Routine pre-treatment with clopidogrel before diagnostic coronary angiography: the question is right, but what about the answer?

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This editorial refers to ‘Clopidogrel pre-treatment in stable angina: for all patients >6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8† by P. Widimsky et al., on page 1495

Dual antiplatelet therapy is the mainstay of antiplatelet treatment in percutaneous coronary interventions (PCIs) with stent implantation, as well as in acute coronary syndromes (ACS) with and without ST segment elevation.1–3 In ACS, dual antiplatelet therapy has been shown to reduce the risk of death and myocardial infarction (MI), both at the initial phase and in the long term. In the setting of stent implantation, dual antiplatelet therapy has been shown to reduce the risk of major adverse cardiac events (MACEs) and stent thrombosis, as compared with various other antithrombotic regimens. Ticlopidine was the first thienopyridine to be used in the setting of stent implantation, but, over time, clopidogrel has proven to be better tolerated and more efficacious.4 However, clopidogrel is a prodrug, which requires a two-step metabolism in the liver to be transformed into its active metabolite. Its onset of action is quite slow, and the level of inhibition of platelet aggregation (IPA) achieved with the recommended regimen is quite low compared with other compounds.5,6 This implies that if clopidogrel is administered at the time of stent implantation, the level of IPA could be quite low during the critical 3–4 h after the procedure.

Two solutions have been proposed to overcome this problem. The first is to administer clopidogrel long before the procedure. This strategy has been shown to be efficacious in three different settings. In the CREDO study, it was shown that better outcome following stent implantation could be achieved if clopidogrel was administered >14 h before the procedure.7 In PCI-CURE and CLARITY, pre-treatment with clopidogrel was shown to lead to better efficacy. The risk reduction for death or MI at 30 days following PCI was in the range of 25% when data from CREDO, PCI-CURE, and CLARITY were pooled.8–11 In addition, no significant increase in the bleeding risk was observed in this meta-analysis, where the odds ratio for major or minor bleeding was 1.21 (95% CI 0.85–1.72, P = 0.29) for pre-treatment vs. no pre-treatment. Based on these data, the most recent guidelines make clopidogrel pre-treatment a class I recommendation (300 mg at least 6 h before PCI).2,12

The other possible solution is to deliver higher doses of clopidogrel. Loading doses of 600 mg and even 900 mg have been tested on surrogate end-points exploring platelet function. These doses have been shown to lead to faster onset of action, and a higher level of IPA. Although neither of these doses is currently approved, the 600 mg dose is widely used in routine practice, and has been shown to be more efficacious than the standard 300 mg loading dose in small trials, mostly with surrogate end-points.

In this context, the study by Widimsky and collaborators13 addresses an important issue frequently encountered in routine practice, namely administration of a loading dose of clopidogrel to patients scheduled for diagnostic coronary angiography with intent to perform PCI, if the lesions are amenable to angioplasty. This means that many of the patients who receive a loading dose of clopidogrel will not undergo stent implantation, and will thus be exposed to the potential risk of this strategy, particularly bleeding at the puncture site, without the perspective of a beneficial effect. This type of strategy—namely patients submitted to diagnostic procedures ‘loaded’ with clopidogrel—has never been compared with a strategy of elective administration of a high loading dose of clopidogrel in the catheterization laboratory in the case of PCI. For this reason, the authors’ intent is sound, and the message for the cardiological community is important, i.e. to determine whether or not elective administration of a high loading dose at the time of PCI will lead to fewer bleeding...
complications without compromising safety, particularly occurrence of MI post-PCI.

The results show that elective administration of a 600 mg loading dose of clopidogrel, as compared with pre-treatment, does not significantly increase the risk of MACEs, whereas it results in a lower risk of bleeding complications in the whole cohort of patients. When considering only patients submitted to PCI, the difference is even more striking. Elective treatment does not lead to a significant increase in MACEs, but does lead to a significant risk reduction for bleeding (7.1 vs. 0.7%, pre-treatment vs. no pre-treatment). Will these results change practice, and incite interventional cardiologists to reconsider pre-treatment with clopidogrel in patients taken to the cathlab for suspected coronary artery disease? Will these findings lead to a change in the recommendations in future guidelines addressing the pharmacological environment of PCI? This might be premature, for several reasons that merit discussion.

First, the rates of revascularization with PCI are quite low, at ~30%, and, furthermore, the rate of MACEs observed in the PCI population is extremely low, at 1.3 vs. 2.8% for pre-treatment vs. elective administration, respectively. In recent trials that used contemporary therapy, the rate of MACEs, defined as in PRAGUE-8, was in the range of 5% in REPLACE-1, and 6.6–10.5% in ESPRIT (epitfibatide vs. placebo, respectively) at 48 h.14,15 This low rate of events may have substantially altered the statistical power of the study to detect the 2.5% absolute difference in the primary end-point between the two groups, which served to calculate the sample size of the study.

In fact, the reason for the low rate of events is that the rate of MI, defined on the basis of CK-MB release, is nil. However, the rate of MI as defined by the Universal Definition of Myocardial Infarction,14 using troponin release as the qualifying criterion, is much higher: 8.4 vs. 11.9% for pre-treatment vs. no pre-treatment [MI defined as 3 x the upper limit of normal (ULN) of troponin release following PCI]. If the universal definition of MI were used, the rate of primary end-point would then be 9.7 vs. 14.7%, i.e. a substantially higher rate in the group with elective administration of clopidogrel vs. pre-treatment.

Secondly, the rate of bleeding complications observed in patients submitted to PCI is surprisingly high in the group with pre-treatment. These findings contradict the data reported in the meta-analysis by Sabatine and co-workers,11 where there was no significant increase in bleeding with pre-treatment. How can this high risk of bleeding be explained? In fact, the two loading doses tested in this trial are both unapproved. Admittedly, a 600 mg loading dose is widely used in the setting of PCI, but pre-treatment with 600 mg of clopidogrel before diagnostic angiography may not derive a much higher level of IPA at the time of intervention, whereas it may well generate more bleeding. Would the rate of bleeding have been different if the authors had chosen to compare pre-treatment with a 300 mg loading dose prior to diagnostic angiography, with an elective 600 mg loading dose at the time of PCI?

Thirdly, there was no excess bleeding in the population not submitted to PCI. Thus the study did not demonstrate any significant harm in those undergoing diagnostic catheterization without consecutive PCI. In addition, the study was not powered to rule out the benefits observed in previous studies and summarized in the paper by Sabatine and co-workers.11

Finally, one important end-point is not addressed at all in the study by Widimsky et al., namely stent thrombosis.13 It would have been interesting to report the rates of stent thrombosis, if any, particularly within the first 24 h, since the level of IPA may have been very different between the two groups in the few hours following angioplasty.

Therefore, the results of this study—while interesting—cannot be generalized, since they do not answer the question of pre-treatment with a 300 mg loading dose. We cannot assume that pre-treatment with a 600 mg loading dose would result in the same level of bleeding complications as a 300 mg loading dose administered the day before diagnostic coronary angiography. In addition, the results of this study are applicable only in the setting of elective PCI in stable patients, and can certainly not be extrapolated to ACS patients.

In conclusion, the authors have made a concerted effort to clarify a situation that poses a real problem in daily practice, in Europe at any rate. The answer they provide through the results of this study is interesting, but still arguable, in view of the limitations outlined above. In addition, it is likely that these findings will soon be outdated. It has previously been shown that the rate of MACEs following stent implantation is highly dependent on the level of IPA achieved at the time of PCI. The current treatment strategy, particularly the pharmacological approach, in the setting of stent implantation in elective PCI or ACS may be called into question in the near future, when newer intravenous or oral antiplatelet agents with faster onset of action and higher IPA become available. With these new compounds, it may no longer be necessary to consider pre-treatment, since after intravenous or even oral administration of these new agents, >70% IPA can be achieved in half an hour at most.17,18 This would render the questions studied in the PRAGUE 8 study moot.

Conflict of interest: none declared.

References


