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Is sex associated with adverse outcomes after percutaneous coronary intervention for CTO?

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ABSTRACT

Background: Conflicting results have been reported regarding sex differences in percutaneous coronary intervention (PCI), but their potential influence on clinical outcomes after chronic total coronary occlusion (CTO) PCI remains unknown. We aimed to identify sex-related differences in long-term clinical outcomes after CTO PCI.
Methods and results: All consecutive patients undergoing CTO PCI between 2004 and 2012 were included in a prospective registry. Baseline, procedural characteristics and clinical outcomes were compared according to sex. Out of 1343 patients, 194 were female (14.4%). Women were older (68.5 ± 9.9 vs 62.3 ± 10.8 years, $p < 0.001$), more frequently diabetic (33.5% vs 26.4%, $p = 0.026$) and hypertensive (70.1% vs 57.4%, $p < 0,001$), whereas males were more frequently smokers (28.5% vs 15.5%, $p < 0.001$). J-CTO score was similar between both sexes (1.59 ± 0.91 vs 1.51 ± 0.88). The procedural success rate was also similar in men and women (74.0% vs 77.3%, respectively). At 8 years' follow-up, successful CTO PCI was associated with reduced mortality in women (14.8% vs 36.2%, $p = 0.003$) and men (18.5% vs 29.1%, $p < 0.001$). In successful CTO PCI cases, no sex-related differences were observed in terms of major adverse cardiac events.
Conclusions: Our study suggests an equal benefit of CTO interventions with a marked reduction in mortality after successful CTO PCI in women and men alike.

1. Introduction

Percutaneous treatment of coronary chronic total occlusions (CTO) is constantly evolving, with new techniques and devices being developed and adopted every year [1]. Several registries identified global benefits associated with successful CTO treatment such as improvements in symptoms, quality of life, left ventricular ejection fraction and a potential benefit on mortality [2–6]. However, the relative paucity of literature regarding sex-related differences in CTO outcomes [6–11] is a direct consequence of the consistently low number of female patients enrolled in CTO registries. Indeed, ischemic cardiomyopathy affects predominantly male patients and women tend to be older and to have a greater burden of risk factors and comorbidities when their heart condition is diagnosed [12,14]. Several studies on sex-related differences in the setting of ST-elevation myocardial infarction showed higher mortality rates in women and greater delay in initiating medical treatment or reperfusion therapy [15–18]. This is consistent with several studies suggesting differences in outcomes between sexes in overall PCI procedures, with notably more short-term complications in women (coronary perforation, access-related vascular complications, or stent thrombosis) as well as a slightly higher mortality rate, even though this "sex gap" has significantly narrowed in recent years [19–21]. Less is known, however, about the influence of sex on CTO PCI outcomes. Few studies focusing on this issue reported contradictory data [7–11].

We present here the results of our 8-year CTO registry comparing the impact of CTO percutaneous revascularization in men versus women.

2. Methods

From January 2004 to January 2012, all consecutive patients referred for CTO recanalization were included in a single-centre prospective registry. The design of the study is presented in Fig. 1 (online). During the 8-year recruitment period 1343 patients underwent PCI of 1506 CTO lesions (84 patients were treated for more than one CTO during the same intervention or a staged procedure). Another 22 patients who had been

Abbreviations: CABG, coronary artery bypass graft; CTO, coronary chronic total occlusion; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization; TLR, target lesion revascularization.

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previously treated for a CTO presented with a new CTO in the same site, which was subsequently re-treated. The global success rate was 74.5%, including 42 patients with successful PCI after a second attempt. CTO was defined as a complete interruption of anterograde flow of >3 months' estimated duration [22] (Thrombolysis in Myocardial Infarction (TIMI) 0) as assessed by angiography. The duration of the occlusion was estimated on the basis of previous angiographic findings, a history of myocardial infarction in the territory of the occluded artery, or changes in the pattern of angina with consistent electrocardiographic changes. All patients were assessed for ischemia (>10% of the myocardium) or viability in the affected territory before CTO recanalization: 317 patients (23.6%) underwent stress magnetic resonance imaging, 224 patients (16.6%) had a positive single-photon emission computed tomography, 154 (11.4%) had a stress echocardiography and 102 patients underwent a conventional exercise stress test (7.6%). For the remaining 546 patients (40.6%) without formal stress test, we considered as viable/ischemic a heart with: absence of Q waves in the ECG, preserved kinetics of the territory by echocardiography or ventriculography, or the persistence of classic angina without other coronary artery lesions that could explain the symptoms. Procedural success was defined as residual stenosis of <50% of the reference diameter with TIMI 3 flow in the treated vessel. Primary events included: all-cause death, myocardial infarction (MI) and need for revascularization (target vessel revascularization (TVR), target lesion revascularization (TLR), or coronary artery bypass graft (CABG)). MI was defined according to the latest definition provided by the European Society of Cardiology [23]. Cardiac death included all deaths of known or presumed cardiac origin as well as all unexpected deaths of unknown causes. All patients received double antiplatelet therapy for at least 6 months. Recently, Clopidogrel was substituted in some cases by Prasugrel or Ticagrelor, at the discretion of the invasive cardiologist. Procedural, angiographic and demographic data were collected from medical records. Regarding follow-up, patients and their clinical cardiologists were contacted by phone and access to their medical records was requested when necessary. Patients who could not be contacted by any means or who refused to share information about their health status were not included in the follow-up analysis, but their initial data were included in the analysis of baseline characteristics. Follow-up data were successfully obtained in 92.5% of patients, with a median length of 4.2 years (interquartile range 2.5 to 6.7 years). In order to estimate the procedure complexity, the J-CTO score [24] was calculated for each procedure via systematic reviewing of all angiograms by two different operators. All patients signed an informed consent form. The protocol was approved by the local ethics committee and the institutional regulatory authorities and was conducted according to the principles of the Declaration of Helsinki.

Categorical variables were compared with the chi-squared test and are presented as percentages. Continuous variables are expressed as the mean ± standard deviation or mean and interquartile range and were compared using Student *t*-test or the Wilcoxon signed ranks according to their distribution. The cumulative incidence was estimated by the Kaplan-Meier method and differences between groups were assessed by the log-rank test. Cox regression was used to estimate relative risks among groups of patients adjusted according to lesion and procedural characteristics. For statistical analysis, we used the data analysis software SPSS version 20 (IBM, New York).

3. Results

A total of 1144 men (85.6%) and 194 women (14.4%) were referred to our centre for CTO PCI. A year-by-year analysis of our registry showed that the number of women referred for CTO PCI remained constant over time (Fig. 2 online), with percentages of women ranging between 12% to 18%. Table 1 shows baseline population and procedural characteristics of male and female patients who underwent an attempt at CTO recanalization. Women were significantly older and had more frequently diabetes mellitus and hypertension. The right coronary artery was the most frequently treated artery in both sexes, while the left anterior descending artery was targeted more frequently in women compared to men.

Success rates were similar between women and men (77.3 vs 74.0%, $p = 0.323$). Sex was not associated with procedural success (Odds ratio 1.140, confidence interval 0.773–1.681, $p = 0.508$) in multivariate analysis (Table 2). Predictive factors of success in multivariate analysis are summarized Table 2.

MACE at follow-up (4.2 year) in male and female patients who underwent successful versus unsuccessful PCI are displayed in Table 3 (online). Successful CTO-PCI was significantly associated with a lower rate of all-cause death, cardiac death and MACE in both sexes (Table 3 online).

Kaplan-Meier survival curves for cumulative all-cause mortality in male and female patients are displayed in Fig. 3, showing again a survival benefit in successfully revascularized patients of both sexes.

Univariate and multivariate predictors of all-cause mortality and MACE are reported in Table 4 and Table 5 (online). Independent predictors of mortality included: age ($p < 0.001$), acute coronary syndrome at presentation ($p = 0.005$), cardiac arrest at presentation ($p < 0.001$), chronic cardiac failure ($p = 0.001$), insulin-dependent diabetes ($p < 0.001$), previous CABG ($p = 0.04$), intervention performed with intra-aortic balloon pump ($p = 0.03$) and failed CTO PCI ($p = 0.02$).

Independent predictors of MACE included non-silent ischemia ($p = 0.03$), cardiac arrest at presentation ($p < 0.001$), insulin-dependent diabetes ($p < 0.001$), current smoking ($p = 0.008$), previous CABG ($p = 0.04$), femoral access ($p = 0.01$), CTO involving left main ($p = 0.002$), severely calcified lesion ($p = 0.001$) and proximal vessel diameter per 1 mm increment ($p = 0.01$).

For patients with successful CTO-PCI, univariate and multivariate predictors of mortality and MACE are reported in Tables 6 and 7 (online).

Independent predictors of mortality included age ($p < 0.001$), chronic cardiac failure ($p = 0.049$) and insulin-dependent diabetes ($p = 0.001$). Independent predictors of MACE included non-silent ischemia ($p = 0.03$), cardiac arrest at presentation ($p < 0.001$), current smoking ($p = 0.001$), previous CABG ($p = 0.01$), severely calcified lesion ($p < 0.001$) and proximal vessel diameter per 1 mm increment ($p = 0.02$).

Table 1
Baseline patient characteristics and in-hospital outcome in male vs female patients.

Variables	Male ($n = 1144$)	Female ($n = 194$)	*p* Value
*Age (yrs)**	*62.8 ± 11.1*	*68.8 ± 11.2*	*<0.001*
*Hypertension (%)**	*57.4*	*70.1*	*0.001*
*Smoking (%)**	*28.5*	*15.5*	*<0.001*
*Diabetes mellitus (%)**	*26.4*	*33.5*	*0.039*
Hypercholesterolemia (%)	63.1	65.5	0.531
*Peripheral artery disease (%)**	*8.8*	*1.8*	*0.047*
Previous MI (%)	23.1	17.5	0.086
Previous PCI (%)	37.4	31.4	0.113
*Previous CABG (%)**	*8.4*	*3.1*	*0.010*
*Ejection fraction (%)**	*57.4 ± 11.1*	*61.7 ± 10.8*	*<0.001*
Target CTO vessel			
*LAD CTO (%)**	*29.9*	*37.1*	*0.046*
*Circumflex CTO (%)**	*23.9*	*16.5*	*0.022*
RCA CTO (%)	45.9	46.4	0.892
Left main CTO (%)	0.3	0.0	0.626
J-CTO score (0–5)	1.59 ± 0.91	1.51 ± 0.88	0.364
Blunt entry shape (%)	55.8	55.2	0.870
Calcifications (%)	57.4	62.4	0.198
*Bending >45 degrees (%)**	*6.4*	*2.6*	*0.037*
*Occlusion lenght >20 mm (%)**	*36.6*	*27.3*	*0.013*
Retry lesions (%)	3.2	3.1	0.926
Number of vessels diseased (n)	1.85 ± 0.80	1.85 ± 0.78	0.991
Femoral access (%)	37.9	34.5	0.376
Procedural success (%)	74.0%	77.3%	0.323
Stents/patient (n)	1.26 ± 1.07	1.15 ± 0.96	0.286
DES (%)	92.3	92.2	0.815
*Stent length (mm)**	*46.9 ± 25.2*	*41.46 ± 23.90*	*0.008*
Coronary perforation (%)	3.5	5.7	0.141
Major vascular complication (%)	1.6	1.5	0.902
Cardiac tamponade (%)	0.4	0.5	0.887

CABG: coronary artery bypass graft; CTO: chronic total occlusion; DES: drug-eluting stent; LAD: left anterior descending; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery.

* $p < 0.05$.

Table 2
Predictors of CTO PCI success.

Variable	Odds ratio	95% confidence interval	*p*-Value
Age	*0.983*	*0.971–0.996*	*0.012*
No hypertension	*1.399*	*1.052–1.861*	*0.021*
No previous CABG	*2.245*	*1.432–3.518*	*0.001*
Tapered entry shape	*1.690*	*1.292–2.212*	*<0.001*
No calcifications	*1.599*	*1.205–2.122*	*0.001*
Occlusion < 20 mm	*1.240*	*1.534–2.629*	*<0.001*
Gender (female)	1.140	0.773–1.681	0.508

CABG: coronary artery bypass graft; CTO: chronic total occlusion; PCI: percutaneous coronary intervention.

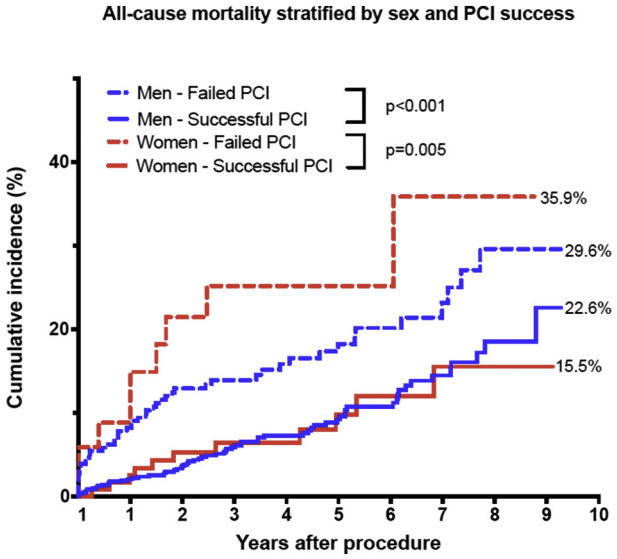

Fig. 3. Cumulative MACE (Death of any cause, MI, TVR and TLR) rates at 8 years follow-up of successful vs failed PCI for CTO in male and female patients.

The survival benefit after successful PCI was similar in men and women (Fig. 4).

The rate of severe peri-procedural complications (vascular-access related bleeding, other severe bleeding, coronary perforation requiring pericardiocentesis, urgent bypass surgery, acute renal failure) remained low (around 1%) and without significant differences between sexes.

4. Discussion

This study describes the impact of sex in patients undergoing CTO PCI. New data have generated 4 main findings: 1/ The proportion of women referred for CTO PCI remained constant over time around 15%, 2/ Women were significantly older and had more frequently diabetes mellitus and hypertension, 3/ Success rates were similar in both sexes, 4/ Successful CTO-PCI was associated with a significantly lower rate of death and MACE in men and women alike.

In accordance with the results reported by Claessen et al. [7] we found that women are under-represented in CTO procedures. Previous registries showed that women account for approximately 30% of all patients treated by PCI, whereas only 14% of our CTO patients were female. Furthermore, a year-by-year analysis showed that the rate of women undergoing CTO recanalization remains almost constant. More recently, in the study by Guelker et al. [8], female patients undergoing CTO PCI accounted for 16% of the study population and in the studies by Karatasakis et al. and Sharma et al. 14% and 20% of the registry population, respectively [25,26] were women.

Older age and a higher rate of diabetes, combined with a lower incidence of typical angina symptoms in women [27,28] probably explain the strikingly low percentage of women recorded in our registry as well as in other CTO registries. This would suggest that women are generally less frequently referred for CTO PCI than men despite the fact that they benefit as much from CTO recanalization as their male counterparts. We recommend, therefore, that substantial efforts should be made in order to identify female candidates for CTO recanalization.

Moreover, differences in baseline characteristics between sexes were well identified in other PCI studies [12–14]. Among these characteristics, those that have emerged as accounting for outcome differences in women are advanced age and a higher rate of diabetes mellitus in women with ischemic cardiomyopathy. These distinctive features were also present in the female patients included in our registry, as shown in Table 1. These results are consistent with the literature regarding the higher rate of diabetes and hypertension in females undergoing PCI in comparison with males [8]. However, as reported in the results section, our statistical analysis did not show any sex-related differences in terms of outcomes.

PCI success rate was also comparable in male and female patients. Lesion complexity was measured by the J-CTO score that takes into account 5 different factors related to the chances of successful revascularization: entry shape of the occlusion, calcification, CTO bend >45°vessel, occlusion length > 20 mm and a previous attempt [24]. We did not find any significant sex-related differences in J-CTO scores. However, by analysing each factor separately, we observed that women had less frequently a CTO lesion >20 mm (27.3% vs 36.6%, $p = 0.013$) and less frequently bends >45° (2.6% vs 6.4%, $p = 0.037$). The sample size may be insufficient to highlight a statistical difference related to sex in the J-CTO score despite less extensive CTO lesion treated in women. These findings could account, albeit partially, for the non-significant lower success rate recorded in men.

It has already been established that successful CTO PCI improves symptoms and quality of life, as well as left ventricular ejection fraction [2] compared with CTO PCI failure. More importantly, recent studies have shown that CTO recanalization may improve long-term survival [4–6]. In our experience, both men and women benefited from improved survival after successful recanalization. These results are in conflict with previously published data by Claessen et al. [7]. Indeed, in a large registry of similar size with a similar percentage of female patients

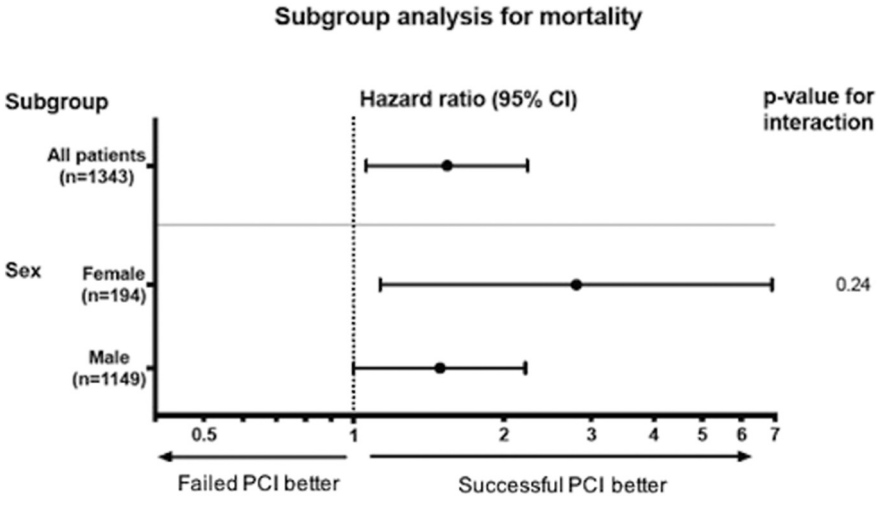

Fig. 4. Sex subgroup analysis for mortality.

(14% vs 14.5% in our study), the survival benefit was observed only in male patients, although sex did not emerge as an independent predictor of mortality in the multivariate Cox analysis. Such differences between Claessen's registry and the analysis reported here may be explained by the fact that patient enrolment in Claessen's registry dates back to 1997. This could account for the lower success rate (68.5% vs 74%), given that fewer dedicated devices were available at that time, and for the lower DES implantation rate (71.7% in women and 64.8% in men in Claessen's registry compared with >92% in our series for both sexes). This in turn may have introduced a bias in the comparison of MACE between both registries. Furthermore, the present registry had a very long follow up duration (mean F.U. of 4.2 years), and we took particular care in documenting the presence of myocardial viability and/or ischemia in all patients before attempting CTO PCI. Indeed, both of these factors are likely to have generated statistical differences. Indeed, the registry by Guelker et al. [8] showed a similar success rate of CTO PCI in both sexes (around 80%) with a similar benefit as did more recent studies [9,10],which are consistent with our findings. The rates of MI and TVR were higher in patients with successful CTO PCI. This could be explained by the fact that a successfully revascularized coronary vessel may be more likely than an already occluded vessel to generate symptoms recurrence or to require a repeat revascularization. Failed CTO PCI resulted in the need for CABG in a subset of patients, probably the most symptomatic, and usually not long after the failed percutaneous attempt. All patients who underwent unsuccessful CTO PCI and in whom TLR was finally achieved were successfully treated by means of CABG surgery. This study is limited by its observational and single-centre nature and by the relatively low number of women who underwent CTO PCI. Several registries and randomized clinical trials focusing on percutaneous revascularization of CTO are currently underway and are expected to provide additional insights into sex-related differences.

5. Conclusion

Our study suggests that equal benefits are derived from CTO interventions regardless of sex. Successful CTO revascularization was associated with significantly lower rates of death, cardiac death and total MACE in men and women alike, in addition to a lower need for CABG in men and a similar trend for women. In accordance with other studies, our findings demonstrate that women are under-referred for CTO PCI in spite of its documented benefits.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.033.

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Conflict of interest

The authors do not have any conflict of interest in the context of the subject of this study.

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