Sex Differences in Long-Term Mortality after Myocardial Infarction: A Systematic Review

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Abstract

Background—Studies of sex differences in long-term mortality after acute myocardial infarction (AMI) have reported mixed results. A systematic review is needed to characterize what is known about sex differences in long-term outcomes and to define gaps in knowledge.

Methods and Results—We searched the Medline database from 1966 to December 2012 to identify all studies that provided sex-based comparisons of mortality after AMI. Only studies with at least five years of follow-up were reviewed. Of the 1,877 identified abstracts, 52 studies met inclusion criteria, of which 39 were included in this review. Most studies included less than one-third women. There was significant heterogeneity across studies in patient populations, methodology, and risk adjustment, which produced substantial variability in risk estimates. In general, most studies reported higher unadjusted mortality for women compared with men at both 5 and 10 years after AMI; however, many of the differences in mortality became attenuated after adjustment for age. Multivariable models varied between studies; however, most reported a further reduction in sex differences after adjustment for covariates other than age. Few studies examined sex-by-age interactions; however several studies reported interactions between sex and treatment, whereby women have similar mortality risk as men after revascularization.

Conclusions—Sex differences in long-term mortality after AMI are largely explained by differences in age, comorbidities, and treatment utilization between women and men. Future

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research should aim to clarify how these differences in risk factors and presentation contribute to the sex gap in mortality.

Keywords

myocardial infarction; sex; women; mortality; follow-up studies; epidemiology

Numerous studies have examined sex differences in the outcomes of patients with acute myocardial infarction (AMI);[1–5] however, most of these studies have focused on outcomes in the first year leaving considerable uncertainty about long-term events. In general, studies of short-term outcomes have reported higher crude mortality for women after AMI, which are largely explained by differences in age and comorbidities between men and women. In addition, these studies have identified an age-sex interaction, whereby younger women are at particularly high risk of mortality after AMI even after adjustment for other prognostic factors.[4, 5] Significantly less is known about sex differences in mortality over the long term. Although several studies have addressed this topic, they differ considerably with respect to inclusion criteria, methodology, and follow-up, making it difficult to interpret these studies at first glance. Whereas some studies show higher mortality for women after AMI, others have reported no difference or even a survival advantage for women. As such, it remains unclear whether sex differences in mortality persist over the long term and which factors contribute to the gap in mortality, if any. As cardiac care improves and patients are living longer after AMI, it has become increasingly important to evaluate the literature on sex differences in long-term outcomes in order to characterize what is known and to define gaps in knowledge. This information can then be used to generate new hypotheses and to inform future research into this field. Additionally, a review of existing studies would help to determine whether the gap in mortality has changed over time by comparing studies published at different time points and whether the gap varies according to initial treatment (coronary intervention or medical management). Clarifying these issues are critical to our understanding of sex differences in coronary heart disease and for improving cardiac care and outcomes in women. In this article, we systematically review the existing literature on sex differences in long-term mortality after AMI in order to summarize study findings, assess heterogeneity across studies, and identify areas where research is needed.

METHODS

Search Strategy

We searched the Medline database from 1966 to December 2012 to identify studies that provided sex-based comparisons of mortality after AMI. The search strategy included the following terms in either the title or abstract of the article: ("myocardial infarction" or "heart attack" or "acute coronary syndrome" or "AMI") AND ("gender" or "sex" or ("men and women") or ("women and men")) AND ("mortality" or "death" or "survival" or "outcome").

Study abstracts were reviewed for mention of AMI and either mortality or survival as an outcome measure. Full-length articles for abstracts meeting these criteria were retrieved and reviewed separately by two reviewers to identify studies that met the full inclusion criteria. To be included in this review, studies had to 1) include both men and women, 2) follow

patients for a maximum follow-up of at least five years, and 3) report at least one of the following: a) mortality or survival rates by sex; b) sex-specific relative risks or hazards ratio for mortality; c) significance tests for comparing mortality or survival in men and women. We chose to examine only studies with at least five years of follow-up in order to focus on mortality well beyond the acute phase. When two or more studies had overlapping study populations, we selected the study with the most in-depth sex analysis. Only published data were reviewed.

Data Extraction and Methodologic Quality

Two trained reviewers extracted the data using a standardized form to ensure systematic data collection. Variables abstracted included information on study participants, outcomes, covariates, and interactions or stratified analyses. We collected data on 1) unadjusted and adjusted mortality risk ratios or risk differences, and 2) sex-specific mortality rates. When risk ratios (relative risks, odds ratios, or hazard ratios) were not reported, we calculated them from the sex-specific crude rates (i.e. cumulative incidence or incidence rates), whenever possible[6–24] Similarly, when age-adjusted risk estimates were not reported but sufficient data were provided,[15, 17–20, 24] we calculated Mantel-Haenszel pooled odds ratios across age strata using the frequency procedure in SAS. Breslow-Day tests for heterogeneity were evaluated in all cases to ensure that it was appropriate to calculate a pooled risk estimate. Study quality was evaluated using a modified STROBE checklist, which included information on study design, patient selection, follow-up, statistical analyses, covariate adjustment, and potential sources of biases.[25]

Analyses

To evaluate whether long-term mortality after AMI differed between men and women, we examined unadjusted, age-adjusted, and multivariate adjusted mortality estimates. Study heterogeneity was evaluated through visual inspection of forest plots and calculation of an I^2 statistic. Originally we had planned to perform a meta-analysis of the study results; however, after examining the literature, it became clear that a meta-analysis was not appropriate due to heterogeneity in study populations, outcome assessment, and covariates in multivariable models. Heterogeneity across studies was evaluated both qualitatively and quantitatively using I-squared statistics. Multiple sub-group analyses were evaluated to identify potential sources of heterogeneity and determine whether estimates could be pooled across some studies; however, all comparisons yielded I^2-statistics >80%. In general, an I^2 statistic >75% reflects high heterogeneity, indicating that it may not be appropriate to calculate a pooled estimate. Therefore, we chose to qualitatively report and compare individual relative risks. Given previous literature indicating an age-sex interaction, we investigated whether a similar interaction was present in studies of long-term mortality. We also reviewed studies for interactions between sex and treatment when available.

Finally, we examined whether specific time trends could be observed in the risk estimates. Adjusted risk ratios for women versus men were plotted by the midpoint of the study recruitment period, and a line was fit to evaluate trends over time. All statistical analyses were performed using a combination of ReviewManager version 5.1.4 (Cochrane Collaboration, Oxford, UK) and SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

The initial search yielded 4,571 titles, from which 1,877 abstracts were reviewed and 52 articles met the full inclusion criteria. Of these, 13 were subsequently excluded for overlapping study populations, leaving a total of 39 studies included in this review (Figure 1). A description of each study is listed in Table 1. Twenty-three studies followed patients for a maximum of five to ten years after AMI, whereas the remaining 16 studies had maximum follow-up periods longer than ten years. The 12 studies that were excluded for overlapping study populations along with the reason for exclusion are listed in Supplementary Table S1.

Study Quality

Of the 39 studies included in this review,[6–24, 26–45] 27 (69%) were designed to specifically examine sex differences in long-term prognosis after AMI.[6, 7, 9, 11, 13–18, 20–24, 27, 30, 31, 35–37, 39–44] The other 12 studies either included sex as a covariate or evaluated it in secondary analyses. We found significant heterogeneity across studies in study design, patient inclusion criteria, follow-up, and covariates, which are summarized in Supplementary Table S2.

Nine studies (23%) had age-specific inclusion criteria, including four studies that required patients to be less than 65 years of age.[14, 23, 35, 45] Although most studies did not specify treatment criteria, three included only patients who had been treated with PCI,[7, 28, 34] and one limited its sample to patients treated with streptokinase.[22]

Follow-up length and measurement varied widely between studies. Of the 39 studies included in this review, 21 measured long-term mortality from admission, nine from discharge, and 15 from timepoints after discharge (Supplementary Table S2). Eight studies reported long-term mortality measured from multiple starting points. Length of follow-up varied from five to 23 years.

Overview of Study Findings

Baseline and Clinical Characteristics—In nearly all studies, women represented less than half of the patients, with 28 studies (72%) containing less than one-third women. Only two studies had samples with a female majority.[33, 43] Although neither of these studies specifically sampled women, both used inclusion criteria that were more common in women (post-AMI heart failure and enrollment in a Medicare program for the elderly).

To determine whether men and women with AMI differed with respect to baseline characteristics and treatment, we qualitatively compared studies that reported the prevalence of these risk factors in men and women (Supplementary Table S3). More studies reported a higher percentage of diabetes, congestive heart failure (CHF), hypertension, depression, and renal dysfunction in female patients, whereas smoking and history of AMI tended to be more prevalent in male patients. Additionally, studies tended to report higher Killip classes and lower rates of PCI, CABG, and fibrinolytic therapy in women.

Unadjusted Mortality—Of the 26 studies reporting mortality five to nine years after AMI, 13 (50%) reported significantly higher mortality for women compared with men, two (8%) reported higher mortality for men, and seven (27%) found nonsignificant differences in mortality between men and women (Table 2). Most of the relative risk estimates for studies finding a higher unadjusted mortality in women were of comparable magnitude ranging from 1.23 to 1.88.

Similar results were observed for studies examining survival beyond ten years. Eleven studies (73%) reported significantly higher mortality for women, and four studies (27%) found no difference. No studies reported higher mortality for men in unadjusted analyses.

To determine whether study results varied by start point of follow-up, we constructed forest plots of the unadjusted risk ratios stratified by these variables (Figures 2 and 3). No consistent patterns were observed by start point of follow-up.

Age-Adjusted Mortality—Thirteen of the 39 studies reported analyses adjusted for age only, and age-adjusted Mantel-Haenszel odds ratios could be calculated for an additional six studies. Age adjustment was performed in a variety of ways, including logistic or proportional hazards regression, Mantel-Haenszel statistics, and direct standardization.

Age adjustment attenuated the association between female sex and increased long-term mortality (Figure 4). Most studies found nonsignificant differences in age-adjusted mortality between men and women, and one study even found a reversal in risk after adjustment for age.[36] Only two studies continued to report a significantly higher age-adjusted risk of mortality for women, which may be due to inadequate adjustment for the effect of age.[6, 18] Benderly et al categorized age into 5-year increments, and Langorgen et al adjusted for age using only two age strata (<60 and 60).

Multivariate-Adjusted Mortality—Twenty-two studies reported multivariate risk estimates (Figure 5); nearly all of which found a reduction in the sex differences after adjustment. Eleven studies reported nonsignificant female-to-male relative risks after adjustment; two reported significantly higher risk for women; and the remaining nine reported lower risk for women. Interestingly, risk ratios for female sex actually switched directions after adjustment in five of these studies.[31, 32, 36, 37, 40] In all five, female sex was significantly associated with increased mortality in unadjusted analyses but became protective after multivariate adjustment.

Stratified Analyses and Interactions

Age—The twelve studies reporting unadjusted age-stratified analyses are presented in Supplementary Figure S1. No consistent patterns were observed when risk ratios were stratified by age, but there appeared to be a trend towards higher mortality for younger women when compared with men of the same age. For example, Alter et al. found that the hazard of five-year death for women compared with men decreased by 14.2% for every 10-year increase in age.[27] Studies examining interactions between sex and age reported mixed results. Two found significant interactions,[9, 27] two reported borderline significant interactions,[36, 43] and four found no interaction.[30, 38, 42, 44] However, it is important to note

that three of the studies reporting nonsignificant interactions restricted their samples to patients within certain age ranges, and thus may not have been equipped to detect an age interaction.[30, 38, 42]

Treatment—Six studies included only patients treated with PCI or presented results stratified by treatment type.[7, 9, 28, 34, 36, 42] When only patients undergoing revascularization (PCI or CABG) were examined, five studies reported nonsignificant unadjusted and adjusted risk ratios for the effect of sex.[7, 9, 28, 36, 42] Only Hosmane et al reported higher risk for women receiving PCI, which may be due to patient selection given their small sample size (98 patients) and high-risk population (patients with cardiac arrest followed by emergent PCI) studied.[34] Only one study reported results for patients receiving medical management only and found significantly higher mortality for women.[42]

Time Trends—Study recruitment periods varied in length from one to 35 years, and data collected by these studies spanned the years 1951 to 2008. All studies examining temporal trends in post-AMI survival found significant increases in survival for both men and women over their study periods.[8, 18, 31, 40]

Given recent improvements in AMI management over the last several decades, we evaluated whether the adjusted risk ratios for women versus men also declined over time (Figure 6). Although risk ratios varied considerably over time, there did appear to be a slight downward trend, suggesting these sex differences have attenuated slightly over time.

DISCUSSION

To our knowledge, this is the first systematic review to evaluate the existing literature on sex differences in mortality after AMI with follow-up periods of five years or longer. Our review included 39 studies evaluating ranges in follow-up from five to 23 years. We found significant heterogeneity in study populations, methodology, and risk adjustment, which produced substantial variability in risk estimates across studies. Although this heterogeneity precludes a formal meta-analysis, several important findings can be deduced from review of the individual studies.

In general, most studies reported higher unadjusted mortality for women compared with men at both five and ten years after AMI. Several factors may explain the observed trend towards higher long-term mortality in women, including differences in age, AMI risk factors, clinical presentation, and treatment. On average, women tend to be older than men at the time of AMI, which may place them at greater risk of mortality in both the short and long term. Indeed, many of the differences in mortality between men and women became attenuated after adjustment in age. In addition, age may also act as an effect modifier. Although studies examining interactions between sex and age reported mixed results, studies examining stratified analyses between by age tended to show that higher mortality for younger women but lower mortality for older women when compared with men of the same age. These findings are consistent with previous reports of sex differences in short-term mortality after AMI. For example, Vaccarino et al. reported an 11.1% increase in the odds of hospital death for women compared with men for every five-year increase in age.[46]

In addition to age, women and men with AMI have different distributions of cardiovascular risk factors and comorbid conditions, which may also explain the observed mortality difference. Consistent with previous literature, we found that studies tended to report a higher prevalence of diabetes, CHF, hypertension, depression, and renal dysfunction in female patients compared with male patients. In addition, most studies reported poorer clinical presentations and higher rates of complications in women, suggesting that women may experience more severe AMIs placing them at higher risk of mortality over the long term. The higher prevalence of cardiovascular risk factors and poorer clinical presentation in women is likely related to their older age at presentation. Because multivariate models varied substantially between studies, it is difficult to determine which factors contributed to the increased mortality in women. However, most studies reported a further reduction in the sex differences after adjustment for covariates other than age.

Finally, there may be an interaction between sex and treatment type. Previous reviews and meta-analyses have proposed that sex differences in treatment utilization may contribute to some of the observed differences in mortality.[47] Although relatively few studies in this review adjusted for treatment in multivariate analyses, all reported nonsignificant or lower risk of mortality for women after adjustment. Similarly, studies examining analyses stratified by treatment type found nonsignificant risk ratios for women versus men among patients undergoing revascularization (PCI or CABG) but significantly higher mortality for women among patients treated with medical management only. These findings suggest an important sex-by-treatment interaction. Although the mechanisms underlying this interaction are unclear, it may be related to improvements in the standard of care for patients with AMI and increased emphasis on prompt intervention in the PCI era.

Indeed, when we examined time trends, we found a slight downward trend suggesting a reduction in sex differences in long-term mortality over time. Given that men and women appear to have similar mortality risk after PCI or CABG, it is not surprising that sex differences have decreased with the widespread adoption of revascularization procedures as the standard of care. However, larger time trend analyses are needed to confirm this observation.

Our findings are consistent with previous systematic reviews of sex differences in short-term mortality after AMI. Nohria et al. concluded that sex-related mortality differences were less related to intrinsic characteristics of coronary disease in women but instead could be largely explained by differences in age, cardiac risk factors, and use of fibrinolytic therapy and aspirin in women versus men.[4] Similarly, Bell and Nappi cited underuse of cardiac procedures and medical therapies in women as an explanation for the worse prognosis in women;[47] and Berger and Brown found that the mortality rate after primary angioplasty for AMI was equal for men and women.[48] Our study adds to these reviews by identifying factors that contribute to sex differences in long-term prognosis after AMI and exploring potential effect modifiers that place women at particularly high risk. In addition, we consider trends in mortality risk ratios over time, which have not been examined in previous reviews.

We observed significant heterogeneity across studies, which precluded us from conducting a formal meta-analysis and limited our ability to draw uniform inferences from all studies

combined. Several studies contained specific treatment, age, or other inclusion criteria, which created large differences in sample characteristics across studies. Covariate selection and definition also varied across studies, and because sex was not the primary focus of several studies, multivariate models may not have adequately controlled for factors associated with sex. Finally, heterogeneity in follow-up assessment may explain some of the discrepancy in long-term risk estimates between studies. Although we stratified results by start point and duration of follow-up, several strata contained only a few studies making it difficult to identify patterns within and across strata.

Inferences from this review may also by limited by potential selection bias in the inclusion of women in these studies. In nearly all studies, women represented the minority with most populations containing less than one-third women. The exclusion of elderly patients in several studies likely explains some of the sex discrepancy in patient inclusion; however, the low percentage of women in these studies may also represent an important diagnosis or hospitalization referral bias. The underrepresentation of women in many of these studies is an important finding in its own right.

The findings in this review have important implications for both clinicians and researchers. We found that differences in age, clinical presentation, and treatment utilization explain much of the disparity in long-term prognosis after AMI between men and women. Future research should aim to clarify how differences in cardiovascular risk factors and clinical presentation contribute to sex differences in long-term mortality. Specifically, research is needed in three areas. First, studies should focus on identifying which patient factors are the strongest confounders in the relationship between sex and mortality in order to identify potential targets for intervention. Second, previous studies have suggested that the prognostic value of certain risk factors may differ by sex. Three studies in this review reported that diabetes, renal insufficiency, and smoking had a stronger effect on mortality in women than in men, whereas respiratory disease and history of CVD were stronger predictors of mortality in men.[6, 8, 41] Future studies should aim to understand how these factors affect men and women differently in order to identify opportunities to improve care in women. Finally, novel strategies for managing these behavioral and clinical risk factors in women are needed, both at the time of presentation and post-hospitalization. This review sets the foundation for future studies that aim to characterize patient factors that drive the sex gap in mortality and propose new approaches for tailoring care to the needs of women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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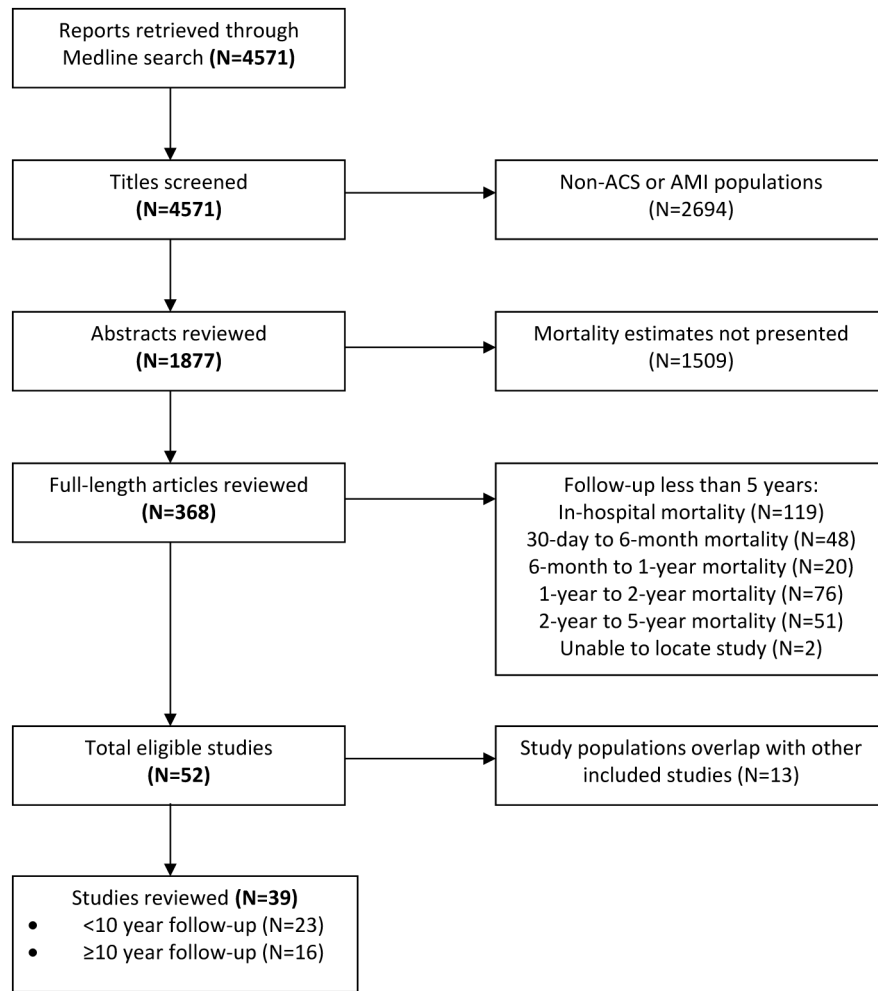
Figure 1.
Flow chart for study retrieval and selection.
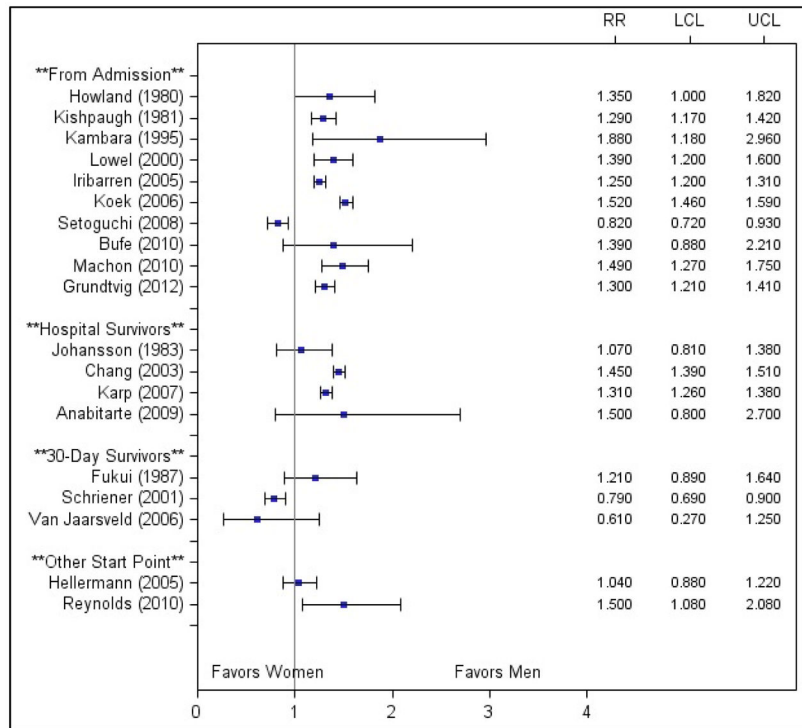
Figure 2.
Unadjusted risk ratios for studies examining 5 to 10 year mortality stratified by start point of follow-up. Abbreviations: LCL, lower confidence limit; RR, risk ratio; UCL, upper confidence limit.
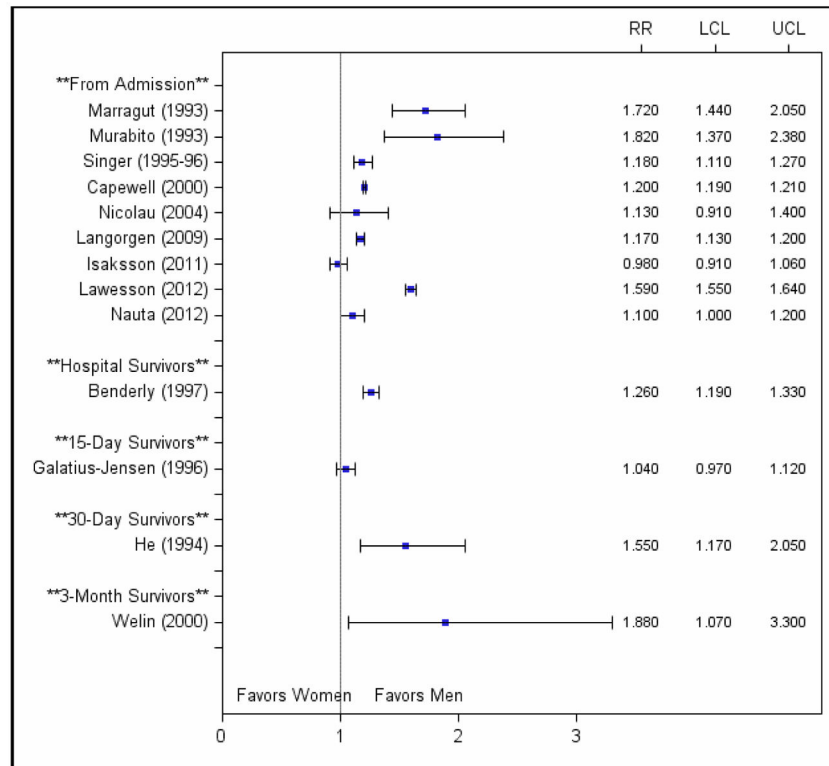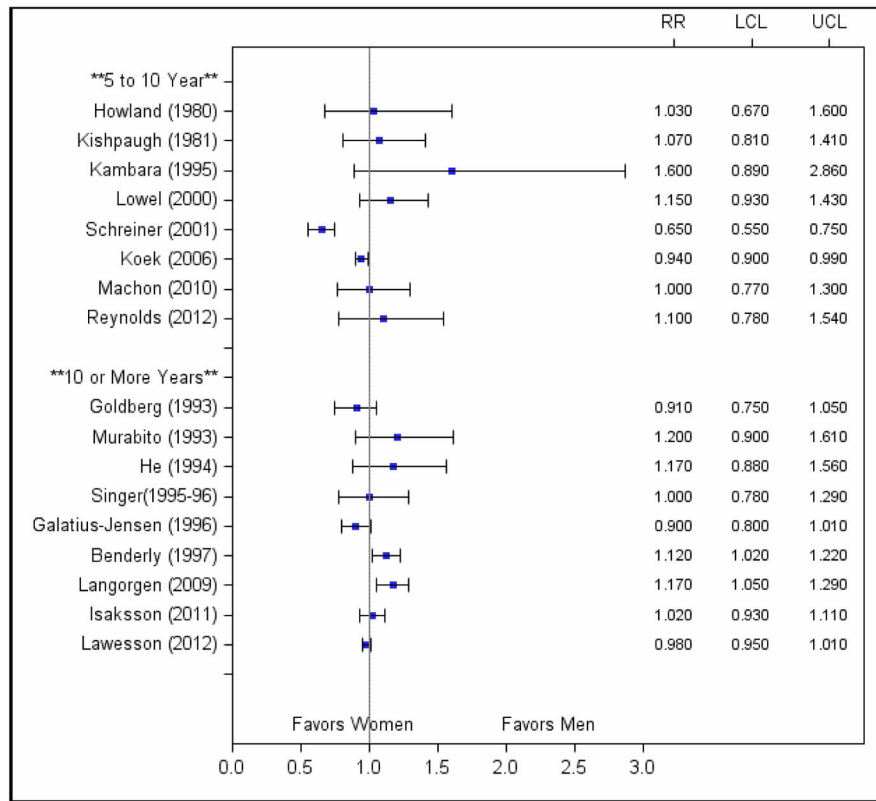
Figure 3.
Unadjusted risk ratios for studies examining 10 or more year mortality stratified by start point of follow-up. Abbreviations: LCL, lower confidence limit; RR, risk ratio; UCL, upper confidence limit.

Figure 4.
Age-adjusted risk ratios for studies stratified by length of follow-up. Abbreviations: LCL, lower confidence limit; RR, risk ratio; UCL, upper confidence limit.

Figure 5.
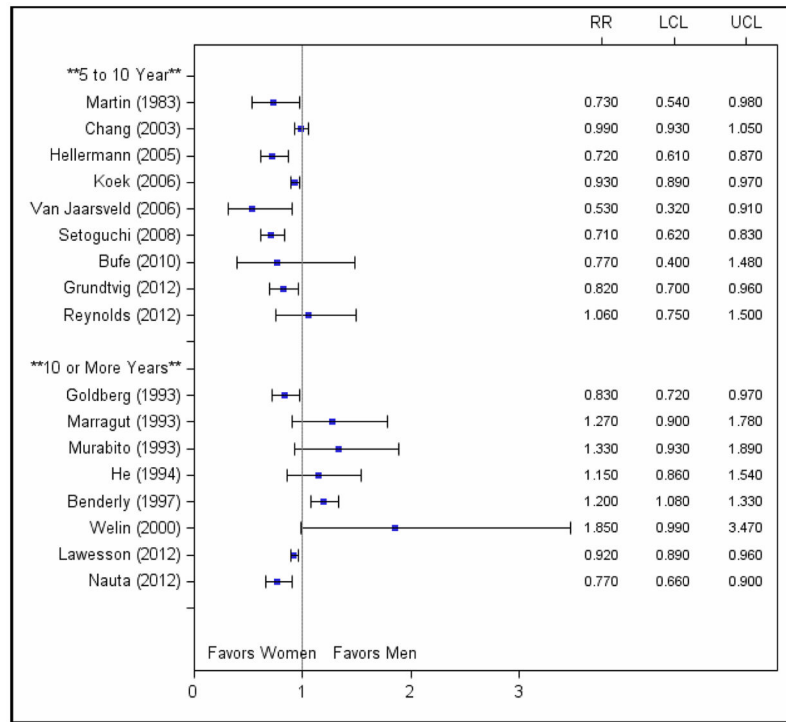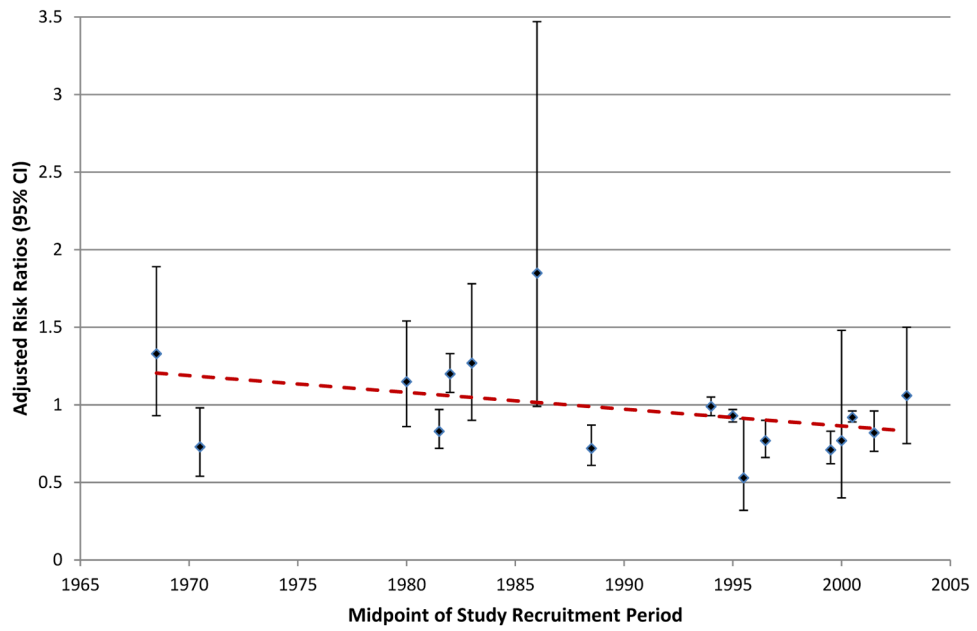Multivariate-adjusted risk ratios for studies stratified by length of follow-up. Abbreviations:
LCL, lower confidence limit; RR, risk ratio; UCL, upper confidence limit.

Figure 6.
Time trends in adjusted risk ratios for women vs. men. Adjusted risk ratios were plotted by mid-point of study recruitment periods.

Table 1

Characteristics of included studies

Study, Year	Study Name, Recruitment Period	Location	Inclusion Criteria	Sample Size (% Women)	Maximum Length of Follow-Up
Alter, 2002[27]	OMID, 1992–1993	Canada	--	25,697 (34.8)	5 years
Chang, 2003[9]	Alberta Ministry of Health, 1993–2000	Canada	First AMI	22,967 (31.2)	5 years
Fukui, 1987[10]	n/a, 1975–1984	Japan	--	790 (23.3)	5 years
Howland, 1980[12]	n/a, 1970–1972	US	--	224 (27.7)	5 years
Kambara, 1995[15]	KYSMI, 1983–1987	Japan	Coronary angiography within 3 months	1000 (18.7)	5 years
Kishpaugh, 1981[17]	n/a, 1970–1972	US	--	2020 (24.9)	5 years
Koek, 2006[36]	Dutch National Hospital Discharge Register, 1995	The Netherlands	First AMI	21,565 (32.9)	5 years
Lowel, 2000[19]	MONICA, 1985–1992	Germany	First AMI Aged <74 years	2210 (25.6)	5 years
Machon, 2010[20]	IBERICA, 1997–2000	Spain	--	1677 (26.8)	5 years
Perers, 2007[41]	Goteborg Swedish Register, 1995–1999	Sweden	STEMI, aged <80 years	546 (30.6)	5 years
Hosmane, 2009[34]	n/a, 2002–2006	US	Cardiac arrest followed by emergent PCI	98 (29.6)	5.5 years
Anabitarte, 2009[28]	Triemli, 1995–?	Switzerland	PCI	978 (19.0)	6 years
Hellermann, 2005[33]	Rochester Epidemiology Project, 1979–1981	US	Heart failure	791 (52.7)	6.6 years
Setoguchi, 2008[43]	n/a, 1999–2000	US	--	1625 (80.5)	6.6 years
Bufe, 2010[7]	n/a, 1999–2001	Germany	PCI	500 (24.8)	7 years
Karp, 2007[16]	Quebec Hospital Discharge Database, 1998–2004	Canada	--	38,543 (38.2)	7 years
Abdulla, 2001[26]	TRACE, 1990–1992	Denmark	--	6676 (33.0)	8 years
Grundtvig, 2011[32]	n/a, 1998–2005	Norway	--	2281 (36.8)	8 years
Iribarren, 2005[13]	n/a, 1995–2002	US	--	30,324 (33.2)	8 years
Van Jaarsveld, 2006[44]	Groningen Longitudinal Aging Study, 1993–1998	The Netherlands	--	198 (38.4)	8 years
Martin, 1983[38]	Perth Coronary Register, 1970–1971	Australia	Aged 30–69 years	666 (25.1)	9 years
Reynolds, 2012[42]	OAT, 2000–2006	US	Total occlusion of infarct-related artery	2201 (22.0)	9 years
Schreiner, 2001[23]	FINMONICA, 1983–1990	Finland	Aged 25–64 years	4900 (25.4)	9 years
Capewell, 2000[8]	Scottish Morbidity Record, 1986–1995	Scotland	First AMI	117,718 (41.8)	10 years
Galatius-Jensen, 1996[30]	Danish Verparamil Infarction Trial, 1979–1981	Denmark	Aged <76 years	3073 (24.0)	10 years
He, 1994[11]	n/a, 1974–1986	China	First AMI	895 (32.8)	10 years

Study, Year	Study Name, Recruitment Period	Location	Inclusion Criteria	Sample Size (% Women)	Maximum Length of Follow-Up
Langorgen, 2009[18]	Western Norway CV Registry, 1979–2001	Norway	First AMI	11878 (35.7)	10 years
Murabito, 1993[39]	Framingham Heart Study, 1951–1986	US	--	385 (30.7)	10 years
Welin, 2000[45]	Goteborg Swedish Register, 1985–1987	Sweden	Aged <65 years	275 (16.4)	10 years
Johansson, 1983[35]	Goteborg Swedish Register, 1968–1977	Sweden	Age <65 years	1521 (17.2)	12 years
Marrugat, 1993[21]	REGICOR, 1978–1988	Spain	Age <74 years	1216 (15.9)	12 years
Nicolau, 2004[22]	n/a, 1985–1997	Brazil	STEMI treated with streptokinase	686 (19.1)	12 years
Benderly, 1997[6]	SPRINT, 1981–1983	Israel	--	4808 (23.3)	13 years
Lawesson, 2012[37]	RIKS-HIA, 1995–2006	Sweden	STEMI	54,146 (34.9)	13 years
Chan, 1989[29]	n/a, 1971–1981	Scotland	Resuscitation from ventricular fibrillation	75 (29.3)	14 years
Goldberg, 1993[31]	Worcester Heart Attack Study, 1975–1981	US	--	3148 (39.1)	14 years
Singer, 1995[24]	Rochester Epidemiology Project, 1960–1979	US	--	1608 (38.0)	23 years
Nauta, 2012[40]	n/a, 1985–2008	The Netherlands	--	14,434 (27.9)	20 years
Isaksson, 2011[14]	Northern Swedish MONICA, 1985–2006	Sweden	Age 25–64 years	8630 (21.6)	23 years

Abbreviations: AMI, acute myocardial infarction; n/a, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 2

Effect of gender on long-term mortality (five or more years) after myocardial infarction

Study, Year	Sample Size	Follow-Up*	Unadjusted				Age-Adjusted		Adjusted for Age and Other Covariates	
			Rate (%)		RR	P or 95% CI	RR	P or 95% CI	RR	P or 95% CI
			Women	Men						
Alter, 2002*	25,697	5 years	--	--	Age-specific	--	--	--	--	--
Capewell, 2000*	117,718	5 years	58.6	45.6	1.29	1.27–1.30	--	--	--	--
		10 years	70.8	59.0	1.20	1.19–1.21	--	--	--	--
Chang, 2003†	22,967	5 years	38.8	26.8	1.45	1.39–1.51	--	--	0.99	0.93–1.05
Fukui, 1987§	651	5 years	27.7	23.2	1.21	0.89–1.64	--	--	--	--
Howland, 1980*	224	5 years	54.0	40.0	1.35	1.00–1.82	1.03	0.67–1.60	--	--
Kambara, 1995*	1,000	5 years	12.4	6.6	1.88	1.18–2.98	1.60	0.89–2.86	--	NS
Kishpaugh, 1981	2,020*	5 years	56.5	43.8	1.29	1.17–1.42	--	--	--	--
	1,495§	5 years	45.3	36.0	1.26	1.09–1.44	--	--	--	--
	1,371#	5 years	50.5	39.0	1.29	1.13–1.48	1.07	0.81–1.41	--	--
Koek, 2006*	21,565	5 years	46.2	33.7	1.52	1.46–1.59	0.94	0.90–0.99	0.93	0.89–0.97
Lowel, 2000	2,210*	5 years	34.2	24.6	1.39	1.20–1.60	1.15	0.93–1.43	--	--
	2,024§	5 years	25.9	18.5	1.40	1.17–1.68	1.12	0.87–1.43	--	--
Machon, 2010	1,677*	5 years	35.0	23.5	1.49	1.27–1.75	1.00	0.77–1.30	--	--
	1,448§	5 years	19.8	13.3	1.49	1.15–1.92	1.05	0.75–1.45	--	--
Perers, 2007§	546	5 years	--	--	--	--	--	NS	--	--
Singer, 1995–96	1,608*	5 years	61.4	50.1	1.23	1.12–1.34	0.99	0.79–1.25	--	--
	1,608*	15 years	74.5	62.9	1.18	1.11–1.27	1.00	0.78–1.29	--	--
	1,014§	5 years	32.0	25.3	1.26	1.03–1.54	0.93	0.68–1.27	--	--
	1,014§	15 years	55.0	44.5	1.24	1.09–1.40	0.95	0.71–1.27	--	--
Hosmane, 2009*	98	5.5 years	--	--	--	--	--	--	5.88	1.15–30.12
Schreiner, 2001§	4,900	5.9 years	17.1	21.7	0.79	0.69–0.90	0.65	0.55–0.75	--	--

Study, Year	Sample Size	Follow-Up*	Unadjusted Rate (%) Women	Men	RR	P or 95% CI	Age-Adjusted RR	P or 95% CI	Adjusted for Age and Other Covariates RR	P or 95% CI
Anabitarte, 2009†	978	3.2 years‡‡	--	--	1.5	0.8–2.7	--	--	--	NS
Hellermann, 2005**	791	6.6 years‡‡	--	--	1.04	0.88–1.22	0.76	p<0.05	0.72	0.61–0.87
Setoguchi, 2008*	1,625	2.2 years‡‡	73.6	79.5	0.82	0.72–0.93	--	--	0.71	0.62–0.83
Bufe, 2010	500*	5.6 years‡‡	17.7	12.8	1.39	0.88–2.21	--	--	0.77	0.40–1.48
	450§	5.6 years‡‡	9.7	6.9	1.43	0.72–2.83	--	--	--	--
Karp, 2007†	38,543	7 years	18.2	13.8	1.31	1.26–1.38	--	--	--	--
Reynolds, 2012††	2,201	7 years	18.2	14.5	1.50	1.08–2.08	1.10	0.78–1.54	1.06	0.75–1.50
Abdulla, 2001§	6,676	8 years	--	--	--	--	--	--	--	NS
Grundtvig, 2012	2,281*	7 years	61.3	47.1	1.30	1.21–1.41	--	--	--	--
	2,013†	7 years	54.7	41.0	1.46	1.31–1.64	--	--	0.82	0.70–0.96
Iribarren, 2005*	30,324	3.5 years‡‡	23.9	19.1	1.25	1.20–1.31	--	--	--	--
Van Jaarsveld, 2006	198*	8 years	--	--	--	--	--	--	0.53	0.32–0.91
	141§	8 years	--	--	0.61	0.27–1.25	--	--	0.31	0.13–0.78
Martin, 1983†	666	9 years	--	--	0.91	NS	--	--	0.73	0.54–0.98
Galatius-Jensen, 1996‡	2,386	10 years	60.9	58.7	1.04	0.97–1.12	0.90	0.80–1.01	--	--
He, 1994§	745	10 years	51.1	35.9	1.55	1.17–2.05	1.17	0.88–1.56	1.15	0.86–1.54
Langorgen, 2009*	9,407	10 years	74.6	64.0	1.17	1.13–1.20	1.17	1.05–1.29	--	--
Murabito, 1993*	385	10 years	69.2	52.8	1.82	1.37–2.38	1.20	0.90–1.61	1.33	0.93–1.89
Welin, 2000‖	275	10 years	35.6	22.2	1.88	1.07–3.30	--	--	1.85	0.99–3.47
Johansson, 1983†	1,521	5 years	20.0	19.0	1.07	0.81–1.38	--	--	--	--
Marragut, 1993	1,216*	5 years‡‡	48.7	28.3	1.72	1.44–2.05	--	--	--	--
	1,061§	5 years‡‡	35.7	19.2	1.86	1.45–2.39	--	--	1.27	0.90–1.78
Nicolau, 2004	686*	5.1 years‡‡	45.6	40.4	1.13	0.91–1.40	--	--	--	NS
	618‡	5.6 years‡‡	35.2	34.9	1.01	0.76–1.33	--	--	--	NS

| Study, Year | Sample Size | Follow-Up* | Unadjusted | | | | Age-Adjusted | | Adjusted for Age and Other Covariates | |
| | | | Rate (%) | | | | | | | |
			Women	Men	RR	P or 95% CI	RR	P or 95% CI	RR	P or 95% CI
Benderly, 1997†	4,808	12 years	65.3	51.8	1.26	1.19–1.33	1.12	1.02–1.22	1.20	1.08–1.33
Lawesson, 2012*	54,146	4.6 years‡‡	45.5	32.3	1.59	1.55–1.64	0.98	0.95–1.01	0.92	0.89–0.96
Chan, 1989†	75	14 years	--	--	--	NS	--	--	--	--
Goldberg, 1993†	3,148	14 years	--	--	>1.0	p<0.05	0.91	0.79–1.05	0.83	0.72–0.97
Nauta, 2012*	14,434	20 years	71.0	65.0	1.10	1.00–1.20	--	--	0.77	0.66–0.90
Isaksson, 2011*	7,466	7.1 years‡‡	35.7	36.3	0.98	0.91–1.06	1.02	0.93–1.11	--	--

*
Long-term mortality calculated from admission

†
Long-term mortality calculated from discharge

‡
Long-term mortality calculated for 15-day survivors

§
Long-term mortality calculated for 30-day survivors

||
Long-term mortality calculated for 3-month survivors

#
Long-term mortality calculated for 4-month survivors

**
Long-term mortality calculated from onset of heart failure.

††
Long-term mortality calculated from randomization (median 8 days after MI).

‡‡
Mean/median length of follow-up when subjects were recruited and followed for varying lengths of time.

Abbreviations: CI, confidence interval; RR, risk ratio.