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Sex Differences in Clinical Profile and Outcome After Percutaneous Coronary Intervention for Chronic Total Occlusion

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ABSTRACT

Background: There are limited data around sex differences in the risk profile, treatments and outcomes of percutaneous coronary intervention (PCI) in chronic total occlusion (CTO) lesions in contemporary interventional practice. We investigated the impact of sex on clinical and procedural characteristics, complications and clinical outcomes in a national cohort.

Methods & results: We created a longitudinal cohort (2006–2018, n = 30,605) of patients with stable angina who underwent CTO PCI in the British Cardiovascular Intervention Society (BCIS) database. Clinical, demographic, procedural and outcome data were analysed in two groups stratified by sex: male (n = 24,651), female (n = 5954). Female patients were older (68 vs 64 years, P < 0.001), had higher prevalence of diabetes mellitus (DM), hypertension (HTN) and prior stroke. Utilization of intravascular ultrasound (IVUS), drug eluting stents (DES), radial or dual access and enabling strategies during CTO PCI were higher in male compared to female patients. Following multivariable analysis, there was no significant difference in in-patient mortality (adjusted odds ratio (OR):1.40, 95 % CI: 0.75–2.61, P = 0.29) and major cardiovascular and cerebrovascular events (MACCE) (adjusted OR: 1.01, 95 % CI: 0.78–1.29, P = 0.96). The crude and adjusted rates of procedural complications (adjusted OR: 1.37, 95 % CI: 1.23–1.52, P < 0.001), coronary artery perforation (adjusted OR: 1.60, 95 % CI: 1.26–2.04, P < 0.001) and major bleeding (adjusted OR: 2.06, 95 % CI: 1.62–2.61, P < 0.001) were higher in women compared with men.

Conclusion: Female patients treated by CTO PCI were older, underwent lesser complex procedures, but had higher adjusted risk of procedural complications with a similar adjusted risk of mortality and MACCE compared with male patients.

Perspective

What's known

There are limited data about clinical profile and outcomes of CTO PCI stratified by sex.

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What's new

After adjustment for baseline differences, women observed higher odds of procedural complications, coronary artery perforations, major bleeding but similar odds of death & MACCE compared with men. Randomised control trial data are needed to validate these observational study findings.

1. Introduction

Chronic total occlusions (CTO) represent an important and distinct subset of coronary artery lesions, present in up to 20 % of patients who undergo coronary angiography [1–3]. Studies have previously reported that successful percutaneous coronary intervention (PCI) of CTO lesions is associated with better control of angina, improvement in quality of life and left ventricular systolic function compared with failed CTO PCI [4–6]. Whilst the majority of patients with CTOs are managed with optimal medical therapy (OMT), a sizeable proportion of these individuals will receive either PCI (10–22 %) or surgical (22–60 %) revascularization [7–9]. CTO PCI is a rapidly evolving area in interventional cardiology, with success rates of >90 % in experienced centres enabled by continued procedural and technological innovation.

Sex disparities have long been known to exist in PCI outcomes. In a recently published pooled patient-level data analysis of 32,877 patients from 21 randomised PCI trials, women had significantly higher rates of MACE, ischaemia-driven target lesion revascularization (but not death) compared to men at five years of follow up after index procedure [10]. Whether such sex disparities exist in CTO PCI is not well studied. Only a few small studies have reported sex-based outcomes following CTO PCI with conflicting results [1,11–14]. In a retrospective cohort study of 780 patients who received PCI for at least one CTO, both sexes had similar procedural success rates and in-patient complications [11]. In contrast, other studies have demonstrated that women had less complex CAD but sustained more procedural complications and bleeding events requiring transfusion [13,15].

We therefore sought to investigate the clinical characteristics, procedural complications and in-hospital adverse outcome in patients with stable angina who underwent successful CTO PCI stratified by sex, in a large unselected national cohort from the PCI database of British Cardiovascular Intervention Society (BCIS).

2. Methods

The current analysis is based on national data for all patients who received CTO PCI in England and Wales from January 2006 to March 2018. The British Cardiovascular Intervention Society (BCIS) records information prospectively on all PCI procedures performed in the United Kingdom (UK). This data collection process is governed by the National Institute of Cardiovascular Outcomes Research (NICOR). Institutional research and ethical board approval were not required for this study as all data were anonymized and routinely collected as part of the national audit. The administrative protocol, governance and quality of these data have previously been validated and published [16–18]. In 2018, approximately 98 % of all PCI procedures performed in the National Health Service (NHS) hospitals in UK were recorded on BCIS database (https://www.bcis.org.uk). The BCIS dataset comprises of 113 variables based on clinical, demographic procedural, and outcomes details with approximately 100,000 new records added each year. Data included patients' clinical and demographic features, risk profile and comorbid conditions as well as aspects of procedural, practice and adjunctive medications. CTO PCI procedures undertaken in the setting of an acute coronary syndrome (ACS), or with incomplete data for age, sex and mortality, were not included in this analysis (Fig. 1). We also analysed in-hospital major adverse cardiovascular and cerebrovascular events (MACCE: defined as a composite of in-hospital mortality, in-hospital myocardial reinfarction [including Q-wave and Non-Q wave MI], emergent target vessel revascularization by PCI or coronary artery bypass grafting (CABG), side branch occlusion, and stroke), procedural complications including coronary perforation, major in-hospital bleeding. In-hospital major bleeding was defined as a composite of clinical tamponade after coronary perforation, intracerebral bleed, gastrointestinal bleed, any blood or platelet transfusion, retroperitoneal hematoma, or an arterial access site haemorrhage requiring delaying discharge or intervention or surgery. We also assessed a composite endpoint of "any procedural complication" which was defined as aortic dissection, coronary perforation, DC cardioversion, heart block requiring pacing, no flow/slow flow phenomenon, need for ventilation or cardiogenic shock-following the procedure. Furthermore, we analysed temporal changes in interventional practice for these patients from 2006 to 2018.

In the BCIS dataset, a CTO lesion is defined as a total occlusion with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 antegrade through the concerned coronary artery segment of >3 months duration [19,20]. We analysed the dataset by the number of enabling strategies used in the index procedure as a surrogate marker of procedural complexity as per our previous BCIS analyses [17,18]. Enabling strategies to facilitate CTO-PCI were described as one of the following: dual arterial access, rotational or laser atherectomy, intravascular ultrasound (IVUS), use of penetration catheters (recorded in the BCIS dataset as Fine cross, corsair, Tornus) or CrossBoss/Stingray balloon.

The CTO PCI cohort was divided into two groups stratified by sex. For descriptive statistical analysis, continuous variables were described as mean or median and standard deviations (SD), interquartile tile ranges (IQR), whereas categorical variables were described using frequencies and proportions. We used chi-square tests to evaluate group differences for categorical variables, whilst students *t*-test or rank sum test were applied for continuous variables. Multiple imputations with chained equations were applied to impute data for all variables with missing records. Multivariable logistic regression analyses were used to analyse the risk of adverse outcomes among two groups. In multivariable analysis, we adjusted for age, radial access, angina class, New York Heart Association (NYHA) class, comorbid conditions (prior history of smoking, myocardial infarction (MI), PCI, coronary artery bypass grafting (CABG) surgery, hypercholesterolemia, hypertension (HTN), peripheral vascular disease (PVD), valvular heart disease, diabetes mellitus (DM), renal disease), ejection fraction (EF), family history of coronary artery disease (CAD), use of circulatory support, use of drug eluting stents (DES), year of procedure & use of enabling strategies. For more clarity, we reported statistical models with complete case analysis as well as with multiple imputations.

As a sensitivity analysis, we implemented propensity score matching (PSM) on imputed data to estimate the average treatment effect (ATE), adjusting for baseline differences between the two groups of interest. Ten imputations were generated. One to one matching with replacements was performed, followed by logistic regression analysis (the sole predictor being group membership) to gain the average treatment effect.

Stata 14.2 statistical package was utilised for all analyses. All statistical analyses were two-tailed, and an alpha of 5 % used throughout.

3. Results

3.1. Study cohort

Our study cohort comprised of 30,605 patients who had successful CTO PCI for stable angina in England and Wales from January 2006 to March 2018 and had data for age, sex and mortality. The process of patients' inclusion and exclusion is presented in Fig. 1. Out of the 30,605 patients in this cohort, 24,651 (81 %) CTO PCI procedures were performed in male and 5954 (19 %) in female patients. Temporal changes in intervention practice from 2006 to 2018 are presented in Fig. 2, with the proportion of women varying between 18 and 22 %.

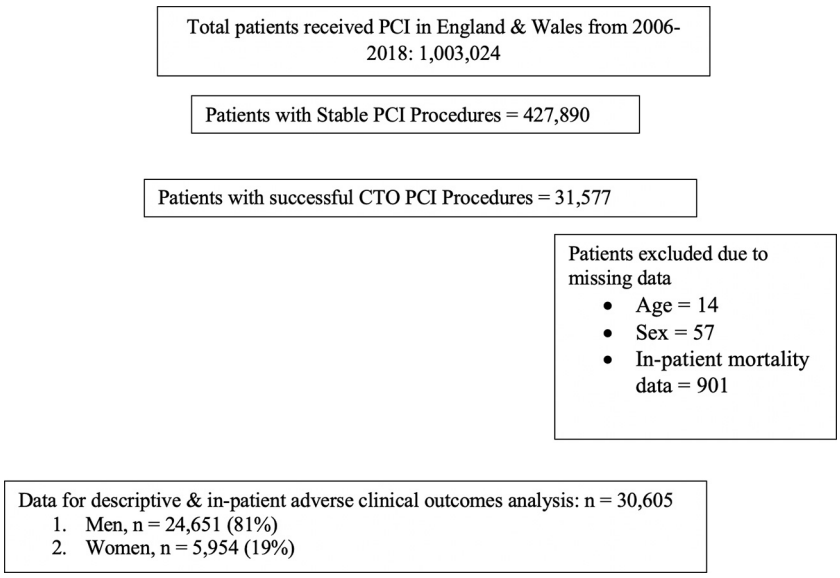

Fig. 1. Consort diagram to show to show all participant inclusion and exclusion.
CTO; Chronic total occlusion, PCI; Percutaneous coronary intervention.

3.1.1. Clinical characteristics

Significant differences were observed in demographics, clinical and procedural characteristics between the two groups (Table 1). Women who received CTO PCI were older, more likely to have more severe angina and breathlessness and had a higher prevalence of DM and HTN. In contrast, the prevalence of smoking history, previous PCI, MI, CABG, and moderate or severe left ventricular systolic dysfunction was significantly higher in men.

Utilization of IVUS, DES, radial or dual access and use of enabling strategies during CTO PCI were higher in men compared to women. Use of dual access (13 % vs 10 %, P < 0.001), IVUS (9 % vs 8 %, P = 0.01), microcatheters (16 % vs 13 %, P < 0.001), CrossBoss/stingray balloon (2.5 % vs 1.9 %, P = 0.01) was more common in men compared with women but use of atherectomy (rotational or laser) (3.8 vs 4.4 %, P = 0.05) and penetration catheters (3 % vs 3 %, P = 0.71) were similar in both sexes. In men, at least one enabling strategy was used in 23 % of cases, two in 8 % and three in 3 % of cases compared to 22 %, 7 % and 2 % respectively in women (P < 0.001).

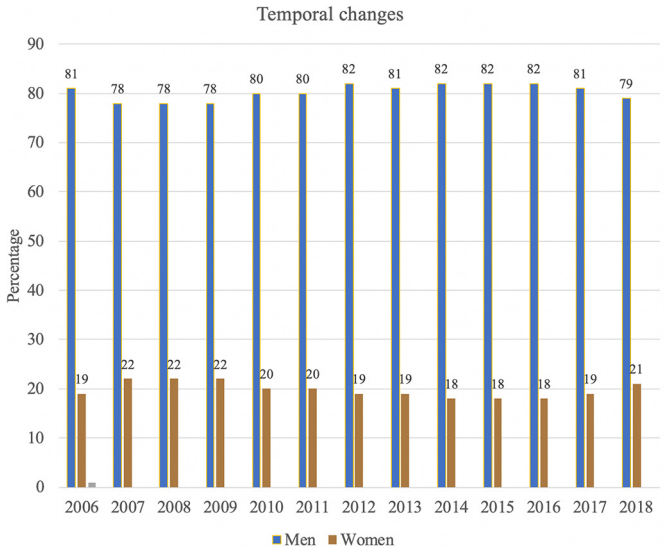

Fig. 2. CTO PCI temporal trends stratified by sex.
CTO; Chronic total occlusion, PCI; Percutaneous coronary intervention.

3.2. Unadjusted clinical outcomes

Unadjusted clinical outcomes are presented in Table 2. The prevalence of crude in-patient death, MACCE and stroke were similar in both sexes. However, the rates of procedural complications (9 % vs 7 %, P < 0.001), coronary artery perforation (2 % vs 1 %, P < 0.001) retroperitoneal haemorrhage (0.3 % vs 0.05 %, P < 0.001) and in-hospital major bleeding (2 % vs 0.87 %, P < 0.001) were higher in women compared to men.

3.3. Adjusted clinical outcomes

The adjusted risk of procedural complications, mortality, and in-hospital MACCE are presented in Table 3. In multivariate analysis on imputed data, after adjustment of baseline covariates, no significant differences were observed for in-patient death (OR: 1.40, CI 0.75–2.61, P = 0.29) and in-patient MACCE (OR: 1.01, 95 % CI: 0.78–1.29, P = 0.96) between CTO PCI procedures undertaken in women and men. The adjusted odds of procedural complications (OR: 1.37, 95 % CI: 1.23–1.52, P < 0.001), coronary artery perforation (OR: 1.60, 95 % CI: 1.26–2.04, P < 0.001), and in-hospital major bleeding (OR: 2.06, 95 % CI: 1.62–2.61, P < 0.001) were higher in female CTO PCI patients compared to male patients. Similar results were obtained in our multivariable complete case analysis (Table 3).

3.3.1. Analysis with propensity score-matching

Finally, we undertook a propensity score matching analysis as a sensitivity analysis (Table 4). We did not observe any difference in in-hospital mortality and MACCE between the two groups. However, similar to the previous multivariable analyses, adjusted odds of procedural complications (OR: 1.52, CI: 1.18–2.10, P < 0.001), coronary artery perforation (OR: 1.54 [1.06–2.02]), and in-hospital major bleeding (OR: 2.12, CI: 1.45–2.18, P – 0.01) were higher in women compared to men.

Our study salient findings are summarised in central illustration figure (Fig. 3).

Table 1
Clinical characteristics.

Variable	Missing data from total	Men (n = 24,651)	Women (n = 5954)	P-value
Median age (IQR)	0	64 (56–71)	68 (61–75)	<0.001
CCS class, Mean (SD)	1782	2.28 (0.83)	2.35 (0.84)	<0.001
NYHA class, Mean (SD)	2833	1.88 (0.77)	1.97 (0.78)	<0.001
Smoking history (%)	3035	14,356 (65 %)	2714 (51 %)	<0.001
Diabetes mellitus (%)	823	5367 (22 %)	1378 (24 %)	0.02
Hypertension (%)	1309	14,388 (61 %)	3855 (67 %)	<0.001
Hypercholesterolemia (%)	1309	15,558 (66 %)	3802 (67 %)	0.40
Previous PCI (%)	469	9088 (37 %)	1797 (31 %)	<0.001
Previous MI (%)	1093	9995 (42 %)	2074 (36 %)	<0.001
Previous CABG (%)	530	3274 (14 %)	480 (8 %)	<0.001
Previous CVA (%)	1309	788 (3 %)	226 (4 %)	0.02
Peripheral vascular disease (%)	1309	1261 (5 %)	280 (5 %)	0.18
Previous renal disease (%)	935	514 (2 %)	109 (2 %)	0.23
Family history of heart disease (%)	3377	11,030 (50 %)	2799 (53 %)	<0.001
Circulatory support (%)	1020	107 (0.45 %)	29 (0.51 %)	0.57
Optical coherence tomography	1466	204 (0.87 %)	44 (0.78 %)	0.51
DES use (%)	367	21,441 (88 %)	5115 (87 %)	0.04
Treated lesion length in mm (IQR)	3400	32 (23–48)	30 (20–48)	<0.001
Stent diameter in mm (IQR)	3796	3.5 (3–3.5)	3 (2.8–3.5)	<0.001
Left ventricular systolic dysfunction				
Good (LVEF >50 %)	10,290	12,153 (76 %)	3073 (81 %)	<0.001
Moderate (LVEF 30–50 %)		2961 (19 %)	613 (16 %)	
Poor (LVEF <30 %)		754 (5 %)	131 (3 %)	
Access				
Femoral (%)	814	14,045 (59 %)	3579 (62 %)	<0.001
Radial (%)	814	12,855 (54 %)	2756 (48 %)	<0.001
Number of stents used				
0	253	1714 (7 %)	396 (7 %)	<0.001
1 (%)		6850 (28 %)	1853 (31 %)	
2 (%)		7178 (29 %)	1744 (30 %)	
≥3 (%)		8711 (36 %)	1906 (32 %)	
RCA as a treating artery	0	12,266 (50 %)	3218 (54 %)	<0.001
LCX as a treating artery	0	6681 (27 %)	1293 (22 %)	<0.001
LAD as a treating artery	0	10,501 (43 %)	2557 (43 %)	<0.001
Enabling strategies use				
No enabling strategies used	51	16,213 (66 %)	4122 (69 %)	<0.001
No of enabling strategies[a] use = 1		5618 (23 %)	1301 (22 %)	
No of enabling strategies[a] use = 2		2082 (8 %)	406 (7 %)	
No of enabling strategies[a] use ≥ 3		696 (3 %)	116 (2 %)	
Details of use of individual CTO enabling strategies				
Dual access	814	3079 (13 %)	588 (10 %)	<0.001
Intravascular ultrasound	1466	2146 (9 %)	457 (8 %)	0.01
Atherectomy (rotational or laser)	1590	896 (3.8 %)	248 (4.4 %)	0.05
Penetration catheters	1590	718 (3 %)	168 (3 %)	0.71
Microcatheters	1590	3743 (16 %)	752 (13 %)	<0.001
CrossBoss/Stingray balloons	1590	579 (2.5 %)	108 (1.9 %)	0.01

CCS; Canadian Cardiovascular Society; CTO; Chronic total occlusion, CVA; Cerebrovascular accident; DES; Drugs eluted stents; IQR; Inter quartile range; LVEF; Left ventricle ejection fraction; MI: Myocardial Infarction, NYHA; New York heart association, PCI; Percutaneous Coronary Intervention, RCA; Right coronary artery, LCX; Left circumflex artery, LAD; Left anterior descending artery, CABG; Coronary artery bypass grafting.

[a] Enabling Strategies to facilitate CTO-PCI were defined as one of the following: dual arterial access, intravascular ultrasound, atherectomy (rotational or laser), penetration catheters (recorded in the BCIS database as Tornus, Asahi Intecc, Santa Ana, CA or Gopher Gold, Vascular Solutions, Minneapolis, MN), microcatheters (fine cross or corsair use), or CrossBoss/Stingray balloon.

4. Discussion

This national analysis of >30,000 CTO PCI procedures undertaken from 2006 to 2018 showed that women who underwent CTO PCI were older, had a higher prevalence of DM and hypertension, but a lower prevalence of a prior PCI, CABG and left ventricular systolic dysfunction compared with men. Utilization of enabling strategies that are surrogates of CTO complexity was used more commonly in men. The crude and adjusted odds of procedural complications, coronary artery perforation, and in-hospital major bleeding were higher in women compared with men, although there was similar risk of in-patient mortality and MACCE among the two cohorts. Our analysis suggests the persistence of sex disparities in in-hospital outcomes in this complex group of patients.

Previous studies have also reported that women who undergo CTO PCI are older, have a higher prevalence of DM, and hypertension but are less likely to have had prior PCI, MI and CABG and severe left ventricular systolic dysfunction [1,13–15,21]. However, there is conflicting data about the association between sex and procedural complications and adverse outcomes following CTO PCI. In a study of 2002 CTO PCI patients (17 % women), men had a higher prevalence of multivessel CAD (83 % vs 74 %, P < 0.001), CTO length > 20 mm (77 % vs 71 %, P = 0.01) and use of a retrograde approach (25 % vs 18 %, P – 003). Despite women having less complex lesions in this study, they sustained more procedural complications (3 % vs 1 %, P = 0.01) and bleeding events requiring transfusion (2 % vs 0.4 %, p = 0.04), which has been confirmed in our study [13]. In an analysis of 1000 CTO PCI patients from the OPEN-CTO registry of 12 US centres, J-CTO scores and strategy to cross the CTO

Table 2
Unadjusted clinical outcomes.

Outcome	Missing data from total	Men	Women	P - value
In hospital major bleeding[a], n (%)	184	214 (0.87 %)	120 (2 %)	<0.001
In-hospital mortality, n (%)	0	41 (0.17 %)	16 (0.27 %)	0.08
In-hospital MACCE[b] (%)	0	343 (1 %)	84 (1 %)	0.91
In-hospital Stroke (%)	459	11 (0.05 %)	6 (0.1 %)	0.09
Procedural complications				
Any procedural complications[c] (%)	1041	1574 (7 %)	503 (9 %)	<0.001
Coronary perforation (%)	1041	248 (1 %)	101 (2 %)	<0.001
Retroperitoneal haemorrhage (%)	1573	11 (0.05 %)	17 (0.3 %)	<0.001
Renal failure or need for dialysis (%)	459	8 (0.03 %)	6 (0.1 %)	0.03

CTO; Chronic total occlusion, MACCE; Major adverse cardiovascular & cerebrovascular events, PCI; Percutaneous Coronary Intervention, TVR; Target vessel revascularization.
[a] Major bleeding: Need blood or platelets transfusions, haemorrhagic stroke, tamponade, retroperitoneal haemorrhage, and access site complication requiring delaying discharge or intervention or surgery.
[b] MACCE; Major adverse cardiovascular & cerebrovascular events (defined as a composite of in-hospital mortality, in-hospital myocardial reinfarction (including Q-wave and Non-Q wave MI), and emergency target vessel revascularization by PCI or CABG, side branch occlusion, Stroke).
[c] Any procedural complication includes Aortic dissection, Coronary perforation, Heart block requiring pacing, DC cardioversion, no flow/slow flow phenomenon, need ventilation, Shock induced by procedure.

lesions were similar in both sexes. However, mean CTO lesion length (58 mm vs 62 mm; p = 0.05), contrast volume (243 ml vs 266 ml, P = 0.04) and radiation dose (17,288 cGy/cm^2 vs 17,576 cGy/cm^2, P < 0.001) were significantly lower in women than in men. Procedural complications like coronary artery perforation, cardiogenic shock, contrast nephropathy and GI bleed were statistically similar in both sexes [14]. At one year follow up, the health status outcomes including angina, quality of life and major adverse cardiovascular events (MACE) were similar in both sexes. In contrast, an observational study of 1343 patients found that despite similar J-CTO scores in both sexes, there was a non-significant trend towards higher coronary perforation (5.7 % vs 3.5 %, P – 0.14) and cardiac tamponade (0.5 % vs 0.4 %, P – 0.89) rates in women [1]. In addition, Guelker and colleagues reported no significant difference in hospital complications between women and men (8.4 % vs 8.1 %, P – 0.9) in 780 consecutive patients (16 % women) who underwent CTO PCI in The Netherlands between 2010 and 2015 [11]. Finally in another study of 1271 patients, that women were older but less likely to undergone CABG with similar J-CTO scores but had more complications including perforation and retroperitoneal bleed [15]. However, all these studies are limited by taking place in very specialised CTO PCI centres, with high volume CTO operators and all are small in sample sizes, which limits the statistical power to draw meaningful results and undertake multivariable analysis. Nevertheless, a common theme is that despite female patients being consistently older than men, they had less advance CAD but higher procedural complications.

The current analysis is based on national data from all PCI centres in England and Wales and the large patient numbers allow sufficient statistical power to assess clinical outcomes between sexes. We observed an under-representation of women patients undergoing CTO procedures for stable angina. Our temporal analysis to assess yearly practice showed that the proportion of female patients who underwent CTO recanalization remains almost unchanged. These findings are consistent with previously published data. Prior registry data shows that women represent approximately 30 % of all patients managed by PCI and 25–28 % of stable angina PCI procedures, whereas the proportion of women in CTO PCI registries ranges from 14 to 23 % [11,21–23]. Older age, the presence of more comorbid conditions, frailty and the perception that women are at an increased risk of procedural complications may prevent some interventional cardiologists from offering CTO PCI in female patients [12]. These differences in the utilization of CTO PCI in women suggest that there are systematic biases with a significant

Table 3
Analysis to assess risk of adverse outcomes following multivariate adjustments.

Outcome[a]	Men	Women
On imputed data		
In hospital major bleeding[b], n = 30,075	Reference	OR: 2.06, 95 % CI: 1.62–2.61, P < 0.001
Any procedural complications[c], n = 30,605	Reference	OR: 1.37, 95 % CI: 1.23–1.52, P < 0.001
Coronary artery perforation as procedural complication, n of observations = 30,605	Reference	OR: 1.60, 95 % CI: 1.26–2.04, P < 0.001
In-hospital mortality n of observations = 30,605	Reference	OR: 1.40, 95 % CI: 0.75–2.61, P = 0.29
In-hospital MACCE[d], n of observations = 30,605	Reference	OR: 1.01, 95 % CI: 0.78–1.29, P = 0.96
Complete case analyses (on non-imputed data)		
In hospital major bleeding[b], n = 14,216	Reference	OR: 3.12, 95 % CI: 2.15–4.52, P < 0.001
Any procedural complications[c], n = 14,159	Reference	OR: 1.40, 95 % CI: 1.99–1.64, P < 0.001
Coronary artery perforation as procedural complication, n of observations = 14,159	Reference	OR: 1.72, 95 % CI: 1.24–2.38, P = 0.001
In-hospital mortality n of observations = 14,344	Reference	OR: 1.37, 95 % CI: 0.61–3.06, P = 0.45
In-hospital MACCE[d], n of observations = 14,344	Reference	OR: 0.95, 95 % CI: 0.67–1.34, P = 0.78

CTO; Chronic total occlusion, PCI; Percutaneous Coronary Intervention, SVG; Saphenous Vein Grafts, TVR; Target vessel revascularization, OR; Odds ratio, CI; Confidence interval, n; number for analysis.
OR; odds ratio.
[a] Adjusted for age, radial access, angina class, NYHA class, comorbid conditions (prior history of smoking, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting surgery, hypercholesterolemia, hypertension, peripheral vascular disease, valvular heart disease, diabetes mellitus, renal disease), ejection fraction, family history of coronary artery disease, use of circulatory support, use of drug eluted stents, year of procedure & use of enabling strategies on imputed data.
[b] Major bleeding: need blood or platelets transfusions, haemorrhagic stroke, tamponade, retroperitoneal haemorrhage and access site complication requiring delaying discharge or intervention or surgery.
[c] Any procedural complication includes Aortic dissection, Coronary perforation, Heart block requiring pacing, DC cardioversion, no flow/slow flow phenomenon, need ventilation, Shock induced by procedure.
[d] MACCE; Major adverse cardiovascular & cerebrovascular events (defined as a composite of in-hospital mortality, in-hospital myocardial reinfarction (including Q-wave and Non-Q wave MI), and emergency target vessel revascularization by PCI or CABG, side branch occlusion, Stroke).

Table 4
Propensity score-matched analysis with average treatment effects on imputed data.

Outcome	Group	Coefficient (95 % CI)	Odds ratio[a] (95 % CI)	P value
In hospital major bleeding[b], n = 30,075	Group 1: CTO PCI in men	Reference		
	Group 2: CTO PCI in women	0.0096093 (0.0038515 to 0.0153671)	OR: 2.12 (1.45–2.18)	0.001
Any procedural complications[c] (n = 30,605)	Group 1: CTO PCI in men	Reference		
	Group 2: CTO PCI in women	0.0216076 (0.0097559 to 0.0334593)	OR: 1.52 (1.18–2.10)	<0.001
Perforation-complications (n = 30,605)	Group 1: CTO PCI in men	Reference		
	Group 2: CTO PCI in women	0.0055269 (0.000673 to 0.0103808)	OR: 1.54 (1.06–2.02)	0.002
In-hospital mortality (n = 30,605)	Group 1: CTO PCI In men	Reference		
	Group 2: CTO PCI in women	0.0011403 (−0.0012196 to 0.0035003)	OR: 1.67 (0.28–3.07)	0.34
In-hospital MACCE[d]	Group 1: CTO PCI in women	Reference		
(n = 30,605)	Group 2: CTO PCI in men	−0.0002124 (−0.0050677 to 0.0046429)	OR: 0.98 (0.63–1.34)	P −0.45

CTO; chronic total occlusion, PCI; percutaneous coronary intervention, OR; odds ratio, CI; confidence interval, n; number for analysis, MACCE; major adverse cardiovascular & cerebrovascular events.

[a] Adjusted for age, radial access, angina class, NYHA class, comorbid conditions (prior history of smoking, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting surgery, hypercholesterolemia, hypertension, peripheral vascular disease, valvular heart disease, diabetes mellitus, renal disease), ejection fraction, family history of coronary artery disease, use of circulatory support, use of drug eluted stents, year of procedure & use of enabling strategies on imputed data.

[b] Major bleeding: Need blood or platelets transfusions, haemorrhagic stroke, tamponade, retroperitoneal haemorrhage and access site complication requiring delaying discharge or intervention or surgery.

[c] Any procedural complication includes Aortic dissection, Coronary perforation, Heart block requiring pacing, DC cardioversion, no flow/slow flow phenomenon, need ventilation, Shock induced by procedure.

[d] MACCE; Major adverse cardiovascular & cerebrovascular events (defined as a composite of in-hospital mortality, in-hospital myocardial reinfarction (including Q-wave and Non-Q wave MI), and emergency target vessel revascularization by PCI or CABG, side branch occlusion, Stroke.

unmet need particularly in women with poorly controlled angina despite optimal medical therapy. We observed higher adjusted odds of peri-procedural complications including major bleeding, coronary perforation and renal failure during CTO PCI procedures undertaken in female patients. Bleeding is one of the important peri-procedural complications observed during PCI procedures. A prior CTO analysis has shown that access site complications were more frequent in femoral compared to radial access (1.5 % vs 0.5 %, P < 0.001) and these were associated with significant increase in transfusion (8 % vs 0.1 %, P < 0.001), procedural coronary complications (17.3 % vs 5.8 %, P < 0.001), major bleeding (8.4 % vs 0.3 %, P < 0.001) and 1-year mortality (4.7 % vs 2.3 %, P = 0.001) [24]. Despite the benefits of radial access, there remains a lower uptake of this approach in women [25,26]. The reasons for some of this difference may be difficult to avoid even for experienced operators. Women have an increased rate of radial access failure due to the relatively small radial artery size and greater risk of radial artery spasm. CTO procedures often require large bore guide catheters (7/8 French) to accommodate more procedural adjuncts which is not always possible in women due to the overall smaller radial artery size.

Gender- and sex-related differences in the bleeding risk are well described [27–29]. Data from the Global Registry of Acute Coronary Events (GRACE) showed that women experienced a 43 % higher relative risk of bleeding during the hospitalization as compared to men [30]. This higher risk of bleeding in women might in part be due to the inappropriate dosing of antithrombotic agents, with a lack of adjustment to body weight [31]. Therefore, special attention should be paid to body weight and anti-thrombotics that should be weight-adjusted. Importantly, more potent P2Y12 receptor inhibition with prasugrel and ticagrelor were associated with higher PCI-related bleeding risks in female vs male patients [32,33], indicating these P2Y12 receptor inhibitors should be avoided in the elective PCI setting. Other mechanisms may also contribute to the increased risk of bleeding complications in women.

Sex specific differences and post menopause changes in coagulation and fibrinolysis have been reported, which may lead to an enhanced

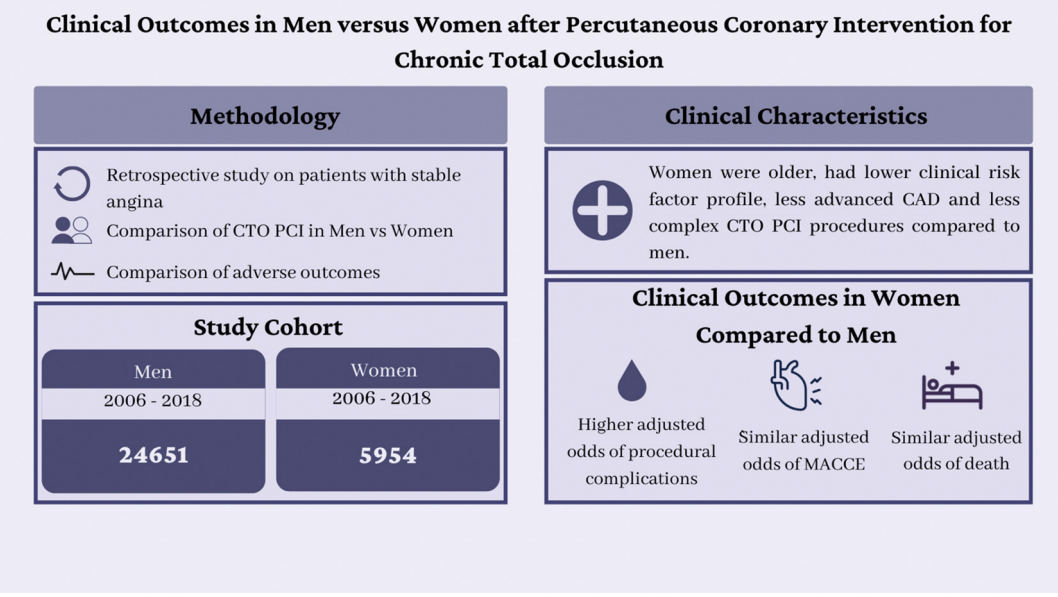

Fig. 3. Central illustration figure.
CTO; Chronic total occlusion, PCI; Percutaneous Coronary Intervention, MACCE; Major adverse cardiovascular & cerebrovascular events.

response to anticoagulants and accompanying excess of bleeding [34]. The increased risk of coronary perforation observed in women may also relate to the vascular effects of estrogen hormone on the arterial tree [35,36] that contribute to arterial fragility and a greater propensity towards coronary perforation. Women undergoing CTO procedures are generally older and are therefore more likely to have calcific coronary disease that increases the risk of coronary perforation, but also less likely to have intravascular imaging, which might translate to underdiagnosed calcific disease, with less accurate stent sizing, therefore increasing the propensity towards perforations [11,21,37].

5. Limitations

This study has several limitations. First, the present study was not a randomised study and data were extracted from a national PCI registry and has all the intrinsic biases attributed to this kind of study design. Second, intraoperative and post procedural complications are self-reported, and do not get formal adjudication, and thus are subject to reporting bias. However, BCIS data are used for publicly reported individual consultant outcomes reports, and all centres and all operators are asked to validate their publicly reported data analysis, so there is a process by which data are re-examined and checked, albeit not independently. Furthermore, this bias should apply both sexes equally and it is unlikely that systematic reporting bias affect one sex more compare to other. Third, the BCIS dataset doesn't record the complexity of CTO lesions according to modern scoring systems (J-CTO or RECHARGE). Fourth, the BCIS database dose not record data regarding procedural time, radiation dose and contrast volume during the CTO PCI procedures. Fifth, BCIS dataset doesn't capture post discharge clinical outcomes and long term follow up data is not available for current cohort. Finally, despite robust multivariable analysis, there is a possibility that unmeasured confounders may contribute to our findings.

6. Conclusion

Our study demonstrates that approximately one in five CTO PCI procedures were undertaken in female patients in contemporary interventional practice in the United Kingdom. Women who received CTO PCI were older, had a different clinical risk factor profile, less advanced CAD and less complex procedures compared to men. We observed higher unadjusted and adjusted odds of procedural complications, coronary artery perforation and major bleeding when CTO PCI was performed in women. However, the clinical endpoints of MACCE and death were similar between the two sexes.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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