SCIENTIFIC EDITORIAL

Pretreatment with P2Y\textsubscript{12} inhibitors in non–ST-segment elevation acute coronary syndrome: Time to revise the guidelines?

Pré-traitement des syndromes coronaires aigus sans sus-décalage du segment ST avec les inhibiteurs de P2Y\textsubscript{12} : l’heure de changer les recommandations?

Guillaume Cayla\textsuperscript{a,b,c}, Jean-Philippe Collet\textsuperscript{a}, Johanne Silvain\textsuperscript{a}, Gilles Montalescot\textsuperscript{a,c,1}

\textsuperscript{a} Institut de Cardiologie, ACTION Group, INSERM CMR937, Pitié-Salpêtrière Hospital (AP–HP), Université Paris 6, Paris, France
\textsuperscript{b} Service de Cardiologie, Hôpital Universitaire Carémeau, Nîmes, France
\textsuperscript{c} Université Montpellier 1, Montpellier, France

Received 21 October 2013; accepted 22 October 2013
Available online 12 December 2013

Antiplatelet agents remain a cornerstone of treatment for acute coronary syndrome. More than 15 years after the introduction of ticlopidine in coronary artery disease, the combination of aspirin with P2Y\textsubscript{12} inhibitors has become a standard of care. However, the optimal timing of the introduction of P2Y\textsubscript{12} inhibitors remains controversial. Clopidogrel is a prodrug that needs hepatic biotransformation in two important steps to irreversibly block the P2\textsubscript{12} receptor. New P2Y\textsubscript{12} inhibitors – namely, prasugrel and ticagrelor – have a simpler hepatic metabolism and induce a rapid and intense level of platelet inhibition [1,2]. These agents are proposed as first-line treatment for non–ST-segment elevation acute coronary syndromes (NSTE-ACS); however, the question of timing of administration has never been addressed [3,4] in a dedicated randomized study. European and American guidelines [5,6] recommend giving P2Y\textsubscript{12} inhibitors as soon as possible; however, the evidence to support this statement is weak. A recent meta-analysis [7] did not show a survival benefit for clopidogrel pretreatment in 37,000 patients undergoing percutaneous coronary intervention (PCI), while there was an excess of major bleeding and little impact on ischemic outcomes.

Abbreviations: CAGB, coronary artery bypass graft; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

\textsuperscript{1} Corresponding author. Bureau 236, Institut de Cardiologie, Pitié-Salpêtrière University Hospital, 47–83, boulevard de l’Hôpital, 75013 Paris, France.

E-mail address: gilles.montalescot@psi.aphp.fr (G. Montalescot).

1875-2136/S — see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.acvd.2013.10.004
The ACCOAST study [8] has addressed the question of optimal timing of \( \text{P}2\text{Y}\text{I}_{12} \) inhibition in patients with non-ST-segment elevation myocardial infarction (NSTEMI) managed invasively within 48 hours of admission. In this study, 4033 patients were randomized to receive prasugrel as pretreatment or to selectively receive prasugrel at the time of PCI. Despite effective platelet inhibition at the time of PCI, pretreatment with prasugrel did not reduce the occurrence of the primary endpoint (a composite of cardiovascular death, myocardial infarction, stroke, urgent revascularization or glycoprotein IIb/IIIa inhibitor rescue therapy) (Fig. 1). Moreover, pretreatment was associated with a twofold increase in major bleeding complications at 7 days. Interestingly, among the 69% of patients who underwent PCI, no evidence of reduction in ischemic complications was observed and pretreatment was associated with a threefold increased risk of major bleeding complications. Finally, there were significantly more major and life-threatening bleeding complications not related to coronary artery bypass graft (CABG) surgery in the pretreatment group than in the control group. These results were consistent across all the subgroups, including in patients in whom radial access was used for PCI.

The results of the ACCOAST study offer new insights into pretreatment with \( \text{P}2\text{Y}\text{I}_{12} \) inhibitors in NSTEMI. The use of new \( \text{P}2\text{Y}\text{I}_{12} \) inhibitors in NSTEMI may be postponed to the time of the decision about PCI, to avoid overtreatment in patients who may need CABG surgery or medical treatment [9]. Can the ACCOAST results be applied to other \( \text{P}2\text{Y}\text{I}_{12} \) inhibitors, such as clopidogrel and ticagrelor? For clopidogrel, the oldest studies suggest a potential benefit for pretreatment when there is a very long delay between randomization and PCI [10,11]. More recent studies have not confirmed the benefit of pretreatment with shorter delays and higher doses of clopidogrel [12,13]. For ticagrelor, in the PLATO trial [4], all patients were pretreated with clopidogrel, ticagrelor or both before PCI; the question of pretreatment has not been addressed for ticagrelor.

The potential risk/benefit ratio for pretreatment with new \( \text{P}2\text{Y}\text{I}_{12} \) inhibitors must now be reconsidered for these agents in NSTEMI. Practical implications may be as follows: in patients with a short delay (<24–48 hours) from admission to angiography, pretreatment should be avoided; in patients with a delay from admission to angiography of >48 hours, pretreatment with either clopidogrel (on the basis of old data) or ticagrelor (without data) may be considered.

**Disclosure of interest**

Prof. Cayla has received consulting fees from AstraZeneca, Eli-Lilly, Daiichi-Sankyo and Abbott; and lecture fees from AstraZeneca, Boston Scientific, Eli-Lilly, Daiichi-Sankyo, Abbott Vascular, Bristol-Myers Squibb, Bayer, Boehringer-Ingelheim, CSL Behring, Iroko Cardio International, Novartis and Pfizer.

Prof. Collet has received research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli-Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Fédération française de cardiologie and Société française de cardiologie; consulting fees from Sanofi-Aventis, Eli-Lilly and Bristol-Myers Squibb; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis and Eli-Lilly.

Dr. Silvain has received research grants from Sanofi-Aventis, Daiichi-Sankyo, Eli-Lilly, INSERM, Fédération française de cardiologie and Société française de cardiologie; consultant fees from Correvio, Daiichi-Sankyo and Eli-Lilly; and lecture fees from AstraZeneca, Boehringer-Ingelheim, Cordis, Daiichi-Sankyo, Eli-Lilly, Stentys and The Medicines Company.

Prof. Montalescot has received research grants to the institution or consulting/lecture fees from Abbott Vascular, Asante, AstraZeneca, Atrium, Bayer, Biotronik, BMS, Boehringer-Ingelheim, Boston Scientific, Choice Pharma, Brahms, CCS, CHUV, Cordis, Daiichi-Sankyo, Duke Institute, Eli-Lilly, Europa, Euro RSCG, Fédération française de cardiologie, Fondation de France, GLG, GSK, HUG, Indegenie, INSERM, Institut de France, Iroko, Lead-up, Medtronic, McKInsey, MSD, Nanospheres, Navigant, Novartis, Pfizer, Portola, Roche, Royal College Physicians, Sanofi-Aventis, Stentys, SGAM, Société française de cardiologie, Springer, Thrombosis Research Institute, The Medicines Company, TIMI group, US Zurich, WebMD and Wolters.
References


