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EDITORIAL COMMENT

Cangrelor

Fixing Life or Just a Leak?*

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Decisions on antiplatelet therapy may appear increasingly complex, and vary according to the clinical situation. Concerning $P2Y_{12}$ antagonists, drug choice, administration route, timing of administration, and duration of therapy need to be factored into the decision making. There are less evidence and poorer recommendations in stable coronary artery disease (CAD) than in acute coronary syndrome (ACS), which all mainly rely on the prevention of periprocedural complications in clinical trials. However, these complications do not share the same definitions, the same prevalence, and the same prognostic value across clinical trials and consequently clinicians are often left with belief more than with hard data to take decisions on antiplatelet therapy for their patients.

In this context, cangrelor appears as a good candidate to simplify the clinician's decision with a rapid onset and offset of platelet inhibition through an intravenous administration. The CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention) trial has already demonstrated a significant reduction of periprocedural ischemic events (1), but whether this benefit is or is not confined to a specific subgroup of patients remains to be thoroughly studied. This is the main interest of the study by Abtan et al. (2) in this issue of *JACC: Cardiovascular Interventions*. The authors highlight the fact that the drug effect is consistent in stable CAD patients (n = 6,358) and ACS patients (n = 4,584) for ischemic, bleeding, and net clinical endpoints, all p values for interaction not being significant. This is a reassuring finding for cangrelor, opening a wide spectrum of indications for the drug.

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Intriguingly, the rate of ischemic events is higher in the stable CAD population than in the ACS patients (6.3% vs. 3.9%). Obviously, it does not mean that stable CAD patients have a worse prognosis than ACS patients. This disconnect finds its explanation in the definitions used to adjudicate ischemic events. The periprocedural myocardial infarction (MI) represented 79.8% of all adjudicated ischemic endpoints and 93.5% in stable CAD patients (373 MI of 399 events). The definitions of periprocedural MI were not the same for ACS and stable CAD patients, although they were all based on the second universal definition of MI published in 2007 (3). In stable CAD patients (with a normal baseline troponin) type 4a MI was simply defined by an elevation above 3-fold the upper limit of normal of cardiac biomarkers (creatine kinase-myocardial band or troponin) post-percutaneous coronary intervention (PCI). In ACS patients (with an elevated baseline troponin), a clinical, electrocardiographic, or angiographic criterion was

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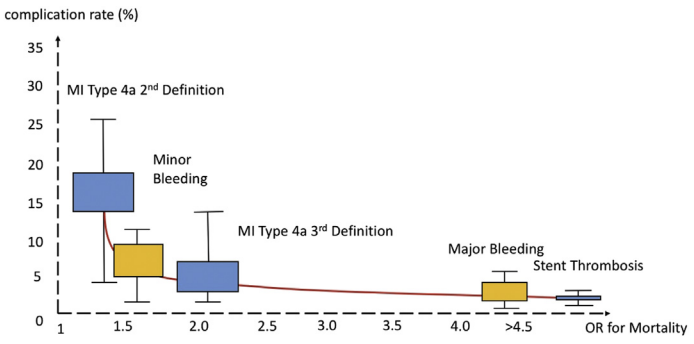
necessary to meet the definition of periprocedural MI. Unfortunately, these results cannot be extrapolated to the third set of universal definitions of MI published in 2012, which are based on high-sensitivity troponin assays and differentiate MI from myocardial injury following PCI (4). The changes of definitions impact the prevalence of events for the same patients as shown by Baker et al. (5) who reported in 7,333 patients undergoing elective PCI a rate of type 4a MI of 31.9% and 2.1% with the second and third sets of definitions of MI, respectively. Thus, not only the definitions differ between ACS and stable CAD patients, but also the definitions evolve over time for the same type of patients. Whether cardiac marker leaks following PCI are adequate surrogate endpoints for mortality and whether this or that set of definitions is more performing to measure prognosis is still debated.

When testing a drug such as cangrelor in a PCI population, it is important to remember that, although we have guidelines dedicated to PCI, PCI is not a disease. It is a procedure applied to a wide spectrum of patients with different clinical presentations and prognosis of coronary disease. Cangrelor has not shown any insinuation of an effect on mortality linked to PCI in comparison with clopidogrel, despite a significant number of patients enrolled. Cangrelor has clearly reduced periprocedural MI, but in a meta-analysis of 15,581 patients, periprocedural MI occurring in 32.9% of the patients was poorly associated with mortality (odds ratio: 1.35; 95% confidence interval: 1.13 to 1.60) with a 16.5-month median follow-up (6). Other large studies failed to find a statistical link between post-procedural troponin and mortality (7). Nevertheless, the loss of myocytes for the cardiologist, similar to the loss of neurons for the neurologist or nephrons for the nephrologist, is an unbearable situation. Moreover, there is no good alternative to evaluate drugs such as cangrelor other than to measure periprocedural leak of troponin. The reality principle does not exclude objectivity (**Figure 1**). The seductive antiplatelet drug has shown so far, to fix the troponin leak but not the life of the patients. However, cangrelor has the potential to reduce hard events. Stent thrombosis, although exposed to similar definition criticisms, is a serious event reduced by cangrelor, both in stable CAD and ACS patients. In addition, the drug, because of its intravenous formulation and fast onset of action, is the only $P2Y_{12}$ antagonist adapted to emergency and high-risk situations when patients cannot swallow or absorb other $P2Y_{12}$ antagonist pills. Shock patients, cardiac arrest patients, and ventilated patients with ongoing ST-segment elevation MI are those who need life-saving drugs at the time of PCI. Unfortunately, they are also those who were excluded from the 3 CHAMPION trials and those the company refused to evaluate so far in new studies.

FIGURE 1 Rate and Prognosis Impact of Periprocedural Complications



Values are mean ± SEM. Figure based on data from references (5,6,10–15).
MI = myocardial infarction; OR = odds ratio.

The safety profile of cangrelor is reassuring, although the safety profile of the CHAMPION PHOENIX trial population is so low that any difference would be difficult to detect. Only 1 patient presented a Thrombolysis In Myocardial Infarction major bleeding event of 2,343 ACS patients randomized to clopidogrel in the CHAMPION PHOENIX trial, whereas the non-coronary artery bypass graft TIMI major bleeding rates on clopidogrel in ACS patients undergoing PCI were 2.2% and 1.8% with ticagrelor and prasugrel, respectively (**Figure 1**) (8,9). In addition to the selection of patients, the delayed administration of clopidogrel in both groups may partly explain the unusually low bleeding event rates observed in the CHAMPION PHOENIX trial. The excellent safety profile of cangrelor in this context adds to the comfort of use for the interventional cardiologist.

In conclusion, there is a strong argument in favor of cangrelor to better control the troponin leak following PCI but no evidence that the drug can improve survival of the patients. Considering the safety hazard of pre-treatment with oral $P2Y_{12}$ antagonists in stable CAD and non-ST-segment elevation-ACS patients, and considering the ease of use and good safety profile of cangrelor, the drug could at least fix the life of the interventional cardiologist!

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