Sex Differences in Long-Term Mortality After Myocardial Infarction

A Systematic Review

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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 acute myocardial infarction. Only studies with at least 5 years of follow-up were reviewed. Of the 1877 identified abstracts, 52 studies met the inclusion criteria, of which 39 were included in this review. Most studies included fewer 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 acute myocardial infarction; 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 acute myocardial infarction are largely explained by differences in age, comorbidities, and treatment use between women and men. Future research should aim to clarify how these differences in risk factors and presentation contribute to the sex gap in mortality. (Circulation. 2014;130:757-767.)

Key Words: epidemiology □ follow-up studies □ mortality □ myocardial infarction □ sex □ women

Numerous studies have examined sex differences in the outcomes of patients with acute myocardial infarction (AMI); 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 is 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. 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. Thus, it remains unclear whether sex differences in mortality persist over the long term and which factors contribute to the gap in mortality, if any.

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Clinical Perspective on p 767

As cardiac care improves and patients live longer after AMI, it has become increasingly important to evaluate the literature on sex differences in long-term outcomes 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 is 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 to summarize study findings, to assess heterogeneity across studies, and to 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 reviewed and reviewed separately by 2 reviewers to identify studies that met the full inclusion criteria. To be included in this review, studies had to include both men and women, had to follow patients for a maximum follow-up of at least 5 years, and had to report at least 1 of the following: mortality or survival rates by sex, sex-specific relative risks or hazards ratio for mortality, and significance tests for comparing mortality or survival in men and women. We chose to examine only studies with at least 5 years of follow-up to focus on mortality well beyond the acute phase. When ≥2 studies had overlapping study populations, we selected the study with the most in-depth sex analysis. Only published data were reviewed.

**Data Extraction and Methodological 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 unadjusted and adjusted mortality risk ratios or risk differences and on 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 (ie, cumulative incidence or incidence rates) whenever possible.6–24 Similarly, when age-adjusted risk estimates were not reported but sufficient data were provided,25,27–29 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 by use of a modified STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist, which included information on study design, patient selection, follow-up, statistical analyses, covariate adjustment, and potential sources of bias.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 $F$ statistic. Originally, we had planned to perform a meta-analysis of the study results; however, after an examination of the literature, it became clear that a meta-analysis was not appropriate because of the heterogeneity in study populations, outcome assessment, and covariates in multivariable models. Multiple subgroup analyses were evaluated to identify potential sources of heterogeneity and to determine whether estimates could be pooled across some studies; however, all comparisons yielded $F$ statistics >80%. In general, an $F$ 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 with 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 4571 titles, from which 1877 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 study6–24,26–45 is given in Table 1. Twenty-three studies followed up patients for a maximum of 5 to 10 years after AMI, whereas the remaining 16 studies had maximum follow-up periods >10 years. The 12 studies that were excluded for overlapping study populations, along with the reason for exclusion, are listed in Table I in the online-only Data Supplement.

**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...
Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Name, Recruitment Period</th>
<th>Location</th>
<th>Inclusion Criteria</th>
<th>Sample Size (% Women)</th>
<th>Maximum Length of Follow-Up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alter et al, 2002</td>
<td>OMID, 1992–1993</td>
<td>Canada</td>
<td>...</td>
<td>25,697 (34.8)</td>
<td>5</td>
</tr>
<tr>
<td>Fukui et al, 1987</td>
<td>N/A, 1975–1984</td>
<td>Japan</td>
<td>...</td>
<td>790 (23.3)</td>
<td>5</td>
</tr>
<tr>
<td>Howland et al, 1980</td>
<td>N/A, 1970–1972</td>
<td>US</td>
<td>...</td>
<td>224 (27.7)</td>
<td>5</td>
</tr>
<tr>
<td>Kambara et al, 1995</td>
<td>KYSMI, 1983–1987</td>
<td>Japan</td>
<td>Coronary angiography within 3 mo</td>
<td>1,000 (18.7)</td>
<td>5</td>
</tr>
<tr>
<td>Koek et al, 2006</td>
<td>Dutch National Hospital Discharge Register, 1995</td>
<td>The Netherlands</td>
<td>First AMI</td>
<td>21,565 (32.9)</td>
<td>5</td>
</tr>
<tr>
<td>Löwel et al, 2000</td>
<td>MONICA, 1985–1992</td>
<td>Germany</td>
<td>First AMI Age &lt;74 y</td>
<td>2,210 (25.6)</td>
<td>5</td>
</tr>
<tr>
<td>Machón et al, 2010</td>
<td>IBERICA, 1997–2000</td>
<td>Spain</td>
<td>...</td>
<td>1,677 (26.8)</td>
<td>5</td>
</tr>
<tr>
<td>Perers et al, 2007</td>
<td>Goteborg Swedish Register, 1995–1999</td>
<td>Sweden</td>
<td>STEMI, age &lt;80 y</td>
<td>546 (30.6)</td>
<td>5</td>
</tr>
<tr>
<td>Hosmane et al, 2009</td>
<td>N/A, 2002–2006</td>
<td>US</td>
<td>Cardiac arrest followed by emergent PCI</td>
<td>98 (29.6)</td>
<td>5.5</td>
</tr>
<tr>
<td>Anabitarte et al, 2009</td>
<td>Triemli, 1995--?</td>
<td>Switzerland</td>
<td>PCI</td>
<td>978 (19.0)</td>
<td>6</td>
</tr>
<tr>
<td>Hellermann et al, 2005</td>
<td>Rochester Epidemiology Project, 1979–1981</td>
<td>US</td>
<td>Heart failure</td>
<td>791 (52.7)</td>
<td>6.6</td>
</tr>
<tr>
<td>Setoguchi et al, 2008</td>
<td>N/A, 1999–2000</td>
<td>US</td>
<td>...</td>
<td>1,625 (80.5)</td>
<td>6.6</td>
</tr>
<tr>
<td>Bufe et al, 2010</td>
<td>N/A, 1999–2001</td>
<td>Germany</td>
<td>PCI</td>
<td>500 (24.8)</td>
<td>7</td>
</tr>
<tr>
<td>Karp et al, 2007</td>
<td>Quebec Hospital Discharge Database, 1998–2004</td>
<td>Canada</td>
<td>...</td>
<td>38,543 (38.2)</td>
<td>7</td>
</tr>
<tr>
<td>Abdulla et al, 2001</td>
<td>TRACE, 1990–1992</td>
<td>Denmark</td>
<td>...</td>
<td>6,676 (33.0)</td>
<td>8</td>
</tr>
<tr>
<td>Grundtig et al, 2011</td>
<td>N/A, 1998–2005</td>
<td>Norway</td>
<td>...</td>
<td>2,281 (36.8)</td>
<td>8</td>
</tr>
<tr>
<td>Iribarren et al, 2005</td>
<td>N/A, 1995–2002</td>
<td>US</td>
<td>...</td>
<td>30,324 (33.2)</td>
<td>8</td>
</tr>
<tr>
<td>Van Jaarsveld et al, 2006</td>
<td>Groningen Longitudinal Aging Study, 1993–1998</td>
<td>The Netherlands</td>
<td>...</td>
<td>1,98 (38.4)</td>
<td>8</td>
</tr>
<tr>
<td>Reynolds et al, 2012</td>
<td>OAT, 2000–2006</td>
<td>US</td>
<td>Total occlusion of infarct-related artery</td>
<td>2,201 (22.0)</td>
<td>9</td>
</tr>
<tr>
<td>Schreiner et al, 2001</td>
<td>FINMONICA, 1983–1990</td>
<td>Finland</td>
<td>Age 25–64 y</td>
<td>4,900 (25.4)</td>
<td>9</td>
</tr>
<tr>
<td>Capewell et al, 2000</td>
<td>Scottish Morbidity Record, 1986–1995</td>
<td>Scotland</td>
<td>First AMI</td>
<td>117,718 (41.8)</td>
<td>10</td>
</tr>
<tr>
<td>Galatius-Jensen et al, 1996</td>
<td>Danish Verapamil Infarction Trial, 1979–1981</td>
<td>Denmark</td>
<td>Age &lt;76 y</td>
<td>3,073 (24.0)</td>
<td>10</td>
</tr>
<tr>
<td>He et al, 1994</td>
<td>N/A, 1974–1986</td>
<td>China</td>
<td>First AMI</td>
<td>895 (32.8)</td>
<td>10</td>
</tr>
<tr>
<td>Langorgen et al, 2009</td>
<td>Western Norway CV Registry, 1979–2001</td>
<td>Norway</td>
<td>First AMI</td>
<td>11,878 (35.7)</td>
<td>10</td>
</tr>
<tr>
<td>Murabito et al, 1993</td>
<td>Framingham Heart Study, 1951–1986</td>
<td>US</td>
<td>...</td>
<td>385 (30.7)</td>
<td>10</td>
</tr>
<tr>
<td>Welin et al, 2000</td>
<td>Goteborg Swedish Register, 1985–1987</td>
<td>Sweden</td>
<td>Age &lt;65 y</td>
<td>275 (16.4)</td>
<td>10</td>
</tr>
<tr>
<td>Johansson et al, 1983</td>
<td>Goteborg Swedish Register, 1968–1977</td>
<td>Sweden</td>
<td>Age &lt;65 y</td>
<td>1,521 (17.2)</td>
<td>12</td>
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<tr>
<td>Marrugat et al, 1993</td>
<td>REGICOR, 1978–1988</td>
<td>Spain</td>
<td>Age &lt;74 y</td>
<td>1,216 (15.9)</td>
<td>12</td>
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<tr>
<td>Benderly et al, 1997</td>
<td>SPRINT, 1981–1983</td>
<td>Israel</td>
<td>...</td>
<td>4,808 (23.3)</td>
<td>13</td>
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<tr>
<td>Lawesson et al, 2012</td>
<td>RIKS-HIA, 1995–2006</td>
<td>Sweden</td>
<td>STEMI</td>
<td>54,146 (34.9)</td>
<td>13</td>
</tr>
<tr>
<td>Chan et al, 1989</td>
<td>N/A, 1971–1981</td>
<td>Scotland</td>
<td>Resuscitation from ventricular fibrillation</td>
<td>75 (29.3)</td>
<td>14</td>
</tr>
<tr>
<td>Singer et al, 1995</td>
<td>Rochester Epidemiology Project, 1960–1979</td>
<td>US</td>
<td>...</td>
<td>1,608 (38.0)</td>
<td>23</td>
</tr>
<tr>
<td>Nauta et al, 2012</td>
<td>N/A, 1985–2008</td>
<td>The Netherlands</td>
<td>...</td>
<td>14,434 (27.9)</td>
<td>20</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; FINMONICA, Finnish Monitoring International Cardiovascular Disease; IBERICA, Investigacion Busqueda Especifica y Registro de Isquemia Coronaria Aguda; KYSMI, Kyoto and Shiga Myocardial Infarction; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; N/A, not applicable; OAT, Occluded Artery Trial; OMID, Ontario Myocardial Infarction Database; PCI, percutaneous coronary intervention; REGICOR, Registre Gironi del Cor; RIKS-HIA, Register of Information and Knowledge about Swedish Heart Intensive Care Admissions; SPRINT, Secondary Prevention Reinfarction Israeli Nifedipine Trial; STEMI, ST-segment–elevation myocardial infarction; and TRACE, Trandolapril Cardiac Evaluation.
Table 2. Effect of Sex on Long-Term Mortality (≥5 Years) After Myocardial Infarction

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Sample Size, n</th>
<th>Follow-Up, y*</th>
<th>Rate, %</th>
<th></th>
<th>Age-Adjusted</th>
<th>Adjusted for Age and Other Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Women</td>
<td>Men</td>
<td>RR</td>
<td>RR or 95% CI</td>
</tr>
<tr>
<td></td>
<td>Rate, %</td>
<td></td>
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<td></td>
<td>Age-specific</td>
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<tr>
<td></td>
<td>Rate, %</td>
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<tr>
<td>Alter et al,27</td>
<td>25697</td>
<td>5</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2002*</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Capewell et al,9</td>
<td>117718</td>
<td>5</td>
<td>58.6</td>
<td>45.6</td>
<td>1.29</td>
<td>1.27–1.30</td>
</tr>
<tr>
<td>2000*</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al,9</td>
<td>22967</td>
<td>5</td>
<td>38.8</td>
<td>26.8</td>
<td>1.45</td>
<td>1.39–1.51</td>
</tr>
<tr>
<td>2003†</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fukui et al,8</td>
<td>651</td>
<td>5</td>
<td>27.7</td>
<td>23.2</td>
<td>1.21</td>
<td>0.89–1.64</td>
</tr>
<tr>
<td>1987§</td>
<td></td>
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<tr>
<td>Howland et al,9</td>
<td>224</td>
<td>5</td>
<td>54.0</td>
<td>40.0</td>
<td>1.35</td>
<td>1.00–1.82</td>
</tr>
<tr>
<td>1980*</td>
<td></td>
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<tr>
<td>Kambara et al,9</td>
<td>1000</td>
<td>5</td>
<td>12.4</td>
<td>6.6</td>
<td>1.88</td>
<td>1.18–2.98</td>
</tr>
<tr>
<td>1995*</td>
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<td></td>
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<tr>
<td>Kishpaugh et al,8</td>
<td>2020*</td>
<td>5</td>
<td>56.5</td>
<td>43.8</td>
<td>1.29</td>
<td>1.17–1.42</td>
</tr>
<tr>
<td>et al,1981†</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Machón et al,20</td>
<td>1677*</td>
<td>5</td>
<td>35.0</td>
<td>23.5</td>
<td>1.49</td>
<td>1.27–1.75</td>
</tr>
<tr>
<td>2010</td>
<td></td>
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<td></td>
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<tr>
<td>Machón et al,21</td>
<td>1448§</td>
<td>5</td>
<td>19.8</td>
<td>13.3</td>
<td>1.49</td>
<td>1.15–1.92</td>
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<td>2006†</td>
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<td></td>
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<tr>
<td>Perers et al,41</td>
<td>546</td>
<td>5</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2007§</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Singer et al,18</td>
<td>1600§</td>
<td>5</td>
<td>61.4</td>
<td>50.1</td>
<td>1.23</td>
<td>1.12–1.34</td>
</tr>
<tr>
<td>1995–1996†</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Schreiner et al,22</td>
<td>1608*</td>
<td>15</td>
<td>74.5</td>
<td>62.9</td>
<td>1.18</td>
<td>1.11–1.27</td>
</tr>
<tr>
<td>et al,2001§</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Anabtarte et al,23</td>
<td>978</td>
<td>3.2‡‡</td>
<td>...</td>
<td>...</td>
<td>1.5</td>
<td>0.8–2.7</td>
</tr>
<tr>
<td>et al,2009†</td>
<td></td>
<td></td>
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<tr>
<td>Hellemann et al,24</td>
<td>791</td>
<td>6.6‡‡</td>
<td>...</td>
<td>...</td>
<td>1.04</td>
<td>0.88–1.22</td>
</tr>
<tr>
<td>et al,2005**</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Setoguchi et al,25</td>
<td>1625</td>
<td>2.2‡‡</td>
<td>73.6</td>
<td>79.5</td>
<td>0.82</td>
<td>0.72–0.93</td>
</tr>
<tr>
<td>2008*</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bufe‡‡*et al,26</td>
<td>500</td>
<td>5.6‡‡</td>
<td>17.7</td>
<td>12.8</td>
<td>1.39</td>
<td>0.88–2.21</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Karp et al,27</td>
<td>38543</td>
<td>7</td>
<td>18.2</td>
<td>13.8</td>
<td>1.31</td>
<td>1.26–1.38</td>
</tr>
<tr>
<td>2007†</td>
<td></td>
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<tr>
<td>Reynolds et al,28</td>
<td>2201</td>
<td>7</td>
<td>18.2</td>
<td>14.5</td>
<td>1.50</td>
<td>1.08–2.08</td>
</tr>
<tr>
<td>et al,2012††</td>
<td></td>
<td></td>
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<tr>
<td>Abdulla et al,29</td>
<td>6676</td>
<td>8</td>
<td>...</td>
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<td>2001§</td>
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<tr>
<td>Grundtvig et al,30</td>
<td>2281*</td>
<td>7</td>
<td>61.3</td>
<td>47.1</td>
<td>1.30</td>
<td>1.21–1.41</td>
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<tr>
<td>et al,2012†</td>
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<td>Iribarren et al,31</td>
<td>30324</td>
<td>3.5‡‡</td>
<td>23.9</td>
<td>19.1</td>
<td>1.25</td>
<td>1.20–1.31</td>
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<tr>
<td>et al,2005*</td>
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it in secondary analyses. We found significant heterogeneity across studies in study design, patient inclusion criteria, follow-up, and covariates, which are summarized in Table II in the online-only Data Supplement.

Nine studies (23%) had age-specific inclusion criteria, including 4 studies that required patients to be <65 years of age. Although most studies did not specify treatment criteria, 3 studies included only patients who had been treated with percutaneous coronary intervention (PCI), and 1 study limited its sample to patients treated with streptokinase.

Follow-up length and measurement varied widely between studies. Of the 39 studies included in this review, 21 measured long-term mortality from admission, 9 from discharge, and 15 from time points after discharge (Table II in the online-only Data Supplement). Eight studies reported long-term mortality measured from multiple starting points. Length of follow-up varied from 5 to 23 years.

Overview of Study Findings

Baseline and Clinical Characteristics

In nearly all studies, women represented fewer than half of the patients, with 28 studies (72%) containing fewer than one-third women. Only 2 studies had samples with a female majority. Although neither of these studies specifically

<table>
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<th>Study, Year</th>
<th>Sample Size, n</th>
<th>Follow-Up, y*</th>
<th>Women</th>
<th>Men</th>
<th>Rate, %</th>
<th>RR</th>
<th>P or 95% CI</th>
<th>Age-Adjusted</th>
<th>Adjusted for Age and Other Covariates</th>
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<td>9</td>
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<td>...</td>
<td>0.91</td>
<td>NS</td>
<td>...</td>
<td>...</td>
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<td>745</td>
<td>10</td>
<td>51.1</td>
<td>35.9</td>
<td>1.55</td>
<td>1.17–2.05</td>
<td>1.17</td>
<td>0.88–1.56</td>
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<td>64.0</td>
<td>1.17</td>
<td>1.13–1.20</td>
<td>1.17</td>
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<td>385</td>
<td>10</td>
<td>69.2</td>
<td>52.8</td>
<td>1.82</td>
<td>1.37–2.38</td>
<td>1.20</td>
<td>0.90–1.61</td>
<td>1.33</td>
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<tr>
<td>Wein et al, 2000</td>
<td>275</td>
<td>10</td>
<td>35.6</td>
<td>22.2</td>
<td>1.88</td>
<td>1.07–3.30</td>
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<td>5</td>
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<td>19.0</td>
<td>1.07</td>
<td>0.81–1.38</td>
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<td>Marrugat et al, 1993</td>
<td>1216*</td>
<td>5‡‡</td>
<td>48.7</td>
<td>28.3</td>
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<td>Goldberg et al, 1993‡</td>
<td>3148</td>
<td>14</td>
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<td>...</td>
<td>&gt;1.0</td>
<td>&lt;0.05</td>
<td>0.91</td>
<td>0.79–1.05</td>
<td>0.83</td>
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<tr>
<td>Nauta et al, 2012*</td>
<td>14434</td>
<td>20</td>
<td>71.0</td>
<td>65.0</td>
<td>1.10</td>
<td>1.00–1.20</td>
<td>...</td>
<td>...</td>
<td>0.77</td>
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<tr>
<td>Isaksson et al, 2011*</td>
<td>7466</td>
<td>7.1‡‡</td>
<td>35.7</td>
<td>36.3</td>
<td>0.98</td>
<td>0.91–1.06</td>
<td>1.02</td>
<td>0.93–1.11</td>
<td>...</td>
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</table>

CI indicates confidence interval; and RR, risk ratio.
*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.
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 (Table III in the online-only Data Supplement). More studies reported a higher percentage of diabetes mellitus, congestive heart failure, 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, coronary artery bypass graft surgery, and fibrinolytic therapy in women.

Unadjusted Mortality

Of the 26 studies reporting mortality 5 to 9 years after AMI, 13 (50%) reported significantly higher mortality for women compared with men, 2 (8%) reported higher mortality for men, and 7 (27%) found nonsignificant differences in mortality between men and women (Table II). Most of the relative risk estimates for studies finding a higher unadjusted mortality in women tended to be more prevalent in male patients. Additionally, studies tended to report higher Killip classes and lower rates of PCI, coronary artery bypass graft surgery, and fibrinolytic therapy in women.

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 6 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 1 study even found a reversal in risk after adjustment for age. Only 2 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. Benderly et al categorized age into 5-year increments, and Langorgen et al adjusted for age using only 2 age strata (<60 and ≥60 years).

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; 2 reported significantly higher risk for women; and the remaining 9
reported lower risk for women. Interestingly, risk ratios for female sex actually switched directions after adjustment in 5 of these studies. 31,32,36,37,40 In all 5 studies, female sex was significantly associated with increased mortality in unadjusted analyses but became protective after multivariate adjustment.

**Stratified Analyses and Interactions**

**Age**
The 12 studies reporting unadjusted age-stratified analyses are presented in Figure I in the online-only Data Supplement. No consistent patterns were observed when risk ratios were stratified by age, but there appeared to be a trend toward higher mortality for younger women compared with men of the same age. For example, Alter et al 27 found that the hazard of 5-year death for women compared with men decreased by 14.2% for every 10-year increase in age.

Studies examining interactions between sex and age reported mixed results. Two found significant interactions, 9,27 2 reported borderline significant interactions, 36,43 and 4 found no interaction. 30,38,42,44 However, it is important to note that 3 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. 7,9,23,34,36,42 When only patients undergoing revascularization (PCI or coronary artery bypass graft surgery) were examined, 5 studies reported nonsignificant unadjusted and adjusted risk ratios for the effect of sex. 7,9,23,36,42 Only Hosmane et al 44 reported higher risk for women receiving PCI, which may be due to patient selection given their small sample size (98 patients) and the high-risk population (patients with cardiac arrest followed by emergent PCI) studied. Only 1 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 1 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 appeared to be a slight downward trend, suggesting these sex differences have attenuated slightly over time.

**Discussion**
To the best of 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 ≥5 years. Our review included 39 studies evaluating ranges in follow-up from 5 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 a review of the individual studies.

In general, most studies reported higher unadjusted mortality for women compared with men at both 5 and 10 years after AMI. Several factors may explain the observed trend toward 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 for age. In addition, age may 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 higher mortality for younger women but lower mortality for older women 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.46 reported an 11.1% increase in the odds of hospital death for women compared with men for every 5-year increase in age.

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 mellitus, congestive heart failure, 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 are 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 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 versus men among patients undergoing revascularization (PCI or coronary artery bypass graft surgery) 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, they may be related to improvements in the standard of care for patients with AMI and increased emphasis on prompt intervention in the PCI era.

![Figure 4. Age-adjusted risk ratios (RRs) for studies stratified by length of follow-up.](http://circ.ahajournals.org/content/early/2014/09/23/CIRCULATIONAHA.114.016041.full.pdf)
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 coronary artery bypass graft surgery, 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 compared with men. Similarly, Bell and Nappi cited underuse of cardiac procedures and medical therapies in women as an explanation for the worse prognosis in women, and Berger and Brown found that the mortality rate after primary angioplasty for AMI was equal for men and women. 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 fewer 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 use 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 3 areas. First, studies should focus on identifying which patient factors are associated with sex. Three studies in this report evaluated diabetes mellitus, renal insufficiency, and smoking had a stronger effect on mortality in women than in men, whereas respiratory disease and history of cardiovascular disease were stronger predictors of mortality in men.6,8,41 Future studies should aim to understand how these factors affect men and women differently 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 after hospitalization. This review sets the foundation for future studies that aim to characterize patient factors that drive the sex gap in mortality and to propose new approaches for tailoring care to the needs of women.

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Disclosures

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References


**CLINICAL PERSPECTIVE**

Studies of sex differences in long-term mortality after acute myocardial infarction (AMI) have reported mixed results, which may be explained by differences in inclusion criteria, methodology, and follow-up. We reviewed 39 studies examining sex differences in mortality ≥5 years after AMI to summarize current knowledge and to identify areas where research is needed. Although there was substantial variability in risk estimates across studies, we found that most studies reported higher unadjusted mortality for women compared with men at both 5 and 10 years after AMI. Many of these differences in mortality became attenuated after multivariable adjustment, suggesting that sex differences in long-term mortality after AMI can be largely explained by differences in age, comorbidities, and treatment. In addition, we identified a possible sex-by-treatment interaction whereby women have a mortality risk similar to that of men after revascularization. The findings in this review have important implications for future research examining sex differences in mortality after AMI. We have highlighted 3 areas of research that are needed: identifying which patient factors contribute most to the sex gap in mortality, understanding how risk factors may affect men and women differently after AMI, and developing novel strategies for managing behavioral and clinical risk factors in women. 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.
Sex Differences in Long-Term Mortality After Myocardial Infarction: A Systematic Review
Emily M. Bucholz, Neel M. Butala, Saif S. Rathore, Rachel P. Dreyer, Alexandra J. Lansky and Harlan M. Krumholz

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SUPPLEMENTAL MATERIAL

Title: Sex Differences in Long-term Mortality after Myocardial Infarction: A Systematic Review
Authors: Emily M. Bucholz, MPH, Neel M. Butala, BA, Saif S. Rathore, MD, PhD, MPH, Rachel P. Dreyer, PhD, Alexandra J. Lansky, MD, Harlan M. Krumholz, MD, SM

Supplemental Tables: 3
Supplemental Figures: 1
### Supplemental Table S1. Characteristics of excluded studies

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<td>Goldberg, 1993</td>
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<td>- Shorter follow-up of 5 years</td>
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<td>- Results are stratified by diabetes</td>
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<td>Isaksson 2011</td>
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<td>- Results stratified by diabetes</td>
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<td>- Shorter follow-up</td>
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REFERENCES


### Supplemental Table S2. Study quality characteristics

<table>
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<th>Study Design</th>
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<td>Hospital/community cohort</td>
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<td>Retrospective study design</td>
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<th>Diagnosis of AMI</th>
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<td>1 of 3 established criteria*</td>
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<td>Discharge diagnosis/ICD-9 codes</td>
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<table>
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<th>Inclusion Criteria</th>
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<td>Specific conditions</td>
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<tr>
<td>Heart failure</td>
<td>31</td>
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<tr>
<td>Cardiac arrest</td>
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<td>Ventricular fibrillation</td>
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<td>Age criteria</td>
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<th>Treatment</th>
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<td>PCI only</td>
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<tr>
<td>Streptokinase only</td>
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<table>
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<th>Follow-Up</th>
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<td>Admission</td>
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<tr>
<td>Discharge</td>
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<td>15 days</td>
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<td>30 days</td>
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<td>3 months</td>
<td>40</td>
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<tr>
<td>After onset of heart failure†</td>
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<td>After randomization§</td>
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<tr>
<td>Multiple start points analyzed</td>
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<table>
<thead>
<tr>
<th>Length of follow-up</th>
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<td>&lt;10 years</td>
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<tr>
<td>≥10 years</td>
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<td>--------------------------------------------------------------</td>
<td>---------------------------------------------------------</td>
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<tr>
<td>Population registries/death certificates</td>
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</tr>
<tr>
<td>Medical records/patient contact</td>
<td>6,26,32</td>
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<tr>
<td>Administrative claims data</td>
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<td>Population registries and medical records</td>
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Provided information on losses to follow-up                  | 8,9,10,13,15,16,18,19,20,21,27,28,30,33,35,36,39,40,41,45 |

* Criteria for diagnosis of AMI included: 1) ischemic symptoms, 2) ECG changes, and 3) elevations in cardiac enzymes
† In study by Hellerman et al, 59% of heart failure episodes occurred within 30 days of MI and 68% within 1 year post-MI
‡ In study by Lowel et al, survival was calculated only among patients who survived first 24 hours of admission.
§ In study by Reynolds et al, median (IQR) time from MI to randomization was 8.5 (5.0, 17.0) in women and 8.0 (5.0, 16.0) in men.
### Supplementary Table S3. Distribution of risk factors, clinical presentation, and treatment in men vs. women across studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Higher Percentage in Women</th>
<th>No Difference Between Genders</th>
<th>Lower Percentage in Women</th>
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<tr>
<td><strong>Risk Factors/Comorbid Conditions</strong></td>
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<td>Diabetes Mellitus</td>
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<td>History of CHF</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Smoking</td>
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<td>Prior MI</td>
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<td>6, 19, 22, 32, 34, 37, 42, 45</td>
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<td>Obesity</td>
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<td>Angina</td>
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<td>Depression/Psychiatric History</td>
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<td>Renal Dysfunction</td>
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<td>Hypercholesterolemia</td>
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<td><strong>Clinical Presentation</strong></td>
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<td>Killip Class 3 or 4</td>
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<td>Anterior MI</td>
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<td>Cardiac Arrest</td>
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<td>CHF/Pulmonary Edema</td>
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<td>Cardiogenic Shock</td>
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<td>Heart block</td>
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<td>CABG</td>
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Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.