BMJ Open

Sex-specific trends in survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. Prospective cohort study.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004598
Article Type:	Research
Date Submitted by the Author:	02-Dec-2013
Complete List of Authors:	Nielsen, Susanne; Institute of medicin, Department of Molecular and Clinical Medicin Björck, Lena; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Berg, Johanna; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Giang, Kok Wai; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Zverkova-Sandström, Tatiana; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Falk, Kristin; Institute of Health and Care Siences, Sahlgrenska Academy, Määttä, Sylvia; Institute of Health and Care Siences, Sahlgrenska Academy, Rosengren, Annika; Department of Molecular and Clinical Medicine, Sahlgrenska Academy
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Epidemiology < TROPICAL MEDICINE, Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

Sex-specific trends in survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. Prospective cohort study.

Nielsen S, MSc[1], Björck L, PhD[1,2], Berg J, MD[1], Giang KW, MSc[1], Zverkova Sandström T, BSc[1], Falk K, PhD[2], Määttä S, PhD[2], Rosengren A, MD, PhD[1]*

[1]Department of Molecular and Clinical Medicine and [2]Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

*Corresponding author: Annika Rosengren, Department of Molecular and Clinical Medicine, Sahlgrenska University, Hospital/Östra sjukhuset, SE-41685, Gothenburg, Sweden. E-mail: annika.rosengren@gu.se; Tel: +46 31343 4086; Fax: +46 31258933

Keywords Myocardial Infarction • Mortality • Survival • Trends • Epidemiology

Word count: Abstract: 265

Manuscript: 2972

ABSTRACT

Objective To examine sex-specific trends in 4-year mortality among young patients with a first acute myocardial infarction (AMI), 1987–2006.

Design: Prospective cohort study

Setting: Sweden.

Participants: We identified 37,276 patients (19.4% women; age, 25–54 years) from the Swedish Inpatient Register, 1987–2006, who had survived 28 days after an AMI.

Outcome measures: Four-year mortality from all causes, and Standard Mortality Ratio (SMR)

Results From the first to last 5-year period, the absolute excess risk decreased from 1.38 to 0.50 and 1.53 to 0.59 per 100 person-years among men aged 25–44 and 45–54 years, respectively. Corresponding figures for women were a decrease from 2.26 to 1.17 and from 1.93 to 1.45 per 100 person-years, respectively. Trends for women were non-linear, decreasing to the same extent as those for men until the third period, then increasing. For the last 5-year period, the standardized mortality ratio for young survivors of AMI compared with the general population was 4.34 (95% confidence interval [CI]: 3.04–5.87) and 2.43 (95% CI: 2.12–2.76) for men aged 25–44 and 45–54 years, respectively, and 13.53 (95% CI: 8.36–19.93) and 6.42 (95% CI: 5.24–7.73) for women. Deaths not associated with cardiovascular causes increased from 21.5% to 44.6% in men and 41.5% to 65.9% in women, respectively.

Conclusion Young male survivors of AMI have low absolute long-term mortality rates, but these rates remain 2- to 4-fold that of the general population. After favourable development until 2001, women now have higher absolute mortality than men and a 6- to 14-fold risk of death compared with healthy women.

Strengths and limitations of this study

- Population-based study, that includes all patients with a first AMI, aged 25-55 years, in Sweden during a period of twenty years.
- Strengths include nationwide coverage, and near-complete follow-up.
- The main limitation is that the used register does not provide data covering clinical characteristics or treatment which could have been valuable to estimate their impact on mortality.

INTRODUCTION

Survival after acute myocardial infarction (AMI) has improved during the last several decades in Sweden and elsewhere.[1-3] Nonetheless, coronary heart disease (CHD) remains a major contributor to morbidity and mortality with more than one in five men and women currently dying from CHD in Europe.[4,5] Survivors of AMI are known to have an impaired prognosis compared with the general population.[6] In a recent UK study, the risk of death of any cause among survivors of a first AMI was twice that of the general English population of equivalent age.[7]

Most patients with AMI are elderly; accordingly, most information on long-term survival is based on patients older than 55 years. However, about one in six AMI survivors is younger than 55 years.[8] Knowledge of the prognosis among young patients with AMI is essential because younger patients stand to lose more of their remaining life years compared with older patients. This applies particularly to women because women have a longer life expectancy.

Further, younger, but not older, women hospitalized with AMI have a worse long-term prognosis than men.[9,10] However, there have since been marked changes in treatment, diagnostic criteria, and post-AMI prognosis. A recent study found that reductions in long-term mortality after 1985 were at least as high for women as for men with AMI,[11] but the study did not specifically report findings for young patients. An additional study, found that reductions in mortality were similar regardless of age but that younger patients are more likely to receive evidence based care.[12]

Few data sets contain a sufficient number of young patients to reliably estimate risk of death compared with the general population. In addition, more information is needed about cause-specific mortality, because an unknown proportion of deaths may not be due to cardiovascular causes, and will thus be less amenable to coronary preventive measures. In the present study, we examined sex-specific trends in long-term survival in a register-based cohort of patients aged 24–54 years hospitalized with a first AMI during 1987–2006, and compared death rates for men and women separately with those of the general population.

METHODS

Registers and study population

Sweden has a publicly financed health care system, with some health care facilities privately run but still fully integrated into the health care system. The Swedish National Inpatient Register (IPR), has established complete national coverage since 1987. Positive predictive values differ among diagnoses in the IPR, but is generally 85–95%;.[13] Diagnoses in the IPR are coded according to the Swedish *International Classification of Diseases* (ICD) system (ICD 8th revision until 1986, 9th revision until 1996, and 10th revision thereafter). In the present study, data from the IPR and the Swedish Cause of Death Registries were linked through personal identity numbers unique to each Swedish citizen. The Swedish Cause of Deaths Registries is based on diagnoses from deaths certificates and captures 99,2% of all deaths.[14]

The present study included all 38,813 patients in Sweden aged 25–54 years and hospitalized with a first AMI in 1987–2006; AMI was defined as a principal discharge code according to the ICD-9: 410 (until 1996) and ICD-10: I21 (from 1997 onward). After excluding 1,537 patients who died during the first 28 days, 37,276 patients (7,229 women and 30,047 men)

with a first AMI remained for analysis. Data from 1980 onward were used to identify first AMIs only, with a time frame of 7 years throughout, to ensure that AMIs registered each year had the same chance of being identified as a first AMI. Criteria for a diagnosis of AMI in Sweden have followed established guidelines, changing after the adoption of new AMI criteria in the year 2000.[15,16] Thus, the characteristics of the AMIs in our analysis changed during the study period. Use of troponins became standard after the year 2000.

Comorbidities were defined by the following main or contributory discharge codes during the preceding 7 years, including the index hospitalization: diabetes (ICD-9 250; ICD-10 E10–E14), hypertension (ICD-9 401–405; ICD-10: I10–I15), valvular disease (ICD-9 394–397, 424; ICD-10 I05–I09, I34–I35), congenital heart disease (ICD-9 745–747; ICD-10 Q20–Q26), stroke (ICD-9 431–434, 436; ICD-10 I61–I64), chronic respiratory disease (ICD-9 490–496; ICD-10 J40–J47), malignancy (ICD-9 140–208; ICD-10 C00–C97), renal failure (ICD-9 584–586; ICD-10 N17–N19), coronary artery bypass grafting (3067, 3066, 3105, 3127, FNA, FNB, FNE, FNC), and percutaneous coronary intervention (3080, FNG 00, FNG 02, FNG 05).

Follow-up

We analysed 4-year all-cause mortality for four 5-year periods (1987–1991, 1992–1996, 1997–2001, and 2002–2006) through the Swedish Cause of Death Registries. The following codes were used for assignment of causes of death among fatal cases: CVD, (390–459, I00–I99), ischaemic heart disease (IHD) (410–414, I20–I25, stroke (430–438, I60–I68), and all other causes (including malignancies; 140-208, C00-C97).

Statistical analysis

Statistical analyses were performed with SAS 9.3, (R version 2.15.1 to obtain the graphs). For comorbidities, $\chi 2$ tests were used to evaluate differences between men and women and for trends; a P-value of ≤ 0.05 was considered significant. To compare mean age within the respective age groups, t-tests were performed.

Standardized mortality ratios (SMR) with 95% confidence intervals (CIs) were calculated as the ratio of the observed to expected number of deaths, estimated from rates in the general Swedish population, by age, gender, and calendar year, using life expectancy tables from Official Statistics of Sweden (SCB).

Absolute excess risk (AER) was estimated and defined as the absolute difference between observed and expected mortality among all patients. The difference between observed and expected deaths, divided by the number of person-years at risk and multiplied by 100, was calculated to derive the AER. The AER calculations add a useful measure of excess risk in absolute terms.

Cox proportional hazard regression, providing hazard ratios (HR) with 95% CIs, was used to estimate age, and gender-specific changes in all-cause mortality over time.[17] The first period (1987–1991) was used as reference; The multivariate models were adjusted for age, diabetes, hypertension, valvular and congenital heart disease, stroke, chronic respiratory disease, malignancy and renal failure. Furthermore, in the final model the periods were also tested for proportionality by interactions of age, time and with significant comorbidities only (men 45-54; malignancies, women, 45-54; chronic respiratory disease).

The Kaplan-Meier method was used to estimate the survival probability. The proportionality assumption of Cox regression was tested by including interactions between covariates (age, sex, and period) with time; neither interaction test was statistically significant.[18] A log-rank test was conducted to study changes in survival between the time periods.

RESULTS

Of the 37,276 patients in the study, 7,905 (21.2%) were aged 25–44 years (19.6% women) and 29,371 (78.8%) were aged 44–54 years (19.3% women). Other than diabetes and hypertension (11% for both), this population had few diagnosed comorbidities (Table 1). Women had more diabetes, hypertension, chronic lower respiratory disease and malignancies than did men ($P < 0.0001$).

Table 1. Baseline characteristics in 37,276 men and women aged <55 years with a first AMI, 1987–2006

	All	Men	Women	P-value
Number of patients	37 276	30 047	7 229	
Age 25-44, n (%)	7 905 (21.2)	6 357 (21.2)	1 548 (21.4)	
Mean age (SD)		40.21 (3.74)	39.84 (4.04)	0.055
Age 44-54, n (%)	29 371(78.8)	23 690 (78.8)	5 681 (78.6)	
Mean age (SD)		50.31 (2.75)	50.39 (2.76)	0.0549
Diabetes, n (%)	4 064 (10.9)	3 017 (10.0)	1 047 (14.5)	<0.0001
Hypertension, n (%)	4110 (11.0)	3141 (10.6)	969 (13.4)	<0.0001
Valvular disease, n (%)	287 (0.77)	211 (0.70)	76 (1.05)	0.0023

Congenital heart disease	36 (0.10)	23 (0.08)	13 (0.18)	0.0111
Stroke, n (%)	412 (1.11)	302 (1.01)	110 (1.52)	0.0002
Chronic lower respiratory disease, n (%)	557(1.49)	368 (1.22)	189 (2.61)	<0.0001
Malignancy, n (%)	354 (0.95)	255 (0.85)	99 (1.37)	<0.0001
Renal failure	230 (0.62)	164 (0.55)	66 (0.91)	0.0003
CABG*, n (%)	253 (0.68)	221 (0.74)	32 (0.44)	0.007
PCI*, n (%)	235 (0.63)	198 (0.66)	37 (0.51)	0.16

*Procedures dating at least 6 months prior to hospitalization for AMI.

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

Supplementary Table 1 shows the comorbidities for each 4-year period. All comorbidities except for congenital heart diseases increased significantly over time. Diabetes and hypertension were the most prevalent comorbidities in both men and women but the rates of other comorbidities remained low even in the last period (<4%).

Expressed as AER for death per 100 person-years over the entire period, the overall rate was 1.18, slightly higher for women (1.32) than for men (0.99) (Table 2). Women aged 25–44 years had a nearly 14-fold higher risk (SMR: 13.9, 95% CI: 11.21–16.86) for death compared with the general population, while men of similar age had an approximately 6-fold increased risk (SMR: 5.99, 95% CI: 5.32–6.70). SMRs in patients aged 45–54 years were lower, namely 3.07 (95% CI: 2.91–3.23) and 5.26 (95% CI: 4.72–5.83) in men and women, respectively.

Table 2. Standardized 4-year mortality ratio by age among 37,276 men and women aged <55 years with a first AMI, 1987–2006

	Age	Observed[a]	Expected[b]	SMR (95% CI)	AR[c]	AER[d]
Men	25-44	288	48	5.99 (5.32-6.70)	1.11	0.97
	45-54	1348	440	3.07 (2.91-3.23)	1.42	0.99
Women	25-44	93	7	13.9 (11.21-16.86)	1.54	1.45
	45-54	347	66	5.26 (4.72-5.83)	1.55	1.28
Men	25-54	1636	488	3.36 (3.19-3.52)	1.35	0.99
Women	25-54	440	73	6.06 (5.51-6.64)	1.55	1.32
All	25-54	2076	378	5.49 (5.25-5.73)	1.39	1.18

[a]Observed number of deaths in the study population, [b]Expected number of deaths in the general population, [c]Absolute risk after 4-year death per 100 person-years, [d]Absolute excess risk after 4-year death per 100 person-years

AMI, acute myocardial infarction; SMR, standardized 4-year mortality ratio; AR, absolute risk; AER, absolute excess risk

Survival in men improved continuously over the four 5-year periods (Figure 1), while the prognosis in women improved until the third period, then reverted to a rate nearly identical to that in the second period (Figure 2).

Table 3 shows mortality by sex, age group, and period. For men aged 25–44 years, the annual excess risk of dying decreased continuously from 1.38 to 0.50 deaths per 100 person-years from the first to last period, with an SMR of 4.34 (95% CI: 3.04–5.87) during the last 5-year period. Corresponding figures for men aged 45–54 were a decrease from 1.53 to 0.59 with an SMR of 2.43 (95% CI: 2.12–2.76) in the last period (2002–2006). Women displayed more

complicated trends, starting from higher absolute risks of dying compared with men, decreasing sharply until a nadir in 1997–2001, and then increasing to 1.17 and 1.45 deaths per 100 person-years in women aged 25–44 and 45–54, respectively, in the last period. This was more than twice the risk in men of the corresponding age groups. Very high SMRs were noted, particularly for the youngest women, at 13.53 (95% CI: 8.36–19.93) in the last period and 6.42 (5.24–7.73) in women aged 45–54 years.

In men aged 25–44 years, the mortality risk decreased by 70% during the study period (multivariable adjusted HR: 0.30, 95% CI: 0.20–0.44). A similar decrease was seen in men aged 45–54 years (multivariable adjusted HR: 0.32, 95% CI: 0.27–0.38). Women aged 25–44 years had an overall decline in mortality risk of approximately 50% (multivariable adjusted HR: 0.47, 95% CI: 0.27–0.83). No significant decrease in mortality risk in the last, compared with the first period was observed in women aged 45–54 years (age-adjusted HR: 0.77, 95% CI: 0.59–1.02), but after adjustment for comorbidities there was a significant decrease in risk (HR: 0.53, 95% CI: 0.39–0.71).

Table 3. Observed versus expected mortality ratio, estimated over 4 years, standardized mortality ratio, absolute risk, absolute excess risk, and hazard ratio for mortality by age group and period among 37,276 men and women aged <55 years with a first AMI

Age, Period	Observed[a]	Expected[b]	SMR (95% CI)	AR[c]	AER[d]	HR (95% CI)[e]	HR (95% CI)[f]
Men 25-44							
1987-1991	113	16	6.88 (5.67–8.20)	1.61	1.38	1.0 (ref)	1.0 (ref)
1992-1996	81	13	6.16 (4.89–7.57)	1.25	1.05	0.76 (0.57–1.01)	0.73 (0.55–0.98)
1997-2001	58	10	5.70 (4.33–7.27)	1.00	0.83	0.60 (0.43–0.82)	0.53 (0.38–0.73)
2002-2006	36	8	4.34 (3.04–5.87)	0.65	0.50	0.41(0.28–0.60)	0.30 (0.20–0.44)
Men 45-54							
1987-1991	465	125	3.72 (3.39–4.07)	2.10	1.53	1.0 (ref)	1.0 (ref)[g]
1992-1996	379	119	3.20 (2.88–3.53)	1.56	1.07	0.74 (0.65–0.85)	0.70 (0.61–0.81)

1997-2001	289	108	2.69 (2.39–3.00)	1.22	0.77	0.57 (0.49–0.66)	0.50 (0.43–0.58)
2002-2006	215	89	2.43 (2.12–2.76)	0.99	0.59	0.47 (0.40–0.56)	0.32 (0.27–0.39)
Women 25-44							
1987-1991	34	2	17.55 (12.15–23.94)	2.39	2.26	1.0 (ref)	1.0 (ref)
1992-1996	28	2	17.99 (11.95–25.27)	2.17	2.05	0.93 (0.56–1.55)	0.85 (0.51–1.42)
1997-2001	10	2	6.07 (2.89–10.42)	0.63	0.52	0.27 (0.13–0.55)	0.28 (0.14–0.56)
2002-2006	21	2	13.53 (8.36–19.93)	1.26	1.17	0.55 (0.32–0.94)	0.47(0.27–0.83)
Women 45-54							
1987-1991	101	15	6.90 (5.62–8.31)	2.25	1.93	1.0 (ref)	1.0 (ref) [h]
1992-1996	76	16	4.63 (3.65–5.73)	1.45	1.14	0.64 (0.48–0.87)	0.56 (0.42–0.76)
1997-2001	68	19	3.58 (2.78–4.48)	1.08	0.78	0.49 (0.36–0.66)	0.44 (0.32–0.60)
2002-2006	102	16	6.42 (5.24–7.73)	1.72	1.45	0.77 (0.59–1.02)	0.53 (0.39–0.71)

[a]Observed number of deaths in the study population, [b]Expected number of deaths in the general population, [c]Absolute risk after 4-year death per 100 person-years, [d]Absolute excess risk after 4-year death per 100 person-years, [e] Age adjusted, [f] Multiadjusted for age, diabetes, hypertension, valvular, congenital heart disease, stroke, chronical respiratory disease, malignancy and renal failure. Adjusted for changes and interaction over time, malignancy ([g]), chronic respiratory disease ([h]).

AMI, acute myocardial infarction; SMR, standardized mortality ratio; AR, absolute risk; AER, absolute excess risk; HR, hazard ratio; CI, confidence interval

Table 4 shows causes of death for the 2,076 deaths that occurred within 4 years in this cohort. Overall, three of four deaths in men were due to CVD (68.2%) with the majority (61.0%) due to IHD, leaving 31.8 % due to other causes, including 10.8% due to malignancies. Women displayed a different pattern, with 47.5% due to CVD (41.1% due to IHD), and 52.5% due to other causes (18.4% due to malignancies).

Table 4. Causes of 2,076 deaths within 4 years among patients aged <55 years with a first AMI[a] during 1987–2006

Cause of death	Total n (%)	Men n (%)	Women n (%)	P-value
	2076	1636	440	
CVD[b]	1325 (63.8)	1116 (68.2)	209 (47.5)	<0.0001
IHD[c]	1179 (56.8)	998 (61.0)	181 (41.1)	<0.0001
Stroke	41 (1.97)	31 (1.89)	10 (2.27)	0.6131
All other causes	751 (36.2)	520 (31.8)	231 (52.5)	<0.0001
Malignancies	257 (12.4)	176 (10.8)	81 (18.4)	<0.0001

[a]AMI, acute myocardial infarction; [b]CVD, cardiovascular disease; [c]IHD, ischaemic heart disease;

In 1987–1991, 74,8% of all deaths within 4 years were due to CVD (78.6% for men and 58.5% for women). However, during the last period, only 48.4% of all deaths were due to CVD (55.4% for men and, notably, only 34.1% for women) (Supplementary Table 2).

DISCUSSION

The present study showed that young male survivors of AMI have low absolute long-term mortality rates; however, these rates remain between 2- and 4-fold those of the general

population. After a favourable development in younger women until 2001, when new criteria for AMI were adopted and troponins became standard, women had higher absolute mortality than men in the last period and showed a dramatically higher risk of death than healthy women. However, fewer than half of all deaths in women were due to CVD in the last period.

Few studies have specifically investigated long-term outcomes in young patients with AMI. One Swedish study based on the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA)[19] investigated all consecutive patients younger than 46 years treated for ST-elevation myocardial infarction (STEMI) in Sweden, 1995–2006 (1,748 men, 384 women). Long-term annual mortality was around 1% with no difference between men and women, similar to our study. Accordingly, in absolute terms and consistent with prior publications from our group,[1] annual mortality rates in AMI survivors younger than 55 years are estimated at about 1%. This is in contrast to older patients in Sweden, among whom annual mortality rates are about 6% for those aged 65–74 years and more than 12% among patients aged 75–84 years).[1] The current low absolute mortality figures are a vast improvement on prior estimates. In a retrospective analysis of 23 published studies from the prethrombolytic era, the annual death rate after the first year in patients with a first AMI was 5% regardless of age or gender.[20] In the late 1980s, the annual mortality for patients younger than 55 years was about 2%.[1]

There are several reasons for the observed decrease in mortality in younger patients with AMI. First, several pharmacological and coronary interventions were developed and implemented during the study period. Nauta et al 2013 showed that patient <55 received evidence-based medical care and reperfusion to a greater extent than elderly patients.[12] Second, some of the decrease is likely due to changes in diagnostic criteria during the study

period, as well as more sensitive methods.[15,21] This may imply that less severe AMIs are detected, with improved survival, but less specificity, as evidenced by increased comorbidities over time and a higher proportion of non-CVD deaths in the last period. Third, there have been changes in clinical presentation, with less severe infarctions,[22,23] and fewer STEMIs.[24] Factors that affect the risk of developing STEMI rather than non-STEMI include smoking[24] and cardioprotective medications that lower the risk.[25] Declining smoking rates and more medications used in primary prevention could thus have contributed to milder infarctions and better survival. Comorbidities increased during the study period. However, this can probably be derived to improvements in clinical reporting. The striking increase in hypertension can also probably be attributed to changes in criteria and guidelines management by the WHO.[26]

There was a continuous decrease in case fatality among men; however, rates in women did not follow the same pattern as in men. Mortality in women decreased until the third period and then increased during the fourth period to the nearly the same level as in the second period. This may have been due to chance because the numbers were limited. However, it could also reflect differences in diagnostics. With increasing use of troponins, the rate of detection has increased, and this effect could be stronger for women than for men. In a study that simultaneously measured CK-MB and troponin,[27] a 64% and 95% increase in the AMI rate among men and women, respectively, was observed when using troponins. Accordingly, the increasing mortality among women hospitalized in 2002–2006 could be due to the capture of other and more complicated types of myocardial damage because an increase in troponin levels is also seen in other conditions.[28] Even so, comorbidities, although increasing over time, were still low in the most recent period.

Few studies have compared mortality rates in young patients with AMI with those in the general population. A record linkage of hospital and mortality data identified 387,452 individuals in England, hospitalized with a main diagnosis of AMI in 2004–2010 and who survived at least 30 days.[7] Long-term risk of death of any cause among survivors of a first AMI was twice that in the English general population of equivalent age, highest among younger patients aged 55–64 years (about 2- to 3-fold for men and women, respectively), and approached the mortality rate of the general population for those aged 85 years or more. Estimates for individuals younger than 55 years were not stated. For the period corresponding to that in the study by Smolina et al.[7] we found mortality ratios of 4.3 and 2.4 for men aged 25–44 and 45–54 years, respectively. For women aged 25–44 years, the estimated mortality ratio was 13.5, but this was based on very few cases (about four deaths per year). The estimate of 6.4 for women aged 45–54 years should be more reliable. It should be noted that women in the general population in this age range have very low mortality rates, which partially explains the high SMRs in women.

The main limitation in the present study is the reliance on administrative registers with no details of clinical characteristics, such as biomarkers, electrocardiographic findings, smoking, medication, hyperlipidemia or family history, and a lack of other clinical information, notably hospital treatment and clinical presentation. Also, we were unable to apply uniform criteria for diagnosis over time. However, the findings should be applicable to current patients with AMI in an industrialized modern country. The quality of the data is obviously of fundamental importance, but validation studies of the IPR indicate reasonable accuracy.[13,29] Incorrect death certificates could lead to uncertainty with respect to attributing cause of death[14], but IHD diagnoses has been estimated to be correct in 87% although the data from this study were collected two decades ago. [30]

The strengths of the study include nationwide coverage with virtually no loss to follow-up and the large sample size. Given the low mortality in absolute terms, larger populations are needed, particularly for women, because they constitute less than 20% of the AMI population younger than 55 years.

Conclusions

These data extend and update what is currently known about sex-specific absolute and relative survival in patients with AMI younger than 55 years, with a large population of more than 35,000 cases during a 20-year period. Among patients surviving for 28 days after AMI, the annual mortality rates are now comparatively low at approximately 1%. Given the much lower mortality in this age group in the general population, young survivors of AMI, particularly women, remain at a much higher risk of death, much of this, however, due to non-CVD causes. Accordingly, while mortality is low in absolute terms, younger women with AMI lose the survival advantage women normally have over men. Additional strategies to bring mortality closer to that which would be expected for this age group are needed, in particular for women.

Contributors

Study concept, design: SN, AR, LB, JB, KWG. Analysis and interpretation of data: SN, TZS, AR, LB, JB, KWG. Drafting and revised the manuscript: SN, LB, JB, KWG, TZS, KF, SM, AR. Critical revision of the final version of the manuscript: all authors. SN, LB, JB, KWG, TZS, KF, SM, AR. Guarantor: AR

Funding

This work was supported by the Swedish Research Council [grant number VR 521-2010-2984]; the Swedish Heart-Lung Foundation [grant number 2012-0325]; and the Swedish Council for Working Life and Social Research [grant number Epilife 2006-1506], the VGR region and the Swedish state under the ALF-LUA agreement.

Competing interests:

None declared.

Ethical approval

All personal identifiers were removed and replaced with a sequential number in the final data set. The protocol was approved by the regional Ethics Board of Gothenburg.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

REFERENCES

1. Dudas K, Lappas G, Rosengren A. Long-term prognosis after hospital admission for acute myocardial infarction from 1987 to 2006. *Int J Cardiol* 2012;**155**:400-405.
2. Langorgen J, Igland J, Vollset SE, *et al*. Short-term and long-term case fatality in 11 878 patients hospitalized with a first acute myocardial infarction, 1979-2001: the Western Norway cardiovascular registry. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:621-627.

3. Hardoon SL, Whincup PH, Petersen I, *et al*. Trends in longer-term survival following an acute myocardial infarction and prescribing of evidenced-based medications in primary care in the UK from 1991: a longitudinal population-based study. *J Epidemiol Community Health* 2011;**65**:770-774.

4. Rayner M, Allender S, Scarborough P. Cardiovascular disease in Europe. *Eur J Cardiovasc Prev Rehabil* 2009;**16 Suppl 2**:S43-S47.

5. Nichols MTN, Scarborough P, Luengo-Fernandez R, *et al*. *European Cardiovascular Disease Statistics 2012*. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis; 2012.

6. Fagring AJ, Lappas G, Kjellgren KI, *et.al.* Twenty-year trends in incidence and 1-year mortality in Swedish patients hospitalised with non-AMI chest pain. Data from 1987-2006 from the Swedish hospital and death registries. *Heart* 2010;**96**:1043-1049.

7. Smolina K, Wright FL, Rayner M, *et al*. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. *Circ Cardiovasc Qual Outcomes* 2012;**5**:532-540.

8. Gale CP, Cattle B, Woolston A,*et al*. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. *Eur Heart J* 2012;**33**:630-639.

9. Rosengren A, Spetz CL, Koster M, *et al*. Sex differences in survival after myocardial infarction in Sweden; data from the Swedish National Acute Myocardial Infarction Register. *Eur Heart J* 2001;**22**:314-322.

10. Vaccarino V, Krumholz HM, Yarzebski J, *et al*. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;**134**:173-181.

11. Nauta ST, Deckers JW, van Domburg RT,*et al*. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. *Circulation* 2012;**126**:2184-2189.

12 Nauta ST, Decker JW, Akkerhuis KM, *et al*. Age-dependent care and long-term (20 year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008. *Int. J Cardiol* 2013;**167**:693-697

13. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.

14 Swedish National Board of Health and Welfare, Cause of death statistics - history, production methods and reliability. 2010. http://www.socialstyrelsen.se/publikationer2010/2010-4-33 (Accessed 16 sept 2013)

15. Alpert JS, Thygesen K, Antman E, *et al*. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;**36**:959-969.

16. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, *et al*. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;**90**:583-612.

17. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol* 1972;**34**:187-220.

18. Allison PD. *Survival Analysis Using SAS: A Practical Guide*. Cary, NC: SAS Institute; 2010.

19. Lawesson SS, Stenestrand U, Lagerqvist B, *et al*. Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST-elevation myocardial infarction. *Heart* 2010;**96**:453-459.

20. Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. *Arch Intern Med* 2002;**162**:2405-2410.

21. Parikh NI, Gona P, Larson MG, *et al*. Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart study. *Circulation* 2009;**119**:1203-1210.

22. Myerson M, Coady S, Taylor H, *et al*. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2009;**119**:503-514.

23. Goff DC Jr, Howard G, Wang CH, *et al*. Trends in severity of hospitalized myocardial infarction: the atherosclerosis risk in communities (ARIC) study, 1987-1994. *Am Heart J* 2000;**139**:874-880.

24. Bjorck L, Rosengren A, Wallentin L, *et al*. Smoking in relation to ST-segment elevation acute myocardial infarction: findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions. *Heart* 2009;**95**:1006-1011.

25. Bjorck L, Wallentin L, Stenestrand U, *et al*. Medication in relation to ST-segment elevation myocardial infarction in patients with a first myocardial infarction: Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). *Arch Intern Med* 2010;**170**:1375-1381.

26. Luepker RV, Duval S, Jacobs DR Jr, *et al*. The effect of changing diagnostic algorithms on acute myocardial infarction rates. *Ann Epidemiol* 2011;**21**:824-829.

27 World Health Organization, international Society of hypertension Writing Group. 2003 World Health Organization (WHO)/International Society og Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983-1992

28. Meier MA, Al-Badr WH, Cooper JV, *et al*. The new definition of myocardial infarction: diagnostic and prognostic implications in patients with acute coronary syndromes. *Arch Intern Med* 2002;**162**:1585-1589.

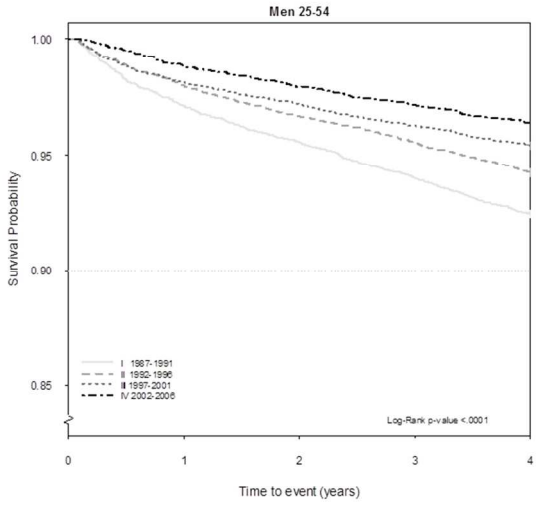
29. Hammar N, Alfredsson L, Rosen M, *et al*. . A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. *Int J Epidemiol* 2001;**30 Suppl 1**:S30-S34.

30 Johansson LA, Björkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995. *J Clin Epidemiol* 2009;62:1202-1209

FIGURE LEGENDS

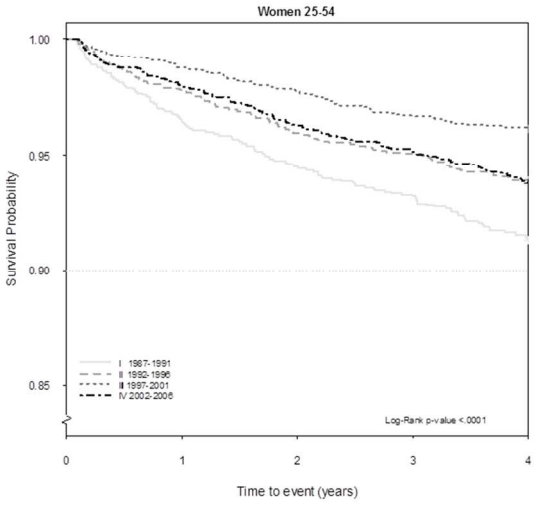
Figure 1 Four-year trend in survival probability by period and time among men (n 30 047) aged 25–54 years with a first AMI

Figure 2 Four-year trend in survival probability by period and time among women (n 7 229) aged 25–54 years with a first AMI



No at risk	0	1	2	3	4
1987-1991	7628	7404	7288	7169	7050
1992-1996	7946	7783	7678	7589	7486
1997-2001	7558	7412	7345	7273	7212
2002-2006	6915	6831	6770	6717	6664

Figure 1, Four-year trend in survival probability by period and time among men (n 30 047) aged 25–54 years with a first AMI
254x190mm (300 x 300 DPI)



No at risk	0	1	2	3	4
1987-1991	1556	1501	1470	1450	1421
1992-1996	1693	1655	1624	1609	1589
1997-2001	2014	1988	1968	1947	1936
2002-2006	1966	1926	1892	1870	1843

Figure 2 Four-year trend in survival probability by period and time among women (n 7 229) aged 25–54 years with a first AMI
254x190mm (300 x 300 DPI)

Supplemental Table 1: Baseline characteristics by period among 37,276 men and women with a first AMI, 1987–2006

		1987-1991	1992-1996	1997-2001	2002-2006	p for trend
Number of patients	Men	7628 (83.1)	7946 (82.4)	7558 (79.0)	6915 (77.9)	
Number of patients	Women	1556 (16.9)	1693 (17.6)	2014 (21.0)	1966 (22.1)	
Diabetes	Men	542 (7.11)	728 (9.16)	814 (10.8)	933 (13.5)	<.0001
	Women	200 (12.9)	244 (14.4)	276 (13.7)	327 (16.6)	0.0043
Hypertension	Men	451 (5.91)	655 (8.24)	807 (10.7)	1228 (17.8)	<.0001
	Women	106 (6.81)	188 (11.1)	252 (12.5)	423 (21.52)	<.0001
Valvular disease	Men	35 (0.47)	34 (0.43)	53 (0.70)	89 (1.29)	<.0001
	Women	11 (0.71)	16 (0.95)	17 (0.84)	32 (1.63)	0.0125
Congenital heart disease	Men	7 (0.09)	1 (0.01)	6 (0.08)	9 (0.13)	0.2212
	Women	1 (0.06)	3 (0.18)	4 (0.20)	5 (0.25)	0.1981
Stroke	Men	36 (0.47)	52 (0.65)	40 (0.53)	174 (2.52)	<.0001
	Women	10 (0.64)	18 (1.06)	21 (1.04)	61 (3.10)	<.0001
Chronic lower resp disease	Men	61 (0.80)	77 (0.97)	86 (1.14)	144 (2.08)	<.0001
	Women	26 (1.67)	41 (2.42)	46 (2.28)	76 (3.87)	0.0001

Malignancy	Men	11 (0.14)	24 (0.30)	55 (0.73)	165 (2.39)	<.0001
	Women	10 (0.64)	17 (1.00)	14 (0.70)	58 (2.95)	<.0001
Renal failure	Men	7 (0.09)	25 (0.31)	47 (0.62)	85 (1.23)	<.0001
	Women	3 (0.19)	15 (0.89)	13 (0.65)	35 (1.78)	<.0001

Supplemental Table 2: Cause of death by period for 2,076 deaths within 4 years among patients with a first AMI during 1987–2006

Cause of death	Total n (%)	Men n (%)	Women n (%)	p-value
1987-1991	713	578 (81.1)	135 (18.9)	
CVD	533(74.8)	454(78.6)	79 (58.5)	<.0001
IHD	481 (67.5)	405 (70.1)	76 (56.3)	0.0021
Stroke	18 (2.52)	16(2.77)	2 (1.48)	0.3909
All other causes	180 (25.3)	124 (21.5)	56 (41.5)	<.0001
Malignancies	55 (7.71)	39 (6.75)	16 (11.9)	0.0454
1992-1996	564	460 (81.6)	104 (18.4)	
CVD	369 (65.4)	318 (69.1)	51 (49.0)	<.0001
IHD	337 (59.8)	295 (64.1)	42 (40.4)	<.0001
Stroke	6 (1.06)	5 (1.09)	1 (0.96)	0.9104
All other causes	195 (34.6)	142 (30.9)	53 (51.0)	<.0001
Malignancies	79 (14.01)	57 (12.4)	22 (21.2)	0.0201
1997-2001	425	347 (81.7)	78 (18.4)	
CVD	242 (56.9)	205 (59.1)	37 (47.4)	0.0606
IHD	216 (50.8)	182 (52.5)	34 (43.6)	0.1573
Stroke	5 (1.18)	3 (0.86)	2 (2.56)	0.2084
All other causes	183 (43.1)	142 (40.9)	41 (52.6)	0.0606
Malignancies	63 (14.8)	52(15.0)	11 (14.1)	0.8428
2002-2006	374	251 (67.1)	123 (32.9)	
CVD	181 (48.4)	139 (55.4)	42 (34.1)	0.0001
IHD	145 (38.8)	116 (46.2)	29 (23.6)	<0.0001

Stroke	12 (3.21)	7 (2.79)	5 (4.07)	0.5106
All other causes	193 (51.6)	112 (44.6)	81(65.9)	0.00001
Malignancies	60 (16.0)	28 (11.2)	32 (26.0)	0.0002

AMI, acute myocardial infarction; IHD, ischaemic heart disease; CVD, cardiovascular disease

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract Title: Sex-specific trends in survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. Prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Please see page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Please see page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses Please see page 5
Methods		
Study design	4	Present key elements of study design early in the paper Please see page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Please see page 5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Please see page 5-6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls N/A *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed N/A

		Case-control study—For matched studies, give matching criteria and the number of controls per case N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Please see page 5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Please see page 5-6
Bias	9	Describe any efforts to address potential sources of bias N/A
Study size	10	Explain how the study size was arrived at N/A. All patients in Sweden in the relevant age group were included.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Please see page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Please see page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions Please see page 7-8
		(*c*) Explain how missing data were addressed N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Loss to follow-up negligible *Case-control study*—If applicable, explain how matching of cases and controls was addressed N/A *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy N/A
		(*e*) Describe any sensitivity analyses N/A

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Please see page 5
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Please see page 5-6
		(b) Indicate number of participants with missing data for each variable of interest N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) Please see page 6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Please see Table 2 and 3 , and page 15.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure N/A
		Cross-sectional study—Report numbers of outcome events or summary measures N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Please see Table 2 and 3, and statistical methods.
		(*b*) Report category boundaries when continuous variables were categorized Done
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Please see Tables 2 and 3.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity

		analyses Please see page 15
Discussion		
Key results	18	Summarise key results with reference to study objectives Please see page 15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Please see page 18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Please see page 15-19
Generalisability	21	Discuss the generalisability (external validity) of the study results Please see page 18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Please see page 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Sex-specific trends in four-year survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. A register-based cohort study.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004598.R1
Article Type:	Research
Date Submitted by the Author:	03-Apr-2014
Complete List of Authors:	Nielsen, Susanne; Institute of medicin, Department of Molecular and Clinical Medicin Björck, Lena; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Berg, Johanna; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Giang, Kok Wai; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Zverkova-Sandström, Tatiana; Department of Molecular and Clinical Medicine, Sahlgrenska Academy Falk, Kristin; Institute of Health and Care Siences, Sahlgrenska Academy, Määttä, Sylvia; Institute of Health and Care Siences, Sahlgrenska Academy, Rosengren, Annika; Department of Molecular and Clinical Medicine, Sahlgrenska Academy
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Epidemiology < TROPICAL MEDICINE, Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

Sex-specific trends in four-year survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. A register-based cohort study.

Nielsen S, MSc[1], Björck L, PhD[1,2], Berg J, MD[1], Giang KW, MSc[1], Zverkova Sandström T, BSc[1], Falk K, PhD[2], Määttä S, PhD[2], Rosengren A, MD, PhD[1]*

[1]Department of Molecular and Clinical Medicine and [2]Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

*Corresponding author: Annika Rosengren, Department of Molecular and Clinical Medicine, Sahlgrenska University Hospital/Östra, SE-41685, Gothenburg, Sweden. E-mail: annika.rosengren@gu.se; Tel: +46 31343 4086; Fax: +46 31258933

Keywords Myocardial Infarction • Mortality • Survival • Trends • Epidemiology

Word count: Abstract: 269

Manuscript: 3400

ABSTRACT

Objective To examine sex-specific trends in 4-year mortality among young patients with a first acute myocardial infarction (AMI), 1987–2006.

Design: Prospective cohort study

Setting: Sweden.

Participants: We identified 37,276 cases (19.4% women; age, 25–54 years) from the Swedish Inpatient Register, 1987–2006, who had survived 28 days after an AMI.

Outcome measures: Four-year mortality from all causes, and Standard Mortality Ratio (SMR)

Results From the first to last 5-year period, the absolute excess risk decreased from 1.38 to 0.50 and 1.53 to 0.59 per 100 person-years among men aged 25–44 and 45–54 years, respectively. Corresponding figures for women were a decrease from 2.26 to 1.17 and from 1.93 to 1.45 per 100 person-years, respectively. Trends for women were non-linear, decreasing to the same extent as those for men until the third period, then increasing. For the last 5-year period, the standardized mortality ratio for young survivors of AMI compared with the general population was 4.34 (95% confidence interval [CI]: 3.04–5.87) and 2.43 (95% CI: 2.12–2.76) for men aged 25–44 and 45–54 years, respectively, and 13.53 (95% CI: 8.36–19.93) and 6.42 (95% CI: 5.24–7.73) for women. Deaths not associated with cardiovascular causes increased from 21.5% to 44.6% in men and 41.5% to 65.9% in women, respectively.

Conclusion Young male survivors of AMI have low absolute long-term mortality rates, but these rates remain 2- to 4-fold that of the general population. After favourable development until 2001, women now have higher absolute mortality than men and a 6- to 14-fold risk of death compared with women in the general population.

Strengths and limitations of this study

- Population-based study, that includes all cases with a first AMI, aged 25-55 years, in Sweden during a period of twenty years.
- Strengths include nationwide coverage, and near-complete follow-up.
- The main limitation is that the used register does not provide data covering clinical characteristics or treatment which could have been valuable to estimate their impact on mortality.

INTRODUCTION

Survival after acute myocardial infarction (AMI) has improved during the last several decades in Sweden and elsewhere.[1-3] Nonetheless, coronary heart disease (CHD) remains a major contributor to morbidity and mortality with more than one in five men and women currently dying from CHD in Europe.[4,5] Survivors of AMI are known to have an impaired prognosis compared with the general population.[6] In a recent study from England, the long-term risk of death of any cause among survivors of a first AMI was twice that of the general English population of equivalent age.[7]

Most patients with AMI are elderly; accordingly, most information on long-term survival is based on patients older than 55 years. However, about one in six AMI survivors is younger than 55 years.[8] Knowledge of the prognosis among young patients with AMI is essential because younger patients stand to lose more of their remaining life years compared with older patients. This applies particularly to women because women have a longer life expectancy.

Further, younger, but not older, women hospitalized with AMI have a worse long-term prognosis than men as shown in analyses of patient populations dating from the 1980s and 1990s.[9,10] However, there have since been marked changes in treatment, diagnostic criteria, and post-AMI prognosis. A recent study found that reductions in long-term mortality after 1985 were at least as high for women as for men with AMI,[11] but the study did not specifically report findings for young patients. An additional study, found that reductions in mortality were similar regardless of age but that younger patients are more likely to receive evidence based care.[12]

Few data sets contain a sufficient number of young patients to reliably estimate risk of death compared with the general population. In addition, more information is needed about cause-specific mortality, because an unknown proportion of deaths may not be due to cardiovascular causes, and will thus be less amenable to coronary preventive measures. In the present study, we examined sex-specific trends in long-term survival in a register-based cohort of patients aged 25–54 years hospitalized with a first AMI during 1987–2006, and compared death rates for men and women separately with those of the general population.

METHODS

Registries and study population

Sweden has a publicly financed health care system, with some health care facilities privately run but still fully integrated into the health care system. The Swedish National Inpatient Register (IPR), has established complete national coverage since 1987. One study stated that positive predictive values (PPV) differ among diagnoses in the IPR, but are generally 85–95%. PPV for myocardial infarction was about 98-100% and the sensitivity was 77-91.5%.[13] Another validation study concluded that the accuracy of correct diagnosis in AMI was 86 % regardless (1987-1995) of age and gender. [14] More recent data are lacking. Diagnoses in the IPR are coded according to the Swedish International Classification of Diseases (ICD) system (ICD 8th revision until 1986, 9th revision until 1996, and 10th revision thereafter). In the present study, data from the IPR and the Swedish Cause of Death Register were linked through personal identity numbers unique to each Swedish citizen. The Cause of Death Register is based on diagnosis from death certificates. In 2008, 0.8% of death certificates were missing or insufficient (2.7%) [15]. Validity for a correct diagnosis of ischemic heart disease in the general population in 1995 was 87%.[16]

The present study included all 38,836 cases (31216 men, 7620 women) in Sweden aged 25–54 years, discharged from hospital after a first AMI in 1987–2006; AMI was defined as a principal discharge code according to the ICD -8 : 410 (until 1987), ICD-9: 410 (until 1996) and ICD-10: I21 (from 1997 onward). After excluding 1,560 cases who died during the first 28 days 1169 men (3.01% of cases) median age; 50, and 391 women (1.01% of cases) median age; 49.0, 37,276 cases (7,229 women and 30,047 men) with a first AMI remained for analysis. Data from 1980 onward were used to identify first AMIs only, with a time frame of 7 years throughout, to ensure that AMIs registered each year had the same chance of being identified as a first AMI. Due to the 7-years time frame, 443 cases were recurrent AMI after seven years (53 women median age; 52, 390 men median age; 51) Criteria for a diagnosis of AMI in Sweden have followed established guidelines, changing after the adoption of new AMI criteria in the year 2000.[17,18] Thus, the characteristics of the AMIs in our analysis changed during the study period. Use of troponins became standard after the year 2000.

Comorbidities were defined by the following main or contributory discharge codes during the preceding 7 years, including the index hospitalization: diabetes (ICD-9 250; ICD-10 E10–E14), hypertension (ICD-9 401–405; ICD-10: I10–I15), valvular disease (ICD-9 394–397, 424; ICD-10 I05–I09, I34–I35), congenital heart disease (ICD-9 745–747; ICD-10 Q20–Q26), stroke (ICD-9 431–434, 436; ICD-10 I61–I64), chronic respiratory disease (ICD-9 490–496; ICD-10 J40–J47), malignancy (ICD-9 140–208; ICD-10 C00–C97), renal failure (ICD-9 584–586; ICD-10 N17–N19), coronary artery bypass grafting (3067, 3066, 3105, 3127, FNA, FNB, FNE, FNC), and percutaneous coronary intervention (3080, FNG 00, FNG 02, FNG 05).

Follow-up

We analysed 4-year all-cause mortality for four 5-year periods (1987–1991, 1992–1996, 1997–2001, and 2002–2006) through the Swedish Cause of Death Register. The following codes were used for assignment of causes of death among fatal cases: CVD, (390–459, I00–I99), ischaemic heart disease (IHD) (410–414, I20–I25, stroke (430–438, I60–I68), and all other causes (including malignancies; 140-208, C00-C97).

Statistical analysis

Statistical analyses were performed with SAS 9.3, (R version 2.15.1 to obtain the graphs). For comorbidities, $\chi 2$ tests were used to evaluate differences between men and women and for trends; a P-value of ≤ 0.05 was considered significant. To compare mean age within the respective age groups, t-tests were performed.

Standardized mortality ratios (SMR) with 95% confidence intervals (CIs) were calculated as the ratio of the observed to expected number of deaths, for 4-year follow up by each period ,estimated from rates in the general Swedish population, by gender, age and calendar year, using life expectancy tables from Official Statistics of Sweden (SCB).

To examine the excess mortality risk in the study population the absolute risk (AR) was calculated separately for both the general population and the study population by dividing the observed mortality with person time. This yields an average annual excess risk for each period. The absolute excess risk (AER) is the difference between the observed and the expected AR. For standardization purposes, the estimates were then multiplied by 100 person-years. The AER calculations add a useful measure of excess risk in absolute terms. Life expectancy tables from Official Statistics of Sweden (SCB) were used to calculate the expected mortality in the Swedish general population by gender, age and calendar year.

Cox proportional hazard regression, providing hazard ratios (HR) with 95% CIs, was used to estimate age, and gender-specific changes in all-cause mortality over time.[19] The first period (1987–1991) was used as reference; The multivariable models were adjusted for age, diabetes, hypertension, valvular and congenital heart disease, stroke, chronic respiratory disease, malignancy and renal failure. Furthermore, in the final model the periods were also tested for proportionality by interactions of age, time and with significant comorbidities only (men 45-54; malignancies, women, 45-54; chronic respiratory disease).

The Kaplan-Meier method was used to estimate the survival probability. The proportionality assumption of Cox regression was tested by including interactions between covariates (age, gender, and period) with time; neither interaction test was statistically significant.[20] A log-rank test was conducted to study changes in survival between the time periods.

RESULTS

Of the 37,276 cases in the study, 7,905 (21.2%) were aged 25–44 years (19.6% women) and 29,371 (78.8%) were aged 44–54 years (19.3% women). Other than diabetes and hypertension (11% for both), this population had few diagnosed comorbidities (Table 1). Women had more diabetes, hypertension, chronic lower respiratory disease and malignancies than did men ($P <$ 0.0001).

Table 1. Baseline characteristics in 37,276 men and women aged <55 years with a first AMI, 1987–2006

	All	Men	Women	P-value

Number of cases	37 276	30 047	7 229	
Age 25-44, n (%)	7 905 (21.2)	6 357 (21.2)	1 548 (21.4)	
Mean age (SD)		40.21 (3.74)	39.84 (4.04)	0.055
Age 44-54, n (%)	29 371(78.8)	23 690 (78.8)	5 681 (78.6)	
Mean age (SD)		50.31 (2.75)	50.39 (2.76)	0.0549
Diabetes, n (%)	4 064 (10.9)	3 017 (10.0)	1 047 (14.5)	<0.0001
Hypertension, n (%)	4110 (11.0)	3141 (10.6)	969 (13.4)	<0.0001
Valvular disease, n (%)	287 (0.77)	211 (0.70)	76 (1.05)	0.0023
Congenital heart disease	36 (0.10)	23 (0.08)	13 (0.18)	0.0111
Stroke, n (%)	412 (1.11)	302 (1.01)	110 (1.52)	0.0002
Chronic lower respiratory disease, n (%)	557(1.49)	368 (1.22)	189 (2.61)	<0.0001
Malignancy, n (%)	354 (0.95)	255 (0.85)	99 (1.37)	<0.0001
Renal failure	230 (0.62)	164 (0.55)	66 (0.91)	0.0003
CABG*, n (%)	253 (0.68)	221 (0.74)	32 (0.44)	0.007
PCI*, n (%)	235 (0.63)	198 (0.66)	37 (0.51)	0.16

*Procedures dating at least 6 months prior to hospitalization for AMI

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

Supplementary Table 1 shows the comorbidities for each 4-year period. All comorbidities except for congenital heart diseases increased significantly over time. Diabetes and hypertension were the most prevalent comorbidities in both men and women but the rates of other comorbidities remained low even in the last period (<4%).

During the study period (1987-2006) annual rate per 100.000 population in men and women aged 25-54 years surviving a first AMI for at least 28 days decreased from 92.3 per 100.000 in 1987 to 72.1 in 2006 (Figure 1). Women, on the other hand, showed a different pattern with an increase from 17.4 per 100.000 in 1987 to 22.3 in 2006 (p for men <0.0001, for women 0.0003).

Survival in men improved continuously over the four 5-year periods (Figure 2), while the prognosis in women improved until the third period (1997-2001), then reverted to a risk nearly identical to that in the second period (Figure 3).

Table 2 shows mortality by sex, age group, and period. For men aged 25–44 years, the annual excess risk of dying decreased continuously from 1.38 to 0.50 deaths per 100 person-years from the first to last period, with an SMR of 4.34 (95% CI: 3.04–5.87) during the last 5-year period. Corresponding figures for men aged 45–54 were a decrease from 1.53 to 0.59 with a SMR of 2.43 (95% CI: 2.12–2.76) in the last period (2002–2006). Women displayed more complicated trends, starting from higher absolute risks of dying compared with men, decreasing sharply until a nadir in 1997–2001, and then increasing to 1.17 and 1.45 deaths per 100 person-years in women aged 25–44 and 45–54, respectively, in the last period. This was more than twice the risk in men of the corresponding age groups. Very high SMRs were noted, particularly for the youngest women, at 13.53 (95% CI: 8.36–19.93) in the last period and 6.42 (5.24–7.73) in women aged 45–54 years.

In men aged 25–44 years, the mortality risk decreased by 70% during the study period (multivariable adjusted HR: 0.30, 95% CI: 0.20–0.44). A similar decrease was seen in men aged 45–54 years (multivariable adjusted HR: 0.32, 95% CI: 0.27–0.38). Women aged 25–44

years had an overall decline in mortality risk of approximately 50% (multivariable adjusted HR: 0.47, 95% CI: 0.27–0.83). No significant decrease in mortality risk in the last, compared with the first period was observed in women aged 45–54 years (age-adjusted HR: 0.77, 95% CI: 0.59–1.02), but after adjustment for comorbidities there was a significant decrease in risk (HR: 0.53, 95% CI: 0.39–0.71).

Table 2. Observed versus expected mortality ratio, estimated over 4 years, standardized mortality ratio, absolute risk, absolute excess risk, and hazard ratio for mortality by age group and period among 37,276 men and women aged <55 years with a first AMI.

Age, Period	Observed[a]	Expected[b]	SMR (95% CI)	AR[c]	AER[d]	HR (95% CI)[e]	HR (95% CI)[f]
Men 25-44							
1987-1991	113	16	6.88 (5.67–8.20)	1.61	1.38	1.0 (ref)	1.0 (ref)
1992-1996	81	13	6.16 (4.89–7.57)	1.25	1.05	0.76 (0.57–1.01)	0.73 (0.55–0.98)
1997-2001	58	10	5.70 (4.33–7.27)	1.00	0.83	0.60 (0.43–0.82)	0.53 (0.38–0.73)
2002-2006	36	8	4.34 (3.04–5.87)	0.65	0.50	0.41(0.28–0.60)	0.30 (0.20–0.44)
Men 45-54							
1987-1991	465	125	3.72 (3.39–4.07)	2.10	1.53	1.0 (ref)	1.0 (ref)[g]
1992-1996	379	119	3.20 (2.88–3.53)	1.56	1.07	0.74 (0.65–0.85)	0.70 (0.61–0.81)

1997-2001	289	108	2.69 (2.39–3.00)	1.22	0.77	0.57 (0.49–0.66)	0.50 (0.43–0.58)
2002-2006	215	89	2.43 (2.12–2.76)	0.99	0.59	0.47 (0.40–0.56)	0.32 (0.27–0.39)
Women 25-44							
1987-1991	34	2	17.55 (12.15–23.94)	2.39	2.26	1.0 (ref)	1.0 (ref)
1992-1996	28	2	17.99 (11.95–25.27)	2.17	2.05	0.93 (0.56–1.55)	0.85 (0.51–1.42)
1997-2001	10	2	6.07 (2.89–10.42)	0.63	0.52	0.27 (0.13–0.55)	0.28 (0.14–0.56)
2002-2006	21	2	13.53 (8.36–19.93)	1.26	1.17	0.55 (0.32–0.94)	0.47(0.27–0.83)
Women 45-54							
1987-1991	101	15	6.90 (5.62–8.31)	2.25	1.93	1.0 (ref)	1.0 (ref) [h]
1992-1996	76	16	4.63 (3.65–5.73)	1.45	1.14	0.64 (0.48–0.87)	0.56 (0.42–0.76)
1997-2001	68	19	3.58 (2.78–4.48)	1.08	0.78	0.49 (0.36–0.66)	0.44 (0.32–0.60)
2002-2006	102	16	6.42 (5.24–7.73)	1.72	1.45	0.77 (0.59–1.02)	0.53 (0.39–0.71)

[a]Observed number of deaths in the study population, [b]Expected number of deaths in the general population, [c]Absolute risk per 100 person-years, [d]Absolute excess risk per 100 person-years, [e] Age adjusted, [f] Multiadjusted for age, diabetes, hypertension, valvular, congenital heart disease, stroke, chronical respiratory disease, malignancy and renal failure. Adjusted for changes and interaction over time, malignancy ([g]), chronic respiratory disease ([h]).

AMI, acute myocardial infarction; SMR, standardized mortality ratio; AR, absolute risk; AER, absolute excess risk; HR, hazard ratio; CI, confidence interval

Table 3 shows causes of death for the 2,076 deaths that occurred within 4 years in this cohort. In 1987–1991, 74,8% of all deaths within 4 years were due to CVD (78.6% for men and 58.5% for women) with a majority to IHD. However, during the last period (2002-2006), only 48.4% of all deaths were due to CVD (55.4% for men and, notably, only 34.1% for women)

Table 3: Cause of death by period for 2,076 deaths within 4 years among men and women aged <55 years with a first AMI during 1987–2006

Cause of death	Total n (%)	Men n (%)	Women n (%)	p-value
1987-1991	713	578 (81.1)	135 (18.9)	
CVD	533(74.8)	454(78.6)	79 (58.5)	<.0001
IHD	481 (67.5)	405 (70.1)	76 (56.3)	0.0021
Stroke	18 (2.52)	16(2.77)	2 (1.48)	0.3909
All other causes	180 (25.3)	124 (21.5)	56 (41.5)	<.0001
Malignancies	55 (7.71)	39 (6.75)	16 (11.9)	0.0454
1992-1996	564	460 (81.6)	104 (18.4)	
CVD	369 (65.4)	318 (69.1)	51 (49.0)	<.0001
IHD	337 (59.8)	295 (64.1)	42 (40.4)	<.0001
Stroke	6 (1.06)	5 (1.09)	1 (0.96)	0.9104
All other causes	195 (34.6)	142 (30.9)	53 (51.0)	<.0001
Malignancies	79 (14.01)	57 (12.4)	22 (21.2)	0.0201
1997-2001	425	347 (81.7)	78 (18.4)	
CVD	242 (56.9)	205 (59.1)	37 (47.4)	0.0606
IHD	216 (50.8)	182 (52.5)	34 (43.6)	0.1573
Stroke	5 (1.18)	3 (0.86)	2 (2.56)	0.2084

All other causes	183 (43.1)	142 (40.9)	41 (52.6)	0.0606
Malignancies	63 (14.8)	52(15.0)	11 (14.1)	0.8428
2002-2006	374	251 (67.1)	123 (32.9)	
CVD	181 (48.4)	139 (55.4)	42 (34.1)	0.0001
IHD	145 (38.8)	116 (46.2)	29 (23.6)	<0.0001
Stroke	12 (3.21)	7 (2.79)	5 (4.07)	0.5106
All other causes	193 (51.6)	112 (44.6)	81(65.9)	0.00001
Malignancies	60 (16.0)	28 (11.2)	32 (26.0)	0.0002

AMI, acute myocardial infarction; IHD, ischaemic heart disease; CVD, cardiovascular disease

DISCUSSION

The present study showed that young male survivors of AMI have low absolute long-term mortality rates; however, these rates remain between 2- and 4-fold those of the general population. After a favourable development in younger women until 2001, when new criteria for AMI were adopted and troponins became standard, women had higher absolute mortality than men in the last period and showed a dramatically higher risk of death than healthy women. However, fewer than half of all deaths in women were due to CVD in the last period.

Few studies have specifically investigated long-term outcomes in young patients with AMI. One Swedish study based on the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA)[21] investigated all consecutive patients younger than 46 years treated for ST-elevation myocardial infarction (STEMI) in Sweden, 1995–2006 (1,748 men, 384 women). Long-term annual mortality was around 1% with no difference between men and women, similar to our study. Accordingly, in absolute terms and consistent

with prior publications from our group,[1] annual mortality rates in AMI survivors younger than 55 years are estimated at about 1%. This is in contrast to older patients in Sweden, among whom annual mortality rates are about 6% for those aged 65–74 years and more than 12% among patients aged 75–84 years).[1] The current low absolute mortality figures are a vast improvement on prior estimates. In a retrospective analysis of 23 published studies from the prethrombolytic era, the annual death rate after the first year in patients with a first AMI was 5% regardless of age or gender.[22] In the late 1980s, the annual mortality for patients younger than 55 years was about 2%.[1]

There are several reasons for the observed decrease in mortality in younger patients with AMI. First, several pharmacological and coronary interventions were developed and implemented during the study period. Nauta et al 2013 showed that patient <55 received evidence-based medical care and reperfusion to a greater extent than elderly patients.[12] Second, some of the decrease is likely due to changes in diagnostic criteria during the study period, as well as more sensitive methods.[17,23] This may imply that less severe AMIs are detected, with improved survival, but less specificity, as evidenced by increased comorbidities over time and a higher proportion of non-CVD deaths in the last period. Third, there have been changes in clinical presentation, with less severe infarctions,[24,25] and fewer STEMIs.[26] Factors that affect the risk of developing STEMI rather than non-STEMI include smoking[26] and cardioprotective medications that lower the risk.[27] Declining smoking rates and more medications used in primary prevention could thus have contributed to milder infarctions and better survival. Comorbidities increased during the study period. However, this can probably at least partly be derived to improvements in clinical reporting due to financial incitements. [13] The striking increase in hypertension can also probably be attributed to changes in criteria and guidelines management by the WHO.[28]

There was a continuous decrease in case fatality among men; however, rates in women did not follow the same pattern as in men. Mortality in women decreased until the third period and then increased during the fourth period to nearly the same level as in the second period. This may have been due to chance because the numbers were limited. However, it could also reflect differences in diagnostics. With increasing use of troponins, the rate of detection has increased, and this effect could be stronger for women than for men. In a study that simultaneously measured CK-MB and troponin,[29] a 64% and 95% increase in the AMI rate among men and women, respectively, was observed when using troponins. Accordingly, the increasing mortality among women hospitalized in 2002–2006 could be due to the capture of other and more complicated types of myocardial damage because an increase in troponin levels is also seen in other conditions.[30] Even so, comorbidities, although increasing over time, were still low in the most recent period. Since the most marked change between the third and the fourth period of our study was the change from CK-MB to troponins as the predominant marker for myocardial damage, we speculate that the additional AMIs captured by this more sensitive method are clinically different, not only in being smaller but also to an unknown extent reflecting myocardial damage not due to atherosclerotic disease. Circumstantial evidence for this might be derived from the increasing and much higher proportion of non-CVD deaths, as well as more comorbidities, in women compared to men over the study period. In the present study the results showed an increased rate of survivors but a decreasing trend in death in CVD among young women. These results strengthen that the increased all-cause mortality is likely a result of a combination between the use of troponin and increasing comorbidities.

Few studies have compared mortality rates in young patients with AMI with those in the general population. A record linkage of hospital and mortality data identified 387,452 individuals in England, hospitalized with a main diagnosis of AMI in 2004–2010 and who survived at least 30 days.[7] Long-term risk of death of any cause among survivors of a first AMI was twice that in the English general population of equivalent age, highest among younger patients aged 55–64 years (about 2- to 3-fold for men and women, respectively), and approached the mortality rate of the general population for those aged 85 years or more. Estimates for individuals younger than 55 years were not stated in the study by Smolina, et al., but we have since been provided with information that mortality ratios were 2.6 for men and 5.6 for women aged 30-54 years after 4 years, which is more or less comparable to our findings (Smolina K, personal communication). For the period corresponding to that in the study by Smolina et al.[7] we found mortality ratios of 4.3 and 2.4 for men aged 25–44 and 45–54 years, respectively. For women aged 25–44 years, the estimated mortality ratio was 13.5, but this was based on very few cases (about four deaths per year). The estimate of 6.4 for women aged 45–54 years should be more reliable. It should be noted that women in the general population in this age range have very low mortality rates, which partially explains the high SMRs in women.

The main limitation in the present study is the reliance on administrative registers with no details of changes in several characteristics, such as biomarkers, electrocardiographic findings, smoking, medication, hyperlipidemia, family history, ethnicity and socioeconomic status and a lack of other clinical information, notably hospital treatment and clinical presentation. Also, we were unable to apply uniform criteria for diagnosis over time. This limits considerably the interpretation that can be made, however, the findings should be applicable to current patients with AMI in an industrialized modern country. The quality of

the data is obviously of fundamental importance, but validation studies of the IPR indicate reasonable accuracy.[13,14] Incorrect death certificates could lead to uncertainty with respect to attributing cause of death[15], but IHD diagnoses has been estimated to be correct in 87% for ischemic heart disease although the data from this study were collected two decades ago. [16] The causes of death are also considered to be more reliable for the younger population than for the elderly population. [15]

The strengths of the study include nationwide coverage with virtually no loss to follow-up and the large sample size. Given the low mortality in absolute terms, larger populations are needed, particularly for women, because they constitute less than 20% of the AMI population younger than 55 years.

Conclusions

These data extend and update what is currently known about sex-specific absolute and relative survival in patients with AMI younger than 55 years, with a large population of more than 35,000 cases during a 20-year period. Among patients surviving for 28 days after AMI, the annual mortality rates are now comparatively low at approximately 1%. Given the much lower mortality in this age group in the general population, young survivors of AMI, particularly women, remain at a much higher risk of death, much of this, however, due to non-CVD causes. Accordingly, while mortality is low in absolute terms, younger women with AMI lose the survival advantage women normally have over men. Additional strategies to bring mortality closer to that which would be expected for this age group are needed, in particular for women.

Funding

This work was supported by the Swedish Research Council [grant number VR 521-2010-2984]; the Swedish Heart-Lung Foundation [grant number 2012-0325]; and the Swedish Council for Working Life and Social Research [grant number Epilife 2006-1506], the VGR region and the Swedish state under the ALF-LUA agreement.

Contributors

Study concept, design: SN, AR, LB, JB, KWG. Analysis and interpretation of data: SN, TZS, AR, LB, JB, KWG. Drafting and revised the manuscript: SN, LB, JB, KWG, TZS, KF, SM, AR. Critical revision of the final version of the manuscript: all authors. SN, LB, JB, KWG, TZS, KF, SM, AR. Guarantor: AR

Competing interests:

None declared.

Data sharing statement

No additional data are available.

Ethical approval

All personal identifiers were removed and replaced with a sequential number in the final data set. The protocol was approved by the regional Ethics Board of Gothenburg.

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES

1. Dudas K, Lappas G, Rosengren A. Long-term prognosis after hospital admission for acute myocardial infarction from 1987 to 2006. *Int J Cardiol* 2012;**155**:400-405.
2. Langorgen J, Igland J, Vollset SE, *et al*. Short-term and long-term case fatality in 11 878 patients hospitalized with a first acute myocardial infarction, 1979-2001: the Western Norway cardiovascular registry. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:621-627.
3. Hardoon SL, Whincup PH, Petersen I, *et al*. Trends in longer-term survival following an acute myocardial infarction and prescribing of evidenced-based medications in primary care in the UK from 1991: a longitudinal population-based study. *J Epidemiol Community Health* 2011;**65**:770-774.
4. Rayner M, Allender S, Scarborough P. Cardiovascular disease in Europe. *Eur J Cardiovasc Prev Rehabil* 2009;**16 Suppl 2**:S43-S47.
5. Nichols MTN, Scarborough P, Luengo-Fernandez R, *et al*. *European Cardiovascular Disease Statistics 2012*. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis; 2012.
6. Fagring AJ, Lappas G, Kjellgren KI, *et.al.* Twenty-year trends in incidence and 1-year mortality in Swedish patients hospitalised with non-AMI chest pain. Data from 1987-2006 from the Swedish hospital and death registries. *Heart* 2010;**96**:1043-1049.
7. Smolina K, Wright FL, Rayner M, *et al*. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. *Circ Cardiovasc Qual Outcomes* 2012;**5**:532-540.

8. Gale CP, Cattle B, Woolston A,*et al*. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. *Eur Heart J* 2012;**33**:630-639.

9. Rosengren A, Spetz CL, Koster M, *et al*. Sex differences in survival after myocardial infarction in Sweden; data from the Swedish National Acute Myocardial Infarction Register. *Eur Heart J* 2001;**22**:314-322.

10. Vaccarino V, Krumholz HM, Yarzebski J, *et al*. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;**134**:173-181.

11. Nauta ST, Deckers JW, van Domburg RT,*et al*. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. *Circulation* 2012;**126**:2184-2189.

12 Nauta ST, Decker JW, Akkerhuis KM, *et al*. Age-dependent care and long-term (20 year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008. *Int. J Cardiol* 2013;**167**:693-697

13. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.

14. Hammar N, Alfredsson L, Rosen M, *et al*. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. *Int J Epidemiol* 2001;**30 Suppl 1**:S30-S34.

15 Swedish National Board of Health and Welfare, Cause of death statistics - history, production methods and reliability. 2010. *(In Swedish)* http://www.socialstyrelsen.se/publikationer2010/2010-4-33 (Accessed 16 sept 2013)

16. Johansson LA, Björkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995. *J Clin Epidemiol* 2009;62:1202-1209

17. Alpert JS, Thygesen K, Antman E, *et al*. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;**36**:959-969.

18. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, *et al*. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;**90**:583-612.

19. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol* 1972;**34**:187-220.

20. Allison PD. *Survival Analysis Using SAS: A Practical Guide*. Cary, NC: SAS Institute; 2010.

21. Lawesson SS, Stenestrand U, Lagerqvist B, *et al*. Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST-elevation myocardial infarction. *Heart* 2010;**96**:453-459.

22. Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. *Arch Intern Med* 2002;**162**:2405-2410.

23. Parikh NI, Gona P, Larson MG, *et al*. Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart study. *Circulation* 2009;**119**:1203-1210.

24. Myerson M, Coady S, Taylor H, *et al*. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2009;**119**:503-514.

25. Goff DC Jr, Howard G, Wang CH, *et al*. Trends in severity of hospitalized myocardial infarction: the atherosclerosis risk in communities (ARIC) study, 1987-1994. *Am Heart J* 2000;**139**:874-880.

26. Bjorck L, Rosengren A, Wallentin L, *et al*. Smoking in relation to ST-segment elevation acute myocardial infarction: findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions. *Heart* 2009;**95**:1006-1011.

27. Bjorck L, Wallentin L, Stenestrand U, *et al*. Medication in relation to ST-segment elevation myocardial infarction in patients with a first myocardial infarction: Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). *Arch Intern Med* 2010;**170**:1375-1381.

28. World Health Organization, international Society of hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-1992

29 Luepker RV, Duval S, Jacobs DR Jr, et al. The effect of changing diagnostic algorithms on acute myocardial infarction rates. Ann Epidemiol 2011;**21**:824-829.

30. Meier MA, Al-Badr WH, Cooper JV, *et al*. The new definition of myocardial infarction: diagnostic and prognostic implications in patients with acute coronary syndromes. *Arch Intern Med* 2002;**162**:1585-1589.

FIGURE LEGENDS

Figure 1 Annual rate per 100.000 population in men and women aged 25-54 years surviving a first AMI for at least 28 days.

Figure 2 Four-year trend in survival probability by period and time among men (n 30 047) aged 25–54 years with a first AMI

Figure 3 Four-year trend in survival probability by period and time among women (n 7 229) aged 25–54 years with a first AMI

Sex-specific trends in *four-year* survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. *A register-based cohort study.*

Nielsen S, MSc[1], Björck L, PhD[1,2], Berg J, MD[1], Giang KW, MSc[1], Zverkova Sandström T, BSc[1], Falk K, PhD[2], Määttä S, PhD[2], Rosengren A, MD, PhD[1]*

[1]Department of Molecular and Clinical Medicine and [2]Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

*Corresponding author: Annika Rosengren, Department of Molecular and Clinical Medicine, Sahlgrenska University Hospital/Östra, SE-41685, Gothenburg, Sweden. E-mail: annika.rosengren@gu.se; Tel: +46 31343 4086; Fax: +46 31258933

Keywords Myocardial Infarction • Mortality • Survival • Trends • Epidemiology

Word count: Abstract: 269

Manuscript: 3400

ABSTRACT

Objective To examine sex-specific trends in 4-year mortality among young patients with a first acute myocardial infarction (AMI), 1987–2006.

Design: Prospective cohort study

Setting: Sweden.

Participants: We identified 37,276 cases (19.4% women; age, 25–54 years) from the Swedish Inpatient Register, 1987–2006, who had survived 28 days after an AMI.

Outcome measures: Four-year mortality from all causes, and Standard Mortality Ratio (SMR)

Results From the first to last 5-year period, the absolute excess risk decreased from 1.38 to 0.50 and 1.53 to 0.59 per 100 person-years among men aged 25–44 and 45–54 years, respectively. Corresponding figures for women were a decrease from 2.26 to 1.17 and from 1.93 to 1.45 per 100 person-years, respectively. Trends for women were non-linear, decreasing to the same extent as those for men until the third period, then increasing. For the last 5-year period, the standardized mortality ratio for young survivors of AMI compared with the general population was 4.34 (95% confidence interval [CI]: 3.04–5.87) and 2.43 (95% CI: 2.12–2.76) for men aged 25–44 and 45–54 years, respectively, and 13.53 (95% CI: 8.36–19.93) and 6.42 (95% CI: 5.24–7.73) for women. Deaths not associated with cardiovascular causes increased from 21.5% to 44.6% in men and 41.5% to 65.9% in women, respectively.

Conclusion Young male survivors of AMI have low absolute long-term mortality rates, but these rates remain 2- to 4-fold that of the general population. After favourable development until 2001, women now have higher absolute mortality than men and a 6- to 14-fold risk of death compared with *women in the general population*.

Strengths and limitations of this study

- Population-based study, that includes all *cases* with a first AMI, aged 25-55 years, in Sweden during a period of twenty years.
- Strengths include nationwide coverage, and near-complete follow-up.
- The main limitation is that the used register does not provide data covering clinical characteristics or treatment which could have been valuable to estimate their impact on mortality.

INTRODUCTION

Survival after acute myocardial infarction (AMI) has improved during the last several decades in Sweden and elsewhere.[1-3] Nonetheless, coronary heart disease (CHD) remains a major contributor to morbidity and mortality with more than one in five men and women currently dying from CHD in Europe.[4,5] Survivors of AMI are known to have an impaired prognosis compared with the general population.[6] In a recent study *from England, the long-term* risk of death of any cause among survivors of a first AMI was twice that of the general English population of equivalent age.[7]

Most patients with AMI are elderly; accordingly, most information on long-term survival is based on patients older than 55 years. However, about one in six AMI survivors is younger than 55 years.[8] Knowledge of the prognosis among young patients with AMI is essential because younger patients stand to lose more of their remaining life years compared with older patients. This applies particularly to women because women have a longer life expectancy.

Further, younger, but not older, women hospitalized with AMI have a worse long-term prognosis than men *as shown in analyses of patient populations dating from the 1980s and 1990s.*[9,10] However, there have since been marked changes in treatment, diagnostic criteria, and post-AMI prognosis. A recent study found that reductions in long-term mortality after 1985 were at least as high for women as for men with AMI,[11] but the study did not specifically report findings for young patients. An additional study, found that reductions in mortality were similar regardless of age but that younger patients are more likely to receive evidence based care.[12]

Few data sets contain a sufficient number of young patients to reliably estimate risk of death compared with the general population. In addition, more information is needed about cause-specific mortality, because an unknown proportion of deaths may not be due to cardiovascular causes, and will thus be less amenable to coronary preventive measures. In the present study, we examined sex-specific trends in long-term survival in a register-based cohort of patients aged *25*–54 years hospitalized with a first AMI during 1987–2006, and compared death rates for men and women separately with those of the general population.

METHODS

Registries and study population

Sweden has a publicly financed health care system, with some health care facilities privately run but still fully integrated into the health care system. The Swedish National Inpatient Register (IPR), has established complete national coverage since 1987. *One study stated that* positive predictive values (PPV) differ among diagnoses in the IPR, but *are* generally 85–95%. *PPV for myocardial infarction was about 98-100% and the sensitivity was 77-91.5%.*[13] *Another validation study concluded that the accuracy of correct diagnosis in AMI was 86 % regardless (1987-1995) of age and gender.*[14] *More recent data are lacking.* Diagnoses in the IPR are coded according to the Swedish *International Classification of Diseases* (ICD) system (ICD 8th revision until 1986, 9th revision until 1996, and 10th revision thereafter). In the present study, data from the IPR and the Swedish Cause of Death Register were linked through personal identity numbers unique to each Swedish citizen. *The Cause of Death Register is based on diagnosis from death certificates. In 2008, 0.8% of death certificates were missing or insufficient (2.7%)* [15]*. Validity for a correct diagnosis of ischemic heart disease in the general population in 1995 was 87%.*[16]

The present study included all 38,836 cases (31216 men, 7620 women) in Sweden aged 25–54 years, discharged from hospital after a first AMI in 1987–2006; AMI was defined as a principal discharge code according to the ICD -8 : 410 (until 1987), ICD-9: 410 (until 1996) and ICD-10: I21 (from 1997 onward). After excluding 1,560 cases who died during the first 28 days 1169 men (3.01% of cases) median age; 50, and 391 women (1.01% of cases) median age; 49.0, 37,276 cases (7,229 women and 30,047 men) with a first AMI remained for analysis. Data from 1980 onward were used to identify first AMIs only, with a time frame of 7 years throughout, to ensure that AMIs registered each year had the same chance of being identified as a first AMI. Due to the 7-years time frame, 443 cases were recurrent AMI after seven years (53 women median age; 52, 390 men median age; 51) Criteria for a diagnosis of AMI in Sweden have followed established guidelines, changing after the adoption of new AMI criteria in the year 2000.[17,18] Thus, the characteristics of the AMIs in our analysis changed during the study period. Use of troponins became standard after the year 2000.

Comorbidities were defined by the following main or contributory discharge codes during the preceding 7 years, including the index hospitalization: diabetes (ICD-9 250; ICD-10 E10–E14), hypertension (ICD-9 401–405; ICD-10: I10–I15), valvular disease (ICD-9 394–397, 424; ICD-10 I05–I09, I34–I35), congenital heart disease (ICD-9 745–747; ICD-10 Q20–Q26), stroke (ICD-9 431–434, 436; ICD-10 I61–I64), chronic respiratory disease (ICD-9 490–496; ICD-10 J40–J47), malignancy (ICD-9 140–208; ICD-10 C00–C97), renal failure (ICD-9 584–586; ICD-10 N17–N19), coronary artery bypass grafting (3067, 3066, 3105, 3127, FNA, FNB, FNE, FNC), and percutaneous coronary intervention (3080, FNG 00, FNG 02, FNG 05).

Follow-up

We analysed 4-year all-cause mortality for four 5-year periods (1987–1991, 1992–1996, 1997–2001, and 2002–2006) through the Swedish Cause of Death Register. The following codes were used for assignment of causes of death among fatal cases: CVD, (390–459, I00–I99), ischaemic heart disease (IHD) (410–414, I20–I25, stroke (430–438, I60–I68), and all other causes (including malignancies; 140-208, C00-C97).

Statistical analysis

Statistical analyses were performed with SAS 9.3, (R version 2.15.1 to obtain the graphs). For comorbidities, $\chi 2$ tests were used to evaluate differences between men and women and for trends; a P-value of ≤ 0.05 was considered significant. To compare mean age within the respective age groups, t-tests were performed.

Standardized mortality ratios (SMR) with 95% confidence intervals (CIs) were calculated as the ratio of the observed to expected number of deaths, *for 4-year follow up by each period* ,estimated from rates in the general Swedish population, by gender, age and calendar year, using life expectancy tables from Official Statistics of Sweden (SCB).

To examine the excess mortality risk in the study population the absolute risk (AR) was calculated separately for both the general population and the study population by dividing the observed mortality with person time. This yields an average annual excess risk for each period. The absolute excess risk (AER) is the difference between the observed and the expected AR. For standardization purposes, the estimates were then multiplied by 100 person-years. The AER calculations add a useful measure of excess risk in absolute terms. Life expectancy tables from Official Statistics of Sweden (SCB) were used to calculate the expected mortality in the Swedish general population by gender, age and calendar year.

Cox proportional hazard regression, providing hazard ratios (HR) with 95% CIs, was used to estimate age, and gender-specific changes in all-cause mortality over time.[19] The first period (1987–1991) was used as reference; The *multivariable* models were adjusted for age, diabetes, hypertension, valvular and congenital heart disease, stroke, chronic respiratory disease, malignancy and renal failure. Furthermore, in the final model the periods were also tested for proportionality by interactions of age, time and with significant comorbidities only (men 45-54; malignancies, women, 45-54; chronic respiratory disease).

The Kaplan-Meier method was used to estimate the survival probability. The proportionality assumption of Cox regression was tested by including interactions between covariates (age, *gender,* and period) with time; neither interaction test was statistically significant.[20] A log-rank test was conducted to study changes in survival between the time periods.

RESULTS

Of the 37,276 cases in the study, 7,905 (21.2%) were aged 25–44 years (19.6% women) and 29,371 (78.8%) were aged 44–54 years (19.3% women). Other than diabetes and hypertension (11% for both), this population had few diagnosed comorbidities (Table 1). Women had more diabetes, hypertension, chronic lower respiratory disease and malignancies than did men ($P < 0.0001$).

Table 1. Baseline characteristics in 37,276 men and women aged <55 years with a first AMI, 1987–2006

	All	Men	Women	P-value

Number of cases	37 276	30 047	7 229	
Age 25-44, n (%)	7 905 (21.2)	6 357 (21.2)	1 548 (21.4)	
Mean age (SD)		40.21 (3.74)	39.84 (4.04)	0.055
Age 44-54, n (%)	29 371(78.8)	23 690 (78.8)	5 681 (78.6)	
Mean age (SD)		50.31 (2.75)	50.39 (2.76)	0.0549
Diabetes, n (%)	4 064 (10.9)	3 017 (10.0)	1 047 (14.5)	<0.0001
Hypertension, n (%)	4110 (11.0)	3141 (10.6)	969 (13.4)	<0.0001
Valvular disease, n (%)	287 (0.77)	211 (0.70)	76 (1.05)	0.0023
Congenital heart disease	36 (0.10)	23 (0.08)	13 (0.18)	0.0111
Stroke, n (%)	412 (1.11)	302 (1.01)	110 (1.52)	0.0002
Chronic lower respiratory disease, n (%)	557(1.49)	368 (1.22)	189 (2.61)	<0.0001
Malignancy, n (%)	354 (0.95)	255 (0.85)	99 (1.37)	<0.0001
Renal failure	230 (0.62)	164 (0.55)	66 (0.91)	0.0003
CABG*, n (%)	253 (0.68)	221 (0.74)	32 (0.44)	0.007
PCI*, n (%)	235 (0.63)	198 (0.66)	37 (0.51)	0.16

*Procedures dating at least 6 months prior to hospitalization for AMI

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

Supplementary Table 1 shows the comorbidities for each 4-year period. All comorbidities except for congenital heart diseases increased significantly over time. Diabetes and hypertension were the most prevalent comorbidities in both men and women but the rates of other comorbidities remained low even in the last period (<4%).

During the study period (1987-2006) annual rate per 100.000 population in men and women aged 25-54 years surviving a first AMI for at least 28 days decreased from 92.3 per 100.000 in 1987 to 72.1 in 2006 (Figure 1). Women, on the other hand, showed a different pattern with an increase from 17.4 per 100.000 in 1987 to 22.3 in 2006 (p for men <0.0001, for women 0.0003).

Survival in men improved continuously over the four 5-year periods (Figure *2*), while the prognosis in women improved until the third period *(1997-2001),* then reverted to a *risk* nearly identical to that in the second period (Figure *3*).

Table *2* shows mortality by sex, age group, and period. For men aged 25–44 years, the annual excess risk of dying decreased continuously from 1.38 to 0.50 deaths per 100 person-years from the first to last period, with an SMR of 4.34 (95% CI: 3.04–5.87) during the last 5-year period. Corresponding figures for men aged 45–54 were a decrease from 1.53 to 0.59 with *a* SMR of 2.43 (95% CI: 2.12–2.76) in the last period (2002–2006). Women displayed more complicated trends, starting from higher absolute risks of dying compared with men, decreasing sharply until a nadir in 1997–2001, and then increasing to 1.17 and 1.45 deaths per 100 person-years in women aged 25–44 and 45–54, respectively, in the last period. This was more than twice the risk in men of the corresponding age groups. Very high SMRs were noted, particularly for the youngest women, at 13.53 (95% CI: 8.36–19.93) in the last period and 6.42 (5.24–7.73) in women aged 45–54 years.

In men aged 25–44 years, the mortality risk decreased by 70% during the study period (multivariable adjusted HR: 0.30, 95% CI: 0.20–0.44). A similar decrease was seen in men aged 45–54 years (multivariable adjusted HR: 0.32, 95% CI: 0.27–0.38). Women aged 25–44

years had an overall decline in mortality risk of approximately 50% (multivariable adjusted HR: 0.47, 95% CI: 0.27–0.83). No significant decrease in mortality risk in the last, compared with the first period was observed in women aged 45–54 years (age-adjusted HR: 0.77, 95% CI: 0.59–1.02), but after adjustment for comorbidities there was a significant decrease in risk (HR: 0.53, 95% CI: 0.39–0.71).

Table 2. Observed versus expected mortality ratio, estimated over 4 years, standardized mortality ratio, absolute risk, absolute excess risk, and hazard ratio for mortality by age group and period among 37,276 men and women aged <55 years with a first AMI.

Age, Period	Observed[a]	Expected[b]	SMR (95% CI)	AR[c]	AER[d]	HR (95% CI)[e]	HR (95% CI)[f]
Men 25-44							
1987-1991	113	16	6.88 (5.67–8.20)	1.61	1.38	1.0 (ref)	1.0 (ref)
1992-1996	81	13	6.16 (4.89–7.57)	1.25	1.05	0.76 (0.57–1.01)	0.73 (0.55–0.98)
1997-2001	58	10	5.70 (4.33–7.27)	1.00	0.83	0.60 (0.43–0.82)	0.53 (0.38–0.73)
2002-2006	36	8	4.34 (3.04–5.87)	0.65	0.50	0.41(0.28–0.60)	0.30 (0.20–0.44)
Men 45-54							
1987-1991	465	125	3.72 (3.39–4.07)	2.10	1.53	1.0 (ref)	1.0 (ref)[g]
1992-1996	379	119	3.20 (2.88–3.53)	1.56	1.07	0.74 (0.65–0.85)	0.70 (0.61–0.81)

1997-2001	289	108	2.69 (2.39–3.00)	1.22	0.77	0.57 (0.49–0.66)	0.50 (0.43–0.58)
2002-2006	215	89	2.43 (2.12–2.76)	0.99	0.59	0.47 (0.40–0.56)	0.32 (0.27–0.39)
Women 25-44							
1987-1991	34	2	17.55 (12.15–23.94)	2.39	2.26	1.0 (ref)	1.0 (ref)
1992-1996	28	2	17.99 (11.95–25.27)	2.17	2.05	0.93 (0.56–1.55)	0.85 (0.51–1.42)
1997-2001	10	2	6.07 (2.89–10.42)	0.63	0.52	0.27 (0.13–0.55)	0.28 (0.14–0.56)
2002-2006	21	2	13.53 (8.36–19.93)	1.26	1.17	0.55 (0.32–0.94)	0.47(0.27–0.83)
Women 45-54							
1987-1991	101	15	6.90 (5.62–8.31)	2.25	1.93	1.0 (ref)	1.0 (ref) [h]
1992-1996	76	16	4.63 (3.65–5.73)	1.45	1.14	0.64 (0.48–0.87)	0.56 (0.42–0.76)
1997-2001	68	19	3.58 (2.78–4.48)	1.08	0.78	0.49 (0.36–0.66)	0.44 (0.32–0.60)
2002-2006	102	16	6.42 (5.24–7.73)	1.72	1.45	0.77 (0.59–1.02)	0.53 (0.39–0.71)

[a]Observed number of deaths in the study population, [b]Expected number of deaths in the general population, [c]*Absolute risk per 100 person-years,* [d]*Absolute excess risk per 100 person-years,* [e] Age adjusted, [f] Multiadjusted for age, diabetes, hypertension, valvular, congenital heart disease, stroke, chronical respiratory disease, malignancy and renal failure. Adjusted for changes and interaction over time, malignancy ([g]), chronic respiratory disease ([h]).

AMI, acute myocardial infarction; SMR, standardized mortality ratio; AR, absolute risk; AER, absolute excess risk; HR, hazard ratio; CI, confidence interval

Table 3 shows causes of death for the 2,076 deaths that occurred within 4 years in this cohort. In 1987–1991, 74,8% of all deaths within 4 years were due to CVD (78.6% for men and 58.5% for women) *with a majority to IHD.* However, during the last period *(2002-2006),* only 48.4% of all deaths were due to CVD (55.4% for men and, notably, only 34.1% for women)

Table 3: Cause of death by period for 2,076 deaths within 4 years among men and women aged <55 years with a first AMI during 1987–2006

Cause of death	Total	Men	Women	p-value
	n (%)	n (%)	n (%)	
1987-1991	713	578 (81.1)	135 (18.9)	
CVD	533(74.8)	454(78.6)	79 (58.5)	<.0001
IHD	481 (67.5)	405 (70.1)	76 (56.3)	0.0021
Stroke	18 (2.52)	16(2.77)	2 (1.48)	0.3909
All other causes	180 (25.3)	124 (21.5)	56 (41.5)	<.0001
Malignancies	55 (7.71)	39 (6.75)	16 (11.9)	0.0454
1992-1996	564	460 (81.6)	104 (18.4)	
CVD	369 (65.4)	318 (69.1)	51 (49.0)	<.0001
IHD	337 (59.8)	295 (64.1)	42 (40.4)	<.0001
Stroke	6 (1.06)	5 (1.09)	1 (0.96)	0.9104
All other causes	195 (34.6)	142 (30.9)	53 (51.0)	<.0001
Malignancies	79 (14.01)	57 (12.4)	22 (21.2)	0.0201
1997-2001	425	347 (81.7)	78 (18.4)	
CVD	242 (56.9)	205 (59.1)	37 (47.4)	0.0606
IHD	216 (50.8)	182 (52.5)	34 (43.6)	0.1573

Stroke	5 (1.18)	3 (0.86)	2 (2.56)	0.2084
All other causes	183 (43.1)	142 (40.9)	41 (52.6)	0.0606
Malignancies	63 (14.8)	52(15.0)	11 (14.1)	0.8428
2002-2006	374	251 (67.1)	123 (32.9)	
CVD	181 (48.4)	139 (55.4)	42 (34.1)	0.0001
IHD	145 (38.8)	116 (46.2)	29 (23.6)	<0.0001
Stroke	12 (3.21)	7 (2.79)	5 (4.07)	0.5106
All other causes	193 (51.6)	112 (44.6)	81(65.9)	0.00001
Malignancies	60 (16.0)	28 (11.2)	32 (26.0)	0.0002

AMI, acute myocardial infarction; IHD, ischaemic heart disease; CVD, cardiovascular disease

DISCUSSION

The present study showed that young male survivors of AMI have low absolute long-term mortality rates; however, these rates remain between 2- and 4-fold those of the general population. After a favourable development in younger women until 2001, when new criteria for AMI were adopted and troponins became standard, women had higher absolute mortality than men in the last period and showed a dramatically higher risk of death than healthy women. However, fewer than half of all deaths in women were due to CVD in the last period.

Few studies have specifically investigated long-term outcomes in young patients with AMI. One Swedish study based on the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA)[21] investigated all consecutive patients younger than 46 years treated for ST-elevation myocardial infarction (STEMI) in Sweden, 1995–2006 (1,748 men, 384 women). Long-term annual mortality was around 1% with no difference

between men and women, similar to our study. Accordingly, in absolute terms and consistent with prior publications from our group,[1] annual mortality rates in AMI survivors younger than 55 years are estimated at about 1%. This is in contrast to older patients in Sweden, among whom annual mortality rates are about 6% for those aged 65–74 years and more than 12% among patients aged 75–84 years).[1] The current low absolute mortality figures are a vast improvement on prior estimates. In a retrospective analysis of 23 published studies from the prethrombolytic era, the annual death rate after the first year in patients with a first AMI was 5% regardless of age or gender.[22] In the late 1980s, the annual mortality for patients younger than 55 years was about 2%.[1]

There are several reasons for the observed decrease in mortality in younger patients with AMI. First, several pharmacological and coronary interventions were developed and implemented during the study period. Nauta et al 2013 showed that patient <55 received evidence-based medical care and reperfusion to a greater extent than elderly patients.[12] Second, some of the decrease is likely due to changes in diagnostic criteria during the study period, as well as more sensitive methods.[17,23] This may imply that less severe AMIs are detected, with improved survival, but less specificity, as evidenced by increased comorbidities over time and a higher proportion of non-CVD deaths in the last period. Third, there have been changes in clinical presentation, with less severe infarctions,[24,25] and fewer STEMIs.[26] Factors that affect the risk of developing STEMI rather than non-STEMI include smoking[26] and cardioprotective medications that lower the risk.[27] Declining smoking rates and more medications used in primary prevention could thus have contributed to milder infarctions and better survival. Comorbidities increased during the study period. However, this can probably *at least partly* be derived to improvements in clinical reporting *due to financial incitements.* [13]

The striking increase in hypertension can also probably be attributed to changes in criteria and guidelines management by the WHO.[28]

There was a continuous decrease in case fatality among men; however, rates in women did not follow the same pattern as in men. Mortality in women decreased until the third period and then increased during the fourth period *to nearly* the same level as in the second period. This may have been due to chance because the numbers were limited. However, it could also reflect differences in diagnostics. With increasing use of troponins, the rate of detection has increased, and this effect could be stronger for women than for men. In a study that simultaneously measured CK-MB and troponin,[29] a 64% and 95% increase in the AMI rate among men and women, respectively, was observed when using troponins. Accordingly, the increasing mortality among women hospitalized in 2002–2006 could be due to the capture of other and more complicated types of myocardial damage because an increase in troponin levels is also seen in other conditions.[30] Even so, comorbidities, although increasing over time, were still low in the most recent period. *Since the most marked change between the third and the fourth period of our study was the change from CK-MB to troponins as the predominant marker for myocardial damage, we speculate that the additional AMIs captured by this more sensitive method are clinically different, not only in being smaller but also to an unknown extent reflecting myocardial damage not due to atherosclerotic disease. Circumstantial evidence for this might be derived from the increasing and much higher proportion of non-CVD deaths, as well as more comorbidities, in women compared to men over the study period. In the present study the results showed an increased rate of survivors but a decreasing trend in death in CVD among young women. These results strengthen that the increased all-cause mortality is likely a result of a combination between the use of troponin and increasing comorbidities.*

Few studies have compared mortality rates in young patients with AMI with those in the general population. A record linkage of hospital and mortality data identified 387,452 individuals in England, hospitalized with a main diagnosis of AMI in 2004–2010 and who survived at least 30 days.[7] Long-term risk of death of any cause among survivors of a first AMI was twice that in the English general population of equivalent age, highest among younger patients aged 55–64 years (about 2- to 3-fold for men and women, respectively), and approached the mortality rate of the general population for those aged 85 years or more. *Estimates for individuals younger than 55 years were not stated in the study by Smolina, et al., but we have since been provided with information that mortality ratios were 2.6 for men and 5.6 for women aged 30-54 years after 4 years, which is more or less comparable to our findings (Smolina K, personal communication).* For the period corresponding to that in the study by Smolina et al.[7] we found mortality ratios of 4.3 and 2.4 for men aged 25–44 and 45–54 years, respectively. For women aged 25–44 years, the estimated mortality ratio was 13.5, but this was based on very few cases (about four deaths per year). The estimate of 6.4 for women aged 45–54 years should be more reliable. It should be noted that women in the general population in this age range have very low mortality rates, which partially explains the high SMRs in women.

The main limitation in the present study is the reliance on administrative registers with no details of *changes in several* characteristics, such as biomarkers, electrocardiographic findings, smoking, medication, hyperlipidemia, family history, *ethnicity and socioeconomic status* and a lack of other clinical information, notably hospital treatment and clinical presentation. Also, we were unable to apply uniform criteria for diagnosis over time. *This limits considerably the interpretation that can be made, h*owever, the findings should be

applicable to current patients with AMI in an industrialized modern country. The quality of the data is obviously of fundamental importance, but validation studies of the IPR indicate reasonable accuracy.[13,14] Incorrect death certificates could lead to uncertainty with respect to attributing cause of death[15], but IHD diagnoses has been estimated to be correct in 87% *for ischemic heart disease* although the data from this study were collected two decades ago. [16] *The causes of death are also considered to be more reliable for the younger population than for the elderly population.* [15]

The strengths of the study include nationwide coverage with virtually no loss to follow-up and the large sample size. Given the low mortality in absolute terms, larger populations are needed, particularly for women, because they constitute less than 20% of the AMI population younger than 55 years.

Conclusions

These data extend and update what is currently known about sex-specific absolute and relative survival in patients with AMI younger than 55 years, with a large population of more than 35,000 cases during a 20-year period. Among patients surviving for 28 days after AMI, the annual mortality rates are now comparatively low at approximately 1%. Given the much lower mortality in this age group in the general population, young survivors of AMI, particularly women, remain at a much higher risk of death, much of this, however, due to non-CVD causes. Accordingly, while mortality is low in absolute terms, younger women with AMI lose the survival advantage women normally have over men. Additional strategies to bring mortality closer to that which would be expected for this age group are needed, in particular for women.

Contributors

Study concept, design: SN, AR, LB, JB, KWG. Analysis and interpretation of data: SN, TZS, AR, LB, JB, KWG. Drafting and revised the manuscript: SN, LB, JB, KWG, TZS, KF, SM, AR. Critical revision of the final version of the manuscript: all authors. SN, LB, JB, KWG, TZS, KF, SM, AR. Guarantor: AR

Funding

This work was supported by the Swedish Research Council [grant number VR 521-2010-2984]; the Swedish Heart-Lung Foundation [grant number 2012-0325]; and the Swedish Council for Working Life and Social Research [grant number Epilife 2006-1506], the VGR region and the Swedish state under the ALF-LUA agreement.

Competing interests:

None declared.

Ethical approval

All personal identifiers were removed and replaced with a sequential number in the final data set. The protocol was approved by the regional Ethics Board of Gothenburg.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

REFERENCES

1. Dudas K, Lappas G, Rosengren A. Long-term prognosis after hospital admission for acute myocardial infarction from 1987 to 2006. *Int J Cardiol* 2012;**155**:400-405.

2. Langorgen J, Igland J, Vollset SE, *et al*. Short-term and long-term case fatality in 11 878 patients hospitalized with a first acute myocardial infarction, 1979-2001: the Western Norway cardiovascular registry. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:621-627.

3. Hardoon SL, Whincup PH, Petersen I, *et al*. Trends in longer-term survival following an acute myocardial infarction and prescribing of evidenced-based medications in primary care in the UK from 1991: a longitudinal population-based study. *J Epidemiol Community Health* 2011;**65**:770-774.

4. Rayner M, Allender S, Scarborough P. Cardiovascular disease in Europe. *Eur J Cardiovasc Prev Rehabil* 2009;**16 Suppl 2**:S43-S47.

5. Nichols MTN, Scarborough P, Luengo-Fernandez R, *et al*. *European Cardiovascular Disease Statistics 2012*. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis; 2012.

6. Fagring AJ, Lappas G, Kjellgren KI, *et.al.* Twenty-year trends in incidence and 1-year mortality in Swedish patients hospitalised with non-AMI chest pain. Data from 1987-2006 from the Swedish hospital and death registries. *Heart* 2010;**96**:1043-1049.

7. Smolina K, Wright FL, Rayner M, *et al*. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. *Circ Cardiovasc Qual Outcomes* 2012;**5**:532-540.

8. Gale CP, Cattle B, Woolston A,*et al*. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. *Eur Heart J* 2012;**33**:630-639.

9. Rosengren A, Spetz CL, Koster M, *et al*. Sex differences in survival after myocardial infarction in Sweden; data from the Swedish National Acute Myocardial Infarction Register. *Eur Heart J* 2001;**22**:314-322.

10. Vaccarino V, Krumholz HM, Yarzebski J, *et al*. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;**134**:173-181.

11. Nauta ST, Deckers JW, van Domburg RT,*et al*. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. *Circulation* 2012;**126**:2184-2189.

12 Nauta ST, Decker JW, Akkerhuis KM, *et al*. Age-dependent care and long-term (20 year) mortality of 14,434 myocardial infarction patients: Changes from 1985 to 2008. *Int. J Cardiol* 2013;**167**:693-697

13. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.

14. Hammar N, Alfredsson L, Rosen M, *et al*. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. *Int J Epidemiol* 2001;**30 Suppl 1**:S30-S34.

15 Swedish National Board of Health and Welfare, Cause of death statistics - history, production methods and reliability. 2010. *(In Swedish)* http://www.socialstyrelsen.se/publikationer2010/2010-4-33 (Accessed 16 sept 2013)

16. Johansson LA, Björkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995. *J Clin Epidemiol* 2009;62:1202-1209

17. Alpert JS, Thygesen K, Antman E, *et al*. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of

Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;**36**:959-969.

18. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, *et al*. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;**90**:583-612.
19. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol* 1972;**34**:187-220.
20. Allison PD. *Survival Analysis Using SAS: A Practical Guide*. Cary, NC: SAS Institute; 2010.
21. Lawesson SS, Stenestrand U, Lagerqvist B, *et al*. Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST-elevation myocardial infarction. *Heart* 2010;**96**:453-459.
22. Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. *Arch Intern Med* 2002;**162**:2405-2410.
23. Parikh NI, Gona P, Larson MG, *et al*. Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart study. *Circulation* 2009;**119**:1203-1210.
24. Myerson M, Coady S, Taylor H, *et al*. Declining severity of myocardial infarction from 1987 to 2002: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2009;**119**:503-514.
25. Goff DC Jr, Howard G, Wang CH, *et al*. Trends in severity of hospitalized myocardial infarction: the atherosclerosis risk in communities (ARIC) study, 1987-1994. *Am Heart J* 2000;**139**:874-880.

26. Bjorck L, Rosengren A, Wallentin L, *et al*. Smoking in relation to ST-segment elevation acute myocardial infarction: findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions. *Heart* 2009;**95**:1006-1011.

27. Bjorck L, Wallentin L, Stenestrand U, *et al*. Medication in relation to ST-segment elevation myocardial infarction in patients with a first myocardial infarction: Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). *Arch Intern Med* 2010;**170**:1375-1381.

28. World Health Organization, international Society of hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-1992

*29 Luepker RV, Duval S, Jacobs DR Jr, et al. The effect of changing diagnostic algorithms on acute myocardial infarction rates. Ann Epidemiol 2011;**21**:824-829.*

30. Meier MA, Al-Badr WH, Cooper JV, *et al*. The new definition of myocardial infarction: diagnostic and prognostic implications in patients with acute coronary syndromes. *Arch Intern Med* 2002;**162**:1585-1589.

FIGURE LEGENDS

Figure 1 Annual rate per 100.000 population in men and women aged 25-54 years surviving a first AMI for at least 28 days.

Figure *2* Four-year trend in survival probability by period and time among men (n 30 047) aged 25–54 years with a first AMI

Figure *3* Four-year trend in survival probability by period and time among women (n 7 229) aged 25–54 years with a first AMI

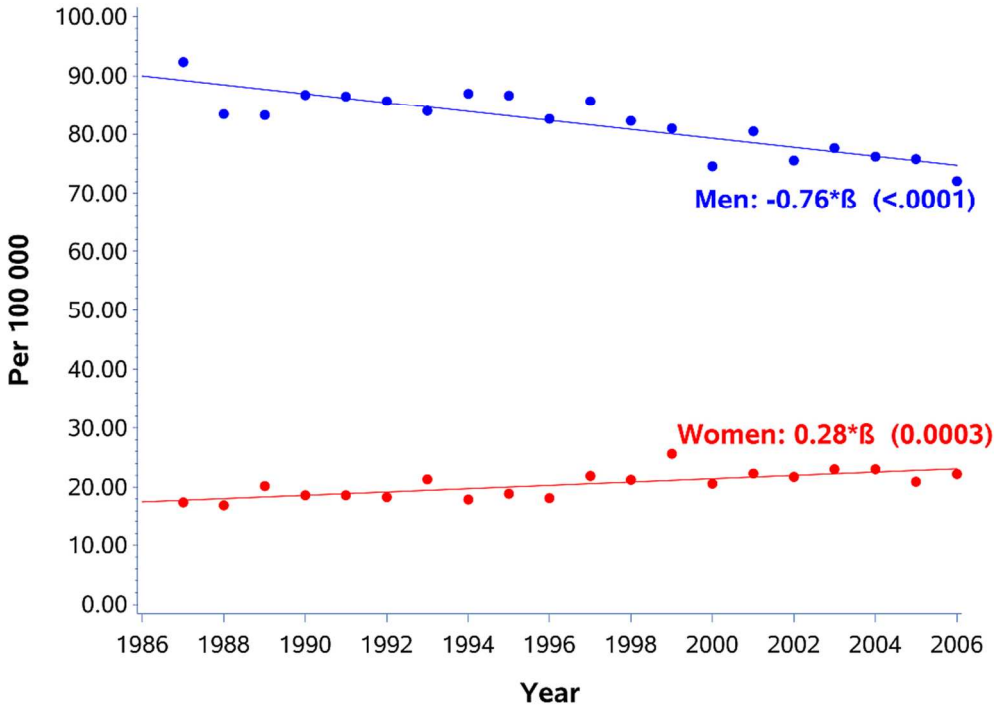


Figure 1 Annual rate per 100.000 population in men and women aged 25-54 years surviving a first AMI for at least 28 days.
90x64mm (300 x 300 DPI)

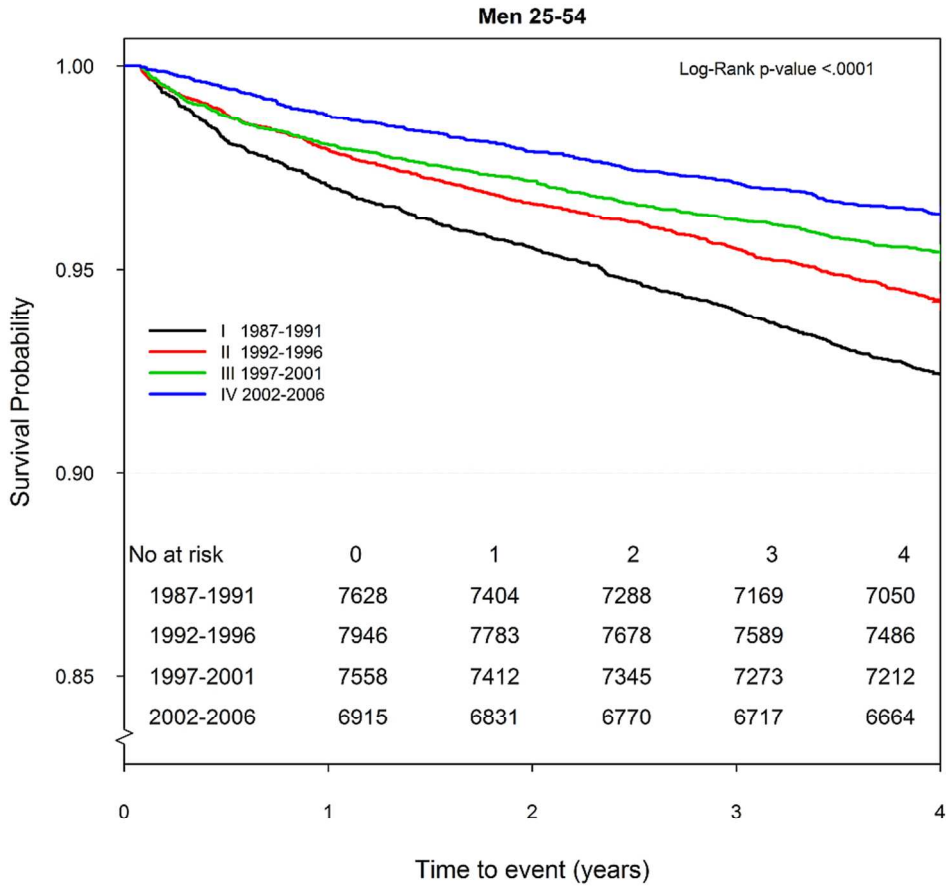


Figure 2 Four-year trend in survival probability by period and time among men (n 30 047) aged 25–54 years with a first AMI
90x90mm (300 x 300 DPI)

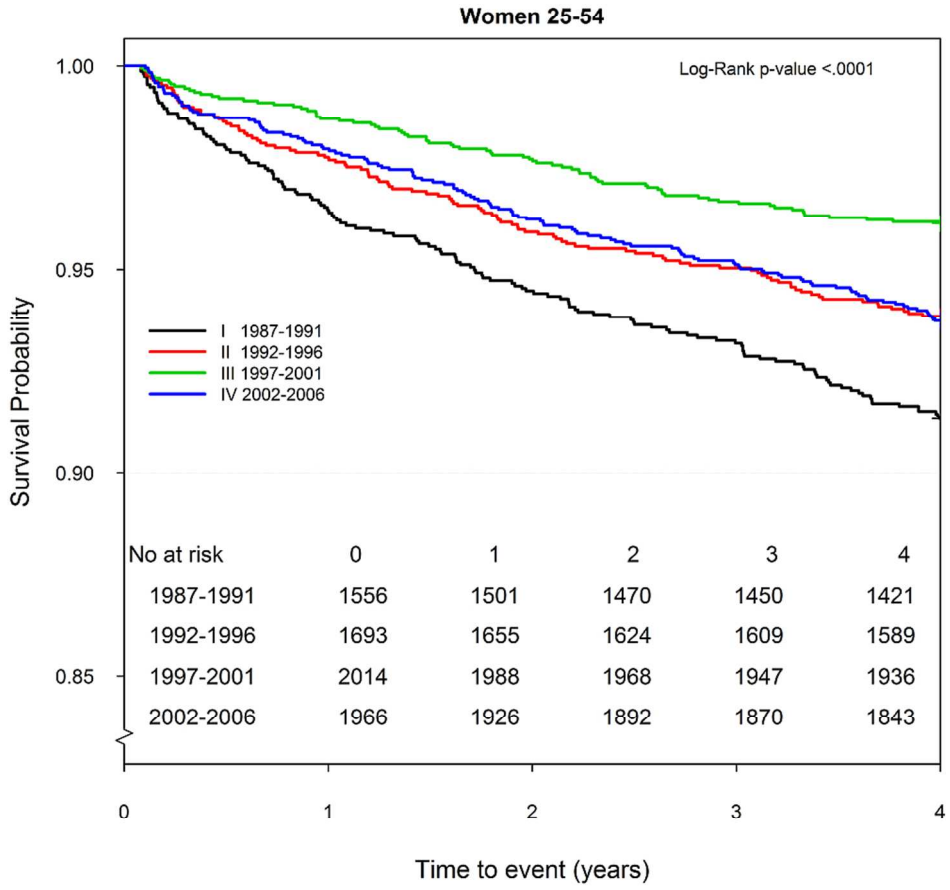


Figure 3 Four-year trend in survival probability by period and time among women (n 7 229) aged 25–54 years with a first AMI
90x90mm (300 x 300 DPI)

Supplemental Table 1: Baseline characteristics by period among 37,276 men and women with a first AMI, 1987–2006

		1987-1991	1992-1996	1997-2001	2002-2006	p for trend
Number of cases	Men	7628 (83.1)	7946 (82.4)	7558 (79.0)	6915 (77.9)	
Number of cases	Women	1556 (16.9)	1693 (17.6)	2014 (21.0)	1966 (22.1)	
Diabetes	Men	542 (7.11)	728 (9.16)	814 (10.8)	933 (13.5)	<.0001
	Women	200 (12.9)	244 (14.4)	276 (13.7)	327 (16.6)	0.0043
Hypertension	Men	451 (5.91)	655 (8.24)	807 (10.7)	1228 (17.8)	<.0001
	Women	106 (6.81)	188 (11.1)	252 (12.5)	423 (21.52)	<.0001
Valvular disease	Men	35 (0.47)	34 (0.43)	53 (0.70)	89 (1.29)	<.0001
	Women	11 (0.71)	16 (0.95)	17 (0.84)	32 (1.63)	0.0125
Congenital heart disease	Men	7 (0.09)	1 (0.01)	6 (0.08)	9 (0.13)	0.2212
	Women	1 (0.06)	3 (0.18)	4 (0.20)	5 (0.25)	0.1981
Stroke	Men	36 (0.47)	52 (0.65)	40 (0.53)	174 (2.52)	<.0001
	Women	10 (0.64)	18 (1.06)	21 (1.04)	61 (3.10)	<.0001
Chronic lower resp disease	Men	61 (0.80)	77 (0.97)	86 (1.14)	144 (2.08)	<.0001
	Women	26 (1.67)	41 (2.42)	46 (2.28)	76 (3.87)	0.0001

Malignancy	Men	11 (0.14)	24 (0.30)	55 (0.73)	165 (2.39)	<.0001
	Women	10 (0.64)	17 (1.00)	14 (0.70)	58 (2.95)	<.0001
Renal failure	Men	7 (0.09)	25 (0.31)	47 (0.62)	85 (1.23)	<.0001
	Women	3 (0.19)	15 (0.89)	13 (0.65)	35 (1.78)	<.0001

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract Title: Sex-specific trends in survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. Prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Please see page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Please see page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses Please see page 5
Methods		
Study design	4	Present key elements of study design early in the paper Please see page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Please see page 5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Please see page 5-6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls N/A *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed N/A

		Case-control study—For matched studies, give matching criteria and the number of controls per case N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Please see page 5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Please see page 5-6
Bias	9	Describe any efforts to address potential sources of bias N/A
Study size	10	Explain how the study size was arrived at N/A. All patients in Sweden in the relevant age group were included.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Please see page 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Please see page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions Please see page 7-8
		(*c*) Explain how missing data were addressed N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Loss to follow-up negligible *Case-control study*—If applicable, explain how matching of cases and controls was addressed N/A *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy N/A
		(*e*) Describe any sensitivity analyses N/A

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Please see page 5
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Please see page 5-6
		(b) Indicate number of participants with missing data for each variable of interest N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) Please see page 6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Please see Table 2 and 3 , and page 15.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure N/A
		Cross-sectional study—Report numbers of outcome events or summary measures N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Please see Table 2 and 3, and statistical methods.
		(*b*) Report category boundaries when continuous variables were categorized Done
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Please see Tables 2 and 3.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity

		analyses Please see page 15
Discussion		
Key results	18	Summarise key results with reference to study objectives Please see page 15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Please see page 18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Please see page 15-19
Generalisability	21	Discuss the generalisability (external validity) of the study results Please see page 18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Please see page 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.