Smoking and Clopidogrel Response Revisited
Hemoglobin Levels Explaining the Smoker’s Paradox*

Dirk Sibbing, MD, Lisa Gross, MD

Cigarette smoking constitutes a major health hazard contributing significantly to cardiovascular morbidity and mortality. The effects of smoking on the pharmacokinetics and pharmacodynamics of clopidogrel have been the subject of numerous reports over the last decade (Table 1) (1–24). The data on the association of smoking and platelet responsiveness to adenosine diphosphate-receptor blocking drugs like clopidogrel are inconsistent and controversial with studies variably showing: 1) no association; 2) a positive (higher on-treatment platelet reactivity in smokers) association; or 3) a negative (lower on-treatment platelet reactivity in smokers) association. Regarding the “negative association,” meaning lower on-treatment platelet reactivity or greater platelet suppression, this unexpected benefit of an enhanced clopidogrel effect was termed the “new smoker’s paradox.” Although a potential mechanism for such surprising results of a heightened antiplatelet drug effect among active smokers might be related to the induction of CYP1A2 and CYP2B6 activity by smoking (15,17,25,26), which in turn may accelerate the in vivo bioactivation of clopidogrel, numerous confounders may have influenced the results of the respective studies.

In this issue of JACC: Cardiovascular Interventions, Kim et al. (24) performed extensive analyses to examine whether the postulated association of smoking and an enhanced clopidogrel response is maintained after adjusting for patients’ hemoglobin levels. Focusing on hemoglobin levels seems intuitive, bearing in mind that active smokers are known to have higher hemoglobin levels (27) than non-smokers and also considering that higher hemoglobin or hematocrit levels are associated with lower platelet P2Y12 reaction units (PRU) when using the VerifyNow device (28). Indeed, in a study cohort of 1,314 clopidogrel-treated patients with recent percutaneous coronary intervention, the authors were able to confirm the known inverse correlation between PRU and hemoglobin levels (r = –0.389; p < 0.001).

Although unadjusted analyses showed lower PRU levels in current smokers versus nonsmokers (as prior studies had observed), after adjusting for hemoglobin levels, no difference in PRU levels remained between non-smokers and current-smokers (224.1 vs. 225.3, respectively; P adj = 0.813). Kim et al. (24) are to be commended for this important study, and the results lend support to the hypothesis that hemoglobin levels are a key driver for the observed ex-vivo phenomenon (new smoker’s paradox) of lower on-treatment platelet reactivity levels and/or an enhanced response to adenosine diphosphate inhibitors like clopidogrel in active smokers in most of the studies published so far. However, the following points are worth mentioning.

A major limitation of the study by Kim et al (24) is the lack of pharmacokinetic data on clopidogrel active metabolite generation among smokers versus non-smokers. It must be emphasized that most of the studies investigating the issue of smoking and drug response focused on pharmacodynamic testing with different platelet function assays. Pharmacokinetic
data were collected in the PARADOX (Influence of Smoking Status on Prasugrel and Clopidogrel Treated Subjects Taking Aspirin and Having Stable Coronary Artery Disease) study (17), a randomized, double-blind, crossover study among nonsmokers (n = 56) and smokers (n = 54). Although PARADOX showed lower clopidogrel active metabolite exposure in non-smokers versus smokers, the authors of that study were unable to show a significant relation between CYPIA2 activity and clopidogrel pharmacokinetics.

Additionally, the sample size of the study by Kim et al. (24) does not allow drawing meaningful conclusions on the influence of smoking on clinical outcome. In this respect it is reassuring to see that 2 large-scale, clinical trials (PLATO [PLATelet inhibition and patient Outcomes] and TRITON-TIMI 38 [A Comparison of Prasugrel (CS-747) and Clopidogrel in Acute Coronary Syndrome Subjects Who Are to Undergo Percutaneous Coronary Intervention-Thrombolysis In Myocardial Infarction 38]) (13,29) of contemporary antiplatelet treatment among ACS patients demonstrated a lack of interaction between smoking and clinical outcome when testing prasugrel or ticagrelor versus clopidogrel. Thus, although a minor impact of smoking may exist on the level of platelet inhibition, it is unlikely to confer a meaningful effect on clinical outcome.

Finally, in the present study, Kim et al. (24) focused their research solely on clopidogrel-treated patients, without validating their findings in patients treated with the novel potent P2Y<sub>12</sub> inhibitors prasugrel or ticagrelor. The recently published COPTER (Cigarette Smoking on Platelet Reactivity) study by Patti et al. (23), a prospective cross-over study, did evaluate the effects of smoking on platelet reactivity among smokers with recent percutaneous coronary intervention for ST-segment elevation myocardial infarction and chronic treatment with clopidogrel (n = 59), prasugrel (n = 71), or ticagrelor (n = 75). Interestingly,
Patti et al. (23) found a significant reduction of PRU values after a 15-day period of smoking cessation and a re-increase of platelet reactivity after a further 15 days of smoking resumption. These modest but significant variations were consistent across the 3 studied anti-platelet agents, and the results of the COPTER study when compared with the study by Kim et al. (24) emphasize the inconsistency that still exists in this field of research.

Several other unresolved issues remain, and further studies in larger cohorts treated with different P2Y₁₂ inhibitors are needed, ideally including pharmacokinetic, pharmacodynamic, and clinical outcome data. Despite the existing gaps in knowledge, the findings by Kim et al. (24) are important because they sound a note of caution toward a possible “benefit” of smoking on antiplatelet drug response, which was suggested by some prior studies.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Dirk Sibbing, Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 Munich, Germany. E-mail: dirk@sibbing.net

**REFERENCES**