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Gender differences in percutaneous coronary intervention for chronic total occlusions from the ERCTO study

Alexandre Avran MD[1] | Andrea Zuffi MD[2] | Cecilia Gobbi MD[2] | Alessio Gasperetti MD[3] | Marco Schiavone MD[4,5] | Gerald S. Werner MD, PhD[6] | Mashayekhi Kambis MD[7] | Nicolas Boudou MD[8] | Alfredo R. Galassi MD[9] | George Sianos MD, PhD[10] | Moussa Idali MD[2] | Roberto Garbo MD[11] | Andrea Gagnor MD[12] | Gabriele Gasparini MD[13] | Alexander Bufe MD[14] | Leszek Bryniarski MD, PhD[15] | Artis Kalnins MD[16] | Daniel Weilenmann MD[17] | Jaroslaw Wojcik MD[18] | Pierfrancesco Agostoni MD[19] | Nenad Z. Bozinovic MD[20] | Mauro Carlino MD[21] | Sergey Furkalo MD[22] | David Hildick-Smith MD[23] | Laurent Drogoul MD[24] | Julien Lemoine MD[25] | Antonio Serra MD, PhD[26] | Stefano Carugo MD[27] | Imre Ungi MD[28] | Joseph Dens MD[29] | Nicolaus Reifart MD, PhD[30] | Joseph Cosma MD[2] | Vincenzo Mallia MD[27] | Giuseppe Vadalà MD[31] | Giuseppe Biondi-Zoccai MD, PhD[32,33] | Carlo Di Mario MD, PhD[34]

[1]Centre Hospitalier de Valenciennes, Valenciennes, France

[2]Cardiology Unit, Saint Martin Private Hospital Center, Caen, France

[3]Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[4]Cardiology Unit, ASST Fatebenefratelli Sacco—Luigi Sacco, University Hospital, University of Milan, Milan, Italy

[5]Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

[6]Medizinische Klinik I Klinikum Darmstadt, Darmstadt, Germany

[7]Division of Cardiology and Angiology II, University Heart Center Freiburg-Bad Krozingen, Bad Krozingen, Germany

[8]Interventional Cardiology, Clinique Saint Augustin, Bordeaux, France

[9]Department of Promise, Cardiovascular Medicine, University of Palermo, Palermo, Italy

[10]AHEPA University Hospital, Thessaloniki, Greece

[11]Maria Pia Hospital, GVM Care & Research, Turin, Italy

[12]Department of Invasive Cardiology, Maria Vittoria Hospital, Turin, Italy

[13]Department of Invasive Cardiology, Humanitas Clinical and Research Center, IRCCS, Rozzano, Italy

[14]Heart Center Krefeld, University Witten/Herdecke, Witten, Germany

[15]II Department of Cardiology and Cardiovascular Interventions, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

[16]Clinic of Cardiovascular Diseases, Riga East Clinical University Hospital, Riga, Latvia

[17]Cardiology, Cantonal Hospital St Gallen, Sankt Gallen, Switzerland

[18]Hospital of Invasive Cardiology IKARDIA, Lublin, Poland

[19]HartCentrum, Ziekenhuis Netwerk Antwerpen (ZNA) Middelheim, Antwerp, Belgium

[20]University Clinical Niš, Niš, Serbia

[21]Cardio-Thoracic-Vascular Department, Interventional Cardiology Unit, IRCCS, San Raffaele Scientific Institute, Milan, Italy

[22]National Institute of Surgery and Transplantology NAMS, Kiev, Ukraine

[23]Sussex Cardiac Centre, Brighton, UK

[24]Clinique Saint George, Nice, France

[25]Department of Cardiology, Clinique Louis Pasteur, Nancy, France

[26]Department of Cardiology, Interventional Cardiology Unit, Hospital de la Santa Creu i Sant Pau, University of Barcelona, Barcelona, Spain

[27]Department of Cardiology, Fondazione IRCCS Ospedale Maggiore Policlinico di Milano and Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[28]Department of Invasive Cardiology, University of Szeged, Szeged, Hungary

[29]Hospital Oost-Limburg, Genk, Belgium

[30]Department of Cardiology, Main Taunus Heart Institute, Bad Soden, Germany

[31]Division of Cardiology, University Hospital "P. Giaccone", Palermo, Italy

[32]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

[33]Mediterranea Cardiocentro, Napoli, Italy

[34]Department of Clinical & Experimental Medicine, University Hospital Careggi, Florence, Italy

Correspondence
Cecilia Gobbi, MD, Cardiology Unit, Saint Martin Private Hospital Center, 18 Rue des Roquemonts, 14000 Caen, France.
Email: cecilia_gobbi@hotmail.it

Abstract

Background: Gender-specific data addressing percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) in female patients are scarce and based on small sample size studies.

Aims: We aimed to analyze gender-differences regarding in-hospital clinical outcomes after CTO-PCI.

Methods: Data from 35,449 patients enrolled in the prospective European Registry of CTOs were analyzed. The primary outcome was the comparison of procedural success rate in the two cohorts (women vs. men), defined as a final residual stenosis less than 20%, with Thrombolysis In Myocardial Infarction grade flow = 3. In-hospital major adverse cardiac and cerebrovascular events (MACCEs) and procedural complications were deemed secondary outcomes.

Results: Women represented 15.2% of the entire study population. They were older and more likely to have hypertension, diabetes, and renal failure, with an overall lower J-CTO score. Women showed a higher procedural success rate (adjusted OR [aOR] = 1.115, confidence interval [CI]: 1.011–1.230, $p = 0.030$). Apart from previous myocardial infarction and surgical revascularization, no other significant gender differences were found among predictors of procedural success. Antegrade approach with true-to-true lumen techniques was more commonly used than retrograde approach in females. No gender differences were found regarding in-hospital MACCEs (0.9% vs. 0.9%, $p = 0.766$), although a higher rate of procedural complications was observed in women, such as coronary perforation (3.7% vs. 2.9%, $p < 0.001$) and vascular complications (1.0% vs. 0.6%, $p < 0.001$).

Conclusions: Women are understudied in contemporary CTO-PCI practice. Female sex is associated with higher procedural success after CTO-PCI, yet no sex differences were found in terms of in-hospital MACCEs. Female sex was associated with a higher rate of procedural complications.

KEYWORDS
chronic total occlusion, female sex, gender differences, major adverse cardiac and cerebrovascular events, percutaneous coronary intervention

1 | INTRODUCTION

Sex differences may influence presentations, outcomes, and management of coronary artery disease (CAD).[1] Nevertheless, studies and registries focused on sex-related differences in chronic total occlusion (CTO) undergoing revascularization are scarce, and women appear to be underrepresented in CTO procedures, accounting only for 14%–21% of patients included in CTO registries and trials.[2] It has been postulated that women with CTOs are preferably managed with conservative medical therapy (MT) alone, rather than with invasive strategies (percutaneous coronary intervention [PCI] or coronary artery bypass graft, [CABG]).[3]

Several studies have demonstrated that CTO PCI success rate is overall comparable among the two genders.[4–6] Despite a less complex anatomy, procedural complications have been observed in females undergoing CTO revascularization more frequently.[7] Besides that, an increase of complex percutaneous revascularization procedures in women has been described over the last decade.[8] Therefore, aim of our study was to identify sex-related differences in both baseline and procedural characteristics, in relation to procedural success, as well as in-hospital clinical outcomes after CTO-PCI, analyzing data from a large, prospective, multicenter, real-world CTO registry (the European Registry of CTOs [ERCTO]).

2 | METHODS

2.1 | Design and study population

All data were collected from the prospective ERCTO, which is currently the largest multicenter prospective real-world CTO registry, including more than 35,000 patients treated by expert operators at several centers across Europe. All patients included in this registry have been treated for one or more CTO lesions, involving a main coronary artery (>2.5 mm) or a bypass conduit. The registry structure has been already described elsewhere.[9,10] Briefly, data collection was carried out at 85 centers across Europe and all patients undergoing CTO PCI at these centers were prospectively enrolled from January 1, 2008 to the end of December, 2019. There were no specific exclusion criteria. Treatment indications were symptomatic myocardial ischemia and/or evidence of reversible myocardial ischemia and/or viability demonstration in case of akinesia in the CTO territory, documented by perfusion imaging or stress testing. This manuscript complies with each institutional review board's policy and with local national regulations. The study was performed in accordance with the Helsinki declaration.

2.2 | Definitions

Coronary CTO was defined as a Thrombolysis In Myocardial Infarction (TIMI) grade 0 flow within the occluded segment, with an estimated duration of at least 3 months.[9] Angina was assessed according to the Canadian Cardiovascular Society (CCS) classification. Procedural success was defined as a final residual stenosis less than 20%, with a TIMI grade flow 3.[9] Major adverse cardiac and cerebrovascular events (MACCEs) were defined as a composite of cardiac death, myocardial infarction (MI), stroke, stent thrombosis, and further need for target vessel revascularization (TVR).[11] Stent thrombosis was defined according to the definition of the Academic Research Consortium. Major bleeding was defined as a hemoglobin level reduction >3 g/dL or need of blood transfusion. Vascular complications were defined as femoral or radial artery hematoma requiring intervention or prolonged hospital stay, occlusion, embolization, dissection, pseudoaneurysm, and arteriovenous fistula. A procedure-related contrast-induced nephropathy (CIN) was defined as an increase of 25% or 0.5 mg/dL in serum creatinine at 48 h after PCI, compared with baseline values.[12]

2.3 | Angiographic procedures

All procedures were performed according to the Euro CTO Club Consensus.[13] Choice of CTO revascularization strategy was left to the operator's discretion, accounting for the angiographic lesions' characteristics and their personal skills. Sequence of use of guidewire, microcatheter or stent was completely dependent on the operator's judgment, to perform the most appropriate CTO technique. The complexity of CTO lesion was assessed using the Japanese CTO (J-CTO) score (0 = easy, 1 = intermediate, 2 = difficult, ≥3 = very difficult).[14] CTO PCIs with retrograde approach were included either as a first-attempt procedures or as a bail-out strategy after prior failed antegrade attempts. Several strategies were used, including the antegrade single-wire technique, the parallel-wires technique, the antegrade dissection and re-entry technique, and retrograde wiring through collateral vessels, such as simple retrograde wiring, kissing wires, the knuckle technique, the controlled antegrade retrograde tracking (CART) and the reverse controlled antegrade and retrograde tracking (reverse CART).

2.4 | Data collection and study outcomes

The investigators collected data regarding demographics, personal medical history, cardiovascular risk factors, procedural and periprocedural information. In-hospital details regarding MACCE occurrence were collected by physicians through the revision of clinical source documentation. All data were centralized in a de-identified database. Patients were divided into two different cohorts, according to their gender (women vs. men). The primary outcome of our study was the comparison of procedural success rate in the two cohorts, defined as a final residual stenosis less than 20%, with TIMI grade flow = 3. In-hospital MACCEs and procedural complications, defined as coronary perforations, major bleedings, and vascular complications, were deemed secondary outcomes.

2.5 | Statistical analysis

Normality of distribution of all continuous variables was tested with a Shaphiro–Wilk test. Continuous variables were reported as mean ± standard deviation (s.d.) or as median [inter-quartile range (1st–3rd quartile)] if normally or nonnormally distributed, respectively. Categorical variables were reported as count (%). Comparisons have been performed using a χ^2 test or a Fisher's exact test between categorical variables, and a Student's *t*-test or a Mann–Whitney U test between numerical variables, as appropriate according to their distribution. A logistic regression was performed to assess the associations between baseline and procedural characteristics and clinical outcomes. Univariable analyses were performed at first; all variables reaching a threshold *p* value 0.10 were then fit into a multivariable model to adjust for confounders. An additional logistic regression was performed stratifying by patient sex, to assess whether per-group specific outcome predictors were present. The output was reported as odds ratios (OR) or adjusted OR (aORs). A two-sided *p* value < 0.05 was considered significant throughout the manuscript. Analysis has been performed using STATA v. 14.0 (StataCorp LLC).

3 | RESULTS

3.1 | Sex differences in baseline characteristics

Women represented 15.2% (*n* = 5389/35,449) of the entire cohort, with an increasing trend of enrollment during the most recent timeframes of the study (15.3% in 2008–2010, 15.0% in 2010–2013, 17.0% in 2014–2016 and 18.0% in the years 2016–2019). Women were older (67.9 ± 10.3 vs. 64.0 ± 10.5 years, $p < 0.001$) and more likely to suffer from hypertension (80.6% vs. 74.1%, $p < 0.001$), diabetes (34.7% vs. 28.9%, $p < 0.001$). A normal left ventricular ejection fraction (73.8% vs. 69.6%, $p < 0.001$) and a lower estimated glomerular filtration rate (64.8 ± 26.1 vs. 75.7 ± 30.5 mL/min/1.73 m^2, $p < 0.001$) were more common in the female cohort. Moreover, women (25.4%) were more likely (21.1%) to report severe angina symptoms (CCS class III or IV, $p < 0.001$). Women showed a lower prevalence of prior MI (32.3% vs. 36.4%, $p < 0.001$), previous PCI and previous CABG, and a lower rate of three-vessel disease when compared with men. Complete baseline characteristics of the entire cohort have been reported in Table 1.

3.2 | CTO localizations and angiographic characteristics

The right coronary artery (RCA) was the most frequent target of CTO revascularization, with no significant differences (54.5% vs. 53.4%, $p = 0.149$) between the two groups. Women presented an overall lower J-CTO score (2.02 ± 1.26 vs. 2.23 ± 1.27, $p < 0.001$). Specifically, they were more likely to present tapered stumps in the CTO proximal cap (45.1% vs. 40.8%, $p = 0.011$), a shorter lesion length (25.5 ± 14.2 mm vs. 28.1 ± 15.3 mm, $p < 0.001$), and fewer moderate-to-severe calcifications (40.1% vs. 43.1%, $p < 0.001$). According to collateral connection (CC) grade estimation, women showed thread-like collateral connections (CC1 43.5% vs. 40.2%, $p < 0.001$) more frequently, while men presented a higher rate of side-branch like connections (CC2) (34.7% vs. 32.9%, $p = 0.009$). Angiographic characteristics of the entire cohort have been reported in Table 2.

3.3 | CTO procedural characteristics and techniques

A primarily antegrade approach was the preferential strategy in female patients (81.3% vs. 76.0% $p = 0.002$), while retrograde and hybrid approach in their counterpart male patients (24.0% vs. 18.7%, $p < 0.001$). In both strategies, true-to-true lumen techniques were more often employed to recanalize CTO in females, while dissection-reentry techniques were used in male patients more often. Total contrast volume (230.5 ± 134.0 vs. 258.6 ± 150.1 mL, $p < 0.001$), fluoroscopic time (33.3 ± 27.3 vs. 39.0 ± 31.7, $p < 0.001$), as well as overall procedural time (100.0 ± 52.0 vs. 109.7 ± 58.3, $p < 0.001$) were significantly lower in females. Procedural characteristics have been summarized in Table 3.

3.4 | Primary and secondary outcomes: Differences and predictors

Regarding the primary outcome, CTO recanalization rate was higher in women (87.3% vs. 86.3%, $p = 0.046$). As for secondary outcomes, no significant differences in terms of in-hospital MACCEs were detected among the two cohorts (0.9% vs. 0.9%, $p = 0.766$). Procedural complications, such as coronary perforation (3.7% vs. 2.8%, $p < 0.001$), vascular complications (1.0% vs. 0.6%, $p < 0.001$) and major bleeding (0.4% vs. 0.2%, $p < 0.001$) were more likely to occur in females. No significant gender differences were found in the incidence of CIN (0.8% vs. 0.6%, $p = 0.056$). The complete analysis of study outcomes has been reported in Table 3.

The impact of baseline and procedural characteristics on primary and secondary outcomes was tested through univariable and multivariable regression analysis (Figure 1). Female sex was an independent predictor of CTO recanalization success both at univariate (OR 1.092, CI 1.001–1.191, $p = 0.046$) and multivariate analysis (OR 1.115, CI 1.011–1.230, $p = 0.030$) (Table 4). Besides the influence of gender, estimated diameter vessel, a tapered stump (OR 2.149, CI 1.986–2.325, $p < 0.001$) and the use of 7/8F guiding catheter were independent predictors of procedural success as well. On the other hand, older age, previous MI, CABG, retrograde approach (OR 0.555 [0.514–0.599], $p < 0.001$), ostial occlusion, presence of moderate to severe calcifications, occlusion length, and in-CTO bend were all found to be independent predictor of procedural failure. Interestingly, when stratifying by sex, no

TABLE 1 Baseline characteristics of the study cohort.

35,449 total patients	Men (=30,060)	Women (=5389)	*p*
Age (years), mean ± s.d.	64.0 ± 10.5	67.9 ± 10.3	**<0.001**
Body mass index (kg/m^2), mean ± s.d.	28.7 ± 9.5	28.5 ± 12.5	<0.272
Family history of CAD, *n* (%)	8992 (29.9%)	1687 (31.3%)	**0.040**
Hypertension, *n* (%)	22,282 (74.1%)	4345 (80.6%)	**<0.001**
Dyslipidemia, *n* (%)	22,086 (73.5%)	3998 (74.2%)	0.273
Diabetes, *n* (%)			
Insulin dependent	2969 (9.9%)	730 (13.6%)	**<0.001**
Non-insulin dependent	5710 (19%)	1138 (21.1%)	<**0.001**
Former or current smoker, *n* (%)	16,930 (56.3%)	1903 (35.3%)	**<0.001**
Peripheral artery disease, *n* (%)	3059 (10.2%)	553 (10.3%)	0.849
eGFR (mL/min), mean ± s.d	75.7 ± 30.5	64.8 ± 26.1	**<0.001**
Prior stroke, *n* (%)	814 (2.7%)	189 (3.5%)	**<0.001**
CCS III/IV, *n* (%)	6338 (21.1%)	1371 (25.4%)	**<0.001**
Previous MI, *n* (%)	10,935 (36.4%)	1739 (32.3%)	**<0.001**
Previous PCI, *n* (%)	15,001 (49.9%)	2412 (44.8%)	**<0.001**
Previous CABG, *n* (%)	3914 (13.0%)	573 (10.6%)	**<0.001**
LVEF, *n* (%)			
<35%	2105 (7.0%)	310 (5.8%)	**0.008**
35%–50%	6368 (21.2%)	985 (18.3%)	<**0.001**
≥50%	20,908 (69.6%)	3978 (73.8%)	<**0.001**
NA	679 (2.3%)	116 (2.2%)	0.627
Number vessel disease, *n* (%)			
One-vessel disease	11,196 (37.3%)	2297 (42.6%)	**<0.001**
Two-vessel disease	9182 (30.6%)	1604 (29.8%)	0.251
Three-vessel disease	9545 (31.8%)	1472 (27.3%)	**<0.001**
CTO artery, *n* (%)			
Bypass venous	314 (1.0%)	36 (0.7%)	**0.010**
Bypass arterial	19 (0.1%)	4 (0.1%)	0.770
Main secondary branches	1136 (3.8%)	150 (2.8%)	**0.003**
Right coronary artery	16,063 (53.4%)	2937 (54.5%)	0.149
Left anterior descending	7503 (25.0%)	1490 (27.7%)	**<0.001**
Left circumflex coronary	4784 (15.9%)	727 (13.5%)	**<0.001**
Left main	160 (0.5%)	16 (0.3%)	**0.023**

Note: Bold values are statistically significant.

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CTO, coronary total occlusion; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention.

differences in procedural success predictors related to CTO characteristics have been found; only 2 baseline characteristics (previous MI and CABG) resulted significantly and negatively associated with the primary outcome in males, but not in females.

Besides older age, dyslipidemia, retrograde approach, a higher J-CTO score, distal vessel disease, occlusion length, lower vessel diameter and presence of calcifications, female sex has been found to be an independent predictor of coronary perforations at multivariate

TABLE 2 CTO lesion anatomic and angiographic characteristics.

	Men	Women	p
J CTO Score, mean ± s.d.	2.23 ± 1.27	2.02 ± 1.26	**<0.001**
J CTO 0	1889 (9.6%)	475 (13.2%)	<**0.001**
J CTO 1	3952 (20.1%)	822 (22.9%)	
J CTO 2	5.416 (27.5%)	981 (27.3%)	
J CTO 3	5074 (25.8%)	830 (23.1%)	
J CTO 4	2791 (14.2%)	428 (11.9%)	
J CTO 5	550 (2.8%)	56 (1.6%)	
Visual estimation diameter (mm), mean ± s.d.	2.8 ± 0.7	2.7 ± 0.7	**<0.001**
Visual estimation length (mm), mean ± s.d.	28.1 ± 15.3	25.5 ± 14.2	**<0.001**
Collateral filling, *n* (%)			
Only bridging	16 (0.1%)	2 (0.1%)	0.284
Contralateral	13,872 (46.2%)	2509 (46.6%)	0.587
Ipsilateral	6781 (22.6%)	1217 (22.6%)	0.968
Ipsi- and contralateral	7360 (24.5%)	1287 (23.9%)	0.343
Collateral Connection (CC), *n* (%)			
N/A	4098 (13.6%)	664 (12.3%)	0.009
CC0	3458 (11.5%)	610 (11.3%)	0.696
CC1	12,072 (40.2%)	2344 (43.5%)	**<0.001**
CC2	10,432 (34.7%)	1771 (32.9%)	**0.009**
In CTO bend, *n* (%)			
<45°	24,512 (80.7%)	4383 (81.3%)	**0.025**
≥45°	5548 (18.5%)	1006 (18.7%)	0.713
Calcification, *n* (%)			
None/mild	17,104 (56.9%)	3226 (59.9%)	<**0.001**
Moderate/severe	12,956 (43.1%)	2163 (40.1%)	<**0.001**
Stump, *n* (%)			
Blunt stump	12,067 (40.1%)	1924 (35.7%)	<**0.001**
Tapered stump	17,993 (59.9%)	3465 (64.3%)	**0.011**

Note: Bold values are statistically significant.

Abbreviations: CC, collateral connection; CTO, chronic total occlusion; N/A, not available.

analysis (OR 1.268 [1.040–1.545], $p = 0.018$). Female sex was also found to be independently associated with vascular complications (OR 1.822 [1.330–2.498], $p < 0.001$). When stratifying by sex, a retrograde approach, the presence of peripheral artery disease, and the use of guiding catheter greater than 6 Fr were independent predictors of vascular complications in females. The whole output of the regression analysis has been reported in Tables 5 and 6.

4 | DISCUSSION

This study from the ERCTO registry currently represent the largest analysis assessing gender differences in CTO-PCI.

The main results from our study are as follows (Central image 1):

1. Women represented 15.2% of the entire cohort and showed a slightly higher procedural success when compared to men (87.3% vs. 86.3%, $p = 0.046$).
2. Female sex was an independent predictor of CTO recanalization success both at univariate (OR 1.092, CI 1.001–1.191, $p = 0.046$) and multivariate analysis (OR 1.115, CI 1.011–1.230, $p = 0.030$).
3. A gender-stratified analysis showed no differences in procedural success predictors related to coronary anatomy or CTO characteristics in the two study cohorts.
4. In-hospital MACCEs after a CTO procedure were similar in the two different study cohorts (0.9% vs. 0.9%, $p = 0.766$).

TABLE 3 CTO procedure characteristic, in-hospital outcome and complications.

	Men	Women	*p*
Radial Access, *n* (%)	11,600 (38.6%)	1902 (35.3%)	**<0.001**
Contralateral injection, *n* (%)	19,301 (64.2%)	3268 (60.6%)	**<0.001**
Guiding catheter (Fr), *n* (%)			
5/6 Fr	10,522 (35%)	2296 (42.6%)	**< 0.001**
7/8 Fr	19,259 (64.1%)	3037 (56.3%)	**<0.001**
N° DES, mean ± s.d.	2.0 ± 1.3	1.8 ± 1.2	**<0.001**
Total length DES (mm), mean ± s.d.	56.2 ± 37.1	49.9.1 ± 33.6	**<0.001**
Max diameter DES (mm), mean ± s.d.	3.2 ± 0.5	3.0 ± 0.4	**<0.001**
Final success, *n* (%)	25,953 (86.3%)	4707 (87.3%)	**0.046**
Procedural time (min.), mean ± s.d.	109.7 ± 58.3	100.0 ± 52.0	**<0.001**
Fluoroscopic time (min.), mean ± s.d.	39.0 ± 31.7	33.3 ± 27.3	**<0.001**
Dye (mL), mean ± s.d.	258.6 ± 150.1	230.5 ± 134.0	**<0.001**
Antegrade approach, *n* (%)	22,316 (76.0%)	4107 (81.3%)	**0.002**
Single wire, step up/step down, parallel wire (%)	16,618 (74.5%)	3220 (78.4%)	**<0.001**
Dissection re-entry primarily or provisional, STAR*, *n* (%)	3793 (16.9%)	607 (14.8%)	0.082
Retrograde/hybrid approach, *n* (%)	7080 (24.0%)	943 (18.7%)	**<0.001**
Wire crossing, touching wire, n (%)	3735 (52.7%)	572 (60.6%)	**<0.001**
Reversed CART, CART**, *n* (%)	3345 (47.2%)	371 (39.3%)	**<0.001**
In-hospital outcome			
MACCEs, *n* (%)	269 (0.9%)	46 (0.9%)	0.766
Cardiac death, *n* (%)	60 (0.2%)	9 (0.2%)	0.617
MI, *n* (%)	139 (0.5%)	24 (0.5%)	0.865
Re-PCI, *n* (%)	32 (0.1%)	4 (0.1%)	0.342
Emergency CABG, *n* (%)	14 (0.1%)	4 (0.1%)	0.407
Stent thrombosis, *n* (%)	33 (0.1%)	3 (0.1%)	0.251
Stroke, *n* (%)	16 (0.1%)	3 (0.1%)	0.943
Procedural complication			
Coronary perforation, *n* (%)	833 (2.8%)	198 (3.7%)	**<0.001**
Dissection/thrombus of donor artery, *n* (%)	221 (0.7%)	49 (0.9%)	0.176
Vascular complications, *n* (%)	172 (0.6%)	54 (1.0%)	**<0.001**
Major bleeding (Hb<3 g/dL), *n* (%)	56 (0.2%)	22 (0.4%)	**0.001**
Prolonged hospitalization, *n* (%)	72 (0.2%)	2 (0.4%)	**0.047**
CIN, *n* (%)	183 (0.6%)	45 (0.8%)	0.056

Note: Bold values are statistically significant.

Abbreviations: CABG, coronary artery bypass graft; CART**, controlled antegrade and retrograde tracking; CIN, contrast induced nephropathy; CTO, chronic total occlusion; DES, drug eluting stent; Fr, French, N/A, not available; MACCEs (death, MI, rePCI, stent thrombosis, stroke), major adverse cardiac cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; STAR*, subintimal tracking and reentry.

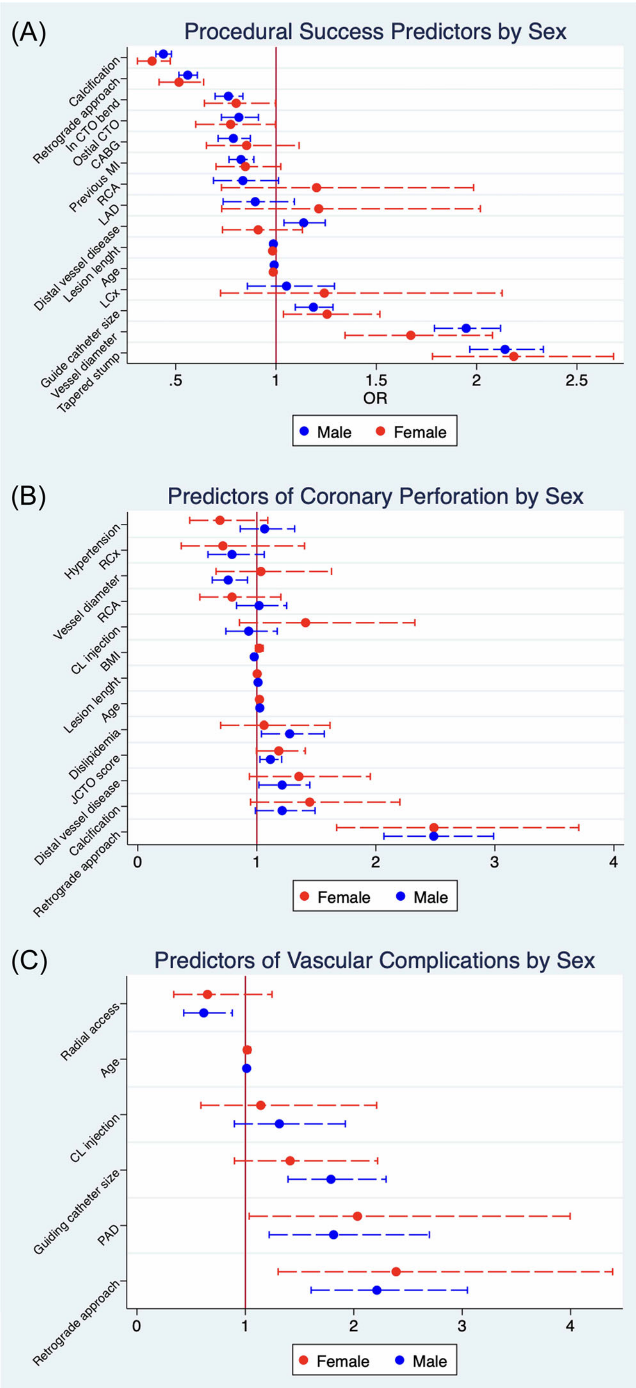


FIGURE 1 (A) Multivariate predictors of procedural success stratified by sex (male = blue; female = red). (B) Multivariate predictors of coronary perforation stratified by sex (male = blue; female = red). (C) Multivariate predictors of vascular complications stratified by sex (male = blue; female = red). BMI, body mass index; CABG, coronary artery bypass graft; CL, contralateral; CTO, coronary total occlusion; LAD, left anterior descending; LCX, left circumflex coronary; MI, myocardial infarction; PAD, peripheral artery disease; RCA, right coronary artery. [Color figure can be viewed at wileyonlinelibrary.com]

5. Procedural complications, defined as coronary perforation, overall vascular complications, and major bleedings were more likely to occur in women than in men.

4.1 | Women and CTO: Truly underrepresented and undertreated?

In our study, women represented the 15.2% of the entire cohort. When comparing our results to the other largest CTO trials, it should be reported that, in the EUROCTO trial, enrolling 396 symptomatic patients with at least one CTO (randomized to PCI plus optimal MT vs. optimal MT alone), women accounted for 17% vs. 14% of CTO patients in the two cohorts, respectively.[15] Moreover, in the DECISION-CTO trial, enrolling 834 patients who were randomized to PCI vs. OMT, women accounted for 17% and 19% of patients in both groups.[16] However, these rates merely describe what percentage of CTO patients enrolled in these studies were females. Whether women underrepresentation in CTO registries is due to a real lower prevalence of CTO in women or just due to a referral selection bias is still unclear. Indeed, to properly evaluate CTO rates in women, it would be necessary to either perform cardiac computed tomography angiographies or cardiac catheterizations on large cohorts of women, or to reexamine several female coronary angiographies, and then reporting how many were noted to show CTOs in comparison to their male counterparts, which is obviously beyond the scope of our study. Thus, if the lower rate of women with CTOs reported in our study and in pre-existing studies represents only a poor recruitment or referral for invasive treatment strategies, might not be excluded completely, since this data is subject to several bias related to trials and studies design. However, it should be underlined that the strength of our report relies in the extensive number of patients enrolled in a prospective real-word registry, that may have mitigated a certain selection bias, at least to some extent, thus reflecting most patients being referred for CTO in general practice patterns more accurately. Finally, this finding needs to be confirmed in futures studies to give a definite answer.

Interestingly, significant gender differences were observed in clinical presentation, with women being older and reporting more cardiovascular comorbidities such as diabetes, hypertension and renal failure and severe symptoms, as documented by differences in CCS class. It is indeed well-known that women tend to show delayed medical presentations, both in chronic and in acute coronary syndrome settings, resulting in underdiagnosis and subsequent undertreatment of cardiac events. Moreover, despite a similar CAD severity, women are also more likely to be medically managed and less likely to be referred for PCI or CABG than men.[1,17] This latter clarification may partially explain why women are still underrepresented in worldwide registries and trials, as also our findings suggest. Thus, the higher number of CTO CABG lesions in the male counterparts and the lower J-CTO score in women, leading to

TABLE 4 Predictors of procedural success.

	Univariate			Multivariate			Male multivariate			Female multivariate		
	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*
Age	0.989	[0.986–0.992]	**<0.001**	0.990	[0.987–0.993]	**<0.001**	0.991	[0.987–0.994]	**<0.001**	0.896	[0.977–2.995]	**0.003**
Female sex	1.092	[1.001–1.191]	**0.046**	1.115	[1.011–1.230]	**0.030**						
Hypertension	0.979	[0.911–1.053]	0.577									
BMI	0.998	[0.995–1.001]	0.161									
Diabetes	0.950	[0.880–1.025]	0.189									
Previous MI	0.857	[0.804–0.912]	**<0.001**	0.829	[0.773–0.889]	**<0.001**	0.825	[0.766–0.890]	**<0.001**	0.847	[0.701–1.124]	0.086
CABG	0.614	[0.566–0.667]	**<0.001**	0.798	[0.725–0.877]	**<0.001**	0.787	[0.710–0.872]	**<0.001**	0.853	[0.753–1.115]	0.245
LAD	1.170	[1.089–1.258]	**<0.001**	0.931	[0.775–1.119]	0.449	0.896	[0.736–1.092]	0.276	1.213	[0.729–2.019]	0.457
LCX	1.373	[1.253–1.505]	**<0.001**	1.071	[0.885–1.297]	0.481	1.052	[0.857–1.291]	0.625	1.241	[0.724–2.127]	0.433
RCA	0.842	[0.792–0.895]	**<0.001**	0.874	[0.730–1.047]	0.144	0.835	[0.688–1.012]	0.067	1.202	[0.728–1.985]	0.472
Ostial CTO	0.647	[0.592–0.707]	**<0.001**	0.806	[0.727–0.894]	**<0.001**	0.815	[0.728–0.912]	**<0.001**	0.774	[0.600–0.997]	**0.048**
Retrograde ap.	0.472	[0.442–0.504]	**<0.001**	0.555	[0.514–0.599]	**<0.001**	0.560	[0.516–0.608]	**<0.001**	0.516	[0.416–0.639]	**<0.001**
Calcifications	0.392	[0.365–0.420]	**<0.001**	0.430	[0.396–0.466]	**<0.001**	0.438	[0.401–0.478]	**<0.001**	0.382	[0.309–0.472]	**<0.001**
J-CTO score	0.647	[0.625–0.668]	**<0.001**									
Occl. lenght	0.979	[0.977–0.981]	**<0.001**	0.986	[0.984–0.988]	**<0.001**	0.987	[0.984–0.989]	**<0.001**	0.982	[0.977–0.989]	**<0.001**
Dist vesl dis	0.848	[0.789–0.910]	**<0.001**	1.023	[0.864–1.200]	**0.465**	1.138	1.039-1.245	0.005	0.911	0.733 1.131	0.400
Vessel diam	1.443	[1.393–1.495]	**<0.001**	1.906	[1.762–2.062]	**<0.001**	1.947	[1.790–2.119]	**<0.001**	1.671	[1.344–2.079]	**<0.001**
Catheter 7/8F	1.120	[1.052–1.193]	**<0.001**	1.196	[1.111–1.286]	**<0.001**	1.187	[1.096–1.284]	**<0.001**	1.254	[1.037–1.517]	**0.020**
Stump tapered	2.735	[2.547–2.938]	**<0.001**	2.149	[1.986–2.325]	**<0.001**	2.141	[1.965–2.332]	**<0.001**	2.185	[1.780–2.682]	**<0.001**
In CTO-bend	0.678	[0.630–0.729]	**<0.001**	0.769	[0.707–0.837]	**<0.001**	0.762	[0.696–0.835]	**<0.001**	0.801	[0.643–0.998]	**0.048**

Note: Bold values are statistically significant.

Abbreviations: ap., approach; BMI, body mass index; CABG, coronary artery bypass graft; CTO, chronic total occlusion; Dist. Ves. Dis., distal vessel disease; diam., diameter; LAD, left anterior descending; LCX, left circumflex coronary; MI, myocardial infarction; occl., occlusion; RCA, right coronary artery.

TABLE 5 Predictors of Coronary Perforations.

	Univariate			Multivariate			Male multivariate			Female multivariate		
	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*
Age	1.024	[1.018 –1.030]	**<0.001**	1.025	[1.017–1.033]	**<0.001**	1.026	[1.017–1.035]	**<0.001**	1.023	[1.003–1.042]	**0.022**
Female sex	1.338	[1.143 –1.567]	**<0.001**	1.268	[1.040–1.545]	**0.018**						
BMI	0.988	[0.976 –0.999]	**0.048**	0.989	[0.973–1.004]	0.167	0.979	[0.960–1.023]	0.632	1.020	[0.988–1.053]	0.218
eGFR	1.000	[0.999 –1.000]	0.403									
Diabetes	0.999	[0.853 –1.169]	0.989									
Dyslipidemia	1.209	[1.043 –1.401]	**<0.011**	1.230	[1.023–1.479]	**0.027**	1.276	[1.039–1.567]	**0.020**	1.061	[0.697–1.614]	0.783
Hypertension	1.222	[1.046 –1.426]	**<0.011**	0.992	[0.818–1.203]	0.935	1.065	[0.861–1.318]	0.558	0.690	[0.437–1.092]	0.113
LAD	0.900	[0.777–1.041]	0.156									
LCX	0.702	[0.579 –0.852]	**<0.001**	0.787	[0.602–1.030]	0.082	0.792	[0.590–1.062]	0.120	0.715	[0.365–1.401]	0.329
RCA	1.316	[1.160 –1.494]	**<0.001**	0.975	[0.811–1.172]	0.788	1.019	[0.830–1.251]	0.856	0.792	[0.521–1.202]	0.274
Contralateral injection	1.609	[1.398 –1.851]	**<0.001**	1.008	[0.818–1.241]	0.944	0.932	[0.741–1.171]	0.544	1.410	[0.854–2.328]	0.179
Retrograde approach	2.818	[2.485 –3.195]	**<0.001**	2.480	[2.098–2.931]	**<0.001**	2.486	[2.068–2.989]	**<0.001**	2.488	[1.671–3.705]	**<0.001**
J-CTO	1.369	[1.290 –1.452]	**<0.001**	1.126	[1.046–1.212]	**0.002**	1.114	[1.027–1.209]	**0.009**	1.185	[1.018–1.407]	**0.046**
Distal vessel disease	1.690	[1.477 –1.933]	**<0.001**	1.239	[1.057–1.451]	**0.008**	1.213	[1.017–1.445]	**0.032**	1.354	[0.938–1.954]	0.106
Visual estimated length	1.017	[1.013–1.020]	**<0.001**	1.009	[1.004–1.014]	**<0.001**	1.010	[1.005–1.016]	**<0.001**	1.003	[0.990–1.016]	0.626
Visual estimated diameter	1.087	[0.991–1.189]	**0.074**	0.797	[0.667–0.952]	**0.012**	0.760	[0.626–0.922]	**0.005**	1.034	[0.657–1.627]	0.884
Calcifications	2.033	[1.768–2.338]	**0.001**	1.250	[1.039–1.503]	**0.018**	1.213	[1.017–1.490]	**0.046**	1.445	[1.048–2.202]	**0.048**

Note: Bold values are statistically significant.

Abbreviations: BMI, body mass index; CTO, chronic total occlusion; GFR, glomerular filtration rate; LAD, left anterior descending; LCX, left circumflex coronary; RCA, right coronary artery.

TABLE 6 Predictors of vascular complications.

	Univariate			Multivariate			Male multivariate			Female multivariate		
	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*
Age	1.015	[1.002–1.028]	**0.020**	1.013	[0.999–1.026]	0.058	1.011	[0.997–1.027]	0.128	1.017	[0.989–1.046]	0.235
Female	1.759	[1.294–2.391]	**<0.001**	1.822	[1.330–2.498]	**<0.001**						
BMI	0.990	[0.967–1.015]	0.432									
eGFR	1.000	[0.999–1.000]	0.931									
Diabetes	1.010	[0.726–1.405]	0.954									
Dyslipidemia	1.166	[0.924–1.734]	0.143									
Hypertension	1.251	[0.901–1.736]	0.181									
Radial access	0.558	[0.414–0.753]	**<0.001**	0.624	[0.457–0.853]	**0.003**	0.616	[0.432–0.879]	**0.008**	0.650	[0.412–0.987]	**0.042**
Contralateral injection	1.733	[1.280–2.346]	**<0.001**	1.261	[0.907–1.751]	0.167	1.314	[0.898–1.922]	0.160	1.142	[0.590–2.211]	0.694
Size guiding Catheter 7/8F	1.969	[1.608–2.411]	**<0.001**	1.690	[1.359–2.102]	**<0.001**	1.789	[1.393–2.298]	**<0.001**	1.412	[1.299–2.220]	**0.013**
PAD	2.016	[1.439–2.825]	**<0.001**	1.858	[1.320–2.615]	**<0.001**	1.814	[1.219–2.698]	**0.003**	2.034	[1.036–3.996]	**0.039**
Retrograde approach	2.556	[1.961–3.331]	**<0.001**	2.251	[1.696–2.988]	**<0.001**	2.212	[1.607–3.048]	**<0.001**	2.391	[1.302–4.388]	**0.05**

Note: Bold values are statistically significant.

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; PAD, peripheral artery disease.

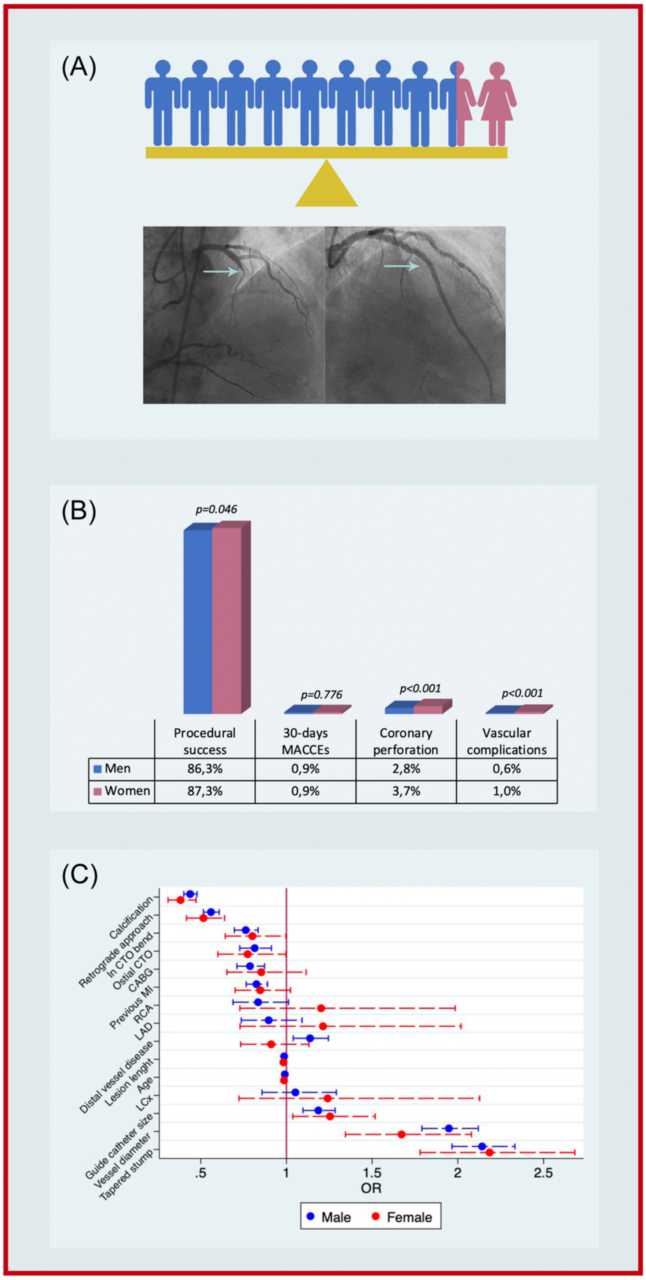
potential easier revascularization procedures in this cohort, may have further decreased the rate of females left undertreated, reducing their potential underrepresentation in our study.

4.2 | Gender differences in procedural success

In our study, women showed a slightly significant overall higher procedural success when compared with men (87.3% vs. 86.3%, $p = 0.046$). This finding was confirmed at univariate and multivariate analysis, where female sex emerged as an independent predictor of CTO recanalization success (OR 1.115, CI 1.011–1.230, $p = 0.030$ at multivariate analysis). This finding is in contrast with recent retrospective studies, that have failed to find significant gender differences in procedural CTO success. Nevertheless, it should be underlined that, at baseline, these studies were not able to detect significant differences in lesion complexity, when expressed in J-CTO score.[4,5,7,18] Moreover, the small differences detected among the two genders in our ERCTO study, might be due to the extensive number of patients enrolled ($n = 35{,}449$) when compared with other studies mentioned above. On the other hand, our results are in line with a recent updated meta-analysis including 14 studies, reporting a higher success rate in women when compared with men, showing a lower median overall CTO-score.[19] In a recent analysis from PROGRESS-CTO registry, Kostantinis et al. reported an overall technical (89.2% vs. 85.6%; $p < 0.001$) and procedural (87.2% vs. 84.4%; $p = 0.003$) success rates (defined as achievement of technical success without any in-hospital MACE) that were both higher in women, corroborating our findings.[20]

The higher procedural success is indeed in line with the significantly lower lesion complexity that we found in the women cohort as well, as confirmed by their lower median J-CTO score. The more true-to-true technique success in women, both with an antegrade and retrograde approach, might indicate that the lesions in women might be softer and maybe younger. Thus, the higher complexity of CTO in men have required a "hybrid strategy" more frequently, combining both an antegrade and a retrograde approach.[21] A less frequent use of a retrograde approach could be also explained by the presence of threadlike connections unsuitable for a retrograde approach in women (CC1). Our findings are also in line with a recent study from Yetkin et al.,[22] showing that female sex was independently associated with poor coronary collateral vessel development in patients with CTO. The exact pathophysiological mechanisms still remains to be clarified, but it has been supposed that the reduction of estrogen levels during and after menopause might have a negative impact on arteriogenesis.[23]

Differences in procedural times and overall contrast doses confirm the lower complexity of CTO revascularization procedures in women. The lower previous surgical revascularization rate that was noticed in women, is another possible explanation of the lower CTO complexity in this cohort. Indeed, it has been suggested that CABG may accelerate native flow-limiting lesion progression resulting in a complete obstruction and in an increase of the CTO complexity (e.g., heavily calcified lesions).[24] Interestingly, a gender-stratified analysis showed no differences in procedural success predictors related to coronary anatomy or CTO characteristics in our cohorts.



CENTRAL IMAGE 1 (A) Women were underrepresented in our prospective ERCTO, representing 15.2% of the entire cohort including 35,449 patients undergoing CTO-PCI (light blue arrows) at several European Institutions. (B) Women showed an overall higher procedural success (CTO recanalization rate) and a higher rate of procedural complications, while no differences were detected in MACCEs. (C) Procedural success predictors stratified by gender. CTO, coronary total occlusion; MACCEs, Major Adverse Cardiac Cerebrovascular events; PCI, percutaneous coronary intervention. [Color figure can be viewed at wileyonlinelibrary.com]

4.3 | Gender differences in MACCEs

In our analysis, the number of in-hospital MACCEs was overall low, with no significant differences in the two study cohorts (men = 0.9% vs. women = 0.9%; $p = 0.766$). At multivariate analysis, the only MACCEs predictors were a previous CABG and diabetes. When considering other studies that evaluated in-hospital MACCEs, our rates are fairly in line with those reports. Specifically, Brilakis et al.[25] found an incidence of procedural-related MACE of 1.6%. If this rate may appear slightly different at a first glance, it should be noted that we considered MACCEs (defined as composite of death, MI, stroke, stent thrombosis, and further need for TVR), not including cardiac tamponade, that would have surely increased this rate. Moreover, in another report from Siudak et al.,[26] evaluating 14.903 CTO-PCI procedures, the authors found an incidence of composite procedural mortality, myocardial infarction, and stroke of 0.7%. This latter data is in line with our report. However, due do the intrinsic nature of our study, a certain grade of complication rate underreporting might not be completely excluded.

When considering the impact of gender on MACCEs, our findings are in line with other studies that have not reported sex-related differences in terms of MACCEs both at short and long-term follow-up.[11–13] Nevertheless, a recent subanalysis from our registry, has shown that female sex was an independent predictor of long-term MACCEs, but only considering patients who underwent a CTO PCI with a retrograde recanalization approach.[10] Interestingly, a recent study from the PROGRESS-CTO from 2012 to 2022 found an overall incidence of 2.0% of in-hospital MACE, that was higher in women (2.9% vs. 1.8%; $p = 0.005$), differently from our report, that did not detected differences among groups regarding in-hospital MACCEs. This finding could be explained by the different definitions that were used when comparing these two studies, with MACE including cardiac tamponade requiring pericardiocentesis, that was more likely to occur in women (1.5% vs. 0.7%; $p = 0.001$). Additionally, overall in-hospital mortality did not differ among groups in both studies, with Kostantinis et al. reporting an overall rate of 0.5% versus our 0.2% rate.[20]

Furthermore, Claessen et al.[18] reported that men had a greater reduction in terms of MACE rate after successful CTO PCI compared with women and also Flores-Umanzor et al.,[27] analyzing 1248 patients (16% women), reported that female sex was an independent predictor for cardiac mortality at long-term follow-up. As also these authors suggested, one possible explanation may be the limited sample size of the female cohort in these studies. All these studies, despite involving a lower number of patients, have reported a longer follow-up when compared with our analysis, and this may have influenced this comparison. Finally, a recent meta-analysis by Mannem et al. including nine observational studies (last on in 2017), found that sex difference is not an independent risk factor of MACCE,[28] corroborating our findings.

4.4 | Gender differences in procedural complications

In our study, female patients presented a higher incidence of periprocedural complications, such as coronary perforation, vascular complications, and major bleeding. At univariate and multivariate analysis, female sex was found to be an independent predictor of both coronary perforations and vascular complications. Coronary perforations were also predicted by older age, dyslipidemia, retrograde approach, higher J-CTO score, distal vessel disease, occlusion length, lower vessel diameter and presence of calcifications, whereas vascular complications were associated with the use of 7/8F size-guiding catheter, PAD and retrograde approach as well. These findings are in line with other studies, highlighting how women usually experience a higher rate of procedural complications, despite showing a less complex lesion anatomy.[7,8] The higher rate of coronary perforations (women = 3.7% vs. men = 2.8%, $p < 0.001$) might be due to a smaller vessel size, thus leading to a higher rate of coronary artery injury and a higher incidence of bleeding.[3] Previous reports using intravascular ultrasound have confirmed that women tend to have smaller coronary diameter even when adjusting for body surface area, which may expose this cohort to coronary perforation more frequently, due to a potential use of oversized balloons and stents.[29]

In our study, female sex was also independently associated to vascular complications, due to a more frequent use of the femoral access route, which is generally preferred for procedural aspects, such as the use of larger sheaths, that are often difficult to handle through smaller radial access (more common in women).[30] Furthermore, a smaller femoral artery diameter when compared with men, may predispose women to develop major bleedings and more severe vascular complications. Lastly, despite several baseline risk factors for CIN were more frequently found in the female cohort, such as older age, pre-existing renal failure and diabetes, no statistically significant gender differences were found in the in-hospital CIN rate, with only a modest trend toward significance. This finding may be explained by the lower total contrast dose that was used in women when compared with men, which is the main determinant of the CIN development and might have counterbalanced the higher baseline risk of the female cohort.

4.5 | Limitations

Our study has several limitations. The first limitation is the non-randomized nature of this multicenter registry of unselected patients undergoing CTO PCI procedures. Although women represented a small percentage of the entire cohort (15.2%), this low enrollment rate was overall mitigated by the very large sample size of the entire cohort of our registry, being the mirror of a "real-world" setting that currently tends to underdescribe women in CTO-PCI procedures, as also highlighted in other studies, as discussed above. Second, although this registry had a prospective nature, all deaths and complications could be not centrally adjudicated by an independent central committee. Therefore, a potential risk of underreporting MACCEs and procedural complications should be considered. Nevertheless, most complication are self-evident, easy to define and uncontroversial. Third, it should be underlined that the evaluation of clinical outcomes, due the nature of our report, was though limited to an in-hospital follow-up and did not cover a long-term period. Fourth, patients' enrollment has taken place over several years, thus potentially resulting in different approaches and materials; this may have led to an improved procedural success rate in the late study period. Fifth, CTO procedures were performed by CTO-dedicated expert operators, and therefore our results do not necessarily reflect the success rate of CTO PCI across not-experienced operators. Lastly, laboratory follow-up was neither mandatory nor standardized across centers, so that a certain rate of laboratory-diagnosed complications underdetection and/or underreporting (such as CIN and periprocedural MI) should be considered.

5 | CONCLUSION

In this multicentered European real-world CTOs registry, women represented 15.2% of the entire cohort and showed an overall higher procedural CTO recanalization rate. While no gender differences were detected in in-hospital MACCEs after a CTO procedure, procedural complications were more likely to occur in women than in men. A gender-stratified analysis showed no differences in procedural success predictors related to coronary anatomy or CTO characteristics in the two study cohorts.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Cecilia Gobbi http://orcid.org/0000-0002-5211-6510
Gerald S. Werner http://orcid.org/0000-0002-6011-0135
Alfredo R. Galassi http://orcid.org/0000-0002-9366-2251
Pierfrancesco Agostoni http://orcid.org/0000-0002-1505-9369
Mauro Carlino http://orcid.org/0000-0003-2326-4749
Giuseppe Vadalà http://orcid.org/0000-0003-0869-4855
Giuseppe Biondi-Zoccai http://orcid.org/0000-0001-6103-8510

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