Discontinuation of Smokeless Tobacco and Mortality Risk after Myocardial Infarction

Running title: Arefalk et al.; Snus Cessation and Post-MI Mortality

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Abstract

**Background**—Based on indications of increased risk for fatal myocardial infarction (MI) in snus users, we hypothesized that discontinuation of snus use after an MI reduces 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 under the age of 75 underwent a structured examination two months post-discharge (the baseline of the present study). We investigated risk of mortality in post-MI snus quitters (n=675) relative to post-MI continuous snus users (n=1799) using Cox proportional hazards analyses. During follow-up (mean 2.1 years), 83 participants died. The mortality rate in post-MI snus quitters was 9.7 (95% confidence interval 5.7 to 16.3)/1000 person-years-at-risk and in post-MI continuous snus users 18.7 (14.8 to 23.6)/1000 person-years-at-risk. Adjusting for age and gender, post-MI snus quitters had half the mortality risk of post-MI continuous snus users (hazard ratio 0.51; 95% CI 0.29 to 0.91). In a multivariable-adjusted model, the hazard ratio was 0.57 (95% CI 0.32 to 1.02). The corresponding estimate for post-MI smoke quitters vs. post-MI continuous smokers was 0.54 (95% CI 0.42 to 0.69).

**Conclusions**—In this study, discontinuation of snus use post-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 post-MI should be discouraged.

**Key words:** myocardial infarction, mortality, risk factor, prognosis, Smokeless tobacco
Introduction

The use of oral moist snuff, a form of smokeless tobacco, is increasing worldwide. The largest snuff market is in the United States with an annual consumption of 1.7 billion cans, and an annual market growth rate of more than 5% during the past five 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, producing a relatively sterile product with lower levels of carcinogenic nitrosamines, the nicotine levels are similar to traditional U.S. moist snuff brands.3

Smoking cessation after a myocardial infarction 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 include reports on acute autonomic and hemodynamic effects such as endothelial dysfunction5,6 and increased blood pressure, heart rate and blood levels of adrenaline.7,8 No increased risk of myocardial infarction incidence has been observed in previous studies,9-16 although two meta-analyses have reported a seemingly increased risk for fatal myocardial infarction,17,18 suggesting that snus use may predispose to arrhythmic or other serious complications of myocardial infarction. Nicotine exposure has also in animal studies been associated with increased vulnerability for ventricular fibrillation following myocardial infarction.19-21 Further, snus use may be associated with higher risk of heart failure, an important myocardial infarction sequel.22 No previous study has addressed the question whether snus users who suffer a myocardial infarction benefit from discontinuation of snus use.

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

Study sample

We included patients in the SWEDHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies; a Swedish nation-wide quality register; www.swedeheart.org) databases RIKS-HIA and SEPHIA, for this study. Patients with myocardial infarction who were admitted to a coronary care unit in Sweden between 2005 and 2009 were initially recorded in RIKS-HIA. At present 73 out of 74 hospitals in Sweden contribute to the database, where about 100 variables are continuously recorded. In the secondary prevention database SEPHIA, patients under the age of 75 were systematically followed up two months post-discharge. At present, 62 out of 73 Swedish hospitals engaged in RIKS-HIA also participate in SEPHIA. The SEPHIA two-month examination was used as the baseline of the present study. We excluded participants that lacked information on smoked and/or smokeless tobacco use (n=1,963), rendering a total sample of 20,911 individuals eligible for the present study. For individuals who had more than one myocardial infarction during these years, baseline data were updated at all subsequent two months post-discharge visits, rendering a total number of observations of 21,210, from which study samples were drawn. Our primary study sample was restricted to all subjects who were using snus at the time of the myocardial infarction, and examined two months post-discharge (n=2,474). Our secondary study sample was defined as all subjects who were smoking at the time of the myocardial infarction, and examined two months post-discharge (n=6,934). Due to differences in treatment and prognosis given different severity of myocardial infarction, we also analyzed risk of mortality in subsamples based on type of myocardial infarction, STEMI/LBBB (snus users n=1,048; smokers n=3,282) and NSTEMI (snus users n=1,411; smokers n=3,629), 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, two months after a myocardial infarction, information was collected through face-to-face interviews using a questionnaire (available on www.ucr.uu.se/sephia). Some data presented in this study (left ventricular systolic function, type of myocardial infarction and the proportion that underwent coronary intervention during hospital stay) were collected at the time of the myocardial infarction (www.ucr.uu.se/rikshia).

Snus exposure was classified into four categories; Post-myocardial infarction (MI) snus users (participants that continued to use snus after their MI), post-MI snus quitters (participants that stopped using snus at the time of their MI), pre-MI snus quitters (participants that already had stopped using snus, prior to admission for their MI) and never snus users. The same classification system was used for smoking exposure. Fasting blood samples were collected and analysed for lipid and glucose levels. Body mass index (kg/m²) was calculated and waist circumference measured. Office supine blood pressure was measured. Heart rhythm was established using an electrocardiogram. 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 seven day recall question at the baseline examination and defined as number of episodes of exercise >30 minutes the past week, grouped into four categories: 0, 1-3, 4-7 and >7 episodes/week.
Occupation status was defined as employed, unemployed and retired. About 80% of the participants had undergone echocardiography during hospitalization for a myocardial infarction; left ventricular systolic function was graded into four categories: normal (left ventricular ejection fraction >50%), mild impairment (40-50%), moderate impairment (30-39%) and severe impairment (<30%). Type of myocardial infarction (STEMI/LBBB or NSTEMI) at presentation and the proportion that underwent coronary intervention during the hospital stay was defined. Presence of dyspnoea and angina were classified according to definitions of the New York Heart Association (NYHA) and the Canadian Cardiovascular Society (CCS), respectively. The presence of diabetes (ICD-10 code E10-14), previous myocardial infarction (ICD-10 code I21-23), stroke (ICD-10 code I60-64) or heart failure (ICD-10 code I50) was defined through record linkages to the Swedish Hospital Discharge Register, and the diabetes diagnosis was supplemented by presence, within two weeks before or after the baseline examination, of a fasting plasma glucose ≥ 7.0 mmol/L and/or HbA1c ≥ 6.5 % and/or use of hypoglycemic drug therapy. Hypertension was defined as use of antihypertensive medication at the time of or prior to admission for myocardial infarction, or a systolic blood pressure at or above 140 mm Hg, or a diastolic blood pressure at or above 90 mm Hg at baseline.

No nation-wide specific program for discontinuation of tobacco was provided. All patients were offered to participate in the standardized nurse-led cardiac rehabilitation program, where tobacco was one of the subjects discussed. Smoking cessation is a key quality measure for secondary prevention in SWEDHEART, but the use of tobacco of any form after a myocardial infarction is discouraged. Due to the lack of such evidence, advice regarding discontinuation of smokeless tobacco has from a clinical perspective not been as prioritized as for smoking.
Follow-Up and Outcome Measures

Follow-up commenced at the SEPHIA two-month examination (2005-2009) and continued until death or Dec 31, 2009. The primary endpoint in the present study was death from any cause. Register data for mortality was available from the Swedish Census, where all deceased individuals in Sweden are registered. Secondary endpoints were: (1) a composite of repeat myocardial infarction, stroke, heart failure (ICD-10 codes as above) and cardiovascular mortality (ICD-10 codes I00-99); (2) cardiovascular mortality; and (3) non-cardiovascular mortality. For secondary endpoints follow-up commenced at the SEPHIA two-month examination (2005-2008) and continued until an endpoint or Dec 31, 2008, whichever occurred first.

Statistical Analyses

Cox proportional hazards models were used to investigate the mortality risk in post-MI snus quitters vs. post-MI snus users (continuing users). The following models were analyzed:

A:  Model adjusted for age as timeline and gender.
B:  Model similar to A, but further adjusted for past and present smoking exposure using a four-category smoking covariate (post-MI use, post-MI cessation, pre-MI cessation and never-use).
C:  Model similar to B, but further adjusted for occupation status and participation in cardiac rehabilitation program. The directed acyclic graph (DAG) approach was used to identify the main model C. The principle of the DAG approach is to use causal diagrams when selecting statistical models in epidemiologic studies, in order to minimize potential bias.25
D:  Model adjusted for age as timeline and a propensity score derived from the variables gender, smoking exposure (covariate similar to the one used in previous models), diabetes, hypertension, systolic and diastolic blood pressures, body mass index, waist circumference,
LDL/HDL-ratio, type of myocardial infarction, occupation status, physical activity (four levels), participation in cardiac rehabilitation program, treatment with aspirin, any other platelet inhibitors (primarily clopidogrel), betablockers, statins and renin-angiotensin-aldosteron system inhibitors (angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers). Additional information about the propensity score used in Model D is available as online supplemental data. This model was designed to account for long-term risk factors as well as differences in post-MI lifestyle changes and treatments, but was not identified using DAGs and is therefore considered a secondary, mechanistic, model.

A secondary study sample was used to investigate mortality risk in post-MI smoke quitters vs. 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 four-category snus exposure covariate in models B, C and D. Missing data on covariates was imputed with an iterative (MCMC) method. A sensitivity analysis using 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 investigated mortality rates also in the subsample (n=1540) without post-MI smokers and post-MI dual quitters, to assess residual risk of smoking or concomitant smoke quitting 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. As the behaviors of patients can change significantly from two months after a myocardial infarction and have important mortality implications, we investigated the agreement of tobacco exposure classification at baseline and at a second follow up visit, one
year after the myocardial infarction, using the Kappa statistic. In order to assess the impact of the fact that patients are 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 four-category smoking covariate or gender were investigated as deviations from multiplicativity in models B (and similarly for quitting smoking). Proportional hazard assumptions were confirmed graphically and by Schoenfeld’s tests. Two-tailed tests were used, with 95% confidence limits. All analyses were conducted using Stata 11.1 or 12.1 (StataCorp, College Station, USA).

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 18.9 [95% confidence interval (CI) 14.8-23.6]/1000 person-years at risk [PYAR]).

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 [5.7-16.3]/1000 PYAR, for post-MI snus users 18.7 [14.8-23.6]/1000 PYAR, and the cumulative hazard of mortality is presented in Figure 1.

In a model adjusted for age and gender (Table 2, model A), post-MI snus quitters had nearly 50% lower mortality rate during follow up than those who continued to use snus. In model B, further adjusting for past and present smoking exposure, snus use cessation post-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 confidence intervals (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 [11.3-16.2]/1000 PYAR and for post-MI smokers 28.4 [24.2-33.3]/1000 PYAR (Figure 2). Post-MI smoke quitters also had circa 50% lower mortality rate than those who continued to smoke. The results were essentially unchanged when adjusting 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 datasets (HR 0.53, 95% CI 0.29-0.96). In model C, quitting snus was associated with a HR for mortality of 0.59 (0.28-1.28) in people with an NSTEMI, and 0.62 (0.25-1.55) in people with a STEMI/LBBB (Figure 3). In the subsample with available data on secondary outcomes, 2% of patients had a cardiovascular event. Among these, 37% had repeat myocardial infarctions, 11% had strokes, 25% were hospitalized for heart failure and 78% suffered cardiovascular death. Of all deaths, 51% were from cardiovascular causes. Snus cessation was associated with a HR of 0.38 (0.11-1.32) for cardiovascular events, 0.56 (0.16-2.0) for cardiovascular mortality, and 0.43 (0.15-1.27) for non-cardiovascular 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 [5.1-18.8]/1000 PYAR and for post-MI snus users 17.2 [12.6-23.6]/1000 PYAR. In dual users, the main model C rendered HR of 0.37 (0.05-2.9) for snus quitting, 0.59 (95 % CI 0.28-1.24) for smoke quitting and 0.31 (0.10-0.98) for dual quitting, relative to not quitting either tobacco form. The vast majority of patients were classified in the same tobacco exposure group at baseline and one year after their MI.
(Kappa for snus = 0.72, Kappa 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), implying that the primary models are adequate. No deviations
from multiplicativity (p> 0.42 for all interaction terms) or proportionality of hazards (all
Schoenfeld’s test p>0.42) were observed. Excluded patients (n=1,963) were older, had more
comorbidities, and were less often treated with PCI for an NSTEMI, relative to the participants
included in this study.

Discussion

Primary observations

In this large prospective cohort study, discontinuation of snus use, after a myocardial infarction,
was associated with a nearly halved mortality risk. This association seemed to be independent of
age, gender and smoking habits, as well as of many other relevant covariates. Notably the benefit
of snus use cessation after a myocardial infarction 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

There are, to our knowledge, 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 one
exception based primarily on tobacco chewers,26 no increase in risk of myocardial infarction
incidence has been observed.9-16 The risk of myocardial infarction mortality has been elevated in
some studies,15,27 suggesting an increased case fatality rate, with a 13% increased risk in a 2009
meta-analysis, and a 28% increased risk in a 2012 pooled meta-analysis.

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. In our study the corresponding estimate was 46%, suggesting 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, as several electrophysiologic experimental studies have indicated an arrhythmogenic potential of nicotine. One experimental study in healthy dogs revealed dose-dependent proarrhythmia (both of benign and malignant nature) following nicotine infusion and a previous study also demonstrated a significant reduction of the electrical ventricular fibrillation threshold following nicotine intake. In two post-infarction studies in dogs; nicotine infusion was shown to facilitate or promote the induction of ventricular fibrillation, as well as result in a more complex electrophysiological pattern after the induction of ventricular fibrillation.

Another possible mechanism is snus-related myocardial dysfunction. In a post-infarction study, nicotine-exposed rats had impaired myocardial healing and altered left ventricular remodelling as compared to controls, suggesting that the continuing snus users may be more prone to develop left ventricular dysfunction as a consequence to the myocardial infarction. The use of snus also induces acute hemodynamic effects such as endothelial dysfunction, increased blood pressure and heart rate and increased blood levels of adrenaline. Since 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
non-ischemic origin. In our study, as the echocardiography was performed during hospital stay and not at baseline two months post-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.

Of interest, nicotine may promote tumor growth and metastasis, and the benefit of stopping snus use might be a decrease in both cardiovascular and cancer mortality. Although estimated with poor precision, we observed similar associations with both cardiovascular and non-cardiovascular mortality. This supports possible non-cardiovascular beneficial effects of quitting snus.

Finally, those who stopped using snus post-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 post-MI. Although the estimates for snus quitting post-MI were attenuated only marginally in the models adjusting for several covariates and the results remained essentially the same in the subsample without smokers and dual quitters, residual confounding still is 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.

**Strengths and limitations**

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

Several limitations in the present study should be borne in mind. As the baseline was two months post-discharge, this is a cohort of MI survivors. The number of snus users or quitters who
died during hospital stay or within two months post discharge, is unknown. Previous meta analyses have indicated that MI mortality is elevated in snus users.\textsuperscript{17,18} The effect of snus use cessation post-MI seen in our study, could therefore be an underestimation of the true effect. Although the study sample included all consecutive patients nationwide and therefore of maximal possible size, the number of deaths was limited in the smallest groups, giving wide confidence intervals. 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 excluding 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 from concurrent tobacco use or abstinence on the participants’ blood pressure levels, heart rate levels or electrocardiograms 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 is necessary. Unfortunately, the lack of information 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, i.e. patients with poor life expectancy from non-cardiac 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 older than 75 years of age were not included. According to the SEPHIA instructions, patients should be classified as ex-tobacco users if > one month since quitting, but we cannot exclude the possibility that some patients with a more recent
cessation may also have been classified as ex-users. The cohort consisted of persons with a recent myocardial infarction 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 a myocardial infarction was associated with a nearly halved mortality risk, similar to that associated with smoking cessation. These observations suggest that the use of snus post-MI should be discouraged.

Acknowledgments: All authors have participated and contributed sufficiently in the work to take public responsibility for the content. Dr Arefalk and Dr Sundström had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures: None.

References:


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3. Stepanov I, Jensen J, Hatsukami D, Hecht SS. New and traditional smokeless tobacco:


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</table>

| Sinus rhythm on ECG*              | 14060/14649 (96) | 1163/1216 (96) | 454/464 (98) | 1746/1794 (97) | 2822/2886 (98) |

| Systolic blood pressure (mmHg)    | 132.4 (18.9)     | 132.2 (18.1)   | 131.8 (18.3) | 131.2 (19.6) | 131.3 (18.7) |
| Diastolic blood pressure (mmHg)  | 76.9 (10.3)      | 78.4 (10.4)    | 77.9 (9.8)   | 77.2 (10.8)  | 77.2 (10.3)  |
| Body mass index (kg/m²)           | 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)    |

<table>
<thead>
<tr>
<th>On treatment with:</th>
<th>(n=21213)</th>
<th>(n=1797)</th>
<th>(n=675)</th>
<th>(n=2674)</th>
<th>(n=4256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>20019 (94)</td>
<td>1691 (94)</td>
<td>651 (96)</td>
<td>2531 (95)</td>
<td>4080 (96)</td>
</tr>
<tr>
<td>Other platelet-inhibitors</td>
<td>17077 (81)</td>
<td>1488 (83)</td>
<td>568 (84)</td>
<td>2256 (84)</td>
<td>3524 (83)</td>
</tr>
<tr>
<td>Betablockers</td>
<td>19289 (91)</td>
<td>1646 (91)</td>
<td>627 (93)</td>
<td>2433 (91)</td>
<td>3903 (92)</td>
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<tr>
<td>Statins</td>
<td>19918 (94)</td>
<td>1683 (94)</td>
<td>655 (97)</td>
<td>2483 (93)</td>
<td>4061 (95)</td>
</tr>
<tr>
<td>RAAS-blockage (ACEI and/or ARB)</td>
<td>15730 (74)</td>
<td>1259 (70)</td>
<td>497 (74)</td>
<td>1902 (71)</td>
<td>3060 (72)</td>
</tr>
<tr>
<td>Participation in cardiac rehabilitation program</td>
<td>6725 (32)</td>
<td>497 (28)</td>
<td>251 (37)</td>
<td>571 (21)</td>
<td>1318 (31)</td>
</tr>
<tr>
<td>Physical activity; episodes of exercise&gt;30 minutes, the past week *</td>
<td>0: 4040 (19)</td>
<td>363 (20)</td>
<td>77 (11)</td>
<td>755 (28)</td>
<td>796 (19)</td>
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<td></td>
<td>1-3: 4632 (22)</td>
<td>412 (23)</td>
<td>140 (21)</td>
<td>642 (24)</td>
<td>893 (21)</td>
</tr>
<tr>
<td></td>
<td>4-6: 4821 (23)</td>
<td>391 (22)</td>
<td>153 (23)</td>
<td>515 (19)</td>
<td>915 (21)</td>
</tr>
<tr>
<td></td>
<td>&gt;7: 7720 (36)</td>
<td>631 (35)</td>
<td>305 (45)</td>
<td>762 (28)</td>
<td>1652 (39)</td>
</tr>
<tr>
<td>Occupation status *</td>
<td>(n=20803)</td>
<td>(n=1773)</td>
<td>(n=661)</td>
<td>(n=2608)</td>
<td>(n=4141)</td>
</tr>
<tr>
<td>Employed</td>
<td>8650 (42)</td>
<td>945 (53)</td>
<td>414 (63)</td>
<td>1113 (43)</td>
<td>2218 (54)</td>
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<tr>
<td>Unemployed</td>
<td>574 (3)</td>
<td>58 (3)</td>
<td>18 (3)</td>
<td>168 (6)</td>
<td>181 (4)</td>
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<tr>
<td>Retired</td>
<td>11579 (56)</td>
<td>770 (43)</td>
<td>229 (35)</td>
<td>1327 (51)</td>
<td>1742 (42)</td>
</tr>
</tbody>
</table>

Data are number of individuals (percent, whole numbers) or means (standard deviations, one decimal).

*: Variable available in subsample

Abbreviations: MI, myocardial infarction; NSTEMI, Non ST-Elevation Myocardial Infarction; STEMI, ST-Elevation Myocardial Infarction; LBBB, Left Bundle Branch Block; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; ECG, electrocardiogram; RAAS, Renin-Angiotensin-Aldosteron-System; ACEI, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin 2 Receptor Blocker.

Data are based on a sample of 21220 observations, contributed by 20911 subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PYAR</th>
<th>Cases</th>
<th>Models A</th>
<th>Models B</th>
<th>Models C</th>
<th>Models D</th>
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</thead>
<tbody>
<tr>
<td>Snus exposure categories</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-MI snus users (n=1799)</td>
<td>3694</td>
<td>69</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>Ref</td>
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<tr>
<td>Post-MI snus quitters (n=675)</td>
<td>1450</td>
<td>14</td>
<td>0.51</td>
<td>0.55</td>
<td>0.57</td>
<td>0.55</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(0.29-0.91)</td>
<td>(0.30-0.97)</td>
<td>(0.32-1.02)</td>
<td>(0.31-0.99)</td>
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<tr>
<td>Smoking exposure categories</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Post-MI smokers (n=2675)</td>
<td>5253</td>
<td>149</td>
<td>ref</td>
<td>ref</td>
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<tr>
<td>Post-MI smoke quitters (n=4259)</td>
<td>8864</td>
<td>120</td>
<td>0.50</td>
<td>0.50</td>
<td>0.54</td>
<td>0.54</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(0.39-0.63)</td>
<td>(0.39-0.63)</td>
<td>(0.42-0.69)</td>
<td>(0.43-0.71)</td>
</tr>
</tbody>
</table>

Estimates presented in models A-D are hazard ratios (95% confidence intervals). Separate models are presented for snus and smoking exposure categories.

Models A: adjusted for age and gender.
Models B: as models A, but further adjusted for past and present smoking and snus exposure respectively, by using four-category tobacco exposure covariates (post-MI use, post-MI cessation, pre-MI cessation and never-use).
Models C: models similar to B, but further adjusted for occupation status and participation in cardiac rehabilitation program. In order to minimize potential bias, the directed acyclic graph approach was used to identify the main
models C.
Models D: adjusted for age and a propensity score derived from the variables gender, smoking exposure (covariate similar to the one used in previous models), diabetes, hypertension, systolic and diastolic blood pressures, body mass index, waist circumference, LDL/HDL-ratio, type of myocardial infarction, occupation status, physical activity (four levels), participation in cardiac rehabilitation program, treatment with aspirin, any other platelet inhibitors (primarily clopidogrel), betablockers, statins and RAAS inhibitors (ACEI and/or ARB). These models were designed to account for long-term risk factors as well as differences in post-MI lifestyle changes and treatments, but were not identified using DAGs and are therefore considered secondary, mechanistic models.

Abbreviations: PYAR, person-years-at-risk; IR, incidence rate (per 1000 PYAR); MI, myocardial infarction; LDL, low density lipoprotein; HDL, high density lipoprotein; STEMI, ST-elevation myocardial infarction; LBBB, left bundle branch block; NSTEMI, Non ST-elevation myocardial infarction; RAAS, renin-angiotensin-aldosterone system; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.
Figure Legends:

**Figure 1.** Cumulative Incidence of Total Mortality by Snus Exposure Categories in Patients Recently (<2 months) Hospitalized for Myocardial Infarction (n=2,474), Sweden 2005-2009.

**Figure 2.** Cumulative Incidence of Total Mortality by Smoking Exposure Categories in Patients Recently (<2 months) Hospitalized for Myocardial Infarction (n=6,934), Sweden 2005-2009.

**Figure 3.** Mortality Rate by Tobacco Exposure Categories in Patients Recently (<2 months) Hospitalized for Different Types of Myocardial Infarction, Sweden 2005-2009. Abbreviations and models as in Table 2.

**Figure 4.** Rate of Cardiovascular Events, Cardiovascular Mortality and Non-Cardiovascular Mortality by Tobacco Exposure Categories in Patients Recently (<2 months) Hospitalized for Myocardial Infarction, Sweden 2005-2008. Cardiovascular events is a composite of repeat myocardial infarction, stroke, heart failure and cardiovascular mortality. Abbreviations and models as in Table 2.
Figure 1

Cumulative Hazard of Mortality (%)

- Post-MI Snus Users
- Post-MI Snus Quitters

Log-Rank Test p=0.02

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-MI Snus Users</td>
</tr>
<tr>
<td>0</td>
<td>1771</td>
</tr>
<tr>
<td>0.5</td>
<td>1534</td>
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<tr>
<td>1</td>
<td>1278</td>
</tr>
<tr>
<td>1.5</td>
<td>1083</td>
</tr>
<tr>
<td>2</td>
<td>873</td>
</tr>
</tbody>
</table>
Figure 2

Cumulative Hazard of Mortality [%]

Time (Years)

Number at Risk
Post-MI Smokers 2624 2264 1900 1569 1222
Post-MI Smoke Quitters 4228 3719 3105 2588 2086

Log-Rank Test p<0.0001
Discontinuation of Smokeless Tobacco and Mortality Risk after Myocardial Infarction
Gabriel Arefalk, Kristina Hambraeus, Lars Lind, Karl Michaëlsson, Bertil Lindahl and Johan Sundström

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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).