Association of Smoking Cessation and Weight Change With Cardiovascular Disease Among Adults With and Without Diabetes

Carole Clair, MD, MSc
Nancy A. Rigotti, MD
Bianca Porneala, MD
Caroline S. Fox, MD, MPH
Ralph B. D’Agostino Sr, PhD
Michael J. Pencina, PhD
James B. Meigs, MD, MPH

Objective  To test the hypothesis that weight gain following smoking cessation does not attenuate the benefits of smoking cessation among adults with and without diabetes.

Main Outcome Measure  Incidence over 6 years of total CVD events, comprising coronary heart disease, cerebrovascular events, peripheral artery disease, and congestive heart failure.

Results  After a mean follow-up of 25 (SD, 9.6) years, 631 CVD events occurred among 3251 participants. Median 4-year weight gain was greater for recent quitters without diabetes (2.7 kg [interquartile range {IQR}, −0.5 to 6.4]) and with diabetes (3.6 kg [IQR, −1.4 to 8.2]) than for long-term quitters (0.9 kg [IQR, −1.4 to 3.2]) and nonsmokers. Pooled Cox proportional hazards models were used to estimate the association between quitting smoking and 6-year CVD events and to test whether 4-year change in weight following smoking cessation modified the association between smoking cessation and CVD events.

Conclusions and Relevance  In this community-based cohort, smoking cessation was associated with a lower risk of CVD events among participants without diabetes, and weight gain that occurred following smoking cessation did not modify this association. This supports a net cardiovascular benefit of smoking cessation, despite subsequent weight gain.

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cern because it is a risk factor for poor diabetes control and increased risk of morbidity and mortality. Weight control is a key factor in diabetes management to prevent microvascular and CVD complications. The effect on CVD of potential weight gain following smoking cessation is not well understood. One study indirectly assessed the association of weight gain following smoking cessation with CVD in Japanese men without diabetes and estimated that successful quitters had a 24% decreased risk of coronary heart disease (CHD) compared with smokers despite weight gain, but that study did not measure actual CHD events. Among patients with diabetes, studies have demonstrated the CVD benefits of quitting smoking, but none have assessed the effect on CVD of weight change following smoking cessation.

The aim of this study was to assess the association between 4-year weight gain following smoking cessation and CVD event rate among adults with and without diabetes. We tested the hypothesis that quitting smoking decreases CVD risk compared with continuing smoking, regardless of any weight gain associated with smoking cessation, in adults with and without diabetes.

METHODS
Study Population and Study Sample
We analyzed data from the Offspring cohort of the Framingham Heart Study. The Framingham Offspring cohort began in 1971 and enrolled 5124 children and spouses of children of the original Framingham Heart Study cohort. As previously described, participants of the Offspring cohort underwent repeated examinations approximately every 4 to 6 years. The present study sample comprised 3251 adult participants free of CVD at the beginning of examination 3. The Boston Medical Center institutional review board approved the study. All participants provided written informed consent.

Assessment of Diabetes, Smoking, Weight, and Weight Change
At each examination, participants underwent a physical examination that included medical history and collection of fasting blood samples for lipid profile and measurement of blood glucose levels. Participants were considered to have diabetes if they had fasting plasma glucose levels of 126 mg/dL (7 mmol/L) or greater or if they were treated with insulin or an oral hypoglycemic agent. In the Offspring study, 99% of the cases of diabetes are type 2 diabetes. Type 1 diabetes was not excluded from our analyses.

Participants were classified as current smokers, former smokers, and non-smokers based on self-reported data at each examination. Current cigarette smoking was defined as regularly smoking cigarettes at any time during the prior year. For former smokers, information on the exact smoking cessation date and therefore time since quitting was not available. Therefore, we defined recent quitters as participants who reported not smoking at one examination and had reported smoking at the examination 4 years earlier (ie, who had quit for ≤4 years). We defined long-term quitters as participants who reported not smoking for 2 or more consecutive examinations after an examination at which they had been a smoker (ie, who had quit for >4 years).

For secondary analyses, we created another smoking category differentiating sustained smokers (participants who were smokers during the entire duration of the study), never smokers (participants who were never smokers during the entire study), quitters (smokers who had made a quit attempt and remained abstinent for the rest of the study), and relapsers (participants who alternated between smoking and smoking cessation during the study).

Participants were weighed in light street clothes per standard protocol using a calibrated scale, identically at each examination. Height was measured at the baseline examination. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Weight change was calculated at each examination as weight at the current examination minus weight at the previous examination, reflecting 4-year weight change.

At each examination, systolic blood pressure was measured twice after the participant had been sitting at least 5 minutes. The mean value was used for the analyses. Information about alcohol consumption, medication, and family history of diabetes was collected and updated at each examination.

CVD Outcomes
The primary outcome was total CVD events. The Framingham Heart Study defined CVD events as a composite of CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral arterial disease (intermittent claudication), and congestive heart failure. In secondary analyses we considered a more restrictive outcome of hard CHD, defined as myocardial infarction and coronary death only. Surveillance for CVD consisted of regular examinations at the Framingham Heart Study clinic and review of medical records from outside physicians’ offices and hospitalizations. A panel of 3 experienced investigators evaluated all pertinent medical records, including prevalent CVD risk factors, for suspected new events. More details regarding the CVD adjudication methods have been described.

Follow-up time was defined by the time from the baseline examination until the first event date (for participants who had an event) or was censored at the last contact date (for participants who did not have any event or were lost to follow-up) or the date of death (for participants who died of non-CVD causes). There were 3251 participants at examination 3 (1984-1987) and 2394 at examination 8 (2005-2008), meaning that 73.6% of participants had at least 1 period of follow-up. Missing data were excluded from analysis.
SMOKING CESSATION, WEIGHT CHANGE, AND CARDIOVASCULAR DISEASE

Statistical Analysis
The analyses began with the third examination (1984-1987) and extended through December 31, 2011 (end of the eighth examination). To have pools of similar lengths, we pooled examinations 3 and 4 and examinations 5 and 6 and kept examinations 7 and 8 as separate pools; we thus obtained 4 pools of a mean duration of 6 years (ranging from 5.2 to 7.0 years). We examined each 6-year examination pool as a follow-up study and considered smoking status (independent variable) at the beginning of each examination and CVD event (dependent variable) during the 6-year follow-up. At the beginning of each examination, participants who had developed a CVD outcome were removed from the sample. We calculated mean 4-year weight change preceding the beginning of each examination to assess the association with weight gain concomitant with or shortly following smoking cessation.

We calculated age- and sex-adjusted 6-year incidence rates of CVD and corresponding 95% CIs. For each period we estimated the likelihood of a CVD event according to smoking status using Cox proportional hazards models and pooled the results of each model. At each examination, risk factors such as smoking status, weight, blood pressure, and cholesterol level were updated based on new information. Pooling Cox models of each study period allowed consideration of changes in those risk factors over the next period with updated exposures.

Preplanned analyses were conducted separately for study participants with and without diabetes, based on the hypothesis that weight change following smoking cessation might have a different association with CVD events depending on diabetes status. Hazard ratios (HRs) for CVD were calculated for recent quitters, long-term quitters, and nonsmokers compared with smokers. Smokers were chosen as the reference group to assess the association between quitting smoking and CVD as recommended by the 1990 Surgeon General’s report.15

We built minimally adjusted models (adjusted only for age and sex) and models adjusted for CVD risk factors (age, sex, alcohol consumption, self-reported family history of diabetes, high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C] levels, triglyceride level, systolic blood pressure, baseline BMI, taking cholesterol-lowering medication, and taking antihypertensive medication). The choice of the covariates included in the model adjusted for CVD risk factors was based on a priori knowledge. To assess the modification of weight change following smoking cessation on CVD risk, we built a third model adding 4-year weight change prior to the index examination to the CVD risk-factor-adjusted model. We verified the proportional hazards assumption using graphical methods and by including time-dependent covariates in the models.

Secondary analyses used the more restrictive outcome of hard CHD. Minimally adjusted and CVD risk-factor-adjusted pooled Cox models assessed the association between weight gain following smoking cessation and hard CHD. We performed subgroup analyses by amount of weight gain. For these analyses, given the lack of interaction by diabetes, we pooled participants with and without diabetes to have more power and avoid empty categories. We built 3 weight-change categories: participants who lost weight, those who gained 0 to 5 kg, and those who gained 5 kg or more.

Exploratory analyses assessed the association between smoking cessation, weight change, and incidence of high blood pressure and hyperlipidemia. High blood pressure was defined as diastolic blood pressure 90 mm Hg or greater, systolic blood pressure 140 mm Hg or greater, or taking antihypertensive drugs. Hypercholesterolemia was defined as LDL-C level greater than 160 mg/dL (4.1 mmol/L) or taking cholesterol-lowering medications. For these analyses we used pooled logistic regression models with the same time intervals as the pooled Cox regression models. We examined each of the 4 pools as a mini follow-up study and considered smoking status at the beginning of each examination and incidence of high blood pressure or hyperlipidemia during the 6-year follow-up. Participants with high blood pressure or hyperlipidemia were removed from analyses at the beginning of each examination.

We considered a 2-sided P < .05 as statistically significant. For the comparison of weight change between the 4 different smoking categories we used the Bonferroni method to adjust for multiple pairwise comparisons and defined a corrected P value of .01 (4 pairwise comparisons). We tested if there was an interaction between smoking and diabetes by entering an interaction term in the Cox models. The test for trend was calculated by entering the smoking ordinal categories (1 = smokers, 2 = recent quitters, 3 = long-term quitters, 4 = nonsmokers) as a continuous variable in the Cox model. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

RESULTS
From the third examination, 3251 participants underwent follow-up over the course of 4 examinations and contributed 11 148 person-examinations. Baseline characteristics of participants at the beginning of each examination are reported in TABLE 1. Smoking prevalence decreased from 31% at the third examination to 13% at the eighth examination.

Weight gain occurred over 4 years in participants without and with diabetes (TABLE 2). Among participants without diabetes, recent quitters gained significantly more weight (median, 2.7 kg [interquartile range {IQR}, −0.5 to 6.4]) than long-term quitters (0.9 kg [IQR, −1.4 to 3.2]), smokers (0.9 kg [IQR, −1.8 to 4.5]), and nonsmokers (1.4 kg [IQR, −1.4 to 3.6]) (P <.001 for each pairwise comparison). Long-term quitters did not have a statistically significant difference in weight gain compared with nonsmokers and smokers, taking into account Bonferroni adjustment (P = .02 for both comparisons). Among patients with
diabetes, recent quitters also gained significantly more weight (3.6 kg [IQR, -1.4 to 8.2]) than smokers (0.9 kg [IQR, -3.2 to 4.1]), long-term quitters (0.0 kg [IQR, -3.2 to 3.2]), and nonsmokers (0.5 kg [IQR, -2.7 to 3.6]) (P < .001 for each pairwise comparison).

Median 4-year weight change prior to each index examination according to smoking status is shown in eFigure 1, available at http://www.jama.com. Among people without and with diabetes, there was no clear trend in weight change over time for recent quitters (P = .97 and P = .32 for trend, respectively). In contrast, among long-term quitters, weight gain tended to decrease over time (P < .001 and P = .01 for trend).

Diabetes incidence over time according to smoking status is shown in eFigure 2. Smokers had on average a higher incidence of diabetes compared with nonsmokers and long-term quitters. Recent quitters had a lower incidence at the beginning of the study; incidence became greater than that for smokers at examinations 5 and 6 and decreased thereafter.

During follow-up, 631 CVD events occurred in 11 148 person-examinations. Of these, 337 (53.4%) were CHD events (TABLE 3). In study participants without diabetes, age- and sex-adjusted 6-year incidence rates of CVD were higher among smokers, followed by recent quitters, long-term quitters, and nonsmokers (FIGURE 2). The same pattern but with higher rates was observed among study participants with diabetes. There was no evidence of interaction between smoking and diabetes on the risk of CVD (P = .12 for interaction).

The main results for the association between smoking cessation and CVD events are summarized in TABLE 4. Among participants without diabetes, the age- and sex-adjusted incidence rates were lower for nonsmokers (2.43 per 100 person-examinations [95% CI, 1.95-3.03]), recent quitters (3.22 per 100 person-examinations [95% CI, 2.06-4.50]), and long-term quitters (3.06 per 100 person-examinations [95% CI, 2.56-3.67]), compared with smokers (5.89 per 100 person-examinations [95% CI, 4.86-7.11]). In the age- and sex-adjusted model, compared with smokers, HRs for CVD were 0.32 (95% CI, 0.22-0.45) for nonsmokers, 0.50 (95% CI, 0.25-1.00) for recent quitters, and 0.50 (95% CI, 0.37-0.68) for long-term quitters. Adjusting for CVD risk factors did not change this association significantly. Adding weight change to the model adjusted for CVD risk factors did not modify the HRs of CVD for recent and long-term quitters. There was an apparent dose-response relationship with smoking and CVD risk (P < .001 for trend across smoking categories).

Among participants with diabetes, the age- and sex-adjusted incidence rates were lower for nonsmokers (4.70 per 100 person-examinations [95% CI, 3.17-6.89]), recent quitters (6.11 per 100 person-examinations [95% CI, 2.89-12.37]), and long-term quitters (6.53 per 100 person-examinations [95% CI, 4.73-8.96]), compared with smokers (7.03 per 100 person-examinations [95% CI, 4.54-10.63]). In the model adjusted for CVD risk factors, the HR for CVD for nonsmokers was 0.41 (95% CI, 0.19-0.86), for recent quitters 0.49 (95% CI, 0.11-2.16), and for long-term quitters 0.53 (95% CI, 0.27-1.06), compared with smokers. Adjusting for CVD risk factors and weight change did not significantly change these estimates.

In secondary analyses restricting the outcome to hard CHD, 160 events oc-
Table 2. Four-Year Weight Change for Participants

<table>
<thead>
<tr>
<th>No diabetes</th>
<th>Smokers</th>
<th>Recent Quitters</th>
<th>Long-term Quitters</th>
<th>Nonsmokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>978</td>
<td>205</td>
<td>676</td>
<td>920</td>
</tr>
<tr>
<td>BMI at examination 3a</td>
<td>25.4 (4.2)</td>
<td>26.5 (4.6)</td>
<td>25.9 (3.9)</td>
<td>25.4 (4.3)</td>
</tr>
<tr>
<td>Weight at examination 3, kg</td>
<td>73.8 (15.7)</td>
<td>77.3 (15.7)</td>
<td>74.3 (14.3)</td>
<td>71.4 (14.6)</td>
</tr>
<tr>
<td>4-y weight change, kg</td>
<td>Mean (SD) [95% CI]b</td>
<td>1.2 (5.4) [0.9 to 1.4]</td>
<td>3.0 (7.3) [2.4 to 3.7]</td>
<td>0.9 (5.0) [0.7 to 1.0]</td>
</tr>
<tr>
<td>No diabetes</td>
<td>Median (IQR)</td>
<td>0.9 (1.8 to 4.6)</td>
<td>2.7 (0.5 to 6.4)</td>
<td>0.9 (1.4 to 3.2)</td>
</tr>
</tbody>
</table>

| Diabetes | No. of participants | 148 | 31 | 118 | 148 |
| No. of participants | 28.7 (5.2) | 29.8 (5.1) | 29.1 (5.6) | 30.3 (5.8) |
| BMI at examination 3, kg | 84.2 (17.7) | 88.3 (15.8) | 85.8 (17.1) | 84.2 (17.0) |
| 4-y weight change, kg | Mean (SD) [95% CI]b | 0.0 (7.4) [-0.1 to 1.1] | 3.8 (7.6) [2.1 to 5.4] | 0.1 (6.4) [-0.5 to 0.6] | 0.5 (6.7) [-0.1 to 1.1] |
| No diabetes | Median (IQR) | 0.9 (-3.2 to 4.1) | 3.6 (-1.4 to 8.2) | 0.0 (-3.2 to 3.2) | 0.5 (-2.7 to 3.6) |

Abbreviations: BMI, body mass index; IQR, interquartile range.

Table 3. Cardiovascular Disease Events and Coronary Heart Disease Events Counts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CVD events (n = 631 events)</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>337 (53.4)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>147 (23.3)</td>
</tr>
<tr>
<td>Death from CVD</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>73 (11.6)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>67 (10.6)</td>
</tr>
<tr>
<td>Hard CHD events (n = 160 events)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>155 (96.9)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>5 (3.1)</td>
</tr>
</tbody>
</table>

Abbreviation: CHD, coronary heart disease; CVD, cardiovascular disease.

SMOKING CESSATION, WEIGHT CHANGE, AND CARDIOVASCULAR DISEASE

Among participants without diabetes, the age- and sex-adjusted incidence rates were lower for recent quitters (3.93 per 100 person-examinations [95% CI, 1.12-12.28]) and long-term quitters (2.32 per 100 person-examinations [95% CI, 1.18-4.55]), compared with smokers (5.12 per 100 person-examinations [95% CI, 2.33-10.75]). In the age- and sex-adjusted model, compared with smokers, the HRs for CHD were 0.63 (95% CI, 0.22-1.83) for recent quitters and 0.32 (95% CI, 0.18-0.56) for long-term quitters (TABLE 5). Adjusting for CVD risk factors and weight change did not change this association significantly.

Among participants with diabetes, the age- and sex-adjusted incidence rates were lower for recent quitters (5.49 per 100 person-examinations [95% CI, 3.78-7.88]) and long-term quitters (4.84 per 100 person-examinations [95% CI, 4.06-5.77]), compared with smokers (9.30 per 100 person-examinations [95% CI, 7.67-11.22]). In the model adjusted for CVD risk factors, the HR for CHD for recent quitters was 0.40 (95% CI, 0.05-3.17) and for long-term quitters was 0.40 (95% CI, 0.16-1.02), compared with smokers. Adjusting for CVD risk factors and weight change did not significantly change these estimates.

Using the alternate smoking definition, among people without diabetes, quitters had a significantly decreased risk of CVD compared with sustained smokers (HR, 0.46 [95% CI, 0.33-0.63]) in the model adjusted for CVD risk factors (eTable 1). Among relapsers, the point estimate for the association was weaker (HR, 0.60 [95% CI, 0.35-1.04]) and not significant. Adjusting for weight change did not significantly modify these estimates. Among people with diabetes the CVD risk factor–adjusted HR of CVD events was 0.56 (95% CI, 0.28-1.11) for quitters and 0.24 (95% CI, 0.03-1.84) for relapsers, compared with sustained smokers.

In subgroup analyses stratified by amount of weight gain (eTable 2), among participants who lost weight and those who gained 0 to 5 kg, the CVD risk factor–adjusted HRs of CVD were significantly lower only for long-term quitters compared with smokers (HR, 0.41 [95% CI, 0.27-0.63] for those who lost weight and HR, 0.39 [95% CI, 0.25-0.61] for those who gained 0-5 kg). Among participants who gained 5 kg or more there were no statistically significant associations, although numbers of events in these categories were small.

Exploratory analyses were performed to assess the association between smoking cessation and weight gain with high blood pressure (eTable 3) and hyperlipidemia (eTable 4). No statistically significant associations were found for recent quitters or long-term quitters among study participants with or without diabetes.

COMMENT

Concerns have been raised about the potential risks for CVD posed by weight...
gain following smoking cessation. However, in this study, 4-year weight gain associated with smoking cessation did not outweigh the benefits for CVD risk associated with smoking cessation. Among participants without diabetes, recent quitters had an HR of 0.47 and long-term quitters an HR of 0.46 in models adjusted for CVD risk factors, compared with smokers. Among participants with diabetes, there were similar point estimates, although the CVD risk reduction associated with quitting smoking was not statistically significant. We observed similar benefits associated with smoking cessation for total CVD and for fatal and nonfatal CHD, with the cessation benefits not offset by weight gain. An alternate smoking definition that takes into account smoking exposure over time suggested the possibility of a dose-response relationship, with never smokers having the lowest risk of CVD compared with sustained smokers, followed by quitters and relapers. Subgroup analyses by amount of weight gain had small numbers of events in many groups, limiting ability to draw unambiguous conclusions, but suggested that at least among participants who gained less than 5 kg there was a CVD benefit associated with smoking cessation.

The amount of weight gain following smoking cessation was comparable with that observed in other studies. Recent analyses of 3 different US cohorts showed that within each 4-year period participants gained a mean of 1.52 kg, compared with a mean 4-year weight gain of 1.39 kg among participants without diabetes in our study. As observed in our study, weight gain following smoking cessation was observed in recent (≤4 years) quitters but decreased thereafter.

To our knowledge, only 1 study has indirectly assessed the effect of weight gain following smoking cessation. However, in a study of 3 different US cohorts, showed that within each 4-year period participants gained a mean of 1.52 kg, compared with a mean 4-year weight gain of 1.39 kg among participants without diabetes in our study. As observed in our study, weight gain following smoking cessation was observed in recent (≤4 years) quitters but decreased thereafter.

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gain following smoking cessation on CVD in people without diabetes. The investigators followed up 1995 Jap-
nese male workers for 4 years and found that smokers who had successfully quit smoking for at least 6 months gained weight and had a significant worsening of their blood pressure and levels of total cholesterol, triglycerides, and fasting blood glucose. In con-
trast, their HDL-C levels improved, and combined with cessation of smoking, successful quitters had a 24% decreased estimated risk of CHD (using a prediction rule based on CHD risk factors) compared with smokers, despite weight gain. Numerous studies have shown the immediate benefits of smoking cessation on CHD, or on overall and CVD mortality, but they did not take into account the effect of weight change following smoking cessation. Being able to quantify the association of weight gain after smoking cessation with actual CVD risk may allow for better counseling of patients.

There is scant literature related to the effects on CVD of smoking cessation in populations with diabetes. Several studies have shown the benefits of quitting smoking for CHD and all-cause mortality in people with diabetes, but none of these studies accounted for potential weight gain subsequent to smoking cessation in their analyses. In our study, one possible reason for not finding the same significant risk reductions in participants with diabetes as in participants without diabetes is limited power, because point estimates for participants with diabetes were similar to estimates for those without diabetes but not statistically significant.

There are multiple potential mechanisms of the decrease in risk in CVD associated with smoking cessation. Cigarette smoking has short- and long-term cardiovascular effects that are reversible shortly after cessation. Cigarette smoking increases heart rate and myocardial contractility, induces arterial vasoconstriction, increases platelet aggregability, reduces oxygen delivery, and in the long term induces endothelial injury and formation of atheroma. The increase in CVD risk associated with smoking is also mediated through cardiovascular risk factors such as an increase in LDL-C and triglyceride levels, a decrease in HDL-C levels, or an increase in levels of fasting blood glucose. Some of these cardiovascular risk factors, such as HDL-C levels or insulin sensitivity, improve after smoking cessation, independent of potential weight gain.

Strengths of this study include the ability to examine adults with and without diabetes to assess the association between weight change following smoking cessation and CVD. Data on smoking, diabetes, and CVD were collected rigorously at periodic examinations. Weight change was measured, not self-reported, at each examination. We adjusted for many CVD risk factors that could act as confounders. Using pooled Cox models accounted for time-varying covariates such as smoking status, weight, and weight change.

Limitations should also be considered. First, smoking status was self-reported, and there was no biochemical...
SMOKING CESSATION, WEIGHT CHANGE, AND CARDIOVASCULAR DISEASE

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Critical revision of the manuscript for important intellectual content: Clair, Rigotti, Porneala, Fox, D’Agostino, Pencina, Meigs.

Statistical analysis: Clair, Pomeala, D’Agostino, Meigs.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Rigotti reported serving as an unpaid consultant to Pfizer and Aller-Wellbeing Inc; conducting research projects spon- sored by Pfizer and Nabi Biopharmaceuticals; and receiving royalties from UpToDate Inc for chapters re- lated to smoking cessation. Dr Pencina reported serving as a data and safety monitoring board member for Tho- racs. No other authors reported disclosures.

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Previous Presentations: Parts of the data of this manu- script were presented as an oral presentation at the 34th annual meeting of the Society of General Intern- al Medicine in May 2011.

Online-Only Material: Tables 1-4, Figures 1 and 2, and Author Video Interview are available at http://www.jama.com.

Additional Contributions: Peter Shadre, MS (Gen- eral Medicine Division, Massachusetts General Hos- pital, Boston), contributed to the statistical analyses. He was compensated for his work.

REFERENCES


