New Insights for Low Dosing With the New P2Y12 Inhibitors
– Lesson From the East –

Johanne Silvain, MD, PhD; Mathieu Kerneis, MD; Jean Philippe Collet, MD, PhD;
Gilles Montalescot, MD, PhD for the ACTION Study Group

Elective PCI is the last bastion where clopidogrel remains the preferred option in combination with aspirin to prevent recurrent ischemic events. The phenomenon of “resistance” or “non-response” to clopidogrel has been extensively studied and linked to recurrent Cardiovascular events in this setting. However, despite the need for better antplatelet therapy in elective PCI for high-risk cases or high-risk patients as now recommended in the guidelines, there is currently no demonstration of superiority of the new drugs over clopidogrel to prevent periprocedural events and short-term complications such as stent thrombosis. Double dose of clopidogrel loading dose (LD) at 600 mg followed by a double dose (150 mg) of clopidogrel maintenance dose (MD) did not provide much benefit for ischemic events in elective patients, and was even associated with higher major bleeding rates in ACS. Platelet function testing to tailor clopidogrel treatment failed to improve patients’ prognosis in elective PCI, although it did improve pharmacological response. Cangrelor provided an additional degree of reduction of ischemic events, especially acute stent thrombosis, and could be a new costly option. Prasugrel and ticagrelor can overcome high platelet reactivity, but clinical data in elective PCI are missing. Moreover, the risk of bleeding associated which the current standard dosage is a concern in these low-risk patients.

The Asian population also displays a higher PD response to prasugrel and ticagrelor with higher exposure to the active metabolite than do Caucasians, suggesting that these drugs are not suitable at the standard dose regimens.

In the Japanese population, a new low dose of prasugrel has been evaluated in the PRASFIT-ACS trial and tested now in the population undergoing elective PCI. This dosage is supposed to provide an intermediate level of P2Y12 inhibition between 10 mg prasugrel MD and clopidogrel 75 mg MD, with the final aim of having a better risk-benefit ratio. The combination of prasugrel 20 mg LD followed by 3.75 mg MD demonstrated a reduction of MACE from 6.7% to 4.1% (RRR of 39%) vs. the classic clopidogrel dose (300 mg/75 mg) without harm. Bleeding events were even fewer in the prasugrel arm (0% vs. 2.2%) in this double-blind study. These findings are supportive of the PRASFIT-ACS trial in which low-dose prasugrel did reduce ischemic events (MACE) from 11.8% to 9.4% (RRR 23%) without any increase in major bleeding events (1.9% vs. 2.2%). Both studies were underpowered and did not provide adequate statistics to definitely conclude a reduction of ischemic events, and these are major limitations of both PRASFIT-Elective and PRASFIT-ACS. However, the results are consistent across the 2 studies and to a lesser degree, with TRITON and PLATO and the meta-analysis of newer P2Y12 inhibitors when compared with clopidogrel. It must be noted that most of the benefit was found in the first 30 days, which seems logical considering the endpoints and the use of last-generation drug-eluting stents.

In both PRASFIT trials, low-dose prasugrel led to a much better PD response in patients identified as genetic poor metabolizers. Overall, the PD response was always better than
Low Dosing of P2Y12 Inhibitors

In conclusion, low-dose prasugrel appears to work and results suggest that the currently recommended dose regimen may be too strong in certain populations or conditions. We may be entering a new era with prasugrel and ticagrelor, starting an opposite strategy to the one we knew with clopidogrel, when we increased clopidogrel doses to improve efficacy. We are now trying to reduce the doses of the new P2Y12 inhibitors to improve safety.

Disclosures

Professor Montalescot reports receiving consulting fees from Bayer, Boehringer-Ingelheim, Cardiovascular Research Foundation, Europa Organisation, the Gerson Lehman Group, Iroko Cardio International, LeadUp, LLC, Luminess, Mc Kinsey & Company, Inc, Remedica, Servier, TIMI Group, WebMD, and Wolters Kluwer Health; consulting fees and grant support from Bristol-Myers Squibb, AstraZeneca, Biotronik, Eli Lilly, The Medicines Company, Medtronic, Menarini Group, Sanofi-Aventis, Pfizer, and Accutomecs; and grant support from Abbott Vascular, Daiichi-Sankyo, Nanospheres Inc, and Stentys.

Professor Collet reports receiving research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Federation Francaise de Cardiologie, and Societe Francaise de Cardiologie; consulting fees and grant support from Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, and Stentys; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, and Eli Lilly.

Dr Kerneis has received research grants from Federation Francaise de Cardiologie.

Dr Silvain reports receiving research grants to the institution from Boehringer-Ingelheim, Daiichi-Sankyo, Eli Lilly, Braham, Sanofi-Aventis, Federation Francaise de Cardiologie and Socite Francaise de Cardiologie, INSERM; consultant fees from Daiichi-Sankyo, Eli Lilly, AstraZeneca, and the Medicines company; and lecture fees from AstraZeneca, Cordis, Daiichi-Sankyo, Eli Lilly, Iroko Cardio and STENTYS.
References


