Outcomes After Percutaneous Coronary Intervention in Women: Are There Differences When Compared with Men?

Usha Rao,[1] G Louise Buchanan[2] and Angela Hoye[1]

1. Department of Cardiology, Castle Hill Hospital, Kingston upon Hull, UK; 2. Department of Cardiology, Cumberland Infirmary, Newtown Road, Carlisle, UK

Abstract

Despite advances in the diagnosis and treatment of coronary artery disease, there remains evidence of a disparity in the outcomes for women when compared with men. This article provides a review of the evidence for this discrepancy and discusses some of the potential contributing factors.

Keywords

Outcomes, women, percutaneous coronary intervention, men, gender inequality, cardiovascular disease, guidelines-based interventions

Disclosure: The authors have no conflicts of interest to declare.
Received: 10 March 2019 **Accepted:** 10 April 2019 **Citation:** *Interventional Cardiology Review* 2019;14(2):70–5. **DOI:** https://doi.org/10.15420/icr.2019.09
Correspondence: Angela Hoye, Department of Academic Cardiology, Castle Hill Hospital, Kingston upon Hull HU16 5JQ, UK. E: angela.hoye@hull.ac.uk

Cardiovascular disease is a major cause of morbidity and is the leading cause of death in women and men in Western societies.[1] Despite the major advances seen in the field of interventional cardiology and pharmacotherapy, which have translated into better outcomes, a disparity is evident in the clinical outcomes between men and women.

This was clearly evident in a recent systematic review and meta-analysis published in 2018.[2] The authors evaluated the outcome of 1,032,828 patients (258,713 women) included in 49 studies of percutaneous coronary intervention (PCI) with respect to sex. Mortality was significantly lower in male patients at all follow-up time points – in-hospital mortality (OR 0.58; 95% CI [0.52–0.63]; p<0.001); 30-day mortality (OR 0.64; 95% CI [0.61–0.66]; p=0.04); 1-year mortality (OR 0.67; 95% CI [0.60–0.75]; p<0.001); and at least 2-year mortality (OR 0.71; 95% CI [0.63–0.79]; p=0.005). The majority of studies included in the analysis had been published in the last 10 years, indicating that this issue remains relevant to contemporary practice.

The postulated causes for this disparity in PCI outcomes are multifactorial and include atypical presentation in women, delays in diagnosis and treatment in women, as well as the underuse of evidence-based medical therapies in female patients. The issue is compounded by the fact that women are under-represented in major trials, so extrapolating outcome data to the entire population may not necessarily be correct.

Acute Coronary Syndrome

There are pathophysiological differences in the causes of acute coronary syndrome (ACS) with respect to sex. In men, there is typically rupture of a thin-capped atheromatous plaque which triggers thrombosis. Women are more likely to develop thrombosis caused by endothelial erosion.[3] However, there is no evidence to suggest that this difference in pathophysiology should affect the treatment offered to patients. This is different to ACS caused by spontaneous coronary artery dissection (SCAD) which is significantly more likely to occur in women who account for 90% of patients and may be best managed medically.[4]

Despite advancements in the management of ACS, various studies have shown a clear disparity in the clinical outcomes between men and women, with women having worse outcomes.[5–10] Women are more likely to present with atypical symptoms, have delays in the administration of treatment and therefore have longer ischaemic times.[11] There is also evidence to suggest that women with ACS are less likely to receive evidence-based treatments and less likely to undergo cardiac catheterisation and revascularisation.[5–7,9,12–19]

Table 1 demonstrates the in-hospital mortality according to sex in several ACS studies. The proportion of female patients in the studies ranged from 27–41%. The unadjusted mortality is significantly higher in women, although appears less so once adjusted for confounders.[12,16]

A large UK study evaluating the treatment of patients with ACS with respect to sex has been published this year.[20] Women (n=238,489) comprised 34.5% of the study and were older (76.7 years versus 67.1 years) and less likely to present with ST-elevation MI (STEMI) (33.9% versus 42.5%). Women were less likely to receive guideline-indicated care when compared with men including timely reperfusion therapy for STEMI (76.8% versus 78.9%; p<0.001), and timely coronary angiography for non-STEMI (24.2% versus 36.7%; p<0.001).

Women also received sub-optimal medical therapy with less dual antiplatelet therapy (75.4% versus 78.7%) and less secondary prevention therapies (87.2% versus 89.6% for statins, 82.5% versus 85.6% for angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blockers and 62.6% versus 67.6% for beta-blockers; all p<0.001). This

Table 1: In-Hospital Mortality According to Sex in Acute Coronary Syndrome Trials

Study	Patients (n)	Women (%)	Women Mortality (%)	Men Mortality (%)	Significance
Blomkalns et al. 2005[12]	35,875	41.0	5.6	4.3	OR 1.27 (adjusted)
Elkoustaf et al. 2006[23]	1,197	31.8	0.3	1.1	p=0.137
Heer et al. 2006[13]	16,817	34.1	6.8	4.1	p<0.001
Alfredsson et al. 2007[14]	53,781	37.0	7.0	5.0	p=NS
Radovanovic et al. 2007[15]	20,290	28.0	10.7	6.3	p<0.001
Jneid et al. 2008[7]	78,254	39.0	8.2	5.7	p<0.0001
Akhter et al. 2009[16]	199,690	34.1	2.2	1.4	p=0.52 (adjusted)
Al-Fiadh et al. 2011[10]	2,952	27.2	3.9	2.0	p<0.001
Bugiardini et al. 2011[18]	6,558	31.8	3.4	2.2	p=0.0078
Poon et al. 2012[19]	14,196	34.3	2.7	1.6	p<0.001

study demonstrated that the 30-day adjusted mortality was higher for women than men – median 5.2% (interquartile ratio [IQR] 1.8%–13.1%) versus 2.3% (IQR 0.8%–7.1%; p<0.001) and the authors estimated that 8,243 deaths among women could have been prevented over the study period if they had been treated equally to the male patients.

Previous studies have demonstrated that when men and women receive similar treatment (including high use of an early invasive strategy in NSTEMI), there is no significant difference in 1-year mortality for women when compared with men, supporting the need for equality of care.[21–23]

Evidence supports the use of stent implantation for patients with coronary artery disease and ACS. However, a large French registry of 74,389 consecutive patients (30% women) demonstrated a lower rate of PCI with stenting in women having an acute MI (14.2% versus 24.4%; p<0.001).[24] In the same study, the in-hospital mortality was significantly higher in women (14.8% versus 6.1%; p<0.0001). The Women in Innovation Initiative and Drug-Eluting Stents (WIN-DES) collaboration is an initiative set up to specifically evaluate outcomes of drug-eluting stent (DES) implantation in women. Recently published data demonstrates the safety and efficacy of the use of contemporary DES in 2,176 women after acute MI.[25] At 3 years, the use of new-generation DES was associated with lower risk of death, MI or target lesion revascularisation (14.9% versus 18.4%; adjusted HR 0.78; 95% CI [0.61–0.99]) compared with first generation DES, as well as definite or probable stent thrombosis (1.4% versus 4.0%; adjusted HR 0.36; 95% CI [0.19–0.69]).

Invasive Strategy in Non-ST-elevation MI

The benefit of an early invasive strategy for non-ST-elevation MI (NSTEMI) is less clear in women compared with men, with some studies suggesting they might even have worse outcomes. This has been attributed to older age at time of presentation, presence of multiple co-morbidities and smaller body habitus.[26,27] Both the Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC) II and the three Randomised Intervention Trial of unstable Angina (RITA) trials demonstrated a clear benefit for a routine early invasive strategy in men; however women in the invasive strategy groups had worse outcomes.[28,29]

Further analysis of the FRISC II trial demonstrated that the higher event rate in women treated with an early invasive strategy seemed largely due to an increased rate of death and MI in the women who underwent coronary artery bypass grafting (CABG) as the means of revascularisation. Conversely, the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction-18 (TACTICS-TIMI 18) trial did show benefit of an early invasive strategy in both sexes.[30] In patients with elevated biomarkers, there was a reduction in the primary endpoint of death, MI or rehospitalisation for ACS at 6 months.

A subsequent meta-analysis did lend support to the use of an early invasive strategy in women in the presence of elevated biomarkers.[31] Furthermore, the large Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry of 46,455 patients also demonstrated that an early invasive strategy for NSTEMI was associated with a marked and similar reduction in mortality in women (RR 0.46; 95% CI [0.38–0.55]) and men (RR 0.45; 95% CI [0.40–0.52]).[22] These data indicate that in women with elevated biomarkers, an early invasive strategy is warranted and women should therefore be undergoing angiography at a comparable rate to that of their male counterparts.

ST-elevation MI

The literature demonstrates that the benefit of early reperfusion therapy in STEMI in both sexes is unquestionable and this is reflected in current practice guidelines.[32] Nevertheless, women presenting with STEMI are less likely than men to be admitted to a hospital which has the ability to perform PCI.[33]

The mortality rate of women after STEMI is higher than that of men. In one meta-analysis of 68,536 patients (27% female, n=18,555), mortality was higher in women both in hospital (RR 1.93; 95% CI [1.75–2.14]; p<0.001) and at 1 year (RR 1.58; 95% CI [1.36–1.84]; p<0.001).[34] However, women tend to be older and have more co-morbidities with a higher rate of diabetes, hypertension and high cholesterol. When these factors were taken into account, the higher 1-year mortality rate in women was no longer evident in this meta-analysis (RR 0.90; 95% CI [0.69–1.17]; p=0.42).

Contrary to this, a recent study analysed patient-level data from 10 randomised trials and evaluated the rate of death or heart failure hospitalisation within 1 year.[35] The study evaluated 2,632 patients (22% female, n=587) and found that, despite there being no difference in the size of infarct, the adverse event rate was higher in women at 1 year: the mortality was 3.5% versus 1.8%, p=0.01; and death or heart failure

Table 2: Ischaemia Time in Women Versus Men Presenting With ST-elevation MI

Study	Number of Women/ Total Number of Participants (%)	Time from Symptom Onset to Help (Minutes)			Door to Balloon Time (Minutes)		
		Women	Men	p	Women	Men	p
Zimmermann et al. 2009[36]	161/566 (28%)	262 (±235)	236 (±263)	<0.02	57 (±45)	63 ±58	0.4
Ferrante et al. 2011[37]	138/481 (29%)	270 (165–485)	205 (140–395)	0.009	94 (57–148)	76 (52–117)	0.02
Wijnbergen et al. 2013[39]	202/907 (22%)	204 (±135)	176 (±119)	0.005	16 (±6)	16 (±7)	0.97
Otten et al. 2013[40]	708/3,714 (19%) (age<65 years)	165 (110–285)	150 (100–240)	<0.001	45 (30–64)	44 (30–66)	0.32
Otten et al. 2013[40]	1,047/3,032 (35%) (age≥65 years)	180 (120–291)	165 (110–254)	<0.001	48 (33–73)	46 (33–73)	0.12
Velders et al. 2013[41]	868/3,483 (25%)	192 (141–286)*	175 (128–279)*	0.002	46 (33–68)	46 (33–67)	0.4

**Symptom onset to balloon time.*

hospitalisation rate was 7.9% versus 3.4%, p<0.001. When adjusted for age, risk factors and infarct size, the risk of death or heart failure hospitalisation was still significantly higher in women (adjusted HR 2.13; 95% CI [1.34–3.38]; p=0.001).

Several studies consistently demonstrate longer ischaemia times for women presenting with STEMI, driven mainly by a delay in seeking help (*Table 2*).[36-41] A large national study from Poland of 26,035 patients (34.5% women), showed that significantly fewer women with STEMI underwent primary PCI within 12 hours from symptom onset (35.8% versus 44.0%; p<0.0001).[38] Both the time between the onset of symptoms to balloon time – 255 minutes (IQR 175–375) versus 241 minutes (IQR 165–360), p<0.0001 – as well as the door to balloon time – 45 minutes (IQR 30–70) versus 44 minutes (IQR 30–68), p=0.032 – were longer.

The multicentre Examining Heart Attacks in Young Women (VIRGO) study evaluated 1,465 patients aged 18 to 55 years admitted with STEMI.[42] This US study was specifically designed to evaluate outcomes in young patients admitted with STEMI with respect to sex and it enrolled more women than men. In accordance with other studies, women were more likely to have atypical symptoms and presented later. Of those patients deemed suitable for reperfusion therapy (women=761; men=477), the study found that women were more likely to be untreated (9% versus 4%; p=0.002) and women who did receive reperfusion experienced a longer delay to receiving therapy.[42]

Mortality in STEMI is strongly associated with ischaemic time – every 30-minute delay of revascularisation increases annual mortality by 7.5%.[43] One contributor to delay is that women do not perceive heart disease as a risk to their own health.[44,45] The delay in women seeking help appears to be irrespective of age.[40,42] It is therefore important that public health campaigns highlight the need for all women to seek medical help promptly. Awareness should be raised among medical professionals to ensure that therapeutic pathways are optimised for women, particularly in those with an atypical presentation.

There is some evidence to suggest that PCI for women presenting with STEMI may be more challenging. Patients who have an unsuccessful PCI procedure for STEMI that fails to restore perfusion have an increased mortality. In a registry of 2,900 consecutive STEMI patients, failed PCI occurred in 4% and was associated with a significantly increased risk of both in-hospital (18% versus 4%) and long-term death (48% versus 14%, p<0.05).[46] In this study, female sex was an independent predictor of PCI failure (OR 1.54; 95% CI [1.01–2.38]) and the authors concluded that special care should be taken when PCI is performed in women who are at higher risk for failure when presenting with STEMI.

Stable Angina

Women are also less likely to receive optimal medical therapy for stable angina compared with men. One observational study evaluated 3,779 patients (42% female) from the Euro Heart Survey.[47] Women were less likely to undergo diagnostic coronary angiography (49% versus 31%; p<0.001), and even in those with proven coronary artery disease (CAD), revascularisation was performed in significantly fewer women than men (adjusted OR 0.70; 95% CI [0.52–0.94]; p=0.019). Women were also less likely than men to receive aspirin (73% versus 81%; p<0.001) and statin therapy (45% versus 51%; p<0.001). Importantly, in patients with confirmed CAD, women were more likely to die (2.9% versus 1.5%) or have MI (5.8% versus 2.7%) during follow-up.

There is some evidence to suggest that women may have poorer outcomes after PCI, both in terms of adverse clinical events as well as target vessel failure.[48–50] One of the possible contributing factors to this could be that women have smaller coronary vessels compared with men. PCI in small vessels is associated with a higher rate of restenosis and target vessel failure. The benefits of using DES rather than a bare metal stent are greater when treating smaller vessels. Contrary to this, the German Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte registry of patients stented between 2005 and 2009 (100,704 stent implantations) found that despite having smaller vessel size, women were significantly less likely to receive a DES compared with men – 28.2 versus 31.3%, adjusted OR 0.93; 95% CI [0.89–0.97].[51]

Numerous studies of DES have demonstrated efficacy irrespective of sex.[52–54] The multicentre Clinical Evaluation of the XIENCE Everolimus Eluting Coronary Stent System in the Treatment of Women With de Novo Coronary Artery Lesions (XIENCE V SPIRIT Women) study specifically evaluated the outcomes of 1,573 women treated with everolimus-eluting stents.[55] The adverse event rate (death, MI or target vessel revascularisation) was 12% at 1 year and 15% at 2 years. These data were compared with male patients enrolled into the SPIRIT V study and once again female patients had a longer delay to therapy. The total referral time for coronary intervention in women was 4 days longer than that for men (p=0.0003). This may be attributed to the fact that women were more likely to have atypical angina (9% versus 6%) or indeed no chest pain (17% versus 13%) compared with men.

Complex Percutaneous Coronary Intervention

The WIN-DES collaboration has published data demonstrating the safety and efficacy of the use of contemporary DES in 4,629 women treated for complex CAD (defined as total stent length >30 mm, two or more stents implanted, two or more lesions treated or bifurcation lesion).[56] Compared with non-complex PCI, women who had complex PCI had a higher 3-year risk of major adverse cardiac events (MACE) (adjusted HR 1.63; 95% CI [1.45 to 1.83]; p<0.0001). The use of new-generation DES for complex PCI, compared with first-generation stents, was associated with significantly lower 3-year risk of MACE (adjusted HR 0.81; 95% CI [0.68–0.96]), target lesion revascularisation (adjusted HR 0.74; 95% CI [0.57–0.95]), and definite or probable stent thrombosis (adjusted HR 0.50; 95% CI [0.30–0.83]).

Left Main Stem Percutaneous Coronary Intervention

Disease of the left main stem (LMS) merits specific attention as revascularisation confers prognostic benefits over and above medical therapy alone. Although CABG is the gold standard, recent trials have supported the concept of PCI as a revascularisation modality for patients without a heavy burden of concomitant disease indicated by a low or intermediate SYNTAX score.[57] The outcome of PCI for LMS disease is dependent on the complexity of disease. Lesions that involve the bifurcation are subject to a higher rate of adverse events, driven mainly by the need for repeat revascularisation.[58] Women may be more likely than men to have disease at the ostium of the LMS.[59] Studies have shown that PCI for ostial LMS disease has a low rate of MACE not significantly different to the results after CABG.[60]

As with other revascularisation trials, women have been relatively under-represented in the studies of LMS disease comparing PCI with CABG. However, a study by Buchanan et al. specifically evaluated the outcomes of 817 women after PCI versus CABG for unprotected LMS disease.[61] Propensity matching was used to identify 175 pairs and demonstrated no difference in death, MI or stroke. There was an increased need for repeat revascularisation in the group treated with PCI compared with the CABG group. This risk of restenosis may be compounded in women because of their smaller vessel size; in one angiographic study, the mean LMS diameter was 3.9 ± 0.4 mm in women versus 4.5 ± 0.5 mm in men.[62]

The Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial was a randomised study designed to specifically evaluate the outcomes of 1,905 patients with LMS disease randomised to either PCI with everolimus-eluting stents versus CABG.[63] At 3 years, PCI was found to be non-inferior to CABG for the primary composite endpoint of death, stroke or MI. However, the study found that women undergoing PCI had worse outcomes (19.7% versus 14.1% for the primary composite endpoint) and might be better treated with CABG.

A recent analysis was undertaken to explore this further.[64] Investigators showed that compared with men, women in the EXCEL trial were older, had a higher rate of hypertension, hyperlipidaemia and diabetes and there were fewer smokers. However, they also had lower coronary anatomic burden and complexity of disease (mean SYNTAX score 24.2 versus 27.2; p<0.001). On multivariate analysis, sex was not an independent predictor of the primary endpoint at 3 years (HR 1.10; 95% CI [0.82–1.48]; p=0.53). However, women treated with PCI had a higher rate of peri-procedural MI compared with men and the authors concluded that sex is an important factor to be considered and that further studies are required to determine the optimal revascularisation modality for women with this type of complex coronary artery disease.

Peri-procedural Complications

A major concern has been that women undergoing PCI have been shown to have higher rates of peri-procedural bleeding and vascular complications compared with men.[26,65–67] Registry data demonstrate that women are more likely to have vascular complications, contrast-induced nephropathy, gastrointestinal bleeding, stroke, infection and death. Women are more likely to suffer femoral complications requiring vascular intervention and retroperitoneal haemorrhage. Major bleeding and receiving a blood transfusion for any reason is strongly associated with MACE and mortality.[68]

The issue of vascular complications and bleeding has been mitigated by the switch to using radial access for PCI. Although women have an increased rate of radial access failure due to the relatively small size and problems of radial artery spasm, this route is still feasible in the vast majority.

The Study of Access Site for Enhancement of Percutaneous Coronary Intervention (SAFE-PCI) involved 1,787 women undergoing either catheterisation or PCI randomised to either radial or femoral access.[69] There was no significant difference in the primary efficacy endpoint, however there were significantly fewer bleeding and vascular complications in the radial group (0.6% versus 1.7%; OR 0.32; 95% CI [0.12–0.90]).

Additional large randomised studies have also supported the use of a radial approach in reducing vascular complications and bleeding.[70,71] One of these, the MATRIX trial, enrolled 8,404 patients (26.7% women) and specifically evaluated the impact of sex.[72] After adjustment, the overall adverse event rate was not significantly different for men versus women, however women still had an overall higher risk of access-site bleeding (RR 0.64; p=0.0016), severe bleeding (RR 0.17; p=0.0012) and need for transfusion (RR 0.56; p=0.0089). The benefit of trans-radial access in reducing MACE was more evident in women than in men and was statistically significantly (RR 0.73; 95% CI [0.56–0.95]; p=0.019) compared with the use of a femoral approach. Notably, although the radial approach was successful in the majority, the crossover rate for those randomised to a radial approach was higher in women than in men (7.6% versus 5.2%).

Conclusion

In contemporary PCI practice, there remains a disparity between the outcomes of women versus men, with women having significantly worse outcomes and a higher mortality. The causes are multifactorial and relate to differences in health-seeking behaviour as well as sub-optimal medical therapy. Women are less likely to undergo cardiac catheterisation and revascularisation; are not treated as quickly as men; and are less likely to receive optimal pharmacotherapy.

There is no data to suggest that women benefit any less than men from guideline-recommended primary and secondary prevention cardiovascular medication and revascularisation. Medical professionals need to ensure that the management of women is not biased by a perception of increased risk, such as bleeding, which might potentially deny women from receiving evidence-based therapies. Future studies should focus on evaluating health behaviours, patterns of disease and clinical outcomes, in a sex-specific way. ■

1. The top 10 causes of death. www.who.int/mediacentre/factsheets/fs310 (accessed 7 May 2019).
2. Guo Y, Yin F, Fan C, Wang Z. Gender difference in clinical outcomes of the patients with coronary artery disease after percutaneous coronary intervention: a systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11644. https://doi.org/10.1097/MD.0000000000011644; PMID: 30045311.
3. Davies MJ. Glagovian remodelling, plaque composition, and stenosis generation. *Heart* 2000;84:461–2. https://doi.org/10.1136/heart.84.5.461; PMID: 11039994.
4. Saw J, Humphries K, Aymong E, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol* 2017;70:1148–58. https://doi.org/10.1016/j.jacc.2017.06.053; PMID: 28838364.
5. Kudenchuk PJ, Maynard C, Martin JS, et al. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). *Am J Cardiol* 1996;78:9–14. https://doi.org/10.1016/S0002-9149(96)00218-4; PMID: 8712126.
6. Mahon NG, McKenna CJ, Codd MB, et al. Gender differences in the management and outcome of acute myocardial infarction in unselected patients in the thrombolytic era. *Am J Cardiol* 2000;85:921–6. https://doi.org/10.1016/S0002-9149(99)00902-9; PMID: 10760327.
7. Anand SS, Xie CC, Mehta S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol* 2005;46:1845–51. https://doi.org/10.1016/j.jacc.2005.05.091; PMID: 16286169.
8. Arslanian-Engoren C, Patel A, Fang J, et al. Symptoms of men and women presenting with acute coronary syndromes. *Am J Cardiol* 2006;98:1177–81. https://doi.org/10.1016/j.amjcard.2006.05.049; PMID: 17056322.
9. Jneid H, Fonarow GC, Cannon CP, et al. Sex differences in medical care and early death after acute myocardial infarction. *Circulation* 2008;118:2803–10. https://doi.org/10.1161/CIRCULATIONAHA.108.789800; PMID: 19064680.
10. Al-Fiadh AH, Andrianopoulos N, Farouque O, et al. Contemporary outcomes in women undergoing percutaneous coronary intervention for acute coronary syndromes. *Int J Cardiol* 2011;151:195–9. https://doi.org/10.1016/j.ijcard.2010.05.018; PMID: 20538357.
11. Milner KA, Vaccarino V, Arnold AL, et al. Gender and age differences in chief complaints of acute myocardial infarction (Worcester Heart Attack Study). *Am J Cardiol* 2004;93:606–8. https://doi.org/10.1016/j.amjcard.2003.11.028; PMID: 14996588.
12. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;45:832–7. https://doi.org/10.1016/j.jacc.2004.11.055; PMID: 15766815.
13. Heer T, Gitt AK, Juenger C, et al. Gender differences in acute non-ST-segment elevation myocardial infarction. *Am J Cardiol* 2006;98:160–6. https://doi.org/10.1016/j.amjcard.2006.01.072; PMID: 16828585.
14. Alfredsson J, Stenestrand U, Wallentin L, Swahn E. Gender differences in management and outcome in non-ST-elevation acute coronary syndrome. *Heart* 2007;93:1357–62. https://doi.org/10.1136/hrt.2006.102012; PMID: 17085528.
15. Radovanovic D, Erne P, Urban P, et al. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20,290 patients from the AMIS Plus Registry. *Heart* 2007;93:1369–75. https://doi.org/10.1136/hrt.2006.106781; PMID: 17933995.
16. Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009;157:141–8. https://doi.org/10.1016/j.ahj.2008.08.012; PMID: 19081410.
17. Hvelplund A, Galatius S, Madsen M, et al. Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. *Eur Heart J* 2010;31:684–90. https://doi.org/10.1093/eurheartj/ehp493; PMID: 19933516.
18. Bugiardini R, Yan AT, Yan RT, et al. Factors influencing underutilization of evidence-based therapies in women. *Eur Heart J* 2011;32:1337–44. https://doi.org/10.1093/eurheartj/ehr027; PMID: 21383003.
19. Poon S, Goodman SG, Yan RT, et al. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. *Am Heart J* 2012;163:66–73. https://doi.org/10.1016/j.ahj.2011.09.025; PMID: 22172438.
20. Wilkinson C, Bebb O, Dondo TB, et al. Sex differences in quality indicator attainment for myocardial infarction: a nationwide cohort study. *Heart* 2019;105:516–23. https://doi.org/10.1136/heartjnl-2018-313959; PMID: 30470725.
21. Mehilli J, Kastrati A, Dirschinger J, et al. Sex-based analysis of outcome in patients with acute myocardial infarction treated predominantly with percutaneous coronary intervention. *JAMA* 2002;287:210–5. https://doi.org/10.1001/jama.287.2.210; PMID: 11779263.
22. Alfredsson J, Lindback J, Wallentin L, Swahn E. Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Eur Heart J* 2011;32:3128–36. https://doi.org/10.1093/eurheartj/ehr349; PMID: 21911338.
23. Elkoustaf RA, Mamkin I, Mather JF, et al. Comparison of results of percutaneous coronary intervention for non-ST-elevation acute myocardial infarction or unstable angina pectoris in men versus women. *Am J Cardiol* 2006;98:182–6. https://doi.org/10.1016/j.amjcard.2006.01.071; PMID: 16828589.
24. Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation* 2007;115:833–9. https://doi.org/10.1161/CIRCULATIONAHA.106.664979; PMID: 17309933.
25. Giustino G, Harari R, Baber U, et al. Long-term safety and efficacy of new-generation drug-eluting stents in women with acute myocardial infarction: From the Women in Innovation and Drug-Eluting Stents (WIN-DES) Collaboration. *JAMA Cardiol* 2017;2:855–62. https://doi.org/10.1001/jamacardio.2017.1978; PMID: 28658478.
26. Duvernoy CS, Smith DE, Manohar P, et al. Gender differences in adverse outcomes after contemporary percutaneous coronary intervention: an analysis from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) percutaneous coronary intervention registry. *Am Heart J* 2010;159:677–83 e1. https://doi.org/10.1016/j.ahj.2009.12.040; PMID: 20362729.
27. Peterson ED, Lansky AJ, Kramer J, et al. National Cardiovascular Network Clinical I. Effect of gender on the outcomes of contemporary percutaneous coronary intervention. *Am J Cardiol* 2001;88:359–64. https://doi.org/10.1016/S0002-9149(01)01679-4; PMID: 11545754.
28. Lagerqvist B, Safstrom K, Stahle E, et al. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. *J Am Coll Cardiol* 2001;38:41–8. https://doi.org/10.1016/S0735-1097(01)01308-0; PMID: 11451294.
29. Clayton TC, Pocock SJ, Henderson RA, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA 3 trial. *Eur Heart J* 2004;25:1641–50. https://doi.org/10.1016/j.ehj.2004.07.032; PMID: 15351164.
30. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA* 2002;288:3124–9. https://doi.org/10.1001/jama.288.24.3124; PMID: 12495392.
31. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;300:71–80. https://doi.org/10.1001/jama.300.1.71; PMID: 18594042.
32. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119–77. https://doi.org/10.1093/eurheartj/ehx393; PMID: 28886621.
33. Fang J, Alderman MH. Gender differences of revascularization in patients with acute myocardial infarction. *Am J Cardiol* 2006;97:1722–6. https://doi.org/10.1016/j.amjcard.2006.01.032; PMID: 16765121.
34. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. *JAMA Intern Med* 2014;174:1822–30. https://doi.org/10.1001/jamainternmed.2014.4762; PMID: 25265319.
35. Kosmidou I, Redfors B, Selker HP, et al. Infarct size, left ventricular function, and prognosis in women compared to men after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: results from an individual patient-level pooled analysis of 10 randomized trials. *Eur Heart J* 2017;38:1656–63. https://doi.org/10.1093/eurheartj/ehx159; PMID: 28407050.
36. Zimmermann S, Ruthrof S, Nowak K, et al. Short-term prognosis of contemporary interventional therapy of ST-elevation myocardial infarction: does gender matter? *Clin Res Cardiol* 2009;98:709–15. https://doi.org/10.1007/s00392-009-0055-8; PMID: 19690904.
37. Ferrante G, Corrada E, Belli G, et al. Impact of female sex on long-term outcomes in patients with ST-elevation myocardial infarction treated by primary percutaneous coronary intervention. *Can J Cardiol* 2011;27:749–55. https://doi.org/10.1016/j.cjca.2011.07.002; PMID: 21924580.
38. Sadowski M, Gasior M, Gierlotka M, et al. Gender-related differences in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry. *EuroIntervention* 2011;6:1068–72. https://doi.org/10.4244/EIJV6I9A186; PMID: 21518678.
39. Wijnbergen I, Tijssen J, van't Veer M, et al. Gender differences in long-term outcome after primary percutaneous intervention for ST-segment elevation myocardial infarction. *Catheter Cardiovasc Interv* 2013;82:379–84. https://doi.org/10.1002/ccd.24800; PMID: 23553888.
40. Otten AM, Maas AH, Ottervanger JP, et al. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. *Eur Heart J Acute Cardiovasc Care* 2013;2:334–41. https://doi.org/10.1177/2048872612475270; PMID: 24338292.
41. Velders MA, Boden H, van Boven AJ, et al. Influence of gender on ischemic times and outcomes after ST-elevation myocardial infarction. *Am J Cardiol* 2013;111:312–8. https://doi.org/10.1016/j.amjcard.2012.10.007; PMID: 23159214.
42. D'Onofrio G, Safdar B, Lichtman JH, et al. Sex differences in reperfusion in young patients with ST-segment-elevation myocardial infarction: results from the VIRGO study. *Circulation* 2015;131:1324–32. https://doi.org/10.1161/CIRCULATIONAHA.114.012293; PMID: 25792558.
43. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004;109:1223–5. https://doi.org/10.1161/01.CIR.0000121424.76486.20; PMID: 15007008.
44. Mosca L, Mochari H, Christian A, et al. National study of women's awareness, preventive action, and barriers to cardiovascular health. *Circulation* 2006;113:525–34. https://doi.org/10.1161/CIRCULATIONAHA.105.588103; PMID: 16449732.
45. Mosca L, Jones WK, King KB, et al. Awareness, perception, and knowledge of heart disease risk and prevention among women in the United States. American Heart Association Women's Heart Disease and Stroke Campaign Task Force. *Arch Fam Med* 2000;9:506–15. https://doi.org/10.1001/archfami.9.6.506; PMID: 10862212.
46. Barbash IM, Ben-Dor I, Torguson R, et al. Clinical predictors for failure of percutaneous coronary intervention in ST-elevation myocardial infarction. *J Interv Cardiol* 2012;25:111–7. https://doi.org/10.1111/j.1540-8183.2011.00707.x; PMID: 22372924.
47. Daly C, Clemens F, Lopez Sendon JL, et al. Gender differences in the management and clinical outcome of stable angina. *Circulation* 2006;113:490–8. https://doi.org/10.1161/CIRCULATIONAHA.105.561647; PMID: 16449728.
48. Ellis SG, Roubin GS, King SB 3rd, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. *Circulation* 1988;77:372–9. https://doi.org/10.1161/01.CIR.77.2.372; PMID: 2962787.
49. Argulian E, Patel AD, Abramson JL, et al. Gender differences in short-term cardiovascular outcomes after percutaneous coronary interventions. *Am J Cardiol* 2006;98:48–53. https://doi.org/10.1016/j.amjcard.2006.01.048; PMID: 16784919.
50. Lansky AJ, Ng VG, Mutlu H, et al. Gender-based evaluation of the XIENCE V everolimus-eluting coronary stent system: clinical and angiographic results from the SPIRIT III randomized trial. *Catheter Cardiovasc Interv* 2009;74:719–27. https://doi.org/10.1002/ccd.22067; PMID: 19530147.
51. Russ MA, Wackerl C, Zeymer U, et al. Gender based differences in drug eluting stent implantation – data from the German ALKK registry suggest underuse of DES in elderly women. *BMC Cardiovasc Disord* 2017;17:68. https://doi.org/10.1186/s12872-017-0500-y; PMID: 28241861.
52. Lansky AJ, Costa RA, Mooney M, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. *J Am Coll Cardiol* 2005;45:1180–5. https://doi.org/10.1016/j.jacc.2004.10.076; PMID: 15837246.
53. Solinas E, Nikolsky E, Lansky AJ, et al. Gender-specific outcomes after sirolimus-eluting stent implantation. *J Am Coll Cardiol* 2007;50:2111–6. https://doi.org/10.1016/j.jacc.2007.06.056; PMID: 18036446.
54. Mikhail GW, Gerber RT, Cox DA, et al. Influence of sex on long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent: results of the 'TAXUS Woman' analysis. *JACC Cardiovasc Interv* 2010;3:1250–9. https://doi.org/10.1016/j.jcin.2010.08.020; PMID: 21232718.
55. Morice MC, Mikhail GW, Mauri I, et al. SPIRIT Women, evaluation of the safety and efficacy of the XIENCE V everolimus-eluting stent system in female patients: referral time for coronary intervention and 2-year clinical outcomes. *EuroIntervention* 2012;8:325–35. https://doi.org/10.4244/EIJV8I3A51; PMID: 22829508.
56. Giustino G, Baber U, Aquino M, et al. Safety and efficacy of new-generation drug-eluting stents in women undergoing complex percutaneous coronary artery revascularization: from the WIN-DES collaborative patient-level pooled analysis. *JACC Cardiovasc Interv* 2016;9:674–84. https://doi.org/10.1016/j.jcin.2015.12.013; PMID: 27056305.
57. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;1:219–27. PMID: 19758907.
58. Naganuma T, Chieffo A, Meliga E, et al. Long-term clinical outcomes after percutaneous coronary intervention for ostial/mid-shaft lesions versus distal bifurcation lesions in unprotected left main coronary artery: the DELTA Registry (drug-eluting stent for left main coronary artery disease): a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv* 2013;6:1242–9. https://

doi.org/10.1016/j.jcin.2013.08.005; PMID: 24355114.
59. Yildirimturk O, Cansel M, Erdim R, et al. Coexistence of left main and right coronary artery ostial stenosis: demographic and angiographic features. *Int J Angiol* 2011;20:33–8. https://doi.org/10.1055/s-0031-1272550; PMID: 22532768.
60. Guo CL, Yu XP, Yang BG, et al. Long-term outcomes of PCI vs. CABG for ostial/midshaft lesions in unprotected left main coronary artery. *J Geriatr Cardiol* 2017;14:254–60. https://doi.org.10.11909/j.issn.1671-5411.2017.04.004; PMID: 28663763.
61. Buchanan GL, Chieffo A, Meliga E, et al. Comparison of percutaneous coronary intervention (with drug-eluting stents) versus coronary artery bypass grafting in women with severe narrowing of the left main coronary artery (from the Women-Drug-Eluting stent for LefT main coronary Artery disease Registry). *Am J Cardiol* 2014;113:1348–55. https://doi.org/10.1016/j.amjcard.2014.01.409; PMID: 24581924.
62. Dodge JT Jr, Brown BG, Bolson EL, Dodge HT. Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. *Circulation* 1992;86:232–46. https://doi.org/10.1161/01.CIR.86.1.232; PMID: 1535570.
63. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016;375:2223–35. https://doi.org/10.1056/NEJMoa1610227; PMID: 27797291.
64. Serruys PW, Cavalcante R, Collet C, et al. Outcomes after coronary stenting or bypass surgery for men and women with unprotected left main disease: The EXCEL Trial. *JACC Cardiovasc Interv* 2018;11:1234–43. https://doi.org/10.1016/j.jcin.2018.03.051; PMID: 29976359.
65. Scott P Farouque O, Clark D. Percutaneous coronary intervention in women: should management be different? *Interventional Cardiology* 2014;6:527–36. https://doi.org/10.2217/ica.14.51.
66. Perdoncin E, Duvernoy C. Treatment of coronary artery disease in women. *Methodist Debakey Cardiovasc J* 2017;13:201–8. doi: 10.14797/mdcj-13-4-201. PMID: 29744012
67. Jibran R, Khan JA, Hoye A. Gender disparity in patients undergoing percutaneous coronary intervention for acute coronary syndromes – does it still exist in contemporary practice? *Ann Acad Med Singapore* 2010;39:173–8. PMID: 20372751.
68. Romaguera R, Wakabayashi K, Laynez-Carnicero A, et al. Association between bleeding severity and long-term mortality in patients experiencing vascular complications after percutaneous coronary intervention. *Am J Cardiol* 2012;109:75–81. https://doi.org/10.1016/j.amjcard.2011.08.007; PMID: 21962994.
69. Rao SV, Hess CN, Barham B, et al. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: the SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial. *JACC Cardiovasc Interv* 2014;7:857–67. https://doi.org/10.1016/j.jcin.2014.04.007; PMD: 25147030.
70. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 2011;377:1409–20. https://doi.org/10.1016/S0140-6736(11)60404-2; PMID: 22090240.
71. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018; 392:835–48. https://doi.org/10.1016/S0140-6736(18)31714-8; PMID: 30153988.
72. Gargiulo G, Ariotti S, Vranckx P, et al. Impact of sex on comparative outcomes of radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: data from the randomized MATRIX-Access trial. *JACC Cardiovasc Interv* 2018;11:36–50. https://doi.org/10.1016/j.jcin.2017.09.014; PMID: 29301646.