

Is it naïve to load only clopidogrel-naïve patients prior to PCI?

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This editorial refers to ‘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’[†], by S. Di Sciascio et al., on page 1337

Percutaneous coronary intervention (PCI) has become the predominant form of coronary revascularization in Europe and the USA. Although overall a safe procedure, PCI may be complicated by adverse events, with myocardial infarction (MI) and bleeding being the most frequent and important contributors to mortality and morbidity after the procedure. It is estimated that ~25% of patients undergoing PCI may have significant post-procedural myonecrosis, as identified by creatinine kinase (CK) and CK-MB isoenzyme elevations, and that up to 50% of PCI patients develop post-procedural troponin elevations.¹ The development of strategies that help prevent post-procedural MI has therefore been a major research interest in the field of interventional cardiology.

Ever since the late 1990s, it is generally accepted that platelets, adhering and aggregating at sites of endothelial injury and mechanical plaque disruption, are the key determinants of PCI-related myocardial necrosis. Accordingly, several trials, including the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial,² demonstrated that dual antiplatelet therapy with aspirin plus thienopyridines is efficient in reducing post-PCI ischaemic complications. Since then, dual antiplatelet therapy with the thienopyridine clopidogrel and aspirin has become an integral part of PCI treatment of patients presenting with various forms of coronary artery disease—ST elevation myocardial infarction (STEMI), non-ST elevation acute coronary syndrome (NSTEMI/ACS), and stable angina.

An important limitation of clopidogrel, however, lies in its pharmacokinetic and pharmacodynamic properties.³ Clopidogrel is a prodrug that has to undergo two sequential cytochrome P-450 (CYP)-dependent oxidation steps after intestinal absorption in order to be converted into its active metabolite. This leads to delayed onset of action and interindividual variability in the platelet

response to clopidogrel. In an effort to reduce this limitation, a high loading dose of clopidogrel has been used prior to PCI in previous studies, showing clinical advantages as compared with placebo.^{4–6} The optimal loading dose of clopidogrel has been the focus of several recent studies, which support the superiority of the 600 mg dose.^{7,8} Currently, a high loading dose of clopidogrel is recommended by the guidelines of the European Society of Cardiology to be administered in all patients undergoing PCI.

In addition to improved antiplatelet regimens, another significant milestone in the recent history of PCI was the development of the drug-eluting stent (DES), substantially reducing coronary restenosis, the major limitation of PCI in the bare metal stent (BMS) era. Although DES have indisputably improved patient outcomes, they require a protracted dual antiplatelet therapy compared with BMS. As a result of the broad application of DES, large numbers of patients presenting for PCI to interventional cardiology centres in Europe and the USA nowadays are no longer clopidogrel naïve, but are already on chronic clopidogrel therapy. An important yet unanswered question is therefore whether patients on maintenance therapy with clopidogrel should also be given a booster load, similar to clopidogrel-naïve subjects. Intuitively, one would expect that patients treated chronically with clopidogrel might not necessarily benefit from reloading prior to a repeat PCI. However, recent studies have suggested that—most probably due to interindividual variability in P450-dependent biotransformation—residual platelet aggregation persists in a substantial number of patients despite chronic clopidogrel treatment, affecting cardiovascular outcomes after repeat PCI.⁹ On average, the magnitude of maximal inhibition of platelet aggregation in patients who receive a dose of 75 mg/day is 30–50%.^{10,11} Correspondingly, further platelet inhibition can be achieved with clopidogrel loading in patients on the currently recommended maintenance dose of 75mg/day.^{10,11} Recent studies evaluating clopidogrel loading dose such as the current Clopidogrel Optimal Dose Usage to Reduce Recurrent Events (CURRENT-OASIS 7) trial,⁷ included both clopidogrel-naïve patients and patients on clopidogrel maintenance therapy. Nevertheless, the clinical benefit of

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reloading patients on chronic clopidogrel therapy when they present for PCI has not been addressed specifically to date.

The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-4 RELOAD) randomized trial is, therefore, an important trial, as it addresses this short-coming.¹² Five hundred and three patients with significant coronary artery disease suitable for percutaneous intervention who were on clopidogrel therapy for >10 days were enrolled into the multicentre, double-blinded ARMYDA-4 RELOAD trial. Two hundred and fifty-two patients were assigned to receive 600 mg of clopidogrel reloading and 251 patients were assigned to receive placebo. After PCI, all patients received aspirin indefinitely and continued clopidogrel for at least 1 month, irrespective of the randomization assignment. The primary endpoint was 30-day incidence of major adverse cardiac events (MACEs). The primary endpoint occurred in 6.7% of patients in the reload vs. 8.8% in the placebo arm ($P=0.50$). Bleeding complications did not differ between the two groups (6% in both groups). A pre-specified subgroup analysis revealed a significant interaction between treatment effect and mode of presentation: reloading significantly reduced MACEs in ACS patients but not in patients presenting with stable angina.

The discussion on the potential implications of the ARMYDA-4 RELOAD trial should take into account its limitations. The total number of patients enrolled in this trial is relatively low to enable strong analyses of clinical endpoints, especially when these analyses are also extended to subgroups. In addition, although the definition of post-procedural MI—the major driver of the primary endpoint in the ARMYDA-4 RELOAD trial—followed criteria selected by task force experts, the clinical relevance of a troponin elevation after PCI has still not been evaluated to the same degree as was done for CK-MB elevation. However, the results of the ARMYDA-4 RELOAD trial have two major implications for daily clinical practice: first, reloading of patients on chronic clopidogrel therapy is safe as it does not result in excess bleeding. This is in line with results that have been observed previously after loading clopidogrel-naïve patients undergoing PCI.⁵ Secondly, reloading results in a significantly lower incidence of adverse events at 30 days after PCI in patients with ACS. The latter finding is consistent with the concept that ACS patients respond less well to clopidogrel—most probably due to a higher degree of platelet activation—and hence benefit most from a more profound, drug-induced inhibition of platelet function.¹³

Reloading in the ARMYDA-4 RELOAD trial also resulted in a 24% reduction in the incidence of the primary endpoint in the overall population including both ACS and stable angina patients. Although this difference was not statistically significant, the lack of significance of the primary endpoint might simply result from the limited sample size of the trial, rather than from the lack of efficacy of the reloading regimen. This might be particularly relevant for patients with stable angina and low event rates after PCI. A low platelet response to clopidogrel is associated with an increased risk of ischaemic events even after PCI in stable angina patients;¹⁴ therefore, additional studies with larger numbers of patients are warranted in order to answer the important question, whether low risk patients on chronic clopidogrel therapy can safely undergo PCI without the need of clopidogrel reloading.

So how best to incorporate the findings of the ARMYDA-4 RELOAD trial into our daily management of patients on clopidogrel maintenance therapy who require PCI? The present study clearly suggests that it is advisable to reload with clopidogrel all patients presenting with ACS. For patients with stable angina in the ARMYDA-4 RELOAD trial, reloading with clopidogrel did not lead to any clinical benefit. On the other hand, it did not result in an increase in the risk of bleeding. In daily routine practice, it is almost impossible to be certain that the patient has been compliant with clopidogrel therapy unless platelet function studies are performed. For these reasons, a high-dose reloading might be beneficial even in patients on maintenance clopidogrel therapy who need PCI for stable angina.

Several point-of-care assays have been validated to evaluate the platelet reactivity in patients on clopidogrel therapy, including multiple electrode platelet aggregometry and the Verify Now P2Y12 assay. Reactivity to clopidogrel assessed by point-of-care tests correlates well with the risk of ischaemic events early after PCI,¹⁴ and selection of the clopidogrel loading dose on the basis of platelet function testing has been shown to improve outcomes of PCI patients.¹⁵ The latter approach might be a reasonable alternative for guiding the decision to carry out clopidogrel reloading in low-risk patients undergoing PCI.

In the near future, recommendations on reloading of PCI patients that are on clopidogrel maintenance therapy will also have to consider the availability of novel ADP receptor antagonists with altered pharmacodynamic and pharmacokinetic properties. Compared with clopidogrel, prasugrel, ticagrelor, cangrelor, and elinogrel show lower interindividual variability in platelet response and no measurable vulnerability to genetic variation in CYP isoenzymes. In view of these recent developments in the field of antiplatelet therapy, the issue of reloading patients on chronic clopidogrel therapy might need to be revisited.

Conflict of interest: none declared.

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CARDIOVASCULAR FLASHLIGHT

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Coronary fistulas are not always bad: coronary artery to coronary artery fistula as a very unusual collateral pathway

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A 57-year-old man presented to the emergency room with light-headedness. There was no prior history of chest pain but his electrocardiography showed Q-waves, ST-segment elevation, and negative T-waves in V1–3. Echocardiography showed apical dyskinesia and an ejection fraction of 40–45%. Coronary angiography showed that the right and the circumflex artery were normal. The left anterior descending artery (LAD) was occluded just after the origin of first diagonal and septal branches. The apical part of the LAD was filling with Rentrop grade 2 collaterals from the right coronary. There was a fistula originating from the proximal LAD that, after a meandering superior, anterior, and inferior course, drain into the junction of the mid-LAD with second septal branch (Panels A and B). It drew a star-like picture. The fistula served as a collateral circulation between the proximal and mid-LAD coronary artery.

Three-dimensional volume-rendering images of computed tomography revealed that the fistula leaves the interventricular sulcus in superior and anterior direction between the auricle of the left atrium and the pulmonary artery, then rightward course on the anterior aspect of the pulmonary artery (Panel C). It then went inferiorly toward to anterior interventricular sulcus, and drained into junction of the mid-LAD with the second septal branch just after the occlusion.

To our knowledge, coronary to coronary fistula has not been previously reported. We postulated that the occlusion of the LAD resulted in activation and growing of the fistula, leading to the formation of this unique source of blood for the occluded LAD.

