Chapter 13
Gender Differences in Outcome After Coronary Revascularization

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Since the introduction of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), coronary revascularization played an important role in reducing cardiovascular mortality over 40–50 years, especially in patients presenting ST-segment elevation myocardial infarction (STEMI). While the benefit of coronary revascularization has been shown both in men and women, cumulating evidences regarding prevalence of coronary artery diseases and clinical outcomes after coronary revascularization revealed apparent sex differences. Women were associated with greater unadjusted peri-procedural mortality following PCI or CABG [1–8], suggesting the older age and presence of comorbidities in women. In terms of long-term outcomes, women as compared with men were associated with lower adjusted 10-year risks for all-cause death after PCI, [9] while long-term mortalities following CABG were similar between men and women [10]. While lower coronary disease burden, lower prevalence of epicardial endothelial dysfunction, and differences in the clinical management following coronary revascularization might possibly explain the observed differences in clinical outcomes between men and women, underlying pathophysiological sex differences on coronary revascularization remains largely unclear.

It is well-known that women are generally 10 years older than men when presenting with coronary artery disease [11–13], because of the protective effects of estrogen until their menopause. This concept has been indirectly supported by observations young women with hypoestrogenemia [14]. In the nation-wide registries of coronary artery disease, despite older age and greater prevalence of traditional risk factors such as hypertension and diabetes, women less likely to have

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Table 13.1 Baseline patient characteristics between men and women in large-scale registries

	GWTG-CAD [1]		German Society of Cardiology [2]		BWGIC registry [3]	
	Men	Women	Men	Women	Men	Women
No of patients	47,556	30,698	65,972	24,262	95,030	35,955
Age	64.7 ± 14.1	72.6 ± 14.2	68 (60–74)	72 (65–78)	64.8 ± 11.6	70.3 ± 11.3
Diabetes	28.0%	32.8%	25.0%	29.8%	20.3%	26.8%
Hypertension	57.7%	67.8%			52.9%	63.3%
Hyperlipidemia	36.1%	33.0%			58.4%	58.9%
Smoking	32.8%	21.6%			30.8%	19.8%
Heart failure	12.8%	20.0%				
Previous MI	21.2%	18.3%			17.9%	12.3%
Previous PCI			51.6%	42.9%	29.9%	25.4%
Previous CABG			16.5%	10.1%	10.8%	7.4%
Poor LV function			13.4%	8.9%		
Renal insufficiency	9.5%	10.9%	16.7%	16.5%	3.1%	3.6%

Data were derived from [1–3]

Baseline characteristics between men and women in GWTG-CAD, German Society of cardiology, and BWGIC registry. Women were generally older and had a greater prevalence of traditional risk factors, while women were less likely to have previous history of coronary artery disease. *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *LV* left ventricular

previous history of coronary artery disease, have a lower extent of coronary artery disease (i.e. lower number of diseased vessels) and present less often with STEMI (Table 13.1) [1–3].

In the sub-analysis of PROSPECT study evaluating serial assessments of three-vessel coronary arteries by virtual histology intravascular ultrasound, young women (<65 years old, N = 88) had a fewer number of fibroatheromas (2.0 vs. 3.0, p = 0.007) and non-culprit lesions per patient (4.0 vs. 5.0, p = 0.004) with smaller plaque volumes (46.8% vs. 47.7%, p = 0.04), and more fibrotic plaques (4.4% vs. 2.2%, p = 0.03) than men in the same age group (N = 398) [15]. ADAPT-DES study also showed lower prevalence of plaque rupture and thin-cap fibroatheroma in young women (<65 years old) as compared with young men [16]. Although Bharadwaj et al. based on optical coherence tomography and near infrared spectroscopy (NIRS) failed to show sex-specific differences in plaque characteristics [17], Haaf et al. reported a tendency towards lower NIRS-derived lipid core burden index (LCBI) in women as compared with men [18]. Men as compared with women also seem to have more diffuse epicardial endothelial dysfunction, which is a known precursor of atherosclerosis [19]. Pathophysiological mechanisms of smaller disease burden in women are largely unknown. We may speculate that not only the absence of protective effect of estrogen but also more smoking may be associated with endothelial dysfunction and the subsequent higher prevalence of atherosclerosis in men as compared with women.

The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study demonstrated that functional flow reserve (FFR)-guided PCI improved outcomes compared with an angiography-guided PCI [20]. In a subanalysis of this study, the benefit of FFR-guided PCI was observed in both men and women [21]. It is noteworthy that FFR values in the similar degree of stenosis were significantly higher in women than in men (0.75 ± 0.18 vs. 0.71 ± 0.17, P = 0.001). While microvascular dysfunction and/or smaller myocardial mass could be a possible explanations of this finding, several studies have been conducted to elucidate the difference in microvascular dysfunction between men versus women. Coronary flow reserve (CFR), which was regarded as an indicator for coronary microvascular dysfunction, showed a linear association with adverse outcomes [22]. Maximal CFR was significantly lower in women than men (2.80 vs. 3.30, P < 0.001) [19, 23], suggesting greater prevalence of microvascular dysfunction in women. On the other hand, Kobayashi et al. measured the index of microcirculatory resistance (direct measurements of coronary microvasculature), which was similar between men and women, suggesting larger resting coronary flow with no significant difference in microvascular dysfunction [23]. Further studies are needed to elucidate the difference in coronary physiology between men versus women.

In addition to the clinical presentation, women and men differ substantially in diagnostic evaluation and their management. Women seem to derive more prognostic information from an anatomical assessments such as cardiac computed tomography, whereas men tend to derive similar prognostic value from both anatomical assessments and stress testing such as exercise electrocardiography, stress echocardiography, and stress nuclear [24]. Recently, high-sensitivity assays for measurements of cardiac troponins emerged as a clinical decision making tool to detect chronic myocardial injury [25]. While high-sensitivity troponin T was an independent predictor for all-cause mortality in both sex (Men: HR 6.45, 95%CI 4.68–8.87, P < 0.001, Women: HR 4.29, 95%CI 2.36–9.03, P < 0.001), difference between high and normal high-sensitivity troponin T values appeared to be more marked in men [26]. It remains unclear whether there are sex-specific differences in the clinical phenotype of coronary artery disease, or in sex-specific bias of diagnostic testing, or both. In the outpatient setting among patients with suspected coronary disease, women undergo coronary revascularization less frequently than men [27, 28]. Since sex-specific difference in clinical presentation, diagnostic evaluation and management may widely varied among different cultures and countries, world-wide survey is warranted to characterize those differences.

Although women represented >30% of patients undergoing PCI, only a small proportion of women are enrolled in randomized clinical trials comparing stent type. To clarify safety and efficacy between stent types, several meta-analyses have been conducted and showed no significant interaction between gender and stent type: between first generation DES (sirolimus eluting stent or paclitaxel-eluting stent) versus bare-metal stent (BMS); [29–31] and between second generation DES (everolimus-eluting stent) versus first generation DES (paclitaxel-eluting stent) [32]. In a large-scale patient-level pooled analysis including a total of 11,557 women, newer-generation DES are associated with an improved safety profile

compared with early generation DES and BMS [33]. A nation-wide analysis of the CathPCI registry also showed favorable risk reductions for major adverse cardiac events following DES implantation as compared with BMS in both men and women without significant interaction [34]. Given these observations, women should be treated using newer-generation DES.

Diagnosis of STEMI is associated with high risk of major adverse cardiac events. In a large-scale Get With the Guidelines-Coronary Artery Disease (GWTG-CAD) registry, there were no significant adjusted risks for in-hospital mortality rates between women and men in the overall acute myocardial infarction cohort (adjusted OR 1.04, 95%CI 0.99–1.10), while there was a significant difference in the STEMI cohort (10.2% vs. 5.5%, P < 0.001, adjusted OR 1.12, 95%CI 1.02–1.23) [1]. The underuse of evidence-based treatments and delayed reperfusion among women were reported to be possible explanations for the greater risks of adverse events following STEMI in women [1]. More recently, in a large scale German PCI registry (N = 185,312), female sex was shown to be associated with 20% increase risks of in-hospital death (adjusted OR 1.19, 95%CI 1.06–1.33) and major adverse cardiac events (adjusted OR 1.19, 95%CI 1.07–1.34), while there was no difference among patients undergoing PCI for stable coronary artery disease, or non-ST-segment acute coronary syndrome [2]. While gender difference may be a possible explanations for these findings, large-scale prospective imaging studies are warranted.

Duration of dual antiplatelet therapy (DAPT) is determined based on ischemic events versus bleeding risks [35]. While female sex was regarded as a predictor of bleeding events following DAPT [36], a pre-specified sub-analysis of PRODIGY study showed no significant interaction between sex and duration of DAPT (6-month vs. 24-month) on both ischemic and bleeding endpoints [37]. It is of note that neither DAPT score [38], PARIS score [39], nor PRECISE-DAPT score [40] included sex as a potential confounder.

As relatively small number of women were included in the clinical trials, differences in the benefit of PCI in a specific subset have not been well investigated so far. In patients with unprotected left main stenting, adjusted 2-year risks of death (HR 1.12, 95%CI 0.80–1.56), cardiac death (HR 1.05, 95%CI 0.70–1.57) or death/myocardial infarction (HR 0.53, 95%CI 0.19–1.47) were not significant between men (N = 1048) and women (N = 404) [41]. Further studies are needed to confirm these observation.

Sex differences in patients undergoing CABG has not been well investigated so far. In the BARI 2D trial comparing PCI versus CABG in patients with type 2 diabetes, no sex differences were observed in clinical outcomes after adjustment for difference in baseline variables throughout 5 years, while number of patients were limited (Men: N = 1666, Women: N = 702) [42]. In large-scale single center studies (N >10,000), female sex was independently associated with an increased risk of short-term mortality after CABG surgery [7, 8], but it was no longer an independent risk factor for all-cause mortality in the long-term outcomes following CABG [10].

In conclusion, female sex is associated with greater short-term mortality following coronary revascularization, mainly driven by older age and greater prevalence of

comorbidities, while long-term outcomes after coronary revascularization is similar between men and women, or even better in women as compared with men. Sex difference in coronary disease burden, coronary physiology, response to diagnostic testing, and clinical management may play an important role in the observed difference in clinical outcomes between men and women. Further studies are needed to elucidate role of gender in determining short-term and long-term outcome following coronary revascularization.

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