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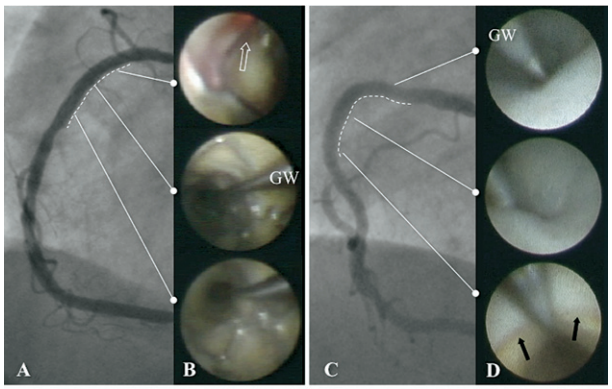

Figure 2 **Coronary Angioscopic Images 8 Months After SES and ZES Implantation**

Left images (A, B) show a sirolimus-eluting stent (SES) (3.5 × 23 mm) implanted case, and **right images (C, D)** show a zirolimus-eluting stent (ZES) (3.5 × 23 mm) implanted case, both at the proximal portion of the right coronary artery. **(A, C)** Angiograms at follow-up revealed no restenosis. **(B)** Angioscopic images of SES indicated grade 1 neointimal coverage throughout the stent, with mural red thrombus adhesion observed at the proximal site of the stent. Further, yellow plaques were observed underneath the stent (the entire segment of the stent placed in the vascular wall was yellow). **(D)** In contrast, ZES showed grade 3 neointimal coverage throughout the stent. Yellow plaques existed in the distal native coronary artery adjacent to the distal end of the stent. The vascular wall showed mild yellow saturation, while the stent portion was covered with white-gray neointima with no yellow plaques observed **(D, bottom image)**. **Open arrow** = mural red thrombus; **solid arrows** = boundary line of the neointimal coverage; GW = guidewire.

at 21 days after the placement in the rabbit iliac arteries (4). All thrombi observed in this study were found at grade 0/1 sites; the dominant pattern in ZES-implanted vessels in this study was grade 2/3 with less adhesion of thrombus. The ZES-implanted vessels were associated with significantly less yellow plaques than SES. Yellow plaque is also reduced by BMS placement, because both the stent and the YP underneath the stent are covered by neointimal development (5). The ZES is likely to have a "sealing" effect, because ZES shows NIC more like that of BMS. These angioscopic findings suggest that arterial endothelial healing of ZES at 8 months after stent placement was more competent than SES. In general, mean in-stent LL below 0.65 mm with stent platforms is associated with TLR rates below 10% (6). Considering the risk of stent thrombosis due to incomplete NIC, it is preferable for DES to have sufficient neointimal volume no greater than LL of 0.65 mm.

Although the single-center, nonrandomized, matched-control, and observational nature with a small sample size of this study should be noted as a limitation, this study suggests that arterial endothelial healing after stenting is more competent in ZES than in SES. Optimal LL might be desirable for adequate arterial endothelial healing after stenting.

Masaki Awata, MD
***Shinsuke Nanto, MD, PhD, FACC**
Masaaki Uematsu, MD, PhD, FACC
Takakazu Morozumi, MD, PhD
Tetsuya Watanabe, MD, PhD
Toshinari Onishi, MD
Osamu Iida, MD
Fusako Sera, MD
Jun-ichi Kotani, MD, PhD, FACC
Masatsugu Hori, MD, PhD, FACC
Seiki Nagata, MD, PhD

*Cardiovascular Division
Kansai Rosai Hospital
3-1-69 Inabaso
Amagasaki, 660-8511
Japan
E-mail: snanto@kanrou.net

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Letters to the Editor

Adjusting Clopidogrel Loading Doses According to Vasodilator-Stimulated Phosphoprotein Index: On Time, Too Early, or Too Late?

We have read with great interest the report from Bonello et al. (1). The authors have to be congratulated on publishing the first article to show the clinical benefit of tailored antiplatelet therapy. We would like to address a few comments to the authors.

The clinical evidence supporting the clinical predictive value of the vasodilator-stimulated phosphoprotein (VASP) index is quite low (2,3), and additional large-sample size studies may be required to validate a definite cutoff. The authors used a cutoff of 50%, previously associated with post-percutaneous coronary interven-

tion (PCI) ischemic events, in a small sample size, single-center study (2) with good negative predictive value but poor specificity.

Is it too early? Indeed, before adapting clopidogrel loading dose, maybe we should define a consensual definition of nonresponse?

The difference observed between both groups is highly significant, with no clinical events in the VASP-guided group. This result could suggest that all post-PCI ischemic events are related to nonresponse to clopidogrel, which is probably excessive. These recurrences involve a complex and multifactorial process. The recent TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) study showed that, even with a more potent P2Y12 inhibitor, the rate of recurrent events significantly decreased but continued to exist (4).

The authors reported no excess of major bleeding in the VASP-guided group and concluded that the strategy is safe. However, the sample size of the present study does not allow for such a definite conclusion. What would be the bleeding complications in a broad population of such strategy? Moreover, in the whole population, 52% of the patients had VASP >50%, suggesting the use of this strategy in more than one-half of the PCI patients. Then, will the increased length in hospital stay be acceptable for the public health system?

Is it too late? Indeed, in the near future, the alternative in nonresponders might be to switch to alternative drugs such as prasugrel. Then, the variability of response to clopidogrel would become a resolved issue.

***Thomas Cuisset, MD**
Corinne Frere, MD, PhD
Jacques Quilici, MD
Marie Christine Alessi, MD, PhD
Jean Louis Bonnet, MD

*CHU Timone
Cardiology
264 rue Saint Pierre
13385, Marseille
France
E-mail: thomascuisset@voila.fr

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Reply

We thank Dr. Cuisset and colleagues for their critical review of our study (1). Many studies have suggested a stepwise relationship between platelet reactivity (PR) and ischemic recurrences after percutaneous coronary intervention (PCI), and the vasodilator-stimulated phosphoprotein index has been used extensively used in these trials. The threshold used to define low response in the present study was chosen according to its clinical and biological relevance (2–5). Further, this cut-off value exhibits a very high negative predictive value and a low positive predictive value, which illustrate the fact that, although ischemic recurrences are multifactorial, PR plays a key role.

Dr. Cuisset and colleagues seem to misunderstand available data on PR and the hypothesis tested in our study. The interindividual variability observed between patients in response to clopidogrel means that the effect of a 2,400-mg loading dose for low responders is inferior to that of 600 mg for good responders! Indeed, available data support the fact that the response to the drug, and not the dose, determines the outcome.

Finally, Dr. Cuisset and colleagues question the relevance of the present study with regard to the future marketing of prasugrel. The present trial is a landmark study demonstrating that PR is a modifiable risk factor for recurrent ischemic events and therefore of major interest not only for clopidogrel but for all other antiplatelet therapies that will be developed. Further, consistent with our results, researchers from the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) study observed that greater PR inhibition, as achieved by prasugrel, compared with standard clopidogrel therapy, resulted in lower rates of ischemic events in patients undergoing PCI for acute coronary syndromes (6). However, achieving 90% PR inhibition with prasugrel resulted in a significant increase in major bleedings. Accordingly, the authors do not support the use of prasugrel for large subgroups of patients, including the elderly, those patients of low weight, those patients with previous stroke, and those patients undergoing elective PCI, which make up more than half of our patients. In addition, finding a threshold of PR to decrease ischemic events could be of great interest for the new P2Y12 ADP-receptor inhibitors to increase their risk/benefit ratio. Until prasugrel is available, platelet monitoring of the response to clopidogrel carries a potential clinical benefit for patients undergoing PCI. We believe that it is never too late to improve both our practice and patient outcomes.

***Laurent Bonello, MD**
Laurence Camoin-Jau, MD, PhD
Stéphane Arques, MD
Paul Barragan, MD
Francoise Dignat-George, PhD
Franck Paganelli, MD

*Département de Cardiologie
Hôpital Universitaire Nord
Chemin des Bourrely
13015, Marseille
France
E-mail: laurentbonello@yahoo.fr

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