Smoking and cardiovascular diseases – is there more paradox than expected?

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Smoking and cardiovascular diseases – is there more paradox than expected?

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Brief title: Smoking cessation paradox

Keywords: clopidogrel, P2Y₁₂ receptor, platelet reactivity, smoking, smoking cessation, smokers’ paradox
Abstract

Cardiovascular diseases, including acute coronary syndromes (ACS), are a major cause of death among tobacco smokers. Epidemiological studies have demonstrated that long-term prognosis is worse in smokers with ACS than in non-smokers. 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 “smokers’ paradox”. The smokers’ paradox may be due to enhanced platelet response to clopidogrel therapy in active smokers versus non-smokers caused by hepatic cytochrome P450 activation resulting in increased clopidogrel active metabolite generation. Another paradox has been reported after smoking cessation. Smoking cessation in clopidogrel-treated patients after percutaneous coronary intervention (PCI) 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 clopidogrel-treated patients. More potent P2Y₁₂ inhibitors may be considered in selected patients who stop smoking after PCI. 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 heightening of thrombotic risk related to smoking cessation.
Abbreviations

ACS – acute coronary syndrome

PCI – percutaneous coronary intervention

PRU – platelet reactivity unit

HPR – high platelet reactivity

CYP – cytochrome

LoF – loss-of-function

STEMI – ST-elevation myocardial infarction

NSTEMI – non-ST-elevation myocardial infarction

PAD – peripheral artery disease
Introduction

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

Smoking as a classical cardiovascular risk factor

The prevalence of cigarette smoking in general population is decreasing [5] but still smoking is 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, dyslipidaemia, vascular and haemodynamic 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 haemorrhage [8]. Higher levels of homocysteine, tissue factor (TF), and decreased tissue plasminogen activator factor (tPA) activity and matrix metalloproteinases were observed among 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 haemodynamic changes are mediated mainly by nicotine.

Smoking is the second leading factor that influences the risk of myocardial infarction (MI) (OR 2.87 [2.58-3.19]) [13]. Even the lowest exposure to smoking with only one 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 one to 10 cigarettes daily have higher mortality 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 two 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].

**Smokers’ 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 versus non-smokers after ACS remains unclear [19,20]. Although epidemiological studies have proven that long-term prognosis in smokers is worse than that in non-smokers, some studies have suggested that active smokers exhibit better in-hospital and short-term follow-up outcomes - a phenomenon called the “smokers’ paradox” [19] (Table 1). The first information about a potential smokers’ paradox was noted in patients with ACS treated with fibrinolytic agents in the GUSTO I trial. Non-smokers 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 deaths among smokers and non-smokers is also not known. However, the data
remained favourable for smoking, even after adjustment for age, gender and comorbidities. In another retrospective analysis, this protective effect of smoking expanded beyond 6 months of observation and was also preserved at 12-month, an observation that may have been affected by lower comorbidities, including diabetes mellitus and heart failure [22].

Beyond more favourable 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 heightened clot formation and strength, and had denser clots, and altered fibrin architecture [24] with thinner fibres [25]. Opposing theories have been postulated of enhanced or lowered sensitivity to the effect of fibrinolytic agents. It has been reported that smokers may have less severe stenosis and therefore, a better outcome after thrombolysis. [26]. However, thinner fibres and denser clots among smokers may be more resistant to fibrinolytic agents, such as t-PA [25].

**Smokers’ paradox in the era of percutaneous coronary interventions (PCI)**

The majority of data regarding influence of smoking on clinical outcomes in the PCI era are derived from trials with patients treated also with P2Y_{12} inhibitors. However, a smokers’ paradox was not observed in trials in patients treated with early PCI, which excluded patients treated with clopidogrel [27]. There are occasional information in patients treated with ticlopidine. In CADILLAC trial patients with ST-elevation myocardial infarction (STEMI) treated with ticlopidine were randomized to angioplasty or stenting with or without abciximab [28]. Despite high proportion of smoking patients (40%) no substantial differences in clinical
outcomes were observed regarding 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 trials on PCI in ACS with clopidogrel, a new smokers’ paradox became apparent where the short-term prognosis for clopidogrel-treated smokers was better than non-smokers [29] (Table 2). A retrospective analysis of landmark large randomized multicentre trials including CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction 28) with ST-elevation myocardial infarction (STEMI) patients, CURE-OASIS 4 (Clopidogrel in Unstable Angina to Prevent Recurrent Events) non ST- elevation myocardial infarction (NSTEMI) patients, CURRENT PCI-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions) ACS patients, or trials which included both ACS or non-ACS patients such as CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) including ACS, stroke, peripheral artery disease (PAD) patients, CREDO (Clopidogrel for the Reduction of Events During Observation) patients with coronary artery disease (CAD), CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) CAD, PAD and cerebral arteries disease patients, strongly suggested that the beneficial effect of clopidogrel vs placebo or high dose clopidogrel vs. standard clopidogrel (e.g. CURRENT PCI-OASIS 7) was confined to smokers. This phenomenon can be regarded as a clinical smokers’ paradox [30]. A pharmacodynamic smokers’ paradox was first reported by Bliden et al. in 2008 in patients undergoing PCI who were treated with clopidogrel. Current smokers on chronic clopidogrel therapy displayed significantly lower platelet aggregation and ADP-stimulated active GP IIb/IIIa expression compared with non-smokers (p ≤ 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 non-smokers (p ≤ = 0.05). In a multivariate Cox regression analysis, current smoking was an independent predictor of low platelet aggregation (p = 0.0001). This effect of smoking of post-treatment platelet aggregation on clopidogrel therapy was observed regardless of age, body mass index, and diabetes [29]. The impact of smoking on platelet function appeared dose-responsive. An analysis of variance in patients on chronic clopidogrel therapy demonstrated significantly lower 5 μmol/l and 20 μmol/l ADP-induced platelet aggregation in patients currently smoking ≥1/2 pack/day compared with non-smokers and patients currently smoking <1/2 pack/day (p < 0.05) [31].

Early after the approval of clopidogrel, it appeared that ~ 30% of patients were resistant to and were at increased risk for recurrent thrombotic events [32,33]. Clopidogrel is a prodrug, that requires hepatic two step metabolism for conversion to an active metabolite. Several cytochromes are involved in clopidogrel metabolism: CYP2C19, CYP3A4/5, CYP1A2, CYP2B6 and CYP2C9 [34]. The CYP2C19 loss-of-function allele has been linked to high platelet reactivity (HPR) during clopidogrel therapy. Patients carrying a CYP2C19 loss-of-function allele who had been stented and were treated with aspirin and clopidogrel had higher overall platelet reactivity and a greater frequency of HPR compared to 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 [36,33].

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

Trials evaluating more potent oral P2Y₁₂ inhibitors than clopidogrel in ACS have exposed another explanation for the smokers’ 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 of ACS patients 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 TRITON, smoking status was not well quantified, being only reported as "tobacco use"; not allowing determination of whether smoking was ongoing and its extent. “Prior use” and “never used” were combined into one 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 the smoking compared to non-smokers. As compared to TRITON, 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 > 1 month earlier or if they smoked less than one cigarette, cigar, or equivalent tobacco per day. Patients were defined as non-smokers if they did not smoke currently or previously [41]. In the PLATO analysis of smoking effect, ex-smokers and non-smokers were combined. Ticagrelor significantly reduced ischemic events irrespective of smoking status with a numerically greater benefit suggested in smokers where the adjusted hazard ratio
(aHR) of 0.83 was observed in habitual smokers and 0.89 in ex/non-smokers 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 TRILOGY ACS (Spontaneous MI After Non-ST Segment Elevation Acute Coronary Syndrome Managed Without Revascularization), a trial of medically managed ACS patients, 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 non-smokers. In TRILOGY, current smoking was defined as smoking 1 cigarette/day or stopped within last month, ex-smoking if stopped >1 month earlier; and non-smoking if not smoking either currently or previously. There was a nearly 50% reduction in the occurrence of the primary endpoint with prasugrel compared to clopidogrel in smokers, whereas no difference was observed in non-smokers [HR 0.54 and HR 1.06, respectively; p$_{interaction}$ = 0.0002].

Similar findings in smokers and non-smokers were observed for cardiovascular death [HR 0.48 and HR 1.12, respectively; p$_{interaction}$=0.0018], and for MI [HR 0.62 and HR 0.98, respectively; p$_{interaction}$=0.0403] [42]. In a meta-analysis derived from the data of TRITON and TRILOGY a positive effect of prasugrel treatment was seen only among smokers [43].

Although a greater treatment effect of the new oral P2Y$_{12}$ inhibitors versus clopidogrel may have been expected in non-smokers since the antiplatelet effects of new agents do not appear to be influenced by smoking, the opposite was observed. The findings suggesting greater clinical efficacy in smokers in these 3 trials therefore cannot be explained by a greater difference in PD 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 non-smokers 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 non-smokers. A cumulative body of observations indicate that the pathobiology of thrombosis differs between smokers and non-smokers 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 rare [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 complications 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. 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 (PRU) and a higher frequency of high platelet reactivity (HPR) after smoking cessation. In the study of Park, smoking status was ascertained by 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 [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 the 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 loss-of-function (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 finding is consistent with that in 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 smoking cessation paradox?**

What are the clinical implications of smoking cessation in clopidogrel-treated patients. There is still lack of clinical data with hard end-points in this group of patients. It can be hypothesized that these patients may be at a paradoxically higher risk of cardiovascular complications due to increased platelet aggregation. It has been reported that even a small increase in platelet activity alters clinical outcomes [52]. Similar changes to those observed after smoking cessation in platelet function have been linked to an increase in periprocedural myocardial infarction [53] and high platelet reactivity is an independent predictor of early
stent thrombosis [54]. This body of evidence suggests that the potential modest increase in platelet reactivity observed in clopidogrel-treated patients 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 randomised to either standard (75 mg) or double dosing of clopidogrel (150 mg) [55]. In the platelet sub-study of the GRAVITAS trial, the difference in platelet aggregation between smokers and non-smokers treated with clopidogrel was observed only in patients treated with the standard dose of clopidogrel, not in those treated with the double dose [56]. In the CURRENT PCI-OASIS 7 trial investigating double vs standard dose of clopidogrel in patients early after ACS, double dose clopidogrel reduced the primary outcome by 34%, whereas the benefit was not seen among non-smokers [57]. This finding supports the potential use of the double dose of clopidogrel following smoking cessation. The direct-acting P2Y₁₂ inhibitor, ticagrelor should be preferentially used in all ACS patients unless contraindicated according to the European Society of Cardiology (ESC) guidelines. As a direct-acting agent, ticagrelor may overcome a potential smoking cessation paradox in ACS patients. Another option to consider would be treatment with prasugrel, a thienopyridine that is metabolized in a one-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 smoking cessation. But this group of patients requires special interest. 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.
Table 1. Smokers’ paradox in STEMI patients treated with thrombolysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Group of patients</th>
<th>Number of patients (n)</th>
<th>Follow-up</th>
<th>Current smokers* (n)</th>
<th>Former smokers* (n)</th>
<th>Never smokers* (n)</th>
<th>Adjusted mortality rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO-1 [21]</td>
<td>STEMI</td>
<td>40599</td>
<td>30 days</td>
<td>17507</td>
<td>11117</td>
<td>11975</td>
<td>1.25 (95%CI 1.11-1.39) never vs current smokers</td>
</tr>
<tr>
<td>Barbash et al. [22]</td>
<td>STEMI</td>
<td>8259</td>
<td>6 months</td>
<td>3649</td>
<td>2244</td>
<td>2366</td>
<td>1.35 (95%CI 1.12-1.61) never vs current + former smokers</td>
</tr>
</tbody>
</table>

*smoking status based on patient’s declaration
Table 2. Smokers’ paradox in patients treated with clopidogrel

<table>
<thead>
<tr>
<th>Study</th>
<th>Group of patients</th>
<th>Number of patients (n)</th>
<th>Follow-up</th>
<th>Current smokers* (n)</th>
<th>Former smokers* (n)</th>
<th>Never smokers* (n)</th>
<th>Primary clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE [60]</td>
<td>ACS, stroke PAD</td>
<td>19185</td>
<td>1 to 3 years</td>
<td>5688</td>
<td>4135</td>
<td>Reduction in primary outcome: HR 0.76 among clopidogrel treated smokers vs HR 0.99 among non-smokers/ex-smokers</td>
<td></td>
</tr>
<tr>
<td>CLARITY TIMI 28 [61]</td>
<td>STEMI</td>
<td>3429</td>
<td>30 days</td>
<td>1697 Subgroups: 1-9 cigarettes/day ≥10 cigarettes/day</td>
<td>1732 (not current smoker)</td>
<td>OR 0.49 vs 0.72 (Pinteraction=0.0004) ≥10 cigarettes/day vs &lt;10 cigarettes/day</td>
<td></td>
</tr>
<tr>
<td>CHARISMA [62]</td>
<td>CAD, PAD, cerebral artery disease</td>
<td>12152</td>
<td>28 months</td>
<td>2419</td>
<td>6260</td>
<td>3473</td>
<td>All cause mortality clopidogrel treated patients HR 0.68 vs 0.95 vs HR 1.14 (Pinteraction=0.018) current vs former vs never smoker</td>
</tr>
<tr>
<td>CURRENT PCI [63]</td>
<td>ACS</td>
<td>17263</td>
<td>30 days</td>
<td>6394</td>
<td>10862</td>
<td>Double vs standard dose clopidogrel among smokers HR 0.66 vs 0.96 (Pinteraction=0.031)</td>
<td></td>
</tr>
</tbody>
</table>

*smoking status based on patient’s declaration
Focus box

- Smoking cessation is the most important single lifestyle intervention in secondary prevention of CVD
- Paradoxically smoking cessation may be associated with diminished effect of clopidogrel
- Not only patients who continue but also who withdraw smoking require special clinical attention
- More potent P2Y_{12} inhibition might be required in patients after PCI who withdraw smoking
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