EDITORIAL

Smoker's paradox: controversy remains

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The study by Bujak et al,[1] based on 3 large Polish registries of acute myocardial infarction (MI), addresses an important, clinically relevant, and undertreated risk factor in patients with ST-segment elevation MI (STEMI)—smoking, which is the leading factor negatively impacting outcomes of MI survivors.[2] Smoking cessation interventions are among the most cost-effective lifestyle modifications; nevertheless, a substantial number of patients with coronary artery disease continue to smoke.[3] The presented study was yet another attempt to refute the so-called "smoker's paradox." However, the interaction between smoking and MI seems to be more complex and equivocal than meets the eye.

Previous epidemiologic studies have shown that smokers generally have a worse long-term prognosis than nonsmokers. However, some researchers have suggested that active smokers achieve better cardiovascular outcomes during hospitalization and in short-term follow-up—a phenomenon referred to as the smoker's paradox.[4] It was observed for the first time among patients with acute coronary syndromes treated with fibrinolytic agents in the GUSTO I trial.[5] In that study, the rates of in-hospital and 30-day mortality were significantly higher among the nonsmokers than the smokers, even after adjustment for age and comorbidities. Most of the data regarding the influence of smoking on clinical outcomes in the percutaneous coronary intervention (PCI) era were derived from trials in patients treated with $P2Y_{12}$ inhibitors. The paradoxical short-term beneficial effect of smoking on the cardiovascular outcomes was demonstrated in landmark clinical trials that evaluated the efficacy of clopidogrel across the spectrum of coronary artery disease.[6] Lower platelet aggregation during clopidogrel treatment in the smokers, as compared with the nonsmokers, was reported in pharmacodynamic studies, which identified current smoking as an independent predictor of low platelet aggregation regardless of age, body mass index, and presence of diabetes.[6] That effect was further supported by the results of a prospective study involving patients with an objectively confirmed active smoking status, who were treated with clopidogrel. After quitting smoking, the participants exhibited a subsequent increase in platelet reactivity.[7] Such a paradox was not observed in the trials on the treatment with ticagrelor, prasugrel, or a double dose of clopidogrel.[8-10] In all previous studies, the paradoxical beneficial effect of smoking was only observed in the short-term follow-up.

The study by Bujak et al[1] included data of one of the largest cohorts of patients with STEMI treated with primary PCI. The risk factors that were previously observed in the smoking STEMI patients were analyzed in the study. The smokers were significantly younger and more frequently male. They also had a lower prevalence of multiple risk factors for MI, such as hypertension, diabetes, obesity, hypercholesterolemia, chronic kidney disease, previous coronary disease including MI, and interventional treatment. Moreover, the group of smokers was characterized by greater left ventricular ejection fraction, and less frequently presented with heart failure and a history of sudden cardiac arrest. Based on the previous studies, the lower all-cause mortality at 12 and 36 months observed among the smokers, as compared with the nonsmokers, was not surprising. However, after correcting for differences in patient characteristics, a multivariable analysis revealed that tobacco use was an independent risk factor for mortality at 36 months (hazard ratio, 1.11; 95% CI, 1.06–1.18; P <0.001).[1] Nevertheless, the data presented by Bujak et al[1] could not refute the existence of the smoker's paradox.

No previous studies have reported the long-term beneficial impact of smoking. The smoker's paradox was only observed in the short-term follow-up and during clopidogrel treatment. Despite a large amount of data analyzed by Bujak et al,[1] information was lacking on prehospital death, the proportion of patients treated with $P2Y_{12}$ inhibitors, clopidogrel, prasugrel and ticagrelor, as well as objective confirmation of smoking and smoking cessation, along with the number of patients who quit or continued smoking during the follow-up. Nevertheless, we

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Received: September 1, 2023.
Accepted: September 4, 2023.
Published online: September 29, 2023.
Pol Arch Intern Med. 2023; 133 (9): 16565
doi:10.20452/pamw.16565

agree with the authors that their study "undermines the myth of beneficial effects of smoking on the prognosis in STEMI patients, and hopefully will contribute to tackling one of the biggest public health threats, that is, widespread tobacco use." This interesting article definitely confirms that smoking is a significant risk factor for long-term mortality following STEMI. However, the issue regarding the short-term prognosis and the unequivocal presence of a pharmacodynamic smoker's paradox related to clopidogrel treatment remain subjects that warrant further investigation. Notably, the prevention of potentially paradoxical negative effects of smoking cessation on platelet function in patients treated with clopidogrel may be a goal of future clinical practice.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

HOW TO CITE Ramotowski B, Budaj A. Smoker's paradox: controversy remains. Pol Arch Intern Med. 2023; 133: 16565. doi:10.20452/pamw.16565

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