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Outcome Comparison of 600- and 300-mg Loading Doses of Clopidogrel in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

Results From the ARMYDA-6 MI (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Myocardial Infarction) Randomized Study

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Objectives The purpose of this study was to compare 600- and 300-mg clopidogrel loading doses in patients with ST-segment elevation myocardial infarction (STEMI).

Background Given the high thrombotic risk of patients with STEMI, greater platelet inhibition may improve outcome in those patients receiving percutaneous coronary intervention (PCI). Although observational data suggest that pretreatment with a 600-mg clopidogrel loading dose may be more effective than the 300-mg regimen in primary PCI, this hypothesis has never been tested in a randomized study.

Methods A total of 201 patients undergoing primary PCI for STEMI randomly received a 600-mg (n = 103) or 300-mg (n = 98) clopidogrel loading dose before the procedure. The primary endpoint was the evaluation of the infarct size, defined as the area under the curve of cardiac markers.

Results Infarct size was significantly lower in the high-dose regimen: median creatine kinase-myocardial band 2,070 ng/ml (interquartile range [IQR]: 815 to 2,847 ng/ml) versus 3,049 ng/ml (IQR: 1,050 to 7,031 ng/ml) in the 300-mg group, p = 0.0001; troponin-I 255 ng/ml (IQR: 130 to 461 ng/ml) versus 380 ng/ml (IQR: 134 to 1,406 ng/ml), p < 0.0001. In the 600-mg arm, Thrombolysis In Myocardial Infarction flow grade <3 after PCI was less frequent (5.8% vs. 16.3%, p = 0.031), left ventricular ejection fraction at discharge was improved (52.1 ± 9.5% vs. 48.8 ± 11.3%, p = 0.026), 30-day major adverse cardiovascular events were fewer (5.8% vs. 15%, p = 0.049), and bleeding/entry site complications were not increased (secondary endpoints).

Conclusions In STEMI patients, pre-treatment with a 600-mg clopidogrel loading dose before primary PCI was associated with a reduction of the infarct size compared with a 300-mg loading dose, as well as with improvement of angiographic results, residual cardiac function, and 30-day major adverse cardiovascular events; further studies are warranted to evaluate impact of such strategy on survival. (J Am Coll Cardiol 2011;58:1592–9) © 2011 by the American College of Cardiology Foundation

Therapy with clopidogrel represents a cornerstone in patients undergoing percutaneous coronary intervention (PCI), including primary intervention for ST-segment elevation myocardial infarction (STEMI) (1–4). Large randomized trials used a 300-mg clopidogrel loading dose in patients with STEMI treated with PCI (4); however, patients

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with STEMI have a high thrombotic risk, thus greater platelet inhibition at the time of PCI might improve the angiographic results and translate into lower periprocedural ischemic events. Furthermore, the adequacy of platelet response to standard doses of clopidogrel, mainly in the setting of acute coronary syndromes, remains a debated issue in interventional cardiology (5–8). Previous randomized studies demonstrated in patients undergoing nonurgent PCI a significant reduction of early cardiac events after pretreatment with a 600-mg compared with a 300-mg clopidogrel loading dose (9,10). Recent observational data suggest that in patients with STEMI treated with primary PCI, the use of a 600-mg clopidogrel loading dose is associated with improvement of procedural angiographic endpoints and safely decreases the rate of adverse event compared with the 300-mg regimen (11–14); to date, no study evaluated this approach in a prospective, randomized protocol. Thus, the ARMYDA (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty) study group designed the randomized ARMYDA-6 MI to evaluate in the setting of urgent PCI for STEMI the impact of pretreatment with a 600-mg versus a 300-mg clopidogrel loading dose on efficacy and safety outcomes.

Abbreviations and Acronyms

AUC = area under the curve
CK-MB = creatine kinase-myocardial band
IQR = interquartile range
MACE = major adverse cardiovascular event(s)
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Methods

Study population and design. ARMYDA-6 MI is an international, multicenter, randomized, prospective trial performed at 5 institutions (Campus Bio-Medico University of Rome; Semmelweis University Heart Center of Budapest; Clinical Center of Serbia, Medical School of Belgrade; Cardiovascular Center, OLV Hospital of Aalst; Vito Fazzi Hospital of Lecce). Consecutive patients with STEMI undergoing primary PCI were included; STEMI was defined as symptoms of acute myocardial ischemia lasting >30 min with symptom onset <12 h, and ST-segment elevation >0.1 mV in at least 2 leads on the electrocardiogram (15). Exclusion criteria were rescue PCI after thrombolysis, cardiogenic shock, platelet count $<70 \times 10^9$/l, or treatment with clopidogrel within 10 days from randomization. A total of 201 patients fulfilling the enrollment criteria were randomized to receive a 600-mg (n = 103) or 300-mg (n = 98) loading dose of clopidogrel at the time of the first medical contact at the center performing primary angioplasty (i.e., in the emergency department before sending patient to the catheterization lab) (Fig. 1). Eligible patients were assigned to 600 or 300 mg clopidogrel using an electronic spreadsheet indicating the group assignment by random numbers; randomization blocks were created and distributed to the 5 centers. Physicians performing the follow-up assessment were not aware of the randomization assignment.

All interventions were performed using the standard technique. All patients received an intravenous dose of 500 mg aspirin and unfractionated heparin (70 IU/kg body weight) before intervention. Thrombus aspiration and gly-

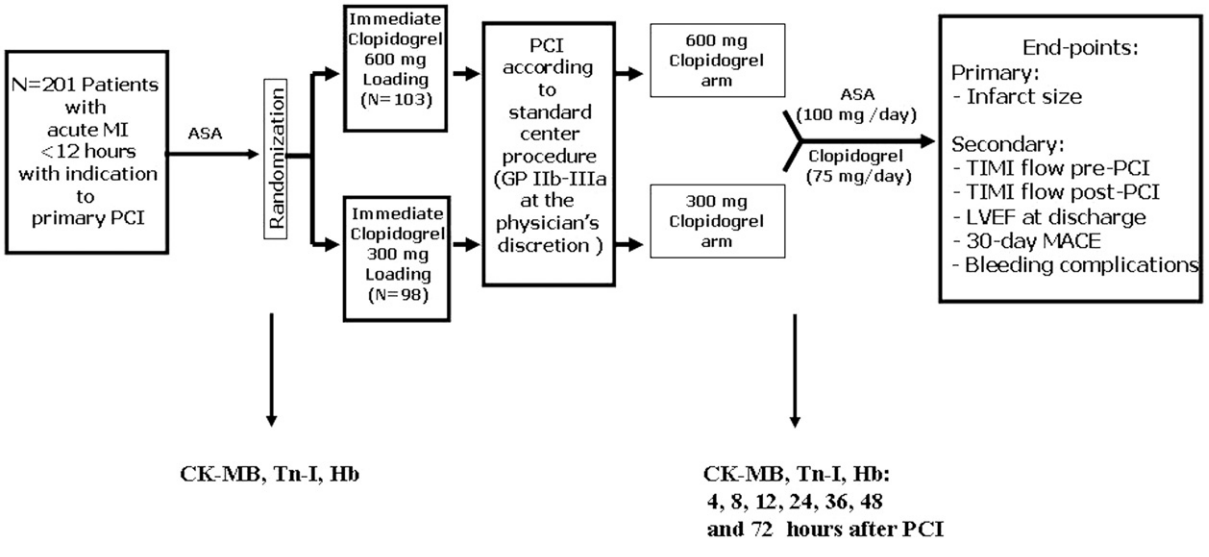

Figure 1 Design of ARMYDA-6 MI Trial

ASA = aspirin; CK-MB = creatine kinase-myocardial band; GP = glycoprotein; Hb = hemoglobin; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; Tn = troponin.

coprotein IIb/IIIa inhibitors were used at the operator's discretion. After the intervention, in all patients, aspirin (100 mg/day) was indefinitely continued, and clopidogrel was prescribed at the conventional maintenance dose of 75 mg/day from the day after PCI up to 1 year.

Blood samples were collected before the PCI and at 4, 8, 12, 24, 36, 48, and 72 h after the procedure to measure creatine kinase-myocardial band (CK-MB) (mass), troponin-I (mass), and hemoglobin levels. One-month clinical follow-up was performed by office visit of all study patients. Each patient gave informed consent to participate in the study. The study was approved by the institutional review boards of the participating institutions. The present study was not supported by any industry sponsorship.

Endpoint definitions. The primary endpoint of the ARMYDA-6 MI trial was the evaluation of the infarct size, defined as CK-MB and troponin-I area under the curve (AUC), calculated by the linear trapezoidal method (16). If baseline or 72-h values were missing, the value was set to 0, whereas missing intermediate values were substituted by linear interpolation. For patients dying in the first 72 h after enrollment, the AUC was set as the largest AUC recorded in the study.

The following secondary endpoints were investigated:

1. Prevalence of Thrombolysis In Myocardial Infarction (TIMI) flow grade >1 at the diagnostic coronary angiography before PCI and of TIMI flow grade <3 after PCI (17).
2. Left ventricular ejection fraction by transthoracic echocardiography at discharge.
3. The incidence of major adverse cardiovascular events (MACEs) (e.g., death, repeat myocardial infarction, target vessel revascularization, stroke) at 30 days. Reinfarction (18) was defined as recurrent symptoms with: a) re-elevation of CK-MB by at least 33% (if ≥2 times normal) or 100% (if <2 times normal) from the preceding nadir at <24 h after PCI; b) new Q waves or re-elevation of CK-MB to >3 times normal at 24 h to discharge; and/or c) new Q waves or re-elevation of CK-MB to >2 times normal after discharge. Target vessel revascularization included ischemia-driven bypass surgery or repeat PCI of the infarct-related artery;
4. Occurrence of bleeding/entry site complications: a) 30-day major bleeding defined as intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of >5 g/dl according to the TIMI criteria (19); b) 30-day minor bleeding (clinically overt hemorrhage associated with a decrease in hemoglobin of ≤5 g/dl) (19); and/or c) hematoma >10 cm, pseudoaneurysm, or arteriovenous fistula.

Statistics. Based on previous evidence of primary PCI outcomes (20), we assumed that an infarct size determined by the CK-MB AUC of 5,000 ng/ml with an SD of 3,500 ng/ml could be expected in the 300-mg group. Predicting a 20% reduction in the infarct size in the 600-mg group, a minimum total number of 182 patients was needed to achieve an 80% power with a 2-sided α value of 0.05 to detect such a difference. Anticipating a 10% dropout rate of patients in whom complete serial measurements of CK-MB would not be obtained, enrollment was set to at least 200 patients.

Continuous variables in the 2 arms were compared by *t* test for normally distributed values (as assessed by Kolmogorov-Smirnov test); otherwise, the Mann-Whitney *U* test was used. Proportions were compared by the Fisher exact test when the expected frequency was <5; otherwise the chi-square test was applied. Event-free survival analysis was performed by the Kaplan-Meier method with log-rank test group comparison. Normally distributed variables were expressed as mean ± SD, whereas non-normally distributed variables were expressed as median and interquartile range. A p value <0.05 (2-tailed) was considered significant. Analysis was performed with SPSS version 12.0 (SPSS Inc., Chicago, Illinois) software.

Results

Study population. Clinical and procedural variables were not different in the 2 arms and are shown in Tables 1 and 2, respectively; symptoms-to-balloon time were also similar (600 mg: 283 ± 183 min vs. 300 mg: 288 ± 223 min; p = 0.86), as well as clopidogrel load-to-balloon time (35 ± 34 min vs. 39 ± 41 min; p = 0.45). Procedure success was achieved in all patients. Four of 103 patients (3.9%) in the 600-mg group and 5 of 98 (5.1%) in the 300-mg group had no-reflow phenomenon (p = 0.94), defined as a decrease of TIMI flow grade ≥1 after initial successful reperfusion of the culprit artery not due to abrupt vessel closure, spasm, dissection, or significant residual stenosis.

Primary endpoint. Infarct size, measured by AUC of cardiac markers, was significantly reduced in patients randomized to the high-dose clopidogrel regimen: median CK-MB, 2,070 ng/ml (interquartile range [IQR]: 815 to 2,847 ng/ml) versus 3,049 ng/ml (IQR: 1,050 to 7,031 ng/ml) in the 300-mg group, p = 0.0001; troponin-I, 255 ng/ml (IQR: 130 to 461 ng/ml) versus 380 ng/ml (IQR: 134 to 1,406 ng/ml), p < 0.0001 (Fig. 2).

Secondary endpoints. Overall, 21.4% of patients (22 of 103) in the 600-mg arm versus 12.2% (12 of 98) in the 300-mg arm had TIMI flow grade >1 at the diagnostic coronary angiography before PCI (p = 0.12); high-dose clopidogrel loading was associated with significantly lower incidence of TIMI flow grade <3 after the intervention (5.8%, 6 of 103 patients, vs. 16.3%, 16 of 98; p = 0.031) (Table 2). Left ventricular ejection fraction early after PCI was similar in the 2 arms (43.2 ± 10.4% vs. 41.8 ± 14.1%; p = 0.42), but was higher at discharge in the 600-mg regimen (52.1 ± 9.5% vs. 48.8 ± 11.3%; p = 0.026).

The incidence of 30-day MACE was reduced in the 600-mg group: 5.8% (6 of 103 patients) versus 15.0% (15 of

Table 1 Clinical Characteristics in the 2 Arms

	600-mg Clopidogrel (n = 103)	300-mg Clopidogrel (n = 98)	p Value
Age, yrs	62 ± 11	65 ± 14	0.09
Male	73 (71)	60 (61)	0.20
Systemic hypertension	64 (62)	65 (66)	0.64
Diabetes mellitus	22 (21)	29 (30)	0.24
Hyperlipidemia	51 (50)	45 (46)	0.71
Active smokers	58 (56)	42 (43)	0.08
Previous myocardial infarction	8 (7)	12 (12)	0.41
Previous percutaneous coronary intervention	5 (5)	10 (10)	0.24
Previous bypass surgery	1 (1)	0 (0)	0.98
Body mass index, kg/m^2	27.8 ± 5.5	27.0 ± 5.3	0.30
Chronic renal failure	9 (9)	7 (7)	0.88
Serum creatinine, mg/dl	1.04 ± 0.74	1.08 ± 1.40	0.80
Hemoglobin, g/dl	14.2 ± 1.4	13.9 ± 1.8	0.19
Symptoms-to-balloon time, min	283 ± 183	288 ± 223	0.86
First medical contact-to-randomization time	20 ± 9	21 ± 11	0.48
Clopidogrel load-to-balloon time, min	35 ± 34	39 ± 41	0.45
Site of infarction			
Anterior, anterolateral, anteroseptal	43 (42)	40 (41)	0.99
Inferior, inferoposterior, inferolateral	60 (58)	58 (59)	0.99
Killip class III–IV	22 (21)	23 (24)	0.85
LVEF (acute phase), %	43.2 ± 10.4	41.8 ± 14.1	0.42
Medical therapy			
Aspirin	103 (100)	98 (100)	—
Statins	88 (85)	79 (81)	0.75
ACE inhibitors/sartans	62 (60)	56 (57)	0.77
Beta-blockers	68 (66)	63 (64)	0.91
Proton pump inhibitors	82 (80)	78 (80)	0.86

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction.

98) in the 300-mg group (p = 0.049). Individual components of this composite endpoint are shown in Table 3; in particular, in the high-dose clopidogrel regimen, 4 patients died (vs. 7), 1 required target vessel revascularization (vs. 7), and 1 had reinfarction (vs. 5). Target vessel revascularization within 30 days due to stent thrombosis occurred in 1 patient in the 600-mg arm and in 4 patients in the 300-mg arm; target vessel revascularization in the remaining 3 patients in the lower dose regimen group was performed in 2 because of recurrent angina with angiographic evidence of coronary thrombosis distal to the stented segment and in 1 patient because of hemodynamic impairment associated with low distal flow.

Definite stent thrombosis by the Academic Research Consortium definition (21) occurred in 1 patient in the 600-mg group versus 2 in the 300-mg group, whereas definite or probable stent thrombosis occurred in 1 versus 4, respectively. MACE-free survival curves in the 2 arms at 1 month are reported in Figure 3.

The safety endpoint did not differ in the 600- and 300-mg arms (Table 3): major bleeding at 1 month occurred in 1.9% versus 2.0% of patients, nonentry site minor bleeding in 7.8% versus 6.1%, and entry site complications in 2.9% versus 3.1%. No patient had post-procedure thrombocytopenia with platelet count $<70 \times 10^9$/l.

Discussion

This randomized study demonstrates that pre-treatment with a 600-mg clopidogrel loading dose before primary PCI compared with the 300-mg regimen decreases the infarct size (as determined by both CK-MB and troponin-I release) in patients with STEMI. Pre-treatment with a higher clopidogrel dose may also improve TIMI flow at the end of the procedure and left ventricular function at discharge and may reduce clinical events at 1 month.

There is a strong rationale for using an "aggressive" antiplatelet strategy in patients with STEMI undergoing primary PCI; in fact, the time from administration of antiplatelet drugs to intervention is reduced in those patients, and there is increased platelet activation (22), which may limit the effects of antiplatelet agents, especially at standard doses (23). In patients with STEMI, a correlation between platelet reactivity and the extent of myocardial necrosis has also been demonstrated (24), and platelet reactivity on admission significantly predicts the risk of MACE during follow-up after PCI (22); moreover, platelet

Table 2 Angiographic/Procedural Characteristics

	600-mg Clopidogrel (n = 103)	300-mg Clopidogrel (n = 98)	p Value
Type of vessel			
Left anterior descending	40 (38)	38 (36)	0.93
Left circumflex	31 (29)	34 (32)	0.73
Right coronary artery	33 (31)	32 (31)	0.96
Saphenous vein graft	2 (2)	1 (1)	0.99
Multivessel coronary disease	37 (36)	42 (43)	0.39
Multivessel PCI	3 (3)	7 (7)	0.29
Approach			
Femoral	74 (72)	72 (74)	0.92
Radial	29 (28)	26 (26)	0.92
Type of intervention			
Balloon only	1 (1)	1 (1)	0.50
Stent	102 (99)	97 (99)	0.50
Use of drug-eluting stents	11 (11)	19 (19)	0.13
Total stent length, mm	22.0 ± 6.2	20.9 ± 7.9	0.27
Stent diameter, mm	3.1 ± 0.6	3.1 ± 0.5	0.98
No. of stents per patient	1.38 ± 0.98	1.29 ± 0.59	0.43
Direct stenting	42 (41)	37 (38)	0.77
Thrombus aspiration	19 (18)	14 (14)	0.55
Glycoprotein IIb/IIIa inhibitors	58 (56)	48 (49)	0.37
Intra-aortic balloon pump	1 (1)	2 (2)	0.97
TIMI flow pre-PCI >1	22 (21)	12 (12)	0.12
TIMI flow post-PCI <3	6 (6)	16 (16)	0.031

Values are n (%) or mean ± SD.
PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

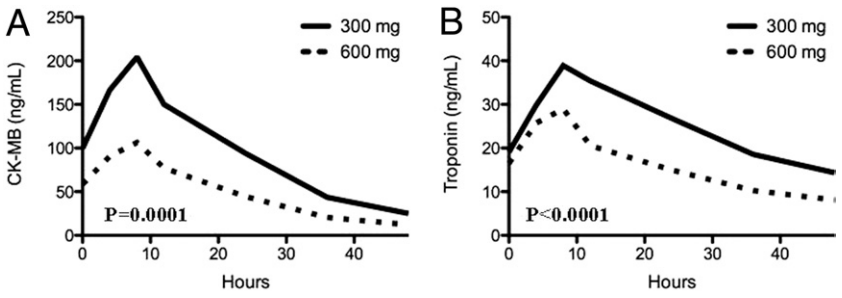

Figure 2 Primary Study Endpoint

Infarct size in the 2 arms by area under the curve of creatine kinase-myocardial band (CK-MB) **(A)** and troponin-I **(B)**.

reactivity at baseline influences the angiographic success of the intervention (22), and platelet-mediated impairment of microcirculation may advance the reperfusion injury of the area at risk (25,26). In patients with STEMI undergoing primary PCI, an early further increase in platelet reactivity has been observed after the procedure despite a 300-mg clopidogrel loading (27), reflecting procedural platelet activation, enhanced platelet consumption, and microparticle formation; of note, the degree of this post-PCI increase in platelet reactivity affects the subsequent clinical outcome (27). Finally, delays in drug absorption and/or metabolism in the acute infarction setting might further affect pharmacokinetics and pharmacodynamics of oral antiplatelet agents (13). Thus, platelet inhibition represents an important target of treatment beyond pure mechanical intervention because patients with STEMI, in the context of high thrombotic and inflammatory activation, are at higher risk of ischemic events and may derive the greatest benefit from a strategy of more intense platelet suppression. Use of newer, more potent antiplatelet drugs (e.g., prasugrel, ticagrelor) instead of clopidogrel significantly decreased the incidence of ischemic events in patients with acute coronary syndromes undergoing PCI, also including those with STEMI (28–30), but at the price of increased bleeding events, which may in turn worsen the prognosis (31,32). However, a direct comparison of prasugrel and pretreatment with 600 mg clopidogrel in clinical trials in patients undergoing PCI has never been performed (33).

Table 3 Ischemic and Safety Outcomes in the 2 Arms

	600-mg Clopidogrel (n = 103)	300-mg Clopidogrel (n = 98)	p Value
30-day MACE	6 (5.8)	15 (15.0)	0.049
Individual components			
Death	4 (3.9)	7 (7.1)	0.48
Reinfarction	1 (0.98)	5 (5.1)	0.19
TVR	1 (0.98)	7 (7.1)	0.06
Stroke	0	1 (1.0)	0.98
Death + reinfarction	5 (4.9)	12 (12.2)	0.10
Death + reinfarction + stroke	5 (4.9)	13 (13.2)	0.07
Death + reinfarction + TVR	6 (5.8)	14 (14.2)	0.08
Definite or probable stent thrombosis	1 (0.98)	4 (4.1)	0.34
Safety endpoint			
30-day major bleeding	2 (1.9)	2 (2.0)	0.65
30-day minor bleeding	8 (7.8)	6 (6.1)	0.86
Entry-site complications	3 (2.9)	3 (3.1)	0.72

Values are n (%).
MACE = major adverse cardiovascular event(s); TVR = target vessel revascularization.

A 600-mg clopidogrel load produces a faster antiplatelet effect than the 300-mg dose, with a maximal platelet inhibition achieved 2 h after drug administration (vs. 12 h) (34,35); moreover, the higher dose regimen significantly reduced the rate of nonresponders in patients treated with PCI from 28% to 8% (36). Previous randomized studies demonstrated that pre-treatment with a 600-mg clopidogrel loading dose improves the clinical outcome in patients undergoing nonurgent PCI. In particular, the 600-mg regimen was associated in the ARMYDA-2 trial (9) with a 52% relative risk reduction of 30-day adverse events compared with the 300-mg dose, and this benefit was mainly driven by prevention of periprocedural myocardial infarction; the higher regimen was also superior for early ischemic endpoints in a randomized study specifically including patients with non–ST-segment elevation acute coronary syndrome (10). More recently, in a prespecified subanalysis of the CURRENT–OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Antiplatelet Strategy for Interventions 7) trial (37), the combination of a 600-mg clopidogrel loading dose followed by a 150-mg daily dose given for 7 days significantly decreased the incidence of MACEs at 1 month versus the conventional strategy (300-mg loading dose followed by 75 mg/day) in patients with acute coronary syndrome undergoing PCI. Improvement of endothelial function and reduction of inflammation might also be associated with the benefit of the higher clopidogrel maintenance dose beyond the expected stronger platelet inhibition (38). To date, only observational investigations (11–14) evaluated the comparison of a 600-mg versus a 300-mg clopidogrel loading dose in patients with STEMI undergoing PCI; in those studies,

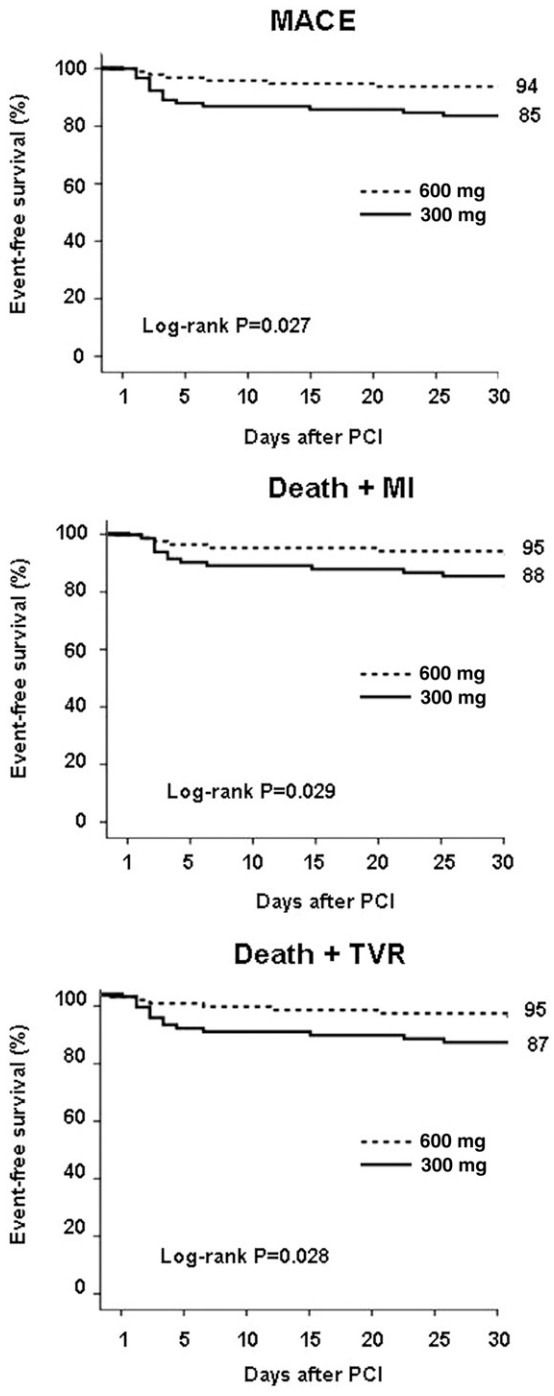

Figure 3 MACE-Free Survival Curves at 1 Month in the 600-mg Versus 300-mg Clopidogrel Arms

TVR = target vessel revascularization; other abbreviations as in Figure 1.

the higher loading dose regimen was associated with a better outcome, with lower 30-day rates of the composite endpoints including death, myocardial infarction, stroke, and urgent revascularization (11), as well as mortality and stent thrombosis (13) and fewer cardiac events at 1 year (14). Of note, the latest published guidelines on myocardial revascularization (39) recommend a 600-mg clopidogrel loading dose in the context of primary PCI for STEMI, with Class of Recommendation I and Level of Evidence: C, given the absence of randomized studies.

The multicenter ARMYDA-6 MI trial demonstrates in a randomized protocol that a 600-mg clopidogrel loading dose compared with the 300-mg regimen significantly decreases the extent of the myocardial necrosis after primary PCI. As observed in this study, this may be a consequence of higher patency rates of the infarct-related artery at the time of the intervention, as well as of achieving a better coronary flow after the procedure. When PCI is performed very early after clopidogrel administration, as typically occurs in the setting of STEMI (a mean of 36 min in our study), pre-treatment with a 600-mg loading dose allows stronger platelet inhibition at the time of the procedure. This may translate into a reduction of the thrombotic burden, reduced platelet-related intraprocedural events, decreased reperfusion injury, and subsequent reduction of the infarct size; the latter in ARMYDA-6 MI was paralleled by improved left ventricular function at discharge. A more intense periprocedural platelet inhibition might also have a favorable impact on the clinical prognosis in patients undergoing primary PCI, as suggested by the reduction of 30-day MACE with the 600-mg clopidogrel regimen, which was mainly driven by prevention of early reinfarction and urgent target vessel revascularization. No excess bleeding complications were observed with the higher loading dose, and this confirms the results of a recent post hoc analysis from the HORIZONS-MI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial (13).

Study limitations. ARMYDA-6 MI was not powered for the evaluation of clinical endpoints; thus, the lower incidence of adverse events at 1 month in the 600-mg arm (secondary endpoint) needs to be confirmed in larger randomized studies. We measured the infarct size by AUC of CK-MB and troponin-I; although this is considered a reliable measure of the extent of the infarct, evaluation of this parameter by magnetic resonance imaging would have been more accurate. Further investigation is warranted to evaluate the impact of the observed improvement in angiographic results, infarct size, and cardiac function by high-dose clopidogrel on survival.

Conclusions

ARMYDA-6 MI demonstrates that a 600-mg clopidogrel loading dose is safe and more effective than the 300-mg regimen in the context of primary PCI for STEMI. The results provide a randomized contribution supporting the use of 600 mg clopidogrel as the loading dose of choice in these patients. Although prasugrel and ticagrelor have a higher recommendation grade (I B) (39) in patients undergoing primary PCI for STEMI, our results may have relevance with regard to practice patterns because clopi-

dogrel is nevertheless still widely used in those patients, especially in the presence of high bleeding risk features, such as bleeding-prone gastrointestinal or genitourinary lesions, older age, low body weight, and previous stroke.

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REFERENCES

1. Steinhubl SR, Berger PB, Mann JT 3rd, et al., for the CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.
2. Mehta SR, Yusuf S, Peters RJ, et al., for the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
3. Sabatine MS, Cannon CP, Gibson CM, et al., for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179–89.
4. Sabatine MS, Cannon CP, Gibson CM, et al., for the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pre-treatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA 2005;294:1224–32.
5. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
6. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention. Results of the ARMYDA-PRO (Antiplatelet Therapy for Reduction of MYocardial Damage During Angioplasty–Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol 2008;52:1128–33.
7. Di Sciascio G, Patti G, Pasceri V, Colonna G, Mangiacapra F, Montinaro A, for the ARMYDA-4 RELOAD Investigators. Clopidogrel reloading in patients undergoing percutaneous coronary intervention on chronic clopidogrel therapy: results of the ARMYDA-4 RELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. Eur Heart J 2010;31:1337–43.
8. Di Sciascio G, Patti G, Pasceri V, Gatto L, Colonna G, Montinaro A, for the ARMYDA-5 PRELOAD Investigators. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. J Am Coll Cardiol 2010;56:550–7.
9. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of peri-procedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. Circulation 2005;111:2099–106.
10. Cuisset T, Frere C, Quilici J, et al. Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. J Am Coll Cardiol 2006;48:1339–45.
11. Jung JH, Min PK, Lee SH, et al. Clopidogrel pretreatment before primary percutaneous coronary stenting in patients with acute ST-segment elevation myocardial infarction: comparison of high loading dose (600 mg) versus low loading dose (300 mg). Coron Artery Dis 2009;20:150–4.
12. Mangiacapra F, Muller O, Ntalianis A, et al. Comparison of 600 versus 300-mg clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary coronary angioplasty. Am J Cardiol 2010;106:1208–11.
13. Dangas G, Mehran R, Guagliumi G, et al., for the HORIZONS-AMI Trial Investigators. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. J Am Coll Cardiol 2009;54:1438–46.
14. Choi CU, Rha SW, Oh DJ, et al. Standard versus high loading doses of clopidogrel in Asian ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention: insights from the Korea Acute Myocardial Infarction Registry. Am Heart J 2011;161:373–82.
15. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557–67.
16. Vollmer RT, Christenson RH, Reimer K, Ohman EM. Temporal creatine kinase curves in acute myocardial infarction: implications of a good empiric fit with the log-normal function. Am J Clin Pathol 1993;100:293–8.
17. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. N Engl J Med 1985;312:932–6.
18. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) investigators. Circulation 1998;98:734–41.
19. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) trial-phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1–11.
20. Fernández-Avilés F, Alonso JJ, Peña G, et al., for the GRACIA-2 (Groupo de Análisis de Cardiopatía Isquémica Aguda) Investigators. Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial. Eur Heart J 2007;28:949–60.
21. Mauri L, Hsieh W, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.
22. Campo G, Valgimigli M, Gemmati D, et al. Value of platelet reactivity in predicting response to treatment and clinical outcome in patients undergoing primary coronary intervention: insights into the STRATEGY study. J Am Coll Cardiol 2006;48:2178–85.
23. Ernst NM, Suryapranata H, Miedema K, et al. Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction. J Am Coll Cardiol 2004;44:1187–93.
24. Frossard M, Fuchs I, Leitner JM, et al. Platelet function predicts myocardial damage in patients with acute myocardial infarction. Circulation 2004;110:1392–7.
25. Uren NG, Crake T, Lefroy DC, DeSilva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. N Engl J Med 1994;331:222–7.
26. Gawaz M, Neumann FJ, Ott I, Schiessler A, Schomig A. Platelet function in acute myocardial infarction treated with direct angioplasty. Circulation 1996;93:229–37.
27. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171–5.
28. Montalescot G, Wiviott SD, Braunwald E, et al., for the TRITON-TIMI 38 Investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723–31.
29. Wiviott SD, Braunwald E, McCabe CH, et al., for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

30. Cannon CP, Harrington RA, James S, et al., for the PLATelet inhibition and patient Outcomes (PLATO) Investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010;375:283–93.
31. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774–82.
32. 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.
33. Pasceri V, Patti G, Di Sciascio G. Prasugrel versus clopidogrel. N Engl J Med 2008;358:1298–9.
34. Muller I, Seyfarth M, Rudiger S, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart 2001;85:92–3.
35. Leimbach ME, Peyrou V, Marzec UM, Chronos NAF, King SB, Harker LA. Single-dose clopidogrel inhibition of platelet adenosine receptor function in patients with atherosclerotic coronary artery disease. Circulation 1999;100 Suppl I:I681.
36. Gurbel PA, Bliden KP, Hayes KM, Yoho JA, Herzog WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. J Am Coll Cardiol 2005;45:1392–6.
37. Mehta SR, Tanguay JF, Eikelboom JW, et al., for the CURRENT-OASIS 7 Trial Investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010; 376:1233–43.
38. Patti G, Grieco D, Dicuonzo G, Pasceri V, Nusca A, Di Sciascio G. High versus standard clopidogrel maintenance dose after percutaneous coronary intervention and effects on platelet inhibition, endothelial function, and inflammation. Results of the ARMYDA-150 mg randomized study. J Am Coll Cardiol 2011;57:771–8.
39. European Association for Percutaneous Cardiovascular Interventions, Wijns W, Kolh P, Danchin N, et al. 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 2010;31: 2501–55.

Key Words: acute myocardial infarction ■ clopidogrel ■ infarct size ■ outcome ■ percutaneous coronary intervention.

APPENDIX

For a list of the investigators participating in the ARMYDA-6 MI trial, please see the online version of this article.