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Tanush Gupta
New York Medical College

Dhaval Kolte
New York Medical College

Sahil Khera
New York Medical College

Prakash Harikrishnan
New York Medical College

Marjan Mujib
New York Medical College

See next page for additional authors

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ORIGINAL RESEARCH

Smoker's Paradox in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

Tanush Gupta, MD; Dhaval Kolte, MD, PhD; Sahil Khera, MD; Prakash Harikrishnan, MD; Marjan Mujib, MD, MPH; Wilbert S. Aronow, MD; Diwakar Jain, MD; Ali Ahmed, MD, MPH; Howard A. Cooper, MD; William H. Frishman, MD; Deepak L. Bhatt, MD, MPH; Gregg C. Fonarow, MD; Julio A. Panza, MD

***Background*—**Prior studies have found that smokers undergoing thrombolytic therapy for ST-segment elevation myocardial infarction have lower in-hospital mortality than nonsmokers, a phenomenon called the "smoker's paradox." Evidence, however, has been conflicting regarding whether this paradoxical association persists in the era of primary percutaneous coronary intervention.

***Methods and Results*—**We used the 2003–2012 National Inpatient Sample databases to identify all patients aged ≥18 years who underwent primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Multivariable logistic regression was used to compare in-hospital mortality between smokers (current and former) and nonsmokers. Of the 985 174 patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, 438 954 (44.6%) were smokers. Smokers were younger, were more often men, and were less likely to have traditional vascular risk factors than nonsmokers. Smokers had lower observed in-hospital mortality compared with nonsmokers (2.0% versus 5.9%; unadjusted odds ratio 0.32, 95% CI 0.31–0.33, $P<0.001$). Although the association between smoking and lower in-hospital mortality was partly attenuated after baseline risk adjustment, a significant residual association remained (adjusted odds ratio 0.60, 95% CI 0.58–0.62, $P<0.001$). This association largely persisted in age-stratified analyses. Smoking status was also associated with shorter average length of stay (3.5 versus 4.5 days, $P<0.001$) and lower incidence of postprocedure hemorrhage (4.2% versus 6.1%; adjusted odds ratio 0.81, 95% CI 0.80–0.83, $P<0.001$) and in-hospital cardiac arrest (1.3% versus 2.1%; adjusted OR 0.78, 95% CI 0.76–0.81, $P<0.001$).

***Conclusions*—**In this nationwide cohort of patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, we observed significantly lower risk-adjusted in-hospital mortality in smokers, suggesting that the smoker's paradox also applies to ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. **(*J Am Heart Assoc*. 2016;5:e003370 doi: 10.1161/JAHA.116.003370)**

Key Words: primary percutaneous coronary intervention • smoker's paradox • smoking • ST-segment elevation myocardial infarction

Cigarette smoking is the leading preventable cause of premature death in the United States. Approximately one-third of all coronary artery disease (CAD) deaths in the United States annually are attributable to smoking.[1] Some prior studies, however, have suggested the existence of a "smoker's paradox," implying that the outcomes of acute myocardial infarction (MI) may be more favorable in smokers than in nonsmokers.[2–6] More recently, smoking has also been shown to be associated with lower in-hospital mortality in patients with acute ischemic stroke, acute heart failure, and cardiac arrest.[7–10]

This phenomenon of smoker's paradox was first introduced into scientific discourse >25 years ago, when studies in the prethrombolytic era showed that smokers with acute MI

From the New York Medical College, Valhalla, NY (T.G., S.K., P.H., M.M., W.S.A., D.J., H.A.C., W.H.F., J.A.P.); Brown University/Rhode Island Hospital, Providence, RI (D.K.); Veterans Affairs Medical Center, Washington, DC (A.A.); Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA (D.L.B.); David Geffen School of Medicine, University of California at Los Angeles, CA (G.C.F.).

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Correspondence to: Wilbert S. Aronow, MD, Macy Pavilion, Room 148, New York Medical College, 100 Woods Road, Valhalla, NY 10595. E-mail: wsaronow@aol.com

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experienced lower mortality compared with nonsmokers.[3–5,11] Similar findings of paradoxical associations with smoking were also seen subsequently in randomized clinical trials investigating thrombolytic therapy for ST-segment elevation MI (STEMI).[2,12,13] These paradoxically lower mortality rates were largely attributed to a cumulative effect of younger age, fewer comorbidities, lesser extent of CAD, and more aggressive treatment of acute MI in smokers. Alternatively, pathophysiological differences between smokers and nonsmokers with acute MI have also been postulated as a basis for this paradox, including a greater thrombus burden in smokers, leading to greater efficacy of thrombolytic therapy,[14–16] and greater responsiveness to antiplatelet therapies.[17–20] Whether a true biochemical basis exists for the smoker's paradox remains inconclusive.

The majority of STEMI patients in current practice are treated with primary percutaneous coronary intervention (pPCI); however, studies of STEMI patients undergoing pPCI have found conflicting evidence regarding whether the smoker's paradox exists in this population.[21–24] We sought to determine the association of smoking status with in-hospital outcomes in STEMI patients undergoing pPCI, using data from the National Inpatient Sample (NIS) databases from 2003 to 2012.

Methods

Data Source

Data were obtained from the 2003–2012 NIS databases. The NIS is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the US Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).[25] The NIS includes deidentified patient data on demographics, admission diagnosis, comorbidities, procedures, and outcomes from all nonfederal, short-term, general, and other specialty acute care hospitals in the United States. Patients admitted under observation status or those admitted to psychiatric or rehabilitation hospitals, long-term care facilities, and chemical dependence units are not included. The database is composed of a random 20% sample of all hospitalized patients from participating states (44 states in 2012) in a given year. During 2003–2011, the NIS was constructed using data from all inpatient discharges (100%) from a random 20% sample of all reporting hospitals (stratified by hospital ownership, patient volume, urban or rural location, teaching status, and geographic region). In 2012, the database was redesigned to include data from a 20% sample of discharges from all participating hospitals (100%). The new design of the NIS delivers more precise and stable weighted estimates and reduces the margin of error.[26] To account for these changes in the sampling methodology, a new set of weights called "trend weights" were provided from 2012 data and for data from the previous years to allow the use of 2012 data along with the previous years' data.[27]

The New York Medical College institutional review board deemed this study exempt because the HCUP-NIS is a publicly available database containing deidentified patient information.

Study Population

We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 410.01 to 410.61, 410.81, and 410.91 to identify all patients aged ≥18 years with the primary diagnosis of STEMI. We chose the primary diagnosis because it is considered the principal reason for hospital admission. Patients who underwent thrombolysis (ICD-9-CM codes 99.19, V45.88) were excluded. STEMI patients undergoing pPCI were recognized as those who underwent PCI (ICD-9-CM codes 00.66, 36.01, 36.05, 36.06, 37.07) on the day of hospital admission and constituted our final study cohort (n=958 174).[28] Smokers (both current and former) were then identified using ICD-9-CM code 305.1 or V15.82 (n=438 954). Patients who did not have either of these diagnosis codes were considered nonsmokers (n=546 220). Prior studies have indicated that these codes have sensitivity of 100%, specificity of 32%, and accuracy of 66% to identify smokers in administrative databases, with little evidence of documentation bias.[29]

Outcomes Measures

Our primary outcome of interest was all-cause in-hospital mortality defined as "died" in the NIS database. We used average length of stay, postprocedure hemorrhage, and incidence of in-hospital cardiac arrest as secondary outcomes. The ICD-9-CM codes used to identify these conditions are provided in Table 1.

Patient and Hospital Characteristics

Baseline patient characteristics used included demographics (age, sex, race, primary expected payer, median household income for patient ZIP code, weekday versus weekend admission), all comorbidities from the Elixhauser Comorbidity Index (acquired immune deficiency syndrome, alcohol abuse, deficiency anemia, rheumatoid arthritis/collagen vascular diseases, chronic blood loss anemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes [uncomplicated], diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, chronic renal failure, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity,

Table 1. ICD-9-CM and CCS Codes Used to Identify Comorbidities and Complications

Variable	Source	Codes
Comorbidities		
Dyslipidemia	CCS	53
Known CAD	ICD-9-CM	414.00–414.07
Family history of CAD	ICD-9-CM	V17.3
Prior myocardial infarction	ICD-9-CM	412
Prior PCI	ICD-9-CM	V45.82
Prior coronary artery bypass surgery	ICD-9-CM	V45.81
Atrial fibrillation	ICD-9-CM	427.31
Carotid artery disease	ICD-9-CM	433.10
Dementia	ICD-9-CM	290.xx, 294.1x, 294.2x, 294.8, 331.0–331.12, 331.82, 797
In-hospital complications		
Postprocedure hemorrhage	ICD-9-CM	998.11, 998.12, 285.1
In-hospital cardiac arrest	ICD-9-CM	99.60, 99.63

CAD indicates coronary artery disease; CCS, Clinical Classification Software; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PCI, percutaneous coronary intervention.

paralysis, peripheral vascular disease, psychosis, pulmonary circulation disorders, solid tumor without metastasis, valvular disease, and weight loss),[30,31] and other clinically relevant comorbidities (dyslipidemia, known CAD, family history of CAD, prior MI, prior PCI, prior coronary artery bypass grafting, atrial fibrillation, carotid artery disease, and dementia). A combination of ICD-9-CM codes and HCUP Clinical Classification Software codes were used to identify baseline characteristics (Table 1). Hospital-level variables such as census region (Northeast, Midwest, South, and West), location (rural or urban), bed size (small, medium, or large), and teaching status were also included.

Statistical Analysis

Weighted estimates were obtained by applying trend weights to the unweighted discharge data. We initially compared patient demographics, hospital characteristics, and comorbidities between smokers and nonsmokers using the Pearson chi-square test for categorical variables and the Student *t* test for continuous variables to identify significant univariate associations. Multivariable logistic regression was used to compare in-hospital outcomes (in-hospital mortality, postprocedure hemorrhage, incidence of in-hospital cardiac arrest) between smokers and nonsmokers undergoing pPCI for STEMI. Variables included in the regression model were baseline demographics, hospital characteristics, comorbid conditions, and STEMI location (anterior, inferior, or other). Race and ethnicity data were missing for 14.6% of the study population and thus were not included in the regression model. We also compared in-hospital mortality separately between current smokers and nonsmokers and between former smokers and nonsmokers to assess whether there was any heterogeneity in the association of smoking status with in-hospital mortality when these groups were studied separately. Average length of stay was compared for smokers and nonsmokers using linear regression models. Given the positively skewed distribution, log transformation of length of stay was used as the dependent variable. To study whether the association of smoking with in-hospital mortality in the study cohort differed by age, we performed the multivariable analysis in different age strata (ie, <40, 40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years). We also repeated the multivariable analysis in subgroups stratified by admission year to assess whether the association of smoking with in-hospital mortality persisted equally throughout the study period. To explore whether the difference in in-hospital mortality between smokers and nonsmokers with STEMI in our study was driven by differences in baseline characteristics between hospitalized smokers and nonsmokers in general, we analyzed the association of smoking with risk-adjusted in-hospital mortality in patients hospitalized with hip fractures (ICD-9-CM codes 820.0x, 820.1x, 820.2x, 830.3x, 820.8, and 820.9) or with severe sepsis (ICD-9-CM code 995.92) during the same time period using the same multivariable regression models.

Statistical analysis was performed using IBM SPSS Statistics 21.0 (IBM Corp). A 2-sided *P* value of <0.05 was used to assess for statistical significance for all analyses. Categorical variables are expressed as percentages and continuous variables as mean±SD. Odds ratio (OR) and 95% CIs were used to report the results of logistic regression.

Results

Baseline Characteristics

From 2003 to 2012, of the 985 174 STEMI patients aged ≥18 years who underwent pPCI, 438 954 (44.6%) were smokers (either current or former). Smokers were, on average, ≈8 years younger than nonsmokers (mean age 56.6 versus 64.3 years; *P*<0.001) and more likely to be white men. Smokers were less likely to have atrial fibrillation, congestive heart failure, diabetes mellitus, hypertension, or chronic renal failure but more often had known CAD, history of prior MI, dyslipidemia, alcohol abuse, drug abuse, and chronic pulmonary disease (*P*<0.001 for all comparisons). Smokers were less likely to have anterior wall STEMI and more likely to have inferior wall STEMI (*P*<0.001) (Table 2).

Table 2. Baseline Demographics, Hospital Characteristics, and Comorbidities of Patients Aged ≥18 Years With STEMI Undergoing Primary Percutaneous Coronary Intervention

Variable	Nonsmokers, % (n=546 220)	Smokers , % (n=438 954)	*P* Value
Age, mean±SD (years)	64.3±13.2	56.6±11.3	<0.001
Women	31.7	24.3	<0.001
Race			<0.001
White	78.0	81.7	
Black	6.8	7.3	
Hispanic	8.1	5.6	
Asian or Pacific Islander	2.5	1.5	
Native American	0.5	0.4	
Other	4.0	3.4	
Primary expected payer			<0.001
Medicare	45.6	25.5	
Medicaid	4.8	8.1	
Private insurance	39.7	47.1	
Self-pay	6.2	13.1	
No charge	0.5	1.3	
Other	3.2	4.8	
Weekend admission	26.4	27.4	<0.001
Hospital characteristics			
Bed size*			<0.001
Small	6.3	5.7	
Medium	20.8	21.2	
Large	72.9	73.1	
Urban location	94.3	94.1	<0.001
Teaching hospital	52.6	52.3	0.005
Region			<0.001
Northeast	20.3	18.1	
Midwest	18.4	21.7	
South	42.3	43.7	
West	19.1	16.5	
Median household income (percentile)			<0.001
0–25th	23.4	26.5	
26th–50th	25.2	27.6	
51st–75th	25.3	25.3	
76th–100th	26.1	20.6	
Comorbidities†			
Dyslipidemia	55.2	61.3	<0.001
Known coronary artery disease	86.3	89.1	<0.001
Family history of coronary artery disease	7.3	14.3	<0.001
Prior myocardial infarction	5.5	7.6	<0.001
Prior percutaneous coronary intervention	8.6	10.8	<0.001
Prior coronary bypass surgery	2.4	1.7	<0.001
Carotid artery disease	0.5	0.5	0.93
Dementia	1.1	0.3	<0.001
Atrial fibrillation	11.1	5.8	<0.001
Acquired immune deficiency syndrome	0.1	0.2	<0.001
Alcohol abuse	1.4	4.9	<0.001
Deficiency anemia	8.8	5.4	<0.001
Rheumatoid arthritis/ collagen vascular diseases	1.8	1.4	<0.001
Chronic blood loss anemia	0.8	0.4	<0.001
Congestive heart failure	16.8	9.9	<0.001
Chronic pulmonary disease	9.3	16.6	<0.001
Coagulopathy	3.4	2.0	<0.001
Depression	3.7	4.8	<0.001
Diabetes mellitus (uncomplicated)	23.9	18.9	<0.001
Diabetes mellitus (complicated)	2.6	1.4	<0.001
Drug abuse	1.0	3.4	<0.001
Hypertension	59.2	54.8	<0.001
Hypothyroidism	7.0	4.2	<0.001
Liver disease	0.6	0.8	<0.001
Lymphoma	0.3	0.2	<0.001
Fluid and electrolyte disorder	12.8	8.9	<0.001
Metastatic cancer	0.5	0.3	<0.001
Other neurological disorders	3.4	2.2	<0.001
Obesity	9.9	11.8	<0.001
Paralysis	0.8	0.4	<0.001
Peripheral vascular disease	5.4	6.6	<0.001

Continued

Continued

Table 2. Continued

Variable	Nonsmokers, % (n=546 220)	Smokers , % (n=438 954)	*P* Value
Psychoses	1.1	1.6	<0.001
Pulmonary circulation disorders	<0.1	<0.1	<0.001
Renal failure (chronic)	6.8	3.0	<0.001
Solid tumor without metastasis	0.9	0.7	<0.001
Peptic ulcer (non-bleeding)	<0.1	<0.1	0.12
Valvular disease	0.1	<0.1	<0.001
Weight loss	1.1	0.6	<0.001
STEMI location			<0.001
Anterior STEMI	38.3	33.1	
Inferior STEMI	50.1	57.2	
Other STEMI	11.6	9.7	

STEMI indicates ST-segment elevation myocardial infarction.
*Bed size categories are specific for hospital location and teaching status.
†Comorbidities (including the 29 comorbidities from the Elixhauser Comorbidity Index) were extracted from the database using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis or Clinical Classification Software codes.

In-Hospital Outcomes of Smokers and Nonsmokers With STEMI Undergoing pPCI

In the overall cohort of STEMI patients undergoing pPCI, smoking was associated with lower in-hospital mortality (2.0% versus 5.9%; unadjusted OR 0.32, 95% CI 0.31–0.33, *P*<0.001). This unadjusted mortality difference was attenuated substantially but remained significant after risk adjustment for demographics, hospital characteristics, baseline comorbidities, and STEMI location (adjusted OR 0.60, 95% CI 0.58–0.62, *P*<0.001) (Table 3). When further adjusted for secondary outcomes (in-hospital cardiac arrest, postprocedure hemorrhage), there was no significant change in the association of smoking with in-hospital mortality (adjusted OR 0.61, 95% CI 0.57–0.64, *P*<0.001). Although there were slight year-to-year variations ($P_{interaction}$<0.001), the association between smoking and lower risk-adjusted in-hospital mortality persisted throughout the study period in subgroups stratified by admission year (Table 4).

When in-hospital mortality was compared separately for current smokers versus nonsmokers (1.7% versus 5.9%; unadjusted OR 0.28, 95% CI 0.26–0.29, *P*<0.001; adjusted OR 0.56, 95% CI 0.52–0.60, *P*<0.001) and for former smokers versus nonsmokers (2.9% versus 5.9%; unadjusted OR 0.48, 95% CI 0.44–0.52, *P*<0.001; adjusted OR 0.70, 95% CI 0.64–0.76, *P*<0.001), smoking status was associated with lower risk-adjusted in-hospital mortality in both comparisons, although this association was stronger in current smokers than in former smokers.

Smoking was also associated with shorter average length of stay (3.5 versus 4.5 days; *P*<0.001) and lower incidence of postprocedure hemorrhage (4.2% versus 6.1%; unadjusted OR 0.67, 95% CI 0.66–0.69, *P*<0.001; adjusted OR 0.81, 95% CI 0.80–0.83, *P*<0.001) and in-hospital cardiac arrest (1.3% versus 2.1%; unadjusted OR 0.60, 95% CI 0.58–0.62, *P*<0.001; adjusted OR 0.78, 95% CI 0.76–0.81, *P*<0.001) (Table 3).

Age-Stratified Analysis

To assess whether the younger age of smokers was influencing the association with lower in-hospital mortality, we performed an age-stratified analysis ($P_{interaction}$<0.001). As expected, the proportion of smokers decreased with increasing age, whereas in-hospital mortality increased (Table 5). Mortality differences between smokers and nonsmokers undergoing pPCI for STEMI decreased substantially with

Table 3. In-Hospital Outcomes in Nonsmokers and Smokers With STEMI Undergoing Primary Percutaneous Coronary Intervention

Outcome	Nonsmokers (n=546 220)	Smokers (n=438 954)	Odds Ratio (95% CI)		*P* Value†
			Unadjusted	Adjusted*	
In-hospital mortality	32 321 (5.9%)	8646 (2.0%)	0.32 (0.31–0.33)	0.60 (0.58–0.62)	<0.001
Secondary outcomes					
Postprocedure hemorrhage	33 051 (6.1%)	18 246 (4.2%)	0.67 (0.66–0.69)	0.81 (0.80–0.83)	<0.001
In-hospital cardiac arrest	11 710 (2.1%)	5658 (1.3%)	0.60 (0.58–0.62)	0.78 (0.76–0.81)	<0.001
Average length of stay	4.5±5.5 days	3.5±3.0 days	—	—	<0.001

Rates of in-hospital mortality, postprocedure hemorrhage, and in-hospital cardiac arrest are depicted as n (%) and average length of stay as mean±SD. STEMI indicates ST-segment elevation myocardial infarction.
*Adjusted for age, sex, primary payer status, weekend admission, median household income for patient ZIP code, hospital characteristics (bed size, region, location, teaching status), all Elixhauser comorbidities, other clinically relevant comorbidities (known coronary artery disease, carotid artery disease, atrial fibrillation, dementia, dyslipidemia, family history of coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary bypass surgery), and STEMI location.
†*P* values reported for adjusted comparisons.

Table 4. In-Hospital Mortality by Admission Year for Nonsmokers and Smokers With STEMI Undergoing Primary Percutaneous Coronary Intervention

Year	In-Hospital Mortality, %		Odds Ratio (95% CI)		*P* Value†
	Nonsmokers	Smokers	Unadjusted	Adjusted*	
2003	4.9	1.4	0.27 (0.24–0.30)	0.65 (0.58–0.73)	<0.001
2004	5.4	1.1	0.19 (0.17–0.22)	0.42 (0.37–0.48)	<0.001
2005	5.8	1.3	0.21 (0.19–0.23)	0.44 (0.40–0.50)	<0.001
2006	5.6	1.4	0.24 (0.22–0.26)	0.51 (0.46–0.56)	<0.001
2007	6.2	1.6	0.25 (0.23–0.27)	0.48 (0.43–0.53)	<0.001
2008	6.5	1.8	0.26 (0.24–0.28)	0.50 (0.46–0.55)	<0.001
2009	6.0	2.2	0.36 (0.33–0.38)	0.64 (0.59–0.69)	<0.001
2010	6.0	2.2	0.36 (0.34–0.39)	0.59 (0.55–0.64)	<0.001
2011	6.3	2.8	0.43 (0.40–0.45)	0.69 (0.64–0.74)	<0.001
2012	6.3	2.9	0.44 (0.42–0.47)	0.66 (0.62–0.71)	<0.001

$P_{interaction}$<0.001 for smoking and year. STEMI indicates ST-segment elevation myocardial infarction.
*Adjusted for age, sex, primary payer status, weekend admission, median household income for patient ZIP code, hospital characteristics (bed size, region, location, teaching status), all Elixhauser comorbidities, other clinically relevant comorbidities (known coronary artery disease, carotid artery disease, atrial fibrillation, dementia, dyslipidemia, family history of coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary bypass surgery), and STEMI location.
†*P* values reported for adjusted comparisons.

increasing age; the adjusted OR for association of smoking with mortality increased from 0.37 in patients aged <40 years to 0.77 in those aged 80 to 89 years. Moreover, the association of smoking with lower in-hospital mortality was no longer significant in patients ≥90 years of age.

In-Hospital Mortality in Smokers and Nonsmokers With Hip Fractures or Severe Sepsis

To explore whether the paradoxically lower risk-adjusted in-hospital mortality in smokers with STEMI in our study was driven by differences in baseline demographics and comorbidities between hospitalized smokers and nonsmokers in general, we analyzed the association of smoking status with in-hospital mortality in 2 conditions in which this association has not been previously studied—hip fractures and severe sepsis—using the same regression models. Of the 3 048 272 patients hospitalized with hip fractures from 2003 to 2012, 14.5% were smokers and 85.5% were nonsmokers (mean age 72.5 versus 80.2 years; *P*<0.001). Smoking was associated with lower risk-adjusted in-hospital mortality after multivariable adjustment (1.6% versus 2.8%; unadjusted OR 0.57, 95%

Table 5. In-Hospital Mortality by Age for Nonsmokers and Smokers With STEMI Undergoing Primary Percutaneous Coronary Intervention

Age, y	n	Smoker, %	In-Hospital Mortality, %		Odds Ratio (95% CI)		*P* Value†
			Nonsmokers	Smokers	Unadjusted	Adjusted*	
<40	36 445	62.2	2.8	0.7	0.26 (0.21–0.31)	0.37 (0.30–0.46)	<0.001
40–49	158 936	61.7	2.6	0.8	0.32 (0.30–0.35)	0.44 (0.40–0.48)	<0.001
50–59	289 200	54.1	3.2	1.4	0.42 (0.40–0.44)	0.56 (0.53–0.59)	<0.001
60–69	245 830	42.2	4.9	2.4	0.47 (0.45–0.50)	0.59 (0.56–0.62)	<0.001
70–79	159 348	27.3	7.7	4.2	0.53 (0.50–0.56)	0.69 (0.66–0.73)	<0.001
80–89	85 031	16.0	12.3	7.8	0.61 (0.57–0.65)	0.77 (0.71–0.83)	<0.001
≥90	10 384	9.1	16.3	16.9	1.05 (0.88–1.25)	1.18 (0.97–1.44)	0.10

$P_{interaction}$<0.001 for smoking and age. STEMI indicates ST-segment elevation myocardial infarction.
*Adjusted for sex, primary payer status, weekend admission, median household income for patient ZIP code, hospital characteristics (bed size, region, location, teaching status), all Elixhauser comorbidities, other clinically relevant comorbidities (known coronary artery disease, carotid artery disease, atrial fibrillation, dementia, dyslipidemia, family history of coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary bypass surgery), and STEMI location.
†*P* values reported for adjusted comparisons.

CI 0.56–0.59, $P<0.001$; adjusted OR 0.70, 95% CI 0.69–0.72, $P<0.001$). During the same time period, 3 773 654 patients were hospitalized with sepsis. Of these, 12.4% were smokers. Smokers were younger (63.2 versus 67.4 years; $P<0.001$) and had lower risk-adjusted morality than nonsmokers (26.7% versus 33.8%; unadjusted OR 0.72, 95% CI 0.71–0.72, $P<0.001$; adjusted OR 0.82, 95% CI 0.81–0.83, $P<0.001$).

Discussion

Our analysis of a large real-world nationwide cohort of ≈100 000 STEMI patients undergoing pPCI showed that smokers had lower in-hospital mortality, shorter average length of stay, and lower incidence of postprocedure hemorrhage and in-hospital cardiac arrest than nonsmokers. Even after adjustment for baseline covariates, the adjusted odds of in-hospital mortality were significantly lower in nonsmokers. We also found that the association of smoking with lower risk-adjusted in-hospital mortality differed across age strata, with this paradoxical association being stronger in younger versus older age groups.

Cigarette smoking is an established risk factor for atherosclerotic cardiovascular disease.[1,32] Consistent with this, smokers presenting with STEMI in our study were ≈8 years younger and were less likely to have vascular risk factors than nonsmokers, providing direct evidence for the deleterious effects of cigarette smoking. Despite risk adjustment for these baseline differences, the association of smoking with lower in-hospital mortality persisted. A novel aspect of our study was the additional assessment for potential confounding by examining the association with smoking with in-hospital mortality in patients hospitalized with hip fractures and severe sepsis. We found that smokers had lower risk-adjusted in-hospital mortality than nonsmokers in both these populations. Smokers were ≈8 years younger than nonsmokers among patients with hip fractures, whereas the mean age difference between smokers and nonsmokers was ≈4 years in the sepsis cohort. Interestingly, this translated into a greater beneficial association of smoking with in-hospital mortality in patients hospitalized with hip fractures (adjusted OR 0.70) compared with patients with severe sepsis (adjusted OR 0.82). These findings suggest that the lower risk-adjusted in-hospital mortality in hospitalized smokers was driven in part by residual confounding due to inadequate adjustment for the biological effects of age. It is probable that the lower in-hospital mortality after extensive multivariable risk adjustment in smokers with STEMI in our study also represents continued unmeasured confounding; however, given that the favorable association of smoking with in-hospital mortality after risk adjustment was greater in STEMI patients than in patients with either hip fractures or sepsis, it is possible that underlying biological differences in pathophysiology and response to treatment in smokers versus nonsmokers with STEMI also account, at least in part, for this paradoxical association.

Multiple randomized trials with thrombolytic therapy have reported lower short- and long-term mortality in smokers with STEMI.[12,14,33–35] Although in most[12,34] of these studies, the association between smoking and reduced mortality was no longer significant after baseline risk adjustment, some[2] showed persistent reduced mortality in smokers, even after correction for baseline differences between smokers and nonsmokers. The hypothesized mechanism for superior response of smokers to thrombolytic therapy is that smoking does not affect atherosclerotic plaque vulnerability as much as it increases hypercoagulability. Smoking has been directly associated with a procoagulant state with effects on endothelial dysfunction, increased platelet activation and aggregation, increased circulating levels of fibrinogen, and increased thrombin generation.[36,37] Components of cigarette smoke have also been shown to impair fibrin crosslinking.[38] These findings support the hypothesis that the pathogenesis of STEMI in smokers may be predominantly thrombogenic and less likely atherogenic, making it more amenable to thrombolytic therapy. Studies have shown that smokers with STEMI have better epicardial flow after thrombolytic therapy[34] and improved myocardial perfusion demonstrated by Thrombolysis in Myocardial Infarction perfusion grade.[39]

Data on the association of smoking with in-hospital outcomes in STEMI patients undergoing pPCI are more limited. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, patients with STEMI were randomized to angioplasty with or without abciximab versus stenting with or without abciximab. Smokers had significantly lower mortality than nonsmokers both at 30 days and 1 year; however, smoking was no longer associated with lower 1-year mortality after baseline risk adjustment.[21] A recent single-center retrospective study of 382 STEMI patients presenting for pPCI via field triage showed that current smoking was not predictive of 30-day all-cause mortality or major adverse cardiac events after multivariable risk adjustment; however, given the small sample size and low event rate, the study was underpowered to assess the validity of the smoker's paradox in this patient population.[24] Of note, Zhang et al[40] recently reported the association of smoking with 5-year outcomes of 1800 patients in the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial. Although smoking status was found to be an independent predictor of the primary composite end point of death, MI, and stroke after multivariable risk adjustment, this association was driven by the effect of smoking on subsequent MI, and no statistically significant association with mortality was observed at 5-year follow-up. More important, the SYNTAX trial examined a population of

patients with predominantly stable CAD; therefore, these findings cannot be compared directly with the MI population, in which the smoker's paradox has been classically described. Ours is the largest study to date to investigate the association of smoking with in-hospital outcomes in the pPCI era. In addition, given the large sample size, our study was sufficiently powered to allow for multivariable analysis across all age strata. We observed that the mortality difference between smokers and nonsmokers diminished substantially with increasing age and was no longer significant in nonagenarians with STEMI. These data suggest that the overall association of smoking with lower in-hospital mortality is driven mostly by younger age groups.

A possible biological mechanism to explain the existence of this paradox in the pPCI population could be the increased responsiveness of smokers to antiplatelet therapies, particularly clopidogrel, which is still the predominant $P2Y_{12}$ inhibitor in current practice. In the Clopidogrel and Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI 28) trial, although clopidogrel reduced the rate of the primary end point of a closed infarct–related artery or death and MI before angiography in the entire study population, the benefit was especially marked among patients who smoked $\geq$10 cigarettes per day versus those who did not.[41] Similarly, in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, among the 12 152 participants with established cardiovascular disease, clopidogrel reduced all-cause and cardiovascular mortality at 28 months in current smokers but not in nonsmokers.[18] Similar findings of effect modification of clopidogrel activity by smoking status have been reported in other studies.[17] Pharmacokinetic and pharmacodynamics studies have shown that smokers have greater inhibition of platelet aggregation, lower $P2Y_{12}$ reaction units, and lower odds of high platelet reactivity while on clopidogrel compared with nonsmokers.[19] A proposed mechanism to explain the differential effect of clopidogrel in smokers versus nonsmokers is the induction of cytochrome P450 1A2 and 2B6 enzymes by cigarette smoking, both of which are involved in the hepatic biotransformation of clopidogrel to its active metabolite.[42] There is also some evidence that smoking status potentiates prasugrel activity. A platelet-function substudy of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial, which randomized medically managed ACS patients to prasugrel versus clopidogrel, showed that persistent smokers had lower $P2Y_{12}$ reaction unit values at 6 months in both treatment groups compared with nonsmokers. Nicotine has been shown to be associated with higher $P2Y_{12}$ receptor expression in human platelet lysates; it is possible that the increased density of $P2Y_{12}$ receptors on the platelet surface in both clopidogrel- and prasugrel-treated smokers versus nonsmokers could play a role in the observed effect of smoking on platelet inhibition.[43] In addition, among smokers, the risk of ischemic outcomes was significantly reduced with prasugrel versus clopidogrel.[20] The greater efficacy of prasugrel versus clopidogrel in smokers might be explained, theoretically, by the association of the reported increased density of $P2Y_{12}$ receptors among smokers with a greater risk of ischemic events that is possibly diminished to a greater degree with a more potent $P2Y_{12}$ inhibitor such as prasugrel. A subanalysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial also showed that in patients undergoing pPCI for STEMI, bivalirudin monotherapy was associated with lower 30-day and 1-year mortality compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors in smokers but not in nonsmokers.[44] These data on the differential clinical efficacy of clopidogrel, prasugrel, and bivalirudin in smokers versus nonsmokers could be a possible mechanistic explanation for the association of smoking with lower in-hospital mortality in patients undergoing pPCI for STEMI.

This apparent smoker's paradox should not be viewed as an endorsement or inadvertent benefit of cigarette smoking. Ample evidence shows the harmful nature of smoking, and these modest differences in in-hospital outcomes would likely be offset by the long-term mortality attributable to cigarette smoking. Intensive efforts to encourage smoking cessation as a public health measure to reduce cardiovascular disease should remain an important goal.[45]

Study Limitations

Our present analysis of the association of smoking with in-hospital outcomes in STEMI patients undergoing pPCI has several limitations. It is possible that smokers with STEMI had higher mortality rates before presentation to the hospital than nonsmokers, with those being hospitalized already representing the "survivors." Given the lack of information on out-of-hospital deaths, we were unable to ascertain whether this bias was present in our study cohort. Because of the unavailability of patient charts and medical records, cumulative smoking exposure in terms of number of pack-years could not be quantified, and we were unable to study the association of amount of smoking with outcomes. We were also unable to determine the time of smoking cessation for former smokers. Given the abstracted nature of the data set, we were unable to assess the duration or severity of comorbid conditions. As an administrative database, the accuracy of NIS data depends greatly on the training and expertise of the coders; therefore, there is potential for under- or overestimation of smoking status, STEMI hospitalizations, and in-hospital outcomes based on ICD-9-CM coding. NIS does not have medication

data, so we had no information available on the adjunctive antiplatelet and antithrombotic therapies used with PCI. Given the lack of angiographic data, we were unable to account for the severity of CAD or to assess the procedural success of PCI. Last, outcomes in NIS are limited to in-hospital events, and important data on long-term mortality in smokers versus nonsmokers were not available.

Conclusion

In summary, in our large national unselected cohort of STEMI patients undergoing pPCI, we found that smoking was associated with lower risk-adjusted in-hospital mortality. We also found that the association of smoking with reduced mortality was driven largely by the association of smoking with mortality in younger age groups. Age-stratified analyses also found the smoker's paradox, except in patients aged ≥90 years, suggesting that the average younger age of smokers was not the sole explanation for the paradox. Although weaker in magnitude, similar paradoxical associations of smoking with lower risk-adjusted in-hospital mortality were found in patients hospitalized with hip fractures or severe sepsis during the same study period, implying that the smoker's paradox is related, at least in part, to continued residual measured or unmeasured confounding. Whether pathophysiological differences between smokers and nonsmokers with STEMI also account in part for this paradoxical association needs to be established conclusively by future studies.

Disclosures

Dr Deepak L. Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Vice-Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda. All other authors have no relevant conflicts of interest to disclose.

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Smoker's Paradox in Patients With ST–Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

Tanush Gupta, Dhaval Kolte, Sahil Khera, Prakash Harikrishnan, Marjan Mujib, Wilbert S. Aronow, Diwakar Jain, Ali Ahmed, Howard A. Cooper, William H. Frishman, Deepak L. Bhatt, Gregg C. Fonarow and Julio A. Panza

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