REVIEW ARTICLE

Smoking and cardiovascular diseases: paradox greater than expected?

Bogumił Ramotowski[1], Paul A. Gurbel[2], Udaya Tantry[3], Andrzej Budaj[1]

1 Department of Cardiology, Centre of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland
2 Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, Falls Church, Virginia, United States
3 Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, LifeBridge Health, Baltimore, Maryland, United States

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ABSTRACT

Cardiovascular diseases, including acute coronary syndromes, are a major cause of death among tobacco smokers. Epidemiological studies have demonstrated that long-term prognosis is worse in smokers with acute coronary syndromes than in nonsmokers. However, some studies have suggested that clopidogrel-treated active smokers have better in-hospital and short-term follow-up outcomes, a phenomenon regarded as the smoker's paradox. The smoker's paradox may be due to enhanced platelet response to clopidogrel therapy in active smokers as compared with nonsmokers caused by hepatic cytochrome P450 activation resulting in an increased generation of clopidogrel active metabolite. Another paradox has been reported after smoking cessation. Smoking cessation in clopidogrel-treated patients after percutaneous coronary intervention is associated with increased platelet reactivity and a greater risk of high platelet reactivity. The smoking cessation paradox may increase the risk of thrombotic complications in patients treated with clopidogrel. More potent $P2Y_{12}$ inhibitors may be considered in selected patients who stopped smoking after percutaneous coronary intervention. Further studies are required to determine the optimal antiplatelet strategy for stented patients who effectively quit smoking during clopidogrel treatment. The aim of this review is to discuss the risk of smoking and the potential elevated thrombotic risk related to smoking cessation.

Introduction Cardiovascular diseases (CVDs) account for 31% of all deaths, that is, 17.9 million deaths per year. Tobacco use is among the greatest risk factors for CVD and accounts for 1 in 4 deaths due to CVDs.[1,2] In addition, the 10-year risk of death is doubled in smokers compared with nonsmokers,[3] and smoking is the most important cause of premature death.[4] Apart from the cardiovascular system, smoking affects other systems including respiratory, digestive, endocrine, and genitourinary systems. Interventions to increase smoking cessation are among the most cost-effective lifestyle modifications. The aim of this review was to discuss the risk of smoking and the potential increase of thrombotic risk related to smoking cessation.

Smoking as a classic risk factor for cardiovascular diseases The prevalence of cigarette smoking in general population is decreasing[5] but smoking remains one of the most important modifiable risk factors in primary, secondary, and tertiary prevention of CVD. Smoking cessation in tertiary prevention is the most important single lifestyle intervention and its effect is stronger than lipid profile modification.[6] The devastating effect of tobacco smoke is related to a mixture of more than 7000 chemicals contributing to endothelial dysfunction, inflammation, dyslipidemia, vascular and hemodynamic function, and a prothrombotic state. Cigarette smoking influences all phases of atherosclerosis from endothelial dysfunction to the occurrence of acute coronary syndrome (ACS). Smoking induced activation of inflammation is characterized by increased plasma levels of fibrinogen, C-reactive protein, and interleukin 6.[6,7] In patients with ACS, smoking is associated with higher levels of inflammation markers and infarct zone hemorrhage.[8] Higher levels of homocysteine, tissue factor, and decreased activity of tissue plasminogen activator factor and matrix metalloproteinases were observed among

Correspondence to:
Bogumił Ramotowski, MD, PhD, Department of Cardiology, Centre of Postgraduate Medical Education, Grochowski Hospital, ul. Grenadierów 51/59, 04-073 Warszawa, Poland, phone: +48225152660, email: bramotowski@kkcmkp.pl
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TABLE 1 The smoker's paradox in patients with ST-segment elevation myocardial infarction treated with thrombolysis

Study	Follow-up	Patients, n	Current smokers, n	Former smokers, n	Never smokers, n	Adjusted mortality rates, OR (95% CI)
GUSTO-I[21]	30 d	40 599	17 507	11 117	11 975	1.25 (1.11–1.39)[a]
Barbash et al[22]	6 mo	8259	3649	2244	2366	1.35 (1.12–1.61)[b]

Smoking status was based on patient's declaration.

a Never vs current smokers

b Never vs current + former smokers

Abbreviations: CI, confidence interval; GUSTO-I, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction

smokers.[9] Decreased vasodilatation[10] and diminished nitric oxide bioavailability were also observed in smokers.[11] Other risk factors influenced by smoking are an increase in total cholesterol, decrease in high density cholesterol, and increased insulin resistance.[12] The tobacco-induced hemodynamic changes are mediated mainly by nicotine.

Smoking is the second leading risk factor for myocardial infarction (MI) (odds ratio, 2.87; 95% confidence interval, 2.58–3.19).[13] Even the lowest exposure to smoking with only 1 cigarette daily can drastically increase the risk of coronary artery disease and stroke to about 50% of the risk of smoking 20 cigarettes a day.[14] Even those smoking 1 to 10 cigarettes daily have higher mortality rates and would potentially benefit from smoking cessation.[15] Additionally, passive smoking is related to a higher risk of CVD.[16] However, the harmful effect of smoking is reversible. A significant decrease in cardiovascular risk was observed during the first 2 years after smoking cessation, and after 5 years, inflammation markers normalized.[17] After smoking cessation in patients with CVD, the risk of death was reduced by more than 30%.[18]

Smoker's paradox in the era of fibrinolytic therapy

Although cigarette smoking has been related to poorer long-term prognosis among patients with CVD, the short-term prognosis for smokers as compared with nonsmokers after ACS remains unclear.[19,20] Although epidemiological studies have proven that long-term prognosis in smokers is worse than in nonsmokers, some studies have suggested that active smokers exhibit better in-hospital and short-term follow-up outcomes—a phenomenon called the smoker's paradox[19] (TABLE 1). The potential smoker's paradox was firstly noted in patients with ACS treated with fibrinolytic agents in the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial. Nonsmokers had significantly higher rates of in-hospital and 30-day mortality compared with smokers.[21] However, smokers tended to be younger and had less comorbidities. The rate of prehospital mortality among smokers and nonsmokers is also not known. However, data remained favorable for smoking, even after adjustment for age, gender, and comorbidities. In another retrospective analysis, this protective effect of smoking expanded beyond 6 months of follow-up and was also preserved at 12 months, an observation that may have been affected by lower comorbidities, including diabetes mellitus and heart failure.[22]

Beyond more favorable risk profile with less comorbidities and younger age, the underlying pathophysiology of a potential cardiovascular protective effect of smoking remains unclear. One of the hypotheses addresses the pathophysiology of thrombosis in smokers. Cigarette smoking alters hemostasis and involves multiple mechanisms including changes in endothelial function, platelet activation, and factors influencing activation of pro- and antifibrinolytic systems. Fibrinogen levels are higher in smokers[23] and smokers exhibited increased clot formation and strength, had denser clots and altered fibrin architecture[24] with thinner fibers.[25] Opposing theories have been postulated of enhanced or lowered sensitivity to fibrinolytic agents. It has been reported that smokers may have less severe stenosis and, therefore, better outcomes after thrombolysis.[26] However, thinner fibers and denser clots among smokers may be more resistant to fibrinolytic agents, such as plasminogen activator factor.[25]

Smoker's paradox in the era of percutaneous coronary interventions

The majority of data regarding the influence of smoking on clinical outcomes in the era of percutaneous coronary intervention (PCI) are derived from trials with patients treated also with $P2Y_{12}$ inhibitors. However, the smoker's paradox was not observed in trials in patients treated with early PCI, which excluded patients treated with clopidogrel.[27] Little is known about smoking patients treated with ticlopidine. In the CADILLAC (Controlled Abcximab and Device Investigation to Lower Late Angioplasty Complications) trial, patients with ST-segment elevation myocardial infarction (STEMI) treated with ticlopidine were randomized to angioplasty or stenting with or without abcximab.[28] Despite high proportion of smoking patients (40%) no substantial differences in clinical outcomes were observed with regard to smoking status. The paradoxical effect of smoking on cardiovascular outcomes has been demonstrated in the landmark clinical trials evaluating the efficacy of clopidogrel across the spectrum of coronary artery disease.[29] After careful analysis of large

TABLE 2 The smoker's paradox in patients treated with clopidogrel

Study	Group of patients	Follow-up	Patients, n	Current smokers, n[a]	Former smokers, n[a]	Never smokers, n[a]	Primary clinical outcome	$P_{interaction}$ value
CAPRIE[60]	ACS, stroke PAD	1 to 3 y	19 185	5688	–	4135	Reduction in primary outcome: HR, 0.76 in clopidogrel-treated smokers vs HR, 0.99 in nonsmokers/ex-smokers	0.01
CLARITY TIMI 28[61]	STEMI	30 d	3429	1697	–	1732 (not current smoker)	OR, 0.49 in patients smoking ≥10 cigarettes/d vs OR, 0.72 in patients smoking <10 cigarettes/d	0.0004
CHARISMA[62]	CAD, PAD, cerebral artery disease	28 mo	12 152	2419	6260	3473	All cause mortality in clopidogrel-treated patients: HR, 0.68 in current smokers vs HR, 0.95 in former smokers vs HR, 1.14 in never smokers	0.018
CURRENT PCI[63]	ACS	30 d	17 263	6394	–	10 862	HR, 0.66 in smokers treated with double-dose clopidogrel vs H, 0.96 in smokers treated with standard-dose clopidogrel	0.031

Smoking status was based on patient's declaration.

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; HR, hazard ratio; OR, odds ratio; PAD, peripheral artery disease; others, see **TABLE 1**

trials on PCI in ACS with clopidogrel, a new smoker's paradox became apparent where the short-term prognosis for smokers treated with clopidogrel was better than nonsmokers[29] (**TABLE 2**). A retrospective analysis of landmark large randomized multicenter trials included the following studies: the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction 28) study on patients with STEMI, the CURE-OASIS 4 (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study on patients with non–ST-segment elevation myocardial infarction, the CURRENT PCI-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events / Optimal Antiplatelet Strategy for Interventions) study on patients with ACS, or trials which included both patients with or without ACS such as the CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) study including patients with ACS, stroke, peripheral artery disease, the CREDO (Clopidogrel for the Reduction of Events During Observation) study on patients with coronary artery disease (CAD), the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) study on patients with CAD, PAD, and cerebral arteries disease.[30] The study strongly suggested that the beneficial effect of clopidogrel as compared with placebo or high dose clopidogrel as compared with standard clopidogrel (eg, CURRENT PCI-OASIS 7) was confined to smokers. This phenomenon can be regarded as a clinical smoker's paradox.[30] A pharmacodynamic smoker's paradox was first reported by Bliden et al[29] in patients undergoing PCI who were treated with clopidogrel. Current smokers on long-term clopidogrel therapy displayed significantly lower platelet aggregation and ADP-stimulated active glycoprotein IIb/IIIa expression compared with nonsmokers ($P \leq 0.0008$ for both). Similarly, current smokers treated with 600 mg of clopidogrel displayed greater platelet inhibition and lower active GP IIb/IIIa expression compared with nonsmokers ($P \leq 0.05$). In a multivariate Cox regression analysis, current smoking was an independent predictor of low platelet aggregation ($P = 0.0001$). This effect of post-treatment platelet aggregation in smokers on clopidogrel therapy was observed regardless of age, body mass index, and diabetes.[29] The impact of smoking on platelet function appeared to be dose-responsive. The analysis of variance in patients on long-term clopidogrel therapy demonstrated significantly lower 5 µmol/l and 20 µmol/l ADP-induced platelet aggregation in patients currently smoking at least half a pack per day compared with nonsmokers and patients currently smoking less than half a pack per day ($P < 0.05$).[31]

Early after the approval of clopidogrel, it appeared that approximately 30% of patients were resistant to and were at increased risk for recurrent thrombotic events.[32,33] Clopidogrel is a prodrug that requires 2-step metabolism involving liver enzymes to be converted to an active metabolite. Several cytochromes are involved in clopidogrel metabolism: *CYP2C19, CYP3A4/5, CYP1A2, CYP2B6*, and *CYP2C9*.[34] The *CYP2C19*

loss-of-function (LoF) allele has been linked to high platelet reactivity (HPR) during clopidogrel therapy. Patients carrying a *CYP2C19* LoF allele who had been stented and were treated with aspirin and clopidogrel had higher overall platelet reactivity and a greater frequency of HPR compared with wild type.[35]

In a genome wide association study carriage of a LoF was linked to higher platelet reactivity and greater post-PCI ischemic events.[33,36]

In the prospective PARADOX study,[37] the effect of smoking status on the pharmacokinetics and pharmacodynamics of clopidogrel and prasugrel was explored, and a greater antiplatelet effect of clopidogrel was observed in smokers than in nonsmokers. The PARADOX trial was the first prospective study to demonstrate greater platelet inhibition by clopidogrel in smokers who were actively smoking, which was determined by measurement of cotinine. It has been shown that cigarette smoking increases hepatic *CYP1A2* activity.[38] The PARADOX study also demonstrated lower clopidogrel active metabolite exposure of clopidogrel in nonsmokers relative to smokers. Prasugrel was associated with greater active metabolite exposure and pharmacodynamic effects than clopidogrel regardless of smoking status. Park et al[39] analyzed 9 single-nucleotide polymorphisms and found an enhanced clopidogrel effect only among smokers who were *CYP1A2* AA allele carriers.

Trials evaluating more potent oral $P2Y_{12}$ inhibitors than clopidogrel in patients with ACS have exposed another explanation for the smoker's paradox beyond enhanced clopidogrel active metabolite exposure and pharmacodynamic efficacy in smokers. Treatment with prasugrel versus clopidogrel was associated with a reduction in the occurrence of thrombotic events in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) trial in patients with ACS undergoing PCI. In a subanalysis, prasugrel therapy was associated with fewer events regardless of smoking status. However, a numerically greater treatment effect was observed in smokers. In the TRITON-TIMI 38 trial, smoking status was not well quantified, being only reported as "tobacco use," which does not allow to determine whether smoking was ongoing and what its extent was. "Prior use" and "never used" were combined into 1 group.[40] Ticagrelor was compared to clopidogrel in the PLATO (Platelet Inhibition and Patients Outcomes) trial and a greater treatment effect of ticagrelor was suggested in smokers compared with nonsmokers. As compared with the TRITON-TIMI 38 study, smoking was defined as "habitual" if patients smoked 1 cigarette, cigars, or equivalent tobacco per day. Ex-smokers were defined as those who smoked and stopped more than 1 month earlier or if they smoked less than one cigarette, cigar, or equivalent tobacco per day. Patients were defined as nonsmokers if they did not smoke currently or previously.[41] In the PLATO analysis of smoking effect, ex-smokers and nonsmokers were combined. Ticagrelor significantly reduced ischemic events irrespective of smoking status with a numerically greater benefit suggested in smokers where the adjusted hazard ratio of 0.83 was observed in habitual smokers and 0.89 in ex/nonsmokers for the primary endpoint; 0.77 and 0.89, respectively, for all cause death; 0.76 and 0.87, respectively for vascular death and MI; and 0.65 and 0.81, respectively for any stent thrombosis.[41] In the TRILOGY ACS (Spontaneous MI After Non-ST Segment Elevation Acute Coronary Syndrome Managed Without Revascularization) trial in medically managed patients with ACS, ischemic events did not differ between prasugrel and clopidogrel. However, a significant treatment benefit was observed from more potent $P2Y_{12}$ blockade in smokers than in nonsmokers. In the TRILOGY trial, current smoking was defined as smoking 1 cigarette per day or stopped within last month, ex-smoking if stopped more than 1 month earlier; and nonsmoking if not smoking either currently or previously. There was a nearly 50% reduction in the occurrence of the primary endpoint with prasugrel compared with clopidogrel in smokers, whereas no difference was observed in nonsmokers (hazard ratio [HR], 0.54 and HR, 1.06, respectively; $P_{\text{interaction}} = 0.0002$). Similar findings in smokers and nonsmokers were observed for cardiovascular death (HR, 0.48 and HR, 1.12, respectively; $P_{\text{interaction}} = 0.0018$), and for MI (HR, 0.62 and HR, 0.98, respectively; $P_{\text{interaction}} = 0.0403$).[42] In a meta-analysis derived from the data of the TRITON-TIMI 38 and TRILOGY trials, a positive effect of prasugrel treatment was seen only among smokers.[43]

Although a greater treatment effect of the new oral $P2Y_{12}$ inhibitors as compared with clopidogrel may have been expected in nonsmokers since the antiplatelet effects of new agents do not appear to be influenced by smoking, the opposite was observed. Therefore, the findings suggesting greater clinical efficacy in smokers in these 3 trials cannot be explained by a greater difference in pharmacodynamics between clopidogrel and its comparator. Moreover, the greater treatment effect of more potent platelet inhibitors in smokers is not explained by greater thrombotic risk in smokers. Earlier trials have reported variable thrombotic event rates in smokers relative to nonsmokers treated with aspirin alone.[30] Thus, in addition to enhancing clopidogrel active metabolite generation, it has been hypothesized that smoking creates a vascular disease state that is more responsive to $P2Y_{12}$ inhibition and that differs from nonsmokers. A cumulative body of research indicates that the pathobiology of thrombosis differs between smokers and nonsmokers and that this fundamental difference may affect the clinical response to specific antithrombotic agents as observed in clinical trials.[19]

Despite the widely documented enhanced treatment effect of active smoking in clopidogrel-treated patients observed in large scale trials, data on the impact of smoking cessation are scarce,[44] and most data on tobacco use, as noted above, were ascertained by self-reporting.[45,46]

Smoking cessation paradox The adverse effect of smoking on cardiovascular outcomes is well-documented. Smoking is related to thromboembolic events in patients with CAD; however, in clopidogrel-treated patients, the effect of smoking remains less clear. Previous studies have repeatedly shown that smoking is associated with enhanced antiplatelet effects of clopidogrel.[31,37] A reduction in platelet inhibition by clopidogrel may therefore occur after smoking cessation and is supported by Park et al[45] who reported in the CROSS-VERIFY (Measuring Clopidogrel Resistance to Assure Safety after PCI using VerifyNow) Asian cohort that there was an increase of 20 platelet reactivity units (PRUs) and a higher frequency of HPR after smoking cessation. In the study by Park et al,[45] smoking status was ascertained by a participant self-report and was not verified by a biomarker, such as the measurement of urine cotinine concentration. Urine cotinine concentration has been reported to be a stronger predictor of cardiovascular risk than self-reporting of smoking cessation.[47]

In most large randomized trials that assessed the clinical efficacy of clopidogrel, smoking was assessed only at baseline, and the proportion of patients who stopped smoking while on clopidogrel treatment was unknown.[48,49] An increase in platelet reactivity in this patient group might influence clinical outcomes and smoking cessation was also related to an increased frequency of HPR.[45] A prospective study of the effect of objectively confirmed smoking cessation on platelet reactivity in clopidogrel-treated patients has recently been completed.[50] In a study by Ramotowski et al,[50] multivariable regression analysis demonstrated that smoking cessation is the most important independent risk factor for HPR. It strongly supports the theory about the increase in the frequency of HPR following smoking cessation. Interesting relation linking smoking cessation and *CYP2C19* LoF was observed in which LoF carriers who stopped smoking had the highest PRUs, whereas those with the wild type who continued smoking had the lowest PRUs. *CYP2C19*2* LoF was associated with a lower level of platelet inhibition among smokers. This is consistent with previous studies, which showed that the *CYP2C19* LoF allele was the most prominent genetic variation attenuating the clopidogrel effect.[51] Smoking cessation influenced another factor related to the diminished effect of clopidogrel, which might be contributed to the clinical outcomes. The devastating nature of smoking seems to be prolonged even after cessation of active habit due to increased platelet reactivity.

How to deal with the smoking cessation paradox? There is still lack of clinical data with hard endpoints regarding the relevance of smoking cessation in patients treated with clopidogrel. It can be hypothesized that these patients may be at a paradoxically higher risk of cardiovascular events due to increased platelet aggregation. It has been reported that even a small increase in platelet activity alters clinical outcomes.[52] Changes similar to those observed in platelet function after smoking cessation have been linked to an increase in periprocedural MI,[53] and HPR is an independent predictor of early stent thrombosis.[54] The current evidence suggests that the potential modest increase in platelet reactivity observed in patients treated with clopidogrel who stopped smoking may have clinical relevance. To overcome the risk of higher platelet reactivity, treatment with an increased dose of clopidogrel may be considered. In the GRAVITAS (Gauging Responsiveness With A Verify-Now Assay—Impact on Thrombosis and Safety) trial, patients with high on-clopidogrel platelet reactivity were randomized to either standard (75 mg) or double dose of clopidogrel (150 mg).[55] In the platelet substudy of the GRAVITAS trial, the difference in platelet aggregation between smokers and nonsmokers treated with clopidogrel was observed only in patients treated with standard doses of clopidogrel, not in those treated with double doses.[56] In the CURRENT PCI-OASIS 7 trial investigating double as compared with standard doses of clopidogrel in patients early after ACS, double-dose clopidogrel reduced the primary outcome by 34%, whereas the benefit was not seen among nonsmokers.[57] This finding supports the potential use of the double dose of clopidogrel following smoking cessation. The direct-acting $P2Y_{12}$ inhibitor, ticagrelor should be preferentially used in all patients with ACS unless contraindicated according to the European Society of Cardiology guidelines. As a direct-acting agent, ticagrelor may overcome a potential smoking cessation paradox in patients with ACS. Another option to consider would be treatment with prasugrel, a thienopyridine that is metabolized in a 1-step metabolic pathway, and whose pharmacodynamics effect is independent of smoking status.[37] Switching to prasugrel may decrease the periprocedural injury also in patients with stable CAD.[58] The systemic exposure to prasugrel metabolite has been reported not to be affected by smoking status.[59]

Conclusions Smoking cessation is the most important single intervention reducing thrombotic complications in primary, secondary, and tertiary prevention of CAD. There is no doubt that all smoking patients after PCI should be encouraged to stop smoking. But this group of patients requires particular attention. Paradoxically, a large body of evidence has demonstrated that smoking enhanced the pharmacodynamic and clinical effects of clopidogrel. Therefore, cessation of smoking in clopidogrel-treated patients after PCI may

be associated with a negative influence on pharmacodynamic and short-term clinical outcomes. Awareness of this interesting paradox has stimulated further investigations of the effects of smoking cessation on the pharmacokinetics and pharmacodynamics of clopidogrel in stented patients. The results of these studies will assist in determining whether more potent $P2Y_{12}$ inhibition should be considered in these patients.

ARTICLE INFORMATION

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REFERENCES

1 World Heart Day. World Health Organization. https://www.who.int/cardiovascular_diseases/world-heart-day/en/. Accessed June 1, 2019.

2 Smoking and cardiovascular disease. Centers for Disease Control and Prevention. https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/pdfs/fs_smoking_CVD_508.pdf. Accessed June 1, 2019.

3 Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003; 24: 987-1003.

4 Jha P. Avoidable global cancer deaths and total deaths from smoking. Nat Rev Cancer. 2009; 9: 655-664.

5 Polakowska M, Kaleta D, Piotrowski W, et al. Tobacco smoking in Poland in the years from 2003 to 2014. Multicentre National Population Health Examination Survey (WOBASZ). Pol Arch Intern Med. 2017; 127: 91-99.

6 Erhardt L. Cigarette smoking: an undertreated risk factor for cardiovascular disease. Atherosclerosis. 2009; 205: 23-32.

7 Sunyer J, Forastiere F, Pekkanen J, et al. Interaction between smoking and the interleukin-6 gene affects systemic levels of inflammatory biomarkers. Nicotine Tob Res. 2009; 11: 1347-1353.

8 Haig C, Carrick D, Carberry J, et al. Current smoking and prognosis after acute ST-segment elevation myocardial infarction: new pathophysiological insights. JACC Cardiovasc Imaging. 2018; 12: 993-1003. [Epub ahead of print].

9 Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis. 2003; 46: 91-111.

10 Zeiher AM, Schachinger V, Minners J. Long-term cigarette smoking impairs endothelium-dependent coronary arterial vasodilator function. Circulation. 1995; 92: 1094-1100.

11 Barua RS, Ambrose JA, Eales-Reynolds LJ, et al. Dysfunctional endothelial nitric oxide biosynthesis in healthy smokers with impaired endothelium-dependent vasodilatation. Circulation. 2001; 104: 1905-1910.

12 Salahuddin S, Prabhakaran D, Roy A. Pathophysiological mechanisms of tobacco-related CVD. Glob Heart. 2012; 7: 113-120.

13 Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364: 937-952.

14 Hackshaw A, Morris JK, Boniface S, et al. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018; 360: j5855.

15 Inoue-Choi M, Liao LM, Reyes-Guzman C, et al. Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health-AARP Diet and Health Study. JAMA Intern Med. 2017; 177: 87-95.

16 Heidrich J, Wellmann J, Heuschmann PU, et al. Mortality and morbidity from coronary heart disease attributable to passive smoking. Eur Heart J. 2007; 28: 2498-2502.

17 Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. PLoS Med. 2005; 2: e160.

18 Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA. 2003; 290: 86-97.

19 Gurbel PA, Baker BA, Bailey WL, et al. Unravelling the smokers' paradox: cigarette smoking, high-risk coronary artery disease and enhanced clinical efficacy of oral $P2Y_{12}$ inhibitors. Thromb Haemost. 2014; 11: 1187-1190.

20 Swiger KJ, Yousuf O, Bliden KP, et al. Cigarette smoking and clopidogrel interaction. Curr Cardiol Rep. 2013; 15: 361.

21 Barbash GI, Reiner J, White HD, et al. Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol. 1995; 26: 1222-1229.

22 Barbash GI, White HD, Modan M, et al. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. Circulation. 1993; 87: 53-58.

23 Dotevall A, Johansson S, Wilhelmsen L. Association between fibrinogen and other risk factors for cardiovascular disease in men and women. Results from the Göteborg MONICA survey 1985. Ann Epidemiol. 1994; 4: 369-374.

24 Barua RS, Sy F, Srikanth S, et al. Effects of cigarette smoke exposure on clot dynamics and fibrin structure: an ex vivo investigation. Arterioscler Thromb Vasc Biol. 2010; 30: 75-79.

25 Barua RS, Sy F, Srikanth S, et al. Acute cigarette smoke exposure reduces clot lysis -association between altered fibrin architecture and the response to t-PA. Thromb Res. 2010; 126: 426-430.

26 Grines CL, Topol EJ, O'Neill WW, et al. Effect of cigarette smoking on outcome after thrombolytic therapy for myocardial infarction. Circulation. 1995; 91: 298-303.

27 Aune E, Røislien J, Mathisen M, et al. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. BMC Med. 2011; 9: 97.

28 Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med. 2002; 346: 957-966.

29 Bliden KP, Dichiara J, Lawal L, et al. The association of cigarette smoking with enhanced platelet inhibition by clopidogrel. J Am Coll Cardiol. 2008; 52: 531-533.

30 Gurbel PA, Nolin TD, Tantry US. Clopidogrel efficacy and cigarette smoking status. JAMA. 2012; 307: 2495-2496.

31 Ueno M, Ferreiro JL, Desai B, et al. Cigarette smoking is associated with a dose-response effect in clopidogrel-treated patients with diabetes mellitus and coronary artery disease: results of a pharmacodynamic study. JACC Cardiovasc Interv. 2012; 5: 293-300.

32 Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004; 109: 3171-3175.

33 Tantry US, Navarese EP, Bliden KP, et al. Acetylsalicylic acid and clopidogrel hyporesponsiveness following acute coronary syndromes. Kardiol Pol. 2018; 76: 1312-1319.

34 Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos. 2010; 38: 92-99.

35 Gurbel PA, Shuldiner AR, Bliden KP, et al. The relation between CYP2C19 genotype and phenotype in stented patients on maintenance dual antiplatelet therapy. Am Heart J. 2011; 161: 598-604.

36 Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA. 2009; 302: 849-857.

37 Gurbel PA, Bliden KP, Logan DK, et al. The influence of smoking status on the pharmacokinetics and pharmacodynamics of clopidogrel and prasugrel: the PARADOX Study. J Am Coll Cardiol. 2013; 62: 505-512.

38 Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. Clin Pharmacokinet. 1999; 36: 425-438.

39 Park KW, Park JJ, Jeon KH, et al. Enhanced clopidogrel responsiveness in smokers: smokers' paradox is dependent on cytochrome P450 CYP1A2 status. Arterioscler Thromb Vasc Biol. 2011; 31: 665-671.

40 Hochholzer W, Trenk D, Mega JL, et al. Impact of smoking on antiplatelet effect of clopidogrel and prasugrel after loading dose and on maintenance therapy. Am Heart J. 2011; 162: 518-526.e5.

41 Cornel JH, Becker RC, Goodman SG, et al. Prior smoking status, clinical outcomes, and the comparison of ticagrelor with clopidogrel in acute coronary syndromes-insights from the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J. 2012; 164: 334-342.e1.

42 Cornel JH, Ohman EM, Neely B, et al. Impact of smoking status on platelet function and clinical outcomes with prasugrel vs. clopidogrel in patients with acute coronary syndromes managed without revascularization: insights from the TRILOGY ACS trial. Am Heart J. 2014; 168: 76-87.e1.

43 Ye Y, Xie H, Zhao X, Zhang S. Smoking and prasugrel. Int J Cardiol. 2013; 168: 1590-1591.

44 Patti G, Polacco M, Taurino E, et al. Effects of cigarette smoking on platelet reactivity during P2Y12 inhibition in patients with myocardial infarction undergoing drug-eluting stent implantation: results from the prospective cigarette smoking on platelet reactivity (COPTER) study. J Thromb Thrombolysis. 2016; 41: 648-653.

45 Park KW, Kang SH, Kang J, et al. Enhanced clopidogrel response in smokers is reversed after discontinuation as assessed by VerifyNow assay: additional evidence for the concept of "smokers' paradox". Heart. 2012; 98: 1000-1006.

46 Park MB, Kim CB, Nam EW, Hong KS. Does South Korea have hidden female smokers: discrepancies in smoking rates between self-reports and urinary cotinine level. BMC Womens Health. 2014; 14: 156.

47 Kunutsor SK, Spee JM, Kieneker LM, et al. Self-reported smoking, urine cotinine, and risk of cardiovascular disease: findings from the PREVEND (Prevention of Renal and Vascular End-Stage Disease) prospective cohort study. J Am Heart Assoc. 2018; 7: e008726.

48 Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345: 494-502.

49 Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006; 354: 1706-1717.

50 Ramotowski B, Witowicz A, Bracha J, Budaj A. Impact of smoking cessation on platelet aggregation in clopidogrel-treated patients after PCI. Eur Heart J. 2017; 38 (suppl 1): ehx504.P4430.

51 Sibbing D, Bernlochner I, Kastrati A, et al. Current evidence for genetic testing in clopidogrel-treated patients undergoing coronary stenting. Circ Cardiovasc Interv. 2011; 4: 505-513.

52 Brar SS, ten Berg J, Marcucci R, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. J Am Coll Cardiol. 2011; 58: 1945-1954.

53 Mangiacapra F, Patti G, Peace A, et al. Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. Am J Cardiol. 2010; 106: 619-623.

54 Geisler T, Zurn C, Simonenko R, et al. Early but not late stent thrombosis is influenced by residual platelet aggregation in patients undergoing coronary interventions. Eur Heart J. 2010; 31: 59-66.

55 Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA. 2011; 305: 1097-1105.

56 Reed GW, Cannon CP, Waalen J, et al. Influence of smoking on the antiplatelet effect of clopidogrel differs according to clopidogrel dose: insights from the GRAVITAS trial. Catheter Cardiovasc Interv. 2017; 89: 190-198.

57 Bossard M, Granger CB, Tanguay JF, et al. Double-dose versus standard-dose clopidogrel according to smoking status among patients with acute coronary syndromes undergoing percutaneous coronary intervention. J Am Heart Assoc. 2017; 6: e006577.

58 Tomaniak M, Kołtowski L, Kochman J, et al. Can prasugrel decrease the extent of periprocedural myocardial injury during elective percutaneous coronary intervention? Pol Arch Intern Med. 2017; 127: 730-740.

59 Wrishko RE, Ernest CS 2nd, Small DS, et al. Population pharmacokinetic analyses to evaluate the influence of intrinsic and extrinsic factors on exposure of prasugrel active metabolite in TRITON-TIMI 38. J Clin Pharmacol. 2009; 49: 984-998.

60 Ferreiro JL, Bhatt DL, Ueno M, et al. Impact of smoking on long-term outcomes in patients with atherosclerotic vascular disease treated with aspirin or clopidogrel: insights from the CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events). J Am Coll Cardiol. 2014; 63: 769-77.

61 Desai NR, Mega JL, Jiang S, et al. Interaction between cigarette smoking and clinical benefit of clopidogrel. J Am Coll Cardiol. 2009; 53: 1273-1278.

62 Berger JS, Bhatt DL, Steinhubl SR, et al. Smoking, clopidogrel, and mortality in patients with established cardiovascular disease. Circulation. 2009; 120: 2337-2344.

63 Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet. 2010; 376: 1233-1243.