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Randomized Comparison of Oral $P2Y_{12}$-Receptor Inhibitor Loading Strategies for Transitioning From Cangrelor

The ExcelsiorLOAD2 Trial

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ABSTRACT

OBJECTIVES This randomized trial tested whether early loading with prasugrel can provide sufficient platelet inhibition even when given at the start of a 2-h infusion of cangrelor.

BACKGROUND Effective platelet inhibition with intravenous cangrelor reduces the risk of ischemic complications during percutaneous coronary intervention (PCI). Transitioning to oral therapy with clopidogrel or prasugrel is only recommended after discontinuation of cangrelor due to drug interactions. Given the long half-life of prasugrel, this drug could achieve effective platelet inhibition even when given early under cangrelor and thereby prevent a transient gap in platelet inhibition.

METHODS This trial randomized 110 $P2Y_{12}$-receptor blocker–naive patients undergoing PCI with use of cangrelor to loading with prasugrel 60 mg or ticagrelor 180 mg at the start of cangrelor (n = 45 each) or loading with clopidogrel 600 mg after discontinuation of cangrelor (n = 20). The primary endpoint was the proportion of patients without high on-treatment platelet reactivity 1 h after stopping cangrelor.

RESULTS The 3 groups were well balanced with respect to clinical parameters. One hour following discontinuation of cangrelor, the primary endpoint was seen in 65.0% of patients on clopidogrel versus 95.6% with ticagrelor and 93.3% with prasugrel (p for superiority of prasugrel vs. clopidogrel = 0.003; p of prasugrel vs. ticagrelor = 0.65). The 30-day incidence of ischemic and bleeding events was similar in all groups.

CONCLUSIONS Prasugrel 60 mg given at the start of a 2-h infusion of cangrelor can provide a sufficient platelet inhibition post-cangrelor. This approach prevents the transient gap in platelet inhibition seen with oral loading after discontinuation of cangrelor. (Impact of Extent of Clopidogrel-Induced Platelet Inhibition during Elective Stent Implantation on Clinical Event Rate – Advanced Loading Strategies [ExcelsiorLOAD2]; DRKS00009739)
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Sufficient platelet inhibition is key for prevention of ischemic complications in patients undergoing percutaneous coronary intervention (PCI) (1,2). Current American and European guidelines recommend the use of dual antiplatelet therapy with aspirin and a $P2Y_{12}$-receptor blocker in this setting (3,4). The clinical importance of a sufficient $P2Y_{12}$-receptor inhibition already at start of PCI

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ABBREVIATIONS AND ACRONYMS

ADP = adenosine diphosphate

AU × min = aggregation units per min

PCI = percutaneous coronary intervention

was underscored by a recent trial comparing the intravenous $P2Y_{12}$-receptor blocker cangrelor with clopidogrel loading given directly before PCI (5). Cangrelor provides an immediate onset of antiplatelet effect, whereas for clopidogrel, it takes at least 2 h to become effective (6–8). This initial short gap in peri-interventional platelet inhibition was associated with a significant increase in peri-interventional myocardial infarction and stent thrombosis.

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There is a competitive interaction of the active metabolites of clopidogrel and prasugrel with cangrelor at the level of the $P2Y_{12}$-receptor as demonstrated by in vitro studies (9,10). Therefore, the U.S. label of cangrelor recommends transitioning to these oral $P2Y_{12}$-receptor blockers only following discontinuation of cangrelor (11). Ticagrelor is the only oral $P2Y_{12}$-receptor blocker without any known interaction with cangrelor, which enables administration at any time during the infusion (12). Due to the short half-life of the active metabolite of clopidogrel (13,14), this drug can only provide sufficient $P2Y_{12}$ inhibition when given after discontinuation of cangrelor (15). However, this transitioning leads to a gap in post-interventional platelet inhibition (15,16). Even though there was no safety signal for this post-interventional gap in studies with cangrelor (5,17), there are still safety concerns in particular for patients at high ischemic risk.

Limited data for prasugrel indicate that this drug might be administered up to 30 min before discontinuation of cangrelor (16). This approach might reduce the post-interventional gap in platelet inhibition, but cannot prevent it (16). However, pharmacokinetic data indicate that it should be possible for prasugrel to achieve sufficient platelet inhibition even when given more than 1 h before discontinuation of cangrelor (18–20). This assumption is based on studies focusing on the half-life of the active metabolite of prasugrel demonstrating that it is with about 7 h significantly longer as compared with clopidogrel (18–20). Such an approach has the potential of avoiding the post-interventional gap in platelet inhibition. However, there are no pharmacodynamic data supporting this approach so far.

Thus, this prospective, randomized trial examined whether early loading with prasugrel already at the start of a 2-h infusion of cangrelor can achieve a more constant antiplatelet effect following cangrelor as compared with loading with clopidogrel post-cangrelor and whether this effect is comparable to early loading with ticagrelor.

METHODS

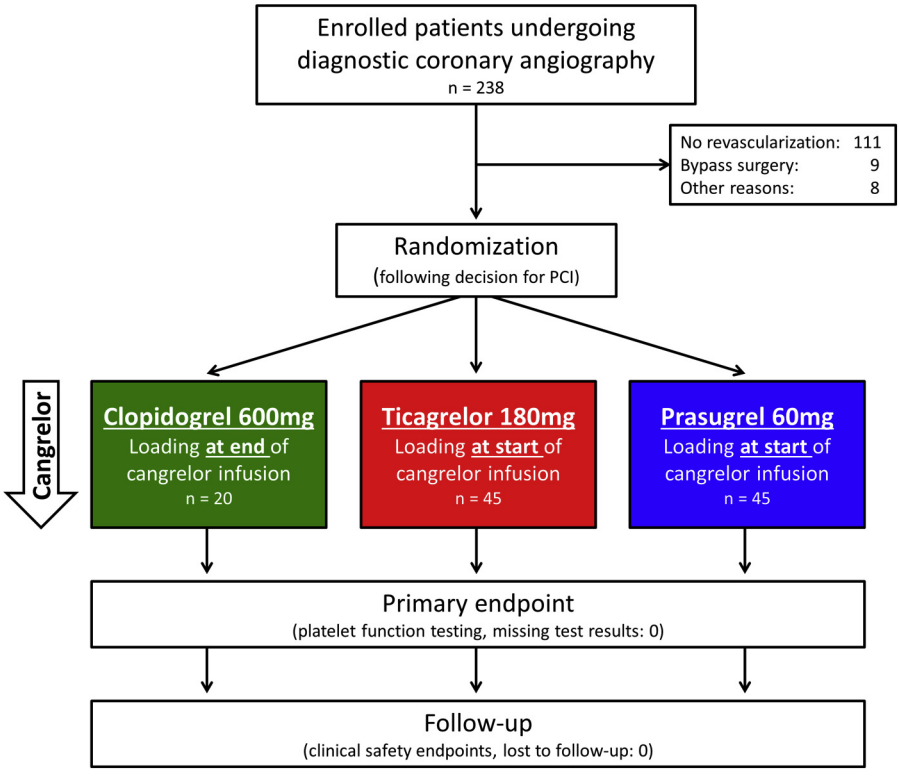
STUDY DESIGN AND OBJECTIVES. The ExcelsiorLOAD2 (Impact of Extent of Clopidogrel-Induced Platelet Inhibition during Elective Stent Implantation on Clinical Event Rate–Advanced Loading Strategies) trial was designed as a three-armed, controlled PROBE (Prospective, Randomized, Open, Blinded End-points) Phase IIIb trial (**Figure 1**). Patients were enrolled into this trial at the University Heart Center in Bad Krozingen, Germany, from January 2016 until May 2016. The study was approved by the ethics committee of the University of Freiburg (Germany) and the regulatory agency (Federal Institute for Drugs and Medical Devices, Bonn, Germany), and has been registered at the German Clinical Trial Register (DRKS00009739).

The objective of the ExcelsiorLOAD2 trial was to compare the pharmacodynamic effectiveness of different oral loading regimes for transitioning from cangrelor administered either at the start of cangrelor immediately before coronary intervention (prasugrel 60 mg, ticagrelor 180 mg) or immediately after discontinuation of cangrelor (clopidogrel 600 mg). The prasugrel arm represented the experimental group, the other 2 arms the control groups. The primary endpoint was the proportion of patients without high on-treatment platelet reactivity defined as platelet aggregation of <468 aggregation units per min (AU × min) (Multiplate Test, Roche Diagnostics, Mannheim, Germany) determined 1 h after stopping cangrelor. Secondary endpoints included analysis of pharmacodynamic effectiveness at other time points following loading and clinical endpoints (all fatal, ischemic, and hemorrhagic events) within 30 days following loading.

STUDY POPULATION. Patients with obstructive coronary heart disease and planned coronary stent implantation were eligible if they were pre-treated with aspirin and ≥18 years of age. Key exclusion criteria were acute myocardial infarction, acute bleeding, treatment with any $P2Y_{12}$-receptor blocker, fibrinolytic agents, or glycoprotein IIb/IIIa inhibitors within 7 days before enrollment, contraindication for aspirin or any of the study medications, oral anticoagulation, or any severe disorder of the coagulation system. Given the label of prasugrel, patients with a history of transient ischemic attack or stroke were also excluded. Patients with unstable angina could be enrolled in this trial.

After diagnostic angiography, patients were randomized when decision for PCI was made. Randomization codes were computer generated with a block

FIGURE 1 Trial Flow Chart



PCI = percutaneous coronary intervention.

size of 22. Treatment with cangrelor was initiated immediately before start of coronary intervention (intravenous bolus of 30 μg/kg of body weight followed by an infusion of 4 μg/kg/min) and continued according to label for at least 2 h or the duration of the procedure, whichever was longer. Patients randomized to prasugrel 60 mg or ticagrelor 180 mg received the oral loading dose together with the intravenous bolus of cangrelor immediately before coronary intervention. Patients randomized to clopidogrel 600 mg were loaded directly after discontinuation of cangrelor. The rationale for loading with clopidogrel only following stopping cangrelor was that this reflects the recommended transitioning strategy from cangrelor as evaluated in large randomized trials (5,17), and that a previous study has shown that clopidogrel 600 mg, when given at the start of a 2-h infusion of cangrelor, does not provide a relevant $P2Y_{12}$-receptor inhibition following discontinuation of cangrelor (15).

Following coronary intervention, all patients were treated with a daily maintenance dose of aspirin 100 mg and clopidogrel 75 mg for at least 30 days. Patients randomized to ticagrelor 180 mg received an additional loading dose of clopidogrel 600 mg on the next day on the basis of previous data and recommendations (21,22). All other medications and procedures were left to the discretion of the treating physicians. All patients gave written informed consent before angiography or any study procedure.

LABORATORY PROCEDURES. Blood samples for platelet function testing were drawn before loading, at end of cangrelor infusion, and every 30 min thereafter for up to 2 h, and on day 1 before intake of clopidogrel. Blood was collected into 2.7-ml tubes containing r-hirudin (45 μg/ml, Sarstedt AG & Co., Nuembrecht, Germany). Adenosine diphosphate (ADP) (6.4 μmol/l)-induced platelet aggregation was assessed in whole blood by impedance aggregometry according to the manufacturer's instructions (ADP test, Multiplate Analyzer, Roche Diagnostics). Results were expressed as AU × min. High on-treatment platelet reactivity was defined as ≥468 AU × min

according to previously published data and recommendations of a consensus document (2,23).

ADJUDICATION AND DEFINITION OF CLINICAL ENDPOINTS. All patients were followed for 30 days. In addition to results obtained from clinical follow-up, an automated computer algorithm reported any additional diagnostic procedure or even minor change in biomarkers, as well as any additional appointment, for example, to the out-patient department within follow-up. All reported potential clinical events were adjudicated by 2 independent cardiologists blinded to randomized treatment (M.A. and C.S.).

Myocardial infarction was classified according to the Third Universal Definition of Myocardial Infarction (24). High-sensitivity cardiac troponin T (Roche Diagnostics) was tested in all patients at 8, 16, and 24 h following coronary intervention. To fulfill the definition of a myocardial infarction associated with PCI (type 4a), an elevation of high-sensitivity cardiac troponin T >5× the 99th percentile upper reference limit was needed. In addition to a significant rise and fall in troponin, new typical cardiac symptoms, electrocardiogram changes, or imaging results were needed for diagnosis.

Bleeding was classified according to the consensus report from the BARC (Bleeding Academic Research Consortium) and the TIMI (Thrombolysis In Myocardial Infarction) criteria (25). To detect even minimal bleeding events, the vascular access site of all patients was examined by dedicated nurses directly following intervention as well as on the next day.

STATISTICS AND POWER CALCULATION. Primary analysis was the comparison of the proportion of patients with no high on-treatment platelet reactivity of clopidogrel 600 mg and prasugrel 60 mg 1 h after discontinuation of cangrelor (Fisher exact test for superiority, alpha level of 2.5%). Given an incidence of the primary endpoint of 45% for clopidogrel and 89% for prasugrel on the basis of the results of the ExcelsiorLOAD (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate-Advanced Loading Strategies) trial (26), 20 patients had to be enrolled in the clopidogrel group and 45 in the prasugrel group to detect superiority of prasugrel at a power of 90%. The sample size of 45 in the ticagrelor group is based on the sample size of the prasugrel group because almost no data were available for early platelet reactivity assessed with the used platelet function assay in patients loaded with ticagrelor. The modified intention-to-treat-population including all randomized patients being treated at least with the study loading dose was used for these analyses.

In general, discrete variables are reported as counts (percentages) and continuous variables as median (interquartile range). For discrete variables, differences between groups were tested by Fisher exact test. For continuous variables, the Kruskal-Wallis test was employed. Dunn nonparametric comparison was used for post hoc testing after a Kruskal-Wallis test. Repeated measures analyses based on regression modeling and including platelet function results at all time points following discontinuation of cangrelor were used to test for differences between groups. The Bonferroni correction was used for post hoc testing. In 2-sided tests, a p value <0.05 was regarded as significant. Statistical analyses were run with IBM SPSS Statistics, version 22 (IBM Corporation, Armonk, New York).

RESULTS

STUDY POPULATION. Baseline characteristics of the 110 randomized patients were well balanced between cohorts (**Table 1**). Patients were predominantly male, mean age was 69 years, 22% had diabetes, and 48% were diagnosed with 3-vessel disease. Radial access for intervention was used in 74%. Cangrelor was given for 120 ± 10 min in the vast majority of patients. Infusion with cangrelor was stopped early in 16 patients (ticagrelor n = 7; prasugrel n = 7; clopidogrel n = 2) after a median time of 90 min (range 66 to 107 min) due to change of revascularization strategy (n = 2), technical or vascular access site items (n = 10), or bleeding/adverse effects (n = 4). Two patients received cangrelor for more than 130 min due to a longer duration of intervention.

PHARMACODYNAMIC RESULTS. The proportion of patients with high on-treatment platelet reactivity tested 1 h after stopping cangrelor infusion was found in 35.0% of patients loaded with clopidogrel 600 mg, in 4.4% of patients receiving ticagrelor 180 mg, and in 6.7% of patients on prasugrel 60 mg (p for superiority of prasugrel vs. clopidogrel = 0.003; p for comparison of prasugrel and ticagrelor = 0.65) (**Figure 2**). Starting from 30 min after discontinuation of cangrelor, patients randomized to clopidogrel showed the highest proportion of patients with high on-treatment platelet reactivity of up to 35%. Even 2 h after stopping cangrelor and loading with clopidogrel, 1 of 5 patients continued to have an insufficient antiplatelet response. The proportion of patients randomized to loading with prasugrel or ticagrelor with high on-treatment platelet reactivity was low and did not show a strong relapse (maximum 4.4% with ticagrelor and 11.3% with prasugrel at 90 min). At day 1 following

loading, the vast majority of patients in all 3 cohorts were below the threshold of high on-treatment platelet reactivity. A repeated measures analysis including all time points following discontinuation of cangrelor showed that the incidence of high on-treatment platelet reactivity differed significantly between time points ($p < 0.001$) and randomized groups ($p = 0.003$). Post hoc testing showed that there was a significant difference between clopidogrel versus ticagrelor and prasugrel ($p = 0.002$ and $p = 0.04$, respectively), but not between ticagrelor and prasugrel ($p = 0.66$).

One patient in the prasugrel arm received cangrelor for 145 min. This patient did not show high on-treatment platelet reactivity at any time-point following discontinuation of cangrelor.

Analyzing platelet reactivity as a continuous variable demonstrated similar findings (Figure 3). There were no significant differences between the 3 cohorts before start of cangrelor as well as at the end of cangrelor infusion ($p = 0.43$ and $p = 0.25$, respectively). However, at any time point following cangrelor, platelet reactivity differed significantly between time points ($p < 0.001$) and randomized groups ($p = 0.001$) as demonstrated by repeated measures analysis. There was a significant difference between clopidogrel and ticagrelor ($p = 0.001$), and ticagrelor and prasugrel ($p = 0.04$), but not between clopidogrel and prasugrel ($p = 0.18$), as demonstrated by post hoc testing. At day 1 following loading, platelet reactivity was not different between the ticagrelor and prasugrel cohorts ($p = 0.91$), but was significantly lower in both cohorts as compared with the clopidogrel cohort ($p = 0.007$ and $p = 0.009$, respectively).

There were no sex-based differences in antiplatelet response to the 3 study regimes.

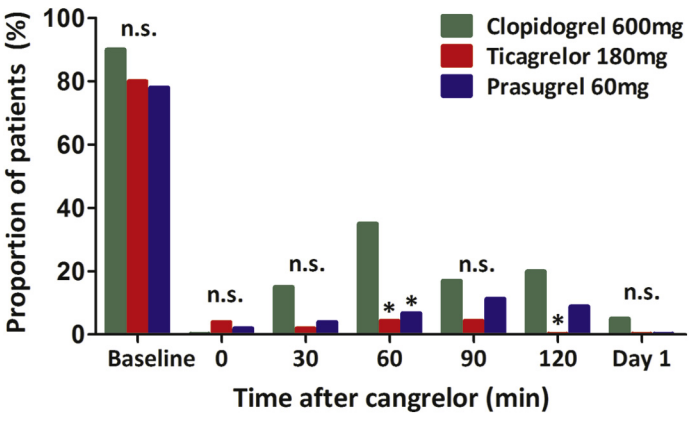
CLINICAL SAFETY PARAMETERS. Complete clinical follow-up was available from all randomized patients. A fatal event occurred in 1 patient randomized to ticagrelor 180 mg (cardiac tamponade several hours after complex PCI followed by prolonged and refractory cardiogenic shock) (Table 2). The incidence of ischemic and bleeding events was comparable between randomized cohorts. Peri-interventional myocardial infarctions on the basis of cardiac troponin testing according to current guidelines were seen in up to 11% of patients. None of the peri-interventional myocardial infarctions were associated with a rise in creatine kinase-myocardial band more than 3-fold the upper limit of normal, nor did any of these events lead to a reintervention. No case of stent thrombosis occurred during follow-up.

TABLE 1 Baseline Characteristics

	Clopidogrel 600 mg (n = 20)	Ticagrelor 180 mg (n = 45)	Prasugrel 60 mg (n = 45)
Age (yrs)	69 (62–76)	69 (63–75)	70 (61–75)
Female	7 (35)	10 (22)	8 (18)
Active smoker	4 (20)	5 (11)	7 (16)
Arterial hypertension	16 (80)	36 (80)	38 (84)
Hypercholesterolemia	17 (85)	43 (96)	38 (84)
Diabetes mellitus	5 (25)	10 (22)	9 (20)
Body mass index (kg/m^2)	28.4 (25.3–32.8)	27.8 (24.8–30.3)	28.0 (25.5–31.0)
Hemoglobin (g/dl)	14.6 (13.3–14.9)	14.5 (13.4–15.4)	14.8 (13.9–15.6)
Glomerular filtration rate (ml/min)	87 (70–98)	81 (67–99)	94 (71–112)
High-sensitivity troponin T (ng/l)	9 (5–14)	12 (6–18)	11 (7–26)
Time of cangrelor infusion (min)	120 (115–121)	120 (115–120)	120 (117–122)
Previous balloon angioplasty	5 (25)	17 (38)	13 (29)
Previous CABG	3 (15)	6 (13)	8 (18)
Previous myocardial infarction	2 (10)	5 (11)	4 (9)
Reduced LV ejection fraction*	3 (15)	10 (22)	7 (16)
Coronary angiography result			
1-vessel disease	6 (30)	10 (22)	12 (27)
2-vessel disease	6 (30)	12 (27)	11 (24)
3-vessel disease	8 (40)	23 (51)	22 (49)
Treated vessel			
Left main	3 (15)	4 (9)	3 (7)
Left anterior descending	13 (65)	23 (51)	22 (49)
Left circumflex	6 (30)	28 (62)	22 (49)
Right coronary artery	2 (10)	10 (22)	10 (22)
Bypass	1 (5)	1 (2)	3 (7)
Radial access	12 (60)	35 (78)	34 (76)
Sheath size >6-F	1 (5)	2 (4)	2 (4)

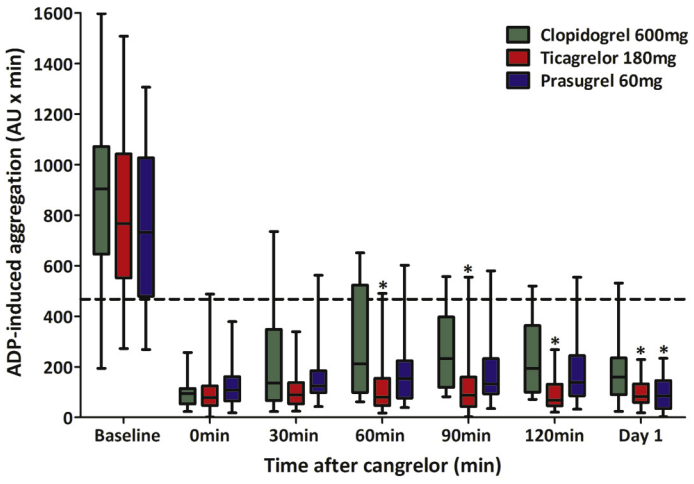
Values are median (interquartile range) or n (%). There were no significant differences between the 3 groups ($p > 0.15$ for all comparisons). *Left ventricular ejection fraction <55%.
CABG = coronary artery bypass surgery; LV = left ventricular.

FIGURE 2 Proportion of Patients With High On-Treatment Platelet Reactivity



*$p < 0.01$ as compared with clopidogrel 600 mg. n.s. = not significant.

FIGURE 3 ADP-Induced Platelet Reactivity as a Linear Variable



*p < 0.01 as compared with clopidogrel 600 mg (post hoc testing with Dunn nonparametric comparison following the Kruskal-Wallis test). **Whiskers** indicate the 95% percentile. **Dashed line** indicates the cutoff for high on-treatment platelet reactivity (468 AU × min). ADP = adenosine diphosphate; AU × min = aggregation units per min.

Bleeding events were mainly mild and located at the vascular access site. The only major bleeding event was the cardiac tamponade mentioned before. None of the bleeding events require surgical treatment.

DISCUSSION

This prospective, randomized trial compared the peri-interventional pharmacodynamics of loading with prasugrel 60 mg or ticagrelor 180 mg at the start of a 2-h infusion of cangrelor or loading with clopidogrel 600 mg after discontinuation of cangrelor in $P2Y_{12}$-receptor blocker naive patients undergoing PCI. Key findings are that loading with 60 mg of prasugrel can provide effective platelet inhibition even when given 2 h before discontinuation of cangrelor despite the known competitive interaction of the active metabolites of both drugs shown by in vitro studies. This approach can effectively prevent the transient gap in platelet inhibition seen in this trial with loading with clopidogrel that was also previously described for loading with prasugrel after stop of cangrelor. These data also support previous studies describing a relatively long half-life of the active metabolite of prasugrel as compared with clopidogrel (18–20). The incidence of patients with high on-treatment platelet reactivity post-cangrelor with prasugrel was similar to the incidence seen with ticagrelor even if the absolute values of platelet reactivity were lower with ticagrelor. Because other studies indicate that the level of platelet inhibition is similar with both potent oral $P2Y_{12}$-receptor blockers (27), the later finding might indicate some minor level of interaction of cangrelor and prasugrel. All 3 loading strategies appeared to be safe with respect to clinical outcomes and in particular to bleeding.

The highest risk for ischemic events in patients undergoing PCI is seen in the peri-interventional phase and the first few days following intervention (3,4,28). Thus, it appears reasonable to aim for a sufficient platelet inhibition in particular during this early period. For the very early phase during PCI, stronger platelet inhibition has been associated with less ischemic events including peri-interventional myocardial infarction and stent thrombosis as demonstrated by pharmacodynamic studies and clinical trials evaluating faster-acting $P2Y_{12}$-inhibitors and pre-treatment strategies, although the results for pretreatment are conflicting (1–5,29). Even if dedicated trials focusing on the early period following PCI are sparse, studies analyzing the impact of interruption of antiplatelet therapy report a significantly increased risk for major ischemic events in particular in this early period (30).

To avoid a post-interventional gap in platelet inhibition, early transitioning to oral therapy with ticagrelor appears to be the optimal strategy because this drug has no known interaction with cangrelor due to its relatively long half-life and its reversible mode of action (12). Potential limitations for this approach are that some patients might have contraindications to ticagrelor (3,4), there is limited availability of ticagrelor in some countries, and patients

TABLE 2 Clinical Safety Parameters Within 30 Days of Enrollment

	Clopidogrel 600 mg (n = 20)	Ticagrelor 180 mg (n = 45)	Prasugrel 60 mg (n = 45)
Death*	0	1 (2.2)	0
Myocardial infarction†	0	2 (4.4)	5 (11.1)
TIMI bleeding			
Minor	1 (5.0)	2 (4.4)	1 (2.2)
Major	0	1 (2.2)	0
BARC 3-5 bleeding			
BARC 3a	1 (5.0)	1 (2.2)	1 (2.2)
BARC 5	0	1 (2.2)	0
Location of bleeding			
Vascular access site	1 (5.0)	1 (2.2)	1 (2.2)
Hematuria	0	1 (2.2)	0
Pericardial	0	1 (2.2)	0

Values are n or n (%). There was no stroke or urgent revascularization during follow-up. There were no significant differences between the 3 groups (p > 0.15 for all comparisons). *Cardiac tamponade several hours following percutaneous coronary intervention with prolonged and refractory cardiogenic shock. †Coded according to Universal Definition of Myocardial Infarction (all events were Type 4a myocardial infarctions).

BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis In Myocardial Infarction.

undergoing elective PCI need to be transitioned to maintenance therapy with clopidogrel. However, there are safety concerns for switching from ticagrelor to thienopyridines (31). According to the results of a recent trial, there appears to be an interaction when thienopyridines are given on top of ticagrelor, similar as for cangrelor, leading to a transient gap in platelet inhibition (31).

Compared to ticagrelor, there is no known interaction of prasugrel with clopidogrel given the irreversible mode of action of both compounds (32,33). Pharmacodynamic data also indicate that transitioning from prasugrel to ticagrelor is feasible (34). Thus, for patients not eligible for loading and long-term therapy with ticagrelor, prasugrel can be seen as the ideal drug for early loading in patients receiving cangrelor. As demonstrated by this trial, it can become effective and prevent the post-cangrelor gap in platelet inhibition, and as demonstrated by previous data, transitioning to other oral strategies is possible without interactions.

The only study so far that has investigated strategies using prasugrel for transitioning from cangrelor evaluated post-cangrelor platelet reactivity after cessation of cangrelor when prasugrel was given up to 1 h before discontinuation of cangrelor (16). Even if the results were limited by the small sample size (3 to 6 patients per group) and the experimental setting without PCI, the data of this trial indicated that prasugrel might become effective when given up to 1 h before stop of cangrelor and that this early oral loading might reduce, but cannot completely prevent, the transient recovery of platelet reactivity (16). The results of our trial extend these previous findings by showing that earlier loading with prasugrel 2 h before discontinuation of cangrelor can become effective in a clinical setting and that this earlier approach is associated with almost no transient recovery of platelet reactivity. Similar to our trial, this previous study only evaluated platelet reactivity and not levels of active metabolites of prasugrel. However, on day 1 following loading, there was still an effective platelet inhibition seen with prasugrel before intake of the first maintenance dose of clopidogrel. Because cangrelor has a rapid offset of antiplatelet effects (7), this finding provides evidence that prasugrel can provide a sufficient and constant antiplatelet effect when given together with cangrelor and that the results seen within the first hours following discontinuation of cangrelor are not just a remaining effect of cangrelor.

Taken together, the results of our trial indicate that a more flexible use of prasugrel for transitioning from cangrelor is possible. This facilitates clinical routine because strict timing of loading with prasugrel or stop of cangrelor infusion is not mandatory anymore. With this strategy, down-titration of intensity of antiplatelet long-term strategy to clopidogrel is also possible without the risk for a transient gap in platelet inhibition.

STUDY LIMITATIONS. This trial is only powered for pharmacodynamic endpoints. Even if there was no significant difference between groups regarding clinical endpoints, the clinical efficacy and safety of the tested approach can only be validated by a larger randomized trial. The results of this trial do not prove noninferiority of prasugrel to ticagrelor even if the incidence of patients with high on-treatment platelet reactivity post-cangrelor was similar in both groups. Active metabolites of the tested drugs were not determined. However, in previous studies, levels of platelet reactivity and not of metabolite levels were associated with clinical outcome. The consistent low platelet reactivity with prasugrel at day 1 following loading and before intake of the first maintenance dose indicate that the remaining plasma concentrations of the active metabolite of prasugrel at time of discontinuation of cangrelor were sufficient for an effective platelet inhibition. The results of this trial are based on a single platelet function assay, and this study did only test loading with prasugrel at the start of cangrelor but not at a later point of time. Thus, further studies are needed to confirm these findings and evaluate different loading strategies with prasugrel.

CONCLUSIONS

Despite the known interaction of active metabolites of prasugrel and cangrelor, loading with prasugrel 60 mg given at the start of a 2-h infusion of cangrelor can provide a sufficient platelet inhibition post-cangrelor. This approach prevents the transient gap in platelet inhibition seen with oral loading with clopidogrel or prasugrel after discontinuation of cangrelor. Although definite proof for the clinical safety and efficacy of this regimen is lacking as well as confirmation in future studies, it might be considered as an option for transitioning from cangrelor to oral therapy as an alternate to ticagrelor particularly in high-risk settings.

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PERSPECTIVES

WHAT IS KNOWN? In patients undergoing PCI with the use of cangrelor, loading with clopidogrel 600 mg at the end of cangrelor infusion causes a transient gap in platelet inhibition.

WHAT IS NEW? Loading with prasugrel 60 mg given 2 h before end of infusion with cangrelor can provide a sufficient platelet inhibition post-cangrelor despite the known interaction of active metabolites of prasugrel and cangrelor. This approach prevents the transient gap in platelet inhibition seen with an oral loading with clopidogrel or prasugrel after discontinuation of cangrelor, and might be considered as an option for transitioning from cangrelor to oral therapy as an alternate to ticagrelor, particularly in high-risk settings.

WHAT IS NEXT? Because definite proof for the safety and efficacy of loading with prasugrel under cangrelor is lacking, further evaluation of this strategy in a prospective outcome trial is needed.

REFERENCES

1. Hochholzer W, Trenk D, Bestehorn HP, et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. J Am Coll Cardiol 2006;48:1742–50.

2. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–73.

3. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.

4. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2014;35:2541–619.

5. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368:1303–13.

6. Hochholzer W, Trenk D, Frundi D, et al. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. Circulation 2005;111:2560–4.

7. Ferreiro JL, Ueno M, Angiolillo DJ. Cangrelor: a review on its mechanism of action and clinical development. Expert Rev Cardiovasc Ther 2009;7:1195–201.

8. Angiolillo DJ, Schneider DJ, Bhatt DL, et al. Pharmacodynamic effects of cangrelor and clopidogrel: the platelet function substudy from the cangrelor versus standard therapy to achieve optimal management of platelet inhibition (CHAMPION) trials. J Thromb Thrombolysis 2012;34:44–55.

9. Dovlatova NL, Jakubowski JA, Sugidachi A, Heptinstall S. The reversible P2Y antagonist cangrelor influences the ability of the active metabolites of clopidogrel and prasugrel to produce irreversible inhibition of platelet function. J Thromb Haemost 2008;6:1153–9.

10. Judge HM, Buckland RJ, Jakubowski JA, Storey RF. Cangrelor inhibits the binding of the active metabolites of clopidogrel and prasugrel to P2Y receptors in vitro. Platelets 2015:1–5.

11. U.S. Label of Kengrexal (Cangrelor). Available at: https://chiesiusa.com/wp-content/uploads/kengreal-us-prescribing-information.pdf. Accessed October 29, 2016.

12. Schneider DJ, Agarwal Z, Seecheran N, Keating FK, Gogo P. Pharmacodynamic effects during the transition between cangrelor and ticagrelor. J Am Coll Cardiol Intv 2014;7:435–42.

13. Tuffal G, Roy S, Lavisse M, et al. An improved method for specific and quantitative determination of the clopidogrel active metabolite isomers in human plasma. Thromb Haemost 2011;105:696–705.

14. Wallentin L, Varenhorst C, James S, et al. Prasugrel achieves greater and faster P2Y12receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. Eur Heart J 2008;29:21–30.

15. Steinhubl SR, Oh JJ, Oestreich JH, Ferraris S, Charnigo R, Akers WS. Transitioning patients from cangrelor to clopidogrel: pharmacodynamic evidence of a competitive effect. Thromb Res 2008;121:527–34.

16. Schneider DJ, Seecheran N, Raza SS, Keating FK, Gogo P. Pharmacodynamic effects during the transition between cangrelor and prasugrel. Coron Artery Dis 2015;26:42–8.

17. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 2009;361:2330–41.

18. Farid NA, Smith RL, Gillespie TA, et al. The disposition of prasugrel, a novel thienopyridine, in humans. Drug Metab Dispos 2007;35:1096–104.

19. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. J Clin Pharmacol 2010;50:126–42.

20. Small DS, Li YG, Ernest CS 2nd, et al. Integrated analysis of pharmacokinetic data across multiple clinical pharmacology studies of prasugrel, a new thienopyridine antiplatelet agent. J Clin Pharmacol 2011;51:321–32.

21. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y-receptor inhibitors in patients with coronary artery disease. Nat Rev Cardiol 2016;13:11–27.

22. Gurbel PA, Bliden KP, Butler K, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. Circulation 2010;121:1188–99.

23. Sibbing D, Braun S, Morath T, et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009;53:849–56.

24. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–67.

25. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

26. Hochholzer W, Amann M, Titov A, et al. Randomized Comparison of Different Thienopyridine Loading Strategies in Patients Undergoing Elective Coronary Intervention: the ExcelsiorLOAD trial. J Am Coll Cardiol Intv 2015;9:219–27.

27. Rollini F, Franchi F, Cho JR, et al. A head-to-head pharmacodynamic comparison of prasugrel vs. ticagrelor after switching from clopidogrel in patients with coronary artery disease: results of a prospective randomized study. Eur Heart J 2016;37:2722–30.

28. Schuhlen H, Kastrati A, Dirschinger J, et al. Intracoronary stenting and risk for major adverse

cardiac events during the first month. Circulation 1998;98:104–11.

29. Bellemain-Appaix A, O'Connor SA, Silvain J, et al. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. JAMA 2012;308:2507–16.

30. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

31. Angiolillo DJ, Curzen N, Gurbel P, et al. Pharmacodynamic evaluation of switching from ticagrelor to prasugrel in patients with stable coronary artery disease: results of the SWAP-2 Study (Switching Anti Platelet-2). J Am Coll Cardiol 2014;63:1500–9.

32. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007;116:2923–32.

33. Angiolillo DJ, Saucedo JF, Deraad R, et al. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: results of the SWAP (SWitching Anti Platelet) study. J Am Coll Cardiol 2010;56:1017–23.

34. Franchi F, Faz GT, Rollini F, et al. Pharmacodynamic Effects of Switching From Prasugrel to Ticagrelor: results of the prospective, randomized SWAP-3 study. J Am Coll Cardiol Intv 2016;9:1089–98.

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