Randomized Trial of High Loading Dose of Clopidogrel for Reduction of Periprocedural Myocardial Infarction in Patients Undergoing Coronary Intervention

Results From the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) Study*

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Background—Aggressive platelet inhibition is crucial to reduce myocardial injury and early cardiac events after coronary intervention. Although observational data have suggested that pretreatment with a high loading dose of clopidogrel may be more effective than a conventional dose, this hypothesis has never been tested in a randomized trial.

Methods and Results—A total of 255 patients scheduled to undergo percutaneous coronary intervention were randomized to a 600-mg (n=126) or 300-mg (n=129) loading regimen of clopidogrel given 4 to 8 hours before the procedure. Creatine kinase MB, troponin I, and myoglobin levels were measured at baseline and at 8 and 24 hours after intervention. The primary end point was the 30-day occurrence of death, myocardial infarction (MI), or target vessel revascularization. The primary end point occurred in 4% of patients in the high loading dose versus 12% of those in the conventional loading dose group (P=0.041) and was due entirely to periprocedural MI. Peak values of all markers were significantly lower in patients treated with the 600-mg regimen (P=0.038). Safety end points were similar in the 2 arms. At multivariable analysis, the high loading regimen was associated with a 50% risk reduction of MI (OR 0.48, 95% CI 0.15 to 0.97, P=0.044). An incremental benefit was observed in patients randomized to the 600-mg dose who were receiving statins, with an 80% risk reduction.

Conclusions—Pretreatment with a 600-mg loading dose of clopidogrel 4 to 8 hours before the procedure is safe and, as compared with the conventional 300-mg dose, significantly reduced periprocedural MI in patients undergoing percutaneous coronary intervention. These results may influence practice patterns with regard to antiplatelet therapy before percutaneous revascularization.

Key Words: angioplasty ■ trials ■ myocardial infarction ■ stents ■ clopidogrel

Periprocedural myocardial infarction can be significantly reduced and outcome improved with appropriate pharmacological treatment before percutaneous intervention, as demonstrated by the ARMYDA trial (Atorvastatin for Reduction of MYocardial Damage during Angioplasty). To evaluate whether aggressive antiplatelet therapy with clopidogrel would achieve similar clinical benefits, and in the context of current uncertainty about what constitutes optimal antithrombotic therapy with percutaneous intervention, the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study group designed a randomized protocol to test the hypothesis of whether a high loading dose of clopidogrel would influence outcome.

Platelet reactivity plays a key role in the pathogenesis of ischemic complications after coronary angioplasty. Accordingly, platelet inhibition with a thienopyridine (ticlopidine or clopidogrel) or with glycoprotein IIb/IIIa receptor antagonists has significantly reduced periprocedural myocardial injury and cardiac events, primarily in higher-risk patients. Use of clopidogrel is associated with higher platelet inhibition, lower adverse events after intervention, and a better safety profile as compared with ticlopidine. Currently, the 300-mg loading dose of clopidogrel given at least 6 hours before the procedure represents the conventional antiplatelet regimen before percutaneous intervention. A higher load-
ing dose with 600 mg of clopidogrel causes an earlier and stronger inhibition of adenosine diphosphate (ADP)-induced platelet activation than does the 300-mg loading regimen\(^1\); observational data\(^2\) have suggested a significant reduction of 30-day cardiac events with this high dose of clopidogrel versus ticlopidine in patients undergoing coronary stenting. No previous study has investigated in a head-to-head comparison high versus conventional loading regimens of clopidogrel. Thus, we have performed the first prospective, randomized trial to evaluate the safety and efficacy of pretreatment with a 600-mg versus a 300-mg loading dose of clopidogrel in improving ischemic complications during coronary intervention.

**Methods**

**Study Population and Design**

ARMYDA-2 is a multicenter, randomized, prospective, double-blind clinical trial performed at 2 Italian institutions (Campus Bio-Medico University of Rome and Vito Fazzi Hospital of Lecce) (Figure 1). Patients who met the inclusion criteria were (1) patients with typical effort angina, positive stress test (ECG, nuclear scan, or stress echo), and indication for coronary angiography; or (2) patients with a non–ST-segment–elevation acute coronary syndrome who were scheduled to undergo coronary angiography. Exclusion criteria were primary intervention for acute myocardial infarction, baseline levels of creatine kinase MB (CK-MB) above the upper normal limit, contraindications to antithrombotic or antiplatelet therapy (including platelet count <70x10^3/L), high risk of bleeding, coronary artery bypass grafting in the previous 3 months, and treatment with clopidogrel within 10 days from randomization. From March 1, 2004, a total of 329 patients who fulfilled the enrollment criteria were randomized to a 600-mg (n=163) or 300-mg (n=166) loading dose of clopidogrel 4 to 8 hours before diagnostic cardiac catheterization. Eligible patients were assigned to 600 or 300 mg of clopidogrel through the use of an electronic spreadsheet that indicated the group assignment by random numbers. Randomization blocks were created and distributed to the 2 centers. Physicians performing the procedure and the follow-up assessment were not aware of the randomization assignment. After coronary angiography, 74 patients (37 in each randomization arm) who did not receive angioplasty were excluded from the study (44 were treated medically and 30 with elective bypass surgery). Two hundred fifty-five patients with significant coronary artery disease (reduction of the lumen diameter of \(\geq 70\%\)) that was deemed responsible for myocardial ischemia and suitable for treatment with percutaneous intervention were enrolled and represent the study population. Of the 255 study patients, 126 were randomized to a 600-mg and 129 to a 300-mg loading dose of clopidogrel. In these patients, revascularization was performed immediately after diagnostic angiography.

All interventions were performed via the femoral approach with the standard technique. All patients without contraindications were pretreated before intervention with aspirin (100 mg/d); they received aspirin (100 mg/d) indefinitely and continued clopidogrel (75 mg/d) for up to 1 month (6 months in patients receiving drug-eluting stents and 9 months in those treated for an acute coronary syndrome), irrespective of randomization assignment. Before intervention, patients received weight-adjusted intravenous heparin, with target activated clotting times of >300 seconds in the absence of glycoprotein IIb/IIIa inhibitor therapy and 200 to 300 seconds when a glycoprotein IIb/IIIa receptor antagonist was used. Use of a glycoprotein IIb/IIIa receptor antagonist was allowed at the operator’s discretion. Procedural success was defined as a reduction of stenosis to <30% residual narrowing. The arterial sheaths were removed when the activated clotting time was <180 seconds.

In all 255 patients, blood samples were drawn before and at 8 and 24 hours after the procedure to detect CK-MB (mass), troponin I (mass), and myoglobin levels. Further measurements were obtained in case of postprocedural symptoms suggestive of myocardial ischemia. Measurements of CK-MB, troponin I, and myoglobin were performed by using the Access 2 Immunochemiluminometric assay (Beckman Coulter).\(^1\) Upper normal limits were defined as the 99th percentile of normal population with a total imprecision of \(<10\%\), according to the Joint European Society of Cardiology/American College of Cardiology guidelines.\(^1\) Normal limits were \(\leq 4\) ng/mL for CK-MB, \(\leq 0.08\) ng/mL for troponin I, and \(\leq 80\) ng/mL for myoglobin. C-reactive protein (CRP) levels were available before percutaneous intervention and at 24 hours after the procedure in 235 of the 255 patients (114 in the 600-mg and 121 in the 300-mg loading dose group). CRP was assayed by the KRYPTOR ultrasensitive immunofluorescent assay (BRAHMS), with a detection limit of 0.06 mg/L. One-month clinical follow-up was obtained by office visit in all study patients. Each patient gave informed consent to participate in the study. The Institutional Review Boards of the institutions...
involved approved the study. The trial was not supported by any external source of funding.

End Points
The primary end point was the occurrence of death, myocardial infarction, or target vessel revascularization up to 30 days after the procedure. Myocardial infarction was defined as a postprocedural increase of CK-MB >3 times above the upper normal limit, according to the consensus statement of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention.13 Target vessel revascularization included bypass grafting or percutaneous intervention on the original coronary vessel(s).

Secondary end points included (1) any postprocedural increase of markers of myocardial injury above upper normal limits (CK-MB, troponin I, myoglobin); (2) mean peak values of CK-MB, troponin I, and myoglobin after intervention; and (3) occurrence of any of the following vascular/hemorrhagic complications: (a) major bleeding, defined as intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of >5 g/dL, according to the Thrombolysis in Myocardial Infarction criteria; (b) minor bleeding (clinically overt hemorrhage associated with a fall in hemoglobin ≤5 g/dL); (c) entry-site complications (hematoma, pseudoaneurysm, or arteriovenous fistula); and (d) thrombocytopenia with platelet count <70×10^9/L, or side effects requiring interruption of clopidogrel.

Statistics
According to a recent observational study, a 600-mg loading dose of clopidogrel before percutaneous intervention may reduce occurrence of postprocedural ischemic complications by about 45%.2 Thus, if we expected an incidence of postprocedural CK-MB elevation of 35% in the conventional loading dose group (as reported in the control group of the first ARMYDA study1), a sample size of at least 35% in the high loading dose group was expected an incidence of postprocedural ischemic complications by about 45%.2 Thus, if we expected an incidence of postprocedural CK-MB elevation of 35% in the conventional loading dose group (as reported in the control group of the first ARMYDA study1), a sample size of at least 222 patients would provide a >80% power to detect a difference in major complications with an α (probability value) of 0.05 (GB-STAT V6 software). Continuous variables between groups were compared by t test for normally distributed values; otherwise the Mann-Whitney U test was used. Proportions were compared by χ² test or Fisher exact test when appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) assessing the risk of the primary end point according to potential confounding variables were assessed by logistic regression. The following parameters were evaluated first in a univariate model: age; sex; center of enrollment; use of β-blockers, statins, ACE inhibitors, or glycoprotein IIb/IIIa inhibitors; diabetes; dyslipidemia; systemic hypertension; systemic hypertension; cigarette smoking; clinical pattern (stable versus unstable coronary syndrome); left ventricular ejection fraction; type of lesion (A/B1 versus B2/C); multivessel intervention; stent length; use of direct stenting; duration of balloon inflations; and use of high-pressure postdilatation. Variables with a probability value <0.15 were then entered into a multivariable logistic regression analysis. Results are expressed as mean±SD unless otherwise specified. A probability value <0.05 (2 tailed) was considered significant. Analysis was performed with GB-STAT V6 software.

Results
Study Population
Clinical and procedural variables in the 2 arms (600-mg and 300-mg loading dose of clopidogrel) are indicated in Tables 1 and 2, respectively. Timing of clopidogrel administration before intervention was similar in both groups (6±0.8 versus 6±1 hours, P=0.88). Sex, cardiovascular risk factors, clinical presentation, left ventricular function, blood creatinine levels, medical treatment at the time of intervention, coronary anatomy, lesion type, procedural characteristics, use of drug-eluting stents, diameter and length of implanted stents, and IIb/IIIa inhibitor infusion were also similar in both groups, but the high-dose group tended to be younger and more frequently had multivessel interventions. Procedural success was obtained in all patients in the 300-mg group and in all but 1 patient (99%) of the 600-mg group (in this patient a total chronic occlusion could not be crossed with the wire). Two patients (1 in each group) had no-reflow phenomenon, which significantly improved after administration of intracoronary nitrates and glycoprotein IIb/IIIa inhibitors. No procedural side branch (≥2 mm) closure occurred. No patient required emergency coronary artery bypass grafting. An abrupt vessel closure (2 hours after the index procedure) due to coronary dissection occurred in 1 patient in the high-dose group and was successfully treated with implantation of 2 other stents; this patient had CK-MB elevation fulfilling the criteria for myocardial infarction.

After diagnostic angiography, 30 patients had an indication for bypass surgery and were excluded from the study although they had received the randomly assigned loading dose of clopidogrel. They underwent elective surgical revascularization a mean of 15 days later (in all cases at least 7 days after discontinuation of clopidogrel, according to American College of Cardiology/American Heart Association practice guidelines). No increased risk of perioperative bleeding was observed in those who received the high loading dose regimen.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High Loading Dose (n=126)</th>
<th>Conventional Loading Dose (n=129)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutions of enrollment</td>
<td>Campus Bio-Medico University 88 (70) 90 (70) 0.90</td>
<td>Vito Fazzi Hospital 38 (30) 39 (30) 0.90</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63±10 65±10 0.027</td>
<td>Male sex</td>
<td>98 (78) 98 (76) 0.85</td>
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<tr>
<td>Diabetes mellitus</td>
<td>39 (31) 41 (32) 0.99</td>
<td>Systemic hypertension</td>
<td>81 (64) 82 (64) 0.99</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>88 (70) 80 (62) 0.24</td>
<td>Current smokers</td>
<td>20 (16) 20 (16) 0.93</td>
</tr>
<tr>
<td>Family history</td>
<td>26 (21) 19 (15) 0.28</td>
<td>Previous myocardial infarction</td>
<td>41 (33) 48 (37) 0.52</td>
</tr>
<tr>
<td>Previous coronary intervention</td>
<td>16 (13) 20 (16) 0.64</td>
<td>Previous bypass surgery</td>
<td>6 (5) 7 (5) 0.97</td>
</tr>
<tr>
<td>Clinical pattern</td>
<td>Non–ST-elevation acute coronary syndrome</td>
<td>Stable angina</td>
<td>94 (75) 97 (75) 0.97</td>
</tr>
<tr>
<td></td>
<td>Left ventricular ejection fraction, %</td>
<td>52±5 54±6 0.53</td>
<td>Multivessel coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Blood creatinine, mg/dL</td>
<td>1.0±0.5 1.0±0.5 0.82</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>105 (83) 96 (74) 0.11</td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td>95 (75) 97 (75) 0.91</td>
<td>Values are given as n (%) or mean±SD.</td>
</tr>
</tbody>
</table>
Conventional loading dose is even more significant (5% versus 15%; \(P=0.014\)). Comparison of CK-MB and troponin I levels is indicated in Figure 3.

Mean preprocedural levels of the 3 markers were similar in the 2 groups (Figure 4). CK-MB values were within normal limits in all patients by enrollment criteria; 12 patients (10%) in the 600-mg versus 11 (9%) in the 300-mg group had baseline elevated troponin I levels (\(P=0.95\)). After the procedure, peak values of all markers were significantly lower in patients treated with the high loading dose of clopidogel compared with conventional dose: CK-MB, 3.0±4.2 versus 4.9±7.2 ng/mL (\(P=0.038\)); troponin I, 0.33±0.65 versus 0.81±1.74 ng/mL (\(P=0.021\)); and myoglobin, 84±86 versus 105±113 ng/mL (\(P=0.002\)), respectively (Figure 4).

No patient in either group had postprocedural major bleeding or required transfusions. Minor bleeding was observed in 1 patient in the 600-mg group (gingival bleeding during glycoprotein IIb/IIIa infusion) and in 1 patient in the 300-mg group (urethral bleeding). A groin hematoma developed in 9 and 6 patients \(P=0.56\), respectively, but there were no local vascular complications requiring surgery. No patient had postprocedural thrombocytopenia with a platelet count \(<70\times10^9/L\). There were no significant side effects in either group requiring interruption of clopidogrel.

CRP levels before and 24 hours after the procedure were not significantly different in the 2 arms: baseline, 4.3±7.0 mg/L in the 600-mg dose versus 4.9±8.7 mg/L in the 300-mg dose group (\(P=0.70\)); after intervention, 7.8±10.8 mg/L versus 10.4±22 mg/L (\(P=0.90\)). Comparison of ΔCRP levels (CRP after intervention minus CRP before intervention) between the 2 study arms showed a nonsignificant trend.
toward a lower ΔCRP in the high-dose group (3.7±7.3 mg/L versus 5.4±18.6 mg/L; \( P=0.2 \)).

Multivariable Analysis
Multivariable analysis (Figure 5) identified pretreatment with the 600-mg loading dose of clopidogrel as an independent predictor of decreased risk of periprocedural myocardial infarction (OR 0.48, 95% CI 0.15 to 0.97; \( P=0.044 \)). Pretreatment with statins also had a protective effect (OR 0.28, 95% CI 0.10 to 0.84; \( P=0.020 \)). An additive reduction in the risk of myocardial infarction was found in patients randomized to 600-mg loading regimen of clopidogrel who were taking statins before intervention (OR 0.20, 95% CI 0.10 to 0.74; \( P=0.017 \)).

Discussion
ARMYDA-2 is the first randomized trial to support previous observational data that have implied that a 600-mg loading dose of clopidogrel is associated with improved outcome, as compared with a 300-mg dose, in patients undergoing coronary stenting. The present study demonstrates that the higher
loading dose is more effective than the conventional dose in preventing ischemic complications and that this effect is due entirely to protection from periprocedural injury.

Clopidogrel is a potent antiplatelet agent, inhibiting the ADP receptor and affecting intracellular signaling events that modulate ADP-induced platelet activation. Because of its safety profile and results of clinical trials, clopidogrel has become the standard treatment for reducing subacute thrombosis after stent implantation. Two large studies in patients with acute coronary syndromes have shown that pretreatment with clopidogrel (given a mean of 6 days before intervention in the observational PCI-CURE [Percutaneous Coronary Intervention—Clopidogrel in Unstable angina to prevent Recurrent Events] and 3 to 24 hours in the randomized CREDO [Clopidogrel for the Reduction of Events During Observation] trial) may have beneficial effects, possibly by decreasing periprocedural ischemia and distal embolization, protecting the microvascular bed, and counterbalancing the postprocedural “procoagulant status.” Accordingly, current common clinical practice is pretreatment with a 300-mg loading dose of clopidogrel at least 6 hours before the procedure in patients with acute coronary syndromes, as well as in those undergoing elective intervention. The use of a 300-mg loading dose of clopidogrel derives from dose-finding data on healthy volunteers; however, patients with coronary artery disease may have enhanced platelet reactivity as compared with healthy individuals, possibly requiring more aggressive platelet inhibition. Peak plasma concentration ($C_{\text{max}}$) of the active drug influences platelet aggregation after first administration in a dose-dependent manner, and in patients undergoing coronary stenting, a 600-mg loading dose of clopidogrel has been associated with approximately 30% and 25% of the ADP-induced platelet aggregation rate at 6 and 24 hours, respectively, compared with 45% and 40% after a 300-mg dose. Thus, a more rapid and intense platelet suppression represents the rationale for pretreatment with 600-mg loading dose of clopidogrel. Furthermore, a high loading regimen of clopidogrel might reduce the rate of nonresponders (about 30% after conventional dose) and prevent the reduction of platelet inhibition by concomitant use of statins metabolized by cytochrome P450.

It has been suggested that clopidogrel may improve inflammation, our results showed only a trend toward lower postprocedural variations of CRP levels after the high versus the conventional loading dose of clopidogrel; this may also be due to the frequent pretreatment with statins (about 80% of the study population). Moreover, clopidogrel may influence linking mechanisms between thrombosis and inflammation by reducing platelet–leukocyte and platelet–endothelial interactions, independently of CRP levels. These effects might contribute to reduce myocardial necrosis due to microembolization during intervention.

The ARMYDA-2 trial has demonstrated that high-dose clopidogrel is not associated with important side effects or bleeding complications, but we cannot comment on possible bleeding risk if bypass surgery is performed on an emergency basis in patients receiving a 600-mg loading dose of the drug. Multivariable analysis confirmed that its clinical benefit was independent of possible confounding factors and other concomitant therapies, with an average 50% risk reduction of periprocedural myocardial infarction.

Even small postintervention increases of CK-MB levels may be associated with higher mortality at follow-up. Indeed, other studies have demonstrated a significant correlation between the degree of CK-MB or troponin I elevation and mortality risk or early cardiac complications. Different thresholds have been used in several contemporary interventional cardiology trials to define occurrence of myocardial infarction: creatine kinase >2 times upper normal limit, CK-MB >3 times, CK-MB >2 times or CK-MB >1 time. In our study, the protective effect of a high loading dose of clopidogrel on myocardial injury is demonstrated by using any of the specific cutoff points for definition of myocardial infarction and is confirmed by the postprocedural reduction of all 3 markers, including troponin I, which has a better sensitivity for myocardial damage. Furthermore, the benefit was not driven by a relatively small number of patients in the 300-mg group who had large infarctions, but primarily was due to a significant reduction of >3 times postprocedural increases of cardiac markers in the high-dose arm. Although 25% of the patients in ARMYDA-2 had unstable coronary syndromes,
the overall incidence of periprocedural myocardial injury was lower than that observed in the ARMYDA trial (26% versus 35% of any postprocedural CK-MB increase, respectively, in the 2 control arms), which enrolled only patients with stable angina. As already mentioned, this is probably due to pre-treatment with statins; accordingly, in ARMYDA-2 an incremental benefit was observed in patients randomized to the 600-mg loading dose of clopidogrel who were receiving statins. The present study did not include patients with ST-segment–elevation myocardial infarction or with non–ST-segment–elevation acute coronary syndromes and elevated baseline CK-MB levels; thus, our results cannot be directly extrapolated to those higher-risk populations. Use of glycoprotein IIb/IIIa inhibitors was limited in the ARMYDA-2 trial, reflecting European practice and the relatively low risk of the study population. Although it is likely that higher-risk patients needing emergency procedures may obtain a clinical benefit from a high loading regimen of clopidogrel, our results cannot directly support the hypothesis that high-dose clopidogrel can be used as a substitute for glycoprotein IIb/IIIa inhibitors at this time. Conversely, this study may support the use of 600-mg loading regimen of clopidogrel in addition to the conventional pharmacological treatment for percutaneous intervention (including glycoprotein IIb/IIIa inhibitors when needed).

A limitation of the study is that the sample size was calculated on assumptions related to any postprocedural increase of CK-MB levels, instead of the primary end point of the trial. This allowed us to enroll fewer patients at the cost of a reduced power with regard to the primary end point. Although no significant complications related to the higher loading dose were observed, the study may also be underpowered to draw definitive conclusions about its safety.

In conclusion, the ARMYDA-2 trial shows that pretreatment with a 600-mg loading dose of clopidogrel given 6 hours before the procedure is safe and, as compared with the 300-mg dose, reduces periprocedural myocardial infarction and improves short-term prognosis in patients undergoing percutaneous revascularization. The low risk of this pharmacological regimen may support its routine use in patients before planned coronary angioplasty and may influence practice patterns with regard to antiplatelet therapy before percutaneous intervention.

Appendix
Participating Investigators in the ARMYDA-2 Trial

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