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Smoking Interaction with Clopidogrel; Another Smoker's Paradox?

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The American Heart Association estimates that one in five deaths from cardiovascular disease are directly linked to cigarette smoking. Individuals who smoke are two to six times more likely to develop coronary artery disease than nonsmokers. However, individuals who quit smoking will reduce their risk to levels equivalent to those of a nonsmoker within three years.

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Exposure to cigarette smoke is an established risk factor for coronary heart disease in both Western and Asian countries. The multivariate relative risk of coronary heart disease mortality for current smokers was 1.8-3.7 compared to nonsmokers.¹⁾ Poor prognosis in smokers results from: 1) induction of hypercoagulability due to increased platelet activation, dyslipidemia, and endothelial dysfunction; 2) increased catecholamine release leading to increased heart rate, blood pressure, coronary vasoconstriction, and even arrhythmogenic effect; and 3) reduction in oxygen delivery due to increased carbon monoxide levels.²⁾

The term of "smoker's paradox" has been coined by Barbash et al.³⁾ who reported better outcomes among the smokers receiving thrombolytic therapy for acute myocardial infarction. Similarly, Cohen et al.⁴⁾ reported that cigarette smoking was associated with a lower rate of subsequent target lesion revascularization in patients undergoing percutaneous coronary intervention (PCI). Hasdai et al.⁵⁾ reported that current smokers during an

index percutaneous intervention had fewer adverse events in the univariable analysis than the nonsmokers and former smokers. This improved can be explained in part by better covariables such as younger age or a more favorable clinical and angiographic profile. Therefore, this term may be misleading.⁶⁾

Clopidogrel, an inhibitor of the platelet P2Y₁₂ adenosine diphosphate receptor, improves prognosis in patients with acute coronary syndrome (ACS). However, there is significant response variability and a diminished clopidogrel response is associated with an increased risk of ischemic events.⁷⁾ Smoking induces cytochrome P450 1A2 (CYP1A2), a hepatic enzyme involved in the metabolism of clopidogrel. Clopidogrel shows better inhibition of platelet aggregation in smokers than nonsmokers,⁸⁾ and smokers are less likely to be hyporesponders than nonsmokers.⁹⁾

In this issue of the Journal, Cho et al.¹⁰⁾ investigated the association between smoking status and post-clopidogrel platelet reactivity in patients with acute myocardial infarction. Differences in the clinical situation and timing of the platelet test could explain the differences with the Bliden study.⁸⁾ The decreases in CYP1A2 activity induced by smoking may also disappear after three days.

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial compared long-term clopidogrel 75 mg/day vs. placebo in patients at high risk for cardiovascular events, and clopidogrel significantly reduced mortality in smokers but not in former or never-smokers.¹¹⁾ In addition to CYP1A2 activation by smoking, smokers may simply be a higher-risk group because of enhanced platelet activity and therefore benefit more from antithrombotic intervention. The Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction 28 (CLARITY-TIMI 28) trial compared the effect of clopidogrel on angiographic and cli-

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nical outcomes in 3,429 ST elevation myocardial infarction patients by smoking intensity: not current smokers (n=1,732), and smokers of 1 to 9 (n=206), 10 to 19 (n=354), 20 to 29 (n=715), and ≥ 30 cigarettes/day (n=422). Clopidogrel reduced the primary end point of a closed infarct-related artery or death/myocardial infarction, particularly among those who smoked ≥ 10 cigarettes/day.¹²⁾ The CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions) trial, which tested high-dose vs. usual-dose clopidogrel in ACS patients undergoing PCI, showed that smokers (vs. nonsmokers) had significant benefit with the higher clopidogrel dose.

Smoking increases the risk for cardiovascular events and mortality in patients with established cardiovascular disease, but clopidogrel treatment may be more effective in smokers. Therefore, the interaction of smoking with acute myocardial infarction deserves further study in more patients using designs that show fewer time limitations.

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