Significance of Smoking in Patients Receiving Thrombolytic Therapy for Acute Myocardial Infarction

Experience Gleaned From the International Tissue Plasminogen Activator/Streptokinase Mortality Trial

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Background. Despite the fact that smoking is a well-established risk factor for the development of coronary artery disease, some investigators have noted that hospital mortality after acute myocardial infarction is lower in patients who smoke than in nonsmoking patients. To evaluate the association of smoking with mortality during hospitalization after thrombolytic therapy and 6 months afterward, we analyzed the results of the International Tissue Plasminogen Activator/Streptokinase Mortality Trial.

Methods and Results. Patients were divided into three groups: nonsmokers (those who never smoked), ex-smokers, and active smokers. Multivariate and univariate comparisons were made with respect to baseline characteristics and clinical outcome. There were 2,366 nonsmokers, 2,244 ex-smokers, and 3,469 active smokers. The baseline characteristics of nonsmoking patients differed significantly from the ex-smokers and active smokers. The nonsmoking group included more women than the ex-smokers or active smokers (45% versus 10.6% and 17.6%, respectively), was older (67±10 years versus 64±10 years and 58±11 years), had a higher rate of diabetes mellitus (16.3% versus 11.1% and 7.5%), and had a worse Killip class at admission. Nonsmoking patients and ex-smokers experienced more in-hospital reinfarction than active smokers (4.7% and 5% versus 2.7%, p<0.0001, respectively). Nonsmokers experienced more in-hospital shock than the ex-smokers or active smokers (9.2% versus 6.4% and 5.8%, p<0.0001), stroke (1.9% versus 1.8% and 0.8%, p<0.0001), and bleeding (7.2% versus 6.5% and 4.4%, p<0.0001). They also experienced a higher in-hospital and 6-month mortality (12.8% and 17.6%) than ex-smokers (8.2% and 12.1%) or active smokers (5.4% and 7.8%) (p<0.0001). A multivariate analysis accounting for all baseline characteristics demonstrated a significant association between nonsmoking and increased hospital mortality, with an odds ratio of 1.42 (confidence limits, 1.15–1.72). Among active smokers, there was a nonsignificant trend for mortality rates to decrease with increasing numbers of cigarettes smoked per day.

Conclusions. This retrospective analysis indicates that smokers receiving thrombolytic therapy after acute myocardial infarction have significantly better hospital and 6-month outcome than nonsmokers or ex-smokers. However, smokers sustained their infarction at a significantly earlier age than nonsmokers, and strenuous efforts should continue to be made to decrease the incidence of new and continued smoking. (Circulation 1993;87:53–58)

Key Words • smoking • myocardial infarction • prognosis • mortality • thrombolysis

Many epidemiological studies have shown that cigarette smoking is associated with a higher incidence of myocardial infarction and death from coronary artery disease.1–4 The causal effect of cigarette smoking is further supported by the dose–response relation of smoking and mortality from coronary artery disease and the decreasing mortality risk for ex-smokers.1–6 In addition to accelerating the atherosclerotic process,7 cigarette smoking is known to enhance platelet aggregation and thrombosis8,9 and lower the baseline fibrinolytic activity in blood.10 Smoking also damages endothelial cell lining,8 increases sympathetic discharge,9,11 lowers the ventricular fibrillation threshold,12 and is arrhythmogenic.13 It is interesting that despite the solid and significant evidence of the deleterious effect of smoking on coronary artery disease, some investigators have noted that among hospitalized patients with acute myocardial in-
paroxysmal atrial fibrillation, patients who smoke appear to have a better prognosis than nonsmokers.\textsuperscript{14–25} Only four studies, however, have differentiated between nonsmokers and ex-smokers,\textsuperscript{15,20,23,25} and only three\textsuperscript{22,23,25} evaluated the role of smoking in patients receiving thrombolytic therapy. Neither of these latter studies reported the results of multivariate analysis.

We hereby report the results of a retrospective analysis performed on the effects of smoking in the population of the International Tissue Plasminogen Activator/Streptokinase Trial.

Methods

Study Group

Study subjects—8,387 consecutive patients with acute evolving myocardial infarction from 13 countries—were randomized to receive either recombinant tissue-type plasminogen activator or streptokinase with or without subcutaneous heparin. The study design, the inclusion and exclusion criteria, the trial medications, and the recommended treatments have been described in detail elsewhere.\textsuperscript{36,27}

In this analysis, patients were divided into three groups: nonsmokers (those who never smoked), ex-smokers (those who quit smoking >1 month before index infarction), and active smokers. Univariate comparisons of differences in baseline and outcome variables between the three patient groups were done by \( \chi^2 \) analysis for trends for categorical variables and one-way ANOVA for continuous variables. Multivariate analyses of the effects of all baseline variables as independent variables on each of the various clinical outcomes as dependent variables were done by logistic regression analysis (Biomedical Computer Programs, University of California \textit{BMDP} Program LR).

The clinical outcomes analyzed were hospital and 6-month mortality, in-hospital reinfarction, ventricular fibrillation, stroke, and hemorrhage; and Killip class at discharge. The baseline characteristics analyzed were age (>70 and 60–69 versus <60), sex (female versus male), infarct site (anterior versus inferior), diabetes mellitus (yes versus no), previous infarction (yes versus no), antecedent angina (>1 month and <1 month versus none), history of hypertension (yes versus no), smoking (nonsmokers versus ex-smokers and smokers combined), family history of cardiovascular disease (yes versus no), systolic hypotension at admission (≤95 versus >95 mm Hg), Killip class at entry (>1 versus 1), and time from onset of symptoms to randomization (>3 versus ≤3 hours). For the final analysis, smokers and ex-smokers were combined, because their independent odds ratios were similar. Odds ratios computed from the logistic coefficients are presented in the text followed by 95% confidence limits computed on the basis of the standard error of the coefficients. In this study, smoking status was not assessed after discharge from index hospitalization.

Results

Study Population

Of the 8,387 patients randomized, smoking status was not defined in 75 patients, and baseline data on an additional 53 patients were missing. Thus, 8,259 patients were included in this analysis: 6,317 men 61±11 years old and 1,942 women 67±10 years old \( (p<0.0001) \). Overall, there were 2,366 nonsmokers (1,302 men [55%] and 1,064 women [45%]), 2,244 ex-smokers (2,007 men [89.4%] and 237 women [10.6%]), and 3,649 smokers (3,008 men [82.4%] and 641 women [17.6%]).

The baseline characteristics of all three groups differed significantly (Table 1). Nonsmokers had consistently worse baseline characteristics than active smokers; they were older (67±10 versus 58±11 years), had a higher prevalence of hypertension (43% versus 24%), had a higher rate of diabetes mellitus (16.3% versus 7.5%), a higher rate of antecedent angina ≥1 month (31.7% versus 22.3%) and of Killip class ≥1 at admission (21.3% versus 15.4%), and a higher rate of previous infarction (20.2% versus 13.2%). With the exception of angina and previous myocardial infarction, the rates in ex-smokers were intermediate between active smokers and nonsmokers. For the latter two baseline variables, the rates were highest in ex-smokers: 35.1% for antecedent angina ≥1 month and 28.6% for previous myocardial infarction. All these trends were highly significant \( (p<0.0001) \).

In-Hospital Clinical Outcome

Table 2 presents in-hospital clinical outcome. Non-smoking patients had the worst in-hospital outcome, and patients who were active smokers had the best outcome, with the ex-smokers constituting an intermediate group. Specifically, the nonsmoking patients had high rates of the following in-hospital complications: reinfarctions (4.7% versus 5.0% in ex-smokers and 2.7% in active smokers, \( p<0.001 \)); shock events (9.2% versus 6.4% and 5.8%, \( p<0.0001 \)); strokes (1.9% versus 1.8% and 0.8%, \( p<0.001 \)); bleeding complications (7.2% versus 6.5% and 4.4%, \( p<0.0001 \)); and a worse Killip class at discharge.

In-hospital and 6-month mortality were higher for nonsmokers (302 and 417 of 2,366 patients [12.8% and 17.6%]) than for ex-smokers (185 and 271 of 2,244 patients [8.2% and 12.1%]) or for active smokers (196 and 286 of 3,649 patients [5.4% and 7.8%]) \( (p<0.0001) \) (Figure 1). It is noteworthy that in the active smoking group, there was a nonsignificant trend for mortality rates to decrease with increasing numbers of cigarettes smoked per day.

Mortality was higher for older patients, both men and women, across all smoking subgroups (Table 3). However, in-hospital mortality was highest for nonsmokers and lowest for active smokers, with ex-smokers intermediate for most age and sex categories. The mortality rates in the three smoking groups were similar in all treatment groups (tissue-type plasminogen activator or streptokinase with or without subcutaneous heparin).

Multivariate analysis (Table 4) showed that after all baseline characteristics were accounted for, the increase in mortality for nonsmokers remained highly significant \( (p<0.0001) \), with an independent odds ratio of 1.49 (1.22–1.82). None of the other clinical outcomes during hospitalization were independently associated with nonsmoking.

Discussion

No single epidemiological study contradicts the increased risk associated with smoking with respect to population mortality from coronary artery disease.\textsuperscript{1–6}
Our results in patients treated with thrombolytic therapy as well as data from a few earlier reports (Table 5) are surprising in that they indicate that smoking patients who are hospitalized for acute myocardial infarction have significantly better hospital and 6-month outcome than nonsmokers or, in some aspects, a better prognosis than that of patients who stopped smoking before their acute myocardial infarction. The intermediate outcome of ex-smokers could be a result of inclusion of recent with long-term quitters, the former group sharing similar mortality risk with the active smokers and the latter group sharing the same outcome as nonsmokers. As found by others, smokers not only are significantly younger but also have a more favorable risk profile at admission.

Some of the investigators confronted by these apparently contradictory results explained the worse outcome of nonsmoking patients by their worse baseline risk profile. However, most of these previous studies combined ex-smokers and nonsmokers or excluded ex-smokers altogether. Separation of the ex-smokers precludes the potential confounding resulting

After

in-Hospital Clinical Outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonsmokers (n=2,366)</th>
<th>Ex-smokers (n=2,244)</th>
<th>Active smokers (n=3,649)</th>
<th>p (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinfarction, n (%)</td>
<td>112 (4.7)</td>
<td>112 (5.0)</td>
<td>98 (2.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ventricular fibrillation, n (%)</td>
<td>144 (6.1)</td>
<td>160 (7.1)</td>
<td>252 (6.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Shock, n (%)</td>
<td>218 (9.2)</td>
<td>143 (6.4)</td>
<td>211 (5.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>44 (1.9)</td>
<td>41 (1.8)</td>
<td>28 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhage, n (%)</td>
<td>171 (7.2)</td>
<td>145 (6.5)</td>
<td>160 (4.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>302 (12.8)</td>
<td>185 (8.2)</td>
<td>196 (5.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip class at discharge, n (%)</td>
<td>1,859 (89.9)</td>
<td>1,880 (91.4)</td>
<td>3,241 (93.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>186 (9.0)</td>
<td>155 (7.5)</td>
<td>190 (5.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (0.8)</td>
<td>14 (0.7)</td>
<td>11 (0.3)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td>8 (0.4)</td>
<td>7 (0.3)</td>
<td>16 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

*Both classes 1 and 2 vs. classes 3 and 4 and class 1 vs. classes 2–4.
from the more favorable risk profile and better prognosis in those who were smoking when the myocardial infarction occurred and may reflect the fact that patients with a more adverse risk profile, and thus worse prognosis, quit smoking before the infarction developed. Indeed, as suggested by the increased prevalence of previous infarction and antecedent angina among our ex-smoking patients (Table 1), some may have stopped smoking after a previous infarction.

Although the better survival of smoking patients could reflect other nonidentified favorable baseline characteristics and cessation of smoking after hospital admission, our multivariate analysis comparing the three smoking categories and taking into account all known baseline characteristics showed that nonsmoking was independently associated with increased in-hospital complications and mortality. The increased in-hospital mortality found in the nonsmoking group was further corroborated by the trend showing that mortality was lower among active smokers as the numbers of cigarettes smoked per day decreased. Although this trend was significant only in the univariate analysis, the lack of significance in the multivariate analysis may reflect an insufficient number of cases and/or inaccuracies in the reporting of the number of cigarettes smoked. Most interesting are the findings of significantly higher incremental mortality rates at the 6-month follow-up in the nonsmoking patients (4.8%) compared with ex-smokers (3.9%) and active smokers (2.4%) (p<0.0001).

What might possibly explain these seemingly paradoxical results? Smoking appeared to be a significant predictor for sudden coronary death in both prospective and retrospective studies. In view of the well-recognized effects of smoking on cardiac arrhythmogenicity, coronary thrombosis, vasospasm, and short-term nicotine-induced catecholamine release, it is likely that smoking may induce sudden death. Thus, the apparent difference in prognosis between nonsmokers and active or ex-smokers may have arisen because a larger proportion of smokers died before admission to the hospital.

There is also evidence that the type of lesion that precipitates myocardial infarction in smokers is less severe and is possibly generated by a different mechanism. Myocardial infarction in smokers occurs at an earlier age, accounting for the younger age of smokers hospitalized for acute myocardial infarction in all reports, including our own. The pathophysiological major risk factors for infarction—hypertension, obesity, glucose intolerance, and the more recently recognized factor hyperinsulinemia—have been shown to be strongly correlated to each other in many studies and are hypothesized to be part of a syndrome. However, there is no positive association between smoking and any of these factors. Also, the extent of angiographically recorded coronary lesions may be less in smokers. In the Coronary Artery Surgery Study Registry, the extent of coronary disease (total number of segments with stenosis ≥50% luminal narrowing) was significantly (p<0.05) less in male smokers >45 years of age than in nonsmokers. Since only a very small proportion of our study population underwent coronary angiography (estimated <10%, because only 2.1% underwent coronary angioplasty and 1.3% coronary bypass surgery), it was not possible for us to correlate our findings of the better outcome in smokers with their baseline coronary anatomy.

It is possible that because of the increased thrombogenicity associated with smoking, coronary obstruction in patients who smoke may be more thrombogenic and less atherosclerotic than that of nonsmokers. Thus, smoking patients, when they have a myocardial infarction, may respond better to both spontaneous and

![Figure 1. Bar graph showing hospital and 6-month mortality by patient group and number of cigarettes smoked per day. *By \( \chi^2 \) analysis for trend comparing nonsmokers with ex-smokers and active smokers as three groups.](image-url)
therapeutic thrombolysis and may be left with less
significant atheromatous residual stenosis.

A third possible explanation is that, because the
smoking patients were not allowed cigarettes after
admission to the hospital, the sudden withdrawal of
cigarettes may have had some favorable effect on vas-
cular or hematological systems that discouraged
thrombosis.37

Our findings, however, should not be construed to mean
that smoking is protective. This study represents a retro-
spective subgroup analysis; therefore, it is possible that
unknown variables not examined in our logistic regression
analysis could account for the better outcome in smokers.
Also, although smokers appear to do well after suffering a
myocardial infarction, they compose the biggest group
among our patients with acute myocardial infarction, and
they had infarctions at an earlier age. It is important to
note that because smokers are more likely to suffer
myocardial infarction than nonsmokers, the trend for
overall mortality from myocardial infarction in the general
population is highest in smokers, intermediate in ex-
smokers, and lowest in those who never smoked.1-6 More-
ever, patients with myocardial infarction who smoke at
admission and then stop have a better survival than those
who continue to smoke.18 Although we do not have
information as to how many patients stopped smoking
after admission, it seems likely that many did and that
cessation of smoking and other possibly unidentified base-
line characteristics may have contributed to their better
outcome after discharge.

Similarly, continued smoking after myocardial infarc-
tion was found to be the only identifiable mortality risk
factor after end-systolic volume in multivariate analysis of
a 7-year follow-up of 605 men,38 and continued

### Table 4. Baseline Characteristics Affecting Hospital and 6-Month Mortality*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hospital mortality</th>
<th>6-Month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% Confidence limits</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69 vs. &lt;60 years</td>
<td>2.59 (1.88, 3.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥70 vs. &lt;60 years</td>
<td>6.15 (4.49, 8.43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic hypertension at admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≤95 vs. &gt;95 mm Hg)</td>
<td>4.22 (3.18, 5.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip class at entry (&gt;1 vs. 1)</td>
<td>3.28 (2.66, 1.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Site of infarction (anterior vs. inferior)</td>
<td>1.66 (1.34, 2.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs. no)</td>
<td>1.50 (1.14, 1.98)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Smoking (nonsmokers vs. smokers+ex-smokers)</td>
<td>1.42 (1.15, 1.75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antecedent angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 month vs. no</td>
<td>1.31 (1.00, 1.72)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;1 month vs. no</td>
<td>1.36 (1.08, 1.70)</td>
<td>0.02</td>
</tr>
<tr>
<td>Time from onset of symptoms to randomization (hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;3 vs. ≤3)</td>
<td>1.30 (1.06, 1.59)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous infarction (yes vs. no)</td>
<td>1.09 (0.86, 1.38)</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension (yes vs. no)</td>
<td>1.12 (0.92, 1.38)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*By logistic regression (see "Methods"). Sex, body mass index, hypercholesterolemia, or family history did not have an independent effect.

<table>
<thead>
<tr>
<th>WEINBLATT ET AL.24*</th>
<th>HIEMERS34†</th>
<th>KITCHIN AND POCOCK35‡</th>
<th>SPARROW ET AL.36‡</th>
<th>KELLY ET AL.37‡</th>
<th>ROBINSON ET AL.38†</th>
<th>AIMS39§</th>
<th>WILCOX ET AL.40‖</th>
<th>MUeller ET AL.41¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>881</td>
<td>606</td>
<td>872</td>
<td>458</td>
<td>2,134</td>
<td>977</td>
<td>1,258</td>
<td>2,514</td>
</tr>
<tr>
<td>Multivariate adjustements</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>For age and other variables</td>
<td>For and infarct site</td>
<td>Not performed</td>
<td>Not performed</td>
</tr>
<tr>
<td>Nonsmokers (%)</td>
<td>21.2</td>
<td>24.3</td>
<td>20.7</td>
<td>22.0</td>
<td>16.7</td>
<td>14.4</td>
<td>11.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Ex-smokers (%)</td>
<td>Not defined</td>
<td>23.4</td>
<td>Not defined</td>
<td>Not defined</td>
<td>7.2</td>
<td>Not defined</td>
<td>10.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Active smokers (%)</td>
<td>18.2</td>
<td>20.2</td>
<td>11.0</td>
<td>12.0</td>
<td>5.4</td>
<td>6.5</td>
<td>9.1</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*Probability of death in the 4.5 years after first acute myocardial infarction.
†Total hospital mortality.
‡Current nonsmokers vs. heavy smokers.
§30-Day mortality.
‖6-Month mortality.
¶42-Day mortality.
smoking after thrombolytic therapy for acute myocardial infarction results in an almost fourfold greater risk of reinfarction at 12 months. The risk of having a myocardial infarction in cigarette smokers decreases within a few years of quitting: this may be related to the time that it takes for the fibrinogen level to return to normal after smoking is stopped.

Thus, although these findings warrant further investigation, they in no way argue against continuing vigorous efforts both to prevent young people from taking up smoking and to encourage smokers to stop.

References

Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial.

G I Barbash, H D White, M Modan, R Diaz, J R Hampton, J Heikkila, A Kristinsson, S Moulopoulos, E A Paolasso and T Van der Werf

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