Hazard Function and Secular Trends in the Risk of Recurrent Acute Myocardial Infarction

30 Years of Follow-Up of More Than 775 000 Incidents

Mats Gulliksson, MD; Hans Wedel, PhD; Max Köster, PhD; Kurt Svärdssudd, MD, PhD

Background—The incidence of a first acute myocardial infarction (AMI) has fallen considerably during the last decades. However, no previous studies have analyzed the underlying hazards function of experiencing a recurrent AMI, and none has analyzed the change of risk for a recurrent AMI over the last 3 decades.

Methods and Results—The study was based on the Swedish national myocardial infarction register. The register contained more than 1 million AMI events. After exclusion of events occurring in subjects younger than 20 or older than 84 years and events with uncertain first AMI status, 775 901 events occurring between 1972 and 2001 remained for analysis. During the study period, the risk of a new event among survivors of a previous AMI decreased sharply during the first 2 years after the previous event, had its minimum after 5 years, and then increased slowly again. The risk for a recurrent AMI during the first year after a previous event was fairly stable over the years until the late 1970s and then decreased by 36% in women and 40% in men until the late 1990s, irrespective of age and AMI number, mirroring the incidence decrease over the years for primary events.

Conclusions—The risk of a recurrent AMI event was highly dependent on time from the previous event, a novel finding which may affect risk scoring. There were strong secular trends toward diminishing risk for a recurrent AMI in recent years, even when other outcome affecting variables were taken into account. (Circ Cardiovasc Qual Outcomes. 2009; 2:178-185.)

Key Words: myocardial infarction ■ epidemiology ■ population ■ prevention

The incidence of a first-time acute myocardial infarction (AMI) is decreasing in most industrialized countries.1–3 This decrease is seen in all ages and among both men and women.3 It began in the 1970s in the United States and Australia, and a few years later in Sweden.4 The mortality in AMI has also declined drastically.4 The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) project reported that the CHD mortality decline was on average 2% to 3% annually.1,5 It was estimated that two thirds of this decline was attributable to the decrease in incidence in CHD, whereas the reduction in case fatality rate, death within 28 days, had contributed to the remaining one third.6 In Sweden, the age-standardized reduction of mortality from a first AMI from 1987 to 2004 was more than 40% in both sexes.7 For individuals treated in hospital the age-adjusted case fatality rate fell from more than 32% in 1987 to just over 15% in 2005 for both sexes.7

The decrease in the incidence of a first-time AMI has stimulated interest in determining whether there is a similar decrease in the incidence of recurrent AMIs. A number of studies have analyzed time trends in recurrent AMI events. For example, The Finnish part of the WHO MONICA (FINMONICA) MI Register Study reported a decline in recurrent coronary events contributing importantly to the decline in coronary mortality in Finland in 1983 to 1997,8,9 the Minnesota Heart Survey presented a falling recurrence rate of 20% to 30% in 1985 to 1997 among men but not among women,2,10 and the National Health and Nutrition Examination Survey round 1 (NHANES I) follow-up study covering trends during 1971 to 1992 in the United States showed a decreasing AMI recurrence in all sex and race groups, except for white women.11 A decreasing trend was also described in the Northern Sweden MONICA area 1985 to 1998 for patients surviving the initial 28-day period.12

In Sweden there is a unique possibility of evaluating the hazard function and secular trends in recurrence rate over time, owing to the availability of a reliable large-scale AMI register with national coverage. The aim of this study was to analyze the hazard function in relation to age, sex, AMI number, and calendar year (not shown previously) and, based
Of these, 214 events occurring in 204 subjects below 20 years of age were identified. The problem of identifying the index event is normally confined to the initial period after a register is established. The first observation for an individual during the initial period might not be an index event if the true index event occurred before the register was established. The probability that an observation is a true first AMI thus depends on the length of the preceding incidence-free period. There are 2 possible solutions to the problem: ignoring it, which means that true first recurrent AMIs are contami-
inated with second or later ones, or (standard procedure) to left truncate data from the initial period, i.e., eliminating early observations with uncertain true first AMI status. A sensitivity analysis showed that the effect of truncation would be small to moderate, the hazard function for a first recurrent AMI was as expected somewhat lower (0.25 to 1.5% units) with than with no truncation. Of the 2 solutions, truncation (time window) was chosen, because the bias caused by misclassification of recurrent AMI probably is larger than that caused by a moderate data loss.

A 36-month time window was therefore used, starting when the regions were fully included in the register. All individuals with an event in the time window and all later events for these individuals were therefore excluded. 127,399 events in 88,933 subjects. After this procedure the majority of first observations were true first AMIs with high probability, and the final study population consisted of 775,901 events in 589,341 subjects, generating 2,059,726 person years of observation, 656,316 among women and 1,403,410 among men. More than 95% of the study population was of white race.

As in many other similar registers, a 28-day rule was applied by the register holder, which had the effect that events occurring within 28 days after a previous event were counted as part of the previous event, and were excluded in the analyses. In 32% of those who died, an autopsy was performed, approximately the same proportion in men and women. The autopsy proportion decreased by age, AMI number, and calendar year, and ranged from 45% to 50% in 1972 to 1986% to 25% during the last years of the study period.

To calculate the average 1-year risk of first-ever AMI by age and sex across the study period (shown in Figure 2), information on number of first-ever AMIs by sex and 1-year age groups in the age range 60 to 82 was obtained from the AMI register (nominator). As denominator information on the annual age and sex distribution in the age range 60 to 82 years of the underlying general population of each participating region was used, downloaded from the official Swedish population database by sex and 1-year age groups each year the regions were included in the national AMI register. The Regional Research Ethics Board, Uppsala, approved the project. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

The computerized version of the Cause of Death Register covers all fatalities in Sweden since 1952, and the Hospital Discharge Register all hospital admissions. Sweden is divided into 20 health care regions. The various regions were successively included in the Hospital Discharge Register, the first region being fully included in 1969 and the last in 1987. Diagnoses in the Hospital Discharge Register and the Cause of Death Register were coded according to the International Classification of Diseases (ICD). ICD codes used for myocardial infarction were ICD-8 codes 410.00 to 410.99 (until 1986), ICD-9 code 410 (1987 to 1996), and ICD-10 code I21-I22 (from 1997 on).

The myocardial infarction register contains information on all incidents, which means that patients may have more than one entry depending on the number of incidents experienced. Register variables used in this report were PIN, incident number, incident date, date of admission to and discharge from hospital if applicable, date of death if applicable, sex, and age at incident.

At the time of the study the register contained 1,163,930 event records in 890,791 subjects, first-ever or recurrent AMIs (Figure 1). Of these, 214 events occurring in 204 subjects below 20 years of age and 154,561 events in 132,868 subjects aged 85 or more were excluded, in the youngest subjects because their AMIs may have had other etiologies than usually found, such as congenital heart disease, and in the oldest subjects because of decreasing diagnosis validity in old age. Moreover, all events before a region was fully included in the register were excluded: 105,855 events in 81,455 subjects.

To study recurrent AMIs, the first AMI on an individual basis (index event) should be identified. The problem of identifying the index event is normally confined to the initial period after a register is established. The first observation for an individual during the initial period might not be an index event if the true index event occurred before the register was established. The probability that an observation is a true first AMI thus depends on the length of the preceding incidence-free period. There are 2 possible solutions to the problem: ignoring it, which means that true first recurrent AMIs are contaminated with second or later ones, or (standard procedure) to left truncate data from the initial period, i.e., eliminating early observations with uncertain true first AMI status. A sensitivity analysis showed that the effect of truncation would be small to moderate, the hazard function for a first recurrent AMI was as expected somewhat lower (0.25 to 1.5% units) with than with no truncation. Of the 2 solutions, truncation (time window) was chosen, because the bias caused by misclassification of recurrent AMI probably is larger than that caused by a moderate data loss.

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Statistical Considerations

Data were analyzed with the SAS program package, version 9.1. Summary statistics, such as means, medians, and measures of dispersion were computed with standard parametric methods. Simple differences between groups in continuous variables were computed with Student t-test and differences in proportions with the χ² test.

Hazard function was computed with 2 methods. First a preliminary analysis was performed with the SAS "lifetest" procedure, yielding the main outline of the hazard function but not permitting adjustment for hazard-affecting variables other than time. In the final hazard function analysis a Poisson model was used in a SAS compatible program developed for the database. The logarithm of the hazard rate was modeled as a continuous function of the time-dependent variables by connected linear and quadratic pieces in specified follow-up time intervals. The time-dependent variables (updated once a year) used as covariates were current age, calendar time 1972 to 2001, and time from the previous AMI. Separate
analyses were performed for sex and AMI number. A number of potential interaction terms were tested but none was significant.

In these analyses the relation between the hazard function of the various age, sex, and AMI number groups was found to be approximately proportional. Estimates of change of 1-year hazard rate over calendar time was therefore computed with the Cox proportional hazards regression, modeled by connected linear, quadratic, and cubic pieces in specified calendar year intervals. The model fit, assessed by comparison of crude risk analyzed separately by calendar year, and annual risk across the total follow-up period according to the model, was excellent. In the figure no confidence interval were indicated because they were so small (fractions of a per cent).

Censoring events were death from other causes than AMI during follow-up or no new event by the end of follow-up. The outcome variable was recurrent AMI (first, second, third, fourth, or more as indicated). Individual follow-up time was right truncated at the end of the 22nd year because of small numbers. The average age specific risk of first-ever AMI in men and women during the study period was obtained by dividing the total number of subjects aged 60, 61, 62 years, et cetera, with an index event across the total follow-up period with the number of persons in the corresponding age–sex segment of the general population.

To test for homogeneity of included regional registers, these were divided into 3 groups, those being fully included early, those being included late, and a middle group. The annual risk levels for a first recurrent AMI was computed separately for each group for the years all groups were in the register. There were no detectable differences in risk level, indicating that there was no observable selection bias. Moreover, to be on the safe side all analyses were adjusted for calendar year.

The effects of potential confounders and other effect modifiers on recurrent AMI rate in the Cox analyzes were adjusted for by stratification (sex) or by inclusion as covariates in the model (eg, age at incident, recurrent AMI number, and calendar year of incident as a proxy for changes over time in other outcome affecting variables, such as case fatality rate, AMI treatment given, potential bias caused by differences in regional introduction in the AMI register). Only 2-tailed tests were used. Probability values less than 5% were regarded as statistically significant.

**Results**

**Characteristics of the Study Population**

During the 30-year study period 210 437 women and 378 904 men had an index event, generating 559 665 and 1 232 145 person-years of observation, respectively (Table). Of these, approximately 20% died out of hospital, 78% to 79% were admitted alive to hospital, and 1% occurred while in hospital. Mean age at the first incident was 72.8 years among women (median, 75; interquartile range, 68 to 80) and 68.1 years for men (median, 70; interquartile range, 61 to 76). The median number of days in hospital for patients with AMI occurring out of hospital and surviving until discharge was 9 days among women (mean, 14.3; range, 30.7 days in 1972 to 8.9 days in 2001) and 8 days among men (median, 70; interquartile range, 61 to 76). The median number of days in hospital for patients with AMI occurring out of hospital and surviving until discharge was 9 days among women (mean, 14.3; range, 30.7 days in 1972 to 8.9 days in 2001) and 8 days among men (mean, 70; interquartile range, 61 to 76). The case fatality rate was 24% for women (range, 33.4% in 1972 to 13.8% in 2001) and 19% for men (range, 32.7% in 1972 to 11.3% in 2001).
A total of 61,927 recurrent AMIs occurred among women and 124,633 among men, generating 90,690 and 246,277 person-years of observation, respectively. The mean number of recurrent AMIs per subject was 1.48 among women and 1.42 among men (median 1, interquartile range 1 to 2 in both sexes). Among women 44,499 subjects had a first recurrent AMI, 19,407 had a second, 39,797 had a third, and 25,591 had a fourth or more recurrent AMIs. The corresponding numbers among men were 84,070, 22,922, 72,089, and 37,349. The proportions of patients dead out of hospital, admitted alive to hospital, and AMIs occurring while in hospital were approximately the same as for index events. Mean time interval to a new AMI event was 30.3 months for women (median, 13.7; interquartile range, 4.8 to 57.9) and 39.5 months for men (median, 18.9; interquartile range, 5 to 12). The case fatality rate was approximately the same as for the first event.

### Hazard Function for Recurrent Event

In Figure 2 the risk, or hazard function, for a first recurrent AMI among men and women of various age groups at the index event is shown. The risk, expressed as proportion (%) of patients with an index event experiencing a first recurrent AMI, fell sharply during the first 2 years after the index event, reached a minimum after ≈5 years as assessed from the Poisson analysis output, and then increased slowly over the remaining years of follow-up. The curve shape was fairly similar in both sexes and all age groups, but the general level differed. The risk increased on average by 3.8% (95% CI, 3.7% to 3.9%) per year of age for women and by 3.6% (95% CI, 3.5% to 3.7%) for men. The risk increase was slightly accelerating by age for both men and women (data not shown). Figure 3 shows the hazard function during 1972 to 1979, 1980 to 1989, and 1990 to 1999. The shape of the hazard function was similar in all 3 periods, but the general level decreased over time.

As a contrast to the recurrent AMI risk for those aged 60 years, Figure 2 also shows the risk for an index AMI in men and women aged 60 years. For both risk functions, age 60 corresponds to follow-up year 0, age 61 to year 1, etc. The index AMI risk function ranged from 0.7% and 0.2% for men and women, respectively, at age 60 to 2.7% and 1.8% at age 82. At the point where the recurrent AMI risk curve had its minimum, the risk ratio for a second compared to an index event was 5.5 among men and 10.7 for women. From then on the index and recurrent AMI curves were approximately proportional.

### Table. Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>First AMI</strong> (index event)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total No. of events</td>
<td>210,437</td>
<td></td>
<td>378,904</td>
<td></td>
<td>. . .</td>
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<td>Person years of observation</td>
<td>559,665</td>
<td></td>
<td>1,232,145</td>
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<td>AMI occurrence</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI out of hospital, died before admission</td>
<td>41,499</td>
<td>19.7</td>
<td>82,242</td>
<td>21.7</td>
<td>.001</td>
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<tr>
<td>AMI out of hospital, survived until admission</td>
<td>166,334</td>
<td>79.1</td>
<td>294,089</td>
<td>77.6</td>
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<td>AMI occurred in hospital</td>
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<td>1.2</td>
<td>2,573</td>
<td>0.7</td>
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<tr>
<td>Age at first AMI, y</td>
<td>72.8±9.1</td>
<td>68.1±10.6</td>
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<tr>
<td>No. of hospital days for AMIs occurring out of hospital, surviving</td>
<td>14.3±32.9</td>
<td>11.4±23.7</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case fatality rate within 28 days</td>
<td>23.8</td>
<td></td>
<td>19.3</td>
<td></td>
<td>.001</td>
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<tr>
<td><strong>Recurrent AMI</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Total No. of events</td>
<td>61,927</td>
<td></td>
<td>124,633</td>
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</tr>
<tr>
<td>Person years of observation</td>
<td>93,069</td>
<td></td>
<td>246,277</td>
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<tr>
<td>Mean No. per subject</td>
<td>1.48±0.95</td>
<td></td>
<td>1.42±0.84</td>
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<td>.001</td>
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<tr>
<td>AMI occurrence</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AMI out of hospital, died before admission</td>
<td>13,370</td>
<td>21.6</td>
<td>29,708</td>
<td>23.8</td>
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<tr>
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<td>48,189</td>
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<td>94,384</td>
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<td>AMI occurred in hospital</td>
<td>368</td>
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<td>541</td>
<td>0.4</td>
<td>.001</td>
</tr>
<tr>
<td>Mean time to recurrent AMI, months</td>
<td>30.3±40.1</td>
<td></td>
<td>39.5±47.5</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>No. of hospital days for AMIs occurring out of hospital, surviving</td>
<td>13.9±30.5</td>
<td>11.3±18.9</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case fatality rate within 28 days</td>
<td>23.2</td>
<td></td>
<td>21.3</td>
<td></td>
<td>.001</td>
</tr>
</tbody>
</table>

*Acute myocardial infarction.*
Secular Effects on the Risk of Recurrent Events

In Figure 5 the average risk of a first recurrent AMI during the first year after a previous event is shown for women and men, 70 years of age, over the study period. During the period 1972 to 1979 there was a nonsignificant tendency toward a risk increase. The risk then leveled off and fell by approximately 40% in men and 36% in women, a highly significant decline ($P<0.0001$). The functional form of the risk change was similar in both sexes. The average risk decrease was 2.5% (95% CI, 2.5% to 2.7%) per calendar year for women and 3.1% (95% CI, 3.0% to 3.2%) for men. Supplemental Figure 1 and supplemental Table I show corresponding data for various age groups. The functional form was the same for all age groups but the switch from slowly increasing to decreasing slope tended to come somewhat later by age and the general risk level increased. As shown in Supplemental Figure 3.

Figure 3. Risk (%) of a first recurrent AMI in groups according to time of first AMI (1972 to 1979, 1980 to 1989, and 1990 to 1999).

Figure 4. Risk (%) of a first, second, third, and fourth or more recurrent AMI among men and women 70 years old at the previous event. Female patients at risk: first reinfarction, $n=210\,437$; second, $n=43\,449$; third, $n=11\,940$; fourth or more, $n=6538$. Male patients at risk: first reinfarction, $n=378\,904$; second, $n=89\,407$; third, $n=24\,292$; fourth or more, $n=10\,934$. The rank order of the curves is the same as the rank order of the key to the symbols.
Figure 2 and supplemental Table II the functional form of the change over calendar years was the same irrespective of recurrent AMI number but the general risk level increased with AMI number.

Discussion

The risk for a recurrent AMI thus fell sharply during the first 2 years, then leveled off, reached a minimum after 5 years, and then increased slowly again. This is a novel finding not reported in previous studies. There was no evidence that the shape of the hazard function changed over the time period covered by the study, but the general level of the function became lower beginning in the early 1980s. This is illustrated by the risk of a new event during the first year after a previous event, which was fairly stable until the late 1970s but decreased considerably from then on.

This study was based on data from the Swedish Acute Myocardial Infarction Statistics covering 775,901 events of fatal and nonfatal first and recurrent AMIs between 1972 and 2001 in Swedish men and women aged 20 to 84. The register permits the possibility of studying incidence of recurrent AMI, mortality and case fatality rates, and, because of the possible linkage to the National Population Database, also incidence of first AMI. The register has been shown to be valid and reliable, and the coverage is almost 100%.

The strength of this study is the very large database on AMI, covering events over a long period of time. To the best of our knowledge it is the largest and most long-term register in the world. One limitation of the study is the relatively few pieces of information on individual background variables, such as direct measures of infarction severity, medical treatment, and risk factor profile.

The 28-day rule may have affected the estimation of the risk for a recurrent event. Because recurrent AMIs occurring within 28 days after the previous event were included in the latter and were not included as exposure time in the analyses, the risk decrease for a recurrent AMI is probably underestimated. This means that the initial slope in Figure 2 may be underestimated, making the risk decrease even larger than shown.

Other possible outcome affecting conditions may be variability of coronary care quality, changes in diagnostic AMI criteria, and change of case fatality rate during the study period. However, in Sweden, almost all AMI patients during the study period were admitted to government-run regional hospitals (there are less than 10 private hospitals in the country, and none of these treat AMI patients), each with a catchment-area population of ≈250,000 residents, and provided with a coronary care unit. All hospital admissions are free of charge. The hospitals are supervised by the National Board of Health and Welfare, which regularly collects and publishes data on hospital care outcome for all these hospitals, promoting the adoption of new techniques by the hospitals. This means that the majority of the patients received the state-of-the-art treatment available at the time. Moreover, calendar time was used as a proxy for such changes in the analyses.

The main diagnostic criteria change (inclusion of unstable angina) occurred in 2001, ie, in the last study year. The effect appears to be small. Moreover, there is evidence that AMI damage volume size has decreased during the study period, which may have contributed to the decreasing case fatality rate and AMI recurrence rate. The potential effect of changing case fatality rate was at least partially taken into account in the analyses by calendar time.

The shape of the risk curve during follow-up (hazard function) may have several determinants. The high initial risk may represent the underlying pathophysiological process with a still-unfinished but slowly regressing plaque or embolus production, or other trigger mechanisms. At any rate, the predisposing factors behind the infarction appear to become less active over the first few years. Because the hazard function after the fifth year, with a slow risk increase, is largely proportional to the hazard function for a first-ever event, the risk increase from this time on is probably attributable to the ageing process. Because the shape of the hazard function appeared to be stable across the study period it most certainly represents the natural history of the risk of a recurrent AMI. The highly variable recurrence risk during the first few years after a previous event should be taken into account when discussing recurrence risk with patients.
The change of risk over calendar years is a secular effect. This means, for instance, that 60-year-old people in the 1990s had a lower risk of recurrent AMI than 60-year-old people in the 1980s. In this study we estimated the secular effect by using the average risk during the first year in the hazard function for events during specific years. It is well known that the risk factor panorama affecting the risk of a recurrent AMI is the same as that for a first AMI, as reviewed in the European and US guidelines on cardiovascular disease prevention in clinical practice, the only difference being the larger urge for action in secondary prevention.18,19 It has also been shown that a risk factor change is followed by a change in incidence.3,5,20 In this study the secular effects were parallel and appeared at about the same time for a first AMI and for recurrent AMI. This is an indication that the risk factor change in the population has affected both types of incidents in the same way.

Primary and secondary prevention of coronary heart disease was initiated in the 1960s, a few years after the initiation of the first population-based studies. The effects of such prevention in Sweden became evident in the early 1980s, i.e., later than in Finland and the United States.8–11,17 The risk factor pattern in the general Swedish population has changed dramatically during the past 35 years, with a drop in tobacco smoking among men from 55% and among women from more than 30% to less than 20% in both sexes,20 a considerable drop in blood pressure not only among treated but also in the nontreated segments of the population,21 and a drop in total cholesterol by 1 mmol/L in the middle-aged general population to 5.5 mmol/L.20 Moreover, more than 60% of patients on lipid-lowering treatment reach the treatment goal for cholesterol levels less than 5 mmol/L.22

Few studies have analyzed time trends in recurrent AMI events, and studies that did so were small and covered quite a rather short period of time. The FINMONICA MI Register Study reported a decline in recurrent coronary events in Finland during 1983 to 19978,9 and presented a curvilinear accelerating shape of the decline. This is in accordance with findings in The Minnesota Heart Survey, which presented a falling recurrence rate of 20% to 30% during 1985 to 1997.10 In another US-based study, covering 1987 to 1994, a significant decline of 2.6% per year was seen for recurrent AMI among men but not for women,2 and in the NHANES I follow-up, covering the US population in 1971 to 1992, a decreasing AMI recurrence in all sex and race groups was found, except for white women, among whom the recurrence rate increased.11 A decreasing trend was also described in The Northern Sweden MONICA area in 1985 to 1998 for patients surviving the initial 28-day period.12 We found a considerable decrease of recurrent AMI among both men and women, beginning in the early 1980s. The large dataset permitted the extraction of detailed novel information on secular trends. There is no doubt that secondary prevention efforts since the late 1970s have been effective enough to break the increasing recurrent AMI incidence rate trend and turn it into a decrease. However, more remains to be done.

In conclusion, the risk of a recurrent AMI event was highly dependent on time from the previous event, a novel finding which may affect risk scoring. In addition, sex, age, and AMI number influenced the general risk level. There were strong secular trends in age-sex-AMI-number–specific risk of a recurrent AMI toward diminishing risk in recent years.

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Disclosures
None.

References
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