European Heart Journal (2010) **31**, 1337–1343
doi:10.1093/eurheartj/ehq081

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†

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Received 17 September 2009; revised 9 November 2009; accepted 17 December 2009; online publish-ahead-of-print 2 April 2010

See page 1298 for the editorial comment on this article (doi:10.1093/eurheartj/ehq082)

Aims To evaluate safety and effectiveness of clopidogrel reloading in patients on chronic clopidogrel therapy undergoing percutaneous coronary intervention (PCI).

Methods and results Five hundred and three patients on >10 days clopidogrel therapy (41% with non-ST-segment elevation acute coronary syndrome, ACS) randomly received 600 mg clopidogrel loading 4–8 h before PCI ($n = 252$) or placebo ($n = 251$). Primary endpoint was 30-day incidence of major adverse cardiac events (MACE). In the overall population primary endpoint occurred in 6.7% of patients in the reload vs. 8.8% in the placebo arm [odds ratios (OR) 0.75, 95% confidence intervals (CI) 0.37–1.52; $P = 0.50$]. In stable angina patients, 1-month MACE were not significantly different (7.0 vs. 3.9%; OR 1.84, 0.60–5.88; $P = 0.36$), whereas ACS patients had significant clinical benefit with reloading (6.4 vs. 16.3%; OR 0.34, 95% CI 0.32–0.90, $P = 0.033$ at multivariable analysis; interaction test: $P = 0.01$). There was no excess bleeding in the reload arm (6% in both groups).

Conclusion ARMYDA-4 RELOAD reveals no overall benefit from reloading patients on chronic clopidogrel therapy prior to PCI; the benefit observed in ACS patients is a hypothesis-generating finding that needs to be confirmed by larger studies.

Keywords Percutaneous coronary intervention • Stent • Clopidogrel • Acute coronary syndromes

Introduction

A growing number of patients undergoing percutaneous coronary intervention (PCI) are already on chronic clopidogrel therapy prior to the procedure. This is usually due to previous drug-eluting stent implantation, acute coronary syndromes (ACS) during the preceding year, staged PCI procedures or other atherothrombotic events. Aggregometry studies have shown that a further 600 mg clopidogrel dose in patients on chronic therapy is associated with an additional significant inhibition of residual platelet reactivity;[1] however, the relationship of such laboratory data and clinical outcome has not been characterized. Furthermore, in patients

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†Presented at the Late Breaking Clinical Trials Session, SCAI-ACCi2 Sessions, Chicago, March 29–April 1, 2008.

already receiving clopidogrel, concerns may arise about increased bleeding risk with reloading, or about adequacy of platelet inhibition if no additional load is given.[2] The goal of this randomized study was to evaluate safety and effectiveness of a strategy of 600 mg clopidogrel reloading in patients undergoing PCI whilst on long-term maintenance clopidogrel therapy, and to analyse differences in outcome according to the clinical presentation.

Methods

Study population and design

ARMYDA-4 RELOAD is a multicentre, randomized, prospective, double-blind, clinical trial performed in four Italian Institutions (Campus Bio-Medico University of Rome, Vito Fazzi Hospital of Lecce, San Filippo Neri Hospital of Rome and La Sapienza University of Rome). By protocol, only patients on chronic (>10 days) therapy with clopidogrel (75 mg/day) were enrolled. Clinical enrolment criteria were: (i) stable angina with inducible myocardial ischaemia and indication to coronary angiography, or (ii) non-ST-segment elevation ACS requiring early diagnostic angiography. Excluded were patients undergoing primary PCI for acute ST-segment elevation acute myocardial infarction, with platelet count $<70 \times 10^9$/L, high bleeding risk, and coronary bypass grafting in the previous 3 months. The design of the study is illustrated in *Figure 1*. A total of 647 patients fulfilling the enrolment criteria were randomized and they represent 22% of the PCI patient population of the recruiting centres; 324 patients received, in addition to the chronic daily dose, a further 600 mg clopidogrel administration 4–8 h before diagnostic angiography and 323 received placebo. Eligible patients were assigned to the allocation arm using an electronic spreadsheet indicating the group assignment by random numbers; randomization blocks were created and distributed to all centres. The assigned therapy was fully blinded; physicians entering the patients and those performing the interventions, post-PCI assessment, and events adjudication, were not aware of the randomization assignment; a hospital pharmacist not involved in the trial supplied the drug/placebo to be administered to patients. After coronary angiography, 144 patients (72 in each arm) without indication for PCI were excluded from the study (82 were treated medically and 62 with elective bypass surgery).

Thus, 503 patients with significant coronary artery disease suitable for percutaneous intervention constitute the study population; 252 patients were randomized to 600 mg clopidogrel reloading and 251 to placebo. Revascularization was performed in the same setting as coronary angiography. All interventions were performed with standard technique as previously described,[3–6] utilizing weight-adjusted unfractionated heparin; bivalirudin was used in 14 patients (2.8%). All patients were pre-treated before intervention with aspirin (100 mg/day); after PCI, they received aspirin (100 mg/day) indefinitely and continued clopidogrel (75 mg/day) for at least 1 month (12 months in patients treated for ACS or receiving drug-eluting stents), irrespective of the randomization assignment.

Creatine kinase-MB (mass) and troponin-I (mass) levels were determined at randomization and 8 and 24 h after intervention; further determinations were obtained in presence of symptoms suggestive of myocardial ischaemia. Measurements of creatine kinase-MB and troponin-I values were done using the Access 2 Immunochemiluminometric assay (Beckman Coulter).[7] Upper normal limits were defined as the 99th percentile of normal population with a total imprecision of <10%, according to Joint European Society of Cardiology/American College of Cardiology guidelines.[8] Normal limits were ≤3.6 ng/mL for creatine kinase-MB and ≤0.034 ng/mL for troponin-I.

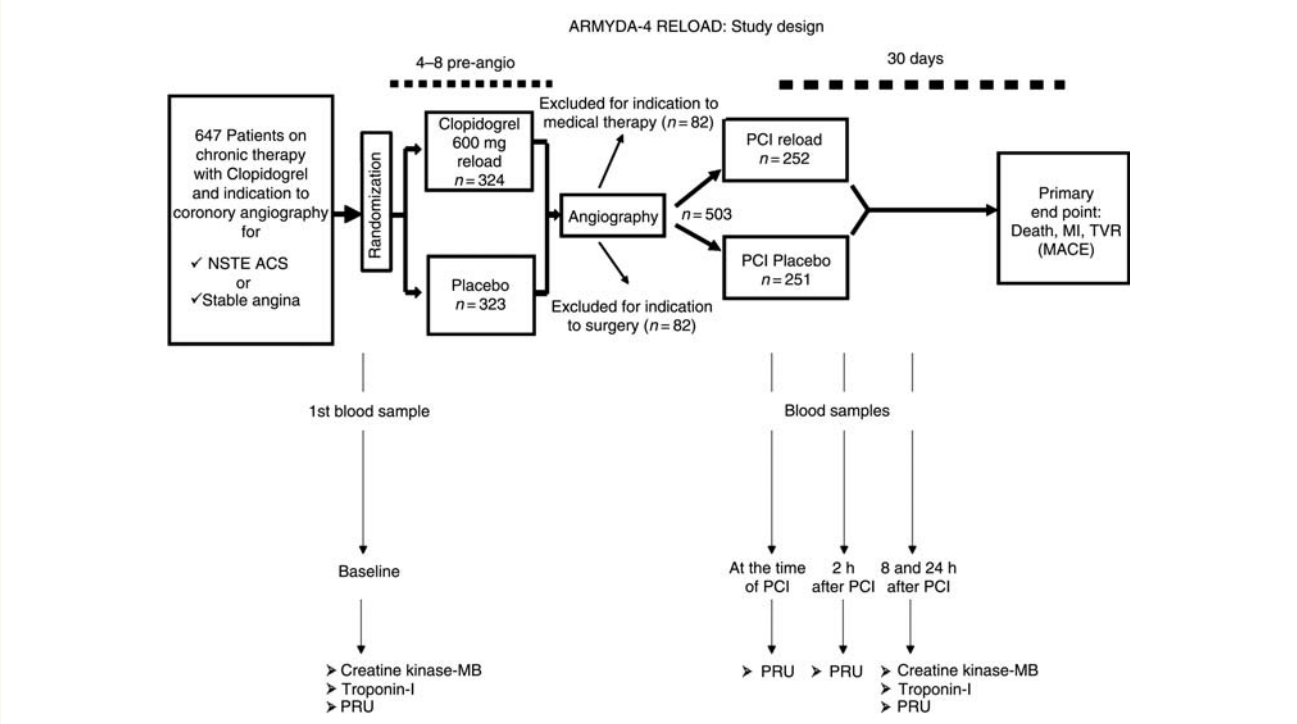

Figure 1 Design of ARMYDA-4 RELOAD trial. MI, myocardial infarction; NSTE ACS, Non-ST-segment elevation acute coronary syndrome; TVR, target vessel revascularization.

One-month clinical follow-up was obtained by office visits in all study patients. Each patient gave informed consent to the study. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Boards of the Institutions involved. The trial was not funded by the industry or other external sources, including grants; funding was derived entirely from internal sources of Campus Bio-Medico University.

Endpoints

Primary endpoint of the ARMYDA-4 RELOAD trial was 30-day incidence of major adverse cardiac events (MACE—death, myocardial infarction, target vessel revascularization). Peri-procedural myocardial infarction was defined following the consensus statement of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention,[9] as a post-PCI increase of cardiac biomarkers (troponin or creatine kinase-MB) $>3 \times$ 99th percentile of the upper reference limit in patients with normal baseline levels of creatine kinase-MB; a subsequent elevation $\geq$50% the baseline value fulfilled the criteria for peri-procedural myocardial infarction in patients with raised baseline levels of creatine kinase-MB.[10]

Target vessel revascularization was defined as repeat PCI or bypass surgery of the treated vessel(s).

Secondary endpoints included:

(i) 30-day incidence of MACE in pre-specified clinical subsets, defined by clinical pattern on admission (i.e. stable angina vs. non-ST-segment elevation ACS), presence or absence of diabetes mellitus and single-vessel vs. multivessel intervention. ACS was defined as rest angina lasting $\geq$10 min within the preceding 24 h in presence of one or more of the following criteria: new ST-segment depression $\geq$1 mm; elevations of the troponin or creatine kinase-MB levels; known coronary artery disease.[11] Diabetes mellitus was defined according to the criteria established by the World Health Organization Report;[12]

(ii) any post-procedural increase of cardiac markers above upper normal limits;

(iii) occurrence of vascular/bleeding complications, defined as: (a) major bleeding (intracranial bleeding or clinically overt bleeding associated with a decrease in haemoglobin $>$5 g/dL, according to the Thrombolysis in Myocardial infarction criteria);[13] (b) minor bleeding (clinically overt haemorrhage associated with a fall in haemoglobin $\leq$5 g/dL); (c) entry-site complications (haematoma $>$5 cm,[11] pseudoaneurysm or arteriovenous fistula).

Statistics

In the ARMYDA-2 trial,[4] the primary endpoint (30-day incidence of death, myocardial infarction, or target vessel revascularization) occurred in 4% of patients in the 600 mg clopidogrel loading dose vs. 12% of those in the 300 mg loading dose group. Accordingly, we expected that a further 600 mg clopidogrel loading pre-PCI in patients on chronic clopidogrel therapy could be associated with a 66% risk reduction of the primary endpoint; thus, hypothesizing a 12% event rate in the placebo arm, a study population of at least 400 patients would be needed to detect such risk reduction with α of 0.05 (two-tailed) and β of 0.8. Continuous variables were compared by *t*-test for normally distributed values (as detected by Kolmogorov–Smirnov test), otherwise the Mann–Whitney *U*-test was used. Proportions were compared by Fisher's exact test when the expected frequency was $<$5, otherwise the chi squared test was applied, and odds ratios (OR) with 95% confidence intervals (CI) were reported. Bonferroni's adjustment was performed for multiple comparisons in subgroup analysis. A multivariable logistic regression model evaluated the comparison of clopidogrel reloading vs. placebo with regard to incidence of MACE in the overall population and in pre-specified subsets, defined by clinical pattern on admission, presence of diabetes mellitus, and multivessel interventions. Results are expressed as mean $\pm$ SD, unless otherwise specified. All calculations were performed by SPSS 12.0 and *P*-values $<$0.05 (two-tailed) were considered significant.

Results

Study population

Main clinical and procedural variables in the two arms are reported in *Tables 1* and *2*, respectively. In particular, there was no difference in timing of study drug administration vs. placebo before PCI (6 $\pm$ 0.6 vs. 6 $\pm$ 0.8 h, $P = 0.98$), diabetes mellitus was present in 33 and 32%, non-ST-segment elevation ACS in 43 and 39%, drug-eluting stents were implanted in 43 and 41%, and almost all patients were on statins (95 and 93%, respectively). Indication for chronic clopidogrel therapy in the majority of patients was recent history of ST or non-ST-segment elevation ACS (79 and 80%) and prior drug-eluting stent implantation (21 and 20%) in the two arms.

Procedural success was obtained in 250/252 patients (99%) of the reload and in 247/251 (98%) in the placebo arm ($P = 0.68$): a total chronic occlusion could not be crossed with the wire in

Table 1 Main clinical features (n = 503 patients)

Characteristic	Clopidogrel reload (n = 252)	Placebo (n = 251)
Age (years)	65 $\pm$ 9	66 $\pm$ 11
Male sex	197 (78)	191 (76)
Diabetes mellitus	83 (33)	80 (32)
Systemic hypertension	192 (76)	198 (79)
Hypercholesterolaemia	204 (81)	201 (80)
Current smokers	45 (18)	50 (20)
Body mass index (kg/m^2)	26.0 $\pm$ 3.2	25.8 $\pm$ 3.3
Previous myocardial infarction	71 (28)	78 (31)
Previous coronary intervention	129 (51)	108 (43)
Previous bypass surgery	25 (10)	20 (8)
Clinical pattern		
Non-ST elevation acute coronary syndrome	109 (43)	98 (39)
Troponin +ve	46 (42)	41 (42)
Stable angina	143 (57)	153 (61)
Left ventricular ejection fraction (%)	54 $\pm$ 7	54 $\pm$ 8
Multivessel coronary artery disease	83 (33)	80 (32)
Blood creatinine (mg/dL)	1.1 $\pm$ 0.6	1.0 $\pm$ 0.7
Aspirin	252 (100)	251 (100)
Statins	239 (95)	233 (93)
Beta-blockers	106 (42)	120 (48)
ACE-inhibitors	207 (82)	203 (81)

Values are given as number of patients (%) or mean $\pm$ SD.

Table 2 Procedural features

Characteristic	Clopidogrel reload ($n = 252$)	Placebo ($n = 251$)
Procedural access		
Femoral artery	212 (84)	213 (85)
Radial artery	40 (16)	38 (15)
Vessel treated	310	311
Left main	6 (2)	6 (2)
Left anterior descending	128 (41)	131 (42)
Left circumflex	74 (24)	68 (22)
Right coronary artery	93 (30)	96 (31)
Saphenous vein graft	9 (3)	10 (3)
Restenotic lesions	28 (11)	20 (8)
Lesion type B2/C	141 (56)	143 (57)
Chronic total occlusions (>3 months)	23 (9)	18 (7)
Multivessel intervention	45 (18)	48 (19)
Type of intervention		
Balloon only	23 (9)	18 (7)
Stent	229 (91)	233 (93)
Bifurcations with kissing balloon	13 (5)	12 (5)
No. of stents per patient	1.12 ± 0.8	1.15 ± 0.9
Stent diameter (mm)	3.10 ± 0.3	3.12 ± 0.5
Total stent length (mm)	22 ± 12	21 ± 11
Use of drug-eluting stents	108 (43)	103 (41)
Direct stenting	88 (35)	93 (37)
No. of pre-dilatations	2.0 ± 2.1	2.0 ± 2.3
Stent deployment pressure (atm)	14.9 ± 2.6	14.7 ± 2.5
Duration of stent deployment (s)	21 ± 9	21 ± 8
Total ischaemia >120 s	58 (23)	55 (22)
Use of post-dilatation	91 (36)	78 (31)
Anti-thrombin regimen during intervention		
Unfractionated heparin	245 (97)	244 (97)
Bivalirudin	7 (3)	7 (3)
Use of IIb–IIIa inhibitors	30 (12)	28 (11)

Values are given as number of patients (%) or mean ± SD.

five patients (two in the reload and three in the placebo arm), and in one patient of the latter group a calcified stenosis on a markedly tortuous vessel was not crossed with the balloon catheter. A total of three patients (two in the reload and one in the placebo arm) had no-reflow phenomenon, which significantly improved after administration of intracoronary nitrates, adenosine, and Glycoprotein IIb/IIIa inhibitors. No evident vessel or side branch (≥2 mm) closure occurred. No patient died or required emergency coronary artery bypass surgery. The only acute stent thrombosis (by ARC definition)[14] occurred at 24 h in a patient of the reload group, treated with PCI without myocardial infarction.

Primary endpoint

The composite primary endpoint of 30-day death, myocardial infarction and target vessel revascularization occurred in 17 of 252 patients (6.7%) in the reload and in 22 of 251 (8.8%) in the placebo group (OR 0.75, 95% CI 0.37–1.52; $P = 0.50$; *Table 3*). Excluding the above-mentioned patient in the reload arm with stent thrombosis without myocardial infarction, incidence of the primary endpoint at 30 days was essentially due to peri-procedural myocardial infarction in both arms: 16/252, 6.3% vs. 22/251, 8.8% (OR 0.71, 95% CI 0.34–1.44; $P = 0.39$).

Secondary endpoints

Subgroup analysis by pre-specified clinical subsets

In the 296 patients with stable angina, difference in MACE between the reload and the placebo arm was not significant (10/143, 7.0% vs. 6/153, 3.9%; OR 1.84, 95% CI 0.60–5.88; $P = 0.36$; *Table 3*). Among the 207 patients with ACS, those randomized to reload had significantly lower MACE vs. placebo: 6.4% (7/109) vs. 16.3% (16/98) (OR 0.35; 95% CI 0.12–0.96; $P = 0.041$); however, as illustrated in detail in *Table 3*, there was no significant difference in MACE according to troponin status: 8.7 vs. 19.5% (OR 0.39, 95% CI 0.09–1.62; $P = 0.25$) in the troponin-positive and 4.8 vs. 14% (OR 0.31, 95% CI 0.06–1.37; $P = 0.15$) in the troponin-negative patients.

Multivariable logistic regression analysis revealed significant additional benefit of clopidogrel reload on 30-day MACE in patients presenting with ACS (OR 0.34, 95% CI 0.32–0.90; RRR 66%; $P = 0.033$) and no benefit in those with stable angina (OR 1.11, 0.92–1.40; $P = 0.40$). Test of interaction[15] comparing the OR of ACS and stable patients was significant ($P = 0.01$).

No outcome improvement with reload was observed in the other pre-specified subgroups: diabetes mellitus vs. no diabetes ($P \geq 0.32$) and single-vessel vs. multivessel PCI ($P \geq 0.42$; *Table 3*).

Cardiac marker elevations

In the overall population, patients randomized to clopidogrel reload had a significantly lower incidence of any post-PCI elevation of creatine kinase-MB above the upper normal limits (23 vs. 32% in the placebo arm, $P = 0.042$); this was mainly driven by the reduction of the proportion of patients with creatine kinase-MB elevation in the ACS group (24 vs. 40%, $P = 0.020$); no change was observed in post-procedural troponin elevation in the two randomization arms (47 vs. 54%, $P = 0.14$).

Bleeding/vascular complications

No patient in the study had major bleeding or required transfusions. Minor bleeding was observed in 6% of patients in either arm (16/252 and 16/251), and it was largely due to entry-site haematomas >5 cm ($n = 28$), with two urethral bleeds, one conjunctival and 1 gum bleeding. Patients with ACS had higher incidence of minor bleeding than those with stable angina (12% vs. 3%; $P = 0.0001$); however, no excess bleeding was observed in the reload arm even in the ACS group.

Outcome of patients randomized but not undergoing PCI

As illustrated in *Figure 1*, after coronary angiography 144 patients (72 in each arm) without indication for PCI were excluded from

Table 3 Individual components of 30-day MACE in the overall cohort and according to clinical presentation, diabetes status, and type of intervention

Population	Cardiac death	MI	TVR	MACE
Overall ($n = 503$)				
Reload ($n = 252$)	–	16 (6.3)	1 (0.4)	17 (6.7)
Placebo ($n = 251$)	–	22 (8.8)	–	22 (8.8)
OR (95% CI)		0.71 (0.34–1.44)		0.75 (0.37–1.52)
P-value		0.39		0.50
Stable angina ($n = 296$)				
Reload ($n = 143$)	–	9 (6.3)	1 (0.7)	10 (7.0)
Placebo ($n = 153$)	–	6 (3.9)	–	6 (3.9)
OR (95% CI)		1.65 (0.52–5.36)		1.84 (0.60–5.88)
P-value		0.51		0.36
ACS ($n = 207$)				
Reload ($n = 109$)	–	7 (6.4)	–	7 (6.4)
Placebo ($n = 98$)	–	16 (16.3)	–	16 (16.3)
OR (95% CI)		0.35 (0.12–0.96)		0.35 (0.12–0.96)
P-value		0.041		0.041
Troponin positive ($n = 87$)				
Reload ($n = 46$)	–	4 (8.7)	–	4 (8.7)
Placebo ($n = 41$)	–	8 (19.5)	–	8 (19.5)
OR (95% CI)		0.39 (0.09–1.62)		0.39 (0.09–1.62)
P-value		0.25		0.25
Troponin negative ($n = 120$)				
Reload ($n = 63$)	–	3 (4.8)	–	3 (4.8)
Placebo ($n = 57$)	–	8 (14)	–	8 (14)
OR (95% CI)		0.31 (0.06–1.37)		0.31 (0.06–1.37)
P-value		0.15		0.15
Diabetes ($n = 163$)				
Reload ($n = 83$)	–	3 (3.6)	1 (1.2)	4 (4.8)
Placebo ($n = 80$)	–	6 (7.5)	–	6 (7.5)
OR (95% CI)		0.46 (0.09–2.18)		0.62 (0.14–2.63)
P-value		0.32		0.53
No diabetes ($n = 340$)				
Reload ($n = 169$)	–	13 (7.7)	–	13 (7.7)
Placebo ($n = 171$)	–	16 (9.4)	–	16 (9.4)
OR (95% CI)		0.81 (0.35–1.84)		0.81 (0.35–1.84)
P-value		0.72		0.72
Single-vessel PCI ($n = 410$)				
Reload ($n = 207$)	–	13 (6.3)	–	13 (6.3)
Placebo ($n = 203$)	–	18 (8.9)	–	18 (8.9)
OR (95% CI)		0.69 (0.31–1.53)		0.69 (0.31–1.53)
P-value		0.42		0.42
Multivessel PCI ($n = 93$)				
Reload ($n = 45$)	–	3 (6.7)	1 (2.2)	4 (8.9)
Placebo ($n = 48$)	–	4 (8.3)	–	4 (8.3)
OR (95% CI)		0.79 (0.13–4.51)		1.07 (0.21–5.56)
P-value		1.00		1.00

Values are given as number of patients (%).
ACS, acute coronary syndrome; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

the study (82 were treated medically and 62 with elective bypass surgery). Of the latter, 31 patients had been randomized to reload and 31 to placebo; they underwent bypass surgery a mean of 12 days later (in all cases at least 5 days after discontinuation of clopidogrel).[16] No excess surgical bleeding was observed in the patients randomized to reload and no MACE at 30 days.

Patients treated medically had no events during follow-up.

Intention-to-treat analysis

In all patients ($n = 647$) randomization was done 4–8 h prior to coronary angiography, but only those undergoing PCI constitute the study group ($n = 503$). An intention-to-treat analysis including all patients reveals a 5% (17/324) overall incidence of MACE in the reload vs. 7% (22/323) in the placebo arm ($P = 0.50$); in the ACS subpopulation the primary endpoint occurred in 5% (7/139) in the reload vs. 13% (16/127) in the placebo arm ($P = 0.048$).

Discussion

The ARMYDA-4 RELOAD trial addresses a relevant clinical issue, i.e. whether a higher level of P2Y12 inhibition with clopidogrel in previously clopidogrel-treated patients will reduce the risk of MACE; those patients represent a significant proportion of patients undergoing PCI (22% in our study). This proportion is likely to increase, owing to the growing number of patients with severe atherothrombotic disease, receiving drug-eluting stents, or undergoing complex, multiple procedures.

An additional antiplatelet effect, adjunctive to that obtained with the currently recommended maintenance dose of clopidogrel might be required pre-PCI in such patients and may potentially improve clinical outcome. To date, only a small study[1] on 20 patients with stable coronary artery disease demonstrated a 68% further inhibition of ADP 5 μmol/L-induced platelet aggregation 6 h after administration of 600 mg clopidogrel loading in patients receiving the chronic 75 mg/day, but no correlation was made with clinical efficacy. A recent study[17] comparing the effects of three reloading-dose strategies on laboratory measures of platelet function in 166 patients on chronic clopidogrel therapy suggests a stepwise per cent increase in inhibition of platelet aggregation 4 h after 300 vs. 600 vs. 900 mg reload (31 vs. 40 vs. 64%), as well as a reduction of inter-individual variability in clopidogrel response; however, the question of the relationship between magnitude of inhibition of platelet aggregation and clinical outcome remains largely unanswered.

The ARMYDA-4 RELOAD trial was designed specifically to evaluate the influence of 600 mg reload on clinical endpoints; furthermore, our aim was to allay fears about additional bleeding risk potentially due to reloading and to identify clinical subgroups that could better benefit from such strategy. Our results indicate that, in the general patient population of chronic clopidogrel users, a pre-PCI 600 mg clopidogrel reloading confers no evident clinical benefit. However, although this appears to be a negative study in the overall comparison and is possibly underpowered for subgroup analysis, the trial suggests that in the ACS population, a reloading strategy may improve outcome, with a 66% relative risk reduction of 30-day MACE ($P = 0.033$). Granted the relatively small size of the subgroups, the significance of the interaction test between angina at presentation and effect of reloading further suggests this hypothesis. Thus, patients with ACS, who are potentially at higher risk of early ischaemic complications after PCI because of enhanced baseline platelet reactivity[18] and have lower inhibition in response to conventional doses of antiplatelet drugs,[19] may derive the greatest benefit from this more aggressive antiplatelet therapy (similar to what was observed with atorvastatin reload in patients on chronic statin therapy).[20]

Importantly, the study shows no major bleeding and no increased bleeding risk with the reload approach; those findings are reassuring considering the strong negative prognostic impact of peri-procedural haemorrhages,[21,22] and may be relevant in the current era of newer, more potent antiplatelet agents.[23] Use of Glycoprotein IIb/IIIa inhibitors was limited in the ARMYDA-4 RELOAD trial, reflecting European practice, therefore the study does not allow to draw conclusions about the bleeding risk if both reloading and Glycoprotein IIb–IIIa inhibitors are utilized.

The study was aimed at evaluating influence on outcome of a 600 mg clopidogrel reload vs. placebo in patients on chronic clopidogrel therapy undergoing PCI. Therefore, patients not receiving PCI were not included in the study group. The randomization was done 'upstream' for two reasons: (i) to allow a preloading time of 4–8 h pre-procedure in the patients assigned to the treatment arm, since by protocol PCI was performed in the same setting as coronary angiography; (ii) in the large majority of patients PCI was either planned or likely, in fact only 22% of the enrolled cohort did not receive PCI after coronary angiography. However, intention-to-treat analysis extended to the whole study cohort of 647 patients gives similar results as related both to the overall population and to the clinical subgroups.

Study limitations

Since the first set of post-PCI enzymes were drawn at 8 h, there could have been up to 16 h gap between baseline and initial post-PCI cardiac enzymes. On the basis of this there may be some challenges in distinguishing a PCI-related event and the normal course of cardiac enzymes based on an index non-ST-segment elevation myocardial infarction.

Secondary analyses are known to be susceptible for a range of statistical problems and need cautious interpretation; however, to address these problems adequately, we pre-specified subgroups to be analysed and prospectively restricted the number of secondary outcomes.[24]

Administration of GPIIb/IIIa receptor blockade during PCI may have blurred the effect of preloading on clinical outcome, although utilized in similar proportion (12 and 11% in both study groups).

Even though in the overall population there was a 24% reduction in the incidence of the primary endpoint in the reload arm, from the results of this study it cannot be concluded that the treatment is effective for all patients.

In conclusion, ARMYDA-4 RELOAD is a hypothesis-generating trial that seems to suggest a clinically driven clopidogrel loading. Given the large proportion of patients undergoing PCI whilst on long-term maintenance clopidogrel therapy, the results of ARMYDA-4 RELOAD may contribute to answering an important scientific and clinical question in contemporary interventional practice;[25] however, its findings need to be confirmed in larger randomized trials.

Conflict of interest: none declared.

Appendix

The following investigators participated in the ARMYDA-4 RELOAD trial:

Chairman of the study: G.D.S., Campus Bio-Medico University, Rome.

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