Smoking cessation and outcome after ischemic stroke or TIA

Katherine A. Epstein, MA
Catherine M. Viscoli, PhD
J. David Spence, MD
Lawrence H. Young, MD
Silvio E. Inzucchi, MD
Mark Gorman, MD
Brett Gerstenhaber, MD
Peter D. Guarino, PhD
Anand Dixit, MD
Karen L. Furie, MD
Walter N. Kernan, MD
For the IRIS Trial Investigators

Correspondence to
Dr. Kernan:
walter.kernan@yale.edu

ABSTRACT

Objective: To assess whether smoking cessation after an ischemic stroke or TIA improves outcomes compared to continued smoking.

Methods: We conducted a prospective observational cohort study of 3,876 nondiabetic men and women enrolled in the Insulin Resistance Intervention After Stroke (IRIS) trial who were randomized to pioglitazone or placebo within 180 days of a qualifying stroke or TIA and followed up for a median of 4.8 years. A tobacco use history was obtained at baseline and updated during annual interviews. The primary outcome, which was not prespecified in the IRIS protocol, was recurrent stroke, myocardial infarction (MI), or death. Cox regression models were used to assess the differences in stroke, MI, and death after 4.8 years, with correction for adjustment variables prespecified in the IRIS trial: age, sex, stroke (vs TIA) as index event, history of stroke, history of hypertension, history of coronary artery disease, and systolic and diastolic blood pressures.

Results: At the time of their index event, 1,072 (28%) patients were current smokers. 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).

Conclusion: 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. *Neurology*® 2017;89:1723–1729

GLOSSARY

ARR = absolute risk reduction; **CI** = confidence interval; **HR** = hazard ratio; **IRIS** = Insulin Resistance Intervention After Stroke; **MI** = myocardial infarction; **RRR** = relative risk reduction.

Stroke is the fifth leading cause of death in the United States and the second leading cause of death worldwide.[1] Tobacco use is estimated to be responsible for 12% to 37% of all stroke events and is therefore a leading preventable cause.[2,3] Other well-documented harms of smoking include coronary and peripheral artery disease, chronic obstructive pulmonary disease, and lung and bladder cancer. Despite decades of research on these adverse effects, 15% of adults in the United States currently smoke cigarettes.[4] Recent American Heart Association guidelines for primary prevention of stroke include Class I recommendations for continued abstinence for nonsmokers and for cessation by current smokers. The recommendation for cessation is based on observational data showing that quitting rapidly reduces a smoker's risk of a first stroke or myocardial infarction (MI) to near that of someone who never smoked.[5]

Smoking cessation might be particularly beneficial for patients who have already had an ischemic stroke or TIA because they are at very high risk for future cardiovascular events.[6] This potential benefit prompted the American Heart Association to issue a Class I recommendation for smoking cessation in the 2014 secondary stroke prevention guidelines, but the level of evidence is only C, meaning that it is based on evaluations of very limited populations, consensus expert opinions, case studies, or accepted standard of care.[6] To better quantify the

Supplemental data
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association between smoking after ischemic stroke or TIA and the risk for adverse health outcomes, we examined the effect of smoking cessation among participants enrolled in the Insulin Resistance Intervention After Stroke (IRIS) trial.

METHODS IRIS study design and procedures. The methods and main results for the IRIS trial have been previously published.[7,8] Briefly, IRIS was a randomized, double-blind, placebo-controlled study in 3,876 insulin-resistant, nondiabetic patients with a recent ischemic stroke or TIA designed to test whether pioglitazone, an insulin-sensitizing drug of the thiazolidinedione class, would reduce the incidence of MI and stroke. From 2005 to 2013, investigators at 179 hospitals and clinics in 7 countries enrolled patients and collected data. Participants were followed up for up to 5 years from randomization or to the last scheduled follow-up contact before August 1, 2015, whichever came first.

Standard protocol approvals, registrations, and patient consents. Informed consent was signed by all patients. The IRIS study was approved by the review committees at the participating sites.

Potentially eligible patients with a qualifying neurologic event within the prior 6 months underwent a screening interview, physical examination, and phlebotomy. Patients were excluded if they met the 2005 American Diabetes Association criteria for diabetes (i.e., fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], repeated and confirmed) or if their hemoglobin A_{1c} was ≥7.0% at the screening blood test. Insulin resistance was defined by a score >3.0 on the homeostasis model assessment–insulin resistance measure.[9] Other major exclusions included history of heart failure or bladder cancer and predicted survival <4 years.

Standardized procedures were used to collect data on each participant's medical history and clinical features associated with increased cardiovascular risk. At baseline, patients were asked about their smoking history, including age at initiation, average number of cigarettes smoked daily, current status (smoking, not smoking), and, for former smokers, the time since most recent cessation. At each annual contact, participants were asked about current smoking status. Adherence to standard preventive therapies for secondary stroke prevention was also ascertained at baseline and annually, including measurement of blood pressure and a medication history. Quarterly interviews inquired about interim health events, including stroke and heart attack. All reported events were submitted to external reviewers for adjudication.

Statistical methods. Study size for the original IRIS trial was determined by a power analysis for its primary research aim.

For this prospective observational cohort study, IRIS participants were classified according to smoking status at the time of randomization: never smokers, former smokers (i.e., stopped smoking before the index stroke or TIA event), quitters (i.e., quit after the index event and not smoking at the time of randomization), or continuing smokers. The primary aim of our analysis was to compare the risk of the composite outcome of stroke, MI, or death in patients who quit smoking vs 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). Participants without outcomes were censored at the time of their last completed follow-up contact. These analyses were not prespecified in the IRIS research protocol or data analysis plan. Rather, the analysis was designed after completion of the IRIS trial because of observational research showing that smoking cessation in patients with established coronary heart disease reduced subsequent all-cause mortality[10] or recurrent cardiovascular events.[11,12]

Cumulative probabilities of outcome-free survival over time by smoking status were calculated by the Kaplan-Meier method,[13] and differences were tested by the log-rank statistic using an α of 0.05 (2 sided). The effect of smoking status on risk was quantified by hazard ratios (HRs; with 95% confidence intervals [CIs]) from Cox proportional hazards models[14] that included baseline cardiovascular risk features and treatment assignment (pioglitazone or placebo). The risk features included in the Cox models were those prespecified as adjustment variables for the IRIS trial and included the following: age, sex, stroke (vs TIA) as the index event, 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 for patients who died during follow-up were classified by an independent committee blinded to treatment assignment and tabulated with standard Centers for Disease Control and Prevention categories,[15] and differences across smoking strata for major categories were tested by the χ^2 statistic.

RESULTS Study population. The study cohort was made up of 3,871 IRIS study participants randomized between February 2005 and January 2013 (5 participants were excluded because of missing smoking information) (figure e-1 at Neurology.org). At the baseline interview, 1,309 participants were classified as never smokers, 1,490 as former smokers, 450 as quitters since the index event, and 622 as continuing smokers. Baseline features for quitters and continuing smokers are displayed in table 1. (Features for all participants by smoking status are shown in table e-1.) Some baseline differences between the 2 smoking groups 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).[16,17] 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).[17] On laboratory testing, quitters had lower fasting glucose, low-density lipoprotein cholesterol, and triglycerides compared to continuing smokers. Among women, quitters had higher high-density lipoprotein 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 in the

Table 1	Baseline features by smoking status at randomization	
Feature	Continuing (n = 622)	Quitter (n = 450)
Demographic features		
Age, mean (SD), y	58 (9)	58 (8)
Male sex, n (%)	410 (66)	295 (66)
Black race, n (%)	120 (20)	61 (14)
Hispanic ethnic group, n (%)	23 (4)	18 (4)
Clinical history, n (%)		
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 Scale score ≥3	36 (6)	57 (13)
Cancer (nonskin) history	26 (4)	20 (4)
Physical examination		
Body mass index, mean (SD), kg/m^2	30 (6)	30 (5)
Abdominal obesity,[b] n (%)	362 (59)	285 (64)
Systolic blood pressure, mean (SD), mm Hg	133 (18)	134 (18)
Diastolic blood pressure, mean (SD), mm Hg	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, n (%)		
Statin	496 (80)	378 (85)
Antithrombotic	616 (99)	445 (99)
Angiotensin II receptor blocker	61 (10)	50 (11)
β-Blocker	197 (32)	113 (25)
Thiazide diuretic	164 (26)	107 (24)
Assigned to pioglitazone, n (%)	323 (52)	215 (48)
Cigarettes per day on average, n (%)		
≥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), y	40 (11)	40 (10)

Abbreviations: HbA$_{1c}$ = hemoglobin A$_{1c}$; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment–insulin resistance; LDL = low-density lipoprotein.

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

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); and prescription drugs (3; 3).

[a] History of hospitalization for MI, coronary artery bypass graft, angioplasty, or stenting.

[b] Waist circumference >88 cm for women or >102 cm for men.

intensity of smoking between quitters and continuing smokers 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, and 4 continuing smokers) did not have complete data on the 8 specified adjustment features and are excluded from the adjusted analyses; 3 outcomes were excluded (figure e-1).

After a median follow-up of 4.8 years, stroke, MI, or death had occurred in 60 patients in the quitter group and in 121 in the continuing smoking group (5-year risk 15.7% vs 22.6%, adjusted HR 0.66, 95% CI 0.48–0.90). Among secondary outcomes, there were nonsignificant reductions in the incidence of stroke and MI during follow-up in quitters compared to continuing smokers (table 2, figure 1, and table e-2). Death occurred in 23 quitters and 66 continuing smokers (5-year risk 6.1% vs 13.1%, adjusted HR 0.49, 95% CI 0.30–0.79). Among major causes of death, the largest difference was observed for cancer: 7 deaths among quitters were attributable to cancer compared to 21 among continuing smokers (1.5% vs 3.4%, $p = 0.07$) (table e-3). A lower percentage of deaths was also observed among quitters resulting from cerebrovascular disease (0.2% vs 1.6%, $p = 0.03$), heart disease (0.7% vs 1.6%, $p = 0.16$), and unknown cause (1.8% vs 2.9%, $p = 0.24$).

At baseline, quitters were slightly more likely than continuing smokers to achieve their preventive health goals: 63% of quitters vs 61% of continuing smokers had blood pressure <140/90 mm Hg; 99% of quitters vs 99% of continuing smokers were on antithrombotics; 85% of quitters vs 80% of continuing smokers were on statins; and 54% of quitters vs 49% of continuing smokers had achieved all 3 of these preventive health goals. During 5 years of follow-up, quitters continued to be more likely to meet their preventive health goals (table e-4). Of note, 145 of 450 quitters reported resuming smoking at ≥1 annual time points during follow-up, and 190 of 622 continuing smokers reported having quit (data not shown).

DISCUSSION The results of this study suggest that quitting smoking within 6 months after an ischemic stroke or TIA will significantly reduce the likelihood of stroke, MI, or death in the next 4.8 years. The observed relative risk reduction (RRR) (34%) and absolute risk reduction (ARR) (6.9%) are comparable to those of most other medical treatments for secondary prevention after stroke, including antiplatelet therapy,[18] statin therapy,[16] blood pressure reduction,[19] and pioglitazone.[7] The exception is anticoagulation for atrial fibrillation,[20] which is associated with substantially greater reductions in relative and absolute risk. The present study supports current guidelines for smoking cessation after stroke or TIA[6] and 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 1 other study that has examined the effect of smoking cessation immediately after stroke. This observational study of 240 smokers with cerebrovascular disease observed a nonsignificant reduction in mortality over 14 months in quitters compared to continuing smokers.[21] Other studies have classified smoking status at the time of the stroke event and were not designed to examine the effect of quitting.[22–24] 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 increases the risk for vascular disease by 2 major mechanisms: induction of a procoagulant state and

Table 2	Risk of outcomes by smoking status at randomization								
	Quitter (n = 450)		Continuing (n = 622)			Cox models			
						Unadjusted		Adjusted[c]	
Outcome	Patients, n[a]	Risk, %[b]	Patients[a]	Risk, %[b]	Risk Δ, %	HR (95% CI)	p Value	HR (95% CI)	p Value
Stroke, 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
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
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

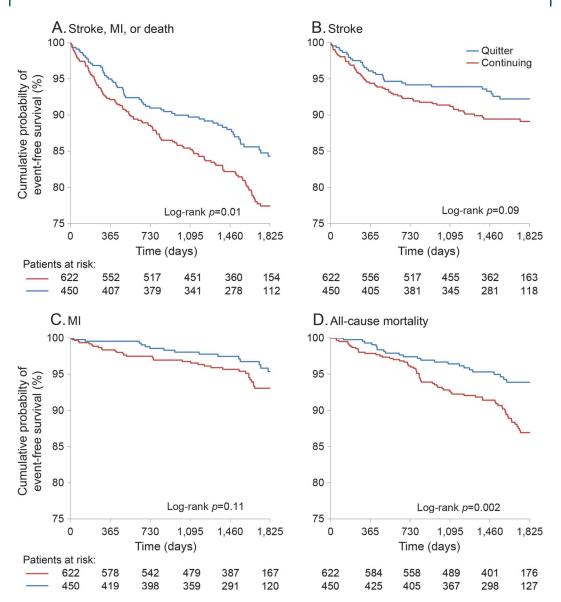Abbreviations: CI = confidence interval; MI = myocardial infarction; HR = hazard ratio.
[a] Number of participants with event.
[b] Five-year risk from lifetable.
[c] Adjusted for 8 prespecified features (age, sex, stroke [vs TIA] as index event, history of stroke, history of hypertension, coronary artery disease, systolic blood pressure, and diastolic blood pressure) and treatment (pioglitazone vs placebo).

Figure 1   Time to outcome events

Time to outcome event by smoking status (quitter = blue line, continuing smoker = red line). (A) Stroke, MI, or death; (B) stroke; (C) MI; and (D) death resulting from any cause. MI = myocardial infarction.

acceleration of atherosclerosis. The procoagulant state is characterized by an increase in platelet aggregation, increased fibrinogen concentration, decrease in fibrinolysis, polycythemia, and high blood viscosity[25] and is rapidly reversible within days of smoking cessation.[26] 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 high-density lipoprotein; and oxidation of low-density lipoprotein).[25] 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.[27,28]

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 that are associated with no significant improvement in survival despite reductions in risk for cardiovascular events.[7,16,19,20] The 1 exception is antiplatelet therapy after a TIA or stroke, which resulted in a smaller but still significant decrease in risk for all-cause mortality after 3 years of therapy (RRR 12%, ARR 1.5%).[29]

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 stroke ($p = 0.03$) and cancer ($p = 0.07$) reached or approached statistical significance. 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. However, we observed a quantitatively large reduction in cancer case fatality in quitters compared with continuing smokers (7 of 31 = 23% vs 21 of 49 = 43%, χ^2 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.[30,31] Mechanisms for the rapid decrease may include enhanced sensitivity to radiation therapy[32] and chemotherapy,[33] elimination of stimulation of tumor growth by nicotine,[34,35] and prevention of death among cancer patients resulting from comorbid pulmonary and cardiovascular disease.[36,37]

The results of this study should be considered in the context of 2 potential sources of bias. Prevention bias refers to the tendency of individuals who make 1 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.[38] Consistent with a prevention bias, quitters were slightly more likely than continuing smokers to have achieved their preventive health goals at baseline and during follow-up. 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 on the basis of features associated with prognosis, the randomized patients may not reflect the true association between smoking and outcomes in the underlying population. In addition to these potential sources of bias, this analysis of 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, nondiabetic 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.

Healthcare providers have a unique opportunity to counsel patients after they have an ischemic stroke or TIA. This article provides a quantitative estimate for the benefits of smoking cessation in this population. 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 of 100 who quit. In simple terms, for every 100 of these patients who manage to quit cigarettes, fully 7 additional patients will survive 5 years without MI or recurrent stroke than otherwise would have. If confirmed, our results suggest that healthcare providers should give very high priority to helping patients quit smoking cigarettes after an ischemic stroke or TIA.

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