Perspective

Interventional Cardiology

Percutaneous coronary intervention in women: should management be different?

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Women undergoing percutaneous coronary intervention (PCI) have poorer unadjusted outcomes as they are older and have greater comorbidity compared with men, but uncertainty remains whether gender affects outcome after these differences in clinical characteristics are taken into account. In this paper, we review recent published evidence comparing outcomes between men and women undergoing PCI. We focus on both acute coronary syndrome and nonacute coronary syndrome presentation, and the risk of bleeding and vascular access complication. We also review how gender is taken into account in recent guidelines and offer a common clinical scenario to illustrate the contemporary management strategies an interventional cardiologist should consider when performing PCI on a female patient.

Keywords: bleeding • female • intervention • myocardial infarction • percutaneous coronary intervention • women

Clinical vignette (e.g., low-body-weight elderly woman with stable angina & severe mid-right coronary artery stenosis)

An 82-year-old woman presents with stable angina pectoris and positive treadmill stress test. She has recently commenced on medical therapy including aspirin, statin, β-blocker and angiotensin-converting enzyme inhibitor with ongoing exertional symptoms and has been referred by her cardiologist for coronary angiography. She has a history of hypertension controlled with medication and a previous transient ischemic attack 6 years ago. She weighs 55 kg and is independent in all daily activities and is active for her age. Angiography reveals diffuse luminal irregularities of the left coronary system, but a severe calcified stenosis is present in the dominant right coronary artery.

How should this patient be treated and are there any specific concerns in terms of procedural and long-term management?

Background

This clinical vignette is not an uncommon scenario faced by an interventional cardiologist. Elderly patients with coronary artery disease (CAD) are more frequently treated with percutaneous coronary intervention (PCI) than ever before [1].

The complexities associated with older patients in terms of both worse procedural and clinical outcomes are well documented and not overlooked by the operator [2,3] with increased use of radial access when feasible [4] and less potent anticoagulants and antiplatelet agents [5] to reduce bleeding complications. What is often not foreseen are the additional procedural risks that female gender confers in addition to the more traditional outcome measures. The importance of female gender for an interventionalist is the main focus of this article.

Women, cardiovascular disease & PCI

The physical differences between men and women provide a possible explanation for differing procedural outcomes when considering PCI. Women tend to be smaller, weigh less are older and have more comorbidities such as diabetes and hypertension [6–10]. Lower BMI in females is associated with worse long-term

Future Medicine part of fsg

outcomes following intervention [11–13] and anatomically, women have smaller coronary artery size [14], radial artery vessel size [15] and an increased risk of radial artery spasm [16].

Certain cardiac conditions are more common in women such as takotsubo cardiomyopathy [17] and spontaneous coronary artery dissection [18]. Hormonal variations are important in the presentations of these conditions. For example, spontaneous dissection is frequently reported during the peripartum period [19], and catecholamine surges are given as an explanation for takotsubo cardiomyopathy, with an increased prevalence in postmenopausal women [20]. Both the oral contraceptive pill and hormone replacement therapy are associated with increased thromboembolic risk and cardiovascular risk [21,22]. The postmenopausal time period has long been associated with cardiovascular risk; however, whether this is an independent cause or an effect of age is debated [23]. From a psychological perspective, females with CAD are more likely to report lower quality of life scores than males [24,25] and have significantly more long-term sick leave following revascularization than men [26].

PCI, women & acute coronary syndrome

Unadjusted mortality for acute coronary syndrome (ACS) is significantly higher compared with men, given the differences in comorbidities (especially age) at presentation. However, uncertainty remains whether gender affects outcome after these differences in background clinical characteristics are taken into account [27]. Early studies revealed a significant discrepancy in outcomes between men and women [28,29], but as interventional treatments and technology have advanced, this difference is less pronounced [30] with evidence that early compared with late intervention offers a better outcome in women [31]. It is therefore not surprising that confusion exists as to the optimal management of acute coronary disease in women.

Whether mode of ACS presentation affects outcome in women is debated [32], but much of the trial data have distinguished between non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) in comparing outcomes between males and females. We will summarize the outcomes of PCI in females in various subsets including STEMI, NSTEMI and stable coronary disease and the implications for clinical practice.

PCI, women & STEMI

The abrupt occlusion of a coronary artery during STEMI is associated with significant morbidity and mortality. In the primary PCI era, multiple factors play a well-established role in determining poor outcomes in STEMI such as delayed presentation, age, comorbidities and clinical status at the time of presentation such as cardiogenic shock. Recently, femoral access compared with radial access, anticoagulant/antiplatelet use, bleeding complications and procedural technique have all been highlighted as potential reasons for poorer outcomes. This diversity of clinical and procedural factors makes any assessment of outcomes based purely on gender arbitrary.

Many trials and registries have found worse outcomes for females with STEMI, but when corrected for baseline comorbidities and age the differences are not significant [33–38]. For example, the CADILLAC trial randomized patients with STEMI to receive either balloon angioplasty or coronary stenting, with or without abciximab. In gender-specific analysis, women had higher rates at 1 year of major adverse cardiac events (MACE; odds ratio [OR]: 1.64; 95% CI: 1.24–2.17), although women receiving stents had a reduction of 1-year MACE from 28.1 to 19.1% ($p = 0.01$). Importantly, there was no excess 1-year mortality (OR: 1.11; 95% CI: 0.53–2.36) after adjustment for comorbidities [39].

In several reviews comparing treatment delay between females and males, time of symptom onset to medical treatment was significantly increased in the female cohort [40,41]. Upon presenting to the emergency department, women are less likely to describe chest pain as a presenting symptom [42,43] and also more likely to be misdiagnosed and discharged from emergency department, specifically in the under 55-year cohort [44]. None the less, women are more likely to respond to national educational programs and early ACS detection promotional initiatives. One study showed a 50% reduction in door-to-balloon time in females (compared with 19% in males) following dedicated patient and physician interventions to improve knowledge about chest pain syndromes to promote early presentation [45].

Women are more likely to present in cardiogenic shock [46] and although largely attributed to older age at presentation, do still appear to have higher adjusted mortality than males in some registries [47,48]. In what would seem a paradox, younger female patients also appear to have a worse prognosis compared with matched male counterparts. In a study by Otten, with 6700 patients with STEMI, young (less than 65 years) females had significantly higher mortality when compared with similar aged men, despite having less obstructive CAD and more often thrombolysis in myocardial infarction (TIMI) III flow before intervention [49]. This finding was shown at both 30 days (hazard ratio: 2.1; 95% CI: 1.3–3.4) and at 1 year (hazard ratio: 1.7; 95% CI: 1.2–2.6) and are similar to findings described by others [6,50].

Incomplete or failed revascularization during PCI is strongly associated with morbidity and mortality in STEMI patients. Female patients are significantly more likely to have unsuccessful culprit lesion revascularization due to failure to cross lesions during STEMI PCI, resulting in worse outcomes [47,51]. Female patients receive less aggressive anticoagulation during PCI and reduced drug-eluting stent use [52,53] though this may be part of a deliberate effort by clinicians to reduce bleeding complications as we will discuss. Results from the EUROTRANSFER study showed that among women presenting with STEMI, early administration of abciximab greater than 30 min prior to primary PCI enhanced pre- and post-procedural myocardial perfusion and improved survival compared with late administration of the drug [54]. As the female subgroup was small in this observational study, additional controlled trials are required to confirm this finding, especially in the bivalirudin and novel antiplatelet era.

There are some positive findings for women in the context of STEMI. No-reflow, often a marker of poor reperfusion and outcome, occurs less frequently in females [55]. Myocardial blush grade after revascularization is an important marker of microvascular coronary flow and has a more significant prognostic impact on mortality in females than males and may provide an important therapeutic target in the future [56].

PCI, women & NSTEMI

NSTEMI is usually not associated with a complete thrombotic occlusion of a coronary artery, but is associated with evidence of myocardial necrosis by elevation of specific cardiac biomarkers such as troponin. The general approach to management is to provide an invasive assessment of the coronary arteries and revascularization with either PCI or CABG when appropriate. Several studies have analyzed whether evidence supports this strategy in women.

Substudy analysis on NSTE ACS had revealed some concerns regarding the benefit of an invasive strategy in females. The FRISC II trial, comparing an early invasive versus a noninvasive approach to NSTEMI management, revealed no significant benefit in women as compared with men [29]. The RITA-3 trial, again comparing an early invasive versus medical management approach to NSTEMI, revealed similar results showing that women did not seem to benefit from an early invasive approach compared with men (adjusted OR: 0.63; 95% CI: 0.41–0.98 for men; and 1.79; 95% CI: 0.95–3.35 for women; interaction p = 0.007) [57]. A recent randomized substudy of the OASIS-5 trial and an accompanying meta-analysis of prior studies of PCI in women presenting with an ACS suggest that women do worse with an early invasive strategy (OR: 1.51; 95% CI: 1.00–2.29) [58]. These studies have had a negative influence in management on women with NSTEMI, with some registries showing females are less frequently referred for intervention and received less revascularization procedures than males [59–62].

In TACTICS-TIMI 18, women with elevated levels of cardiac troponin T did benefit from an early invasive strategy (adjusted OR: 0.47; 95% CI: 0.26–0.83) and the graded benefit based on other risk markers (e.g., ST-segment depression and TIMI risk scores) was similar for women and men [30]. However, it appeared that women at lower risk and those with negative troponin levels tended to have excess events with an invasive strategy. Although this excess did not approach statistical significance, it is comparable with the findings in FRISC II and RITA-3. A meta-analysis of conservative versus invasive management of patients with ACS revealed a significant benefit in males and high-risk females in the invasive cohort; however, biomarker negative females showed no benefit [63]. A review of NSTEMI PCI at the Cleveland Clinic showed an almost twofold increase in mortality in low-risk (less than 60 years and troponin negative) females compared with males who underwent PCI [64].

In conclusion, women with high-risk (generally regarded as biomarker positive) NSTEMI appear to derive benefit from invasive management, while low-risk females do not and a more conservative initial strategy should be strongly considered.

PCI, women & stable coronary disease

The lack of benefit of revascularization in 'low-risk/stable' women without elevated biomarkers is of interest. However, data are lacking regarding PCI in women with stable angina. No mortality benefit with PCI compared with medical management in stable CAD has been documented in either gender. The COURAGE trial is the largest, multicenter trial comparing medical with invasive management of ischemic heart disease to date [65] and there was no benefit in revascularization in terms of myocardial infarction, ACS or death. It should be noted that only 15% of the recruited patients were females; however, on post-hoc analysis there were no gender differences in terms of PCI success or completeness of revascularization [66]. The FAME II study suggested that a fractional flow reserve-guided PCI approach reduces future revascularization rates [67] and this appears to apply to females as much as males [68].

Crucial to all these trials is appropriate medical therapy, and females have been shown to have less aggressive medical therapy compared with males. In an interesting review by Sabouret and colleagues, women are more likely to be managed medically following

ACS and medically managed ACS patients actually received less secondary preventative medications than those who underwent revascularization [69]. Evidence exists that women are less often prescribed aspirin and angiotensin-converting enzyme inhibitors in secondary prevention [70] and statins following intervention [71]. Women are also less likely to be referred to cardiac rehabilitation following myocardial infarction [72].

In the setting of multivessel disease, there have been multiple randomized trials comparing outcomes of PCI versus CABG. Certain selective subgroups including diabetic patients, complex coronary anatomy and patients older than 65 years of age benefit from surgical revascularization. However, when outcome is analyzed by gender, women should be treated similar to men [73–75].

Women & the risk of PCI complications including bleeding & vascular injury

Women are at increased risk of bleeding and vascular complications with PCI. In the setting of ACS, our Australian multicenter registry has previously found female gender to associated with a large increase in bleeding risk with PCI (OR: 4.37; 95% CI: 2.0–9.56; $p < 0.001$) [76], similar to multiple other trials and registries [9,77–81]. In a cohort of 5700 stable angina patients who underwent coronary intervention in our registry, bleeding risk was again increased in females (OR: 2.3; $p < 0.001$) [82].

Major bleeding and receiving a blood transfusion for any reason is strongly associated with MACE and mortality [83,84]. Females are more likely to suffer groin complications in the form of femoral pseudoaneurysm and more likely to require vascular intervention [85]. A study by Farouque *et al.* found female gender was a strong independent predictor of retroperitoneal hemorrhage after PCI (relative risk: 5.4; 95% CI: 2.65–22.73; $p = 0.005$) [86].

The increased bleeding risk in females has led to a greater awareness in the interventional community, with a reduction in major bleeding over the past few years [87]. Women are more sensitive to excess dosing of anticoagulation (especially glycoprotein IIb/IIIa inhibitors) with associated increased bleeding risk [52] and less benefit than males [88]. More stringent weight adjusted dosing of medications and alternative anticoagulants such as bivalirudin have made some impacts in reducing bleeding risk [89]. Bivalirudin as an anticoagulant during PCI in an NSTEMI population has been shown to reduce bleeding yet maintain effectiveness in specific female subgroup analysis [90]. Adopting so-called bleeding awareness strategies (vascular closure devices, bivalirudin, radial approach and their combinations) have also been shown to significantly reduce the number of bleeding complications in women (6.3 vs 3.2%; $p < 0.01$) with a resultant decrease in mortality [91]. Antiplatelet use is also an important consideration, with newer agents such as prasugrel and ticagrelor improving ischemic ACS outcomes. Important caveats with prasugrel are especially relevant in the female population, as there was significant increase in major bleeding and no overall benefit in the subgroup of patients with previous cerebrovascular disease, under 60 kg and over 75 years old [5]. Ticagrelor does not have these restrictions of use and may be of additional benefit [92,93].

Utilizing the radial artery for access has also been shown to significantly reduce bleeding complications and even mortality in all-comer STEMI patients [94,95], with females appearing to derive even more benefit than males [96,97]. Despite the obvious benefits of radial access, there remains a slower uptake of radial PCI in women. In the multicenter NOBORI-2 trial, females were significantly less likely to undergo radial access PCI (33 vs 41.5%; $p < 0.001$) [98].

Why are women at increased risk of bleeding complications? Several possibilities exist, including gender-related differences in arterial structure and function related to the vascular effects of estrogen [99,100]. It is conceivable that such alterations may predispose to arterial fragility and vascular complications. Gender-specific differences and menopause-related changes in coagulation and fibrinolysis have also been documented [101] and this may lead to a more pronounced response to anticoagulants and associated excesses of bleeding. There are also gender differences in arterial mechanical properties, such as increased pulsatility, possibly related to body size, which could increase bleeding risk [102].

There is inconclusive evidence that women are at risk of other complications during PCI such as a significant increase in post-procedural stroke in a single study (OR: 3.2; 95% CI: 1.4–7.4; $p < 0.01$) [103]. Some studies have also shown coronary perforation and tamponade was more common in women [104]; however, in a recent large review of grade III coronary perforations, predictors in PCI were rotablation, complex lesions and IVUS-guided procedures but female gender was not a significant predictor [105].

Guidelines

Despite a wealth of published data on the subject of STEMI and outcomes in women, little is mentioned to distinguish management strategies between genders in either European (ESC) or American (ACC/AHA) STEMI guidelines [106].

ACC guidelines on unstable angina/NSTEMI 2007 (updated 2012) Class 1 recommendations include [107]:

- Women with unstable angina/NSTEMI should be managed with the same pharmacological therapy as men both in the hospital and for secondary prevention, with attention to antiplatelet and anticoagulant doses based on weight and renal function; doses of renally cleared medications should be based on estimated creatinine clearance (level of evidence: B);
- For women with high-risk features, recommendations for invasive strategy are similar to those of men;
- In women with low-risk features, a conservative strategy is recommended (level of evidence: B).

In the European NSTEMI guidelines, the conclusion regarding interventional approach "suggest that a routine early invasive strategy should be considered in women on the same principles as in men." It is acknowledged that "contradictory results have been published with respect to the influence of sex on the treatment effect of an invasive strategy in NSTE-ACS" [108].

While both ACC and ESC revascularization guidelines recommend an invasive strategy for women with positive biomarkers, for biomarker negative cases, women should avoid an early invasive strategy due to the higher event rate [109]. Recent 2013 ESC guidelines for stable CAD acknowledge that there appears to be an increased procedural risk and state that "it may be prudent to adopt a more conservative approach in undertaking PCI and CABG in women" [110].

Conclusion

In the STEMI population, women do benefit from PCI, although there is an increase in bleeding and vascular complications, and younger women are at increased risk than their male contemporaries. In the NSTEMI population, high-risk females appear to gain as much benefit from revascularization as males. However, in low-risk women, careful consideration should be given to medical over invasive management due to lack of demonstrated efficacy.

Stable women undergoing PCI are under-represented in the literature. Women should receive optimal medical management and care should be given regarding increased bleeding risks. In women referred for PCI, an individual approach should be provided and optimal measures utilized to reduce bleeding and vascular access complication, either with radial access, careful dosing of anticoagulants and perhaps use of agents such as bivalirudin.

Clinical vignette & future perspectives

This 82 year old has many markers of high bleeding risk, namely low body weight, age and female gender. This patient has stable angina and although has 'failed' medical therapy, it would be prudent for the interventionalist to ensure that appropriate anti-anginal medication at adequate doses have been administered before recommending PCI. If PCI is performed for symptomatic benefit, the patient should be appropriately consented for the procedure and measures should be taken to minimize the risk of procedure-related bleeding. At our center, we would advocate a radial approach with weight-adjusted unfractionated heparin without routine glycoprotein IIb/IIIa inhibitor use unless required for bailout. For the stable patient, clopidogrel would remain the antiplatelet of choice.

In the future, we envisage development of additional novel agents to improve safety outcomes, specifically focusing on reduced bleeding complications in women. Further refinement of the radial access technique will likely reduce the risk of vascular access complications. In this environment, we propose that age-adjusted complications and outcome between the sexes will be indistinguishable.

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Executive summary

- Women often have delayed presentation of ischemic chest pain with more atypical-type symptoms than men.
- Women undergoing percutaneous coronary intervention (PCI) are older than men, with associated increase in morbidity and mortality.
- Previously, outcomes in PCI for acute coronary syndrome were worse in women; however, recent analyses adjusted for differences in comorbidity have shown that outcomes are improving and are similar to men.
- Bleeding and vascular complications remain the most important problem for women undergoing PCI.
- Novel anticoagulant and antiplatelet agents and radial access for PCI have been utilized with success to reduce bleeding risk.

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