



Sex-Based Differences in Chronic Total Occlusion Management

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Abstract

Chronic total occlusions (CTOs) are an important and increasingly recognized subgroup of coronary lesions, documented in at least 30%, but up to 52% of patients with coronary artery disease (CAD) undergoing coronary angiography. Percutaneous coronary intervention (PCI) of these lesions is increasingly pursued, with excellent success rates.

Purpose of Review It is known that gender differences exist in the presentation of CAD, as well as in clinical outcomes after routine PCI; however, it is not well described how these differences pertain to management of CTOs. This review summarizes the available data regarding sex-based differences in CTO management and outcomes.

Recent Findings Women comprise approximately 20% of CTO registry and trial participants.

Summary As has been demonstrated in PCI studies, women comprise a minority of patients in CTO PCI registries and trials. Sex-based differences exist in complication rates, collateral formation, and outcomes and need further evaluation in future studies.

Keywords Chronic total occlusions (CTOs) · Percutaneous coronary intervention (PCI) · Coronary artery disease (CAD) · ST elevation MI (STEMI) · Coronary artery bypass graft (CABG)

Introduction

A chronic total occlusion (CTO) is defined as an artery with luminal narrowing, leading to thrombolysis in myocardial infarction (TIMI) 0 flow, estimated to be present for at least 3 months. CTOs are present in between 30% and 52% of patients with coronary artery disease [1–6], including up to 10% of patients presenting with ST elevation MI (STEMI) [6]. Despite this significant prevalence, CTO PCI represents only 3.8% of attempted PCI cases according to data from the National Cardiovascular Disease Registry (NCDR) [2, 7].

CTO patients in general are older and are much less likely to undergo revascularization (either by PCI or bypass surgery) than non-CTO patients. Recent data from the Canadian Registry indicates that only 35% of

CTOs underwent an attempt at revascularization, either by PCI (10% of all CTOs) or bypass surgery (25%). Revascularization, when offered, appears to significantly improve quality of life [8].

Percutaneous revascularization of coronary CTOs has evolved from initial techniques relying on antegrade wire escalation [6] to now include subintimal tracking and reentry technique (STAR) [9], antegrade dissection and reentry (ADR) strategy using dedicated catheter and balloon technology, and retrograde techniques. These strategies were organized into a comprehensive “hybrid algorithm.” [10] Establishment and implementation of this systematic “hybrid algorithm” improved procedural success >90%, as well as accessibility to CTO PCI [11].

This evolution has led to an interest in pursuing CTO PCI in patients with appropriate indications, and in whom bypass surgery does not portend additional benefit, or risk is prohibitive. However, in this emerging trend, significant practice heterogeneity persists with regard to referral and management of chronic ischemic heart disease, including patients with CTOs. Women may be particularly vulnerable to treatment variability based on differences in patient presentation and disease manifestation. In this review, we aim to explore the

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available data regarding gender differences in CTO presentation, management, and outcomes.

Sex-Based Disparities in CTO Presentation

Ischemic heart disease remains the leading cause of death for both men and women in the USA. In 2013, nearly 290,000 women died from ischemic heart disease, which totals more deaths than from all cancers combined [12]. Gender differences have long been known to exist in the presentation, outcome, and management of coronary artery disease. Numerous studies indicate that women are less likely than men to be referred for invasive coronary angiography and to undergo revascularization, despite a nearly identical prevalence of coronary disease [13, 14]. This gap has been validated in multiple clinical settings including acute coronary syndrome, acute myocardial infarction, and chronic, stable angina.

Recognizing the signs of ischemic heart disease in women, as in any patient, can be challenging. Rather than “typical” substernal angina, women more often experience pain in the arms, jaw, neck, or infrascapular area, sometimes with associated epigastric discomfort, with or without nausea [15–17]. Prodromal symptoms are unusual, but may include fatigue, sleep disturbances, and shortness of breath. While physical exertion often exposes symptoms in men, women are more apt to develop symptoms in response to an emotional event or psychosocial stressor, and therefore, symptoms may last longer, rather than just throughout the duration of activity [16]. More so than in men, roughly half of women presenting with an acute coronary syndrome do not identify any preceding symptoms whatsoever [15].

The epidemiology of CTOs in women is poorly understood and referral bias limits assessment of their true prevalence in the greater population. This was evaluated in an unselected STEMI population; however, there was no difference in CTO prevalence between men and women [18]. In general, women presenting with CTOs are more likely to be older than men, presumably due to the potentiating protective effects of estrogen, have higher rates of hypertension and diabetes, and less tobacco dependence [7, 19]. Contemporary CTO series are typically comprised of no more than 20% women, which is in line with the overall low inclusion of women in cardiovascular registries and randomized trials [20]. In Outcomes, Patient Health Status, and Efficiency IN Chronic Total Occlusion Hybrid Procedures (OPEN-CTO), 1096 patients underwent CTO PCI and outcomes were reported including technical endpoints, adverse events including coronary

dissection and pericardial tamponade, clinical endpoints such as major adverse cardiovascular events (MACE) and death, and finally, overall success of the procedure. Once again, women comprised just 20% of these patients [21].

Representation of Women in CTO PCI and Outcomes

Women represent 14–21% of patients included in most registries and trials studying CTO PCI outcomes [21–23]. This may reflect a component of selection bias, as there was no difference in CTO prevalence in an unselected population presenting with STEMI [6]. A similar proportion of CTO PCI cases were performed on women in the NCDR CathPCI registry [2]. Despite this likely under-representation of women in registries and trials, several pertinent studies evaluating sex-specific variables and outcomes in CTO PCI are relevant to this discussion.

The Multinational CTO Registry was an observational study consisting of 1791 patients undergoing CTO PCI at three centers in the USA, Italy, and South Korea between 1998 and 2007, where women represented 14% of subjects. Female patients in this population were less likely to have multi-vessel disease, and more often had CTOs located in the left anterior descending (LAD) artery (43% vs 33% in men) [19].

The EXPLORE trial evaluated STEMI presentations with a concurrent CTO in a non-infarct-related artery randomized to primary PCI of culprit lesion alone versus short-term staged CTO PCI. At 4 months, there was an improvement in left ventricular ejection fraction and diastolic volume in the LAD CTO PCI subgroup. The primary endpoint of left ventricular function was not significant in the total cohort, but this subanalysis is certainly hypothesis-generating [23]. As is consistent with previous studies, women comprised a minority of the 304 total patients enrolled. Only 12% of the patients who underwent CTO PCI were women and 8% of the patients randomized to undergo primary PCI without CTO PCI were women. Of the 42 female patients undergoing CTO PCI of the LAD, there was a trend toward improvement of LVEF and LVEDV. This finding was not statistically significant in this study that was not powered for this sub-analysis [23] but in total suggests that LAD CTO PCI in particular may be correlated with recovery of left ventricular systolic function, and that women may be more likely to present with this anatomical finding.

In terms of variables that may have impacted procedural outcomes in the Multinational CTO cohort, women were

found to have shorter CTO lengths and lower frequency of blunt stumps and bridging collaterals, findings that likely contributed to higher success rates in women [19]. This could be based on pathophysiologic differences or may represent differences in selecting women for PCI based on anatomical characteristics. In contrast, other studies found female gender to be an independent risk factor for poor coronary collateral vessel development (CVD) [24] though septal collaterals were a marker for successful PCI in the OPEN-CTO registry [22]. Procedural success was more frequent in women at 75% compared to 67% in men, yet gender was not a significant predictor of failure in the adjusted analysis. While successful CTO PCI was associated with lower 5-year mortality in men, this was not statistically significant in women, though likely underpowered given approximately two early deaths out of the 62 unsuccessful procedures performed in women. The authors did find an interaction between MACE reduction and successful PCI based on gender, but another analysis from the Multinational CTO Registry did not find gender to be a significant predictor of mortality [19]. The relationship between gender and both anatomic and procedural outcomes is thus multifactorial and may represent a hybrid of patient selection, risk aversion, and underlying pathology.

A propensity-matched, observational analysis of patients in the UK enrolled in a CTO registry suggests parallel findings. This database included 1271 patients who underwent CTO PCI between 2011 and 2015. The 20.5% of women patients were older than their male counterparts, less likely to have a history of tobacco use and less likely to have had previous coronary artery bypass grafting [25]. In addition, there was suggestion of lower procedural complexity extrapolated from lower procedural times, lower fluoroscopy doses, and lower volumes of contrast administered, though J-CTO scores were similar between women and men. Similarly, rates of retrograde dissection and reentry (RDR) were lower in women, though it is unclear if this is related to a smaller vessel caliber combined with fewer well developed and easy to navigate collaterals, or related to a lower lesion complexity [26].

In a recent single center, retrospective study analyzing 2002 consecutive patients undergoing CTO PCI between 2005 and 2013, women were more likely than their male counterparts to present with dyspnea, and only 23% endorsed typical anginal symptoms, vs 35% of men presenting with chest pain. If women did present with typical angina, it was more likely to be severe. With regard to burden of disease, as seen in other studies, women were less likely to present with long CTO lesions or multi-vessel disease. With regard to comorbidities, women were more likely than men to have concomitant renal dysfunction, less likely to use tobacco, and less likely to have previously undergone coronary revascularization. Despite these baseline differences, procedural success was no different at 82% in women and 83% in men. Both women and men experienced lower all-cause mortality and

major adverse cardiovascular events (MACE) after successful CTO PCI [26].

Differences in CTO Complication Rates Between Men and Women

Complication rates are known to be higher in CTO vs non-CTO PCI. Among nearly 600,000 patients observed in the NCDR Cath PCI registry between 2009 and 2013, only 3.8% of total PCI volume targeted a CTO lesion but also had a higher rate of major adverse cardiac events (1.6% vs 0.8%) [2]. Generally speaking, patients undergoing CTO PCI vs non-CTO PCI required greater contrast volume and longer fluoroscopy time with lower procedural success (59% vs 96%). In this small portion of patients undergoing CTO PCI in this cohort, 22% were women and gender was not associated with complication rate. Of note, operator experience was found to be directly related to increased procedural success and lower rates of MACE in CTO PCI, but not overall complication rates in this study of elective PCI procedures [2].

Another study examined gender-specific complication rates following CTO PCI performed by high-volume operators, and in contrast, demonstrated post-procedural complications were higher in women than in men [27]. A composite of in-hospital complications were twice as likely in the unmatched cohort, and nearly three times as likely in women in the matched cohort as compared to men. The composite complication endpoint included coronary perforation, acute vessel closure, bleeding (either retroperitoneal bleeding or directly from a femoral access site), myocardial infarction, TIA/stroke, contrast-induced nephropathy, and death. Coronary perforation, bleeding, and contrast-induced nephropathy were all independently observed more frequently in women than men [25]. Perforation rates (Ellis type 3) were 3.1% in women but only 0.5% in men in the unmatched cohort. Interestingly, RDR was less commonly employed as the initial or final strategy in women, though the difference was only significant in the unmatched cohort as the final crossing strategy. This suggests that interventional collaterals may be less favorable in this group of women, who were significantly older than the corresponding male population with 48% of women >70 years old in the study as compared to 29% of men. Interestingly, the complication rate was higher in women despite higher use of antegrade techniques, even though retrograde CTO PCI has been previously associated with increased risk of complications compared to an antegrade approach. Coronary calcification was also related to perforation in women. Therefore, it appears in this elderly

female cohort that this was a contributing factor, perhaps in contrast to perforations related to collateral trauma. Additionally, data comparing female coronary size using intravascular ultrasound (IVUS) have demonstrated that normal coronary artery diameter was lower in women as compared to men, even after adjusting for body surface area, so a propensity to oversize balloons or stents in women may be a contributing factor [28]. Overall, it appears that the propensity of women to present later in life with a heavier burden of calcification is related to this higher rate of perforation, and caution against oversizing stents in vessels that have undergone remodeling in a chronically occluded state, especially in the subintimal track, may be especially relevant to women undergoing CTO PCI.

Female sex is a known risk factor for bleeding complications in the overall PCI population and so these findings in the CTO population may be an extension of overlapping risk factors in the non-CTO female population. The updated Cath PCI risk model found female sex to be the strongest predictor of bleeding with women twice as likely as men to experience access or non-access related post-PCI bleeding (OR 1.97, 95% CI 1.93–2.02) [29]. This appears to be the case regardless of the bleeding avoidance strategy employed. Patients, including women, at increased risk for bleeding have paradoxically seen lower rates of use of bleeding avoidance strategies including bivalirudin in place of heparin, vascular closure devices, and radial access [30].

Radial access is a logical strategy to avoid bleeding complications in women. CTO PCI almost invariably requires dual-injection coronary angiography and so use of at least one femoral artery is common. As such, use of radial-specific 7F slender sheaths and sheathless guide systems are important considerations for the CTO operator as a risk-avoidance strategy. A recent registry-based trial randomizing only women before catheterization to primary radial or femoral strategy failed to show definitive benefit of radial access in women, however [29]. Of note, the study was stopped early due to a lower than anticipated rate of bleeding or vascular complications, and use of other bleeding avoidance strategies with bivalirudin and vascular closure devices in the femoral arm was substantial at approximately 65%. Women in the study preferred radial access, and a trend toward benefit was seen. Notably, 7% in the radial arm crossed over to the femoral access arm to complete the procedure, as compared to 2% in the femoral access arm (HR 3.65, 95% CI 1.45–9.17, $p < 0.01$). In total, it appears that woman, as with other high risk groups, may be overlooked with regard to the use of bleeding avoidance strategies. In the absence of more conclusive data, bleeding risk should be strongly considered in women, in the context of risk factors and propensity for access and non-access site bleeding. Women are also known to be at increased risk for

contrast-induced nephropathy in the overall PCI population, and given that contrast utilization tends to be higher in CTO PCI, it is not surprising that this relationship is present in female CTO PCI patients as well.

Thematic Differences in Women Undergoing CTO PCI

Although all studies to date evaluating gender disparities in the presentation and management of CTOs are observational in nature, and themselves are comprised of a minority of women (typically 20% or less of each study population), multiple notable trends are relevant.

First, it is well established that ischemic heart disease in general tends to present in women at a later age and less likely with “typical” symptoms of chest pain. This is true in the specific CTO population as well. Women are less likely to have invasive evaluation and treatment of both non-CTO and CTO coronary lesions and discrepancies in management warrant further investigation [13, 25, 31].

Secondly, women appear to experience a higher rate of complications than men, particularly coronary perforation and bleeding. Collateral vessels in women appear to be smaller, more tortuous, and more difficult to cross, leading less frequently to successful retrograde approaches, compared with men, and may contribute to these disparate outcomes, as well as older age at presentation, and a higher degree of calcification.

It is clear from the available data that CTO PCI in women is safe and feasible, with similar success rates compared with men, and that women derive significant benefit, including in symptomatology, as well as left ventricular function and tolerance of future coronary events. As discussed above, although not statistically significant, a subgroup analysis of the EXPLORE trial demonstrated a trend toward improvement of LVEF and LVEDV in women who underwent CTO PCI of the LAD [23]. These differences in outcomes between genders are not yet evaluated in the OPEN-CTO study [21, 22].

Conclusion

As the CTO field continues to evolve, better definition of the optimal management of CTOs in all patients is paramount. Patient selection for PCI in stable ischemic heart disease poses significant challenges for randomized trial design. This is further complicated by trial design in the CTO population due to insufficient rates of revascularization by surgery and PCI. Further study of patient-driven outcomes and the morbidity of CTO PCI warrants special attention to sex-specific differences. In the interim, having a high index of suspicion for

ischemic heart disease in women is essential, including for both non-CTO and CTO lesions. Additionally, awareness of the higher complication rate should lead the operator to consider techniques that minimize perforation, bleeding, and other adverse events, on a case-specific basis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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