRU >208 is increased 2-fold as compared with patients with PRU ≤208 (2). On the basis of these assumptions, it was anticipated that 1,075 subjects would need to be randomized to each group.

A blinded interim review performed on March 18, 2011, after 236 patients had completed 6-month follow-up demonstrated that 1 primary endpoint event had occurred, corresponding to an incidence of 0.4% with an upper confidence limit of 1.25%. On the basis of these data, the steering committee decided to terminate the study prematurely for futility.

If not stated otherwise, categorical variables are reported as counts (percentages) and continuous variables as mean ± SD. To compare continuous variables, we used the Student *t* test. Comparisons of proportions were carried out using the Pearson chi-square test of homogeneity. By study design, baseline PRU data were non-normally distributed. Hence, we report PRU data as median (interquartile range) and used the nonparametric Mann-Whitney *U* test for analyzing differences between patients and the Wilcoxon test for within-patient comparisons. For various outcomes, confidence intervals for hazard ratios (under the assumption of proportional hazards)

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and/or relative risks are calculated. Comparison of the treatment groups with respect to ischemic and bleeding events was carried out by time-to-first event analysis using a log-rank test. All confidence intervals are 2-sided with a 95% confidence level, and all hypothesis tests were 2-sided and carried out at a significance level of 0.05. Analyses were performed with SPSS version 15.0 for Windows (SPSS, Chicago, Illinois).

## Results

**Study population.** From July 6, 2009, through March 18, 2011, we screened 3,525 patients. Of 3,283 patients with valid PRU measurements, 625 (19.0%) met the inclusion criterion of PRU >208 and were invited to participate in the randomized study. A total of 202 patients declined participation in the study. We, thus, finally randomized 423 patients, 212 of whom were assigned to prasugrel and 211 to clopidogrel. Within each group, 210 patients received at least 1 dose of the assigned study medication.

There were no significant differences in any of the baseline, clinical, and procedural characteristics between the 2 treatment arms (Table 1). Baseline PRU was well matched between the 2 study groups ( $p = 0.805$ ) (Table 1, Fig. 2).

One hundred forty-seven patients discontinued the study prematurely after a median of 90 days (interquartile range: 44 to 132 days). This was mostly due to early termination of the study ( $n = 118$ ); other reasons included early revocation of consent ( $n = 5$ ) or unwillingness to continue with the study ( $n = 24$ ). Finally, 136 patients assigned to prasugrel and 137 patients assigned

to clopidogrel ultimately completed the study. In the prasugrel arm, we obtained a least 1 valid PRU measurement on study medication in 191 patients and a valid subsequent PRU measurement in 139 patients on the study drug. In the clopidogrel arm, the respective numbers were 197 and 144.

**Correction of HTPR by prasugrel.** At the first blinded PRU measurement in patients on the study drug, which was performed after a median of 90 days (interquartile range: 88 to 94 days), median PRU on prasugrel was significantly lower than that on clopidogrel (Fig. 2). Thus, we observed a substantial decrease in PRU in the prasugrel arm ( $p < 0.001$ ), but only a small, albeit statistically significant ( $p = 0.001$ ), decrease in the clopidogrel arm (Fig. 3). Accordingly, 176 (94.1%) patients of the prasugrel arm and 56 (29.6%) patients randomized to clopidogrel reached a PRU  $\leq 208$  ( $p < 0.001$ ). Comparing the PRU measurements between the 3- and 6-month time points on the study drug, we did not find any significant changes in either the prasugrel or the clopidogrel arm (Fig. 3).

**Clinical outcomes.** As summarized in Table 2, all endpoints analyzed occurred infrequently and without significant differences between the 2 study arms. During the entire study period, we encountered 1 primary efficacy endpoint, which occurred in the clopidogrel arm on day 140 after study entry. The timing of the combined secondary endpoint of cardiovascular death, MI, stroke, or rehospitalization for cardiac ischemic event is shown in Figure 4A. Table 3 shows the primary safety endpoint of TIMI major non-coronary artery bypass graft bleeding, which was reached in 3 patients on prasugrel and 1 patient on clopidogrel. Figure 4B shows the timing of any TIMI bleeds (major, minor, or minimal) during the study period.

**Discussion**

The major findings of TRIGGER-PCI are that prasugrel results in effective platelet inhibition in patients with HTPR after loading and maintenance dosing with clopi-

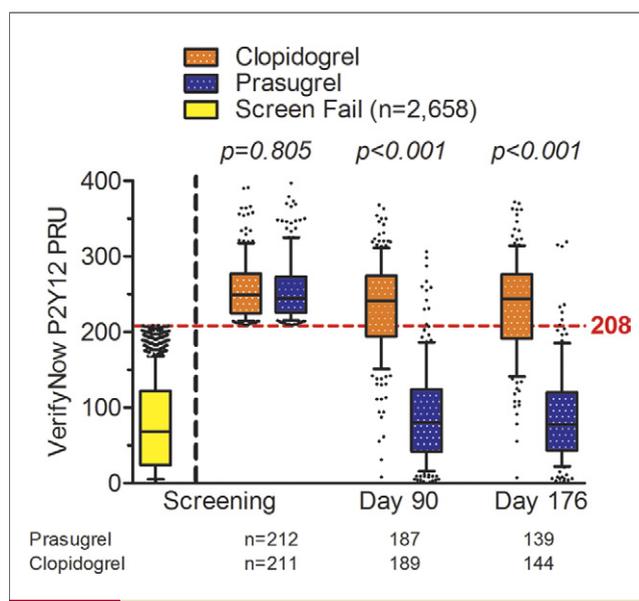
dogrel; however, given the low adverse event rate after elective DES implantation in patients with stable CAD, the clinical utility of this approach could not be demonstrated.

In the present study, after DES placement in patients with stable CAD and HTPR on clopidogrel, switching to prasugrel resulted in a consistent decrease in platelet reactivity, reaching a level comparable to that of clopidogrel-responsive patients. After patients with HTPR were switched to prasugrel, only 5.9% of patients remained above the pre-specified threshold for HTPR. Platelet reactivity on prasugrel was stable during maintenance therapy, with no significant change between the 3- and 6-month on-treatment measurements.

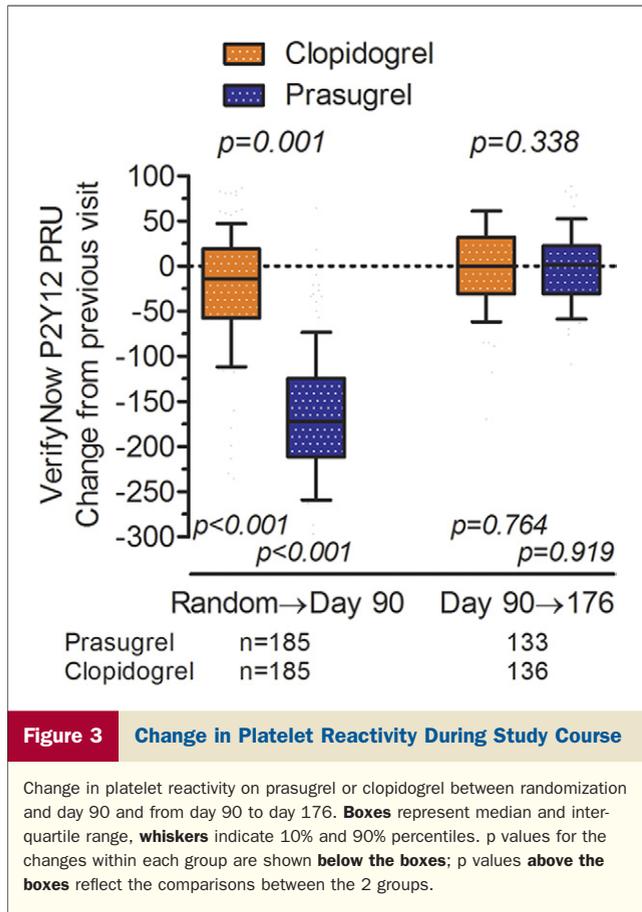
In contrast to the findings in the prasugrel arm, 70% of patients continuing on standard-dose clopidogrel remained in the range of HTPR, a finding that was consistent over time. These findings in the clopidogrel arm of TRIGGER-PCI are consistent with the findings in the control arm of GRAVITAS (Gauging Responsiveness with A VerifyNow assay–Impact on Thrombosis And Safety) (8). Conversely, significantly greater inhibition of platelet reactivity was achieved in the prasugrel arm of TRIGGER-PCI than in the double-dose clopidogrel arm of GRAVITAS (8). Despite the unequivocal pharmacodynamic superiority of prasugrel as tested, TRIGGER-PCI was stopped prematurely for futility due to an event rate that was substantially lower than expected. TRIGGER-PCI enrolled an even lower-risk cohort than GRAVITAS, and in both studies, the 6-month composite rate of cardiac death or myocardial infarction was

<b>Table 1 Baseline Demographic, Clinical, and Procedural Characteristics of the Study Patients</b>			
	<b>Prasugrel (n = 212)</b>	<b>Clopidogrel (n = 211)</b>	<b>p Value</b>
Residual platelet reactivity at randomization, PRU	245 (225–273)	249 (225–277)	0.805
Age, yrs	65.8 ± 8.3	66.3 ± 8.6	0.568
Women	59 (27.8)	57 (27.0)	0.851
Body weight, kg	88.5 ± 17.3	88.6 ± 17.2	0.946
Body mass index, kg/m <sup>2</sup>	29.9 ± 5.3	29.9 ± 5.0	0.967
Current smoker	33 (16.2)	28 (14.0)	0.829
<b>Medical history</b>			
Diabetes mellitus	87 (41.0)	90 (42.7)	0.736
Hypertension	188 (88.7)	188 (89.1)	0.891
Prior myocardial infarction	63 (29.7)	53 (25.1)	0.300
Prior unstable angina	39 (18.4)	40 (19.0)	0.861
Prior PCI	93 (43.9)	95 (45.0)	0.776
Prior CABG	26 (12.3)	30 (14.2)	0.514
Clopidogrel at admission	5 (2.4)	3 (1.4)	0.479
<b>Pharmacotherapy at randomization</b>			
<b>Maximum daily dose of aspirin</b>			
≤100 mg	186 (87.7)	184 (87.2)	0.900
>100–250 mg	2 (0.9)	4 (1.9)	0.408
>250 mg	6 (2.8)	6 (2.8)	0.993
Beta-blocker	161 (75.9)	148 (70.1)	0.179
ACE inhibitor or ARB	163 (76.9)	171 (81.0)	0.294
Calcium-channel blocker	52 (24.5)	49 (23.2)	0.753
Statin	170 (80.2)	161 (76.3)	0.333
Proton pump inhibitor	44 (20.8)	46 (21.8)	0.793
Total no. of DES	1.9 ± 1.2	1.8 ± 1.1	0.638
<b>Total no. of stents per patient</b>			
0	0	0	0.862
1	110 (51.9)	105 (49.8)	
2	53 (25.0)	58 (27.5)	
≥3	49 (23.1)	48 (22.8)	
<b>Type of stent used</b>			
Xience V/Promus	199 (49.9)	207 (53.2)	0.899
Cypher	119 (29.8)	101 (26.0)	
Endeavor	49 (12.3)	24 (6.2)	
Taxus	10 (2.5)	6 (1.5)	
Endeavor Resolute/Resolute Integrity	8 (2.0)	31 (8.0)	
Others	14 (3.5)	20 (5.1)	
Stent length, mm	18.7 ± 7.9	18.5 ± 8.0	0.714
Stent diameter, mm	3.0 ± 0.5	3.0 ± 0.5	0.960
Overlapping stents	59 (27.8)	61 (28.9)	0.377
<b>Type of vessel stented</b>			
Native artery	204 (97.6)	205 (97.2)	0.816
Saphenous vein graft	4 (1.9)	5 (2.4)	
Arterial graft	1 (0.5)	2 (1.0)	

Values are median (interquartile range), mean ± SD, or n (%). Two-sided p values were calculated by Pearson chi-square test for categorical variables, t test for continuous variables or Mann-Whitney U test between patients randomized to prasugrel or clopidogrel. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; DES = drug-eluting stent(s); PCI = percutaneous coronary intervention; PRU = P2Y<sub>12</sub> reaction units.



**Figure 2 Platelet Reactivity in the TRIGGER-PCI Study**  
 Platelet reactivity in screening failures and in patients randomized to prasugrel or clopidogrel. **Boxes** represent median and interquartile range, **whiskers** indicate 10% and 90% percentiles. Screen Fail indicates patients with ≤208 P2Y<sub>12</sub> reaction units (PRU) at screening.



extremely low (0.2% and 2.3%, respectively). The very low 6-month event rate in the present study may be attributed to several factors:

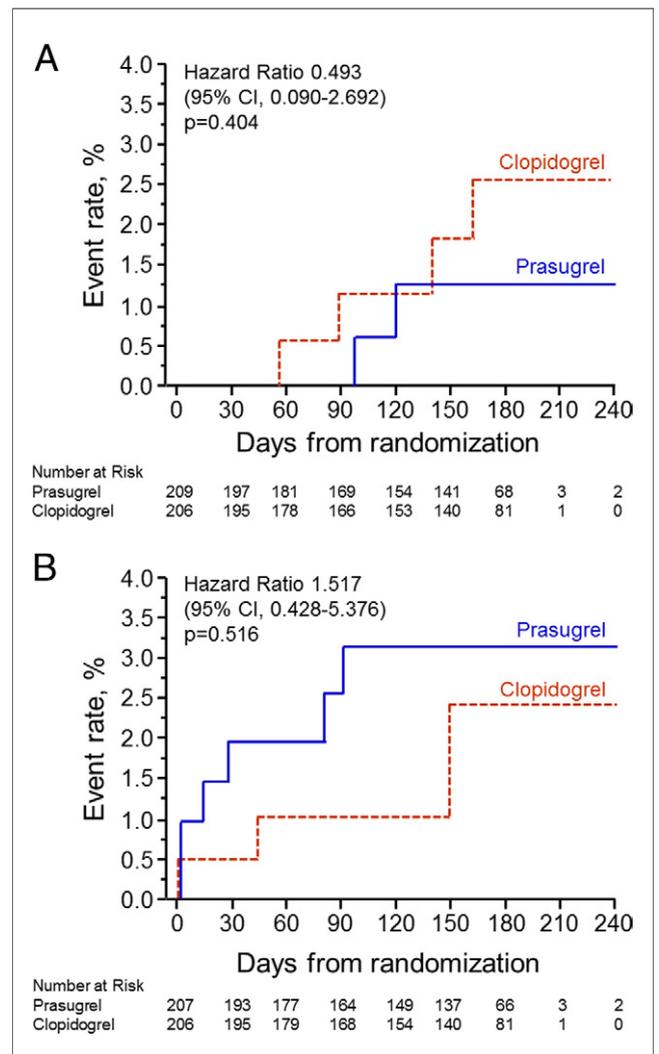
1. During the enrollment period, first-generation DES were largely replaced by new-generation stents, which eventually accounted for 70% of the stents implanted. Recent studies with new-generation DES show substantially better outcomes than with earlier devices (9–11).
2. TRIGGER-PCI excluded patients with peri-interventional ischemic or hemorrhagic complications, which are strongly associated with adverse mid- and long-term outcomes (12).
3. We also did not include any patients with acute coronary syndromes, who have been shown to benefit from intensified antiplatelet therapy with prasugrel or ticagrelor irrespective of the responder status to clopidogrel (13,14).

Exclusion of patients with acute coronary syndromes, procedure-related infarctions, and peri-interventional bleeding events, and improved results with second-generation DES resulted in a cohort that could tolerate high levels of platelet reactivity without a substantial risk of ischemic events after DES placement.

**Implications.** The results of TRIGGER-PCI impact on the concept of personalized antiplatelet therapy in 2 ways:

1) TRIGGER-PCI validated one of the key prerequisites for the utility of personalized antiplatelet therapy by demonstrating that high on-treatment platelet reactivity, if detected, can be reliably corrected by switching from clopidogrel to prasugrel; and 2) conversely, TRIGGER-PCI failed to demonstrate an improvement in clinical outcomes by switching to prasugrel in patients with HTPR on clopidogrel after elective PCI with DES implantation. The low observed ischemic event rate in the control group even without correction of HTPR demonstrates that testing platelet function in such patients for consideration of more intensive antiplatelet therapy is not warranted, especially given the potentially increased risk of bleeding (13,14).

The observations of TRIGGER-PCI, however, do not negate the concept of personalized antiplatelet therapy in



**Table 2** Summary of Primary and Secondary Adjudicated Efficacy Endpoints

	Prasugrel (n = 212)	Clopidogrel (n = 211)	p Value HR (95% CI)
<b>Primary composite efficacy endpoint</b>			
CV death or MI	0 (0.0)	1 (0.5)	NE
<b>Secondary efficacy endpoints</b>			
CV death	0 (0.0)	0 (0.0)	NE
MI	0 (0.0)	1 (0.5)	NE
Definite or probable stent thrombosis	0 (0.0)	0 (0.0)	NE
UTVR	2 (1.0)	1 (0.5)	NE
CV death, MI, or UTVR	2 (1.0)	2 (1.0)	NE
CV death, MI, stroke, or rehospitalization for cardiac ischemic events	2 (1.0)	6 (2.9)	0.404 0.493 (0.090–2.692)
Non-CV death	0 (0.0)	1 (0.5)	NE

Values are n (%). HR and 2-sided 95% CI are derived using Cox proportional hazards model with treatment as a fixed effect with the associated p value based on a log-rank test.

CEC = clinical endpoints committee; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NE = not evaluated due to insufficient data (n = 5); UTVR = urgent target vessel revascularization.

general. The TRIGGER-PCI cohort represented the low-risk end of patients undergoing PCI. The 6-month risk of death and myocardial infarction is substantially higher in patients with acute coronary syndromes, in those undergoing multilesion and/or complex lesion interventions, and had peri-interventional complications not been excluded. Higher-risk populations are likely more dependent on adequate suppression of platelet reactivity for optimal results than the TRIGGER-PCI cohort. Thus, future randomized trials are warranted to examine the risk–benefit ratio of allocating higher-risk patients with stable CAD and high on-clopidogrel platelet reactivity to more potent platelet inhibition before and after PCI. These studies can build on the pharmacodynamic data from TRIGGER-PCI, which

**Table 3** Summary of Safety Endpoints

	Prasugrel (n = 210)	Clopidogrel (n = 210)	p Value HR (95% CI)
Non-CABG TIMI major bleeding	3 (1.4)	1 (0.5)	NE
Non-CABG TIMI fatal bleeding	0	0	NE
Non-CABG TIMI life-threatening bleeding	0	1 (0.5)	NE
Non-CABG TIMI major or minor bleeding	3 (1.4)	2 (1.0)	NE
Non-CABG TIMI major, minor, or minimal bleeding	6 (2.9)	4 (1.9)	0.516 1.517 (0.428–5.376)

Values are n (%). Bleeding was categorized according to the TIMI criteria. HR and 2-sided 95% CI are derived using Cox proportional hazards model with treatment as a fixed effect with the associated p value based on a log-rank test.

CABG = coronary artery bypass grafting; TIMI = Thrombolysis in Myocardial Infarction; other abbreviations as in Table 2.

demonstrates the efficacy of prasugrel in overcoming HTPR on clopidogrel in patients with stable CAD.

**Reprint requests and correspondence:** Dr. Dietmar Trenk, Universitaets-Herzzentrum Freiburg-Bad Krozingen, Klinik fuer Kardiologie und Angiologie, D-79189 Bad Krozingen, Germany. E-mail: dietmar.trenk@herzzentrum.de.

**REFERENCES**

- Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. *Circulation* 2009;119:2625–32.
- Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol* 2008;51:1925–34.
- Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;50:2173–95.
- Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann Intern Med* 1991;115:256–65.
- Schömig A, Schmitt C, Dibra A, et al. One year outcomes with abciximab vs. placebo during percutaneous coronary intervention after pre-treatment with clopidogrel. *Eur Heart J* 2005;26:1379–84.
- Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411–20.
- Zahn R, Hamm CW, Schneider S, et al. Predictors of death or myocardial infarction during follow-up after coronary stenting with the sirolimus-eluting stent. Results from the prospective multicenter German Cypher Stent Registry. *Am Heart J* 2006;152:1146–52.
- Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention. *JAMA* 2011;305:1097–105.
- Raber L, Juni P, Nuesch E, et al. Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. *J Am Coll Cardiol* 2011;57:2143–51.
- Stone GW, Teirstein PS, Meredith IT, et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial. *J Am Coll Cardiol* 2011;57:1700–8.
- Yeung AC, Leon MB, Jain A, et al. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. *J Am Coll Cardiol* 2011;57:1778–83.
- Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol* 2008;51:690–7.
- Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57.
- Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–15.

**Key Words:** clopidogrel ■ coronary disease ■ platelet aggregation ■ prasugrel ■ stent.

**APPENDIX**

For a list of the Steering Committee members, DSMB members, Clinical Endpoints Committee Members, and the Acknowledgments section, please see the online version of this article.