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BRIEF ARTICLE

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.

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

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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[4]. 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, estrogens, 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 subsequently compared women with men. This provided 152 articles. After screening of the full text, a total of 92 articles were found to be relevant and valid.

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[2]. 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[1]	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	706.0	237.1
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

[1]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[6], women who presented with ACS more often had hypertension[7-61], diabetes[7-10,12,13,15-17,20,22-25,27,28,30-32,34-36,38,39,41-43,45-47,49-54,57-66], hypercholesterolemia[7,9,10,13,15-17,21,22,26,28-30,35,36,50], and a history of angina[7,50], heart failure[7,45,47,52,53,59,60,63,64], and cerebrovascular events (CVA)[7,39,47,50,52,63,64] than men. On the other hand, men tended to smoke more[7-10,13-17,19-22,25,26,28,30,31,33-44,46,47,49-51,53-56,62,66] and were more likely to have a history of MI[7-9,14,16,18,19,21-23,28-32,36,39,41,43,45,47,51,53-56,58,64] and prior CABG[7-10,12,13,15-17,23,28,30,31,34,39,43,44,54,55,62-64,67] 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)[68]. 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[69]. Women with ACS more often had a family history of CAD[23,33,70]. However,

Table 2 Prevalence of cardiovascular risk factors and history of myocardial infarction and cardiac surgery stratified by gender

Author study/date	Design	Study population	Patients		Age (mean, yr)		*P*	Hypertension (%)		*P*	Diabetes (%)		*P*	Smoking (%)		*P*	History of MI (%)		*P*	History of cardiac surgery (%)			*P*
			Men	Women	Men	Women		Men	Women		Men	Women		Men	Women		Men	Women			Men	Women	
Reynolds *et al*[30] 2007	RCT	MI	12 498	4090	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
Moriel *et al*[28] 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*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	46	56	0.01	24	21	NS	22	16	NS	42	33	< 0.0001	CABG	10	7	0.06
																				PCI	7	5	0.32
Mehilli *et al*[54] 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*[55] 2002	Pros cohort	MI	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
Toumpoulis *et al*[34] 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
Dallongevillle *et al*[15] 2010	Pros cohort	ACS	6698	2268	62.2	65.8	< 0.0001	80.3	87.9	< 0.0001	33.6	38.4	0.009	19.3	11.0	< 0.0001	19.1	20.6	< 0.0001	CABG	20.4	17.2	< 0.0001
Anand *et al*[9] 2005	Trial	ACS	7726	4836	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*[26] 2002	Retro cohort	AMI	346	136	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
Tizón-Marcos *et al*[33] 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	21	14	0.016
Reina *et al*[51] 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	Total	7.2	12.0	< 0.01
Thompson *et al*[53] 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	28.3	24.6	0.20
Lee *et al*[78] 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	14.7	< 0.001	3.6	2.9	0.239	CABG	0.5	0.3	0.330
																				PCI	4.3	2.8	0.023
Jankowski *et al*[46] 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	8.8	8.5	NS
Duvernoy *et al*[43] 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
Lansky *et al*[22] 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	PCI	12.7	7.1	< 0.001
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001	72.7	81.5	0.0026	25.7	36.3	0.0007	24.0	21.2	0.3711	21.9	13.6	0.0022	Total	34.1	25.5	0.0066
De Luca *et al*[41] 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	5.3	1.7	0.004
De Luca *et al*[42] 2010	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
Bufe *et al*[62] 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
Carrabba *et al*[40] 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

Lawesson *et al*[24] 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	58.0	63.9	0.04	6.6	5.2	0.30	CABG	0.8	0.3	0.25
																				PCI	2.5	1.9	0.46
Berger *et al*[10] 2006	Pros cohort	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
																				PCI	26	24	0.137
Chiu *et al*[13] 2004	Pros cohort	PCI	12 738	5301	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
																				PCI	6	4	< 0.001
Koch *et al*[20] 2003	Pros cohort	CABG	1588	460				51.7	70.2	0.0001	22.5	36.3	0.0001	71.5	49.6	0.0001	14.3	10.7	0.044	CABG	14.4	7.0	0.0001
																				PCI	15.4	16.3	0.6249
Setoguchi *et al*[31] 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

MI: Myocardial infarction; AMI: Acute myocardial Infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; ACS: Acute coronary syndrome; STEMI: ST elevation MI; CAD: Coronary artery disease; NS: Not significant.

a family history of premature CAD was not a risk factor overall for in-hospital mortality[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)[24]. Peirera *et al*[72] 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[73], 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[9,11,18,30,44,49,60]. 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[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[51,60,74]. Nevertheless, even after adjustment for age[18] and other cardiovascular risk factors[9,11], women with ACS were still less likely to have CAG or PCI[45,47,49] (OR, 0.70; 95% CI: 0.64-0.76)[75]. In men and women younger than 46 years, no differences were seen in the number of performed angiograms[24]. In ACS patients who underwent CAG, an equal number of men and women received a PCI afterwards[18,30,60,66]. In STEMI patients, results were inconsistent. Some studies found no significant differences in the number of CAGs and PCIs performed after adjustment for age[40,44,50,51], while Radovanovic *et al* 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)[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 5.6% and 2.9%, respectively, in men[30]. 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[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[13,16,20,22,34,36,43,53,75,76]. Women more often had one-vessel disease[8,19,23,24,34,43,52,62,67] and less often three-vessel disease[8,9,19,23-25,34,43,55,66,67] as shown in Table 3. Multiple vessel disease was associated with a higher mortality rate[77]. 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[23]. Nevertheless, among patients who underwent PCI no differences were seen between men and women in the number of stents placed; 69% *vs* 66%[19] and 77% *vs* 77%[10]. Furthermore, no differences were found in length or diameter of the stents placed, nor in success rate of the performed PCI[25,41,43,46,48,53,56,57,59,78]. 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[14,21].

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		Men	Women		Men	Women	
Lansky *et al*[22] 2005	RCT	AMI + PTCA	1520	562	57.0	66.0	< 0.001	51.1	51.6	NS	15.7	15.3	NS
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001	61.3	74.2	< 0.0001	11.5	4.5	0.0002
Tizón-Marcos *et al*[33] 2009	RCT	PCI	1050	298	59.7	62.5		58	65	0.066	9.8	7.4	0.066
Hirakawa *et al*[19] 2007	Pros cohort	AMI	2048	566	62.92	71.08	< 0.01	60.1	56.0	< 0.05	34.8[1]	40.1[1]	< 0.05
Mueller *et al*[55] 2002	Pros cohort	MI	1033	417	64	68	0.01	24	26	0.45	42	29	0.01
Duvernoy *et al*[43] 2010	Pros cohort	PCI	14 848	7877	61.9	66.9	< 0.001	49.4	55.0	< 0.001	22.8	18.0	< 0.001
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61	14.7	10.3	0.29	48.2	61.2	0.03
Jibran *et al*[81] 2010	Retro cohort	ACS + PCI	331	137	60.7	66.1	< 0.00001	41.1	48.9	0.3	22.7	12.4	0.3
De Luca *et al*[41] 2004	Pros cohort	STEMI	1195	353	59	66	< 0.001	47.9	43.8	NS	20.7	22.3	NS
Bufe *et al*[62] 2010	Pros cohort	STEMI + PCI	376	124	58	65	< 0.001	48.1	54.0	0.031	24.2	21.8	0.667
Lawesson *et al*[24] 2010	Retro cohort	STEMI aged < 46	1748	384	40.8	40.4	0.14	59.3	72.9	< 0.001	33.6	19.2	< 0.001
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	48	50	0.195	18	17	NS
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	4.6	7.3	0.001	73.7	69.3	0.005
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001	43	44	NS	57[1]	56[1]	NS
Vakili *et al*[57] 2001	Retro cohort	PTCA first MI	727	317	59	65	< 0.005	56	59	NS	15	12	NS

[1]More 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*	CABG (%)		*P*	PCI (%)		*P*
			Men	Women	Men	Women		Men	Women		Men	Women	
Reynolds *et al*[30] 2007	RCT	MI	12 498	4090	59.5	67.0	< 0.001	3.4	3.1	0.45	27.4	23.6	< 0.01
Matsui *et al*[26] 2002	Retro cohort	AMI	346	136	62.9	70.4	0.01	4	7	0.179	95	84	0.001
Moriel *et al*[28] 2005	Pros cohort	ACS	820	511	78	79	0.12	7	6	0.47	32	28	0.06
Herlitz *et al*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	9	2	< 0.0001	15	7	NS
Setoguchi *et al*[31] 2008	Pros cohort	AMI	317	1308	80	82	< 0.001	3	3	0.73	10	12	0.40
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001	3	2	NS	95.1	93.8	
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	100	100		1.6	3.1	0.002
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	0.1	0.0	0.179	100	100	
Alfredsson *et al*[11] 2007	Pros cohort	Unstable/NSTEMI	34020	19761	69	73	< 0.001	7	5		18	14	
Lagerqvist *et al*[21] 2001	RCT	AMI	1708	749	64	68	< 0.001	30	24		34	28	
SoS[37] 2004	RCT	Multivessel disease	782	206	60.6	64.7	< 0.001	50.1	52.4		49.9	47.6	
Singh *et al*[79] 2008	Retro cohort	PCI	7616	3365	64.7	69.4		0.8	0.8		100	100	
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61				85.3	84.3	NS

MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; STEMI: ST elevation MI; NS: Not significant.

Table 5 Percentage of peri-procedural complications during index admission stratified by gender

Author study/date	Design	Study population	Patients		Age (mean, yr)		*P*	Complications < admission (%)			*P*
			Men	Women	Men	Women			Men	Women	
Lansky *et al*[22] 2005	RCT	AMI + PTCA	1520	562	57.0	66.0	< 0.001	MACE	3.2	6.4	0.002
								Bleeding	2.0	5.2	0.0003
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001	MACE[1]	1.3	3.2	0.0766
								Vascular[1]	0.6	1.0	0.6844
								MI[1]	1.0	2.9	0.0526
Tizón-Marcos *et al*[33] 2009	RCT	PCI	1050	298	59.7	62.5	< 0.0001	MACE[1]	3.9	3.4	0.86
								Bleeding[1]	1.1	2.4	0.16
								MI[1]	3.5	3.0	0.86
Thompson *et al*[53] 2006	Pros cohort	PCI	807	359	61.7	67.7	< 0.0001	MACE	2.7	3.9	0.29
								Vascular	4.2	12.0	< 0.0001
Jibran *et al*[81] 2010	Retro cohort	ACS + PCI	331	137	60.7	66.1	< 0.0001	MACE[1]	3.9	2.9	0.8
								Access site[1]	1.5	6.2	0.02
								MI[1]	1.5	0.7	1.0
Duvernoy *et al*[43] 2010	Pros cohort	PCI	14 848	7877	61.9	66.9	< 0.001	MACE	4.48	5.19	< 0.001
								Vascular	1.02	3.34	< 0.001
								MI	1.60	1.66	0.70
Bufe *et al*[62] 2010	Pros cohort	STEMI + PCI	376	124	58	65	< 0.001	Shock	10.1	11.3	0.838
								Renal failure	1.3	1.6	0.835
Reynolds *et al*[30] 2007	RTC	MI	12 498	4090	59.5	67.0	< 0.001	CVA[1]	0.2	0.6	< 0.01
								Heart failure	4.0	6.7	< 0.001
								Re-MI	2.7	3.5	0.004
Matsui *et al*[26] 2002	Retro cohort	AMI	346	136	62.9	70.4		Heart failure	16	26	0.013
								Re-MI	5	6	0.568
Moriel *et al*[28] 2005	Pros cohort	ACS	820	511	78	79	0.12	CVA	2	1	0.79
								Heart failure	21	21	0.86
								Re-MI	15	14	0.61
Uva *et al*[35] 2009	RCT	CABG	1485	481	64.7	69.0	0.001	MACE	3.9	6.6	NS
								CVA	0.7	1.2	0.2
								MI	0.7	1.3	0.08
Herlitz *et al*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	Re-MI	4	2	0.02
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	CVA	2.8	4.2	NS
								Bleeding	1.8	1.5	0.592
								MI	0.6	0.7	0.657
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61	MACE	4.2	6.0	0.50
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	MACE	2.9	3.0	0.922
								CVA	0.1	0.2	0.905
								MI	1.6	1.7	NS
								Access site	0.0	0.3	0.018
Chiu *et al*[13] 2004	Pros cohort	PCI	12 738	5301	62.3	66.5	< 0.001	Transfusion	4	12	< 0.001
								Haematoma	5	6	0.568
Setoguchi *et al*[31] 2008	Pros cohort	AMI	317	1308	80	82	< 0.001	CVA	3	4	0.57
Singh *et al*[79] 2008	Retro cohort	PCI	7616	3365	64.7	69.4	0.48	CVA	0.5	0.9	0.29
								MI	1.1	1.4	0.44
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001	Re-MI	3	2	NS

[1]After 30 d. MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; STEMI: ST elevation MI; NS: Not significant; CVA: Cerebrovascular accident; MACE: Major adverse cardiac events.

The proportion of men and women undergoing CABG was equal[10,11,26,28,30-32,37,79] 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[16]. Furthermore, women underwent surgery more commonly on an urgent basis than men[12,16,20,34,36,63,75].

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[7,9,13,18,22,30,36,53,61,64,78,80], while others showed no differences[23,25,28,33-35,38,40,44,46,48,54,56-58,62,81] (Table 5). Particularly at younger ages, women tended to have a greater risk for cardiac events compared with men at the same age[64,82]. This difference disappeared in patients older than 65 years[82,83].

Many discrepancies existed in the short-term mortality rate of patients with ACS. Some studies revealed

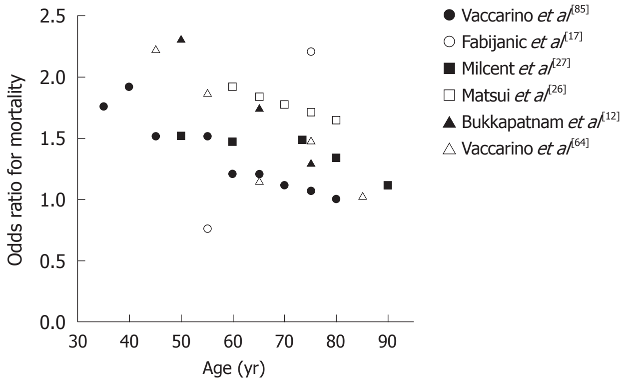

Figure 1 Gender differences in mortality after a myocardial infarction among different age categories. An odds ratio higher than one indicates an increased mortality after a myocardial infarction in women in comparison to men.

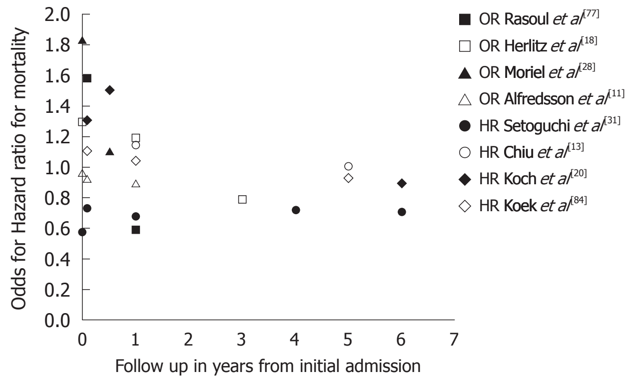

Figure 2 Gender differences in mortality risk in patients with coronary artery disease. An odds/hazard ratio higher than one indicates an increased mortality in women in comparison to men. OR: Odds ratio; HR: Hazard ratio.

a higher short-term mortality risk among women[7,12,17,22,24,27,28,35,36,57,64,78], while others did not[9-11,16,18,26,32-34,46,48,54,59,65,81] (Table 6). As discussed above, older age at presentation was an important confounding factor in this regard[29,39,54,58,75,77,84].

An important finding was that women with ACS had an increased mortality risk at younger ages compared with men of the same age[39,45,52,64]. Figure 1 illustrates the gender differences in mortality after a MI among different age categories. As shown in this Figure, the difference in mortality risk was reduced in older age[12,26,27,64,83,85].

Independent predictors of mortality were old age[20,29,39-41,49,50,54,59,75,77,84], with an OR of 1.06 (95% CI: 1.05-1.07) for each additional year[40,74], diabetes[20,24,29,49,54,62,74,77,84], heart failure[20,29,39], CAD[29], duration of ischemia, multiple vessel disease, history of MI, hypertension[41,77], CVA[77], anemia[20], cardiogenic shock, peripheral vascular disease[39], and ST-elevation[74]. Whether female gender can be considered as an independent risk factor remains unclear. Some studies claimed it could[24,27,51,55,57,75,77], but others showed no significant association after adjustment for risk factors[16,22,29,34,38-40,42-46,49,50,53,54,58,59,61,62,66,80,82,84]. 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)[74]. After adjustment for age and cardiovascular risk factors, the long-term mortality rate was equal for both men and women[13,20,22-24,29,31,32,40,41,44-46,48,49,58-60,62,65,79] or even in favor of women[10,31,34,42,54,55,63,77,84], 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[76,79]. Data were inconsistent on the differences between men and women in the number of readmissions[86-88] and the number of second PCIs[10,18,21,23-26,28,33,35]. 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)[60,89]. 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[89]. Whether this can be explained by the protective mechanism of estrogens in women is still unknown. Estrogens were shown to have an antiinflammatory effect on the vessel wall and induce vasodilatation in coronary arteries[1]. However HRT in post-menopausal women did not lower the risk of mortality from CVD after adjustment for other risk factors[90-92]. HRT is therefore not recommended as primary or secondary prevention of CVD in women[73].

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[24]. 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[13,20,22-24,29,31,32,79]. 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[72].

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

Table 6 Mortality rates in male and female patients with coronary artery disease at admission, at thirty days and after one-year of follow-up

Author study/ date	Design	Study population	Patients		Age (mean, yr)		*P*	Mortality < admission (%)		*P*	Mortality < 30 d (%)		*P*	Mortality < 1 year (%)		*P*
			Men	Women	Men	Women		Men	Women		Men	Women		Men	Women	
Lansky *et al*[22] 2005	RCT	AMI + PTCA	1520	562	57.0	66.0	< 0.001	1.0	3.4	0.0003	1.1	4.6	< 0.001	3.0	7.6	< 0.001
Singh *et al*[79] 2008	Retro cohort	PCI	7616	3365	64.7	69.4	0.48	1.8	2.5	0.38	2	3	0.25	4	4	0.490
Alfredsson *et al*[11] 2007	Pros cohort	Unstable/ NSTEMI	34 020	19 761	69	73	< 0.001	5	7		7	9		16	19	
Setoguchi *et al*[31] 2008	Pros cohort	AMI	317	1308	80	82	< 0.001	14.5	13.9		9.8	8.6		21.5 24.3[3]	18.2 25.0[3]	
Matsui *et al*[26] 2002	RCT	MI	346	136	62.9	70.4		4	4	0.851	4	10	0.013			
Uva *et al*[35] 2009	RCT	CABG	1485	481	64.7	69.0	0.001	0.8	2	0.01	1.2	2.3	0.09			
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	2.7	2.9	0.639	3.7	3.9	0.747			
Moriel *et al*[28] 2005	Pros cohort	ACS	820	511	78	79	0.12	7	12	0.007				19[1]	21[1]	0.480
Herlitz *et al*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	12	14	NS				18	22	0.040
Lawesson *et al*[24] 2010	Retro cohort	STEMI aged < 46	1748	384	40.8	40.4	0.14	1.0	2.9	0.005				2.2	3.7	0.010
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	0.5	0.5	0.918				8.9[2]	10[2]	0.197
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61	2.8	5.2					0	3.4	
Anand *et al*[9] 2005	Trial	ACS	7726	4836	62.7	66.5	0.0001				4.9	4.4	0.23[5]	11.1	9.7	0.040
Tizón-Marcos *et al*[33] 2009	RCT	PCI	1050	298	59.7	62.5	< 0.0001				0.2	0	1.00	0.8	1.0	0.720
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001				6	6.2	NS	9 12[2]	12.5 18[2]	0.600 0.070
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001				0	0		1.0	0.3	0.447
Koch *et al*[20] 2003	Pros cohort	CABG	1588	460							2.5	3.4	0.29	4.2[1] 15.8[4]	7.1[1] 19.6[4]	0.020 0.030
Lagerqvist *et al*[21] 2001	RCT	AMI	1708	749	64	68	< 0.001							5.7	7.2	NS
Chiu *et al*[13] 2004	Pros cohort	PCI	12 738	5301	62.3	66.5	< 0.001							5	7	< 0.001

[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[9,11,18,24,28,30]. 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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