Smoking Paradox in Patients Hospitalized With Coronary Artery Disease or Acute Ischemic Stroke
Findings From Get With The Guidelines

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Background—Smoking is a potent risk factor for coronary artery disease (CAD) and acute ischemic stroke (AIS), but there are numerous reports of lower in-hospital mortality among smokers versus nonsmokers hospitalized for these events.

Methods and Results—We analyzed all consecutive patients hospitalized with a first index CAD (n=158,054) or AIS (n=899,295) event in Get With The Guidelines from 2002 to 2012; 20.4% of AIS and 30.4% of patients with CAD were past-year smokers. Multivariable models and age-stratified analyses were used to estimate the adjusted odds ratio of in-hospital mortality in smokers versus nonsmokers. Smokers were younger, more often male, with fewer vascular risk factors, and were more likely to be admitted to hospitals that were large, academic, or in the South. In-hospital mortality was significantly lower among smokers in both CAD (2.7% versus 5.2%; P<0.0001) and AIS (3.5% versus 5.8%; P<0.0001). The difference between unadjusted and adjusted odds ratios for smoking (0.57 versus 0.86 in CAD; 0.56 versus 0.86 in AIS) indicates the presence of substantial confounding by age and other covariates, but a significant association of past-year smoking remained.

Conclusions—Among patients hospitalized with CAD and AIS, smoking is a risk factor for early age of onset, even among those with few vascular risk factors. The persistent association with lower in-hospital mortality after adjusted and stratified analyses probably represents residual unmeasured confounding, although a biological effect of smoking cannot be excluded. Further clinical and prospective population-based studies are needed to explore variables that contribute to outcomes in these patients. (Circ Cardiovasc Qual Outcomes. 2015;8:S73-S80. DOI: 10.1161/CIRCOUTCOMES.114.001244.)

Key Words: coronary artery disease ■ mortality ■ risk factor ■ smoking ■ stroke
WHAT IS KNOWN

- Smoking is an important risk factor for atherosclerosis and contributes to both coronary artery disease and stroke.
- Paradoxically, previous studies have shown that smoking seems to be associated with lower in-hospital mortality.

WHAT THE STUDY ADDS

- This large, parallel retrospective study allows for rigorous adjustment for potential confounding in assessing the association of smoking with in-hospital mortality among patients with first ever coronary artery disease or stroke admission.
- Smokers have much earlier onset of first atherosclerotic event, but even after extensive risk adjustment and sensitivity analyses, smoking remained associated with lower mortality.
- Future prospective, population-based studies are needed to better understand if this reduced mortality is because of residual confounding or an actual difference in pathophysiology of vascular occlusion in smokers versus nonsmokers.

from large contemporary registries that include measures of stroke severity are lacking. A recent report demonstrated differential rates of increase in smoking cessation counseling provided to patients in the Get With The Guidelines (GWTG) CAD versus Stroke registries, and that there were important differences in the clinical characteristics of patients who received versus did not receive counseling. Because the pathophysiology of AIS has similarities with acute myocardial infarction— notably vascular occlusion because of atherosclerosis, we performed a parallel retrospective analysis of patients in the GWTG-CAD and Stroke registries to evaluate if similar paradoxical associations between smoking and in-hospital mortality were present.

Methods

GWGT Program Design, Case Identification, and Data Abstraction

GWGT is an ongoing voluntary, continuous registry, and performance improvement initiative in cardiovascular disease and stroke. It includes modules that address the hospital-based care of patients with stroke, CAD, heart failure, atrial fibrillation, and in-hospital cardiac arrest. A detailed description of the programs has been previously reported. For the CAD and Stroke modules, sites collect and enter deidentified patient level data on clinical and demographic characteristics, diagnostic testing, treatments, adherence to quality measures, and in-hospital outcomes in patients hospitalized with CAD and Stroke. GWGT—CAD data were available from 2002 when the program launched until 2008 and when the program transitioned to the Action-GWGT Registry in partnership with the American College of Cardiology. GWGT—Stroke was launched in April 2003 and is still actively enrolling patients as a national stroke quality improvement program available to any hospital in United States. Hospitals have continued to join during the past decade.

Trained hospital personnel ascertain consecutive patients admitted with CAD and stroke by either prospective clinical identification, retrospective identification using International Classification of Diseases Ninth Revision discharge codes, or a combination. Data collection and entry is distinct between the 2 modules, and many hospitals participate in only one of the modules. Prospective identification includes regular surveillance of emergency department records (ie, presenting symptoms and chief complaints), ward census logs, or neurological consultations. The eligibility of each case is confirmed at chart review before abstraction. After abstraction by trained personnel at hospital, deidentified patient data are entered into the GWTG database using a Web-based patient management tool (Outcome and Quintiles). Data elements abstracted include patient demographics, medical history and comorbidities, in-hospital treatment and events, discharge treatment and counseling, mortality, and discharge destination.

All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Outcome, A Quintiles Company (Cambridge, MA) served as the registry coordinating center. The Duke Clinical Research Institute (Durham, NC) served as the data analysis center and institutional review board approval was granted to analyze aggregate deidentified data for research purposes.

Patient Population

GWGT-CAD Cohort

In the GWGT-CAD cohort, there were a total of 393,505 consecutive admissions at 421 hospital sites from January 2002 to December 2008. We limited our analysis to patients with the diagnosis of acute myocardial infarction or unstable angina (n=298,198). To explore the association of smoking with in-hospital mortality among patients presenting with the first index event, we excluded patients with a previous history of CAD or MI (n=141,372) and patients from hospitals with >25% medical history panel missing (n=290,71). We also excluded patients with unknown discharge disposition (n=98,38), leaving 117,916 patients for analysis in the CAD cohort.

GWGT-Stroke Cohort

In the GWGT-Stroke cohort, there were a total of 2,175,050 consecutive admissions at 1,706 hospital sites from April 2003 to September 2012. We limited our analysis to patients with the diagnosis of AIS (n=1,338,013). To explore the association of smoking with in-hospital mortality among patients presenting with the first index event, we excluded patients with a previous history of Stroke/transient ischemic attack (n=456,318) and patients from hospitals with >25% medical history panel missing (n=117,29). We also excluded patients with unknown discharge disposition (n=23,338), leaving 846,628 patients for analysis in the AIS cohort.

Because the cases are all deidentified, it is possible that some patients represent multiple case entries across the 2 modules. Because of differences in the data elements collected, the 2 cohorts are separately analyzed in this report.

Definitions

Smoking

The study population was divided into 2 groups based on their past-year smoking status. Information about smoking status was abstracted from the medical record by a trained abstractor and classified according to the GWGT coding instructions, which are derived from the Medicare definition of smoking status. Past-year smokers were defined as any cigarette use within the year preceding the event. Nonsmokers include those who have never smoked and those who have been abstinent for >1 year before the event. The data do not distinguish between former versus never smokers, nor does GWGT collect information on the dose and duration of smoking.
Clinical Outcomes
The primary outcome of interest was in-hospital mortality, which was defined as patients who expired in the emergency department or during the hospital stay. Hospital length of stay and discharge disposition were also analyzed as secondary outcomes. Discharge disposition was divided into home versus inpatient rehabilitation facility/skilled nursing facility.

Statistical Analysis
Patient demographics and clinical variables were analyzed for the 2 cohorts. Percentages were used for categorical variables and medians with interquartile ranges for continuous variables. Categorical data were analyzed by Pearson’s χ² and continuous data by Wilcoxon rank sum test. Logistic regression models with generalized estimating equations were used to account for within-hospital clustering and to compute odds ratios (ORs) for factors associated with in-hospital mortality in CAD and AIS cohorts. Specifically, compound symmetry (or exchangeable) working correlation structure was used in the generalized estimating equations model. In Stroke, there were 1706 hospitals (clusters), and the estimated correlation coefficient for the working exchangeable correlation was 0.0073. In CAD, there were 421 hospitals (clusters), and the estimated correlation coefficient was 0.0118. We first explored the confounding effect of age by developing a logistic model that contained only age and smoking. To develop fully adjusted multivariable models, we tested all available demographic and medical history variables, as well as calendar year, time in program (per year) and treating hospital characteristics. Stroke severity is a critical factor in predicting risk of stroke mortality; however, the most commonly used measure of stroke severity, the National Institutes of Health Stroke Scale (NIHSS), is often not documented in the medical record. To address this, in the GWTG-Stroke cohort we constructed 2 multivariable models: one including NIHSS and another without it. Results from the 2 models were similar, thus we report the ORs from the model including NIHSS as a covariate.

To determine whether the effect of smoking differed by age, we tested whether age-by-smoking interaction terms were statistically significant in the age-adjusted models as well as in the fully adjusted multivariable models. To illustrate the presence of effect modification by age, we repeated the multivariable analysis in different age strata (ie, <50, 50–59, 60–69, 70–79, 80–89, and ≥90). We reran the same multivariable model within each age stratum and report the adjusted ORs with 95% confidence intervals (CIs) for each. To further explore the relationship between age of onset and mortality risk, we also carried out an early onset sensitivity analysis. For both the CAD and the Stroke study populations, patients with age ≥60 years were excluded for this early onset sensitivity analysis. Patients with a medical history of CAD/MI (in the CAD cohort), and medical history of Stroke/transient ischemic attack (in the stroke cohort) were previously excluded in the primary analysis. A model for early onset of disease (<50 years versus 50–59 years) was built for both the CAD and the Stroke data sets using generalized estimating equations logistic regression. The probability of early onset was estimated via covariates observed at admission. Covariates in the model included sex, race, medical history, and body mass index. High risk of early onset was then defined as being above the 90th percentile of the predicted early onset probability. A high-risk indicator for early onset was then used to adjust the relationship between smoking and mortality in both the CAD and the Stroke data sets, following recommendations by VanderWeele et al. Finally, a bootstrap procedure was used to calculate the 95% CI for the point estimates. All P values are 2 sided, with values of P<0.05 considered statistically significant. All analyses were conducted by the statistical division of the Duke Clinical Research Institute using SAS software version 9.1.3 (SAS Institute, Cary, NC).

Results

CAD Cohort
Eighty percent of patients in the CAD cohort had an index diagnosis of acute MI and the overall prevalence of past-year smoking was 30.4% (35 872/117 916). Past-year smokers differed significantly in terms of both demographics and clinical characteristics from nonsmokers (Table 1). Smokers were substantially younger (mean difference, 13.1 years); only 8.6% of past-year smokers were ≥75 years of age compared with 39.9% of nonsmokers. Smokers were more often male and less often had a history of hypertension, dyslipidemia,
heart failure, renal insufficiency, and atrial fibrillation, but more often had COPD and asthma. They had similar rates of in-hospital interventions for coronary artery bypass graft surgery but a greater percentage of smokers underwent percutaneous coronary intervention or reperfusion therapy. We also observed that smokers were more likely to be admitted to hospitals that were large, academic centers, or in the South. Smokers had shorter median hospital length of stay and were more often discharged home, consistent with better short-term outcomes. In-hospital mortality in smokers was nearly half that of nonsmokers (2.7% versus 5.2%; \( P<0.0001 \)).

**AIS Cohort**

In the cohort with an index AIS event, the overall prevalence rate of past-year smoking was 20.4% (172 658/846 628). Differences in demographic and clinical characteristics between past-year smokers and nonsmokers were similar to those seen in the CAD cohort. In the AIS cohort, smokers were also substantially younger (mean difference, 10.5 years), more often male and less often white. They were also less likely to have a history of hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, and heart failure but more often had peripheral vascular disease (note that information on COPD and asthma are not collected in the GWTG-Stroke module). Smokers had less severe strokes on presentation, as measured by the median NIHSS. The rates of use of in-hospital prevention strategies (early antithrombotic therapy, dysphagia screening before oral intake, and deep vein thrombosis prophylaxis) and rates of complications (in-hospital pneumonia) were similar between smokers and nonsmokers, as was the use of intravenous thrombolytic therapy (tissue-type plasminogen activator within 3 hours of last known well). Similar to CAD, smokers in the AIS cohort were more likely to be admitted to hospitals that were large, academic centers, or in the South. Smokers had a shorter median hospital length of stay and were more often discharged home. In-hospital mortality among smokers in the AIS cohort was also half that of nonsmokers (2.7% versus 5.2%; \( P<0.0001 \)).

**Factors Associated With In-Hospital Mortality After CAD or AIS**

Smoking was associated with lower in-hospital mortality in both cohorts, with an unadjusted OR of 0.57 (95% CI, 0.53–0.61) in CAD and 0.56 (95% CI, 0.54–0.58) in AIS. This unadjusted mortality difference attenuated substantially after adjusting for only age with the ORs increasing to 0.98 (95% CI, 0.90–1.06) in the CAD cohort and 0.81 (95% CI, 0.78–0.85) in the AIS cohort. An age-by-smoking interaction term was significant in the CAD model (\( P=0.003 \)) but was not significant in the AIS model (\( P=0.14 \)). When the multivariable model was fully adjusted for all factors including age, we observed an overall OR of 0.86 in both cohorts (CAD: 95% CI, 0.79–0.95; AIS: 95% CI, 0.83–0.89).

We also carried out interaction analyses between race and smoking, and sex and smoking, as they have been previously reported to be associated with in-hospital mortality among the studied groups. The results showed that in the CAD model, race×smoking interaction (\( P=0.29 \)) and sex×smoking interaction (\( P=0.42 \)) were both nonsignificant. But in the AIS model, the race×smoking interaction (\( P<0.0001 \)) and sex×smoking interaction (\( P=0.019 \)) were both significant. When the AIS model was stratified by race, the OR for in-hospital mortality among white smokers (0.91 [95% CI, 0.87–0.95]) was higher than among nonwhite smokers (0.66 [0.61–0.71]). When stratified by sex, the OR for females (0.82 [0.78–0.87]) was similar to males (0.83 [0.79–0.87]), which could have been driven by the large sample size in our study.

Many factors were independently associated with in-hospital mortality in both the CAD and the AIS cohorts (Table 3). Increasing age (per decade), history of diabetes mellitus, and peripheral vascular disease were associated with higher in-hospital mortality in both the CAD and the AIS cohorts, whereas dyslipidemia with lower in-hospital mortality. In the

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**Table 2. Baseline Characteristics, Performance Measures, Hospital Characteristics, and Outcomes of Patients Admitted With Acute Ischemic Stroke by Smoking Status From April 2003 to October 2012**

<table>
<thead>
<tr>
<th>Factor</th>
<th>All (n=899295)</th>
<th>Smokers (n=183234)</th>
<th>Nonsmokers (n=716061)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*,†</td>
<td>70.3±14.8</td>
<td>59.8±12.5</td>
<td>73.0±14.1</td>
</tr>
<tr>
<td>Sex—Male, %*,†</td>
<td>48.5</td>
<td>59.1</td>
<td>45.8</td>
</tr>
<tr>
<td>Race—White, %*</td>
<td>69.3</td>
<td>66.2</td>
<td>70.1</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %*,†</td>
<td>75.3</td>
<td>64.7</td>
<td>78.0</td>
</tr>
<tr>
<td>Dyslipidemia, %*,†</td>
<td>39.0</td>
<td>32.7</td>
<td>40.6</td>
</tr>
<tr>
<td>Diabetes mellitus, %*,†</td>
<td>30.3</td>
<td>24.2</td>
<td>31.8</td>
</tr>
<tr>
<td>Atrial fibrillation, %*,†</td>
<td>17.4</td>
<td>6.3</td>
<td>20.2</td>
</tr>
<tr>
<td>Heart failure, %*</td>
<td>6.2</td>
<td>3.5</td>
<td>6.9</td>
</tr>
<tr>
<td>Peripheral vascular disease, %*</td>
<td>4.3</td>
<td>5.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Carotid stenosis, %*</td>
<td>3.1</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>NIHSS (Med [IQR]*,‡</td>
<td>4 (2–10)</td>
<td>4 (2–9)</td>
<td>4 (2–11)</td>
</tr>
<tr>
<td>In-hospital complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, %*,‡</td>
<td>3.6</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Hospital characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital type—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic, %*,‡</td>
<td>59.3</td>
<td>62.5</td>
<td>58.4</td>
</tr>
<tr>
<td>Region*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast, %</td>
<td>26.2</td>
<td>22.5</td>
<td>27.1</td>
</tr>
<tr>
<td>Mid west, %</td>
<td>20.2</td>
<td>22.6</td>
<td>19.6</td>
</tr>
<tr>
<td>South, %</td>
<td>35.7</td>
<td>40.1</td>
<td>34.6</td>
</tr>
<tr>
<td>West, %</td>
<td>17.9</td>
<td>14.8</td>
<td>18.7</td>
</tr>
<tr>
<td>No. of Beds*</td>
<td>436.3±321.7</td>
<td>453.6±309.0</td>
<td>431.9±324.8</td>
</tr>
<tr>
<td>Length of stay, d*</td>
<td>5.4±6.4</td>
<td>5.3±6.7</td>
<td>5.4±6.3</td>
</tr>
<tr>
<td>Discharge disposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home, %*</td>
<td>52.3</td>
<td>62.7</td>
<td>49.6</td>
</tr>
<tr>
<td>IRF/SNF, %*</td>
<td>43.2</td>
<td>34.4</td>
<td>45.5</td>
</tr>
<tr>
<td>In-hospital mortality, %*</td>
<td>5.3</td>
<td>3.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; IRF, inpatient rehabilitation facility; NIHSS, National Institutes of Health Stroke Scale; and SNF, skilled nursing facility.

*\( P<0.0001 \).

†Difference of >5% between smokers versus nonsmokers.

‡Missing=NIHSS, 42.5% in smokers versus 43.9% in nonsmokers; Pneumonia, 10.4% in smokers versus 11.0% in nonsmokers; and Hospital type, 6.9% in smokers versus 7.4% in nonsmokers.
Table 3. Multivariable Logistic Regression Model of Factors Significantly Associated With In-Hospital Mortality in Acute Ischemic Stroke and CAD Cohorts During the Study Period

<table>
<thead>
<tr>
<th></th>
<th>Acute Ischemic Stroke</th>
<th></th>
<th>CAD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.86</td>
<td>0.83–0.89</td>
<td>0.86</td>
<td>0.79–0.95</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>1.10</td>
<td>1.08–1.11</td>
<td>1.50</td>
<td>1.44–1.55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.15</td>
<td>1.12–1.18</td>
<td>1.26</td>
<td>1.18–1.35</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.86</td>
<td>0.83–0.88</td>
<td>0.60</td>
<td>0.56–0.64</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.19</td>
<td>1.13–1.25</td>
<td>1.31</td>
<td>1.19–1.44</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.25</td>
<td>1.21–1.28</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CAD/Previous MI</td>
<td>1.20</td>
<td>1.17–1.23</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.85</td>
<td>0.83–0.87</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS (per point)</td>
<td>1.12</td>
<td>1.12–1.13</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Race (white versus nonwhite)</td>
<td>1.14</td>
<td>1.10–1.18</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>COPD/Asthma</td>
<td>NS</td>
<td>NS</td>
<td>1.27</td>
<td>1.17–1.37</td>
</tr>
<tr>
<td>Heart failure</td>
<td>NS</td>
<td>NS</td>
<td>1.46</td>
<td>1.35–1.58</td>
</tr>
<tr>
<td>Hypertension</td>
<td>NS</td>
<td>NS</td>
<td>0.85</td>
<td>0.80–0.91</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>NS</td>
<td>NS</td>
<td>1.42</td>
<td>1.28–1.57</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>NS</td>
<td>NS</td>
<td>1.63</td>
<td>1.47–1.80</td>
</tr>
</tbody>
</table>

Acute ischemic stroke model included: NIHSS, sex, age, race, atrial fibrillation/flutter, prosthetic heart valve, previous stroke/TIA, carotid stenosis, diabetes mellitus, peripheral vascular disease, hypertension, dyslipidemia, BMI, calendar time (per year), time in program (per year), annual stroke discharges, bed size, region, and teaching status. CAD model included: age, sex, race, COPD or asthma, diabetes mellitus (combined), heart failure, hypertension, hyperlipidemia, previous MI, peripheral vascular disease, renal insufficiency, insurance, BMI, calendar time (per year), time in program (per year), annual stroke discharges, bed size, region, and teaching status. BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; NS, not significant; and TIA, transient ischemic attack.

Early Onset Sensitivity Analysis

A separate sensitivity analysis was conducted among patients <60 years of age. After regression adjustment for high risk of early onset (<50 years of age), the relationship between smoking and mortality remained significant in both the CAD and the AIS populations (Table 5). The OR for smoking in the AIS model was 0.77 (95% CI, 0.70–0.84) and in the CAD model was 0.72 (95% CI, 0.60–0.86).

Discussion

Our analysis of a large, contemporary national population of patients from >2000 hospitals participating in the GWTG-CAD and GWTG-Stroke programs across the United States demonstrates that smokers present with these acute vascular events at a significantly earlier age, with fewer vascular risk factors, and have lower in-hospital mortality and shorter hospital length of stay when compared with those patients without past-year smoking. Even after adjustment for measured covariates, the adjusted odds of in-hospital mortality were substantially lower in both CAD and AIS cohorts. We also explored the presence of effect modification of smoking across different age strata, that is, whether the association between smoking and mortality differed by age group.

We restricted our cohort to those with a first ever index event so as to avoid any influences because of biological or behavioral responses to a previous vascular event that preceded the index event entered into the registry. This analysis allows us to focus on the age of first vascular event and adjust for that in the models. However, after adjustment for age and other known risk factors in this population with first ever stroke or coronary admission, the paradoxical association between smoking and mortality was in fact stronger in younger versus older age groups in both the CAD and AIS cohorts. This analysis suggests the presence of strong effect modification by age because the association is larger in younger age groups.

This apparent smokers’ paradox should not be interpreted as a benefit of cigarette smoking on mortality in these conditions because our study provides direct confirmatory evidence that the hazardous effects of smoking are manifested as the occurrence of CAD and AIS events years earlier than might otherwise have occurred in the absence of smoking. Although it is likely that unmeasured confounders account for much of the observed association, we cannot exclude the possibility that the biology of these atherosclerotic events is altered by the age of the index event.

The overall prevalence rate of smoking reported in this study is similar to previously published reports. Cigarette smoking is a major risk factor for atherosclerotic vascular diseases. Consistent with this risk, patients who were past-year cigarette smokers in our study presented with CAD or AIS events at substantially younger ages are compared with nonsmokers. They were also less likely to have other traditional...
vascular risk factors compared with nonsmokers. In previous studies, older age has been consistently regarded as the most important factor influencing early prognosis after major atherosclerotic event. In our study, cigarette smokers were on average at least 10 years younger in both the CAD and the AIS cohorts when compared with nonsmokers, and age-related differences contributed to the unadjusted survival differences. Despite adequate adjustment for age and carrying out additional early onset sensitivity analyses, the reduced mortality associated with smoking persisted. Although previous studies have suggested that this persistent association of smoking with lower short-term mortality is because of continued confounding because of substantial age difference, our study is the first to be sufficiently powered to allow for multivariable analyses to be repeated across the full spectrum of age strata and in probability-based, early onset sensitivity analyses.

We hypothesized that because atherosclerosis is such a dominant cause of both these diseases that we might gain insights by evaluating both cohorts simultaneously. We observed that the mortality difference diminished substantially with increasing age, especially in the CAD cohort. In this cohort, association of smoking with lower in-hospital mortality was found only among younger patients, whereas in patients >69 years of age, the rate of mortality reversed and was higher among smokers when compared with nonsmokers, although not statistically significant. These data indicate the overall association of smoking with lower in-hospital mortality in CAD is largely driven by the effect of smoking in younger age groups. In the AIS cohort, although the association of smoking with lower in-hospital mortality attenuated in strength with increasing age, the association persisted in older patients only disappearing after 79 years of age. This finding suggests that there may be either other unmeasured confounders present in the AIS cohort that are not important in explaining CAD mortality, or that the biological effect of smoking on mortality is different between patients with stroke versus CAD. Because of our large sample size and availability of stroke severity measurement in >50% of cases, we were also able to control for initial stroke severity in our model, which has not been previously reported. Despite including the NIHSS that plays a dominant role in predicting inpatient stroke mortality, it is notable to see a persistent association with smoking and mortality among the AIS cohort.

Previous reports have examined the possible biological effects of smoking on various potential mechanisms of initiation and resolution of ischemia in the arterial circulation. Smoking has been associated with increased hematocrit, platelet activation and aggregation, vasoconstriction,
increased circulating levels of fibrinogen, thrombin generation, impaired endogenous fibrinolytic capacity, and increased response to clopidogrel.\textsuperscript{7,35–38} As a result, the pathogenesis of vascular occlusions in smokers may be more because of changes in thrombogenicity than in atherosclerotic plaque rupture or morphology. This may be particularly true in those patients with fewer clinically manifest traditional atherosclerosis risk factors, whereas in nonsmokers, occlusion may be more frequently because of rupture or ulceration of atherosclerotic plaque with formation of platelet-rich clot. All these may reflect a greater propensity for spontaneous thrombolysis or response to therapeutic thrombolysis in smokers, which has been reported in several studies showing the beneficial association of smoking among patients with CAD and AIS receiving thrombolysis.\textsuperscript{3,4,32} In 2 major studies for patients with AIS, both exploring the association among patients who received intravenous thrombolysis, results showed that smoking was independently associated with improved recanalization and reperfusion, indicating that thrombotic therapy appeared to act more effectively in smokers.\textsuperscript{4,32} It is possible that an increased likelihood of spontaneous or pharmacological early recanalization is contributing to greater survival among smokers. In addition, it may be that the prevalence of ischemic stroke subtypes associated with better survival (eg, small vessel atherosclerosis) is more common among smokers than subtypes associated with worse survival (eg, cardioembolism). Because GWTG does not collect ischemic stroke subtypes, we are unable to estimate the association of stroke subtype and mortality.

Our present analysis of smoking and in-hospital mortality has some important limitations. We used the GWTG definition of smoking, which is derived from the Medicare reporting and quality programs that define active smoking as any cigarette use in the past year. Therefore, our cohort of smokers is heterogeneous and includes those whose use in the past year may not be reflective of their cumulative previous exposures. Former heavy smokers who quit >1 year ago because of other comorbid events, which could put them at higher risk of an MI or stroke are not classified as smokers in this study or distinguishable from never smokers. Because of this, we are unable to quantify the smoking exposure and analyze the association of total smoking exposure with the age of onset, mortality, or other outcomes. Although the data abstraction is complete and has been shown to be accurate,\textsuperscript{39} clinical variables and in-hospital complications that are not documented in the medical record could be missing and may contribute to unmeasured confounding. Duration and severity of comorbid conditions were not collected and may also contribute to residual confounding. The impact on mortality of subsequent admissions with stroke or CAD was not evaluated in this model, and might produce different estimates.

In summary, in our large national, contemporary cohort of patients hospitalized with first ever CAD or AIS events, we found that smoking was independently associated with lower rates of in-hospital mortality. Whether this association is driven by unmeasured confounders or by differences in pathophysiological processes of vascular occlusion in smokers versus nonsmokers remains to be established. Further clinical and prospective population-based studies are needed to explore variables that contribute to outcomes in these patients.

Disclosures
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References
5. Grines CL, Topol EJ, O’Neill WW, George BS, Kereiakes D, Phillips HR, Leimberger JD, Wooddief LH, Califf RM. Effect of cigarette smoking on


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