Time trends in STEMI - improved treatment and outcome but still a gender gap: A prospective, observational cohort study from the SWEDEHEART register

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Time trends in STEMI - improved treatment and outcome but still a gender gap

A prospective, observational cohort study from the SWEDEHEART register

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Sofia Sederholm Lawesson has substantially contributed to conception and design of the study. She has handled, analysed and interpreted all the data and drafted the article.

Joakim Alfredsson has substantially contributed to conception and design, help with analyses and interpretation of the data. He has revised the draft critically for important intellectual content and approved the final version to be published.

Mats Fredrikson has substantially contributed with analysing and interpreting the data, revising the draft critically and approved the final version to be published.

Eva Swahn has substantially contributed to conception and design, help with analysing and interpreting the data. She revised the draft critically for important intellectual content and approved the final version to be published.

Summary

Article focus:

With 1) the focus on treatment guidelines, 2) the attention on gender differences in management and outcome and 3) the change in reperfusion strategy in STEMI the last decade, we hypothesised;

- That gender differences in adherence to treatment guidelines would have diminished
- That gender differences in outcome would have decreased

Key messages:

- Management improved and mortality decreased in STEMI patients in the late compared to the early period.
- The gender treatment gap did not decrease between the two time periods.
- The gender outcome gap did not decrease between the two time periods.

Strengths and limitations:

The study included a huge amount of STEMI patients, with enough numbers to assure adequate statistical analyses. SWEDEHEART registry is a unique Swedish National Quality registry, with quality control and audit measures, covering all hospitals in Sweden treating STEMI patients and has standardised criteria for defining MI. Mortality data are complete as the vital status of all Swedish citizens is registered in the Cause of Death Registry. One limitation is the nonrandomised, observational nature. Thus multivariate analyses were used in order to reduce the bias inherent in this type of studies. Adjustments might be influenced by the lack of registration on some possible confounding factors in the data base e.g. non-cardiac co-morbidities and contra-indications for specific treatments.

Abstract

Objective: In ST-elevation myocardial infarction [STEMI] women received less evidence-based medicine [EBM] and had worse outcome during the fibrinolytic era. With the shift to primary percutaneous coronary intervention [pPCI] as preferred reperfusion strategy, we aimed to investigate whether these gender differences has diminished.

Design, setting and patients: Cohort study including consecutive STEMI patients registered 1998 – 2000 (n=15697) and 2004 – 2006 (n=14380) in the Register of Information and Knowledge about Swedish Heart Intensive care Admissions.
Main outcome measures: EBM use, in-hospital and one year mortality.

Results: Reperfusion therapy (pPCI in 9 vs. 68%, early vs. late period) was given to 63 vs. 71% and 64 vs. 75%, women vs. men in the two respective periods, OR 0.86 (95% CI 0.78 – 0.94) and 0.80 (0.73 – 0.89) after multivariable adjustments. In the late period women had 14 – 25% less chance of receiving EBM at discharge (OR 0.75, 95% CI 0.68 – 0.81 thru 0.86, 0.77 – 0.95). Gender differences in the early period were small. In both periods, multivariable adjusted in-hospital mortality was higher in women, OR 1.17 (95% CI 1.02 – 1.14) and 1.21 (1.00 – 1.46). One year mortality was gender equal, HR 0.95 (95% CI 0.87– 1.05) and 0.96 (0.86 – 1.08), after adding EBM to the multivariable adjustments.

Conclusion: In spite of an intense gender debate, focus on guideline adherence and the change in reperfusion strategy the last decade gender differences in use of reperfusion therapy and evidence-based therapy at discharge did not decline during the study period. Moreover, higher mortality in women persisted.

INTRODUCTION

Numerous studies have shown excess mortality in women after myocardial infarction [MI][1, 2] but ST-elevation MI [STEMI] has seldom been separated from non-ST elevation acute coronary syndromes [NSTEACS].[1, 3] Women have been treated less intensively than men [4, 5] with less reperfusion therapy in the STEMI group.[5] Whereas some have found small gender differences in treatment not affecting mortality after MI [3] others have attributed part of the gender gap in outcome to a treatment bias.[1] Higher risk of death and bleeding in women is shown in many fibrinolytic trials. [2, 6] There is less firm evidence that female gender is an independent risk factor for adverse outcome after primary percutaneous coronary intervention [pPCI] which seems to be a better reperfusion strategy for women in particular.[7, 8, 9, 10] Since 2002/2003 there are separate ESC guidelines for STEMI and NSTE ACS recommending pPCI as the preferred reperfusion strategy in STEMI.[11, 12] With the last decade's awareness and debate about ACS from a gender perspective, the focus on adherence to treatment guidelines, and the shift to a reperfusion strategy, we hypothesised that the previously noticed gender differences in STEMI management would have decreased and thus also the gender gap in mortality, especially in the early phase.

Our aim was to evaluate gender differences in management and outcome in STEMI patients in two time periods with different dominating reperfusion strategies, i.e. fibrinolytics and primary PCI, respectively.

METHODS

Patients

Data for this study came from the prospective observational Register of Information and Knowledge about Swedish Heart Intensive care Admissions [RIKS-HIA], since 2009 merged with the Swedish Coronary Angiography and Angioplasty Registry [SCAAR], the Swedish Heart Surgery Registry and the National Registry of Secondary Prevention [SEPHIA] together forming the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies [SWEDEHEART].[13] RIKS-HIA contains information about all patients admitted to coronary care units [CCU] of the participating hospitals in Sweden (95% of the CCUs in Sweden year 2004). Variables including age, sex, smoking habits, co-morbidity, delay-times, symptoms, biochemical markers, results from cardiac investigations, complications, revascularisation procedures, therapies, discharge diagnoses and outcomes during the hospital stay are continuously recorded on-line over the internet. The criteria for the MI diagnosis were standardised and identical for all participating hospitals.[14, 15] The RIKS-HIA register has a continuous internal and external validation of data. The internet-based program for data input has interactive instructions, manuals, definitions and help functions and a number of compulsory variables and inbuilt validity controls. An independent monitor travels to 20 hospitals annually and in each hospital 30 randomly chosen patients in the database are compared with the hospital records. For example year 2005, 95.2% and 2006, 96.5% of the registry input showed agreement with the hospital records.

From the National Cause of Death Register information was available about cause of death and vital status of all Swedish citizens until 31st of December 2007. Regarding co-morbidity, data on previous diagnoses of diabetes, hypertension, MI and previous revascularisation procedures were taken from RIKS-HIA, SCAAR and the Swedish Heart Surgery Registry, which were merged. Previous history of co-morbidities such as chronic obstructive pulmonary disease [COPD], heart failure, chronic kidney disease [CKD], peripheral artery disease [PAD], dementia and cancer was obtained from the National Patient Register, including patients hospitalised in Sweden since 1987. Information on previous history of heart failure or stroke was taken both from RIKSHIA and the National Patient Register. A patient was coded as having the diagnosis if he/she had the diagnosis in either of these registries.

Between 1st January 1995 until 31st December 2006, 54146 patients were admitted to participating CCUs with the first registry recorded diagnosis of STEMI, defined as ST-elevation on admission ECG and a diagnosis of acute MI at discharge. Patients with pacemaker/unknown/unspecified rhythm or bundle branch block on admission were excluded. Two time periods with different dominating reperfusion strategies were chosen (Figure 1); patients admitted 1st of January 1998 until 31st of December 2000 (the early period) and patients admitted 1st of January 2004 until 31st of December 2006 (the late period). The groups were compared and gender comparisons were done in both groups.

Statistical analyses

Continuous variables were summarised by their mean and standard deviation or median and interquartile range as appropriate. Categorical variables were summarised by counts and percentages. Comparisons between different strata were performed by chi-square tests for categorical variables and by student t-tests or Mann Whitney tests for continuous variables. P-values < 0.05 were considered to indicate statistical significance.

Crude, age- and multivariable adjusted odds ratios with 95% confidence intervals were calculated from logistic regression analyses in order to compare the genders regarding use of cardiac procedures, evidence based therapies at discharge and in-hospital mortality. In addition to sex and age, the multivariable adjusted analyses included smoking, previous MI, PCI, coronary artery bypass grafting [CABG], stroke, hypertension, diabetes mellitus, COPD, heart failure, CKD, PAD, dementia, cancer within 3 years, therapies on arrival, interventional hospital and year of inclusion. Regarding use of coronary angiography, reperfusion therapy and in-hospital mortality we also added Killip class on arrival and symptom-to-door time (as a continuous variable in one hour intervals) to the multivariable adjusted analyses. Data from the logistic regression analyses are shown in forest plots.

Hazard ratios with 95% confidence intervals were calculated from Cox proportional hazard regression analyses in order to compare the genders regarding cumulative one year mortality. The first multivariable adjusted analysis included the same variables as first described above. In a second multivariable adjusted analysis we also added reperfusion therapy and evidence-based therapies at discharge (platelet inhibitors, beta-blockers, ACE-inhibitors/ARBs and statins). Data from the Cox regression analyses are shown in forest plots.

Missing values for all variables were controlled (1-2 %). As symptom-to-door time was available for 82 % of the patients a sensitivity analysis was done. Logistic regression analyses regarding use of coronary angiography, reperfusion therapy and in-hospital mortality were done also without incorporating symptom-to-door time. These analyses did not substantially change the results. (Supplementary table)

All statistical analyses were performed with the SPSS (PASW Statistics) Version 18.0 software (SPSS, Inc, Chicago, Ill).

Ethical considerations

The register was approved by the National Board of Health and Welfare and the process of merging the RIKS-HIA register with other registries was approved by the Swedish Data Inspection Board. The study was approved by the ethical committee and complies with the Declaration of Helsinki.

RESULTS

Baseline characteristics

A total of 30 077 STEMI patients were admitted during the two inclusion periods, 15 697 (35% women) in 1998-2000 and 14 380 (35% women) in 2004-2006. In both time periods women were older, had more often diabetes, hypertension, heart failure, COPD, PAD or previous stroke. They had more frequently diuretics, digitalis, calcium-channel blocker and long-acting nitrates on arrival and they had longer delay-times whereas men were more often smokers and were previously revascularised. The mean age was the same in the two time periods. (Table I)

Hospital care

In the early period, coronary angiography was performed in fewer women than men (18 vs. 25%). In the late period the numbers were higher in both genders (66 vs. 82%). (Table I) After multivariable adjustments women had 8 vs. 20% less chance of angiography in early and late periods, respectively (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.83 – 1.02 vs. OR 0.80, 95% CI 0.71 – 0.90). (Figure 2, Supplementary table) Among patients treated with reperfusion therapy 9% were treated with pPCI in the early compared to 68% in the late period. Sixty-three percent of women compared to 71% of men received acute reperfusion therapy in the early compared to 64% and 75% in the late period. (Table II) After multivariable adjustment, women were 14 and 20% less likely to receive reperfusion therapy in the early and late periods, respectively, compared to men (OR 0.86, 95% CI 0.78 – 0.94 vs. OR 0.80, 95% CI 0.73 – 0.89). (Figure 2, Supplementary table) Patients in the early period had more often heart failure and lower Killip class but less major bleedings. In both early and late period, women had more often heart failure and bleeding complications during hospital stay. (Table I)

Therapy at discharge

Evidence-based treatment with statins, platelet inhibitors, beta-blockers and ACE-inhibitors or ARBs were prescribed more often in the late compared to the early period in both genders. All evidence-based therapies were prescribed more seldom to women in both periods. (Table I) Women still had less chance of receiving ACE-inhibitors/ARBs but higher chance of receiving statins after multivariable adjustments in the early period. In the late period women had 14 – 25% less chance of receiving any of these therapies after multivariable adjustments. (Figure 2, Supplementary table)

TABLE I Baseline characteristics, management and outcome

	Early period: Year 1998-2000			**Late period: Year 2004-2006**			**Periods compared**
	Men (n=10151)	*Women (n=5546)*	*p-value*	*Men (n=9386)*	*Women (n=4994)*	*p-value*	*p-value*
Age, in years (standard deviations)	66.4 (12.2)	72.9 (11.5)	<0.001	65.9 (12.2)	72.4 (12.1)	<0.001	0.11
Symptom-to-door time, h:m (IQR)*	2:45 (1:39 – 5:10)	3:15 (1:54 – 6:15)	<0.001	3:00 (1:40 – 5:50)	3:30 (2:00 – 6:30)	<0.001	<0.001‡
Co-morbidity							
Current smoker	2762 (28.9)	1220 (23.8)	<0.001	2680 (30.9)	1224 (27.6)	<0.001	<0.001‡
Previous myocardial infarction	1781 (17.5)	742 (13.4)	<0.001	1062 (11.3)	529 (10.6)	0.19	<0.001†
Previous PCI	287 (2.9)	87 (1.6)	<0.001	372 (4.0)	110 (2.2)	<0.001	<0.001‡
Previous coronary artery bypass grafting	307 (3.1)	58 (1.1)	<0.001	308 (3.3)	82 (1.7)	<0.001	0.05 ‡
Diabetes Mellitus	1758 (17.3)	1198 (21.6)	<0.001	1679 (17.9)	1014 (20.3)	<0.001	0.82
Hypertension	2736 (27.2)	1972 (36.0)	<0.001	3053 (32.8)	2195 (44.5)	<0.001	<0.001‡
Congestive heart failure	586 (5.8)	518 (9.3)	<0.001	406 (4.3)	455 (9.1)	<0.001	<0.001†
Previous stroke	769 (7.6)	509 (9.2)	<0.001	780 (8.3)	523 (10.5)	<0.001	0.04‡
Chronic kidney disease	89 (0.9)	40 (0.7)	0.30	113 (1.2)	72 (1.4)	<0.001	<0.001‡
Chronic obstructive pulmonary disease	448 (4.4)	358 (6.5)	<0.001	465 (5.0)	440 (8.8)	<0.001	<0.001‡

Cancer within 3 years	246 (2.4)	160 (2.9)	0.08	277 (3.0)	149 (3.0)	0.91	0.05‡
Therapy on arrival							
Aspirin	2680 (26.6)	1512 (27.5)	0.25	2127 (22.9)	1440 (29.2)	<0.001	<0.001†
Other platelet inhibitor	37 (0.4)	16 (0.3)	0.43	309 (3.3)	195 (3.9)	0.05	<0.001‡
Beta–blocker	2525 (25.1)	1544 (28.1)	<0.001	2194 (23.6)	1565 (31.8)	<0.001	0.57
ACE inhibitor/ARB	1081 (10.7)	586 (10.7)	0.89	1553 (16.7)	924 (18.7)	0.002	<0.001‡
Statin	750 (7.5)	318 (5.8)	<0.001	1249 (13.4)	621 (12.6)	0.16	<0.001‡
Oral anticoagulant	271 (2.7)	109 (2.0)	0.006	232 (2.5)	119 (2.4)	0.76	0.91
Calcium-channel blocker	1304 (13.0)	786 (14.3)	0.02	1075 (11.6)	722 (14.6)	<0.001	0.04†
Diuretics	1453 (14.4)	1520 (27.7)	<0.001	1182 (12.7)	1407 (28.5)	<0.001	0.04†
Digitalis	388 (3.9)	343 (6.3)	<0.001	156 (1.7)	214 (4.3)	<0.001	<0.001†
Long-acting nitrates	1053 (10.5)	679 (12.4)	<0.001	487 (5.2)	435 (8.8)	<0.001	<0.001†
CCU procedures and therapies							
Echocardiography	6200 (64.2)	2970 (57.8)	<0.001	6842 (73.7)	3282 (66.5)	<0.001	<0.001‡
Coronary angiography	2539 (25.0)	975 (17.6)	<0.001	7686 (81.9)	3316 (66.4)	<0.001	<0.001‡
Reperfusion therapy, all	7194 (70.9)	3500 (63.1)	<0.001	7065 (75.3)	3174 (63.6)	<0.001	<0.001‡
Fibrinolytics	6419 (63.3)	3223 (58.2)	<0.001	1944 (21.0)	1006 (20.4)	0.44	<0.001‡
Primary PCI	713 (7.0)	248 (4.5)	<0.001	4898 (52.2)	2033 (40.7)	<0.001	<0.001‡
Complications							
Killip class II-IV	2912 (29.5)	2077 (38.6)	<0.0	991 (11.1)	847 (18.4)	<0.0	<0.001

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Major bleeding †	67 (1.1)	62 (2.0)	<0.001	104 (1.6)	120 (4.0)	<0.001	<0.001‡
Re-infarction during hospital stay	281 (2.9)	205 (3.9)	0.001	150 (1.6)	94 (1.9)	0.21	<0.001†
Therapy at discharge in hospital survivors							
Aspirin	7994 (87.5)	4004 (86.1)	0.02	8318 (93.6)	4062 (91.2)	<0.001	<0.001‡
Other platelet inhibitor	800 (8.8)	330 (7.1)	0.001	6978 (78.5)	3045 (68.4)	<0.001	<0.001‡
Beta-blocker	7801 (85.4)	3812 (82.1)	<0.001	8105 (91.2)	3895 (87.5)	<0.001	<0.001‡
ACE inhibitor/ARB	3934 (43.4)	1952 (42.4)	0.25	5894 (66.4)	2719 (61.1)	<0.001	<0.001‡
Statin	3991 (44.0)	1757 (38.1)	<0.001	7570 (85.2)	3279 (73.8)	<0.001	<0.001‡
Outcome							
In-hospital mortality	837 (8.3)	800 (14.5)	<0.001	464 (4.9)	521 (10.4)	<0.001	<0.001†
One year mortality	1576 (15.5)	1324 (23.9)	<0.001	961 (10.3)	955 (19.1)	<0.001	<0.001†

Data presented as numbers (percentages) if not otherwise indicated. §Intracranial haemorrhage, mortal bleeding or given blood transfusion in patients treated with reperfusion therapy.† More in early period ‡ More in late period

IQR, interquartile range; PCI, percutaneous coronary intervention; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCU, coronary care unit

Mortality

In-hospital as well as cumulative one year mortality was higher in the early than in the late period in both genders. Women had about twice as high in-hospital as well as one year mortality in both periods. (Table I) After multivariable adjustments the in-hospital mortality was around 20% higher in women in both periods (OR 1.17, 95% CI 1.02 – 1.36 vs. OR 1.21, 95% CI 1.00 – 1.46).The one year mortality was 5 and 11%

higher in women in the early and late period respectively, although it did not reach statistical significance in the early period (hazard ratio [HR] 1.05, 95% CI 0.97-1.14 vs. HR 1.11, 95% CI 1.00 – 1.24). After adding adjustment for reperfusion therapy and evidence-based treatment at discharge, there was no longer any gender difference in long-term mortality (HR 0.95, 5% CI 0.87 – 1.05 vs. HR 0.96, 95% CI 0.86 – 1.08). (Figure 3, Supplementary table)

DISCUSSION

After the reperfusion strategy change patients admitted during the first decade of the 21st century were treated with reperfusion therapy more often than patients admitted during the late 1990s. Anyhow, we did not find a diminished gender gap neither regarding use of reperfusion therapy, nor regarding mortality. Even more surprising was the finding that women had 14-25% less chance of receiving evidence-based cardiovascular treatment in the late period after multivariable adjustments.

Previous trials during the fibrinolytic era have found higher mortality in women, but usually without separating STEMI from NSTE ACS.[1] In STEMI studies, the risk of early death has been 10-25% higher in women after multivariable adjustments [2, 5, 6, 16] although most STEMI-cohorts have been extracted from randomised controlled trials [2, 6] and may not correspond to the real life population. Fibrinolytics has been given to fewer women even if eligibility has been considered.[17] Also in our study women had 14% lower chance of receiving reperfusion therapy in the early group where fibrinolytics accounted for 91% of the reperfusion therapy. As an increased risk of intracranial haemorrhage and other major bleedings has been found in women treated with fibrinolytics,[18] a fear of these dreadful complications may explain some of the observed difference. The well-known longer delay-times in women could be another explanation. In our study women had 30 min longer delay times from symptom onset to arrival to CCU or the cath lab in both time periods. Adjusting for this did not change the results.

As primary PCI has been shown superior to fibrinolytics in reducing mortality after STEMI,[19] it has been recommend in the ESC guidelines since 2003.[20] In Sweden it has been the dominant reperfusion strategy from 2004 and onwards. (Figure 1) During this new pPCI era the evidence that gender per se bears prognostic information is less firm and data is contrasting. [10, 21] When we started our study and formed our hypothesis there were only small and mainly single-centre studies published.[7, 8, 10, 21] The majority of those did not find female gender to be an independent predictor of adverse outcome after pPCI.[7, 10] Mehilli et al found better myocardial salvage in women than in men after pPCI which they speculated could be due to a higher hypoxia tolerance in women because of higher incidence of pre-infarction angina (ischemic pre-conditioning) and more often spontaneous thrombolysis. [22] Also, as pPCI is less time-dependent than fibrinolytics, women could be expected to benefit more than men from a reperfusion strategy change because of their consistently longer symptom-to-door time. [10]

Thus, our hypothesis was that the gender gap in reperfusion therapy would diminish after the shift to a reperfusion strategy that could be more advantageous to women. This hypothesis was not confirmed. The rate of reperfusion in men increased from 70.9% to 75.3% whereas the increase in women was very modest, 63.1% to 63.6%. The reason for the finding is for us unclear. Mean age was the same in the two periods and women had 30 min longer symptom-to-door time in both periods. One possible reason could be higher prevalence of normal coronary arteries in women, which is shown before although mainly in NSTEACS and mixed ACS populations.[23] In our study, during the early period we had coronary angiography findings from few patients (56% of the 3514 patients that underwent coronary angiography). In the late period we had findings on 97 % of the 11 002 examined patients showing that 3% of men and 7 % of women had non-obstructive coronary artery disease. Thus, normal coronary arteries can hardly explain the gap in reperfusion therapy in the early period when fibrinolytics was dominating and angiography seldom performed. In the late period it could account for a small part of the difference in use of primary PCI although it does not explain the gender gap in use of coronary angiography, which also increased between the two time periods.

During the last decade several important randomised controlled trials have been published encouraging more effective secondary prevention in CAD patients.[24, 25] Use of ACE-inhibitors/ARBs, dual platelet inhibition and statins has thus increased dramatically in the STEMI population during this decade and mortality has declined. We found increased use of all secondary prevention drugs, even those with older evidence such as aspirin and beta-blockers. However, the increase of all the evidence-based therapies was more pronounced in men than in women. In spite of the intense focus on the gender aspect in the ACS field during the last two decades, together with the focus on adherence to guidelines, the treatment gap was even more pronounced in the late compared to the early group. Even after multivariable adjustment, women had 14-25% lesser chance of receiving any of these drugs at discharge.

We cannot fully explain this gender gap in management. Maybe a fear of doing harm because of the well-known higher risk of bleeding in women [26] or reports from patients of previous or current adverse effects are reasons for the bias. It has been shown in previous studies that women report side effects more often than men, especially if the same dosages are used. [27] Finally, we could speculate that doctors tend to adapt to new treatment modalities and new guidelines faster in men than in women, especially in older cohorts. We did some subgroup analyses of different age groups (not included in the manuscript) where we found the treatment bias clearest in the oldest cohort.

A more effective reperfusion strategy with pPCI and the increased use of evidence-based treatment has been associated with improved outcome. Thus we found reduced mortality in the late compared to the early period in both genders. However we also found a persistent gender gap both regarding short- and long-term mortality. In-hospital mortality was approximately 20% higher in both time periods consistent with previous STEMI studies focusing on gender from the fibrinolytic era.[2, 5, 6, 16] From the PCI era, two recent publications by Benamer et al and Sadowski et al found that there is still a gender difference in in-hospital mortality among STEMI patients consistent with our findings. [28, 29] In addition, one year mortality was higher in our study, 5 vs. 11% higher in the early and late periods, respectively. If we also incorporated evidence-based treatment at discharge and reperfusion therapy in the multivariable adjustments, there was no longer a significant gender difference in long-term mortality.

In USA, the American College of Cardiology's AMI Guidelines Applied in Practice (GAP) program is proven to increase the use of evidenced based medicine and reduce MI mortality but is less used in women.[30] The results in our study are in concordance with those findings.

Limitations

As in all registries on clinical practice, one limitation is the handling of missing data. In the RIKS-HIA register, we have data for around 95% of the patients for almost all variables that is mandatory for the hospitals to register. Furthermore, as in all observational data sets, the adjustment might be influenced by the lack of registration on some possible confounding factors in the data base e.g. non-cardiac co-morbidities and contra-indications for specific treatments. However a strength is the large number of patients allowing adjustment for baseline differences between the compared groups.

CONCLUSION

Our study showed improved management and reduced mortality in STEMI patients in the late compared to the early period. Adherence to treatment guidelines was better in men than in women. In fact the treatment gap seemed even more pronounced in the new era. Thus a better adherence to treatment guidelines in women is mandatory as it might reduce the differences in long-term outcome between the genders. There is also a great need of studies scrutinising the gender differences in management of STEMI in the new pPCI era.

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Disclosures

None.

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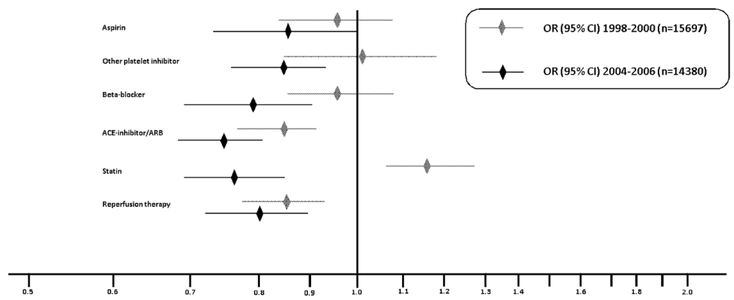
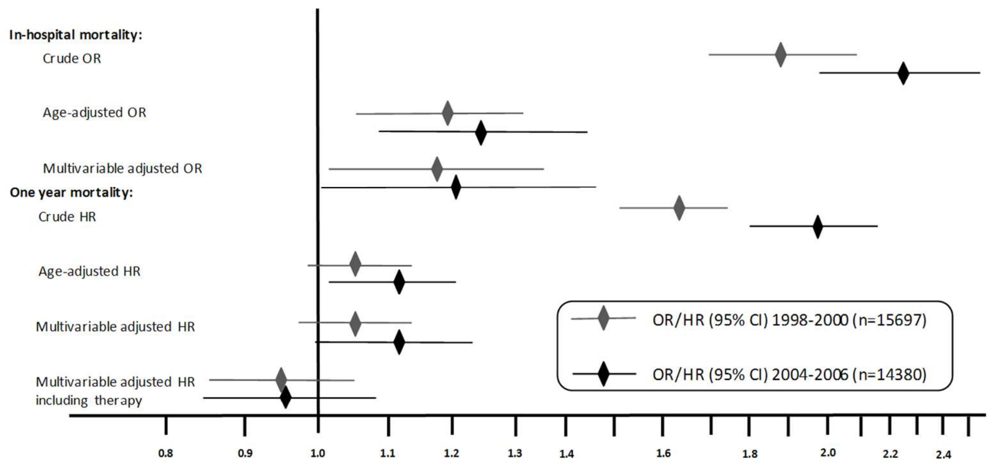


Use of coronary angiography, reperfusion therapy and evidence based therapies at discharge in STEMI patients in two time periods after multivariable adjustments, women vs. men
180x119mm (300 x 300 DPI)



In-hospital and cumulative one year mortality in STEMI patients in two time periods with different dominating reperfusion strategies. Crude, age-adjusted and multivariable adjusted odds and hazard ratios with 95% confidence intervals, women vs. men
295x190mm (120 x 120 DPI)

Abstract

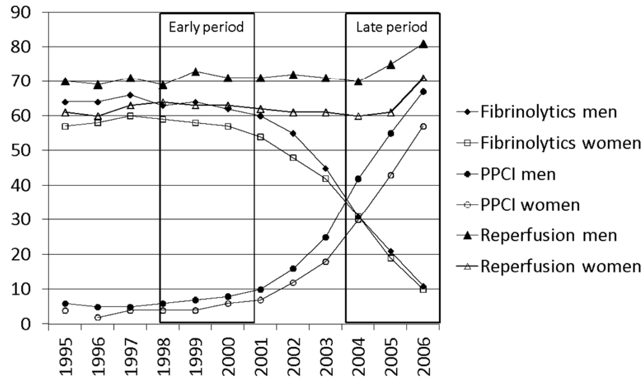
Objective: In ST-elevation myocardial infarction [STEMI] women received less evidence-based medicine [EBM] and had worse outcome during the fibrinolytic era. With the shift to primary percutaneous coronary intervention [pPCI] as preferred reperfusion strategy, we aimed to investigate whether these gender differences has diminished.

Design, setting and participants: Cohort study including consecutive STEMI patients registered 1998 – 2000 (n=15697) and 2004 – 2006 (n=14380) in the Register of Information and Knowledge about Swedish Heart Intensive care Admissions.

Outcome measures: EBM use, in-hospital and one year mortality.

Results: Reperfusion therapy (pPCI in 9 vs. 68%, early vs. late period) was given to 63 vs. 71% and 64 vs. 75%, women vs. men in the two respective periods, OR 0.86 (95% CI 0.78 – 0.94) and 0.80 (0.73 – 0.89) after multivariable adjustments. In the late period women had 14 – 25% less chance of receiving EBM at discharge (OR 0.75, 95% CI 0.68 – 0.81 thru 0.86, 0.77 – 0.95). Gender differences in the early period were small. In both periods, multivariable adjusted in-hospital mortality was higher in women, OR 1.17 (95% CI 1.02 – 1.14) and 1.21 (1.00 – 1.46). One year mortality was gender equal, HR 0.95 (95% CI 0.87– 1.05) and 0.96 (0.86 – 1.08), after adding EBM to the multivariable adjustments.

Conclusion: In spite of an intense gender debate, focus on guideline adherence and the change in reperfusion strategy the last decade gender differences in use of reperfusion therapy and evidence-based therapy at discharge did not decline during the study period. Moreover, higher mortality in women persisted.



Trends in reperfusion therapy among Swedish STEMI patients 1995 – 2006
119x180mm (300 x 300 DPI)

Time trends in STEMI - improved treatment and outcome but still a gender gap: A prospective, observational cohort study from the SWEDEHEART register

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Time trends in STEMI - improved treatment and outcome but still a gender gap

A prospective, observational cohort study from the SWEDEHEART register

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Sofia Sederholm Lawesson has substantially contributed to conception and design of the study. She has handled, analysed and interpreted all the data and drafted the article.

Joakim Alfredsson has substantially contributed to conception and design, help with analyses and interpretation of the data. He has revised the draft critically for important intellectual content and approved the final version to be published.

Mats Fredrikson has substantially contributed with analysing and interpreting the data, revising the draft critically and approved the final version to be published.

Eva Swahn has substantially contributed to conception and design, help with analysing and interpreting the data. She revised the draft critically for important intellectual content and approved the final version to be published.

Summary

Article focus:

With 1) the focus on treatment guidelines, 2) the attention on gender differences in management and outcome and 3) the change in reperfusion strategy in STEMI the last decade, we hypothesised;

- That gender differences in adherence to treatment guidelines would have diminished
- That gender differences in outcome would have decreased

Key messages:

- Management improved and mortality decreased in STEMI patients in the late compared to the early period.
- The gender treatment gap did not decrease between the two time periods.
- The gender outcome gap did not decrease between the two time periods.

Strengths and limitations:

The study included a huge amount of STEMI patients, with enough numbers to assure adequate statistical analyses. SWEDEHEART registry is a unique Swedish National Quality registry, with quality control and audit measures, covering all hospitals in Sweden treating STEMI patients and has standardised criteria for defining MI. Mortality data are complete as the vital status of all Swedish citizens is registered in the Cause of Death Registry. One limitation is the nonrandomised, observational nature. Thus multivariate analyses were used in order to reduce the bias inherent in this type of studies. Adjustments might be influenced by the lack of registration on some possible confounding factors in the data base e.g. non-cardiac co-morbidities and contra-indications for specific treatments.

Abstract

Objective: In ST-elevation myocardial infarction [STEMI] women received less evidence-based medicine [EBM] and had worse outcome during the fibrinolytic era. With the shift to primary percutaneous coronary intervention [pPCI] as preferred reperfusion strategy, we aimed to investigate whether these gender differences has diminished.

Design, setting and participants: Cohort study including consecutive STEMI patients registered 1998 – 2000 (n=15697) and 2004 – 2006 (n=14380) in the Register of Information and Knowledge about Swedish Heart Intensive care Admissions.

Outcome measures: 1. Use of EBM such as reperfusion therapy (pPCI or fibrinolysis) and evidence-based drugs at discharge. 2. In-hospital and one year mortality.

Results: Of those who got reperfusion therapy, pPCI was the choice in 9% in the early period compared to 68% in the late period. In the early period, reperfusion therapy was given to 63% of women vs. 71% of men, p<0.001. Corresponding figures in the late period were 64% vs. 75%, p<0.001. After multivariable adjustments the odds ratios [OR] (women vs. men) were 0.86 (95% CI 0.78 – 0.94) in the early and 0.80 (95% CI 0.73 – 0.89) in the late period. As regards evidence-based secondary preventive drugs at discharge in hospital survivors (platelet inhibitors, statins, ACE-inhibitors/angiotensin receptor blockers [ARB] and beta-blockers) there were small gender differences in the early period. In the late period women had 14 – 25% less chance of receiving these drugs, OR 0.75 (95% CI 0.68 – 0.81) thru 0.86 (95% CI 0.77 – 0.95). In both periods, multivariable adjusted in-hospital mortality was higher in women, OR 1.18 (95% CI 1.02 – 1.36) and 1.21 (1.00 – 1.46). One year mortality was gender equal, HR 0.95 (95% CI 0.87– 1.05) and 0.96 (0.86 – 1.08), after adding EBM to the multivariable adjustments.

Conclusion: In spite of an intense gender debate, focus on guideline adherence and the change in reperfusion strategy the last decade gender differences in use of reperfusion therapy and evidence-based therapy at discharge did not decline during the study period, rather the opposite. Moreover, higher mortality in women persisted.

INTRODUCTION

Numerous studies have shown excess mortality in women after myocardial infarction [MI][1, 2] but ST-elevation MI [STEMI] has seldom been separated from non-ST elevation acute coronary syndromes [NSTEACS].[1, 3] Women have been treated less intensively than men [4, 5] with less reperfusion therapy in the STEMI group.[5] Whereas some have found small gender differences in treatment not affecting mortality after MI [3] others have attributed part of the gender gap in outcome to a treatment bias.[1] Higher risk of death and bleeding in women is shown in many fibrinolytic trials. [2, 6] The last decade there has been a shift in reperfusion strategy in Sweden from fibrinolytic to primary PCI. Simulataneously there has been an increase in use of evidence-based cardiovascular secondary preventive drugs such as statins, P2Y12-inhibitors and ACE-inhibitors/angiotensin receptor blockers [ARBs] and the case fatality has declined. There is less firm evidence that female gender is an independent risk factor for adverse outcome after primary percutaneous coronary intervention [pPCI] which seems to be a better reperfusion strategy for women in particular.[7, 8, 9, 10] Since 2002/2003 there are separate ESC guidelines for STEMI and NSTE ACS recommending pPCI as the preferred reperfusion strategy in STEMI.[11, 12] With the last decade's awareness and debate about ACS from a gender perspective, the focus on adherence to treatment guidelines, and the shift to a reperfusion strategy, we hypothesised that the previously noticed gender differences in STEMI management would have decreased and thus also the gender gap in mortality, especially in the early phase.

Our aim was to evaluate gender differences in management and outcome in STEMI patients in two time periods with different dominating reperfusion strategies, i.e. fibrinolytics and primary PCI, respectively.

METHODS

Patients

Data for this study came from the prospective observational Register of Information and Knowledge about Swedish Heart Intensive care Admissions [RIKS-HIA], since 2009 merged with the Swedish Coronary Angiography and Angioplasty Registry [SCAAR], the Swedish Heart Surgery Registry and the National

Registry of Secondary Prevention [SEPHIA] together forming the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies [SWEDEHEART].[13] The RIK-SHIA/SWEDEHEART register is a large national quality register funded by the National Board of Health and Welfare (Socialstyrelsen). It contains information about all patients admitted to coronary care units [CCU] of the participating hospitals in Sweden (95% of the CCUs in Sweden year 2004). Variables including age, sex, smoking habits, co-morbidity, delay-times, symptoms, biochemical markers, results from cardiac investigations, complications, revascularisation procedures, therapies, discharge diagnoses and outcomes during the hospital stay are continuously recorded on-line over the internet. The criteria for the MI diagnosis were standardised and identical for all participating hospitals.[14, 15] The register has a continuous internal and external validation of data. The internet-based program for data input has interactive instructions, manuals, definitions and help functions and a number of compulsory variables and inbuilt validity controls. An independent monitor travels to 20 hospitals annually and in each hospital 30 randomly chosen patients in the database are compared with the hospital records. For example year 2005, 95.2% and 2006, 96.5% of the registry input showed agreement with the hospital records.

RIKS-HIA/SWEDEHEART is repeatedly further merged with the administrative registers National Cause of Death register and the National Patient Register (National Board of Health and Welfare is responsible for both those registers). The Cause of Death Register covers all Swedish residents, whether the death occurred in Sweden or not, and whether the person in question was a Swedish citizen or not. From this register information was available about cause of death and vital status of all Swedish citizens until 31st of December 2007. Regarding co-morbidity, data on previous diagnoses of diabetes, hypertension, MI and previous revascularisation procedures were taken from RIKS-HIA, SCAAR and the Swedish Heart Surgery Registry, which were merged (today SWEDEHEART). Previous history of co-morbidities such as chronic obstructive pulmonary disease [COPD], heart failure, chronic kidney disease [CKD], peripheral artery disease [PAD], dementia and cancer was obtained from the National Patient Register, including patients hospitalised in Sweden since 1987. Information on previous history of heart failure or stroke was taken both from

RIKSHIA and the National Patient Register. A patient was coded as having the diagnosis if he/she had the diagnosis in either of these registries.

Between 1st January 1995 until 31st December 2006, 54146 patients were admitted to participating CCUs with the first registry recorded diagnosis of STEMI, defined as ST-elevation on admission ECG and a diagnosis of acute MI at discharge. Patients with pacemaker/unknown/unspecified rhythm or bundle branch block on admission were excluded. Two time periods with different dominating reperfusion strategies were chosen (Figure 1); patients admitted 1st of January 1998 until 31st of December 2000 (the early period) and patients admitted 1st of January 2004 until 31st of December 2006 (the late period). The yearly STEMI prevalence was similar and about 5000 (women comprising 33-36%) ranging from 4662 (year 2006) to 5308 (year 2000). The groups were compared and gender comparisons were done in both groups.

Statistical analyses

Continuous variables were summarised by their mean and standard deviation or median and interquartile range as appropriate. Categorical variables were summarised by counts and percentages. Comparisons between different strata were performed by chi-square tests for categorical variables and by student t-tests or Mann Whitney tests for continuous variables. P-values < 0.05 were considered to indicate statistical significance.

Crude, age- and multivariable adjusted odds ratios with 95% confidence intervals were calculated from logistic regression analyses in order to compare the genders regarding use of cardiac procedures, evidence based therapies at discharge and in-hospital mortality. In addition to sex and age, the multivariable adjusted analyses included smoking, previous MI, PCI, coronary artery bypass grafting [CABG], stroke, hypertension, diabetes mellitus, COPD, heart failure, CKD, PAD, dementia, cancer within 3 years, therapies on arrival, interventional hospital and year of inclusion. Regarding use of coronary angiography, reperfusion therapy and in-hospital mortality we also added Killip class on arrival and symptom-to-door time (as a continuous variable in one hour intervals) to the multivariable adjusted analyses. Data from the logistic regression analyses are shown in forest plots.

Hazard ratios with 95% confidence intervals were calculated from Cox proportional hazard regression analyses in order to compare the genders regarding cumulative one year mortality. The first multivariable adjusted analysis included the same variables as first described above. In a second multivariable adjusted analysis we also added reperfusion therapy and evidence-based therapies at discharge (platelet inhibitors, beta-blockers, ACE-inhibitors/ARBs and statins). Data from the Cox regression analyses are shown in forest plots.

Missing values for all variables were controlled (1-2 %). As symptom-to-door time was available for 82 % of the patients a sensitivity analysis was done. Logistic regression analyses regarding use of coronary angiography, reperfusion therapy and in-hospital mortality were done also without incorporating symptom-to-door time. These analyses did not substantially change the results. (Supplementary table)

All statistical analyses were performed with the SPSS (PASW Statistics) Version 18.0 software (SPSS, Inc, Chicago, Ill).

Ethical considerations

The register was approved by the National Board of Health and Welfare and the process of merging the RIKS-HIA register with other registries was approved by the Swedish Data Inspection Board. The study was approved by the ethical committee and complies with the Declaration of Helsinki.

RESULTS

Baseline characteristics

A total of 30 077 STEMI patients were admitted during the two inclusion periods, 15 697 (35% women) in 1998-2000 and 14 380 (35% women) in 2004-2006. The mean age did not differ between the two periods whereas the prevalence of previous MI was lower and the prevalence of COPD and smoking was higher in the late period. In both time periods women were 6.5 years older than men and had more often diabetes, hypertension, heart failure, COPD, PAD or previous stroke whereas men were more often smokers and were previously revascularised.

The use of statins, clopidogrel and ACE-inhibitors/ARB on admission increased between the two time periods. Women were more frequently treated with diuretics, digitalis, calcium-channel blocker and long-acting nitrates on admission in both time periods,.

Women had 30 min longer median symptom-to-door time in both time periods. Also the median time from 1st ECG to needle differed between the genders in both time periods (4 and 5 min respectively), whereas the median time from 1st ECG to balloon only differed in the late time period (5 min). (Table I)

Hospital care

In the early period, coronary angiography was performed in fewer women than men (18 vs. 25%). In the late period the numbers were higher in both genders (66 vs. 82%). (Table I) After multivariable adjustments women had 8 vs. 20% less chance of angiography in early and late periods, respectively (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.83 – 1.02 vs. OR 0.80, 95% CI 0.71 – 0.90). (Figure 2, Supplementary table) Among patients treated with reperfusion therapy 9% (7% of women, 10% of men, Table 1) were treated with pPCI in the early compared to 68% (64% of women, 69% of men, Table 1) in the late period. Sixty-three percent of women compared to 71% of men received acute reperfusion therapy in the early compared to 64% and 75% in the late period. (Table II) After multivariable adjustment, women were 14 and 20% less likely to receive reperfusion therapy in the early and late periods, respectively, compared to men (OR 0.86, 95% CI 0.78 – 0.94 vs. OR 0.80, 95% CI 0.73 – 0.89). (Figure 2, Supplementary table) Patients in the early period had more often heart failure and lower Killip class but less major bleedings. In both early and late period, women had more often heart failure and bleeding complications during hospital stay. (Table I)

Therapy at discharge

Evidence-based treatment with statins, platelet inhibitors, beta-blockers and ACE-inhibitors or ARBs were prescribed more often in the late compared to the early period in both genders. All evidence-based therapies were prescribed more seldom to women in both periods. (Table I) Women still had less chance of receiving

ACE-inhibitors/ARBs but higher chance of receiving statins after multivariable adjustments in the early period. In the late period women had 14 – 25% less chance of receiving any of these therapies after multivariable adjustments, OR 0.75, (95% CI 0.68 – 0.81) thru OR 0.86 (95% CI 0.73 – 1.00). (Figure 2, Supplementary table)

Mortality

In-hospital as well as cumulative one year mortality was higher in the early than in the late period in both genders. Women had about twice as high in-hospital as well as one year mortality in both periods. (Table I) After multivariable adjustments the in-hospital mortality was around 20% higher in women in both periods (OR 1.17, 95% CI 1.02 – 1.36 vs. OR 1.21, 95% CI 1.00 – 1.46).The one year mortality was 5 and 11% higher in women in the early and late period respectively, although it did not reach statistical significance in the early period (hazard ratio [HR] 1.05, 95% CI 0.97-1.14 vs. HR 1.11, 95% CI 1.00 – 1.24). After adding adjustment for reperfusion therapy and evidence-based treatment at discharge, there was no longer any gender difference in long-term mortality (HR 0.95, 5% CI 0.87 – 1.05 vs. HR 0.96, 95% CI 0.86 – 1.08). (Figure 3, Supplementary table)

DISCUSSION

After the reperfusion strategy change patients admitted during the first decade of the 21st century were treated with reperfusion therapy more often than patients admitted during the late 1990s. Anyhow, we did not find a diminished gender gap neither regarding use of reperfusion therapy, nor regarding mortality. Even more surprising was the finding that women had 14-25% less chance of receiving evidence-based cardiovascular treatment in the late period after multivariable adjustments.

Previous trials during the fibrinolytic era have found higher mortality in women, but usually without separating STEMI from NSTE ACS.[1] In STEMI studies, the risk of early death has been 10-25% higher in women after multivariable adjustments [2, 5, 6, 16] although most STEMI-cohorts have been extracted from randomised controlled trials [2, 6] and may not correspond to the real life population. Fibrinolytics has been given to fewer women even if eligibility has been considered.[17] Also in our study women had 14% lower chance of receiving reperfusion therapy in the early group where fibrinolytics accounted for 91% of the reperfusion therapy. As an increased risk of intracranial haemorrhage and other major bleedings has been found in women treated with fibrinolytics,[18] a fear of these dreadful complications may explain some of the observed difference. The well-known longer delay-times in women could be another explanation. In our study women had 30 min longer delay times from symptom onset to arrival to CCU or the cath lab in both time periods. Adjusting for this did not change the results.

As primary PCI has been shown superior to fibrinolytics in reducing mortality after STEMI,[19] it has been recommend in the ESC guidelines since 2003.[20] In Sweden it has been the dominant reperfusion strategy from 2004 and onwards. (Figure 1) During this new pPCI era the evidence that gender per se bears prognostic information is less firm and data is contrasting. [10, 21] When we started our study and formed our hypothesis there were only small and mainly single-centre studies published.[7, 8, 10, 21] The majority of those did not find female gender to be an independent predictor of adverse outcome after pPCI.[7, 10] Mehilli et al found better myocardial salvage in women than in men after pPCI which they speculated could be due to a higher hypoxia tolerance in women because of higher incidence of pre-infarction angina (ischemic pre-conditioning) and more often spontaneous thrombolysis. [22] Also, as pPCI is less time-dependent than fibrinolytics, women could be expected to benefit more than men from a reperfusion strategy change because of their consistently longer symptom-to-door time. [10]

Thus, our hypothesis was that the gender gap in reperfusion therapy would diminish after the shift to a reperfusion strategy that could be more advantageous to women. This hypothesis was not confirmed. The rate of reperfusion in men increased from 70.9% to 75.3% whereas the increase in women was very modest, 63.1% to 63.6%. The reason for the finding is for us unclear. The gender difference in mean age was the same in the two periods and women had 30 min longer symptom-to-door time in both periods. One possible reason could be higher prevalence of normal coronary arteries in women, which is shown before although mainly in NSTEACS and mixed ACS populations.[23] In our study, during the early period we had coronary angiography findings from few patients (56% of the 3514 patients that underwent coronary angiography). In the late period we had findings on 97 % of the 11 002 examined patients showing that 3% of men and 7 % of women had non-obstructive coronary artery disease. Thus, normal coronary arteries can hardly explain the gap in reperfusion therapy in the early period when fibrinolytics was dominating and angiography seldom performed. In the late period it could account for a small part of the difference in use of primary PCI although it does not explain the gender gap in use of coronary angiography, which also increased between the two time periods.

During the last decade several important randomised controlled trials have been published encouraging more effective secondary prevention in CAD patients.[24, 25] Use of ACE-inhibitors/ARBs, dual platelet inhibition and statins has thus increased dramatically in the STEMI population during this decade and mortality has declined. We found increased use of all secondary prevention drugs, even those with older evidence such as aspirin and beta-blockers. However, the increase of all the evidence-based therapies was more pronounced in men than in women. In spite of the intense focus on the gender aspect in the ACS field during the last two decades, together with the focus on adherence to guidelines, the treatment gap was even more pronounced in the late compared to the early group. Even after multivariable adjustment, women had 14-25% lesser chance of receiving any of these drugs at discharge.

We cannot fully explain this gender gap in management. Maybe a fear of doing harm because of the well-known higher risk of bleeding in women [26] or reports from patients of previous or current adverse effects are reasons for the bias. It has been shown in previous studies that women report side effects more often than men, especially if the same dosages are used. [27] Finally, we could speculate that doctors tend to adapt to new treatment modalities and new guidelines faster in men than in women, especially in older cohorts. We did some subgroup analyses of different age groups (not included in the manuscript) where we found the treatment bias clearest in the oldest cohort.

A more effective reperfusion strategy with pPCI and the increased use of evidence-based treatment has been associated with improved outcome. Thus we found reduced mortality in the late compared to the early period in both genders. However we also found a persistent gender gap both regarding short- and long-term mortality. In-hospital mortality was approximately 20% higher in both time periods consistent with previous STEMI studies focusing on gender from the fibrinolytic era.[2, 5, 6, 16] From the PCI era, two recent publications by Benamer et al and Sadowski et al found that there is still a gender difference in in-hospital mortality among STEMI patients consistent with our findings. [28, 29] In addition, one year mortality was higher in our study, 5 vs. 11% higher in the early and late periods, respectively. If we also incorporated evidence-based treatment at discharge and reperfusion therapy in the multivariable adjustments, there was no longer a significant gender difference in long-term mortality.

In USA, the American College of Cardiology's AMI Guidelines Applied in Practice (GAP) program is proven to increase the use of evidenced based medicine and reduce MI mortality but is less used in women.[30] The results in our study are in concordance with those findings.

Limitations

As in all registries on clinical practice, one limitation is the handling of missing data. In the RIKS-HIA register, we have data for around 95% of the patients for almost all variables that is mandatory for the hospitals to register. Furthermore, as in all observational data sets, the adjustment might be influenced by the lack of registration on some possible confounding factors in the data base e.g. non-cardiac co-morbidities, reduced kidney function and contra-indications for specific treatments. Accordingly eligibility for all treatments was not possible to acertain, and might thus differ between the genders. However a strength is the large number of patients allowing adjustment for baseline differences between the compared groups.

CONCLUSION

Our study showed improved management and reduced mortality in STEMI patients in the late compared to the early period. Anyhow the gender difference did not diminish between the two time periods neither regarding management, nor regarding early mortality. Adherence to treatment guidelines was better in men than in women and in fact the treatment gap seemed even more pronounced in the new era. There was also a persistent 20% higher risk of early mortality in women in the new pPCI era, in accordance with the fibrinolytic era. Thus a better adherence to treatment guidelines in women is mandatory as it might reduce the differences in outcome between the genders. There is also a great need of studies scrutinising the gender differences in management of STEMI in the new pPCI era.

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Disclosures

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TABLE I Baseline characteristics, management and outcome

	Early period: Year 1998-2000			**Late period: Year 2004-2006**			**Periods compared**
	Men (n=10151)	*Women (n=5546)*	*p-value*	*Men (n=9386)*	*Women (n=4994)*	*p-value*	*p-value*
Age, in years (standard deviations)	66.4 (12.2)	72.9 (11.5)	<0.001	65.9 (12.2)	72.4 (12.1)	<0.001	0.11
Median symptom-to-door time, h:m (IQR)	2:45 (1:39 – 5:10)	3:15 (1:54 – 6:15)	<0.001	3:00 (1:40 – 5:50)	3:30 (2:00 – 6:30)	<0.001	<0.001‡
Median time from 1st ECG to balloon, h:m (IQR)	1:00 (0:35 – 1:39)	0:58 (0:35 – 1:42)	0.60	1:10 (0:42 – 1:49)	1:15 (0:45 – 1:59)	<0.001	<0.001
Median time from 1st ECG to needle, h:m (IQR)	0:43 (0:27 – 1:05)	0:47 (0:30 – 1:15)	<0.001	0:36 (0:20 – 1:02)	0:41 (0:23 – 1:08)	0.001	<0.001
Co-morbidity							
Current smoker	2762 (28.9)	1220 (23.8)	<0.001	2680 (30.9)	1224 (27.6)	<0.001	<0.001‡
Previous myocardial infarction	1781 (17.5)	742 (13.4)	<0.001	1062 (11.3)	529 (10.6)	0.19	<0.001†
Previous PCI	287 (2.9)	87 (1.6)	<0.001	372 (4.0)	110 (2.2)	<0.001	<0.001‡
Previous coronary artery bypass grafting	307 (3.1)	58 (1.1)	<0.001	308 (3.3)	82 (1.7)	<0.001	0.05 ‡
Diabetes Mellitus	1758 (17.3)	1198 (21.6)	<0.001	1679 (17.9)	1014 (20.3)	<0.001	0.82
Hypertension	2736 (27.2)	1972 (36.0)	<0.001	3053 (32.8)	2195 (44.5)	<0.001	<0.001‡
Congestive heart failure	586 (5.8)	518 (9.3)	<0.001	406 (4.3)	455 (9.1)	<0.001	<0.001†
Previous stroke	769 (7.6)	509 (9.2)	<0.001	780 (8.3)	523 (10.5)	<0.001	0.04‡
Chronic kidney disease	89 (0.9)	40 (0.7)	0.30	113 (1.2)	72 (1.4)	<0.001	<0.001‡
Chronic obstructive pulmonary disease	448 (4.4)	358 (6.5)	<0.001	465 (5.0)	440 (8.8)	<0.001	<0.001‡
Cancer within 3 years	246 (2.4)	160 (2.9)	0.08	277 (3.0)	149 (3.0)	0.91	0.05‡
Therapy on arrival							
Aspirin	2680 (26.6)	1512 (27.5)	0.25	2127 (22.9)	1440 (29.2)	<0.001	<0.001†
Other platelet inhibitor	37 (0.4)	16 (0.3)	0.43	309 (3.3)	195 (3.9)	0.05	<0.001‡
Beta–blocker	2525 (25.1)	1544 (28.1)	<0.001	2194 (23.6)	1565 (31.8)	<0.001	0.57
ACE inhibitor/ARB	1081 (10.7)	586 (10.7)	0.89	1553 (16.7)	924 (18.7)	0.002	<0.001‡
Statin	750 (7.5)	318 (5.8)	<0.001	1249 (13.4)	621 (12.6)	0.16	<0.001‡
Oral anticoagulant	271 (2.7)	109 (2.0)	0.006	232 (2.5)	119 (2.4)	0.76	0.91
Calcium-channel blocker	1304 (13.0)	786 (14.3)	0.02	1075 (11.6)	722 (14.6)	<0.001	0.04†
Diuretics	1453 (14.4)	1520 (27.7)	<0.001	1182 (12.7)	1407 (28.5)	<0.001	0.04†
Digitalis	388 (3.9)	343 (6.3)	<0.001	156 (1.7)	214 (4.3)	<0.001	<0.001†
Long-acting nitrates	1053 (10.5)	679 (12.4)	<0.001	487 (5.2)	435 (8.8)	<0.001	<0.001†
CCU procedures and therapies							
Echocardiography	6200 (64.2)	2970 (57.8)	<0.001	6842 (73.7)	3282 (66.5)	<0.001	<0.001‡
Coronary angiography	2539 (25.0)	975 (17.6)	<0.001	7686 (81.9)	3316 (66.4)	<0.001	<0.001‡
Reperfusion therapy, all	7194 (70.9)	3500 (63.1)	<0.001	7065 (75.3)	3174 (63.6)	<0.001	<0.001‡
Fibrinolysis (% of all patients)	6419 (63.3)	3223 (58.2)	<0.001	1944 (21.0)	1006 (20.4)	0.44	<0.001‡
Fibrinolysis (% of patients receiving reperfusion therapy)	6419 (89.3)	3223 (92.2)	<0.001	1944 (28.0)	1006 (32.4)	<0.001	<0.001
Primary PCI (% of all patients)	713 (7.0)	248 (4.5)	<0.001	4898 (52.2)	2033 (40.7)	<0.001	<0.001‡
Primary PCI (% of patients receiving reperfusion therapy)	713 (9.9)	248 (7.1)	<0.001	4898 (69.3)	2033 (64.1)	<0.001	<0.001
Complications							
Killip class II-IV	2912 (29.5)	2077 (38.6)	<0.001	991 (11.1)	847 (18.4)	<0.001	<0.001
Major bleeding †	67 (1.1)	62 (2.0)	<0.001	104 (1.6)	120 (4.0)	<0.001	<0.001‡
Re-infarction during hospital stay	281 (2.9)	205 (3.9)	0.001	150 (1.6)	94 (1.9)	0.21	<0.001†
Therapy at discharge in hospital survivors							
Aspirin	7994 (87.5)	4004 (86.1)	0.02	8318 (93.6)	4062 (91.2)	<0.001	<0.001‡
Other platelet inhibitor	800 (8.8)	330 (7.1)	0.001	6978 (78.5)	3045 (68.4)	<0.001	<0.001‡
Beta-blocker	7801 (85.4)	3812 (82.1)	<0.001	8105 (91.2)	3895 (87.5)	<0.001	<0.001‡
ACE inhibitor/ARB	3934 (43.4)	1952 (42.4)	0.25	5894 (66.4)	2719 (61.1)	<0.001	<0.001‡
Statin	3991 (44.0)	1757 (38.1)	<0.001	7570 (85.2)	3279 (73.8)	<0.001	<0.001‡
Outcome							
In-hospital mortality	837 (8.3)	800 (14.5)	<0.001	464 (4.9)	521 (10.4)	<0.001	<0.001†
One year mortality	1576 (15.5)	1324 (23.9)	<0.001	961 (10.3)	955 (19.1)	<0.001	<0.001†

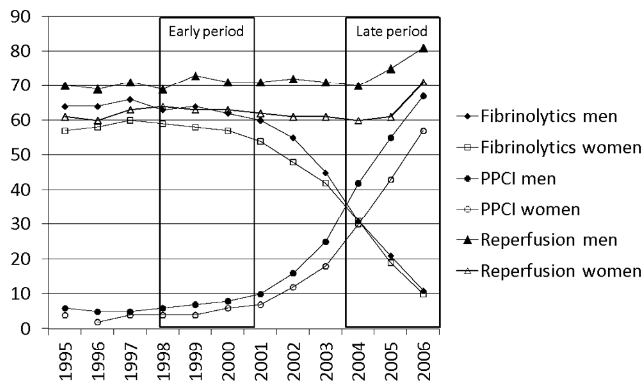
Data presented as numbers (percentages) if not otherwise indicated. §Intracranial haemorrhage, mortal bleeding or given blood transfusion in patients treated with reperfusion therapy.† More in early period ‡ More in late period
IQR, interquartile range; PCI, percutaneous coronary intervention; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCU, coronary care unit

Figure legends

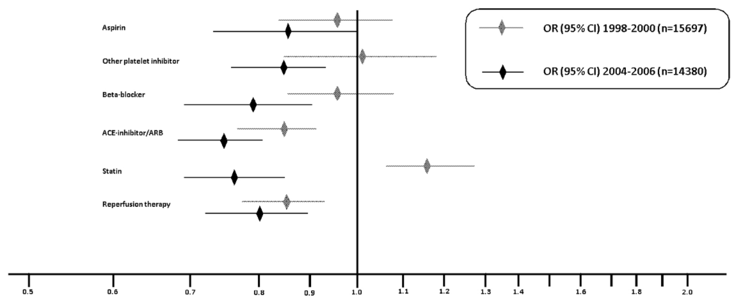
Figure 1. Trends in reperfusion therapy among Swedish STEMI patients 1995 – 2006

Figure 2. Use of coronary angiography, reperfusion therapy and evidence based therapies at discharge in STEMI patients in two time periods after multivariable adjustments, women vs. men

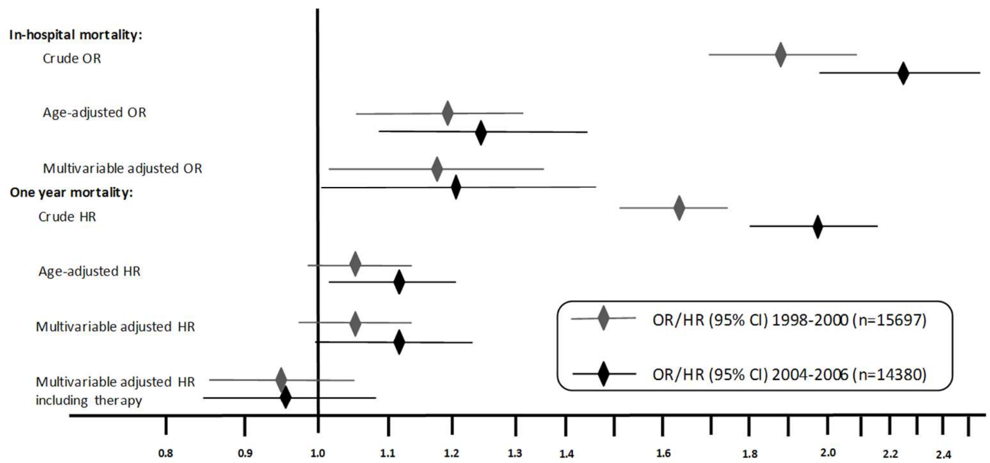
Figure 3. In-hospital and cumulative one year mortality in STEMI patients in two time periods with different dominating reperfusion strategies after multivariable adjustments, women vs. men



Trends in reperfusion therapy among Swedish STEMI patients 1995 – 2006
119x180mm (300 x 300 DPI)



Use of coronary angiography, reperfusion therapy and evidence based therapies at discharge in STEMI patients in two time periods after multivariable adjustments, women vs. men
180x119mm (300 x 300 DPI)



In-hospital and cumulative one year mortality in STEMI patients in two time periods with different dominating reperfusion strategies. Crude, age-adjusted and multivariable adjusted odds and hazard ratios with 95% confidence intervals, women vs. men
295x190mm (120 x 120 DPI)

Figure 1.

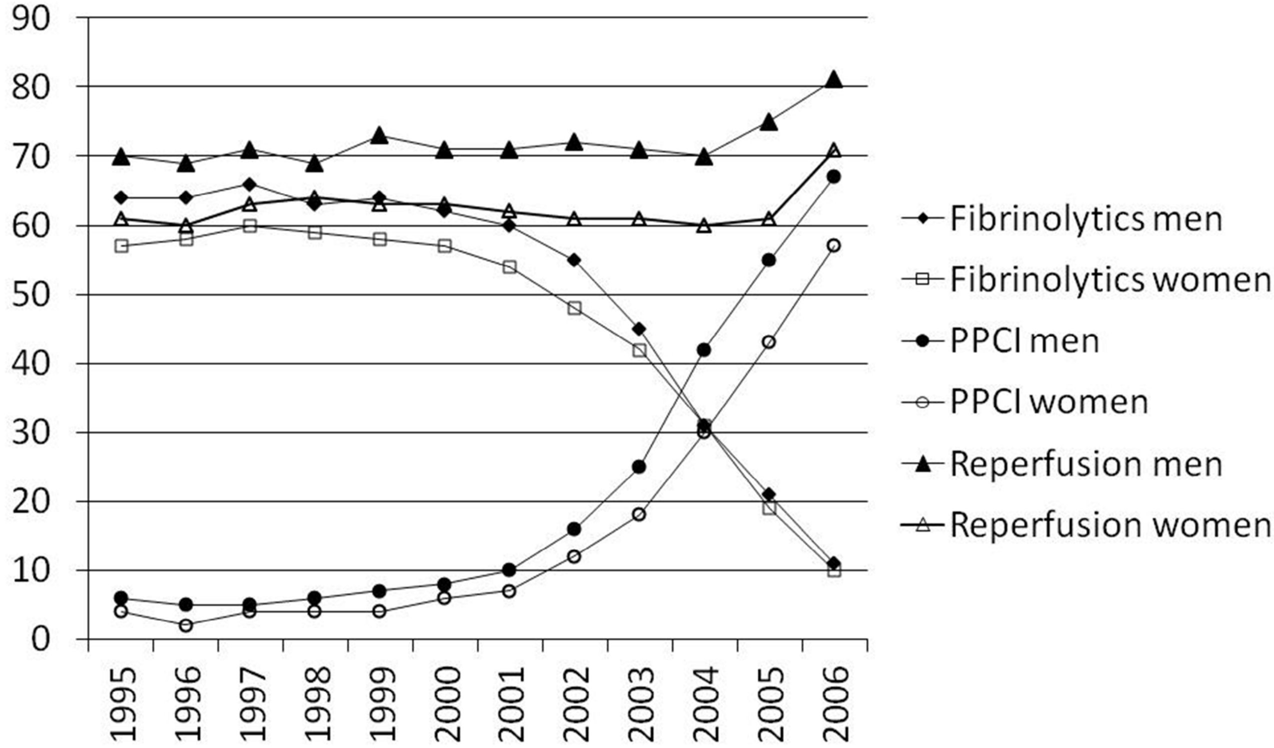

90
80
70
60
50
40
30
20
10
0
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
Fibrinolytics men
Fibrinolytics women
PPCI men
PPCI women
Reperfusion men
Reperfusion women

Figure 2

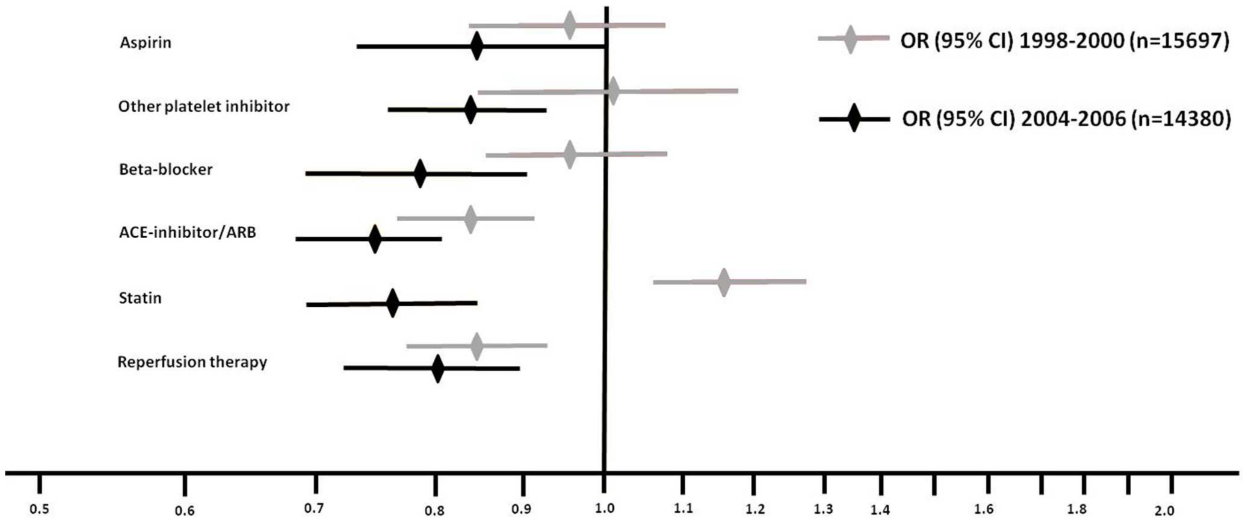
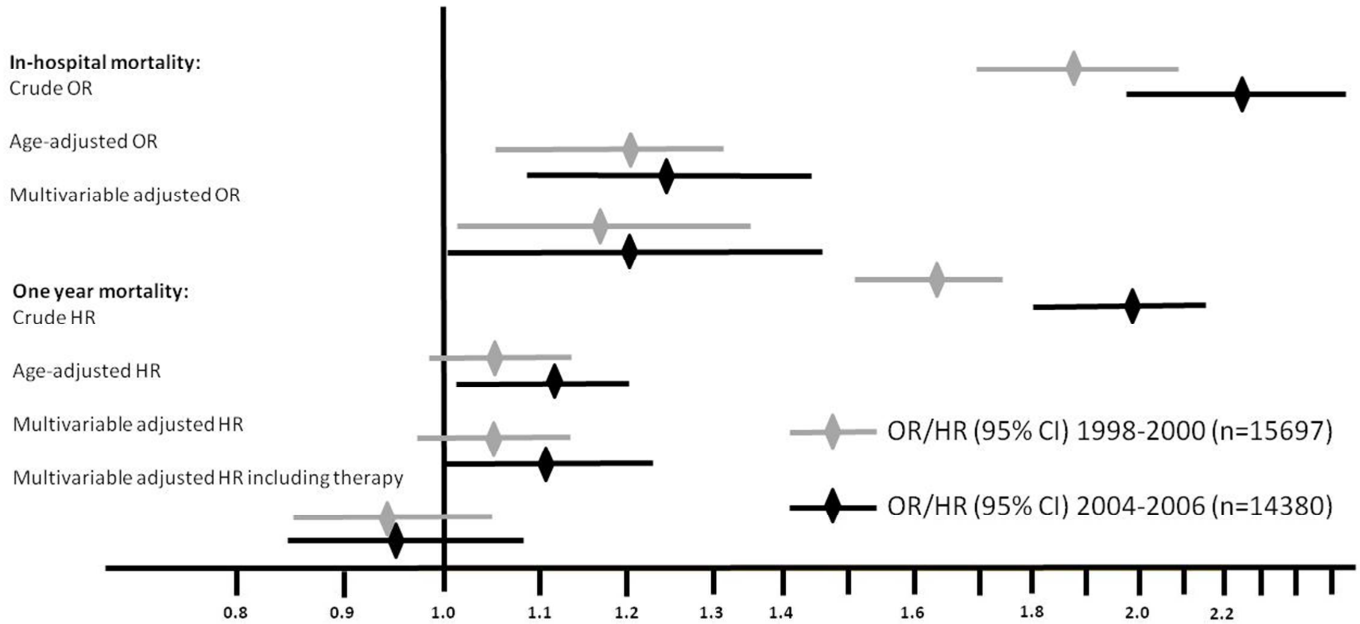

Aspirin
Other platelet inhibitor
Beta-blocker
ACE-inhibitor/ARB
Statin
Reperfusion therapy
OR (95% CI) 1998-2000 (n=15697)
OR (95% CI) 2004-2006 (n=14380)
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.6
1.8
2.0

Figure 3.


In-hospital mortality:
Crude OR
Age-adjusted OR
Multivariable adjusted OR
One year mortality:
Crude HR
Age-adjusted HR
Multivariable adjusted HR
Multivariable adjusted HR including therapy
OR/HR (95% CI) 1998-2000 (n=15697)
OR/HR (95% CI) 2004-2006 (n=14380)
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.6
1.8
2.0
2.2