Review

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Interventional Cardiology

Sex differences in clinical outcomes following coronary revascularization

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There have been several reports suggesting that the response to treatment for patients with significant coronary heart disease was not equal among males and females. Most of the early investigations on sex differences after surgical or percutaneous coronary revascularization suggested worse clinical outcomes in females compared with male counterparts. However, along with the advent of new revascularization techniques and devices, recent trials have shown somewhat narrowed sex-based differences in cardiovascular outcomes. Given that sex-based difference in outcomes and prognosis is still an important ongoing issue, this article systematically reviewed the cumulative evidence from key clinical studies and tried to help guide the physician in making sex-specific treatment decisions for patients with significant coronary heart disease requiring coronary revascularization.

Keywords: coronary artery bypass graft surgery • coronary heart disease • gender • mortality • percutaneous coronary intervention

Ischemic heart disease (IHD) accounts for more than half of cardiovascular deaths in both the males and the females [1]. However, there were numerous sex-based differences in IHD in terms of prevalence, clinical symptoms, diagnostic accuracy, response to treatment and prognosis. Whether these sex-specific differences were directly attributable to true sex-related biologic difference or were caused by the disparities in sociocultural experiences and the prevalence of concomitant risk factors has been debated for decades. Notwithstanding these unclear understandings, treating physicians have believed that diverse treatment modalities in everyday practice might yield comparable efficacy and safety in both males and females, which might not be true.

Clinical evidence regarding treatment and prognosis of various clinical subsets of coronary heart disease (CHD) were largely based on male patients, since females have been under-represented in clinical research trials [2]. And, up to recently, many important studies still are not designed to specifically examine sex-specific differences from the beginning, thus making it difficult to evaluate whether study findings are equally applicable to female as well as male patients. To overcome this 'sex gap' representation, the US NIH instructed to include both males and females in clinical studies and when studied health condition affects both sexes, to analyze data by sex [3]. Moreover, the US FDA recently issued draft guidance on the study and evaluation of sex differences in implantable medical device clinical studies (Box 1) [4].

During the last two decades, there has been a revolutionary change in the field of surgical or percutaneous revascularization treatments for significant CHD. New methods that minimize the invasiveness and risks involved with coronary artery bypass graft (CABG) surgery have been developed, and rapid advancements of novel techniques, devices and adjunctive pharmacotherapies led percutaneous coronary intervention (PCI) to extend its clinical application for more complex subsets of patients. In

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Box 1. Summary of US FDA's guidance on evaluation of sex differences in medical device clinical studies.[†]

Recommendations for achieving representative enrollment
- Provide background sex-specific information for the disease or condition that the device is intended to treat or diagnose in the study and submission documents
- Consider various approaches to enhance enrollment of females in clinical studies

Recommendations for sex-specific statistical analysis
- After overall outcomes have been investigated, the influence of sex on primary end points for both safety and effectiveness (and in some cases for important secondary end points as well) should be assessed
- Discuss with US FDA for the interpretation of sex-specific data in cases where clinically significant differences between the sexes are observed in safety or effectiveness

Recommendations for reporting sex-specific information in summaries & labeling
- Report the number and proportion of subjects by sex who were treated or diagnosed with the device as part of a clinical study
- The results of sex-specific outcome analyses should be presented in the labeling, regardless of whether the analyses are prespecified or *post hoc*

[†]Data taken from [4].

this review, we investigated the cumulative evidence regarding sex-specific differences of clinical outcomes among patients with significant CHD requiring surgical or percutaneous coronary revascularization based on published literatures.

Mechanisms leading to differential sex-specific outcomes in CHD

As illustrated in Figure 1, multiple biological factors contribute to the different outcomes of CHD between females and males. The most obvious biological factor is hormonal difference such that estrogen affords females a protective advantage against CHD before menopause. Female sex hormone, precisely 17 beta-estradiol, modulates cholesterol levels, stimulates nitric oxide and prevents vessel contraction by acting with endothelial and vascular smooth muscle factors [5]. Difference in autonomic responses has also been postulated as a putative mechanism to account for sex-specific outcomes in CHD since vagal activation is more common in females than in males during acute coronary events and this may contribute to antiarrhythmic effects or reduction of ischemic myocardial burden [6]. Difference in coronary vessel caliber might also seem to play a role. Coronary arteries are smaller in females than males independent of body size, and along with different body habitus and smaller heart size, these structural factors may lead to technical difficulties, greater risk of incomplete revascularization and higher rates of restenosis in female patients undergoing either PCI or CABG surgery [7,8].

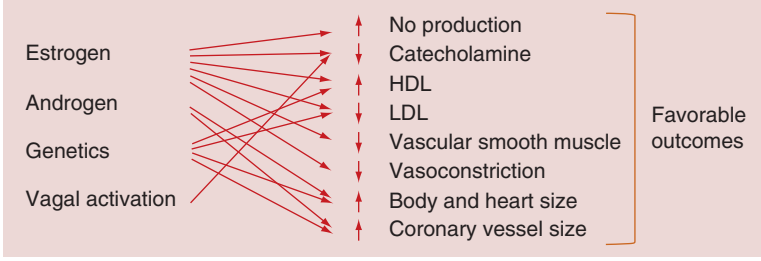

Figure 1. Sex-specific biological mechanisms leading to different sex-specific outcomes in coronary artery disease.

Disparities in the prevalence of risk factors and sociocultural issues, which are frequently proposed in abundant clinical studies, seem to be more plausible explanation leading to different sex-based outcomes. Females are usually older when presenting with CHD, and more likely to have greater risk factor burden or comorbid conditions and more functional disability compared with male counterparts [9]. Furthermore, there are evidences that physician bias and difference in patient behaviors contribute to different referral patterns for noninvasive testing or coronary angiography [10,11]. These biological and nonbiological factors might function independently or synergistically to the sex-specific difference in CHD outcomes.

Sex-specific differences in prevalence, patterns & outcomes of CHD

In general, the prevalence of all forms of CHD (i.e., stable angina or acute coronary syndrome [ACS]) was higher in males than females within each age stratum over 20 years of age, and this finding contributes to the common perception that heart disease is a man's disease [1,12]. However, it is well known that lifetime development of CHD in males and females differ. Some population-based studies, including the INTERHEART study, demonstrated that the first presentation with CHD occurs approximately 8–10 years later among females than males [13]. Although an exact mechanism is still incompletely understood, this later onset of disease in females is speculated to be the

output of hormonal protection from early development of atherosclerosis; since the incidence of CHD sharply increases after menopause and by the age of 70, females have more incidence of CHD as males do.

Sex differences in patterns of CHD presentation were also suggested. Prior studies of elderly patient cohorts indicated that females were more likely to present with atypical forms of chest pain compared with males [14]. This tendency was also consistent even in younger patients with ACS; two recent studies demonstrated that females were more likely to present without chest pain compared with males [15,16]. In addition to the sex differences in diagnostic sensitivity of noninvasive stress tests and ECG [10,17], these disparities in symptom profile might contribute to the delay in seeking medical care as well as the under or misdiagnosis of acute form of CHD, probably affecting the outcome [18,19].

There have been several reports showing sex-specific outcomes of CHD according to different clinical settings such as stable angina or ACS (Table 1). In general, many registries and population-based studies suggested that female patients with CHD might have higher rates of classic risk factors such as hypertension or diabetes, and have lower probability to receive appropriate medical therapy or coronary revascularization compared with male patients [1,11,20–21]. However, this difference of risk-factor profiles did not seem to always translate into poor outcomes with women. Data from the national registers in Finland and Euro Heart Survey described higher mortality for female patients with stable angina at 1–4 years of follow-up [11,21]. But, recent results from the international CLARIFY registry including 30,977 patients with stable CHD demonstrated similar 1-year rate of the composite of cardiovascular death, myocardial infarction (MI), or stroke for men and women [22].

Among ACS patients, sex differences in mortality seem to depend largely on age. Based on US National Registry of Myocardial Infarction and several other studies, younger females (aged <50–55 years) showed a mortality excess compared with aged men presenting with acute MI, whereas significant mortality differences were not found in older population [23–24,27–28]. Although the reason was not fully understood, disproportionate burden of coronary risk factors and comor-

Table 1. Current evidences for sex-specific differences in outcomes of coronary heart disease.

Study (year)	Patients (n)	Characteristics	Clinical setting	Main findings (female vs male)	Ref.
Euro Heart Survey (2006)	3779	Europe, 196 centers, prospective registry	Stable angina	1-year death, MI: 3.7 vs 2.9%; adjusted HR: 2.09 (1.14, 3.85); p = 0.02	[14]
CLARIFY registry (2012)	30,977	International, 45 countries, prospective registry	Stable angina	1-year CV death, MI, stroke: 1.8 vs 1.7%; adjusted HR: 0.93 (0.75, 1.15); p = 0.5 1-year death: 1.6 vs 1.5%; adjusted HR: 0.91 (0.72, 1.13); p = 0.39	[22]
NRMI 2 (1999)	384,878	USA, 1658 centers, prospective cohort	AMI	Hospital death: aged <50 years; 6.1 vs 2.9%; aged 75–79 years; 19.1 vs 18.4%	[23]
USIC registry (2006)	4347	France, nationwide registry	AMI	Hospital death: 16 vs 9%; younger group, adjusted OR: 2.4 (1.4, 4.3); p = 0.003; older group; adjusted OR: 1.2 (0.9, 1.7); p = 0.3 1-year death: 25 vs 16%; younger group: 14 vs 8%, p = 0.0005; older group: 29 vs 27%, p = 0.31	[24]
Berger *et al.* (2009)	136,247	International, pooled data from 11 RCTs	ACS	30-day death: STEMI, 12.3 vs 5.8%, adjusted OR: 1.15 (1.06,1.24); NSTEMI, 6.4 vs 4.3%, adjusted OR: 0.77 (0.63, 0.95); unstable angina, 2.4 vs 2.8%; adjusted OR: 0.55 (0.43, 0.70)	[25]
NRMI (2009)	361,429	USA, 1057 centers, retrospective cohort	AMI	Hospital death: STEMI, unadjusted RR: 1.64 (1.59, 1.69); NSTEMI, unadjusted RR: 1.22 (1.09, 1.15)	[26]

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CV: Cardiovascular; HR: Hazard ratio; MI: Myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; OR: Odds ratio; RCT: Randomized controlled trial; RR: Relative risk; STEMI: ST-segment elevation myocardial infarction.

Table 2. Summary of studies regarding sex-specific outcomes following coronary artery bypass grafting surgery.

Study	Characteristics	n	Main findings (female vs male)	Ref.
Blankstein *et al.*	Isolated CABG, USA, 31 hospitals, 1999–2000	5023 females and 10,417 males	Operative mortality: 4.24 vs 2.23%; risk adjusted mortality: 3.81 vs 2.43%	[37]
CCORP database	Isolated CABG, USA, 121 hospitals, 2003–2004	10,708 females and 29,669 males	Operative mortality: 4.60 vs 2.53%; adjusted OR: 1.61 (1.40, 1.84)	[38]
ASCTS cardiac surgery database	Isolated CABG, Australia, 18 hospitals, 2001–2009	4780 females and 16,754 males	In-hospital mortality: 2.3 vs 1.6%, 30-day mortality: 2.2 vs 1.4%, 7-years survival: 82.8 vs 84.1%	[44]
Ahmed *et al.*	Isolated CABG, Australia, single center, 1996–2004	1114 females and 3628 males	7.9-year mortality: adjusted HR: 0.92 (0.77, 1.11); p = 0.38	[45]
CCN database	Isolated CABG, Canada, population-based cohort, 1991–2002	14,393 females and 51,800 males	11-year mortality: adjusted HR: 0.9 (0.83, 0.98); p < 0.01	[43]
BAR	Isolated CABG, USA and Canada, 18 centers, 1988–1991	489 females and 1340 males	5.4-year mortality: 12.8 vs 12.0%; adjusted RR: 0.60 (0.43, 0.84); p = 0.003	[42]

CABG: Coronary artery bypass graft; HR: Hazard ratio; OR: Odds ratio; RR: Relative risk.

bidities in younger females seemed to account for this age-dependent disparity in mortality among patients presented with acute MI. The mortality gap was also observed by the type of ACS [25]. In this study, among patients with ST-segment elevation myocardial infarction (STEMI), 30-day mortality was higher among females compared with males, whereas in non-STEMI (NSTEMI) and unstable angina, mortality was lower among females. Similarly, the US National Registry of Myocardial Infarction data from 2000 and 2006 showed higher hospital mortality among females in the STEMI population than NSTEMI population [26]. To date, there was also a considerable debate regarding the evidence for the sex difference in long-term outcomes [2], but of note, survival for both the male and female patients after treatment for acute myocardial infarction have improved markedly over decades, suggesting that evidence-based therapies might have equal clinical benefit for both genders [27,29].

Sex-specific outcomes following CABG

Key findings of studies regarding short- and long-term mortality for patients who underwent CABG are summarized in Table 2. Most of early investigations on sex-based differences related to CABG consistently showed that females had considerably higher in-hospital mortality and morbidity than males [30–32]. In accordance with the general CHD population, there were major sex differences in the preoperative risk-factor profiles and surgical factors among patients referred for CABG [30–34]. However, there have been conflicting reports whether this difference in outcomes persists after adjustment for all identifiable risk factors and thus, many investigators still argue that female sex is an independent predictor of poor perioperative outcome [34–38]. Up to date, two meta-analyses exist within this context. Nalysnyk *et al.* [39] suggested that female sex was associated with an increased risk for death (unadjusted odds ratio [OR]: 1.92; 95% CI: 1.48–2.48) after CABG. Consistently, in the more recent contemporary meta-analysis by Takagi *et al.* [35], there was a significant increase in short-term mortality in females compared with male patients (adjusted OR: 1.38; 95% CI: 1.29–1.49; p < 0.001). As a result, several risk models such as EuroSCORE and Society of Thoracic Surgeons (STS) score, which were developed to predict operative mortality, included female sex as a negative prognostic factor [40,41]. Despite these relatively unfavorable early outcomes in females compared with males, once past the perioperative time period, long-term survival for females appeared to be comparable to or even slightly better than for males [42–45].

Underutilization of internal thoracic artery (ITA) in female is one of the major concerns, which has been postulated to explain the different outcomes between both sexes after CABG [34,46]. In contrast with the vein conduits, ITA appears to be virtually resistant to the development of intimal hyperplasia and atherosclerosis combined with intact functional capacity, such as endothelial-dependent vasodilation, after grafting [47]. These unique characteristics led ITA graft to have excellent 5- and 10-year patency rates and compared

with CABG using only venous grafts, the use of at least one ITA is associated with improved short- and long-term survival rates [48–50]. Although the benefits of ITA graft over the saphenous vein graft are not in dispute, a contemporary observational study based on the STS National Cardiac Database including 541,368 patients reported profound underutilization of ITA (OR: 0.62; 95% CI: 0.61–0.63; p < 0.001) in female than male patients [46]. The efforts to eliminate these disparities can be indirectly emphasized based on some reports in that short- and long-term survival rates were not different when ITA was equally used in both sexes [51,52]. In the same context, the use of bilateral ITA was also reported to be less frequent in females compared with males based on several studies [46,53]. This difference is a potential future issue since there are growing burden of published studies showing better long-term survival in patients receiving bilateral ITA compared with single ITA grafting [53–56].

Off-pump CABG (OPCAB), compared with the conventional on-pump CABG, is a less-invasive established technique and has been introduced to eliminate overall operative mortality and morbidity attributable to cardiopulmonary bypass. While this technique was expected to provide some benefits in end-organ function during operation, some technical limitation can result in poor graft quality and incomplete revascularization [57]. Several clinical trials comparing OPCAB with on-pump CABG have failed to demonstrate a difference in long-term clinical outcomes [58–60]. However, at least for the early outcomes, there are some promising results for females after OPCAB compared with on-pump CABG [61–64]. Two studies using Healthcare Company database compared on-pump CABG and OPCAB in 16,871 and 21,902 consecutive females and demonstrated 42% (adjusted OR: 1.42) and 73.3% (adjusted OR: 1.73; 95% CI: 1.22–2.46; p = 0.002) higher mortality rate in patients undergoing on-pump CABG, respectively [62,63]. Another recent study by Puskas *et al.* showed that OPCAB was associated with a significant reduction in death (risk-adjusted OR: 0.39; p = 0.001) in females [61]. Despite these favorable evidences suggesting that OPCAB might be better than on-pump CABG for females, further well-designed studies are needed to define the impact of OPCAB in females, since most current

Table 3. Summary of landmark studies regarding long-term sex-specific outcomes following percutaneous coronary intervention using drug-eluting stents.

Study	Characteristics	Patients (n)	Main findings (female vs male)	Ref.
Mikhail *et al.*	PES, pooled analysis of five RCTs	665 females and 1606 males	5-year mortality: 2.08 vs 1.90%; p = 0.54; adjusted HR: 0.83 (0.60, 1.14) 5-year MI: 1.86 vs 1.60%; p = 0.42; adjusted HR: 1.12 (0.80, 1.58)	[72]
Stefanini *et al.*	SES/PES/ZES, pooled analysis of three RCTs	1164 females and 3721 males	2-year cardiac mortality: 2.9 vs 2.5%; p = 0.43; adjusted OR: 1.04 (0.61, 1.80); p = 0.87 2-year MI: 5.8 vs 4.7%; p = 0.13; adjusted HR: 1.07 (0.75, 1.53); p = 0.71	[77]
Abbott *et al.*	SES/PES, NHLBI registry	486 females and 974 males	1-year mortality: 3.8 vs 3.6%; p = 0.97; adjusted RR: 1.02 (0.54, 1.93); p = 0.95 1-year MI: 4.4 vs 4.5%; p = 0.94, adjusted RR: 1.07 (0.61, 1.89); p = 0.81	[75]
Onuma *et al.*	SES/PES, pooled analysis of two registries	798 females and 2007 males	3-year mortality: 10.2 vs 9.5%; p = 0.52; adjusted HR: 0.92 (0.68, 1.25) 3-year MI: 4.6 vs 4.4%; p = 0.96; adjusted HR: 1.22 (0.79, 1.87)	[74]
Anderson *et al.*	SES/PES/EES/ZES, US NCDR CathPCI registry	134,679 females and 180,283 males	2.5-year mortality: 16.3 vs 15.8%; p = 0.002; adjusted HR: 0.92 (0.90, 0.94) 2.5-year MI: 7.8 vs 7.6%; p = 0.868; adjusted HR: 0.99 (0.95, 1.03)	[73]
Park *et al.*	SES/PES/EES/ZES, pooled analysis of eight RCTs and three observational studies	7180 females and 16,424 males	2.1-year cardiac mortality: 1.4 vs 1.3%; adjusted HR: 1.05 (0.93,1.19); p = 0.41 2.1-year MI: 9.6 vs 7.5%; adjusted HR: 1.27 (1.16, 1.39); p < 0.001	[78]

EES: Everolimus-eluting stent; HR: Hazard ratio; MI: Myocardial infarction; NCDR: National Registry of Myocardial Infarction; OR: Odds ratio; PES: Paclitaxel-eluting stent; RCT: Randomized controlled trial; RR: Relative risk; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

evidences are based on retrospective observational studies.

Sex-specific outcomes following PCI

Sex-specific outcomes after PCI have changed over time along with the advent of the procedural techniques and coronary stent system. Before the introduction of drug-eluting stent (DES), PCI was performed either by conventional balloon angioplasty or implantation of bare-metal stent (BMS). Most of early registries in the balloon angioplasty era found that female patients had lower rates of angiographic success, two- to three-fold higher in-hospital mortality, and worse long-term clinical outcomes compared with male patients [65–67]. Subsequent studies in the BMS era indicated that the outcomes after PCI significantly improved in females and sex-based differences in outcomes have much narrowed [65,68–71].

DESs are currently used in preference to BMS in most cases because they are associated with marked reductions in restenosis and repeat revascularization. Several clinical trials and registries suggested a consistent beneficial effect of DES over BMS equally in both female and male patients [72–75]. A recent analysis from US National Cardiovascular Data Registry CathPCI Registry found that, compared with BMS, DES use was associated with lower long-term likelihood for death (female: adjusted hazard ratio [HR]: 0.78; 95% CI: 0.76–0.81; male: HR: 0.77; 95% CI: 0.74–0.79) and MI (female: adjusted HR: 0.79; 95% CI: 0.74–0.84; male: HR: 0.81; 95% CI: 0.77–0.85) equally in both sexes. Thus, the sex gap in clinical outcomes after PCI appears to significantly decrease with the use of DESs. Currently, there are limited published data focusing on sex-specific outcomes after PCI predominantly using DESs. The long-term sex-specific outcomes of DES-treated patients from recent important studies were summarized in Table 3. Overall, female revealed to have comparable benefits to male from PCI with DES on long-term outcomes. Whether newer-generation DES further benefits in females over early-generation DESs remains to be determined. A recent large-scale analysis of DES-treated females provided a clue for this issue. Stefanini *et al.* pooled data for female participants from 26 randomized trials of DES and analyzed 3-year follow-up outcomes according to the stent type [76]. They found that newer-generation DES was associated with significantly lower rates of death or MI (9.2 vs 10.9%; p = 0.01), definite or probable stent thrombosis (1.1 vs 2.1%; p = 0.03) and target lesion revascularization (6.3 vs 7.8%; p = 0.005) than was the use of early-generation DES in females. As discussed above, the reduction of sex-based differences in outcome after PCI was evident over time, even after rigorous adjustment of these clinical risk profiles. This suggests that improved interventional techniques and devices may have predominantly played a role in the improvement of outcomes in females.

Executive summary

Current problems in conducting clinical trials for evaluation of sex-based differences in patients with coronary heart disease

- Females are under-represented in clinical research trials as well as cardiovascular device trials.
- Many studies are not designed to specifically examine sex-specific difference.

Mechanisms leading to different responses in females compared with males

- Biological factors include differences in sex hormone, autonomic responses and size of heart or coronary vessels.
- Nonbiological factors include differences in the prevalence of cardiovascular risk factors and sociocultural experiences.

Sex-specific differences in prevalence, patterns & outcomes of coronary heart disease

- Conflicting data exist for long-term mortality in patients with stable angina and acute coronary syndrome.
- Younger females show higher short-term mortality compared with male counterparts after acute myocardial infarction.
- Females carry higher hospital mortality after ST-segment elevation myocardial infarction compared with male patients.

Sex-specific outcomes following coronary artery bypass graft

- Female sex is an independent predictor of poor perioperative outcome.
- Long-term survival is comparable to both males and females.
- Internal thoracic artery grafts are underutilized in females compared with male patients.
- Off-pump coronary artery bypass graft showed improved in-hospital survival in female patients.

Sex-specific outcomes following percutaneous coronary intervention

- Differences in outcomes decreased over time from balloon angioplasty era through drug-eluting stent era.
- Both males and females have comparable long-term outcomes after drug-eluting stent implantation.

Future perspective

Although limited in sample number of female gender and study design, current studies have shown somewhat diminished but persistent sex-based differences in clinical outcomes of patients with CHD despite adjustment for other risk factors. Along with the advent of evidence-based medicine in modern medical science and the rapid development of revascularization techniques and medical devices, well-designed future researches including sufficient number of female participants warrant to better understand sex-based differences in CHD. Furthermore, it would be essential that clinical trials and registries should report gender-specific outcomes in terms of treatment effect. And, it was also considered that future clinical practice guidelines might be tailored to be gender-specific for improving the efficient use of various treatment options and targeting at-risk populations of males and females. Most importantly, treating physician should recognize the possibility of sex-specific difference in treatment effect and prognosis and incorporate any opportunities to mitigate these differences in clinical practice

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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