Discontinuation of Smokeless Tobacco and Mortality Risk After Myocardial Infarction

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Background—Given the indications of increased risk for fatal myocardial infarction (MI) in people who use snus, a moist smokeless tobacco product, we hypothesized that discontinuation of snus use after an MI would reduce mortality risk.

Methods and Results—All patients who were admitted to coronary care units for an MI in Sweden between 2005 and 2009 and were <75 years of age underwent a structured examination 2 months after discharge (the baseline of the present study). We investigated the risk of mortality in post-MI snus quitters (n=675) relative to post-MI continuing snus users (n=1799) using Cox proportional hazards analyses. During follow-up (mean 2.1 years), 83 participants died. The mortality rate was 9.7 (95% confidence interval, 5.7–16.3) per 1000 person-years at risk in post-MI snus quitters and 18.7 (14.8–23.6) per 1000 person-years at risk in post-MI continuing snus users. After adjustment for age and sex, post-MI snus quitters had half the mortality risk of post-MI continuing snus users (hazard ratio, 0.51; 95% confidence interval, 0.29–0.91). In a multivariable-adjusted model, the hazard ratio was 0.57 (95% confidence interval, 0.32–1.02). The corresponding estimate for people who quit smoking after MI versus post-MI continuing smokers was 0.54 (95% confidence interval, 0.42–0.69).

Conclusions—In this study, discontinuation of snus use after an MI was associated with a nearly halved mortality risk, similar to the benefit associated with smoking cessation. These observations suggest that the use of snus after MI should be discouraged. **(*Circulation*. 2014;130:325-332.)**

Key Words: mortality ■ myocardial infarction ■ prognosis ■ risk factors ■ smokeless tobacco

The use of oral moist snuff, a form of smokeless tobacco, is increasing worldwide. The largest snuff market is the United States, with an annual consumption of 1.7 billion cans and an annual market growth rate of >5% during the past 5 years.[1] The highest prevalence of snuff use is in Sweden, where 20% of the male and 3% of the female adult population are daily users of snus, the Swedish form of snuff.[2] Although the manufacturing of Swedish snus includes a pasteurization process, which produces a relatively sterile product with lower levels of carcinogenic nitrosamines, the nicotine levels are similar to traditional US moist snuff brands.[3]

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Smoking cessation after a myocardial infarction (MI) reduces the risk of death by one third[4] and is considered a cornerstone of cardiac rehabilitation programs worldwide. Cardiovascular effects of smokeless tobacco have been less studied, but there are reports on acute autonomic and hemodynamic effects such as endothelial dysfunction[5,6] and increased blood pressure, heart rate, and blood levels of adrenaline.[7,8] No increased risk of MI incidence has been observed in previous studies,[9–16] although 2 meta-analyses have reported a seemingly increased risk for fatal MI,[17,18] which suggests that snus use may predispose to arrhythmic or other serious complications of MI. Nicotine exposure has also been associated with increased vulnerability for ventricular fibrillation after MI in animal studies.[19–21] Furthermore, snus use may be associated with a higher risk of heart failure, an important MI sequel.[22] No previous study has addressed the question of whether snus users who have an MI benefit from discontinuation of snus use.

We hypothesized that cessation of snus use after an MI would reduce mortality risk to the same extent as smoking cessation. We investigated this hypothesis in a large prospective sample of patients with a recent MI.

Methods

Study Sample

We included patients in the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies, a Swedish nationwide quality register; http://www.swedeheart.org) databases Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA) and Secondary Prevention after Heart Intensive Care Admission (SEPHIA) for the present study. Patients with MI who were admitted to a coronary care unit in Sweden between 2005 and 2009 were initially recorded in RIKS-HIA. At present, 73 of 74 hospitals in Sweden contribute to the

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database, in which ≈100 variables are recorded continuously.[23] In the secondary prevention database SEPHIA, patients <75 years of age were systematically followed up 2 months after discharge. At present, 62 of 73 Swedish hospitals engaged in RIKS-HIA also participate in SEPHIA. The SEPHIA 2-month examination was used as the baseline of the present study. We excluded participants for whom information on smoking or the use of smokeless tobacco use was lacking (n=1963), rendering a total sample of 20 911 individuals eligible for the present study. For individuals who had >1 MI during these years, baseline data were updated at all subsequent 2-month postdischarge visits, rendering a total of 21 210 observations from which study samples were drawn. Our primary study sample was restricted to all subjects who were using snus at the time of the MI and were examined 2 months after discharge (n=2474). Our secondary study sample was defined as all subjects who were smoking at the time of the MI and were examined 2 months after discharge (n=6934). Because of differences in treatment and prognosis given different severities of MI, we also analyzed the risk of mortality in subsamples based on type of MI, ST-segment–elevation MI (STEMI)/left bundle-branch block (snus users, n=1048; smokers, n=3282) or non-STEMI (snus users, n=1411; smokers, n=3629), as a secondary analysis.

All patients were informed about their participation in the registry and the follow-up and had the right to refuse participation. The registry and the merging of registries were approved by the National Board of Health and Welfare, the Swedish Data Inspection Board, and the Regional Ethical Review Board in Uppsala.

Baseline Examinations

At the baseline examinations, 2 months after an MI, information was collected through face-to-face interviews by use of a questionnaire (available at http://www.ucr.uu.se/sephia). Some data presented in this study (left ventricular systolic function, type of MI, and the proportion who underwent coronary intervention during hospital stay) were collected at the time of the MI (http://www.ucr.uu.se/rikshia).

Snus exposure was classified into 4 categories: Post-MI snus users (participants who continued to use snus after their MI), post-MI snus quitters (participants who stopped using snus at the time of their MI), pre-MI snus quitters (participants who had stopped using snus before admission for their MI), and those who had never used snus. The same classification system was used for smoking exposure. Fasting blood samples were collected and analyzed for lipid and glucose levels. Body mass index was calculated and waist circumference measured. Office supine blood pressure was measured. Heart rhythm was established with an ECG. Participation in a cardiac rehabilitation program (nurse-led general educational program about coronary heart disease) was recorded. Information on current medication was obtained. Level of physical activity was established through a 7-day recall question at the baseline examination and defined as number of episodes of exercise >30 minutes the past week, grouped into 4 categories: 0, 1 to 3, 4 to 7, and >7 episodes per week. Occupation status was defined as employed, unemployed, and retired. Approximately 80% of the participants had undergone echocardiography during hospitalization for an MI. Left ventricular systolic function was graded into 4 categories: Normal (left ventricular ejection fraction >50%), mild impairment (40%–50%), moderate impairment (30%–39%) and severe impairment (<30%). Type of MI (STEMI/left bundle-branch block or non-STEMI) at presentation and the proportion who underwent coronary intervention during the hospital stay were defined. Presence of dyspnea and angina were classified according to definitions of the New York Heart Association and the Canadian Cardiovascular Society, respectively. The presence of diabetes mellitus (*International Classification of Diseases, 10th Revision* [*ICD-10*] code E10–14) and previous MI (*ICD-10* code I21–23), stroke (*ICD-10* code I60–64), or heart failure (*ICD-10* code I50) were defined through record linkages to the Swedish Hospital Discharge Register, and the diabetes mellitus diagnosis was supplemented by the presence, within 2 weeks before or after the baseline examination, of a fasting plasma glucose ≥7.0 mmol/L, hemoglobin A_{1c} ≥6.5%, or use of hypoglycemic drug therapy.[24] Hypertension was defined as use of antihypertensive medication at the time of or before admission for MI, a systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg at baseline.

No nationwide specific program for discontinuation of tobacco was provided. All patients were offered a chance to participate in the standardized nurse-led cardiac rehabilitation program, in which tobacco was one of the subjects discussed. Smoking cessation is a key quality measure for secondary prevention in SWEDEHEART, but the use of tobacco of any form after an MI is discouraged. Because of the lack of such evidence, advice regarding discontinuation of smokeless tobacco, from a clinical perspective, has not been as prioritized as for smoking.

Follow-Up and Outcome Measures

Follow-up commenced at the SEPHIA 2-month examination (2005–2009) and continued until death or December 31, 2009. The primary end point in the present study was death of any cause. Register data for mortality were available from the Swedish Census, in which all deceased individuals in Sweden are registered. Secondary end points were (1) a composite of repeat MI, stroke, heart failure (*ICD-10* codes as above), and cardiovascular mortality (*ICD-10* codes I00–99); (2) cardiovascular mortality; and (3) noncardiovascular mortality. For secondary end points, follow-up commenced at the SEPHIA 2-month examination (2005–2008) and continued until an end point was reached or December 31, 2008, whichever occurred first.

Statistical Analyses

Cox proportional hazards models were used to investigate the mortality risk in post-MI snus quitters versus post-MI snus users (continuing users). The following models were analyzed: Model A was adjusted for age as a timeline and sex. Model B was similar to A but was further adjusted for past and present smoking exposure with a 4-category smoking covariate (post-MI use, post-MI cessation, pre-MI cessation, and never-use). Model C was similar to B but was further adjusted for occupational status and participation in cardiac rehabilitation program. The directed acyclic graph approach was used to identify the main model C. The principle of the directed acyclic graph approach is to use causal diagrams when selecting statistical models in epidemiological studies, to minimize potential bias.[25] Model D was adjusted for age as a timeline and a propensity score derived from the variables sex, smoking exposure (covariate similar to the one used in previous models), diabetes mellitus, hypertension, systolic and diastolic blood pressures, body mass index, waist circumference, low-density lipoprotein/high-density lipoprotein ratio, type of MI, occupational status, physical activity (4 levels), participation in cardiac rehabilitation program, treatment with aspirin, and use of any other platelet inhibitors (primarily clopidogrel), β-blockers, statins, and renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). Additional information about the propensity score used in model D is available in the online-only Data Supplement. This model was designed to account for long-term risk factors and differences in post-MI lifestyle changes and treatments but was not identified by use of directed acyclic graphs and is therefore considered a secondary, mechanistic model.

A secondary study sample was used to investigate mortality risk in post-MI smoke quitters versus post-MI smokers (continuing smokers) for comparison with the main analysis. Models investigated were identical to the above, apart from replacing the smoking covariate with a similar 4-category snus exposure covariate in models B, C, and D. Missing data on covariates were imputed with an iterative (MCMC, or Markov chain Monte Carlo) method. A sensitivity analysis that included only individuals with complete data on all variables in model C was also performed (n=2443). In this study, some of the post-MI snus quitters were post-MI smokers or concomitant post-MI smoke quitters (post-MI dual quitters). We therefore also investigated mortality rates in the subsample (n=1540) without post-MI smokers and post-MI dual quitters, to assess residual risk of smoking or concomitant smoking cessation as a confounding reason for a possible benefit seen with smokeless tobacco quitting. As a secondary analysis, we also wanted to address the effects of tobacco cessation in dual users (n=934), examining the effects of stopping snus, stopping cigarettes, and stopping both. Because the behaviors of patients can change significantly from 2 months after an MI and have important mortality implications, we investigated the agreement of tobacco

exposure classification at baseline and at a second follow-up visit, 1 year after the MI, using the κ-statistic. To assess the impact of the fact that patients were clustered within hospitals, we investigated a shared frailty model, with shared frailty on the hospital level in model C. Interactions between quitting snus and the 4-category smoking covariate or sex were investigated as multiplicative deviations in model B (and similarly for quitting smoking). Proportional hazard assumptions were confirmed graphically and by Schoenfeld tests. Two-tailed tests were used, with 95% confidence limits. All analyses were conducted with Stata 11.1 or 12.1 (StataCorp, College Station, TX).

Results

Characteristics of the cohort are presented in Table 1. Median follow-up time in the total cohort was 1.9 years, and maximum follow-up time was 4.9 years, rendering in total 40 370 person-years at risk (PYAR). During follow-up, 812 of the 20 911 participants died (incidence rate per 1000 PYAR, 18.9; 95% confidence interval [CI], 14.8–23.6).

Snus Cessation and Mortality Risk

In our primary study sample, the median follow-up time was 2.1 years, and 83 of the participants died during follow-up. The incidence rate for post-MI snus quitters was 9.7 (95% CI, 5.7–16.3) per 1000 PYAR, whereas for post-MI snus users, it was 18.7 (95% CI, 14.8–23.6) per 1000 PYAR. The cumulative hazard of mortality is presented in Figure 1.

In a model adjusted for age and sex (Table 2, model A), post-MI snus quitters had nearly 50% lower mortality during follow-up than those who continued to use snus. In model B, with further adjustment for past and present smoking exposure, snus use cessation after MI was still independently associated with a lower rate of total mortality than continued use. In the multivariable-adjusted models C and D, point estimates for post-MI snus quitters were essentially unchanged, albeit with wider CIs (Table 2).

Smoking Cessation and Mortality Risk

In our secondary study sample, the age-adjusted incidence rate for post-MI smoke quitters was 13.5 (95% CI, 11.3–16.2) per 1000 PYAR and for post-MI smokers 28.4 (95% CI, 24.2–33.3) per 1000 PYAR (Figure 2). Post-MI smoke quitters also had ≈50% lower mortality than those who continued to smoke. The results were essentially unchanged when adjusted for past and present snus exposure in model B and in the multivariable-adjusted models C and D (Table 2).

Secondary Analyses

A sensitivity analysis of model C in individuals with complete data on all variables rendered very similar results to the same model using imputed data sets (hazard ratio, 0.53; 95% CI, 0.29–0.96). In model C, quitting snus was associated with a hazard ratio for mortality of 0.59 (95% CI, 0.28–1.28) in people with a non-STEMI and 0.62 (95% CI, 0.25–1.55) in people with an STEMI or left bundle-branch block (Figure 3). In the subsample with available data on secondary outcomes, 2% of patients had a cardiovascular event. Among these, 37% had repeat MIs, 11% had strokes, 25% were hospitalized for heart failure, and 78% had cardiovascular death. Of all deaths, 51% were attributable to cardiovascular causes. Snus cessation was associated with a hazard ratio of 0.38 (95% CI, 0.11–1.32) for cardiovascular events, 0.56 (95% CI, 0.16–2.0) for cardiovascular mortality, and 0.43 (95% CI, 0.15–1.27) for noncardiovascular mortality in the main model C (Figure 4). In the subsample without post-MI smokers and dual quitters, the incidence rates for post-MI snus quitters was 9.8 (95% CI, 5.1–18.8) per 1000 PYAR, and for post-MI snus users, it was 17.2 (95% CI, 12.6–23.6) per 1000 PYAR. In dual users, the main model C rendered an HR of 0.37 (95% CI, 0.05–2.9) for snus quitting, 0.59 (95% CI, 0.28–1.24) for quitting smoking, and 0.31 (95% CI, 0.10–0.98) for dual quitting relative to not quitting either form of tobacco. The vast majority of patients were classified in the same tobacco exposure group at baseline and 1 year after their MI (κ for snus=0.72, κ for smoking=0.77). A version of model C with shared frailty on the hospital level did not perform better than the model without the clustered structure (likelihood ratio test P=0.50), which implies that the primary models were adequate. No deviations from multiplicity (P>0.42 for all interaction terms) or proportionality of hazards (all Schoenfeld test P values were >0.42) were observed. Excluded patients (n=1963) were older, had more comorbidities, and were less often treated with percutaneous coronary intervention for a non-STEMI relative to the participants included in the present study.

Discussion

Primary Observations

In this large, prospective cohort study, discontinuation of snus use after an MI was associated with a nearly halved mortality risk. This association appeared to be independent of age, sex, and smoking habits, as well as of many other relevant covariates. Notably, the benefit of snus use cessation after an MI was similar to the undisputed benefit of smoking cessation, which was confirmed yet again. Results were consistent across a range of subgroups and outcomes, although most secondary analyses were assessed with poor precision.

Comparisons With Previous Studies

To the best of our knowledge, there have been no previous investigations of smokeless tobacco cessation and potential risk reduction of cardiovascular outcomes or total mortality, either in population-based studies or in samples of patients with acute or chronic coronary disease. Apart from 1 exception based primarily on tobacco chewers,[26] no increase in risk of MI incidence has been observed.[9–16] The risk of MI mortality has been elevated in some studies,[15,27] which suggests an increased case-fatality rate, with a 13% increased risk in a 2009 meta-analysis[17] and a 28% increased risk in a 2012 pooled meta-analysis.[18]

In a review and meta-analysis, smoking cessation was associated with a 36% reduction in risk of all-cause mortality among patients with coronary heart disease.[4] In the present study, the corresponding estimate was 46%, which suggests a study sample in line with previous observational secondary prevention studies.

Potential Mechanisms

One possible explanation for our observations is an increased vulnerability to arrhythmic complications in snus users, because several electrophysiological experimental studies

Table 1. Baseline Characteristics by Different Tobacco Exposure Categories in Patients Recently (<2 mo) Hospitalized for MI in Sweden, 2005 to 2009

		Primary Study Sample (n=2474)		Secondary Study Sample (n=6934)	
Variable	Total Sample (n=21 220)	Post-MI Snus Users (n=1799)	Post-MI Snus Quitters (n=675)	Post-MI Smokers (n=2675)	Post-MI Smoke Quitters (n=4259)
Age, y	61.9 (8.5)	58.7 (9.0)	58.4 (8.4)	59.3 (8.7)	58.9 (8.5)
Female sex	5600 (26)	90 (5)	26 (4)	792 (30)	1232 (29)
Snus exposure categories					
Post-MI snus users	1799 (9)	1799 (100)	0 (0)	229 (9)	461 (11)
Post-MI snus quitters	675 (3)	0 (0)	675 (100)	29 (1)	215 (5)
Pre-MI snus quitters	1537 (7)	0 (0)	0 (0)	139 (5)	198 (5)
Never snus users	17 209 (81)	0 (0)	0 (0)	2278 (85)	3385 (79)
Smoking exposure categories					
Post-MI smokers	2675 (13)	229 (13)	29 (4)	2675 (100)	0 (0)
Post-MI smoke quitters	4259 (20)	461 (26)	215 (32)	0 (0)	4259 (100)
Pre-MI smoke quitters	7894 (37)	899 (50)	314 (47)	0 (0)	0 (0)
Never-smokers	6392 (30)	210 (12)	117 (17)	0 (0)	0 (0)
Diabetes prevalence	4931 (23)	426 (24)	131 (19)	609 (23)	807 (19)
Previous stroke	1063 (5)	77 (4)	18 (3)	159 (6)	127 (3)
Previous heart failure	863 (4)	71 (4)	6 (1)	148 (5)	59 (1)
Hypertension	11 891 (56)	943 (52)	345 (51)	1387 (52)	2103 (49)
Type of MI*	n=21 134	n=1789	n=670	n=2666	n=4244
STEMI, LBBB (vs NSTEMI)	8678 (41)	733 (41)	315 (47)	1145 (43)	2137 (50)
Coronary intervention during hospital stay	16 095 (76)	1396 (78)	555 (82)	2098 (78)	3485 (82)
Classification of angina					
Asymptomatic	17 862 (84)	1514 (84)	592 (88)	2200 (82)	3666 (86)
CCS 1	2235 (11)	201 (11)	56 (8)	315 (12)	424 (10)
CCS 2	802 (4)	61 (3)	17 (3)	116 (4)	129 (3)
CCS 3–4	320 (2)	23 (1)	9 (1)	44 (2)	40 (1)
Classification of heart failure					
Asymptomatic	16 176 (76)	1373 (76)	525 (78)	1997 (75)	3231 (76)
NYHA I	2806 (13)	244 (14)	90 (13)	380 (14)	604 (14)
NYHA II	1679 (8)	143 (8)	47 (7)	220 (8)	335 (8)
NYHA III or IV	559 (3)	39 (2)	13 (2)	78 (3)	89 (2)
Left ventricular ejection fraction*	n=16 872	n=1435	n=556	n=2081	n=3526
Normal (>0.5)	10 295 (61)	956 (67)	349 (63)	1233 (59)	2116 (60)
Mild (0.4–0.5)	3766 (22)	284 (20)	122 (22)	489 (23)	793 (22)
Moderate (0.3–0.4)	2153 (13)	150 (10)	63 (11)	265 (13)	454 (13)
Severe (<0.3)	658 (4)	45 (3)	22 (4)	94 (5)	163 (5)
Sinus rhythm on ECG*	14 060/14 649 (96)	1163/1216 (96)	454/464 (98)	1746/1794 (97)	2822/2886 (98)
Systolic blood pressure, mm Hg	132.4 (18.9)	132.2 (18.1)	131.8 (18.3)	131.2 (19.6)	131.3 (18.7)
Diastolic blood pressure, mm Hg	76.9 (10.3)	78.4 (10.4)	77.9 (9.8)	77.2 (10.8)	77.2 (10.3)
Body mass index, kg/m^2	27.4 (4.4)	27.9 (4.4)	27.6 (3.6)	27.0 (4.8)	27.3 (4.5)
Waist circumference, cm	99.6 (12.5)	102.5 (12.2)	101.2 (9.3)	99.1 (12.9)	99.1 (12.8)
Cholesterol, mmol/L	4.1 (0.9)	4.2 (0.9)	4.1 (0.9)	4.3 (1.0)	4.2 (0.9)
LDL/HDL fraction	1.9 (0.9)	2.0 (0.8)	2.1 (1.6)	2.1 (1.1)	2.0 (1.1)
Triglycerides, mmol/L	1.6 (0.9)	1.8 (1.1)	1.7 (1.0)	1.8 (1.1)	1.7 (1.0)
Undergoing treatment with					
Aspirin	20 019 (94)	1691 (94)	651 (96)	2531 (95)	4080 (96)
Other platelet inhibitors	17 077 (81)	1488 (83)	568 (84)	2256 (84)	3524 (83)
β-Blockers	19 289 (91)	1646 (91)	627 (93)	2433 (91)	3903 (92)
Statins	19 918 (94)	1683 (94)	655 (97)	2483 (93)	4061 (95)

(*Continued*)

Table 1. Continued

Variable	Total Sample (n=21 220)	Primary Study Sample (n=2474)		Secondary Study Sample (n=6934)	
		Post-MI Snus Users (n=1799)	Post-MI Snus Quitters (n=675)	Post-MI Smokers (n=2675)	Post-MI Smoke Quitters (n=4259)
RAAS blockage (ACEI or ARB)	15 730 (74)	1259 (70)	497 (74)	1902 (71)	3060 (72)
Participation in cardiac rehabilitation program	6725 (32)	497 (28)	251 (37)	571 (21)	1318 (31)
Physical activity, episodes of exercise >30 min in the past week*	n=21 213	n=1797	n=675	n=2674	n=4256
0	4040 (19)	363 (20)	77 (11)	755 (28)	796 (19)
1–3	4632 (22)	412 (23)	140 (21)	642 (24)	893 (21)
4–6	4821 (23)	391 (22)	153 (23)	515 (19)	915 (21)
>7	7720 (36)	631 (35)	305 (45)	762 (28)	1652 (39)
Occupation status*	(n=20 803)	(n=1773)	(n=661)	(n=2608)	(n=4141)
Employed	8650 (42)	945 (53)	414 (63)	1113 (43)	2218 (54)
Unemployed	574 (3)	58 (3)	18 (3)	168 (6)	181 (4)
Retired	11 579 (56)	770 (43)	229 (35)	1327 (51)	1742 (42)

Data are number of individuals (%) or means (standard deviations; 1 decimal). Data are based on a sample of 21 220 observations contributed by 20 911 subjects. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; CCS, Canadian Cardiovascular Society; HDL, high-density lipoprotein; LBBB, left bundle-branch block; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone system; and STEMI, ST-segment–elevation myocardial infarction.

*Variable available in subsample.

have indicated an arrhythmogenic potential of nicotine. One experimental study in healthy dogs revealed dose-dependent proarrhythmia (both of a benign and a malignant nature) after nicotine infusion,[28] and a previous study also demonstrated a significant reduction of the electric ventricular fibrillation threshold after nicotine intake.[29] In 2 postinfarction studies in dogs, nicotine infusion was shown to facilitate or promote the induction of ventricular fibrillation,[19] as well as resulting in a more complex electrophysiological pattern after the induction of ventricular fibrillation.[20]

Another possible mechanism is snus-related myocardial dysfunction. In a postinfarction study, nicotine-exposed rats had impaired myocardial healing and altered left ventricular remodeling compared with controls,[21] which suggests that the continuing snus users may be more prone to develop left ventricular dysfunction as a result of the MI. The use of snus also induces acute hemodynamic effects such as endothelial dysfunction,[5,6] increased blood pressure and heart rate, and increased blood levels of adrenaline.[7,8] Because hypertension is a well-established risk factor for heart failure, this suggests a possible link. In a previous study, snus use was associated with an increased risk for incident heart failure, both of ischemic and nonischemic origin.[22] In the present study, because echocardiography was performed during the hospital stay and not at baseline 2 months after the MI, any differences in left ventricular function between post-MI snus quitters and post-MI continuing snus users at baseline or during follow-up are unknown.

Nicotine may promote tumor growth and metastasis,[30] and the benefits of stopping snus use might include a decrease in both cardiovascular and cancer mortality. Although estimated with poor precision, we observed similar associations with both cardiovascular and noncardiovascular mortality. This supports possible noncardiovascular beneficial effects of quitting snus.

Finally, those who stopped using snus after an MI participated to a higher extent in the cardiac rehabilitation program, were more physically active, had a lower prevalence of concomitant smoking, and were more inclined to stop smoking after the MI. Although the estimates for snus quitting after an MI were

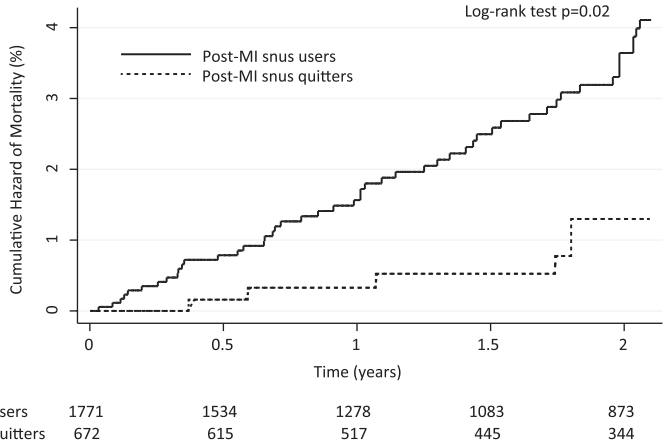

Figure 1. Cumulative incidence of total mortality by snus exposure category in patients recently (<2 months) hospitalized for myocardial infarction (MI; n=2474), Sweden, 2005 to 2009.

Table 2. Mortality Rate by Tobacco Exposure Category in Patients Recently (<2 mo) Hospitalized for MI in Sweden, 2005 to 2009

Variable	PYAR	Cases, n	Model A	Model B	Model C	Model D
Snus exposure categories						
Post-MI snus users (n=1799)	3694	69	Reference	Reference	Reference	Reference
Post-MI snus quitters (n=675)	1450	14	0.51 (0.29–0.91)	0.55 (0.30–0.97)	0.57 (0.32–1.02)	0.55 (0.31–0.99)
Smoking exposure categories						
Post-MI smokers (n=2675)	5253	149	Reference	Reference	Reference	Reference
Post-MI smoke quitters (n=4259)	8864	120	0.50 (0.39–0.63)	0.50 (0.39–0.63)	0.54 (0.42–0.69)	0.54 (0.43–0.71)

Estimates presented in models A through D are hazard ratio (95% CI). Separate models are presented for snus and smoking exposure categories. MI indicates myocardial infarction; and PYAR, person-years-at-risk.

Model A: Adjusted for age and sex.

Model B: As model A but further adjusted for past and present smoking and snus exposure, respectively, by using 4-category tobacco exposure covariates (post-MI use, post-MI cessation, pre-MI cessation, and never-use).

Model C: Model similar to B but further adjusted for occupation status and participation in cardiac rehabilitation program. To minimize potential bias, the directed acyclic graph approach was used to identify the main model C.

Model D: Adjusted for age and a propensity score derived from the variables sex, smoking exposure (covariate similar to the one used in previous models), diabetes mellitus, hypertension, systolic and diastolic blood pressures, body mass index, waist circumference, low-density lipoprotein/high-density lipoprotein ratio, type of MI, occupation status, physical activity (4 levels), participation in cardiac rehabilitation program, treatment with aspirin, treatment with any other platelet inhibitor (primarily clopidogrel), β-blockers, statins, and renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitor or angiotensin 2 receptor blocker). These models were designed to account for long-term risk factors, as well as for differences in post-MI lifestyle changes and treatments, but were not identified by use of directed acyclic graphs and are therefore considered secondary, mechanistic models.

attenuated only marginally in the models that adjusted for several covariates, and the results remained essentially the same in the subsample without smokers and dual quitters, residual confounding remains a possibility. Those who manage to quit using snus may represent a selected group with an overall healthier lifestyle relative to the group that continued to use snus.

Study Strengths and Limitations

This prospective study is based on a large, well-characterized cohort that included both men and women. All exposure and outcome data were collected systematically, and loss to follow-up was minimal.

Several limitations in the present study should be borne in mind. Because the baseline was 2 months after hospital discharge, this is a cohort of MI survivors. The number of snus users or quitters who died during their hospital stay or within 2 months after discharge is unknown. Previous meta-analyses have indicated that MI mortality is elevated in snus users.[17,18] The effect of snus use cessation after MI seen in the present study could therefore be an underestimation of the true effect. Although the study sample included all consecutive patients nationwide and was therefore of maximal possible size, the number of deaths was limited in the smallest groups, which yielded wide CIs. The proportion of never-smoking snus users was limited. Therefore, statistical analyses were based on groups with both current/former smokers and snus users. Residual confounding by smoking is hence possible, but adjustments for smoking exposure in models B, C, and D and subgroup analyses that excluded smokers and dual quitters did not indicate this to be of major concern. No specific instructions were given about abstinence from cigarettes or snus on the day of the baseline examination. Therefore, any influence of concurrent tobacco use or abstinence on the participants' blood pressure levels, heart rate levels, or ECGs is unknown. We lacked information on alcohol use, nicotine replacement therapy, illegal substances, and social group, although we used occupational classification as a psychosocial and socioeconomic proxy. To explore the proarrhythmia hypothesis (or other causes of death) further, a larger sample than the present one is necessary. Unfortunately, the lack of information

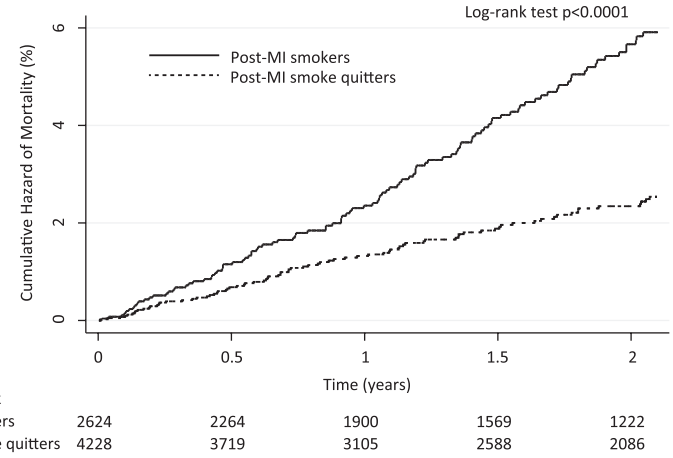

Figure 2. Cumulative incidence of total mortality by smoking exposure category in patients recently (<2 months) hospitalized for myocardial infarction (MI; n=6934), Sweden, 2005 to 2009.

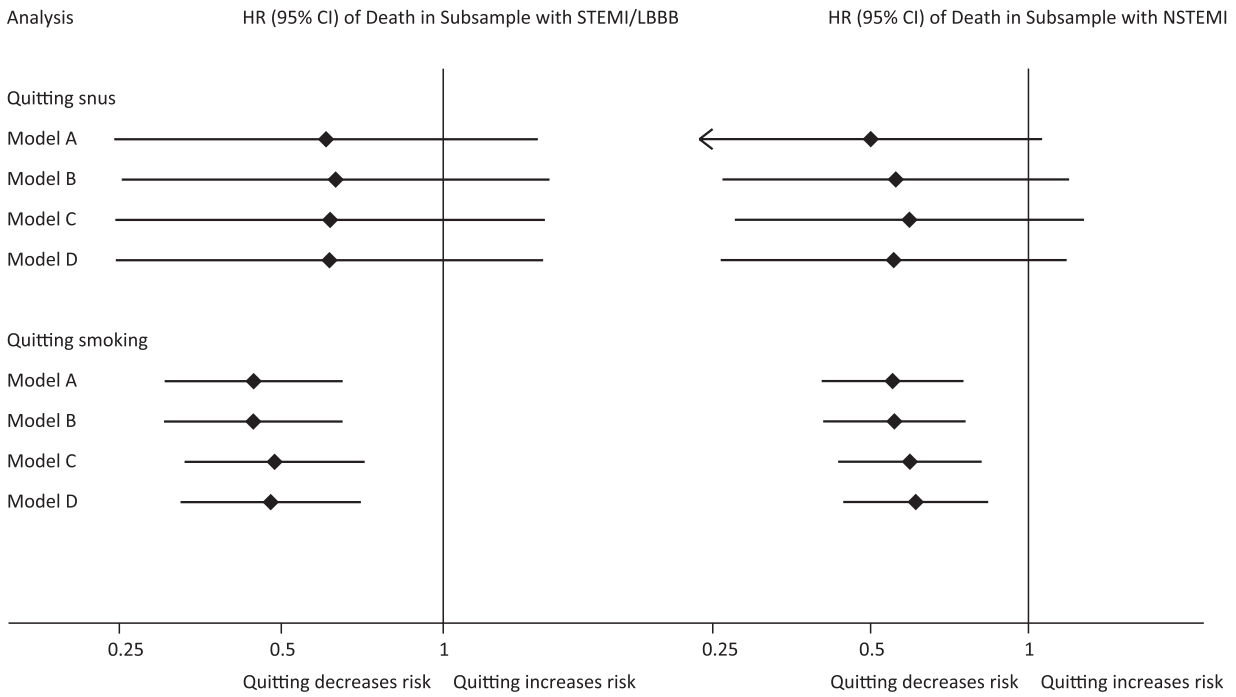

Figure 3. Mortality rate by tobacco exposure category in patients recently (<2 months) hospitalized for different types of myocardial infarction, Sweden, 2005 to 2009. CI indicates confidence interval; HR, hazard ratio; LBBB, left bundle-branch block; and NSTEMI, non–ST-segment–elevation myocardial infarction. Models as in Table 2.

on tobacco doses and usage durations made it impossible for us to study any dose-response relations. Apart from lack of information on tobacco habits, no other exclusion criteria were used (ie, patients with poor life expectancy because of noncardiac causes may have contributed with deaths). If this group had been more (or less) prone to quit snus use, they may have biased the results. This risk is limited because patients >75 years of age were not included. According to the SEPHIA instructions, patients should be classified as ex-tobacco users if it had been >1 month since they quit, but we cannot exclude the possibility that some patients with a more recent cessation date may also have been classified as ex-users. The cohort consisted of people with a recent MI who were of primarily white Northern European descent, and the generalizability to other populations or ethnic groups is unknown.

Conclusions

In this prospective cohort study, discontinuation of snus use after an MI was associated with a nearly halved mortality risk, similar to that associated with smoking cessation. These observations suggest that the use of snus after an MI should be discouraged.

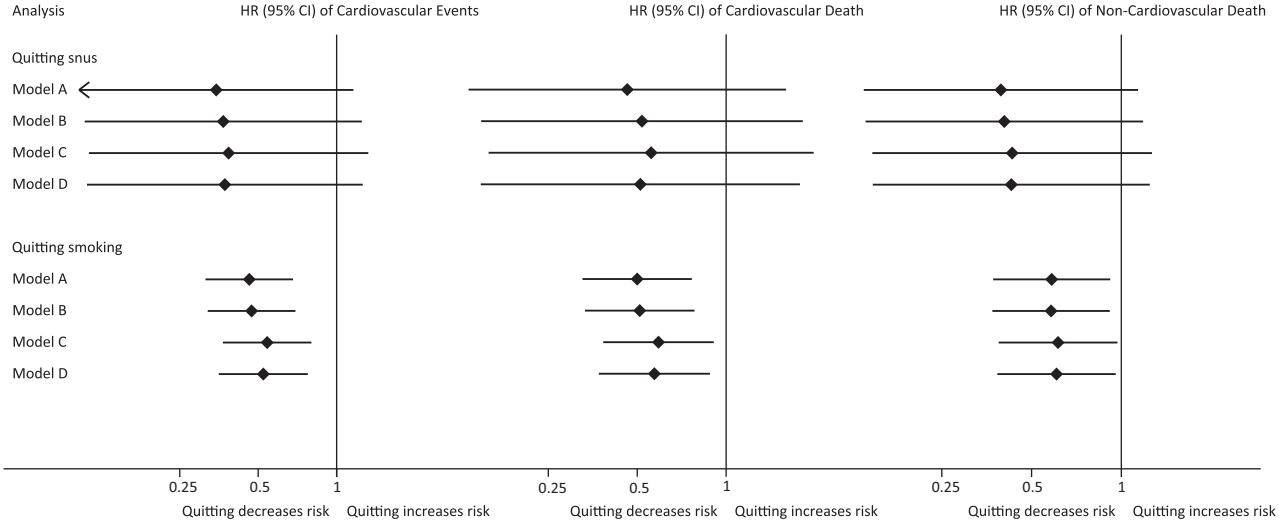

Figure 4. Rate of cardiovascular events, cardiovascular mortality, and noncardiovascular mortality by tobacco exposure category in patients recently (<2 months) hospitalized for myocardial infarction, Sweden, 2005 to 2008. "Cardiovascular events" is a composite of repeat myocardial infarction, stroke, heart failure, and cardiovascular mortality. CI indicates confidence interval; and HR, hazard ratio. Models as in Table 2.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Smokeless tobacco in the form of Swedish snus (oral moist snuff) has been proposed as a safer alternative to smoking. Different snus formulations exist, from loose tobacco to sachets. In Sweden, 20% of adult males and 4% of adult females are estimated to be daily snus users. The sale of snus is illegal in the rest of the European Union but is widespread and increasing in the United States. Previous studies have suggested that use of smokeless tobacco results in an increased risk for fatal myocardial infarction (MI), which indicates that snus use may predispose people to arrhythmic or other serious complications of MIs. No previous study has addressed the question of whether snus users who have an MI benefit from discontinuation. We have investigated associations of snus discontinuation after MI with mortality risk using the Swedish national quality register for myocardial infarctions (SWEDEHEART). Our data indicate that cessation of snus use after MI might be equally beneficial as smoking cessation after MI. The mortality risk was halved in post-MI snus quitters relative to post-MI continuing users. These data are of interest not only to researchers and physicians but also to policy makers and the general public. Ideally, the effects of quitting snus after an MI should be studied in a randomized clinical trial; until then, these observations suggest that the use of snus after MI should be discouraged.

Discontinuation of Smokeless Tobacco and Mortality Risk After Myocardial Infarction

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SUPPLEMENTAL MATERIAL

1) Supplemental Methods:

The propensity score was fitted using the user-written Stata "pscore" algorithm (Becker & Ichino, *Estimation of average treatment effects based on propensity scores.* Stata J 2002;2:358–377), with the independent variables listed in the manuscript. This algorithm uses a logit model, and stratifies individuals in quantiles of the propensity score and checks that the score is balanced between the groups. The latter is done by testing differences in means of all independent variables between snus users and snus quitters within each quantile, using two-sample t-tests. In the present study, all independent variables were well balanced between the snus use groups within all quantiles of the propensity score (all $p>0.05$).