Gender gap in acute coronary heart disease: Myth or reality?

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Abstract

AIM: To investigate potential gender differences in the prevalence of cardiovascular risk factors, cardiovascular disease (CVD) management, and prognosis in acute coronary syndrome (ACS).

METHODS: A systematic literature search was performed through Medline using pre-specified keywords. An additional search was performed, focusing specifically on randomized controlled clinical trials in relation to therapeutic intervention and prognosis. In total, 92 relevant articles were found.

RESULTS: Women with CVD tended to have more hypertension and diabetes at the time of presentation, whereas men were more likely to smoke. Coronary angiography and revascularization by percutaneous coronary intervention were performed more often in men. Women were at a greater risk of short-term mortality and complications after revascularization. Interestingly, women under 40 years presenting with ACS were at highest risk of cardiovascular death compared with men of the same age, irrespective of risk factors. This disadvantage disappeared in older age. The long-term mortality risk of ACS was similar in men and women, and even in favor of women.

CONCLUSION: Mortality rates are higher among young women with ACS, but this difference tends to disappear with age, and long-term prognosis is even better among older women.

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Key words: Cardiovascular disease; Gender; Myocardial infarction; Coronary artery bypass grafting; Percutaneous coronary intervention; Postoperative complications; Mortality; Prognosis; Estrogens

INTRODUCTION

Cardiovascular disease (CVD) is an important cause of death among both men and women. In women, CVD develops 7 to 10 years later than in men, potentially because of a protective effect of estrogens. However, CVD is the main cause of death among women and its occurrence narrows women’s survival advantage over men[1]. In most parts of the world, the mortality rate has declined in the last 30 years, except for Eastern Europe and China[2]. In the
United States in 2007, 391,886 men died because of CVD, compared with 421,918 women[3], while 10 years previously the mortality rate of CVD in men was significantly higher in several countries[4]. Some studies have suggested gender differences in presentation and treatment of CVD and acute coronary syndrome (ACS), but there are many uncertainties and discrepancies between these studies[4,5]. Besides differences in presentation, women also seem to have different abnormalities with regard to electrocardiography and scintigraphy, compared with men[6]. The aim of this review is to provide an overview of what is known nowadays with respect to possible gender differences in cardiovascular risk factors, therapy and prognosis of ACS.

MATERIALS AND METHODS

A systematic literature search was performed through Medline using pre-specified keywords. The following keywords with synonyms were used for selecting relevant studies: CVD, coronary artery disease (CAD), ACS/event, ischemic heart disease, myocardial infarction (MI), gender, sex, women, men, differences, estrogen, hormone replacement therapy (HRT), coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI), revascularization, readmission, postoperative complications, outcome, and hospital mortality. Only studies that included both men and women were eligible for review. Of 2260 articles found, 199 articles appeared relevant after screening of the title and abstract. Furthermore, through a search of the references in the articles obtained by these keywords, 30 additional relevant articles were found.

A more focused exclusion of articles was then performed in relation to therapy and prognosis of ACS. Articles published before 2000 were excluded, because therapy, operative techniques and thereby prognosis have a high tendency to change over time. Selected articles included patients with ACS, unstable angina, acute MI, ST elevation MI (STEMI) and non-STEMI, and subse- following years. Selected articles included both men and women were eligible for review. Of 2260 articles found, 199 articles appeared relevant after screening of the title and abstract. Furthermore, through a search of the references in the articles obtained by these keywords, 30 additional relevant articles were found. A more focused exclusion of articles was then performed in relation to therapy and prognosis of ACS. Articles published before 2000 were excluded, because therapy, operative techniques and thereby prognosis have a high tendency to change over time. Selected articles included patients with ACS, unstable angina, acute MI, ST elevation MI (STEMI) and non-STEMI, and subse-

RESULTS

Epidemiology

The prevalence of CVD increased with age and was higher among men. The prevalence of coronary heart disease (CHD) in the United States was 37.4% in men and 35.0% in women in 2008, with a mortality rate of 48.2% and 51.8% in men and women, respectively, in 2007. The prevalence of CHD in men and women of 20 years and older was 8.3% and 6.1%, respectively. When comparing different countries, France and Japan had the lowest prevalence of CHD for both men and women (Table 1)[3]. Although the incidence of CVD remained higher in men compared with women, figures of the last 30 years showed a declining incidence of CVD in men, while the incidence in women remained relatively stable. In North America CVD is the leading cause of hospital admission for both men and women. However, in women hospital stay tended to be longer and they experienced higher levels of pain, disability and discomfort, compared with men[3]. In the United States in 2007, one out of three deaths was caused by CVD and one out of six was due to CHD. However, the risk of heart disease in women often seemed to be underestimated, with CVD the major cause of death in women older than 75 years[3].

Table 1: Mortality rates of coronary heart disease per 100,000 population by gender[3]

| Country          | Year | Men 35-74 yr | Women 35-74 yr |
|------------------|------|--------------|----------------|
| United States    | 2007 | 153.3        | 60.4           |
| The Netherlands   | 2008 | 66.2         | 22.8           |
| England/Wales    | 2007 | 138.3        | 43.4           |
| Denmark          | 2006 | 84.8         | 32.4           |
| France           | 2007 | 48.4         | 12.2           |
| Germany          | 2006 | 125.3        | 38.2           |
| Italy            | 2007 | 75.6         | 22.2           |
| Russian Federation | 2006 | 716.0        | 257.1          |
| China            | 2000 | 108.3        | 71.9           |
| Japan            | 2008 | 47.6         | 13.8           |
| Australia        | 2006 | 88.9         | 26.8           |
| New Zealand      | 2005 | 138.4        | 47.2           |
| Argentina        | 1996 | 140.3        | 39.4           |

Most recent year available.

Risk factors

The INTERHEART study identified nine different global risk factors for an acute MI, namely smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors. Altogether, they could predict the risk of an acute MI as 90% in men and 94% in women. Although most of these classic risk factors were of equal clinical significance in both men and women[4], women who presented with ACS more often had hypertension[7,50,51], diabetes[7,9,13-17,21,22,26,28,30,35], hypercholesterolemia[7,9,13-17,21,22,26,28,30,35,58], and a history of angina[7,58], heart failure[7,9,13-17,21,22,26,28,30,35] more often than men. On the other hand, men tended to smoke more[7,10-13,17-19,22,25,26,28,30,31,33-34,46,47,49,51,53,56,62,66] and were more likely to have a history of MI[7,9,14,16,18,19,21-23,26,28,30-36,39,41,43,45,47,51,53-65,68,69] and prior CABG[7,10,12,13-15,17,21,23,28,30,31,34,39,43,44,54,55,63,64,67] as shown in Table 2. Although women smoked less, the relative risk (RR) for developing a MI was 1.57 (95% CI: 1.25-1.97) among smoking women in comparison to smoking men and this increased risk was pronounced in women at younger age (< 55 years)[3]. The prevalence of fatal CHD was substantially higher in patients with diabetes, in comparison to patients without diabetes (5.4% vs 1.6%). Among women, this effect of diabetes on mortality was even stronger, with a RR of 3.50 (95% CI: 2.70-4.53), compared with a RR of 2.06 (95% CI: 1.81-2.34) among men with diabetes vs no diabetes[90]. Women with ACS more often had a family history of CAD[23,33,70]. However,
| Author study date | Design | Study population | Patients | Age (mean, yr) | Hypertension (%) | Diabetes (%) | Smoking (%) | History of MI (%) | History of cardiac surgery (%) |
|-------------------|--------|------------------|----------|---------------|-----------------|--------------|-------------|------------------|-------------------------------|
| Reynolds et al. 2007 | RCT MI | 12498 4099 | 59.5 67.0 <0.001 | 29.7 47.3 <0.001 | 14.4 21.0 <0.001 | 49.7 34.3 <0.001 | 16.4 12.5 <0.001 | CABG 3.7 2.2 <0.001 | PCI 7.5 4.5 <0.001 |
| Mortiel et al. 2005 | Pros cohort ACS | 820 511 | 78 79 0.12 | 58 74 <0.001 | 33 40 0.007 | 13 5 <0.001 | 39 29 <0.001 | CABG 14 7 <0.001 | PCI 21 11 <0.001 |
| Herlitz et al. 2009 | Retro cohort AMI | 835 588 | 72.7 79.2 <0.001 | 46 56 0.01 | 24 21 NS | 22 16 NS | 42 33 <0.001 | CABG 10 7 0.06 | PCI 7 5 0.32 |
| Mehilli et al. 2002 | Pros cohort AMI | 1435 502 | 60.7 70.3 <0.001 | 61.0 72.9 <0.001 | 18.0 25.3 <0.001 | 43.1 25.9 <0.001 | 22.1 16.3 0.001 | CABG 6.1 3.4 0.02 | PCI 10.7 7.6 0.04 |
| Mueller et al. 2002 | Pros cohort CABG | 1033 417 | 64 68 0.01 | 60 72 0.01 | 19 23 0.15 | 33 21 0.01 | 37 24 0.01 | CABG 17 6 0.01 | PCI 24 21 0.20 |
| Touboul et al. 2006 | Pros cohort CABG | 2598 1162 | 63.2 66.2 <0.001 | 65.9 79.4 <0.001 | 28.8 45.5 <0.001 | 16.1 12.9 0.011 | 50.7 46.1 0.010 | CABG 7.8 5.3 0.006 | PCI 10.9 12.8 0.093 |
| Dallongeville et al. 2010 | Pros cohort CABG | 6698 2268 | 62.2 65.8 <0.001 | 80.3 87.9 <0.001 | 33.6 38.4 0.009 | 19.3 11.0 <0.001 | 19.1 20.6 <0.001 | CABG 20.4 17.2 <0.001 |
| Anand et al. 2005 | Trial ACS | 7726 4856 | 62.7 66.5 0.0001 | 53 68.8 0.0001 | 20.9 24.6 0.0001 | 76.4 37.4 0.0001 | 36.9 23.9 0.0001 | CABG 13.3 6.8 0.0001 | PCI 11.5 7.2 0.0001 |
| Matsui et al. 2002 | Retro cohort AMI | 346 156 | 62.9 70.4 | 44 54 0.047 | 25 33 0.078 | 60 19 0.001 | 18 15 0.517 | CABG 1 1 0.556 | PCI 12 4 0.016 |
| Tióñ-Marcos et al. 2009 | RCT PCI | 1050 298 | 59.7 62.5 | 49 59 0.004 | 17 20 0.19 | 32 36 0.23 | 45 41 0.19 | CABG 6.3 6.4 1.00 | PCI Total 21 14 0.016 | Total 7.2 12.0 <0.01 |
| Reina et al. 2007 | Pros cohort AMI | 4641 1568 | 64 71 <0.01 | 41.0 61.1 <0.01 | 25.5 41.2 <0.01 | 53.6 15.7 <0.01 | 16.6 13.0 <0.01 | PCI Total 21 14 0.016 | Total 7.2 12.0 <0.01 |
| Thompson et al. 2006 | Pros cohort PCI | 807 359 | 61.7 67.7 <0.001 | 59.3 67.8 0.006 | 23.8 30.1 0.03 | 47.4 38.5 0.005 | 25.2 22.4 0.33 | CABG 8.3 7.2 0.53 | PCI Total 28.3 24.6 0.20 |
| Lee et al. 2008 | Pros cohort STEMI | 2954 1083 | 60.7 72.1 <0.001 | 40.2 59.7 <0.001 | 23.1 31.4 <0.001 | 58.8 47.4 0.007 | 3.6 2.9 0.239 | CABG 0.5 0.3 0.330 | PCI Total 4.3 2.8 0.023 |
| Jankowski et al. 2007 | Pros cohort CAD + PCI | 738 187 | 57.5 60.6 <0.001 | 72.6 87.8 <0.001 | 14.5 21.3 <0.05 | 13.6 6.4 <0.01 | 63.2 66.0 NS | CABG 1.5 0.5 NS | PCI Total 8.8 8.5 NS |
| Davernoy et al. 2010 | Pros cohort PCI | 14848 7877 | 61.9 66.9 <0.001 | 71.0 82.5 <0.001 | 29.2 38.5 <0.001 | 27.3 21.7 <0.001 | 36.0 32.6 <0.001 | CABG 21.5 17.4 <0.001 | PCI 41.8 38.9 <0.001 |
| Lamsky et al. 2005 | RCT AMI + PTCA | 1520 562 | 57.0 66.0 <0.001 | 29.0 59.3 <0.001 | 14.0 25.7 <0.001 | 45.3 37.4 0.001 | 15.7 8.4 <0.001 | CABG 12.7 7.1 <0.001 |
| Lamsky et al. 2009 | RCT PCI | 687 314 | 61.8 65.9 <0.0001 | 72.7 81.5 0.0026 | 23.7 36.3 0.0007 | 24.0 21.2 0.3711 | 21.9 13.6 0.0022 | CABG 34.1 25.5 0.0066 |
| De Luca et al. 2004 | Pros cohort STEMI | 1195 353 | 59 66 <0.001 | 24 39 <0.001 | 8.7 15.8 <0.001 | 52.1 42.7 0.002 | 11.6 7.1 0.014 | CABG 2.1 1.7 NS | PCI Total 5.3 1.7 0.0004 |
| De Luca et al. 2010 | Pros cohort Trail STEMI | 1283 379 | 59 67 <0.001 | 39.1 52.5 <0.001 | 15.3 22.4 <0.001 | 56 36.9 <0.001 | 9.2 7.7 0.35 | Total 7.7 7.6 0.93 |
| Butelle et al. 2010 | Pros cohort STEMI + PCI | 376 124 | 58 65 <0.001 | 66 54.8 0.055 | 11.2 24.2 <0.001 | 67.3 40.3 <0.001 | 11.7 8.9 0.479 | CABG 5.6 0.8 0.046 | PCI 5.6 4.0 0.658 |
| Cannabba et al. 2004 | Pros cohort STEMI | 627 293 | 67.7 76.3 0.001 | 45.3 60.1 <0.001 | 22.7 25.3 0.385 | 34.1 14.3 <0.001 | 17.2 14.7 0.331 | CABG 2.6 1.0 0.129 | PCI 5.9 2.1 0.010 |
a family history of premature CAD was not a risk factor overall for in-hospital mortality\textsuperscript{[71]}. The cardiovascular risk burden tended to be higher in women aged younger than 46 years, compared with men of the same age. Of all patients younger than 46 years presenting with ACS, 78.5% and 25.3% of women, respectively, had one or more than one risk factor for ACS, compared with 71.8% and 17.2%, respectively, among men (\( P = 0.008 \) and \( P < 0.001 \), respectively)\textsuperscript{[24]}.

Peitera et al\textsuperscript{[23]} studied differences in hypertension between men and women as an important risk factor for CVD. Apart from the fact that women received treatment more often, they also had a greater awareness of the risk of hypertension for CVD. In both developing and developed countries, awareness, control and treatment of hypertension was significantly higher in women, compared with men. On the other hand, women were categorized at high-risk of CVD in risk assessment programs if a history of diabetes, stroke or chronic kidney disease was present\textsuperscript{[28,77]}, and all these conditions were generally more prevalent in women, compared with men, as noted above.

Interventions

In the evaluation of CVD, coronary angiography (CAG) was less often performed in women than in men\textsuperscript{[8,19,23-25,34,43,55,66,67]}. Age might be an important confounding factor in this regard, because women present with an ACS 10 years later than men, and CAGs were less likely to be performed in the elderly\textsuperscript{[28]}. Age was found to be a predictor for undergoing PCI, with an odds ratio (OR) of 0.98 (95% CI: 0.97-0.98) for each additional year\textsuperscript{[28,45,47,49]}. Nevertheless, even after adjustment for age\textsuperscript{[28,45,47,49]} and other cardiovascular risk factors\textsuperscript{[45,47,49]}, women with ACS were less likely to have CAG or PCI\textsuperscript{[51,60,74]} (OR, 0.70; 95% CI: 0.64-0.76)\textsuperscript{[73]}. In men and women younger than 46 years, no differences were seen in the number of performed angiograms\textsuperscript{[18]}. In ACS patients who underwent CAG, an equal number of men and women received a PCI afterwards\textsuperscript{[18,9,11,18,30,44,49,60]}. In STEMI patients, results were inconsistent. Some studies found no significant differences in the number of CAGs and PCI\textsuperscript{[11]} performed after adjustment for age\textsuperscript{[18,44,49,60]}; while Radovanovic et al\textsuperscript{[18]} found that women with both STEMI and non-STEMI underwent primary PCI less often (30.9% and 22.0%, respectively) compared with men (40.3% and 30.9%, respectively). This difference persisted after adjustment for cardiovascular risk factors (OR, 0.70) and after adjustment for age alone (OR, 0.71; 95% CI: 0.63-0.80)\textsuperscript{[58,74]}.

The mortality rate for ACS was highest among female patients who did not undergo a CAG; 12.9% vs 4.7% in those who underwent a CAG, compared with men (40.3% and 30.9%, respectively). A higher mortality rate among women compared with men was also reported in patients who suffered a STEMI. A possible explanation may be the higher rate of comorbidity in women and a greater delay between onset of complaints and arrival at the emergency department compared with men. At 6 mo follow-up, no significant differences in mortality were present\textsuperscript{[28]}. Several studies compared the coronary anatomy of men and women presenting with ACS. In general, women tended to have a smaller diameter of coronary arteries, in proportion with the lower body surface area, and this was associated with a higher mortality rate\textsuperscript{[2,13,19,23,30,34,43,55,66,67]}. Women more often had one-vessel disease\textsuperscript{[8,19,23-25,34,43,55,66,67]} and less often three-vessel disease\textsuperscript{[8,19,23-25,34,43,55,66,67]} as shown in Table 3. Multiple vessel disease was associated with a higher mortality rate\textsuperscript{[71]}. In addition, women with ACS had less extensive obstructive CAD, whereas men not only had more lesions, but also lesions of greater length and complexity\textsuperscript{[55]}. Nevertheless, among patients who underwent PCI no differences were seen between men and women in the number of stents placed; 69% vs 66%\textsuperscript{[18]} and 77% vs 77%\textsuperscript{[18]}. Furthermore, no differences were found in length or diameter of the stents placed, nor in success rate of the performed PCI\textsuperscript{[25,41,43,44,49,51,77,89,84]}. It remains uncertain whether women would benefit as much as men from early invasive strategy in the case of an ACS, because the power of the different studies was limited\textsuperscript{[14,20]}.  

| Lawesson et al\textsuperscript{[54]} 2010 | Retro cohort | STEMI aged < 46 | 1748 | 384 | 40.8 | 40.4 | 0.14 | 13.9 | 21.7 | < 0.001 | 12.4 | 18.5 | 0.002 | 56.0 | 63.9 | 0.04 | 6.6 | 5.2 | 0.30 | CABG | 0.8 | 0.3 | 0.25 |
| Berger et al\textsuperscript{[55]} 2006 | PCI | 2953 | 1331 | 61.9 | 66.8 | < 0.001 | 66 | 78 | < 0.001 | 22 | 36 | < 0.001 | 15 | 10 | < 0.001 | 36 | 33 | 0.08 | CABG | 19 | 14 | 0.001 |
| Chiu et al\textsuperscript{[56]} 2004 | Pros cohort | PCI | 12,738 | 5031 | 62.3 | 66.5 | < 0.001 | 58 | 71 | < 0.001 | 24 | 34 | < 0.001 | 21 | 20 | 0.01 | 43 | 42 | 0.29 | CABG | 30 | 21 | < 0.001 |
| Koch et al\textsuperscript{[57]} 2000 | Pros cohort | CABG | 1988 | 460 | 51.7 | 70.2 | 0.001 | 22.5 | 36.3 | 0.001 | 71.5 | 49.6 | 0.0001 | 14.3 | 10.7 | 0.04 | 14.4 | 7.0 | 0.0001 |
| Setoguchi et al\textsuperscript{[58,59]} 2008 | Pros cohort | AMI | 317 | 1308 | 80 | 82 | < 0.001 | 71 | 80 | 0.001 | 33 | 39 | 0.03 | 15 | 10 | 0.01 | 52 | 37 | < 0.001 | CABG | 18 | 13 | 0.03 | PCI | 13 | 9 | 0.02 |
Table 3  Extent of coronary artery disease stratified by gender

| Author study/date       | Design | Study population | Patients | Age (mean, yr) | P    | 1 vessel disease (%) | P    | 3 vessel disease (%) | P    |
|-------------------------|--------|------------------|----------|----------------|------|----------------------|------|----------------------|------|
|                         |        |                  | Men      | Women          |      | Men                  |      | Women                |      |
| Lanksy et al.2005       | RCT    | AMI + PTCA       | 1520     | 562            |      | 57.0                 | 66.0 | < 0.001              | 51.1 | 51.6 | NS                  | 15.7 | 15.3 | NS                  |
| Matsui et al.2002       | Retro cohort | AMI     | 346      | 136            |      | 62.9                 | 70.4 | 0.1                  | 4    | 7    | 0.179               | 95   | 84   | 0.001               |
| Moriel et al.2005       | Pros cohort | ACS      | 820      | 511            |      | 78                   | 79   | 0.12                 | 7    | 6    | 0.47                | 32   | 28   | 0.06                |
| Herlitz et al.2009      | Retro cohort | AMI     | 835      | 588            |      | 72.7                 | 79.2 | < 0.0001             | 9    | 2    | < 0.0001            | 15   | 7    | NS                  |
| Setoguchi et al.2008    | Pros cohort | AMI     | 317      | 1308           |      | 80                   | 82   | < 0.001              | 3    | 3    | 0.73                | 10   | 12   | 0.40                |
| Tillmanns et al.2005    | Pros cohort | STEMI    | 513      | 178            |      | 60                   | 66   | < 0.0001             | 3    | 2    | NS                  | 95.1 | 93.8 | NS                  |
| Toupounovs et al.2006   | Pros cohort | CABG    | 2598     | 1162           |      | 63.2                 | 66.2 | < 0.0001             | 4.6  | 7.3  | 0.001               | 73.7 | 69.3 | 0.005               |
| Berger et al.2006       | Pros cohort | PCI     | 2953     | 1331           |      | 61.9                 | 66.8 | < 0.001              | 0.1  | 0.0  | 0.179               | 100  | 100  | 0.002               |
| Alfredsson et al.2007   | Pros cohort | Unstable/NSTEMI | 34020  | 19761          |      | 69                   | 73   | < 0.001              | 7    | 5    | 18                  | 14   | 14   | 0.67                |
| Lappan et al.2001       | RCT     | AMI         | 1708     | 749            |      | 64                   | 68   | < 0.001              | 30   | 24   | 34                  | 28   | 28   | NS                  |
| Selby2004               | RCT     | Multivessel disease | 782  | 206            |      | 60.6                 | 64.7 | < 0.001              | 50.1 | 52.4 | 49.9                | 47.6 | 47.6 | NS                  |
| Singh et al.2008        | Retro cohort | PCI     | 7616     | 3365           |      | 64.7                 | 69.4 | 0.08                 | 0.8  | 0.5  | 0.179               | 100  | 100  | 0.002               |
| Liu et al.2008          | Pros cohort | STEMI + PCI     | 143      | 116            |      | 68.1                 | 68.7 | 0.61                 | 85.3 | 84.3 | NS                  | 15.7 | 15.3 | NS                  |

1More than single vessel disease. MI: Myocardial infarction; CABG: Coronary artery bypass grafting; STEMI: ST elevation MI; NS: Not significant.

Table 4  Percentage of performed revascularizations stratified by gender

| Author study/date       | Design | Study population | Patients | Age (mean, yr) | P    | CAGB (%) | P    | PCI (%) | P    |
|-------------------------|--------|------------------|----------|----------------|------|----------|------|---------|------|
|                         |        |                  | Men      | Women          |      | Men      |      | Women   |      |
| Reynolds et al.2007     | RCT    | MI               | 1248     | 4090           |      | 59.5     | 67.0 | < 0.001 | 3.4  | 3.1  | 0.45               | 27.4 | 23.6 | < 0.01               |
| Matsui et al.2002       | Retro cohort | AMI     | 346      | 136            |      | 62.9     | 70.4 | 0.01    | 4    | 7    | 0.179               | 95   | 84   | 0.001               |
| Moriel et al.2005       | Pros cohort | ACS      | 820      | 511            |      | 78       | 79   | 0.12    | 7    | 6    | 0.47                | 32   | 28   | 0.06                |
| Herlitz et al.2009      | Retro cohort | AMI     | 835      | 588            |      | 72.7     | 79.2 | < 0.0001| 9    | 2    | < 0.0001            | 15   | 7    | NS                  |
| Setoguchi et al.2008    | Pros cohort | AMI     | 317      | 1308           |      | 80       | 82   | < 0.001 | 3    | 3    | 0.73                | 10   | 12   | 0.40                |
| Tillmanns et al.2005    | Pros cohort | STEMI    | 513      | 178            |      | 60       | 66   | < 0.0001| 3    | 2    | NS                  | 95.1 | 93.8 | NS                  |
| Toupounovs et al.2006   | Pros cohort | CABG    | 2598     | 1162           |      | 63.2     | 66.2 | < 0.0001| 100  | 100  | 1.6                 | 3.1  | 0.002               |
| Berger et al.2006       | Pros cohort | PCI     | 2953     | 1331           |      | 61.9     | 66.8 | < 0.001 | 0.1  | 0.0  | 0.179               | 100  | 100  | 0.002               |
| Alfredsson et al.2007   | Pros cohort | Unstable/NSTEMI | 34020  | 19761          |      | 69       | 73   | < 0.001 | 7    | 5    | 18                  | 14   | 14   | 0.67                |
| Lappan et al.2001       | RCT     | AMI         | 1708     | 749            |      | 64       | 68   | < 0.001 | 30   | 24   | 34                  | 28   | 28   | NS                  |
| Selby2004               | RCT     | Multivessel disease | 782  | 206            |      | 60.6     | 64.7 | < 0.001 | 50.1 | 52.4 | 49.9                | 47.6 | 47.6 | NS                  |
| Singh et al.2008        | Retro cohort | PCI     | 7616     | 3365           |      | 64.7     | 69.4 | 0.08    | 0.8  | 0.5  | 0.179               | 100  | 100  | 0.002               |
| Liu et al.2008          | Pros cohort | STEMI + PCI     | 143      | 116            |      | 68.1     | 68.7 | 0.61    | 85.3 | 84.3 | NS                  | 15.7 | 15.3 | NS                  |

MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; STEMI: ST elevation MI; NS: Not significant.
The proportion of men and women undergoing CABG was equal\cite{12,16,20,34,36,63,75} as shown in Table 4. In women undergoing CABG, the internal mammary artery was used less often than in men. The usage of this artery was associated with a decrease in mortality after CABG\cite{14}. Furthermore, women underwent surgery more commonly on an urgent basis than men\cite{12,14,34,63,75}.

**Prognosis**

Many discrepancies existed between the different studies investigating the prognosis of men and women with an ACS. Some studies showed that women had more complications during hospital admission compared with men\cite{73,13,22,30,33,64,78,80}, while others showed no differences\cite{73,25,28,30,33,41,44,48,54,56,58,72} (Table 5). Particularly at younger ages, women tended to have a greater risk for cardiac events compared with men at the same age\cite{30,81}. This difference disappeared in patients older than 65 years\cite{81}.

Many discrepancies existed in the short-term mortality rate of patients with ACS. Some studies revealed...
a higher short-term mortality risk among women, with others did not (Table 6). As discussed above, older age at presentation was an important confounding factor in this regard.

An important finding was that women with ACS had an increased mortality risk at younger ages compared with men of the same age, with an OR of 1.06 (95% CI: 1.05-1.07) for each additional year; diabetes, heart failure, CAD, duration of ischemia, multiple vessel disease, history of MI, hypertension, CVA, anemia, cardiogenic shock, peripheral vascular disease, and ST-elevation. Whether female gender can be considered as an independent risk factor remains unclear. Some studies claimed it could be (20,24,31,53,77,78), but others showed no significant association after adjustment for risk factors (30,33). After adjustment for several risk factors, female gender persisted as a risk factor for in-hospital mortality in ACS only for patients aged 51-60 years (OR, 1.78; 95% CI: 1.04-3.04). For adjustment for cardiovascular risk factors, the long-term mortality rate was equal for both men and women (5,20,22-24,26-29,31,32,44-48,49,50,53,54,58,61,62,64,66,74,77,78), or even in favor of women (10,31,34,42,54,63,77,78), as shown in Table 6 and Figure 2.

In the past 20-25 years the mortality rate at 30 d after PCI or CABG has declined equally in both men and women (11,77). Data were inconsistent on the differences between men and women in the number of readmissions, and the number of second PCIs (5,10,14,21,22-24,26-28,33,35). Interestingly, differences were found in the restenosis rates after PCI. In the first 6 mo after coronary stenting, restenosis was found in 28.9% of the women, compared with 33.9% of men (P = 0.01). After adjustment of gender, age and multiple risk factors, women showed a 23% risk reduction in angiographic restenosis compared with men (OR, 0.77; 95% CI: 0.63-0.93). Diabetes and small vessel size were identified as the most important predictors of restenosis. However, despite the higher prevalence of diabetes in women and smaller vessel size, women tended to have a lower incidence of restenosis.

Whether this can be explained by the protective mechanism of estrogens in women is still unknown. Estrogens were shown to have an anti-inflammatory effect on the vessel wall and induce vasodilatation in coronary arteries. However HRT in post-menopausal women did not lower the risk of mortality from CVD after adjustment for other risk factors. HRT is therefore not recommended as primary or secondary prevention of CVD in women.

**DISCUSSION**

Women with CVD tended to have more cardiovascular risk factors such as diabetes, hypertension, and hypercholesterolemia when presenting with ACS. More importantly, women with an ACS at a young age had a higher mortality rate during index hospitalization and during 30 d of follow-up compared with men. A possible explanation could be that pre-menopausal women enjoyed some protection against ACS from estrogens and those women who developed ACS despite this hormonal protection were more likely to have a higher cardiovascular risk factor burden leading to a more severe clinical presentation and worse outcome. None of the discussed studies adjusted for the use of hormone therapy among women. This might lead to information bias, because hormone therapy could influence the outcome of women with ACS. In the elderly, the long-term mortality rate was equal for both men and women, and even slightly in favor of women (10,20,22-24,26-29,31,32,77,78). This small advantage in survival might possibly be due to the greater awareness and control of hypertension in women, compared with men, as hypertension is an important risk factor for CVD.

Study results were inconsistent, but it seems that an angiogram was less often performed in women than in men. This phenomenon could partly be explained by the higher average age of women as fewer diagnostic CAG...
| Author study/ date | Design | Study population | Patients | Age (mean, yr) | Mortality < admission (%) | Mortality < 30 d (%) | Mortality < 1 year (%) |
|-------------------|--------|------------------|----------|---------------|--------------------------|---------------------|----------------------|
| Lansky et al. 2015 | RCT    | AMI + PTCA       | Men 1520 | Women 562     | Men 57.0 | Women 66.0 | < 0.001 | Men 1.0 | Women 3.4 | 0.003 | Men 1.1 | Women 4.6 | < 0.001 | Men 3.0 | Women 7.6 | < 0.001 |
| Singh et al. 2008 | Retro cohort | PCI | Men 7616 | Women 3365 | Men 64.7 | Women 69.4 | 0.048 | Men 1.8 | Women 2.5 | 0.38 | Men 2.7 | Women 3 | 0.25 | Men 4 | Women 4 | 0.40 |
| Alfredsson et al. 2007 | Pros cohort | Unstable/ NSTEMI | Men 34020 | Women 39761 | Men 69 | Women 73 | < 0.001 | Men 5 | Women 7 | 0.7 | Men 16 | Women 19 | 0.006 |
| Setoguchi et al. 2008 | Pros cohort | AMI | Men 317 | Women 1308 | Men 80 | Women 82 | < 0.001 | Men 14.5 | Women 13.9 | 0.7 | Men 9.8 | Women 8.6 | 0.25 | Men 21.5 | Women 18.2 | 0.006 |
| Matsui et al. 2002 | RCT | MI | Men 346 | Women 136 | Men 62.9 | Women 70.4 | 0.001 | Men 4 | Women 4 | 0.85 | Men 10 | Women 0.13 | 0.006 |
| Uva et al. 2009 | RCT | CABG | Men 1485 | Women 481 | Men 64.7 | Women 69.0 | 0.001 | Men 0.8 | Women 2 | 0.01 | Men 1.2 | Women 2.3 | 0.09 | 0.006 |
| Toumpoulis et al. 2006 | Pros cohort | CABG | Men 2986 | Women 1162 | Men 63.2 | Women 66.2 | < 0.001 | Men 2.7 | Women 2.9 | 0.65 | Men 3.7 | Women 3.9 | 0.747 | 0.006 |
| Moriel et al. 2005 | Pros cohort | ACS | Men 820 | Women 511 | Men 78 | Women 76 | 0.12 | Men 7 | Women 12 | 0.003 | 19 | 21 | 0.48 | 0.006 |
| Herlitz et al. 2009 | Retro cohort | AMI | Men 835 | Women 588 | Men 72.7 | Women 79.2 | < 0.0001 | Men 12 | Women 14 | NS | 18 | 22 | 0.046 | 0.006 |
| Lawesson et al. 2009 | Retro cohort | STEMI aged < 46 | Men 1748 | Women 384 | Men 40.8 | Women 40.4 | 0.47 | Men 1.0 | Women 2.9 | 0.005 | 2.2 | 3.7 | 0.01 | 0.006 |
| Berger et al. 2006 | Pros cohort | PCI | Men 2953 | Women 1331 | Men 61.9 | Women 66.8 | < 0.001 | Men 0.5 | Women 0.5 | 0.918 | 8.9 | 10 | 0.197 | 0.006 |
| Liu et al. 2008 | Pros cohort | STEMI + PCI | Men 143 | Women 116 | Men 68.1 | Women 68.6 | 0.61 | Men 2.8 | Women 5.2 | 0.006 | 0 | 3 | 0.01 | 0.006 |
| Uva et al. 2005 | Trial | ACS | Men 7726 | Women 4836 | Men 62.7 | Women 66.5 | 0.0001 | Men 4.9 | Women 4.4 | 0.23 | 11.1 | 9.7 | 0.04 | 0.006 |
| Tzoun-Manous et al. 2009 | RCT | PCI | Men 1050 | Women 298 | Men 59.7 | Women 62.5 | < 0.0001 | Men 0.2 | Women 1.0 | 0.08 | Men 1.0 | Women 0.72 | 0.006 |
| Tillmanns et al. 2007 | Pros cohort | STEMI | Men 513 | Women 178 | Men 60 | Women 66 | < 0.0001 | Men 6 | Women 6.2 | NS | 12.5 | 0.60 | 0.006 |
| Lansky et al. 2009 | RCT | PCI | Men 687 | Women 314 | Men 61.8 | Women 65.9 | < 0.0001 | Men 0 | Women 0.3 | 0.44 | 12 | 18 | 0.07 | 0.006 |
| Koch et al. 2003 | Pros cohort | CABG | Men 1588 | Women 46 | Men 2.5 | Women 3.4 | 0.29 | Men 4.2 | Women 7.1 | 0.02 | 15.8 | 19.6 | 0.03 | 0.006 |
| Lagerqvist et al. 2001 | RCT | AMI | Men 1708 | Women 749 | Men 64 | Women 68 | < 0.001 | Men 5 | Women 7 | 0.009 | 5.7 | 7 | 0.02 | 0.006 |
| Chua et al. 2004 | Pros | PCI | Men 1278 | Women 5301 | Men 62.3 | Women 66.5 | < 0.001 | Men 5 | Women 7 | < 0.001 | 0.006 |

1 After 6 mo; 2 After 3 years; 3 After 4 years; 4 After 5 years; 5 Adjusted for age, diabetes, smoking, history of cardiovascular disease, increased cardiac enzymes, region and received therapy. MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; STEMI: ST elevation MI; NS: Not significant.
were performed in both male and female patients of older age. However, where a CAG was performed, women and men received the same therapy for similar vessel disease. No differences between genders were found in the number of performed CABGs.

The current review has several limitations. Most included studies were retrospective in nature and performed a post hoc analysis by stratifying by gender. Included studies were hard to compare due to different patient characteristics; some studies included patients with STEMI, while others also included non-STEMI or patients with unstable angina. Another important limitation is the large difference in mean age between the included men and women across the different studies. Consequently, a comparison between the two genders was very difficult and no firm conclusion can be drawn. In addition, women are still underrepresented in most studies (inclusion rate < 30%). Due to the relatively low incidence of outcomes (e.g. complications, death), greater statistical power is needed to reach statistical significance. Therefore, large prospective observational cohort studies are needed in the future to provide sufficient power to answer the question whether female gender is an independent risk factor for cardiovascular morbidity and mortality.

CVD is the main cause of death among women. The prevalence of CVD is higher among men, but this gap narrows after the menopause. Women present approximately 10 years later with ACS than men, and at the time of presentation have a higher cardiovascular risk factor burden. Women are less often assigned to receive a CAG and subsequently less PCIs are performed. In addition, women have more complications and a higher short-term mortality after revascularization. Finally, mortality rates are higher among young women with ACS, but this difference tends to disappear with age, and long-term prognosis is even better among older women during long-term follow-up.

**COMMENTS**

**Background**

Cardiovascular disease (CVD) is the main cause of death among women and its occurrence narrows women’s survival advantage over men. Many studies investigated gender differences in CVD, but results were inconsistent due to several limitations. Women were generally underrepresented in mainly retrospective studies and a true comparison between genders was difficult due to large differences in age at presentation between the included men and women.

**Research frontiers**

It is important to clarify possible differences between men and women in a large prospective cohort study, with equal numbers of male and female patients. Furthermore, as age is an important confounding factor, men and women of similar age should be compared. A systematic literature search was performed to assess the current state of knowledge on possible gender differences in CVD.

**Innovations and breakthroughs**

In the short-term, women with CVD seem to have a worse outcome compared with men. In particular, young women have an increased mortality risk, but this disadvantage disappears at older age. Moreover, long-term mortality is slightly better in elderly women compared with men.

**Peer review**

This is an interesting meta-analysis on putative gender differences in cardiovascular care.

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