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MINI-FOCUS: PLATELET RESPONSIVENESS

The Antiplatelet Effect of Higher Loading and Maintenance Dose Regimens of Clopidogrel

The PRINC (Plavix Response in Coronary Intervention) Trial

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Objectives This study evaluated the antiplatelet effect of a higher loading and maintenance dose regimen of clopidogrel and a possible drug interaction with verapamil.

Background Clopidogrel loading doses above 600 mg have not resulted in more rapid or complete platelet inhibition. Higher maintenance dosages may be more effective than 75 mg/day.

Methods A double-blind, randomized, placebo-controlled trial was undertaken in 60 patients undergoing percutaneous coronary intervention. All patients received clopidogrel 600 mg at the start of the procedure. Using a 2 × 2 design, patients were allocated to clopidogrel 600 mg given 2 h later or matching placebo, and to verapamil 5 mg intra-arterial or placebo. Platelet function was measured using the VerifyNow P2Y12 analyzer (Accumetrics Ltd., San Diego, California) at 2, 4, and 7 h. Patients were further randomized to receive a clopidogrel 75 or 150 mg once daily, with platelet function assessed after 1 week.

Results Two hours after the second dose of clopidogrel or placebo, platelet inhibition was 42 ± 27% with clopidogrel, compared with 24 ± 22% with placebo ($p = 0.0006$). By 5 h after the second dose, platelet inhibition was 49 ± 30% with clopidogrel, compared with 29 ± 22% with placebo ($p = 0.01$). No drug interaction was seen with verapamil. A clopidogrel maintenance dosage of 150 mg daily for 1 week resulted in greater platelet inhibition than 75 mg daily (50 ± 28% vs. 29 ± 19%, $p = 0.01$).

Conclusions In an unselected population undergoing percutaneous coronary intervention a clopidogrel 1,200-mg loading dose, given as two 600-mg doses 2 h apart, results in more rapid and complete platelet inhibition than a single 600-mg dose. A maintenance dosage of 150 mg daily produces greater platelet inhibition than 75 mg daily. (The PRINC trial; ACTRN12606000129583) (J Am Coll Cardiol Intv 2008;1:612–9) © 2008 by the American College of Cardiology Foundation

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A loading dose of 600-mg clopidogrel given immediately before percutaneous coronary intervention (PCI) achieves greater platelet inhibition and reduces periprocedural myonecrosis, compared with lower dosages (1,2). Three studies have examined whether a 900-mg loading dose might be even more effective. Two showed no further platelet inhibition with 900 mg compared with 600 mg (3,4), but in the third, there was a nonsignificant trend to greater platelet inhibition that was only evident 6 h after dosing (5). Clopidogrel drug levels measured in the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) study suggested that the ceiling effect with clopidogrel 600 mg might be due to saturable intestinal absorption of the drug (3). Split-dose loading with clopidogrel may overcome this limitation and achieve greater platelet inhibition (3,4).

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P-glycoprotein is a drug efflux pump mechanism in the gut that may reduce the intestinal absorption of clopidogrel (6). Verapamil, a vasodilator drug frequently used in the cardiac catheterization laboratory, inhibits p-glycoprotein in the short term but up-regulates it in the long term. Verapamil also inhibits CYP3A4, thereby potentially interfering with clopidogrel pharmacokinetics (7).

We undertook a randomized, placebo-controlled trial to compare the effect of a clopidogrel 1,200-mg split-loading dose with a standard 600-mg loading dose and to assess a possible interaction between verapamil and clopidogrel. A higher maintenance dosage regimen of clopidogrel was also evaluated.

Methods

Study population. The study protocol was approved by the Northern Regional Ethics Committee of New Zealand and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12606000129583). Consecutive patients undergoing elective PCI, who were taking aspirin but not clopidogrel, were enrolled in the study. Exclusion criteria were a bleeding or inherited platelet disorder; gastrointestinal bleeding or gastric ulcer, duodenal ulcer, or gastritis within the last 6 months; sensitivity and/or allergy to aspirin, clopidogrel, or verapamil; renal failure (creatinine clearance estimated glomerular filtration rate: <30 ml/s/m^2); anemia (hemoglobin <11.5 g/dl); thrombocytopenia (platelet count $<150 \times 10^9$/l); use of a glycoprotein IIb/IIIa inhibitor and medications inhibiting CYP3A4. Patients on warfarin were eligible if the international normalized ratio was <1.5 at study entry and warfarin could be withheld for the 7-day study duration.

Study design. The study design had 2 phases: a 2×2 factorial, randomized, placebo-controlled, double-blind study over the first 24 h, followed by a 1-week randomized, placebo-controlled, double-blind study. Randomization was done by computerized pseudorandom number. Clopidogrel was repackaged into gelatin capsules packed with lactose powder to match the appearance of the placebo capsules.

Patients were first randomized in a 2×2 manner to receive either 5-mg intra-arterial verapamil or placebo at baseline and either placebo or 600-mg clopidogrel, 2 h from baseline (Fig. 1). Verapamil 5 mg approximates the dose used in clinical practice. All patients received 600-mg clopidogrel at the start of the PCI procedure, 10 min after administration of verapamil or placebo. Starting the next day, all patients were separately randomized to receive clopidogrel 75 or 150 mg once daily for 1 week, followed by 75 mg once daily thereafter. Adherence to the treatment regimen was assessed by phone interview and pill count.

Blood sampling. Arterial blood was sampled through a 6-F femoral sheath and transferred immediately to 3.2% citrate 2-ml vacutainer tubes (Greiner Vacuette, Greiner, Kremsmuenster, Austria), using a 20-G needle and syringe. After sheath removal, blood was drawn by venipuncture directly into vacutainer tubes. The collection tubes were inverted 4 times to mix the anticoagulant and left for 10 min at ambient temperature (24°C) before testing. Platelet function was tested at baseline, 2, 4, and 7 h from the first clopidogrel loading dose; and at 7 days.

Abbreviations and Acronyms

PCI = percutaneous coronary intervention

PRU = platelet response unit

RPFA = rapid platelet function analyzer

Platelet function analysis. Platelet function was measured using the VerifyNow point-of-care rapid platelet function analyzer (RPFA) and its P2Y12 cartridge (Accumetrics Ltd., San Diego, California). This device uses fibrinogen-coated microbeads, an agonist of adenosine diphosphate (20 mmol/l), and light transmittance through whole blood to measure platelet agglutination. The P2Y12 cartridge result correlates favorably with light transmittance aggregometry (8), with a reported increased sensitivity to the P2Y12 receptor due to the addition of prostaglandin E2 (22 nmol/l) to the reaction chamber (9). Platelet inhibition is reported as the percentage change in the platelet response unit (PRU) from a baseline unit, derived from a second channel run in parallel with the adenosine diphosphate channel using the agonist isothrombin receptor activating peptide.

Antiplatelet drug "resistance" may be assessed as residual post-treatment activity in the target pathway of an antiplatelet agent (10). Nonresponsiveness to clopidogrel was defined as $<10\%$ maximal inhibition at 7 h (11,12).

End points. The study primary end points were RPFA values at 2, 4, and 7 h for verapamil; 4 and 7 h for

clopidogrel loading; and 7 days for the clopidogrel maintenance dose. The 7-h value was considered the peak loading dose effect.

Secondary end points were plasma troponin and creatine kinase at 7 h and safety outcomes including death, myocardial infarction, bleeding events, and adverse drug reactions. Significant bleeding was defined as any intracranial bleeding, hemoglobin decrease of >5 g/dl, bleeding requiring transfusion, femoral hematoma >10-cm diameter, or femoral pseudoaneurysm.

Statistical analysis. With the 2 × 2 design, it was estimated that 120 patients (30 in each group) would provide ~80% power to detect 1 standardized difference between groups in the percentage platelet inhibition, at a significance level of 0.05. An interim analysis was prespecified once 60 patients were enrolled. As verapamil had no effect, the verapamil and placebo results were combined, giving 60 subjects in which to compare the 600-mg and 1,200-mg doses over the first 24 h, and the 75-mg and 150-mg dosages at 1 week.

Chi-square likelihood ratio tests were used to compare categorical outcomes between the different intervention groups; Fisher exact tests were used where more than 25% of the expected counts in a table were less than 5. The Mann-Whitney *U* test was applied to compare continuous measures between groups. Analysis of covariance was used to adjust for baseline PRU and age when comparing percentage platelet inhibition in the 600-mg and 1,200-mg clopidogrel groups and to adjust for baseline PRU, age, and diabetes in the 75-mg and 150-mg clopidogrel groups. Equal variances tests were applied. The effect of the loading dose on platelet inhibition at 1 week was nonsignificant and the results at 1 week, across loading doses, were pooled into just 75-mg and 150-mg groups. A kinetic model on logarithmic scale of hours was used to describe the growth rate of percentage platelet inhibition over time. The model was validated by undertaking linear regression on each patient's percentage platelet inhibition versus the natural logarithm of hours after medication. Coefficient of determinants R^2 were summarized and compared across 2 other kinetic models (Ln[%inhibition] ~ Ln[hours] and %inhibition ~ exp[hours]). Two-sided tests were used in all analyses and a p value <0.05 was considered statistically significant. The software used for the analysis was Statistics Analysis System (version 9.1) and R (version 2.1.1) (SAS Institute, Cary, North Carolina).

Results

Patient characteristics. Patients were well matched between treatment groups with similar baseline demographics, preexisting illnesses, smoking rates, and current medications (Table 1). The average age was greater in the verapamil group, and there were more patients with diabetes in the clopidogrel 150-mg group. Baseline PRU and percentage platelet inhibition did not differ significantly at baseline or 2 h after all patients received the first clopidogrel 600-mg dose. The treatment group numbers differed, as a block randomization schedule was not used, and enrollment was stopped at 60 participants.

All participants completed the treatment allocated in the first stage of the protocol. Three outlier RPFA values were observed at baseline, but were included in the analysis, possibly indicating either sampling error or inadvertent administration of clopidogrel prior to PCI. Three outlier

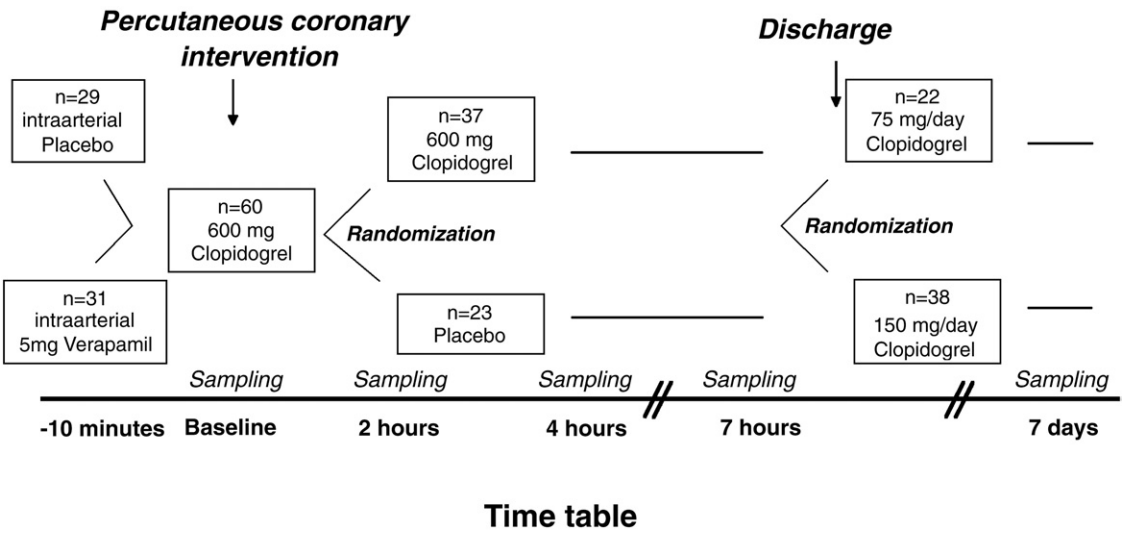

Figure 1. Study Protocol Timeline

The figure shows the PRINC trial protocol.

Table 1. Patient Characteristics

	N = 60	Clopidogrel 600 mg + Placebo (n = 23)	Clopidogrel 600 mg + 600 mg (n = 37)	p Value
Demographics				
Age, yrs, mean (SD)	68 (10)	64 (10)	70 (10)	0.06
Male	50 (83%)	19 (83%)	31 (84%)	>0.9
Caucasian	57 (95%)	22 (96%)	35 (95%)	0.3
BMI, kg/m^2, mean (SD)	29 (4)	28 (4)	29 (5)	0.4
Current smoker	6 (10%)	3 (13%)	3 (8%)	0.7
Baseline PRU	346.2 (58)	335 (45)	353 (64)	0.1
Clinical characteristics				
ASA	59 (98%)	23 (100%)	36 (97%)	>0.9
Statin	56 (95%)	21 (95%)	35 (95%)	>0.9
Beta-blocker	47 (80%)	16 (73%)	31 (84%)	0.3
ACE	33 (56%)	13 (59%)	20 (54%)	0.7
DM	11 (18%)	4 (17%)	7 (19%)	>0.9
HTN	34 (57%)	15 (65%)	19 (51%)	0.3
CHF	2 (3%)	1 (4%)	1 (3%)	>0.9
Prior CABG	6 (10%)	1 (4%)	5 (14%)	0.4
Recent NSTEMI	4 (7%)	2 (9%)	2 (5%)	0.6
Recent STEMI	3 (5%)	2 (9%)	1 (3%)	0.6
Prior PCI	12 (20%)	5 (22%)	7 (19%)	>0.9
PVD	13 (22%)	5 (22%)	8 (22%)	>0.9
Family history of CAD	24 (40%)	12 (52%)	12 (32%)	0.1
Ejection fraction, mean (SD)	68 (16)	63 (24)	71 (11)	0.3
Multiple stents	9 (15%)	2 (9%)	7 (19%)	0.5
DES	21 (35%)	7 (30%)	14 (38%)	0.6

ACE = angiotensin-converting enzyme; ASA =acetylsalicylic acid; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; DES = drug-eluting stent; DM = diabetes mellitus; HTN = hypertension; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PRU = platelet response unit; PVD = pulmonary vascular disease; STEMI = ST-segment elevation myocardial infarction.

values in the post-loading phase, thought to be related to overfilled citrate tubes, were also included. A total of 15 subjects (12 in the 150-mg group and 3 in the 75-mg group) did not have the 1-week follow-up RPFA because they lived more than 2 h from the tertiary PCI center.

Primary outcomes. Platelet inhibition at 2 h did not differ in the group receiving verapamil compared with placebo group (20.9 ± 23.1% vs. 17.0 ± 17.5%, p = 0.4). There was also no difference seen at 4 or 7 h (Table 2).

Platelet inhibition at 4 h differed significantly between the 600-mg loading dose and the 1,200-mg split loading dose (23.7 ± 21.6% vs. 42 ± 26.6%, p = 0.03). This difference was sustained at 7 h (28.7 ± 21.9% vs. 48.9 ± 30.3%, p = 0.03) (Fig. 2) but not at 7 days (35.7 ± 27.3% vs. 44.5 ± 25.8%, p = 0.3). Analysis of the 4- and 7-h results using analysis of covariance to adjust for baseline differences in age, baseline PRU, and any interaction between drugs and dose showed that the treatment group differences remained significantly different (p = 0.01).

The rate of change over time in platelet inhibition in the 1,200-mg split dose group was significantly greater than in the 600-mg group. Linear percentage inhibition change by

Table 2. Percentage Platelet Inhibition (Mean [SD]) in Patients Receiving Clopidogrel and Placebo Compared With Those Receiving Clopidogrel and Verapamil

	Placebo	Verapamil	Unadjusted p Value*	Adjusted p Value†
Baseline	7.4 (15.0)	2.2 (3.9)	0.3	
2 h	17.0 (17.5)	20.9 (23.1)	0.6	0.2
4 h	32.9 (27.1)	37.6 (25.5)	0.4	0.5
7 h	40.4 (30.5)	42.1 (27.8)	0.7	0.3
7 days	40.8 (23.7)	41.1 (28.6)	0.9	0.6

*Mann-Whitney *U* test. †Analysis of covariance, adjusted by baseline platelet response unit and age.

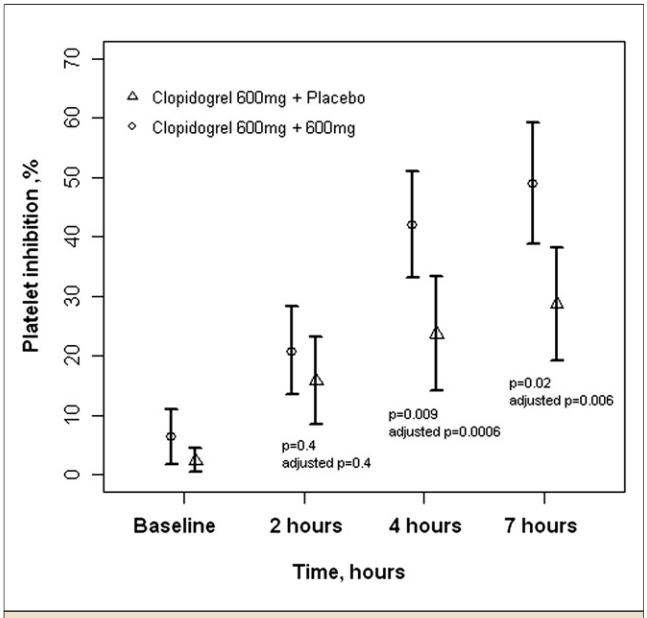

Figure 2. Temporal Dose Response Showing Platelet Inhibition in Patients Receiving 600-mg and 1,200-mg Clopidogrel Loading Doses

The **points** represent the mean platelet inhibition and the **bars** represent the 95% confidence intervals. The unadjusted p value is from Mann-Whitney *U* test. This result was adjusted by baseline platelet response unit and age level using analysis of covariance.

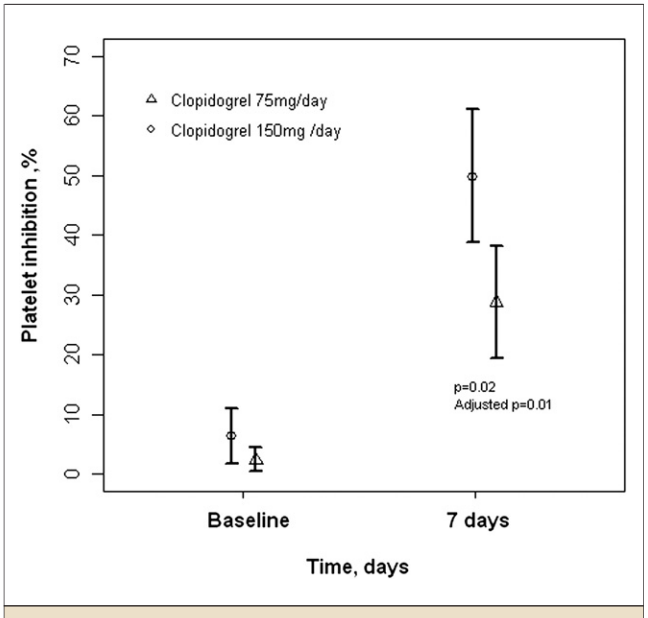

Figure 3. Platelet Inhibition in Patients Receiving 75-mg and 150-mg Once Daily Clopidogrel After 1 Week

Unadjusted p value is from Mann-Whitney *U* test. This result was adjusted by baseline platelet function analyzer level, age, and diabetes using analysis of covariance.

log (hours) was 43% versus 14%, respectively, at 4 h (p = 0.0001) (Table 3).

At 1 week, a significant difference in platelet inhibition was seen between the group receiving 75 mg of clopidogrel compared with the group receiving 150-mg once daily (28.8 ± 19.4% vs. 49.8 ± 27.7%, p = 0.01) (Figs. 3 and 4). The degree of platelet inhibition 7 h after the 1,200-mg loading dose was similar to that achieved after a maintenance dose of 150 mg/day for 7 days.

Secondary outcomes. Troponin levels at 7 h were significantly higher in patients considered nonresponsive to clopidogrel compared with those who were responsive (median: 0.05 [0.01, 0.29] vs. 0.01 [0.01, 0.03], p = 0.05). However, there was no significant difference in 7-h troponin levels between the 1,200-mg and 600-mg loading dose groups (median: 0.04 [0.01, 0.23] vs. 0.01 [0.01, 0.03], p = 0.5).

Table 3. Percentage Platelet Inhibition Growth Rate (Median [IQR]) in Patients Receiving Clopidogrel 600 mg at Baseline Compared With Clopidogrel 600 mg at Baseline and a Second Dose of Clopidogrel 600 mg at 2 h

	Clopidogrel 600 mg + Placebo	Clopidogrel 600 mg + 600 mg	p Value*
2 h	16 (0, 30)	13 (3, 39)	>0.9
4 h	14 (2, 24)	43 (29, 62)	0.0001
7 h	15 (3, 20)	24 (12, 37)	0.009

The data presented are median (IQR). The unit is %change/Ln (hour). *Mann-Whitney *U* test.
CI = confidence interval; IQR = interquartile range.

In the 1,200-mg group, there were 3 gastrointestinal adverse reactions: 1 patient vomited, 1 experienced indigestion, and another developed diarrhea the next day, which was thought to be due to the lactose vehicle in the gelatin capsules.

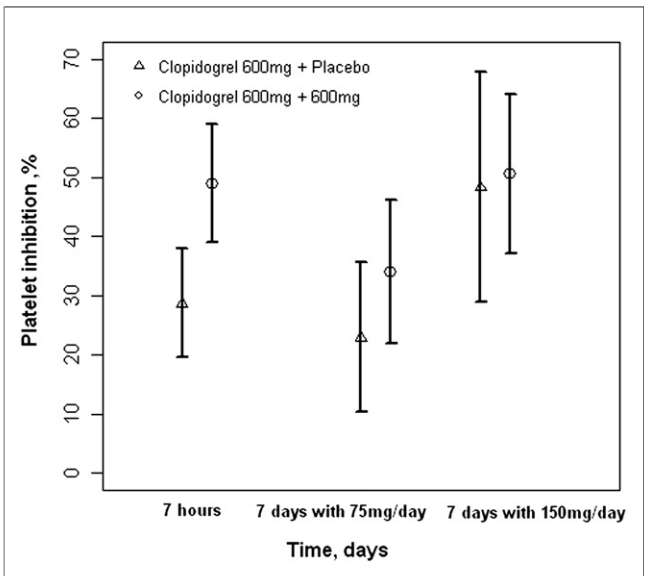

Figure 4. Platelet Inhibition at 7 h and Effect of the Loading Dose on Inhibition at 1 Week

Numbers in each group: 600 mg + 75 mg, n = 10; 1,200 mg + 75 mg, n = 12; 600 mg + 150 mg, n = 13; 1,200 mg + 150 mg, n = 25.

There were 2 significant bleeding events, both femoral hematomas at the groin puncture site and both in study subjects in their 80s. Neither required blood transfusion. One subject was in the 1,200-mg dose and the other in the 600-mg dose group; P2Y12 platelet inhibition at the time of bleeding was 28% and 25%, respectively. There were no spontaneous bleeding episodes. Adherence to treatment at 1 week was 89%.

Discussion

A clopidogrel 1,200-mg loading dose achieves more rapid and complete platelet inhibition than a 600-mg loading dose does, if administered as two 600-mg doses given 2 h apart. Greater platelet inhibition was evident within 2 h of the second 600-mg dose. Until now, the ceiling loading dose of clopidogrel appeared to be 600 mg. Staggered dosing may be more effective by overcoming the saturable nature of intestinal absorption of the parent drug (3). Another possible explanation is that circulating platelets have longer exposure to the primary metabolite of clopidogrel. This primary metabolite has a short half-life and is created by the hepatic biotransformation of the parent drug by cytochrome P450 3A4, 1A2, 2B6, 2C19, and 2C9 (13–15).

Consistent findings were recently reported in the PREPAIR (Clopidogrel 600-mg Double Loading Dose Achieves Stronger Platelet Inhibition than Conventional Regimens) study, which demonstrated that platelet inhibition was increased after a second 600-mg dose of clopidogrel given 18 to 24 h after an initial 600-mg loading dose (16). In another study of patients undergoing stent deployment, a standard clopidogrel 600-mg loading dose was compared with vasodilator-stimulated phosphoprotein–guided clopidogrel reloading, with up to 3 additional daily 600-mg doses (17). The vasodilator-stimulated phosphoprotein–guided treatment group had significantly fewer 30-day adverse cardiac events, with no increased bleeding.

Although a larger trial is needed to confirm the clinical efficacy and safety of this regimen, other studies have related the degree of platelet inhibition to periprocedural myonecrosis (2). In the CREDO (Clopidogrel for Reduction of Events During Observation) study, an early and sustained antiplatelet effect, achieved by dosing more than 6 h before PCI, was necessary to reduce the combined risk of death, myocardial infarction, or urgent target vessel revascularization (18). The ISAR-REACT 2 (Intracoronary Stenting and Antithrombotic REgimen: Rapid Early Action for Coronary Treatment) study demonstrated that clopidogrel 600 mg given 2 h or more before intervention was insufficient to achieve optimal platelet inhibition in high-risk troponin-positive acute coronary syndrome patients. In that study, adding abciximab reduced adverse events (19). It is possible that a clopidogrel regimen with a higher loading and maintenance dosage might have achieved a similar outcome.

Optimal loading dosage regimens of clopidogrel are important because pre-treatment is not always logistically possible or clinically desirable. Clopidogrel loading before angiography in patients who subsequently need early coronary bypass graft surgery is a problem, as it is associated with a 50% increase in major perioperative bleeding (20).

Another major finding is that, in an unselected population, a maintenance clopidogrel dosage of 150 mg daily achieves greater chronic platelet inhibition than the standard regimen of 75 mg daily. This is consistent with a study by Kastrati et al. (21) showing that in patients on chronic clopidogrel 75 mg daily, reloading with 600-mg clopidogrel at the time of coronary intervention achieves greater platelet inhibition. The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study also showed greater platelet inhibition with 150-mg than 75-mg clopidogrel daily. That study selectively enrolled patients with diabetes who had demonstrated a suboptimal response to clopidogrel 75 mg daily, as assessed by light transmittance aggregometry (22). It is at present unclear whether this increased antiplatelet effect will translate into a reduction in adverse clinical events without an undue increase in bleeding. The ongoing CURRENT/OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions) study will answer some of these questions; approximately 14,000 non–ST-segment elevation myocardial infarction patients are being randomly allocated to clopidogrel treatment with either a 600-mg loading dose, followed by 150 mg once daily for the first week of therapy or to a 300-mg loading dose, followed by 75 mg daily (23).

Drug–drug interactions are a common cause of hospital morbidity. Atorvastatin and erythromycin interact with clopidogrel by affecting hepatic biotransformation. Although the ex vivo antiplatelet effect of clopidogrel is reduced, nonrandomized clinical studies to date have not demonstrated worse clinical outcomes (24). Verapamil has mixed and unexpected effects on the intestinal p-glycoprotein efflux pump. Short-term dosing inhibits p-glycoprotein activity, potentially enhancing clopidogrel absorption, whereas longer term dosing up-regulates p-glycoprotein and may have the opposite effect. Verapamil also has an inhibitory effect on cytochrome P450 3A4 metabolism, which could reduce the biotransformation of clopidogrel. We found that a single dose of verapamil did not impair the antiplatelet effect of clopidogrel.

The extent of platelet inhibition at 7 h with the split 1,200-mg loading dose was similar to that achieved with 150-mg clopidogrel daily for 1 week, supporting the idea to use such a regimen in future clinical trials. Although our study lacked sufficient power to determine whether the 1,200-mg loading dose reduced post-PCI troponin eleva-

tion, we did confirm previous reports that those who were unresponsive to clopidogrel were significantly more likely to have periprocedural myonecrosis.

The TRITON–TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction-38) study reported that prasugrel given as a 60-mg loading dose followed by 10-mg/day reduced post-PCI ischemic events compared with clopidogrel 300-mg loading dose and 75 mg/day, although bleeding was increased with prasugrel (25). More recently PRINCIPLE–TIMI-44 (The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction-44) study found that the same prasugrel regimen produced greater platelet inhibition than clopidogrel 600-mg loading followed by 150 mg/day (26). How prasugrel would compare with a clopidogrel 1,200-mg loading regimen remains to be seen. Even with a 1,200-mg loading dose, the range of platelet response appears wider with clopidogrel than prasugrel. Thirteen percent of patients in the present study had <10% inhibition at 7 h; these patients may particularly benefit from prasugrel.

Study limitations. The clopidogrel loading dose of 1,200 mg and maintenance dosage of 150 mg daily appeared to be safe and well tolerated. The small study population precludes an accurate safety assessment, which awaits the results of the OASIS-7 trial. Platelet function was only assessed with the point-of-care platelet function analyzer. The VerifyNow device lacks dynamic range compared with light transmittance aggregometry and loses sensitivity below inhibition levels of 20% (27). However, results from the VerifyNow device correlate well with those of light transmittance aggregometry (8,27) through most of the platelet reactivity range. The results also correlate well with specific markers of P2Y12 platelet activity such as vasodilator-stimulated phosphorylation (9). Pharmacokinetic measurements would have enhanced the study. However the active metabolite of clopidogrel is difficult to measure, requiring a derivatization agent to protect the thiol ester (28). The numbers in the treatment groups in this study were uneven because block randomization was not used and the study was stopped after the planned interim analysis.

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