

significant bleeding (BARC ≥ 2 : 5.3 vs. 2.3%; $p=0.028$). Procedural complications during RA were associated with almost double the incidence of MACE at long-term follow-up (HR 1.92; 95% CI 1.34-2.77, $p<0.001$). When RA was compared with modified balloon angioplasty for the treatment of severely calcified lesions, there was a significant interaction by sex, suggesting that RA may be beneficial in men but not women, although it is important to note that only 23 women were included in this study.¹²⁵ While there are insufficient data available to conclusively determine the safety of atherectomy devices in women, including no studies on laser atherectomy, current evidence suggests that caution is needed when using RA in women.

Intravascular lithotripsy

Intravascular lithotripsy (IVL) emits sonic pressure waves from an angioplasty balloon to fracture circumferential coronary calcium. The safety and effectiveness of IVL was evaluated in 3 single-arm studies, DISRUPT CAD I, II, and III, which enrolled a total of 631 patients.¹²⁶⁻¹²⁸ In a patient-level pooled analysis of 628 patients (22.9% women), women had similar extent and severity of calcium compared with men. Despite women having more comorbidities and smaller vessel size (2.7 ± 0.4 mm vs. 3.0 ± 0.5 mm, $p<0.001$), there were no differences in the primary safety endpoint of 30-day MACE (8.3% vs. 7.1%, $p=0.61$) or the primary effectiveness endpoint defined as stent delivery with a residual in-stent stenosis $\leq 30\%$ without in-hospital MACE (91.7% vs. 92.6%, $p=0.72$) between women and men. Importantly, IVL related serious angiographic complications (flow-limiting dissection, perforation, abrupt closure, slow flow, no-reflow) were uncommon and similar for women and men (1.6% vs. 2.3%, $p=0.75$). While additional evidence is needed, these results taken in the context of outcomes with atherectomy devices suggest that IVL may emerge as a first-line therapy for plaque modification of calcified lesions in women specifically.¹²⁹

Gaps in evidence

- Sex differences in the efficacy and safety of various device-based strategies for calcified plaque modification

Lesion Considerations During Percutaneous Revascularization

Chronic total occlusions

Percutaneous revascularization of chronic total occlusions (CTO) carries high procedural complexity. Although women comprise less than 20% of trial participants, complications after CTO intervention, including coronary perforation, bleeding, and contrast-induced nephropathy are observed more commonly in women.¹³⁰ Nevertheless, a registry of 2002 patients (17% women) suggested that CTO procedural success and mortality reduction is similar in women and men.¹³¹ Furthermore, a meta-analysis of 9 studies including 30,830 CTO patients treated with PCI found that female sex was not an independent risk factor for MACE or PCI success rate.¹³² Overall, these non-randomized studies suggest that female sex should not be a factor in withholding CTO PCI.

Gaps in evidence

- Randomized evidence of medical therapy versus revascularization for CTO in women

Vascular Access in Women

With respect to femoral catheterization, vascular complication rates with vascular closure devices (VCDs) in women are inconsistent across studies.^{133,134} The Instrumental Sealing of Arterial Puncture Site – CLOSURE Device versus Manual Compression (ISAR-CLOSURE) trial reported similar rates of vascular access-site complications in women

receiving a VCD compared with those receiving manual compression (8.6% vs. 9.8%; $p=0.451$),¹³³ whereas other studies have reported reduced or even higher vascular complications with VCD in women.¹³⁵⁻¹³⁷ As such, the optimal manner of achieving hemostasis at the access site in women undergoing transfemoral cardiac catheterization is not defined.

Radial access is recommended in women to reduce bleeding and vascular complications including retroperitoneal hemorrhage (Supplemental Table 4).¹³⁸⁻¹⁴² The MATRIX Access trial randomized 8404 patients (26.6% women) to femoral versus radial access for PCI.¹⁴¹ While women were noted to have a higher bleeding risk compared with men in this trial, the benefit of radial access was relatively greater in women for the primary endpoint of MACCE (composite of death, MI, or stroke; RR 0.73; $p=0.019$) and net adverse events (composite of MACCE or major bleeding; RR 0.73, $p=0.012$).¹⁴¹ In contrast, the Safety and Efficacy of Femoral Access vs Radial Access in ST-Segment Elevation Myocardial Infarction (SAFARI) trial (N=2292), which evaluated radial versus femoral access in the setting of STEMI, did not demonstrate a significant difference in the primary endpoint of all-cause mortality in either women or men.¹⁴³ Nevertheless, a meta-analysis of RCTs including the STEMI-RADIAL trial demonstrated that a radial approach was associated with decreased non-CABG related bleeding (odds ratio [OR] 0.56, 95% CI 0.44-0.72), vascular complications (OR 0.49, 95% CI 0.32-0.75), and MACCE (OR 0.73, 95% CI 0.58-0.93) in women,^{140,144} suggesting that the radial artery should be the preferred access site for women to reduce procedural-related complications. Since women may be more prone to radial artery tortuosity or spasm (which could lead to unsuccessful radial access), administration of vasodilators and anxiolytics as well as procedural techniques to navigate the forearm vascular anatomy should be employed liberally.

Gaps in evidence

- Optimal method of arterial hemostasis in women undergoing transfemoral cardiac catheterization
- Comparative outcomes based on sex of vascular closure devices

Considerations Regarding Adjunctive Antithrombotic and Antiplatelet Pharmacology

Antithrombotic agents for the treatment of acute coronary syndromes

Antithrombotic therapy is the cornerstone of treatment in patients undergoing coronary revascularization, and studies have suggested that women are undertreated with guideline-recommended therapies.^{145,146} Although sex-specific differences in the pharmacokinetic (PK) profiles of antithrombotic drugs may cause variability in pharmacodynamic (PD) responses between women and men and may have a role in modulating bleeding risk, RCTs evaluating antithrombotic medications indicate that both women and men have similar therapeutic benefits.¹⁴⁷⁻¹⁴⁹

Antiplatelet agents for the treatment of acute and chronic coronary syndromes

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) is the standard of care for preventing thrombotic events after PCI (Supplemental Table 5). Increased platelet reactivity has been shown among women receiving aspirin, although these PD differences have not resulted in significant heterogeneity in aspirin efficacy between the sexes.¹⁴⁷⁻¹⁴⁹ Although reduction in ischemic events has been shown to be greater in men with all oral P2Y12 inhibitors, most studies have shown no significant interactions between specific P2Y12 inhibitor treatment and sex,¹⁵⁰ and sex has not been shown to be an independent predictor of bleeding complications with use of specific agents.¹⁵¹

The minimum required duration of use for an oral P2Y12 receptor inhibitor varies according to the clinical setting (Figure 1).¹⁴⁵