Impact of smoking on acute phase outcomes of myocardial infarction

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Objectives **Previous studies have found an apparent paradox in smokers: acute phase outcomes after an acute myocardial infarction are superior to those of nonsmokers. Furthermore, it is reported that smoking has an impact on the metabolism of clopidogrel. This study aimed to examine whether this paradoxical finding exists in patients who undergo drug-eluting stent implantation and are treated with clopidogrel.**

Methods **From April 2003 to June 2010, 1424 consecutive patients with acute myocardial infarction who underwent primary or rescue percutaneous coronary intervention with drug-eluting stent and clopidogrel were enrolled. They were divided into three groups: current smokers ($n=486$); previous smokers ($n=349$); and nonsmokers ($n=589$). The primary end point was a composite of 30-day, all-cause death, nonfatal myocardial infarction, or definite stent thrombosis.**

Results **Compared with nonsmokers, current smokers were younger ($P<0.001$) and more often men ($P<0.001$). They had larger myocardial infarctions than did nonsmokers [maximum troponin I, 8.9 (2.4, 38.4) vs. 6.8 (1.4, 30.1) ng/ml, $P=0.01$]. Current smokers less frequently met the primary end point than did nonsmokers (2.9 vs. 6.1%, $P=0.01$). However, after adjustment for baseline and angiographic characteristics, the beneficial effect of smoking was no longer seen (odds ratio 1.35, confidence interval: 0.53–3.44, $P=0.5$).**

Conclusion **A beneficial effect of smoking ('smoker's paradox') in the unadjusted primary end point continues to be present; however, after adjustment for differences in baseline characteristics, no benefit was detectable.** *Coron Artery Dis* **22:217–222 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Active smoking is associated with a significant increase in the incidence of cardiovascular events and is a major risk factor for ischemic heart disease [1–3]. Paradoxically, previous studies [4–13], mostly from the fibrinolytic era, have found that smokers experience better outcomes after an acute myocardial infarction (AMI) than nonsmokers. Furthermore, smoking seems to potentiate the antiplatelet effect of clopidogrel. It may be that such potentiation plays a role in the paradoxical effect cited above [14]. The existence of a 'smoker's paradox' in the drug-eluting stent (DES) era, in which clopidogrel use is virtually universal, has not been investigated.

This analysis was conducted to evaluate the impact of smoking on 30-day outcomes of patients with AMI who undergo urgent primary or rescue percutaneous coronary intervention (PCI) with DES implantation and who receive clopidogrel as an antiplatelet agent.

Methods

A prospective registry of patients undergoing PCI at our institution is maintained. The registry includes 1424 patients with AMI who underwent primary or rescue PCI including greater than or equal to 1 DES from April 2003 to June 2010. In the registry, a current smoker is defined as an individual who is currently smoking or had stopped within 1 year of admission. A previous smoker was defined as one who smoked for more than or equal to 1 year and who quit more than or equal to 1 year before admission. Accordingly, there were 486 current smokers, 349 previous smokers, and 589 nonsmokers. All patients gave written informed consent for the PCI procedure. This analysis was conducted with the approval of the Institutional Review Board at Washington Hospital Center.

Coronary stent implantation was performed using conventional techniques. The interventional strategy, including the use of anticoagulant regimen and glycoprotein IIb/IIIa

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inhibitors, was left to the discretion of the physician. Intraprocedural anticoagulation was ensured using either unfractionated heparin or bivalirudin. Patients who received bivalirudin were given a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg per hour for the duration of the procedure. If activated clotting time, determined 5 min after the start of the infusion, was less than 250 s, an additional bivalirudin bolus of 0.3 mg/kg was administered. Patients who received unfractionated heparin were given a bolus of 50–70 U/kg, and additional unfractionated heparin was given to achieve an activated clotting time of more than 250 s. All patients received aspirin, 325 mg daily, and continued this dose daily indefinitely. Additional antiplatelet therapy with clopidogrel, 75 mg daily, was instituted in all patients after a loading dose of 300 or 600 mg at the time of PCI. Clopidogrel was recommended for more than or equal to 12 months.

The primary outcome end point was a 30-day composite of all-cause death, nonfatal MI, or definite stent thrombosis. Secondary outcomes include each of the three components of the primary outcome, infarct size (as estimated by myocardial biomarkers), and important in-hospital events. The maximum troponin I level was chosen as the estimate of the infarct size. These biomarkers were routinely measured before and immediately after the procedure and until a peak level was reached. Periprocedural nephropathy was defined as an absolute increase in serum creatinine of more than 0.5 mg/dl after PCI. Critical bleeding was defined as a decrease of more than 15% in hematocrit. Need for transfusion was defined as the need for whole blood or packed red blood cells due to a hemorrhagic event. Target lesion revascularization was defined as a target vessel revascularization for stenosis within a stent or within the 5-mm segments proximal or distal to the stent. Definite stent thrombosis was considered as defined by the Academic Research Consortium [15]. Angiographic success was defined as attainment of Thrombolysis In Myocardial Infarction grade 3 flow and residual stenosis less than 30%.

The demographic, clinical, and procedural data and in-hospital outcomes were collected and entered into a prospective database. The data were obtained from hospital chart review by independent research personnel unaware of the study objectives. All data management and analyses were carried out by a dedicated data-coordinating center (Data Center, Cardiovascular Research Institute, Washington, DC, USA). Clinical follow-up was carried out by trained quality assurance nurses who worked exclusively with the database to determine post-PCI clinical events. Clinical follow-up data were obtained by a telephone interview or office visit. A committee independently adjudicated all clinical events based on primary source documents. The 30-day follow-up information was obtained for all patients.

Normally distributed, continuous variables are expressed as mean ± standard deviation, and compared using an analysis of variance. For variables not normally distributed, median and interquartile ranges are reported and differences were tested using the Kruskal–Wallis rank test. Differences among groups were tested using the χ^2 test or Fisher's exact test. For variables with P value of less than 0.05, we carried out a post-hoc analysis adjusted by multiple comparisons.

The association between end points and smoking status was assessed by univariable and multivariable logistic regression analyses. The nonsmoking group was treated as a reference for comparison. The following independent variables were included in the coronary risk factor model: age, sex, systemic hypertension, hypercholesterolemia, diabetes mellitus, chronic renal insufficiency, body mass index, peripheral artery disease, earlier MI, history of chronic heart failure, previous coronary artery bypass surgery, and previous PCI. In addition, cardiogenic shock at presentation, left ventricular ejection fraction, number of diseased vessels, fibrinolytic agent use, bivalirudin use, glycoprotein IIb/IIIa inhibitor use, number of lesions dilated, treated vessel location, pre-PCI diameter stenosis (%), and angiographic success were included in the final model. Significant variables with a P value of less than 0.05 on univariable analysis were entered into a multivariable logistic regression model to adjust for baseline differences. All variables were entered into the model in their original form without transformation. Statistical analysis was carried out using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA). Statistical significance was accepted for all values of P of less than 0.05.

Results

The baseline clinical characteristics are listed in Table 1. Compared with nonsmokers, current smokers were 11 years younger ($P < 0.001$) and were more often men ($P < 0.001$). Furthermore, current smokers less often reported systemic hypertension ($P < 0.001$), hypercholesterolemia ($P = 0.02$), diabetes mellitus ($P < 0.001$), and chronic renal insufficiency ($P < 0.001$). Moreover, current smokers less often reported a history of chronic heart failure ($P = 0.02$), previous coronary artery bypass graft surgery ($P = 0.02$), and previous PCI ($P = 0.01$). The severity of coronary heart disease was similar between current smokers and nonsmokers.

Significant differences were observed in admission laboratory data. White blood cell count ($P < 0.001$), hematocrit ($P < 0.001$), and platelet count ($P = 0.03$) were each higher in current smokers than in nonsmokers. Use of antithrombotic agents was similar across the three smoking categories. Medications prescribed at discharge were similar among the three groups. Table 2 lists baseline angiographic and procedural characteristics of the three groups based on a by-lesion analysis. Among

Table 1 Patient baseline characteristics based on smoking status

Variable [*n* (%)]	Smoking status					
	Current (*n*=486)	Previous (*n*=349)	Non (*n*=589)	*P* value	p1	p2
Cardiovascular risk factors						
Age (years)	55.6±10.2	67.7±11.6	66.4±13.0	<0.001	<0.001	0.3
Men	351 (72.4%)	247 (70.8%)	348 (59.2%)	<0.001	<0.001	<0.001
Systemic hypertension	358 (74.0%)	307 (88.2%)	484 (82.3%)	<0.001	<0.001	0.02
Hypercholesterolemia[a]	374 (77.4%)	303 (87.8%)	487 (83.1%)	<0.001	0.02	0.05
Diabetes mellitus	108 (22.5%)	119 (34.3%)	210 (36.1%)	<0.001	<0.001	0.6
Chronic renal insufficiency[b]	34 (7.1%)	62 (17.9%)	113 (19.3%)	<0.001	<0.001	0.6
Body mass index	29.0±6.3	28.9±5.8	29.3±6.6	0.6		
Peripheral artery disease	60 (12.4%)	63 (18.3%)	59 (10.1%)	0.001	0.2	<0.001
Cardiac history						
Earlier myocardial infarction	63 (13.1%)	78 (23.4%)	96 (16.6%)	<0.001	0.1	0.01
Chronic heart failure	40 (8.5%)	53 (15.7%)	74 (13.0%)	0.006	0.02	0.3
Previous coronary artery bypass surgery	41 (8.5%)	65 (18.7%)	75 (12.8%)	<0.001	0.02	0.01
Previous percutaneous coronary intervention	66 (14.3%)	93 (27.8%)	111 (20.1%)	<0.001	0.01	0.008
Severity of heart disease						
Cardiogenic shock at presentation	38 (7.9%)	30 (8.7%)	53 (9.1%)	0.8		
Left ventricular ejection function (%)	44±12	43±14	43±0.13	0.7		
Number of diseased vessels	1.8±0.8	2.0±0.9	2.0±0.8	0.1		
Laboratory data						
White blood cells at admission ($\times 10^3/\mu l$)	10.4 (8.3–12.7)	8.7 (7.0–11.7)	8.9 (6.9–11.5)	<0.001	<0.001	0.9
Hematocrit at admission (%)	41.5 (38.1–44.3)	38.7 (35.6–41.9)	39.1 (35.6–42.6)	<0.001	<0.001	0.4
Platelet at admission ($\times 10^3/\mu l$)	234 (198–274)	226 (181–269)	222 (183–269)	0.04	0.03	0.9
Medication before PCI						
Fibrinolytic agent	74 (15.2%)	47 (13.5%)	65 (11.0%)	0.1		
Bivalirudin	257 (52.9%)	210 (60.2%)	329 (55.9%)	0.1		
Glycoprotein IIb/IIIa inhibitor	105 (21.6%)	67 (19.3%)	123 (21.1%)	0.7		
Medication at discharge (*n*=1378)[c]						
Aspirin	469 (98.9%)	333 (97.7%)	555 (97.9%)	0.3		
Clopidogrel	464 (97.9%)	333 (97.7%)	560 (98.9%)	0.3		
Angiotensin-converting enzyme inhibitor	334 (70.6%)	219 (65.0%)	372 (65.8%)	0.2		
β-blocker	430 (90.7%)	309 (90.6%)	513 (90.8%)	0.9		
Statin	426 (90.8%)	301 (88.3%)	515 (91.3%)	0.3		

Values are mean±standard deviation, median (interquartile range), or *n* (%); p1 current smoker vs. nonsmoker; p2 previous smoker vs. nonsmoker.
PCI, percutaneous coronary intervention.
[a]Includes patients with a previously documented diagnosis of hypercholesterolemia. The patient may be treated with diet or medication. A new diagnosis can be made during this hospitalization with an elevated total cholesterol >160 mg/dl. Does not include elevated triglycerides.
[b]Previously diagnosed or treated with medication, diet, or dialysis by a physician. Diagnosis at admission if a baseline creatinine of >2.0 mg/dl is found.
[c]Patients alive at discharge.

Table 2 Angiographic and procedural characteristics of patients based on smoking status

Lesion based	Smoking status					
	Current (*n*=859)	Previous (*n*=633)	Non (*n*=1026)	*P* value	p1	p2
Number of lesions dilated[a]	1.7±0.9	1.7±0.9	1.7±1.8	0.7		
Treated vessel						
Right coronary artery	333 (38.8%)	219 (34.6%)	283 (27.6%)	<0.001	<0.001	0.003
Left main tract	8 (0.9%)	16 (2.5%)	10 (1.0%)	0.01	0.9	0.02
Left anterior descending artery	290 (33.8%)	219 (34.6%)	467 (45.5%)	<0.001	<0.001	<0.001
Left circumflex artery	207 (24.1%)	148 (23.4%)	226 (22.0%)	0.6		
Saphenous vein graft	21 (2.4%)	31 (4.9%)	37 (3.6%)	0.04	0.2	0.2
Prediameter stenosis (%)	87±14	87±13	87±13	0.9		
Angiographic success	837 (97.8%)	609 (97.0%)	1010 (98.8%)	0.03	0.1	0.009

Values are mean±standard deviation or *n* (%); p1 current smoker vs. nonsmoker; p2 previous smoker vs. nonsmoker; Angiographic success was defined as attainment of Thrombolysis In Myocardial Infarction grade 3 flow and residual stenosis <30%.
[a]Per person.

current smokers a significantly greater proportion of treated lesions were located in the right coronary artery ($P<0.001$), whereas in those who did not smoke the most frequently treated artery was the left anterior descending artery ($P<0.001$). Current smokers tended to have low angiographic success rates compared with nonsmokers.

Table 3 lists the incidence of in-hospital adverse events. Current smokers less frequently had periprocedural nephropathy ($P=0.008$) and less often required transfusion ($P=0.001$). The length of hospital stay was shorter in current smokers than in nonsmokers ($P<0.001$). Table 4 lists 30-day adverse cardiac events. The primary end point, a composite of all-cause mortality, MI, and

Table 3 In-hospital outcome and infarct size of patients with acute myocardial infarction based on smoking status

Variable [*n* (%)]	Smoking status					
	Current (*n*=486)	Previous (*n*=349)	Non (*n*=589)	*P* value	p1	p2
In-hospital outcome						
Death	11 (2.3%)	11 (3.2%)	24 (4.1%)	0.2		
Emergent intra-aortic balloon pump	36 (7.4%)	31 (8.9%)	46 (7.9%)	0.7		
Urgent coronary artery bypass graft	3 (0.6%)	2 (0.6%)	7 (1.2%)	0.6		
Recurrent Q-wave myocardial infarction	0	4 (1.2%)	4 (0.7%)	0.04	0.1	0.4
Periprocedural nephropathy	20 (4.4%)	25 (7.9%)	47 (8.7%)	0.03	0.008	0.7
Any neurological event	3 (0.6%)	4 (1.1%)	2 (0.3%)	0.3		
Bleeding (hematocrit drop >15%)	11 (2.4%)	10 (3.0%)	18 (3.2%)	0.7		
Transfusion	21 (4.5%)	27 (8.1%)	55 (9.8%)	0.006	0.001	0.4
Length of stay (days)	3.7±3.7	4.3±5.2	5.0±5.3	<0.001	<0.001	0.2
Intensive care unit (days)	1.8±2.7	1.6±2.3	2.2±3.5	0.1		
Infarct size estimated by troponin I						
Troponin I baseline (ng/ml)	2.9 (0.6–12.6)	2.9 (0.2–13.9)	2.9 (0.4–10.4)	0.5		
Troponin I maximum (ng/ml)	8.9 (2.4–38.4)	6.7 (1.2–31.4)	6.8 (1.4–30.1)	0.04	0.01	0.9

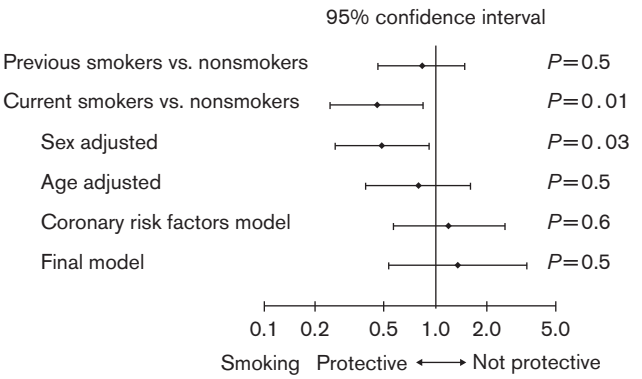
Values are mean±standard deviation, median (interquartile range), or *n* (%); p1 current smoker vs. nonsmoker; p2 previous smoker vs. nonsmoker.

Table 4 Thirty-day outcome of patients with acute myocardial infarction based on smoking status

Variable [*n* (%)]	Smoking status					
	Current (*n*=486)	Previous (*n*=349)	Non (*n*=589)	*P* value	p1	p2
Primary end point						
Death or MI or definite ST	14 (2.9%)	18 (5.2%)	36 (6.1%)	0.04	0.01	0.5
Secondary end point						
Death	13 (2.7%)	13 (3.7%)	30 (5.1%)	0.1		
MI	0	3 (0.9%)	7 (1.2%)	0.03	0.02	0.6
Definite ST	2 (0.4%)	3 (0.9%)	7 (1.2%)	0.4		
Target lesion revascularization	5 (1.0%)	4 (1.2%)	10 (1.7%)	0.6		
Target vessel revascularization	10 (2.1%)	6 (1.8%)	11 (1.9%)	0.9		

Values are *n* (%); p1 current smoker vs. nonsmoker; p2 previous smoker vs. nonsmoker.
MI, myocardial infarction; ST, stent thrombosis.

Fig. 1



Thirty-day composite events of death, myocardial infarction, or stent thrombosis. In univariable analysis for the primary end point, active smoking was significantly protective [odds ratio (OR) 0.46, confidence interval (CI): 0.24–0.86, *P*=0.01], but previous smoking was not (OR 0.84, CI: 0.47–1.5, *P*=0.5). However, when age was adjusted, current smoking was not protective (*P*=0.5). After adjustment of coronary risk factors, likelihood of cardiac adverse events was increased by 20% in current smokers (OR 1.20, CI: 0.57–2.54, *P*=0.7). In the final model including angiographic variables, the likelihood of cardiac adverse events was increased by 35% in current smokers (OR 1.35, CI: 0.53–3.44, *P*=0.5).

definite stent thrombosis, occurred in 68 patients (4.8%). It was encountered less frequently in those who currently smoked than in nonsmokers (2.9 vs. 6.1%, $P = 0.01$). Recurrent MI was less frequently recognized in current smokers than in nonsmokers (0 vs. 1.2%, $P = 0.02$); however, the former had evidence of greater myocardial injury as estimated by the maximum troponin I level (Table 3).

In the univariable analysis for the primary end point, the status of current smoker was significantly protective [odds ratio (OR) 0.46, confidence interval (CI): 0.24–0.86, $P = 0.01$], yet the status of previous smoker was not (OR 0.84, CI: 0.47–1.5, $P = 0.5$) (Fig. 1). When stratified by sex, current smoker status remained protective ($P = 0.03$). However, when adjusted for age, the 'beneficial' effect of smoking status was lost ($P = 0.5$). After adjustment for all coronary risk factors and history of coronary disease events (coronary risk factor model), and in the final model including markers of the severity of cardiac disease, angiographic and procedural variables, there was no protective effect from smoking.

Discussion

The results of our study challenge the 'smoker's paradox' in a population that presents with acute MI and is treated with DES and clopidogrel. Therefore, smoking cessation remains to be an important foundation to preventive care. In contrast to the overwhelming evidence for the health-harming effects of tobacco use, there have been a number of reports indicating that active smokers have lower mortality rates after acute MI [4–14]. Reports of this apparent paradox almost exclusively describe observations in patients treated with fibrinolysis [9–14]. For example, Barbash *et al.* [9] found that active smoking had a beneficial effect on mortality after adjustment of

baseline characteristics in 8387 patients with acute MI who underwent fibrinolysis. In an even larger trial, 40 599 patients from the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries-I fibrinolytic trial [10] were evaluated. Smoking was again shown to be associated with lower mortality even after adjustment of coronary risk factors. Other investigators [6,8,12] showed that active smokers with acute MI were younger and had less comorbidities than nonsmokers and suggested that these differences accounted for 'the smoker's paradox'.

We are aware of only one published description of the relationship of smoking and outcomes in patients with acute MI treated with stenting. Data from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial [4], a randomized evaluation of bare-metal stenting in patients with acute MI, suggested that active smokers had better survival than nonsmokers, but that the effect was entirely explained by differences in baseline risk and angiographic factors.

To further investigate the mechanisms of these observations, analyses from angiographic studies were undertaken to address the putative benefit of active smoking in acute MI. An analysis of data from 1562 participants in the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries-I trial [10], adjusted for angiographic characteristics, concluded that active smoking was not protective. Other studies [4,7,10,11,16] found, as did we, that active smokers have less extensive coronary disease and that the culprit lesion was more often located in the right coronary artery [10,12]. Taken together, these data are consistent with the conclusion that with appropriate adjustment for differences in patient characteristics, there is no 'paradoxical' benefit from smoking.

The possibility of a 'smoker's paradox' associated with fibrinolytic therapy of patients with acute MI is an intriguing alternative to the notion that observed differences are accounted for by patient characteristics. Active smoking is associated with a relatively hypercoagulable state [4,7,11,17]. Furthermore, smokers seem to have a greater thrombotic component to their coronary occlusion [7,11,17] and a relatively smaller atherosclerotic plaque burden. Arguably, fibrinolytic agents may, therefore, be more effective. Such a conclusion is supported by evidence that Thrombolysis In Myocardial Infarction grade 3 flow after fibrinolytic therapy in smokers is more frequent than in nonsmokers [11,13,16–18].

As far as this hypothesis is true, current smokers should have an advantage when treated with clopidogrel. Active smoking is an inducer of CYP1A2, an enzyme actively involved in converting the prodrug clopidogrel to its active form [19]. Consequently, smoking has been associated with both an increase in platelet inhibition and a diminution in platelet aggregation in response to clopidogrel [20]. These observations may have clinical relevance. Recently, in an analysis of a randomized trial of the effects of clopidogrel on outcomes in patients with acute MI treated with fibrinolytic agents, Desai *et al.* [14] found that active smoking positively modified the beneficial effect of clopidogrel as manifested by patients' angiographic and clinical outcomes.

An important strength of this study is the statistical power provided by the large number of patients in whom data were prospectively recorded in accordance with prespecified definitions for the data fields. Moreover, appropriate statistical techniques were used to adjust for differences in baseline variables. The observations reflect a 'real world' experience from a single, very experienced interventional practice. Nevertheless, the conclusions that can be drawn are limited by its observational nature. The limitations of all such studies apply. Unrecognized but pertinent confounders may not have been accounted for in the risk adjustment models. Our registry does not include detailed information regarding the presence and amount of thrombus on angiography, door-to-balloon time, and details of the smoking history.

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