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Smoking cessation and outcome after ischemic stroke or TIA

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Katherine Abigail Epstein

2018

SMOKING CESSATION AND OUTCOME AFTER ISCHEMIC STROKE OR TRANSIENT ISCHEMIC ATTACK

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People who smoke cigarettes are 2-4 times more likely to have a stroke¹ and 2-5 times more likely to have a myocardial infarction² compared with people who do not smoke. On a population level, it is estimated that smoking accounts for 33% of all cardiovascular deaths.³ Fortunately, quitting smoking can rapidly normalize risk. After an MI, smoking cessation reduces the risk of recurrent coronary events to the level of a never-smoker's after 3 years.⁴ While the benefits of smoking cessation in patients with cardiovascular disease are well-known, the benefits of smoking cessation after stroke have never been adequately examined and remain unquantified. In this research, we tested the hypothesis that smoking cessation after an ischemic stroke or transient ischemic attack (TIA) improves outcome, compared to continued smoking. We conducted a prospective observational cohort study of 1072 men and women who were current cigarette smokers at the time they were enrolled in the Insulin Resistance Intervention after Stroke (IRIS) trial. The IRIS trial was conducted during 2005-2015 to test the effectiveness of pioglitazone, compared with placebo, for prevention of stroke or MI among non-diabetic patients with a recent qualifying stroke or TIA; the main finding was that pioglitazone significantly reduced the risk of subsequent stroke or MI.⁵ A tobacco use history was obtained at baseline and updated during annual interviews. Cox regression models were used to estimate the

differences in rates of stroke, MI, or death between quitters and continuing smokers after 4.8 years of IRIS participation. Pre-specified adjustment variables were age, sex, stroke [vs. TIA] as index event, prior history of stroke, history of hypertension, history of coronary artery disease, systolic blood pressure, diastolic blood pressure, and pioglitazone treatment. By the time of randomization, 450 (42%) patients had quit smoking. Among quitters, the 5-year risk of stroke, MI, or death was 15.7%, compared to 22.6% for patients who continued to smoke (adjusted hazard ratio, 0.66; 95% confidence interval, 0.48-0.90). Cessation of cigarette smoking after an ischemic stroke or TIA was associated with significant health benefits over 4.8 years in the IRIS trial cohort.

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INTRODUCTION

Stroke is the fifth leading cause of death in the US and the second leading cause of death worldwide.⁶ Tobacco use results in a strong, dose-dependent increase in stroke risk^{7,8} and is estimated to be responsible for 12-15% of all stroke events.^{9,10} Smoking is therefore a leading preventable cause of stroke. Other well-documented harms of smoking include coronary and peripheral artery disease, chronic obstructive pulmonary disease, and cancer of the lung and urinary bladder. Despite decades of research on these adverse effects, 15% of adults in the US currently smoke cigarettes.¹¹ Use peaks at 21% for persons 25-44 years of age and falls to 7.9% after age 65 years.¹² Recent AHA guidelines for primary prevention of stroke include a Class I recommendation for abstinence from smoking.¹³ Although never smoking is undoubtedly the best strategy for primary prevention of stroke and other smoking-related harms, smoking cessation is increasingly recognized as a powerful intervention that can rapidly diminish risk for stroke or MI, and over time decrease a current smoker's risk to near that of a never-smoker's.¹⁴⁻¹⁸

Patients who have already experienced an ischemic stroke or TIA are at increased risk for future cardiovascular events, and therefore represent a high-risk group for whom interventions are likely to have a large impact.¹⁹ Smoking cessation for these patients is a logical choice for secondary prevention, but there are limited data quantifying the effect of cessation compared to continued smoking after an ischemic stroke or TIA. AHA guidelines for secondary prevention also include a Class 1 recommendation for abstinence or (if applicable) cessation from smoking after an ischemic stroke or TIA, but the level of evidence is only a C, meaning the recommendation is based on very limited populations evaluated, consensus opinions of experts, case studies, and/or accepted standard of care.¹⁹

The Class I recommendation for cessation or abstinence from smoking after a first stroke or TIA is primarily based on research from stroke-free populations showing that smoking cessation in midlife or even late-life is associated with rapid return toward normal of risk for vascular events.²⁰ There is no well-controlled study quantifying the risk reduction in patients who stop smoking after a stroke or TIA. By comparison, there is a substantial body of literature demonstrating the benefits of smoking cessation for patients with CAD²¹⁻²³ or post myocardial infarction.^{4,24} After an MI, smoking cessation reduces the risk of recurrent coronary events to the level of a never-smoker's after 3 years⁴ and the risk of mortality by 46% over 2-10 years. Smoking cessation for patients with CAD is associated with a 36% reduction in mortality over 3-7 years.²² Smoking cessation is a uniquely powerful intervention in secondary prevention of cardiovascular disease. By analogy, it is possible that smoking cessation is a uniquely powerful intervention in secondary prevention of stroke. Quantifying this risk reduction could be very helpful in guiding the efforts of stroke patients and their clinicians in reducing their risk of a future cardiovascular event. Among patients with a first-ever stroke, one third (32-39%) are current smokers, and less than half (22-43%) of these current smokers are able to quit smoking after their stroke.^{25,26} Among those who do quit, many may relapse. One study showed that 43% of smokers initially quit smoking after a stroke, whereas only 28% were still abstinent after 6 months.²⁶ Quantifying the health benefits of quitting smoking after a stroke may help patients and their doctors focus their efforts and attention on this important target for secondary prevention.

STATEMENT OF THE PURPOSE

The purpose of this study was to test the hypothesis that smoking cessation after an ischemic stroke or TIA will improve outcome relative to continued smoking.

The primary outcome was a composite of nonfatal stroke, nonfatal MI, or death. Secondary outcomes included nonfatal stroke alone, nonfatal MI alone, and all-cause death alone.

METHODS

Contribution of the student

The present study was a secondary analysis of the Insulin Resistance Intervention after Stroke (IRIS) dataset that was not pre-specified in the trial protocol. The idea for the study emerged from a conversation between the student and her mentor, Dr. Walter Kernan, on the general problem of over-diagnosis of chronic conditions. When it became apparent that the IRIS trial did not include data that would allow for an analysis of over-diagnosis in stroke, the student and mentor turned to the student's interest in psychiatry and addiction. They realized the IRIS trial data set was distinctive in containing detailed information on patients' tobacco use over 5 years of follow-up. The student then conducted a literature search and discovered a dearth of reliable information about the effects of smoking cessation after a stroke or TIA. She drafted a set of research aims and then worked in collaboration with Dr. Kernan and Dr. Catherine Viscoli to design the analyses and interpret the results. At every step, the student's initial proposals for methods, analysis, and interpretation drove the research and were used as the basis for team discussions. The student wrote the first draft of the manuscript, and revised it in collaboration

with Drs. Kernan and Viscoli. Description of methods for the original IRIS trial are based on Viscoli *et al.* 2014 and Tables 1 and 2 are modified from Viscoli *et al.* 2014, with permission from the authors. Portions of text and tables are drawn verbatim from the student's first author publication.²⁷

Study objective

The IRIS trial (www.clinicaltrials.gov NCT00091949) was an investigator-initiated, international, multicenter, randomized, double-blind, placebo-controlled study in 3,876 nondiabetic patients with insulin resistance and a recent ischemic stroke or TIA. The objective was to evaluate whether pioglitazone, an insulin-sensitizing drug of the thiazolidinedione (TZD) class, when initiated less than 6 months after an ischemic stroke or TIA, reduces the incidence of subsequent stroke and MI. The main finding was that pioglitazone reduced the risk of subsequent stroke or MI.

The objective of this secondary analysis of the IRIS trial was to evaluate whether smoking cessation after an ischemic stroke or TIA is associated with a lower incidence of subsequent nonfatal stroke, nonfatal MI, or all-cause death, compared with continued smoking.

Study population

The study population for this thesis comprised patients who were current cigarette smokers at the time of the ischemic stroke or TIA that qualified them for subsequent enrollment in the IRIS trial. Inclusion and exclusion criteria for the IRIS trial are shown in Table 1. Eligible participants were ≥ 40 years of age, had an ischemic stroke or TIA within the past six months, and had no

prior or current diagnosis of diabetes. An ischemic stroke was defined by focal neurologic deficits persisting for ≥ 24 hours and/or a new area of infarction on brain imaging in an appropriate location. Patients who had isolated symptoms affecting only one eye were required to have imaging evidence of a new ischemic brain abnormality in an appropriate location. After recruitment began in January 2005, the protocol was changed in November 2005 to allow enrollment of participants with nonvalvular atrial fibrillation. In 2006, eligibility was further expanded to include patients with TIAs. A TIA was defined as an acute neurologic change attributable to brain ischemia that lasted ≥ 10 minutes but < 24 hours, without imaging evidence of new cerebral infarction. To enroll patients who likely had a vascular etiology for their symptoms, eligible TIA deficits were limited to hemiplegia or hemiparesis, monoplegia or monoparesis, or a language disturbance besides isolated dysarthria.²⁸ In 2007, eligibility was expanded to include patients with non-focal neurological symptoms (*e.g.*, dizziness, confusion, and headache) lasting ≥ 24 hours and accompanied by a focal abnormality detected on diffusion weighted magnetic resonance imaging (MRI).

Patients with insulin resistance were identified by a value > 3.0 on the Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) (calculated as [fasting insulin, $\mu\text{U/mL}$ x fasting glucose, mmol/L]/22.520). Results from the HOMA-IR are closely associated with results of more complex tests of insulin sensitivity, as well as with glucose intolerance,²⁹ progression to diabetes mellitus type II,^{30,31} metabolic syndrome,³² and cardiovascular disease.^{33,34} A HOMA-IR > 3.0 was selected as the diagnostic criterion for the IRIS trial because this value demarcates the top quartile of nondiabetic patients with insulin resistance in general populations.³⁵ In

epidemiologic studies, this top quartile has increased risk for cardiovascular disease compared with the lower three quartiles.³⁴

Since TZD drugs are known to cause or exacerbate congestive heart failure (CHF), patients with New York Heart Association class 3 or 4 heart failure were excluded, although patients with class 2 CHF (*i.e.*, symptomatic with moderate activity) and an ejection fraction $\geq 40\%$ were initially eligible at US sites. Because pioglitazone can also cause edema, patients with advanced lower extremity edema were also excluded.

In 2007, after new prescribing guidelines for pioglitazone were issued, patients with symptomatic CHF were no longer permitted to participate. In 2008, patients with any history of CHF were excluded. Other external developments during the trial led to several protocol changes to ensure the safety of participants and to conform with changing regulations. When IRIS began in 2005, there was no evidence to suggest a connection between pioglitazone treatment and bladder cancer in humans. Data from other trials subsequently emerged to suggest a possible imbalance of bladder cancer in pioglitazone-treated diabetic patients. The IRIS protocol was then revised in 2007 to exclude patients with a history of bladder cancer. In 2011, in response to an FDA advisory on the topic, patients with specific risk factors for bladder cancer, such as a history of pelvic radiation, cytoxan exposure, or uninvestigated macroscopic hematuria, were excluded as well.

IRIS Trial Procedures

Patients who provided informed consent for the IRIS trial attended a screening visit that included an interview (including smoking history), a physical examination, and fasting blood test (Table 2). Because glucose metabolism may be altered immediately after a stroke,³⁶ the screening test to measure HOMA-IR was conducted a minimum of 14 days after the index stroke or TIA. Blood samples were processed centrally by Esoterix Inc. (Cranford, NJ; Burlington, NC) or an affiliate laboratory. The Linco (St. Charles, MO) human insulin-specific radioimmunoassay (RIA) was used in North America and Australia to measure insulin concentrations in the blood. Because this assay was unavailable in Europe and Israel, the Linco animal serum-free enzyme-linked immunosorbent assay was used and results were converted to RIA values using an internal LINCO correlation equation ($\text{insulin RIA } [\mu\text{U/mL}] = 1.1056 \times (\text{insulin enzyme-linked immunosorbent assay } [\text{uIU/mL}]) + 2.1494$).³⁷

Patients with HOMA-IR >3.0 who had no excluded conditions were randomly assigned in a 1:1 ratio to initial treatment with either 15 mg pioglitazone tablet or placebo tablet daily by mouth. Placebo and active tablets were identical in both appearance and texture. Randomization was conducted using a random permuted block design with variable block sizes that were stratified by site. To hide the allocation sequence, randomization lists were kept only at the central pharmacy and the statistical center.³⁷

After month 4, participants were contacted every 4 months. Each year, in-person assessments were conducted that included a physical examination, Modified Mini-Mental State test,³⁸ fasting blood test, and smoking status. Participants who survived the primary IRIS outcome stroke or MI

were maintained on study medication. The IRIS investigators monitored vascular risk factors, reported them to participants and their physicians annually, and advised participants to achieve their secondary prevention goals. However, providing standard secondary preventive care was the responsibility of each patient's personal physician.³⁷

Smoking history was assessed at screening when participants were asked when (if applicable) they started smoking cigarettes, and when (if applicable) they quit smoking. If they were current cigarette smokers, participants were asked how many cigarettes they smoked per day. At randomization and annually during follow up, participants were asked if they were current smokers.

Participants were followed for 5 years or until the last scheduled contact that occurred before the end date of the trial (July 1, 2015), whichever came first.³⁷

Student Thesis Outcome

The primary outcome for the IRIS trial was time to first occurrence of fatal or non-fatal stroke or fatal or non-fatal MI. However, the primary outcome for the student's thesis was time to first occurrence of non-fatal stroke, non-fatal MI, or all-cause death. All-cause death was included in the student's primary outcome, despite not being part of the primary outcome for the original IRIS trial, because of convincing data showing that cigarette smoking increases risk for all-cause death. Current smokers die at rates three times as high as never-smokers, from cancer, or from vascular, respiratory, and other causes.¹⁸

Primary and secondary outcomes for both the IRIS trial and the student's thesis are shown in Table 3. Clinical event committees for adjudicating neurology, cardiology, and endocrinology events were composed of a chairperson and ≥ 3 specialists. Two reviewers adjudicated each potential outcome, with a third reviewer added if necessary to reach a majority decision. All reviewers were blinded to treatment allocation and smoking status and received training in IRIS outcome criteria. Cause of death was classified by the blinded cardiology committee using documentation provided for each deceased participant, including hospital admission note, hospital discharge summary, or death certificate, if available. Specific categories for causes of death included stroke, MI, congestive heart failure, other cardiac, cancer, infection, other (with specific "other" cause recorded on form), and unknown.

All incident cancers were reviewed and confirmed by a blinded oncologist to determine type and stage. Pathology data was required for confirmation of cancer by the oncology reviewer. In the current analysis, a death was attributed to cancer if the oncologist confirmed a diagnosis of cancer based on pathology data, and the cardiology outcome committee attributed the cause of death to cancer based on available clinical data. Deaths classified as due to cancer by the cardiology committee without confirming pathology data were classified as "other" cause of death. Cancer deaths were assigned a type of cancer based on the primary tumor type as determined by the oncology reviewer, including lung, colon, brain, pancreatic, bladder, prostate, and primary unknown.

Safety outcomes of particular interest included heart failure, bone fracture, and bladder cancer. During the trial, several developments prompted modifications of the protocol and of the

informed consent document. In 2006, a randomized trial reported a higher rate of fractures in women receiving rosiglitazone, another TZD drug.³⁹ In March 2007, the manufacturer of pioglitazone alerted health care providers to a similar finding after analyzing its clinical trial database. In April 2007, the IRIS informed consent was modified to describe this potential new risk of fracture. A query for fractures was added to interviews; already-enrolled participants were asked to complete a retrospective survey asking about fractures, and all participants were advised to follow standard recommendations to optimize bone health. The revised 2007 informed consent also described new information from clinical trials in humans suggesting an association between pioglitazone use and bladder cancer. In 2011, after several observational studies reported higher rates of bladder cancer in diabetic patients treated with pioglitazone^{40,41} the informed consent was again revised and the protocol modified to exclude participants with selected risk factors for bladder cancer. Enrolled participants who were determined to have those risk factors were removed from study medication.³⁷

Patient consents and standard protocol approvals

Informed consent was signed by all participants. The study was approved in each participating center by the responsible ethics committee.

Statistical Methods

Research Design

The student's thesis was designed as an observational analysis of previously-collected data in the IRIS trial.

Sample size and duration of enrollment

The sample size for the original IRIS trial (N=3,136) was determined by a power analysis for its primary research aim. Because the enrollment rate fell below projections, in July 2007 the duration of enrollment was lengthened to achieve the original sample size. In February 2011, the Data Safety Monitoring Board (DSMB) recommended increasing person-years in the trial by further lengthening recruitment to June 2012 and follow-up to June 2015, based on the results of the first blinded interim analysis. In mid-2012, the DSMB allowed continued recruitment at selected high-recruiting sites. Recruitment was terminated on January 15, 2013 with a cohort of 3,876 participants. The present study was a secondary analysis designed to use all the available data from the IRIS trial.

Statistical analyses

IRIS participants were classified according to smoking status at the time of randomization: (a) never smokers, (b) former smokers (*i.e.*, stopped smoking prior to the index stroke or TIA event), (c) quitters (*i.e.*, quit after the index event and not smoking at time of randomization), or (d) continuing smokers. The primary aim of our analysis was to compare the risk of the composite outcome of nonfatal stroke, nonfatal MI, or all-cause death in patients who quit smoking versus patients who continued to smoke after their index event. We also examined risk for the components of this outcome (*i.e.*, stroke alone, MI alone, and all-cause mortality) and the incidence of cancer in quitters compared to continuing smokers. Participants without outcomes were censored at the time of their last completed follow-up contact. These analyses were not pre-specified in the IRIS research protocol or data analysis plan. Rather, these analyses were designed after completion of the IRIS trial to test the widely accepted (but never substantiated)

hypothesis that smoking cessation after stroke improves outcome. This hypothesis was strengthened by observational research showing that smoking cessation in patients with established coronary heart disease reduces subsequent all-cause mortality²² and recurrent cardiovascular events.^{4,24}

All analyses were conducted using the intention-to treat principle (*i.e.*, according to participants' smoking status (quitter versus continuing smoker) at the time of randomization).

Cumulative probabilities of outcome-free survival over time by smoking status were calculated by the method of Kaplan-Meier⁴² and differences were tested by the log-rank statistic using alpha of 0.05 (2-sided). The effect of smoking status on risk was quantified by hazard ratios (with 95% confidence intervals) from Cox proportional hazards models⁴³ that included baseline cardiovascular risk features and treatment assignment (pioglitazone or placebo). The risk features included in the Cox models were those pre-specified as adjustment variables for the IRIS trial, plus pioglitazone treatment, and included the following: age, sex, stroke [vs. TIA] as index event, prior history of stroke, history of hypertension, history of coronary artery disease, systolic blood pressure, and diastolic blood pressure. All adjustment variables were obtained by self-report from participants, except for type of index event (determined by site investigators) and blood pressure (measured at screening blood test). Participants missing information on any of these features are excluded from the adjusted analyses.

Causes of death were tabulated using standard CDC categories⁴⁴ and differences across smoking strata for major categories were tested by the chi-square statistic.

RESULTS

Study Population

The study cohort was derived from 3,871 IRIS study participants who were randomized between February 2005 and January 2013 (five participants were excluded from the original cohort of 3,876 because of missing smoking information). At randomization, 1309 participants were classified as never smokers, 1490 as former smokers, 450 as quitters since the index event, and 622 as continuing smokers. The total sample for the primary analysis comprised the 450 quitters and 622 continuing smokers. Baseline features for quitters and continuing smokers are displayed in Table 4. (Features for all 3,871 IRIS participants with smoking information by smoking status are shown in Table 5.) Some baseline differences between the quitters and continuing smokers were detected and would be expected to reduce risk for vascular outcomes in quitters compared with continuing smokers (*i.e.*, quitters were less likely to report a history of stroke or coronary artery disease before the index event, and were more likely to use statin therapy).^{45,46} Other baseline differences would be expected to increase risk in quitters (*i.e.*, quitters were more likely to enter with a stroke (vs. TIA) and be assigned to receive placebo).⁴⁶ On laboratory testing, quitters had lower fasting glucose, LDL cholesterol, and triglycerides compared to continuing smokers. Among women, quitters had higher HDL cholesterol compared to continuing smokers, but this difference was not as large in men. Quitters more often reported being heavy smokers (*i.e.*, 20+ cigarettes daily) at the time of the index event (60%) compared to continuing smokers

at randomization (27%). However, we do not know if this reflects a true difference between quitters and continuing smokers for intensity of smoking at the time of the index event or a reduction in smoking (or reported smoking) in the latter group between the event and trial entry. The mean reported duration of smoking was 40 years in both groups. A total of 32 participants (10 never smokers, 13 former smokers, 5 quitters, 4 continuing smokers did not have complete data on the eight specified adjustment features and are excluded from the adjusted analyses; 3 outcomes were excluded).

Clinical Outcomes

After a median follow-up of 4.8 years, nonfatal stroke, nonfatal MI, or all-cause death had occurred in 60 patients in the quitter group and 121 in the continuing smoking group (5-year risk, 15.7% vs. 22.6%; adjusted hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.48 to 0.90). Among secondary outcomes, there were non-significant reductions in the incidence of stroke, myocardial infarction, and cancer during follow-up in quitters compared to continuing smokers (Table 6, Figure 1, and Table 7). Death occurred in 23 quitters and 66 continuing smokers (5-year risk, 6.1% vs 13.1%; adjusted HR 0.49; 95% CI 0.30 to 0.79). Among major causes of death, the largest difference was observed for cancer: seven deaths among quitters were attributable to cancer compared to 21 among continuing smokers (1.5% vs 3.4%; p-value, 0.07) (Table 8). A lower percentage of deaths was also observed among quitters from cerebrovascular disease (0.2% vs 1.6%, p-value, 0.03), heart disease (0.7% vs 1.6%; p-value, 0.16), and unknown cause (1.8% vs 2.9%; p-value, 0.24).

At baseline, quitters were slightly more likely than continuing smokers to achieve their preventive health goals: 63% of quitters versus 61% of continuing smokers had a blood pressure <140/90 mmHg; 85% of quitters versus 80% of continuing smokers were on statins; and 54% of quitters versus 49% of continuing smokers had achieved all three of these preventative health goals. However, an identical number of quitters and continuing smokers were on anti-thrombotic therapy at baseline (99%). During five years of follow-up, quitters were more likely to meet their preventative health goals (Table 9).

Of note, 145 of 450 (32%) quitters reported resuming smoking at one or more annual time points during follow-up and 190 of 622 (31%) continuing smokers reported having quit.

DISCUSSION

The results of this study suggest that quitting smoking within six months after an ischemic stroke or TIA will significantly reduce the likelihood of nonfatal stroke, nonfatal MI, or all-cause death in the next 4.8 years. The observed relative risk reduction (RRR) (34%) and absolute risk reduction (ARR) (6.9%) are comparable to other medical treatments for secondary prevention after stroke, including antiplatelet therapy,⁴⁷ statin therapy,⁴⁵ blood pressure reduction,⁴⁸ and pioglitazone.⁵ Different outcome measures among secondary prevention studies make strict comparison impossible. However, reports suggest that aspirin reduces risk of stroke or death by 31%,⁴⁷ high dose statin therapy reduces major cardiovascular events by 20%,⁴⁵ blood pressure lowering therapy with perindopril and indapamide reduces stroke risk by 43%,⁴⁸ and pioglitazone reduces risk for stroke or MI by 26%.⁵ Anticoagulation for atrial fibrillation stands out as a medical treatment for secondary prevention with a substantially greater RRR of 64%,

and a comparable ARR of 8%.⁴⁹ The present study not only supports current guidelines for smoking cessation after stroke or TIA,¹⁹ but also suggests that cessation may be one of the most important single interventions for smokers with an ischemic stroke or TIA.

We are aware of only one other study that has examined the effect of smoking cessation immediately after stroke. This observational study of 105 quitters and 135 continuing smokers with cerebrovascular disease observed a non-significant reduction in mortality over 14 months in quitters compared to continuing smokers.²¹ By contrast, our study looked at 450 quitters and 622 continuing smokers over 4.8 years and had more power to detect a difference in outcome between quitters and continuing smokers. Other studies have classified smoking status at the time of the stroke event and were not designed to examine the effect of quitting.⁵⁰⁻⁵² There have been no clinical trials of smoking cessation after stroke or TIA.

We found that the benefit of smoking cessation emerged early (*i.e.*, within 5 years) after an acute ischemic stroke or TIA, which is consistent with prior research on the vascular effects of smoking. Smoking is thought to increase the risk for vascular disease by two major mechanisms: (1) induction of a pro-coagulant state, and (2) acceleration of atherosclerosis.⁵³ The pro-coagulant state is characterized by an increase in platelet aggregation, increased fibrinogen concentration, decrease in fibrinolysis, polycythemia, and high blood viscosity,⁵³ and is rapidly reversible within days of smoking cessation.⁵⁴ Smoking accelerates atherosclerosis through several pathways, including impaired endothelial function (with decreases in nitric oxide), increased inflammation (through an increase in peripheral leukocytes and inflammatory markers), and lipid modification (increased cholesterol, triglycerides, and low density

lipoprotein, decreased HDL, and oxidation of LDL).⁵³ Although the atherogenic effects of smoking likely take longer to dissipate, several studies have observed that stroke risk declines exponentially after smoking cessation and returns to baseline risk within 5 years of quitting.^{8,55}

Smoking cessation in our study had a particularly large effect on all-cause mortality (RRR, 51%, ARR, 7.0%). This finding suggests that smoking cessation may be distinct from other medical interventions for secondary stroke prevention, which are not associated with significant improvement in survival despite reductions in risk for cardiovascular events.^{5,45,48,49} The one exception is antiplatelet therapy after a TIA or stroke, which results in a smaller but still significant decrease in risk for all-cause mortality after 3 years of therapy (RRR 12%, ARR, 1.5%).⁵⁶

The most common cause of death among IRIS participants was cancer, followed by stroke, heart disease, and respiratory infection. All these causes were reduced among quitters, but only reached or approached statistical significance for stroke ($p=0.03$) and cancer ($p=0.07$). The decreased rate of cancer death observed in quitters compared to continuing smokers is most likely attributable to the beneficial effects of smoking cessation on case fatality. At baseline, quitters and continuing smokers had similar reported cancer histories and similar years of exposure to tobacco. Quitters were slightly less likely to be diagnosed with cancer during five years of follow-up, but this difference was small and not statistically significant. However, we observed a quantitatively large reduction in cancer case fatality in quitters compared with continuing smokers (7/31=23% vs 21/49=43%; Chi square p -value, 0.06). The finding that quitters have lower rates of cancer death relative to continuing smokers is consistent with other

research showing that smoking cessation in patients who already have a cancer diagnosis is associated with a rapid decrease in case fatality.^{57,58} Mechanisms for the rapid decrease may include enhanced sensitivity to radiation therapy⁵⁹ and chemotherapy,⁶⁰ elimination of stimulation of tumor growth by nicotine,^{61,62} and prevention of death among cancer patients from comorbid pulmonary and cardiovascular disease.^{63,64}

The results of this study should be considered in the context of three potential sources of bias. Prevention bias refers to the tendency of individuals who make one healthy choice (*e.g.*, quitting smoking) to make others as well (*e.g.*, taking medication as prescribed, seeing a doctor regularly, exercising) that could improve outcomes.⁶⁵ Consistent with a prevention bias, quitters in this study were slightly more likely than continuing smokers to have achieved their preventative health goals at baseline and during follow-up (Table 9). This small difference between groups may have increased the benefit attributed to smoking cessation in this study, but is probably not large enough to account for the full difference in outcome rates. A second source of bias may have resulted from selective loss of patients from the study cohort between the index event and randomization. If patients who quit smoking after their stroke/TIA and patients who continued to smoke had differing short-term survival or differentially agreed to participate in IRIS based on features associated with prognosis, the randomized patients may not reflect the true association between smoking and outcomes in the underlying population. A third source of potential bias may have resulted from crossover between groups. Since 32% of quitters resumed smoking at one or more time points after randomization, and 31% of continuing smokers quit at one or more time points after randomization, our results may have been biased toward the null. This suggests that magnitude of the benefit from quitting smoking may be even greater than our estimate. In

addition to these potential sources of bias, this analysis on smoking was an unplanned, secondary analysis of data from a randomized clinical trial and the findings, although compelling, must be regarded as hypothesis-generating only. Finally, the IRIS trial enrolled insulin-resistant, non-diabetic patients and our results may not be generalizable to all stroke patients who smoke.

This study also had several notable strengths, including detailed data on smoking, close follow-up of participants, and careful adjudication of outcomes. In addition, quitters and continuing smokers were well balanced in most demographic and clinical characteristics, specifically smoking history, age, and medical comorbidities.

The smoker's paradox

Other researchers have looked at the relationship between smoking at the time of a coronary event or stroke and risk for various outcomes. One surprisingly well-replicated finding among studies in both groups of patients is the "smoker's paradox." The smoker's paradox describes the counterintuitive observation that smokers have better outcomes (improved survival) than non-smokers after an acute coronary event⁶⁶⁻⁶⁹ or acute ischemic stroke.⁷⁰ This paradox may cause patients and clinicians to underestimate the adverse effect of a smoking once clinical disease is evident. The paradox, however, is not due to a beneficial effect of smoking, but rather to bias.

Index event bias

"Index event bias," also called "collider stratification bias"^{71,72} explains why established risk factors for an index event (such as stroke) may not appear to be a risk factor for a recurrence of

that event.⁷¹ Index event bias occurs when a study population is chosen on the basis of a common effect (*e.g.*, stroke) of two or more factors (*e.g.*, smoking, hypertension, *etc.*). Under these conditions, the correlation between the risk factor of interest (*i.e.*, smoking) and the disease (*i.e.*, stroke) are biased toward the null. The risk factor of interest may even appear to be negatively correlated with the outcome of interest.⁷³ A mathematical model of index event bias demonstrates that selection based on an index event can create a spurious negative correlation between the risk factors for the index event and recurrence of the index event. Such a negative correlation does not require any biological connection between the risk factor and outcome, and is purely an artifact.⁷³

Examples of index event bias can be drawn from literature on cardiovascular disease, rheumatic disease, and birth outcomes. The thrombophilia paradox describes the observation that individuals with thrombophilias are at increased risk for a first deep venous thrombosis, but not for recurrence.⁷⁴ The obesity paradox describes the observation that obesity is an established risk factor for coronary artery disease, but is protective against recurrent coronary events.⁷⁵ A patent foramen ovale is a risk factor for an initial cryptogenic stroke, but not for recurrent stroke.⁷⁶ In rheumatic disease, many risk factors (*e.g.*, obesity and smoking) for incident osteoarthritis, rheumatoid arthritis, or psoriatic arthritis appear to be neutral or protective when used to predict disease progression.⁷⁷ Finally, the birth weight paradox describes the observation that low birth weight babies born to mothers who smoke have improved survival.⁷⁸

The mechanism underlying index event bias can be explained by measured and unmeasured risk factors in a population selected on the basis of a known disease. Most studies on coronary artery

disease and stroke have categorized smoking at the time of the vascular event. Based on this categorization, important differences are observed between "smoking" and "non-smoking" groups. In general, smokers with a first vascular event tend to be younger, have fewer atherosclerotic risk factors, and fewer medical comorbidities that increase risk for stroke and MI, such as diabetes and hypertension.⁷⁹ Aside from the unhealthy habit of smoking, smokers with a vascular event tend to be measurably healthier than nonsmokers with a vascular event. These smokers would likely have been spared a vascular event if they had been nonsmokers. The underlying better health of smokers explains why they have a better prognosis than nonsmokers after a vascular event.

While measurable demographic and clinical differences between smokers and nonsmokers may contribute to the observation of a smoker's paradox,⁷⁹ some studies that control for these measurable risk factors still document a residual benefit of smoking.^{67,69} This residual benefit may be explained by differences in unmeasured risk factors between smokers and nonsmokers. On average, individuals with a known risk factor (such as smoking) who have an index event (such as stroke) tend to have fewer unmeasured risk factors than individuals without known risk factors who also have an index event. One example of this phenomenon is observed in low birthweight babies. It has been observed, paradoxically, that low birthweight babies whose mothers smoke have better outcomes than low birthweight babies whose mothers don't smoke. This is because low birthweight babies whose mothers smoke tend have fewer unmeasured risk factors for low birthweight, while low birthweight babies whose mothers don't smoke have some other, more lethal, etiology for low birthweight (*e.g.*, a genetic syndrome). This effect can be observed in the absence of a hypothetical biological benefit of smoking.⁷⁸

Further evidence that index event bias creates a spurious negative correlation between risk factors and recurrence comes from intervention studies demonstrating that modifying risk factors can improve outcomes. Intervention studies have demonstrated that treating hypertension has strong beneficial effects on stroke recurrence.^{80,81} PFO closure in patients with cryptogenic stroke prevents recurrent stroke.⁸² In the present study, smoking cessation reduced risk for the combined outcome of stroke, MI, or death.

One important question is why didn't index event bias obscure the relationship we observed between smoking (versus not smoking) and stroke, MI, or death? Since the participants in the IRIS trial were selected on the basis of their index event, we might expect that the relationship between known risk factors (*i.e.*, smoking) and the outcome to be biased toward the null. However, all participants in the primary analysis were smokers at the time of their stroke. Although our analysis was a prospective cohort study, not a randomized clinical trial, the "intervention," which was smoking cessation, was not differentially related to other vascular risk factors in quitters and continuing smokers.

Although it was not the aim of our study to look for a smoker's paradox (or index event bias), a comparison of patients who smoked at the time of their IRIS index event with patients who were not smoking at that time reveals no evidence for a smoker's paradox (Table 10). Unadjusted analyses reveal that nonsmokers at the time of their index event had significantly lower rates of nonfatal stroke, nonfatal MI, or death than nonsmokers (5-year risk, 16.1% vs. 19.7%;

unadjusted HR 0.80; 95% CI 0.67, 0.95). After adjusting for eight prespecified adjustment variables, this difference is even more apparent (adjusted HR 0.57; 95% CI 0.47, 0.69). Although we did not observe the smokers' paradox in the present study, index event bias is a potentially important issue in stroke recurrence studies. Researchers interested in the relationship between smoking and stroke recurrence should be aware of the index event bias to correctly interpret both past and future studies.

Message for patients

Among 100 patients who continue to smoke after an ischemic stroke or TIA, 23 may be expected to have a stroke, MI, or death within 5 years compared to only 16 out of 100 who quit. In simple terms, for every 100 of these patients who manage to quit cigarettes, fully 7 additional will survive 5 years without MI or recurrent stroke than otherwise would have.

Conclusion

Healthcare providers have a unique opportunity to counsel patients after they suffer an ischemic stroke or TIA. A stroke or TIA can act as a wake-up call for patients, and enhance motivation to make lifestyle changes that could prevent a recurrence. This paper provides a quantitative estimate for the benefits of smoking cessation in this population. Our results suggest that health care providers should give very high priority to helping patients quit smoking cigarettes after an ischemic stroke or TIA.

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Table 1. Final inclusion and exclusion criteria for the IRIS trial**Inclusion criteria**

Ischemic stroke or TIA within 6 months of randomization
 Insulin resistance as defined by HOMA-IR >3.0
 Age $\geq$ 40 years at randomization
 Ability and willingness to provide informed consent

Exclusion criteria

Stroke or TIA related to structural cardiac lesion
 Stroke related to head trauma, proximal arterial dissection, or medical procedures
 Diabetes mellitus
 CHF (NYHA class 1-4) or history of CHF
 History of bladder cancer or high risk for bladder cancer
 Active liver disease
 Inability to participate in follow-up activities
 Irreversible medical condition with predicted survival < 4 years
 Oral or patch estrogen contraceptive use
 Ongoing use of oral corticosteroids
 History of intolerance to a TZD
 Pregnancy, desire to become pregnant, or currently breastfeeding
 Current participation in conflicting clinical trial
 ALT > 2.5 upper limit of normal
 Hemoglobin <8.5 g/dL
 Moderate-to-severe pitting edema of feet or legs
 Carotid surgery or carotid stenting procedure within 14 days of randomization

Abbreviations: *NYHA*, New York Heart Association; *ALT*, Alanine aminotransferase.

Table 2. Timetable of assessments

	Screening	Baseline	Wk 2,4,6,8,10,12	M			Q4M	Q12M	Exit
				4	8	12			
Physical examination	X					X		X	X
Medical history	X	X							
Blood test									
Hemoglobin	X								
HbA1c	X								
Alanine	X					X		X	X
aminotransferase									
Fasting glucose	X					X		X	X
Fasting lipid profile	X					X		X	
Fasting insulin	X					X			
HS C-reactive	X					X			
protein									
NIH Stroke Scale		X							
Medication inventory		X				X		X	X
Modified mini- mental examination		X				X		X	X
Lifestyle survey		X				X		X	X
Safety and outcome screening			X			X	X	X	X
Study medication dose changes			4 and 8 weeks	X	X	X			
Study medication resupply			12 weeks		X	X	X	X	X

Abbreviations: *Q4M*, every months; *Q12M*, annually; *HS*, high-sensitivity; *NIH*, National Institutes of Health

Table 3. Outcomes For The IRIS Trial Compared With Outcomes For The Student's Thesis

Main Study (IRIS trial)	Student's Thesis
Primary Outcome	Primary Outcome
Fatal or nonfatal stroke or fatal or non-fatal MI	Non-fatal stroke, non-fatal MI, or all-cause mortality
Secondary outcomes	Secondary outcomes
Stroke (fatal or non-fatal)	Stroke (fatal or non-fatal)
Acute coronary syndrome (MI or unstable angina)	MI (fatal or non-fatal)
Diabetes onset	All-cause mortality
Cognitive decline	
Stroke, MI, or severe CHF	
All-cause mortality	

Table 4. Baseline Features by Smoking Status at Randomization

Feature	Continuing (n=622)	Quitter (n=450)
Demographic features		
Age, mean (SD), years	58 (9)	58 (8)
Male sex, no. (%)	410 (66)	295 (66)
Black race, no. (%)	120 (20)	61 (14)
Hispanic ethnic group, no. (%)	23 (4)	18 (4)
Clinical history, no. (%)		
Stroke at entry (vs TIA)	533 (86)	416 (93)
Prior stroke (before index event)	85 (14)	41 (9)
Hypertension	453 (73)	310 (69)
Coronary artery disease ^a	88 (14)	38 (8)
Atrial fibrillation	15 (2)	17 (4)
Modified Rankin score 3+	36 (6)	57 (13)
Cancer (non-skin) history	26 (4)	20 (4)
Physical examination		
Body mass index, mean (SD), kg/m ²	30 (6)	30 (5)
Abdominal obesity ^b , no. (%)	362 (59)	285 (64)
Systolic blood pressure, mean (SD), mmHg	133 (18)	134 (18)
Diastolic blood pressure, mean (SD), mmHg	81 (11)	81 (11)
Laboratory data, mean (SD)		
Fasting glucose, mg/dL	99 (10)	97 (10)
HOMA-IR	5.6 (2.8)	5.6 (3.1)
HbA _{1c} , %	5.9 (0.4)	5.8 (0.4)
LDL cholesterol, mg/dL	93 (33)	90 (32)
HDL cholesterol-men, mg/dL	42 (11)	43 (10)
HDL cholesterol-women, mg/dL	49 (13)	54 (14)
Triglycerides, mg/dL	154 (82)	144 (63)
Concomitant medications, no. (%)		
Statin	496 (80)	378 (85)
Antithrombotic	616 (99)	445 (99)
Angiotensin II Receptor Blocker	61 (10)	50 (11)
Beta-blocker	197 (32)	113 (25)
Thiazide diuretic	164 (26)	107 (24)
Assigned to pioglitazone, no. (%)	323 (52)	215 (48)
Cigarettes/day on average, no. (%)		
20±	168 (27)	269 (60)
10-19	205 (33)	117 (26)
<10	243 (39)	59 (13)
Uncertain	6 (1)	5 (1)
Duration of smoking, mean (SD), years	40 (11)	40 (10)

SI conversions: mg/dL to mmol/L: glucose, multiply by 0.0555; cholesterol, multiply by 0.0259; triglycerides, multiply by 0.0113; HbA_{1c} % to mmol/mol: multiply by 10.93 and subtract 23.5 from product.

^aHistory of hospitalization for MI, coronary artery bypass graft, angioplasty or stenting.

^bWaist circumference >88 cms for women; >102 cms for men.

Number of participants with missing data (continuing; quitter): Black race (7; 9); Hispanic ethnic group (1; 4); stroke at entry (2; 1); prior stroke (0; 1); atrial fibrillation (0; 1); body mass index (2; 2); blood pressure (2; 3); LDL (12; 3); HDL-men (2; 1); HDL-women (1; 1); triglycerides (3; 2); prescription drugs (3; 3).

Table 5. Baseline Features by Smoking Status at Randomization

Feature	Continuing n=622		Quitter n=450		Former n=1490		Never n=1309	
Demographic features								
Age, mean (SD), years	58	(9)	58	(8)	66	(10)	63	(11)
Male sex, no. (%)	410	(66)	295	(66)	1083	(73)	747	(57)
Black race, no. (%)	120	(20)	61	(14)	122	(8)	139	(11)
Hispanic ethnic group, no. (%)	23	(4)	18	(4)	51	(3)	55	(4)
Clinical history, no. (%)								
Stroke at entry (vs TIA)	533	(86)	416	(93)	1274	(86)	1148	(88)
Prior stroke (before index event)	85	(14)	41	(9)	206	(14)	156	(12)
Hypertension	453	(73)	310	(69)	1078	(72)	927	(71)
Coronary artery disease ^a	88	(14)	38	(8)	216	(14)	119	(9)
Atrial fibrillation	15	(2)	17	(4)	123	(8)	109	(8)
Modified Rankin score 3+	36	(6)	57	(13)	113	(8)	117	(9)
Cancer (non-skin) history	26	(4)	20	(4)	132	(9)	95	(7)
Physical examination								
Body mass index, mean (SD), kg/m ²	30	(6)	30	(5)	30	(5)	30	(5)
Abdominal obesity ^b , no. (%)	362	(59)	285	(64)	923	(62)	811	(63)
Systolic blood pressure, mean (SD), mmHg	133	(18)	134	(18)	133	(17)	133	(17)
Diastolic blood pressure, mean (SD), mmHg	81	(11)	81	(11)	78	(11)	79	(10)
Laboratory data, mean (SD)								
Fasting glucose, mg/dL	99	(10)	97	(10)	99	(10)	98	(10)
HOMA-IR	5.6	(2.8)	5.6	(3.1)	5.5	(2.7)	5.3	(2.5)
HbA _{1c} , %	5.9	(0.4)	5.8	(0.4)	5.8	(0.4)	5.8	(0.4)
LDL cholesterol, mg/dL	93	(33)	90	(32)	86	(30)	87	(31)
HDL cholesterol-men, mg/dL	42	(11)	43	(10)	45	(12)	44	(11)
HDL cholesterol-women, mg/dL	49	(13)	54	(14)	55	(13)	53	(13)
Triglycerides, mg/dL	154	(82)	144	(63)	138	(71)	137	(73)
Concomitant medications, no. (%)								
Statin	496	(80)	378	(85)	1239	(83)	1071	(82)
Antithrombotic	616	(99)	445	(99)	1477	(99)	1292	(99)
Angiotensin II Receptor Blocker	61	(10)	50	(11)	241	(16)	194	(15)
Beta-blocker	197	(32)	113	(25)	509	(34)	409	(31)
Thiazide diuretic	164	(26)	107	(24)	403	(27)	346	(26)
Assigned to pioglitazone, no. (%)	323	(52)	215	(48)	762	(51)	636	(49)
Cigarettes/day on average, no. (%)								
20±	168	(27)	269	(60)	825	(55)		
10-19	205	(33)	117	(26)	304	(20)		
<10	243	(39)	59	(13)	305	(20)		
Uncertain	6	(1)	5	(1)	56	(4)		
Duration of smoking, mean (SD), years	40	(11)	40	(10)	26	(15)		

SI conversions: mg/dL to mmol/L: glucose, multiply by 0.0555; cholesterol, multiply by 0.0259; triglycerides, multiply by 0.0113; HbA_{1c} % to mmol/mol: multiply by 10.93 and subtract 23.5 from product.

^aHistory of hospitalization for MI, coronary artery bypass graft, angioplasty or stenting.

^bWaist circumference >88 cms for women; >102 cms for men.

Table 6. Risk of Outcomes by Smoking Status at Randomization

Outcome	Quitter (n=450)		Continuing (n=622)		Risk Δ	Cox Models				
						Unadjusted		Adjusted ^c		
	Pts. ^a	Risk ^b	Pts. ^a	Risk ^b		Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P	
Nonfatal stroke, nonfatal MI or death	60	15.7%	121	22.6%	-6.9%	0.66 (0.49, 0.90)	0.009	0.66 (0.48, 0.90)	0.009	
Nonfatal stroke	31	7.8%	61	10.9%	-3.1%	0.68 (0.44, 1.05)	0.08	0.67 (0.43, 1.04)	0.07	
Nonfatal MI	14	4.4%	28	5.9%	-1.5%	0.67 (0.35, 1.28)	0.23	0.74 (0.39, 1.42)	0.37	
Death	23	6.1%	66	13.1%	-7.0%	0.47 (0.29, 0.76)	0.002	0.49 (0.30, 0.79)	0.004	
Cancer ^d	31	8.7%	49	10.0%	-1.3%	0.86 (0.55, 1.35)	0.52	0.87 (0.55, 1.37)	0.56	

^aNumber of participants with event.^b5-year risk from life-table.^cAdjusted for 8 pre-specified features (age, sex, stroke [vs. TIA] as index event, prior history of stroke, history of hypertension, coronary artery disease, systolic blood pressure, and diastolic blood pressure) and treatment (pioglitazone vs placebo).

Table 7. Risk of Outcomes by Smoking Status at Randomization

Outcome				Cox Models			
Baseline Smoking Status	Pts.	Pts w/ Event	5-Year Risk	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P
<u>Stroke, MI or Death</u>							
Continuing	622	121	22.6%	<i>Reference</i>			
Quitter	450	60	15.7%	0.66 (0.49, 0.90)	0.009	0.66 (0.48, 0.90)	0.009
Former	1490	244	18.6%	0.80 (0.64, 0.99)	0.04	0.54 (0.43, 0.68)	<.0001
Never	1309	153	13.3%	0.55 (0.44, 0.70)	<.0001	0.43 (0.33, 0.55)	<.0001
<u>Stroke</u>							
Continuing	622	61	10.9%	<i>Reference</i>			
Quitter	450	31	7.8%	0.68 (0.44, 1.05)	0.08	0.67 (0.43, 1.04)	0.07
Former	1490	100	7.8%	0.65 (0.47, 0.89)	0.008	0.49 (0.35, 0.69)	<.0001
Never	1309	89	7.7%	0.65 (0.47, 0.90)	0.009	0.54 (0.38, 0.76)	0.0004
<u>MI</u>							
Continuing	622	28	5.9%	<i>Reference</i>			
Quitter	450	14	4.4%	0.67 (0.35, 1.28)	0.23	0.74 (0.39, 1.42)	0.37
Former	1490	66	5.4%	0.95 (0.61, 1.48)	0.82	0.76 (0.47, 1.22)	0.25
Never	1309	36	3.1%	0.57 (0.35, 0.93)	0.03	0.51 (0.30, 0.86)	0.01
<u>Death</u>							
Continuing	622	66	13.1%	<i>Reference</i>			
Quitter	450	23	6.1%	0.47 (0.29, 0.76)	0.002	0.49 (0.30, 0.79)	0.004
Former	1490	131	10.4%	0.80 (0.59, 1.07)	0.13	0.39 (0.28, 0.53)	<.0001
Never	1309	62	5.6%	0.42 (0.30, 0.59)	<.0001	0.25 (0.17, 0.36)	<.0001

^aAdjusted for 8 prespecified features and treatment (pioglitazone vs placebo).

Table 8. Causes of Death by Smoking Status at Randomization

Type	Total	Continuing n=622		Quitter n=450		P ^a	Former n=1490		Never n=1309	
		No.	%	No.	%		No.	%	No.	%
Cancer ^b	70	21	3.4%	7	1.5%	0.07	28	1.9%	14	1.1%
Lung	18	10		2			3		2	
Colon	5	1		0			2		2	
Brain	4	0		0			4		0	
Pancreatic	3	0		1			2		0	
Bladder	2	1		0			1		0	
Breast	2	2		0			0		0	
Prostate	2	1		0			1		0	
Primary Unknown	8	1		1			4		2	
Other	26	5		3			11		8	
Cerebrovascular disease	37	10	1.6%	1	0.2%	0.03	18	1.2%	8	0.6%
Heart disease	35	10	1.6%	3	0.7%	0.16	11	0.7%	11	0.8%
Influenza and pneumonia	12	1	0.2%	0	0.0%		9	0.6%	2	0.2%
Accidents and self-harm	9	2	0.3%	1	0.2%		5	0.3%	1	0.1%
Alzheimer's disease	7	0	0.0%	0	0.0%		4	0.3%	3	0.2%
Chronic lower respiratory disease	7	0	0.0%	0	0.0%		6	0.4%	1	0.1%
Other	30	4	0.6%	3	0.7%		18	1.2%	5	0.4%
Unknown ^c	75	18	2.9%	8	1.8%	0.24	31	2.1%	17	1.3%
Total	282	66		23			131		62	

^aP-value from chi-square test for proportions, continuing smokers vs. quitters.

^bDeaths attributed to cancer with confirming pathology data.

^cIncludes 6 deaths attributed to cancer by review committee without pathology-confirmed cancer during follow-up (2 continuing smoker, 1 quitter, 3 former smokers).

Table 9. Participants Meeting Preventive Goals by Time in Trial, by Smoking Status at Randomization

Preventive Goal	Time in Trial	Continuing n=622					Quitter n=450				
		Yes	No	Unk	Out	% At Goal*	Yes	No	Unk	Out	% At Goal*
BP<140/90	Baseline	380	240	2	0	61%	283	164	3	0	63%
	Year 1	369	162	72	19	69%	264	127	43	16	68%
	Year 2	311	154	115	42	67%	239	112	63	36	68%
	Year 3	266	128	135	93	68%	224	91	66	69	71%
	Year 4	226	86	129	181	72%	176	80	72	122	69%
	Year 5	158	64	98	302	71%	126	54	51	219	70%
On Anti-thrombotic	Baseline	616	6	0	0	99%	445	5	0	0	99%
	Year 1	519	27	57	19	95%	387	11	36	16	97%
	Year 2	481	28	71	42	94%	374	6	34	36	98%
	Year 3	415	25	89	93	94%	331	11	39	69	97%
	Year 4	345	16	80	181	96%	281	8	39	122	97%
	Year 5	250	14	56	302	95%	191	10	30	219	95%
On Statin	Baseline	496	123	3	0	80%	378	69	3	0	85%
	Year 1	423	124	56	19	77%	320	78	36	16	80%
	Year 2	391	116	73	42	77%	305	74	35	36	80%
	Year 3	328	113	88	93	74%	273	69	39	69	80%
	Year 4	273	82	86	181	77%	229	62	37	122	79%
	Year 5	192	73	55	302	72%	157	45	29	219	78%
All of Above	Baseline	302	315	5	0	49%	240	204	6	0	54%
	Year 1	276	253	74	19	52%	217	173	44	16	56%
	Year 2	242	222	116	42	52%	192	158	64	36	55%
	Year 3	198	194	137	93	51%	187	128	66	69	59%
	Year 4	171	139	131	181	55%	143	113	72	122	56%
	Year 5	120	102	98	302	54%	103	77	51	219	57%
Non-Smoker	Baseline	0	622	0	0	0%	450	0	0	0	100%
	Year 1	92	458	53	19	17%	307	92	35	16	77%
	Year 2	101	407	72	42	20%	281	97	36	36	74%
	Year 3	103	336	90	93	23%	247	97	37	69	72%
	Year 4	105	253	83	181	29%	205	86	37	122	70%
	Year 5	78	186	56	302	30%	152	51	28	219	75%

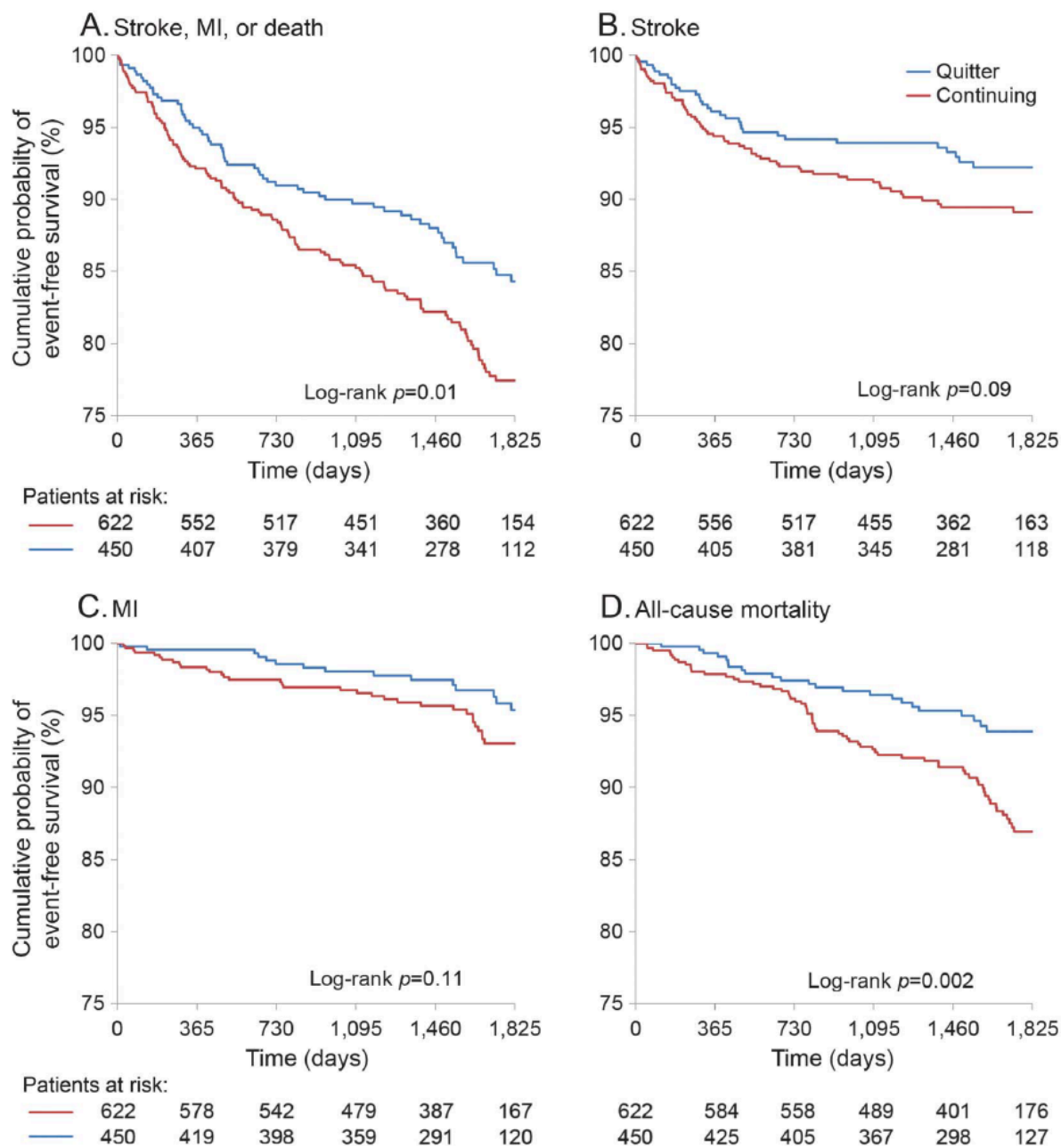
*Proportion of patients with data meeting goal.

Table 10. Risk of Outcomes by Smoking Status at Randomization

Outcome	Nonsmoker (n=2799)		Smoker (n=1072)		Risk Δ	Cox Models				
						Unadjusted		Adjusted ^c		
	Pts. ^a	Risk ^b	Pts. ^a	Risk ^b		Hazard Ratio (95% CI)		P	Hazard Ratio (95% CI)	
Nonfatal stroke, nonfatal MI or death	397	16.1%	181	19.7%	-3.6%	0.80 (0.67, 0.95)	0.01	0.57	(0.47, 0.69)	<0.001
Nonfatal stroke	189	7.8%	92	9.6%	-1.8%	0.75 (0.59, 0.96)	0.02	0.60	(0.46, 0.78)	0.0002
Nonfatal MI	102	4.3%	42	5.3%	-1.0%	0.89 (0.62, 1.28)	0.54	0.72	(0.49, 1.06)	0.09
Death	193	8.1%	89	10.2%	-2.1%	0.80 (0.62, 1.02)	0.08	0.41	(0.31, 0.54)	<0.001

^aNumber of participants with event.^b5-year risk from life-table.^cAdjusted for 8 pre-specified features (age, sex, stroke [vs. TIA] as index event, prior history of stroke, history of hypertension, coronary artery disease, systolic blood pressure, and diastolic blood pressure) and treatment (pioglitazone vs placebo).

Figure 1 Time to outcome events



Time to Outcome Events

Figure 1. Time to Outcome Event, by Smoking Status (Quitter=solid blue line, Continuing smoker=dashed red line); A=Stroke, MI or death; B=Stroke; C=Myocardial infarction; D=death from any cause. MI = Myocardial infarction.