European Heart Journal (2015) **36**, 3189–3198
doi:10.1093/eurheartj/ehv450

Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions

Salvatore D. Tomasello[1], Marouane Boukhris[1†], Simona Giubilato[1], Francesco Marzà[1], Roberto Garbo[2], Gaetano Contegiacomo[3], Antonio Marzocchi[4], Giampaolo Niccoli[5], Andrea Gagnor[6], Ferdinando Varbella[6], Alessandro Desideri[7], Paolo Rubartelli[8], Angelo Cioppa[9], Giorgio Baralis[10], and Alfredo R. Galassi[1*]

[1]Ospedale Cannizzaro, Università di Catania, Via Antonello da Messina 75, Acicastello, 95021 Catania, Italy; [2]Ospedale G. Bosco, Torino, Italy; [3]Casa Di Cura S. Maria, Bari, Italy; [4]Policlinico S. Orsola Malpigli, Bologna, Italy; [5]Ospedale Policlinico Gemelli, Roma, Italy; [6]Ospedale Degli Infermi, Rivoli, Italy; [7]Ospedale S. Giacomo, Castelfranco, Veneto Genova, Italy; [8]Ospedale Villa Scassi, Genova, Italy; [9]Casa di Cura Montevergine, Mercogliano, Italy; and [10]Ospedale S. Croce e Carle, Cuneo, Italy

Received 9 April 2015; revised 24 July 2015; accepted 17 August 2015; online publish-ahead-of-print 2 September 2015

See page 3199 for the editorial comment on this article (doi:10.1093/eurheartj/ehv432)

Background Through contemporary literature, the optimal strategy to manage coronary chronic total occlusions (CTOs) remains under debate.

Objectives The aim of the Italian Registry of Chronic Total Occlusions (IRCTO) was to provide data on prevalence, characteristics, and outcome of CTO patients according to the management strategy.

Methods The IRCTO is a prospective real world multicentre registry enrolling patients showing at least one CTO. Clinical and angiographic data were collected independently from the therapeutic strategy [optimal medical therapy (MT), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG)]; a comparative 1-year clinical follow-up was performed.

Results A total of 1777 patients were enrolled for an overall CTO prevalence of 13.3%. The adopted therapeutic strategies were as follows: MT in 826 patients (46.5%), PCI in 776 patients (43.7%), and CABG in the remaining 175 patients (9.8%). At 1-year follow-up, patients undergoing PCI showed lower rate of major adverse cardiac and cerebrovascular events (MACCE) (2.6% vs. 8.2% and vs. 6.9%; $P < 0.001$ and $P < 0.01$) and cardiac death (1.4% vs. 4.7% and vs. 6.3%; $P < 0.001$ and $P < 0.001$) in comparison with those treated with MT and CABG, respectively. After propensity score-matching analysis, patients treated with PCI showed lower incidence of cardiac death (1.5 vs. 4.4%; $P < 0.001$), acute myocardial infarction (1.1 vs. 2.9%; $P = 0.03$), and re-hospitalization (2.3 vs. 4.4% $P = 0.04$) in comparison with those managed by MT.

Conclusions Our data showed how CTO PCI might significantly improve the survival and decrease MACCE occurrence at 1 year follow-up in comparison with MT and/or CABG.

Keywords Chronic total occlusion • Registry • PCI • CABG • Optimal medical therapy

* Corresponding author. Tel: +39 095 7263122, Fax: +39 095 7263124, Email: argalassi@gmail.com

† Present address: Faculty of Medicine of Tunis, University Tunis El Manar, Tunisia.

Clinical perspective

- Percutaneous coronary intervention (PCI) for coronary chronic total occlusions (CTOs) remains one of the major challenges in interventional cardiology. Only a minority of CTO patients are treated percutaneously, while the majority are referred to surgery or conservatively managed.
- The Italian Registry of Chronic Total Occlusion (IRCTO) provide detailed data on long-term outcome of CTO patients according to the adopted management strategy showing a real benefit of PCI in such a lesions' subset, when compared with medical therapy or surgical revascularization.
- Despite its nonrandomized nature, IRCTO enables multicentre retrospective large real world comparisons of treatment strategies in patients affected by coronary CTOs showing a beneficial impact of PCI on the outcome at 1-year follow-up.
- Randomized trials may give conclusive answers regarding the optimal management strategy of stable CTO patients.

Introduction

Percutaneous coronary intervention (PCI) for coronary chronic total occlusions (CTOs) remains one of the major challenges in interventional cardiology.[1,2] A CTO is a frequent condition encountered in catheterization laboratory and its prevalence in patients undergoing coronary angiography was reported to range from 12 to 20%.[3,4]

Although several observational studies have shown that successful PCI was associated with an improvement of symptoms and quality of life, a reduction in the need for coronary artery bypass grafting (CABG) surgery and an increase in long-term survival,[5–8] only a minority of CTO patients are treated percutaneously.[9] This might be explained by several reasons: the complexity of CTO procedures, which seek for specific equipments and dedicated operators in order to achieve a similar rate of success than non-CTO lesions; the fact that CTO PCIs are time-consuming procedures associated with elevated radiation exposure, increased amount of contrast load and higher risk of procedural complications; and the lack of prospective outcome data in respect to the adopted management strategy for CTO lesion [optimal medical therapy (MT), CABG, or PCI).

The aim of the Italian Registry of Chronic Total Occlusions (IRCTO) was to provide detailed data on prevalence, characteristics, and outcome of CTO patients according to the adopted treatment strategy.

Methods

Study population

The IRCTO is a prospective real world all comers multicentre registry, enrolling patients showing at coronary angiography $\geq$1 CTO in a main coronary artery (vessel size $\geq$2.5 mm). A prior CABG procedure or a life expectancy $<$1 year represented the exclusion criteria. The enrolment started on March 1st 2008 and continued up to 1 year, in 12 high-volume Italian centres, where a total of 15 619 patients underwent coronary angiography during the enrolment period. *Figure 1* shows the flowchart of the study population.

At the enrolment, the participating physicians prospectively inserted all data into a webmaster database. Data collection included patients clinical [age, risk factors, peripheral artery disease, chronic obstructive pulmonary disease, left ventricular ejection fraction (LVEF), chronic renal failure (defined as creatinine clearance $<$60 ml/min), clinical presentation, viability related to CTO vessel and prescribed medication] and angiographic characteristics (CTO artery, presence of multi-vessel coronary disease, presence of blunt stump, severe calcification, bridge collaterals, and CTO length). In case of CTO PCI strategy, procedural data were also collected.

Patients' follow-up was performed either by a clinical visit or by a telephone interview. At follow-up, details regarding major adverse cardiac and cerebrovascular events (MACCE) occurrence, and re-hospitalization for a cardiovascular reason were collected by the physicians through the revision of clinical source documentation. The study was carried out in accordance to the Helsinki declaration; the ethics committee approved the protocol and all patients provided written informed consent.

Definitions and end-points

Coronary CTO was defined as thrombolysis in myocardial infarction (TIMI) Grade 0 flow within the occluded segment with an occlusion duration $>$3 months. The occlusion duration was divided into three levels of certainty: (i) 'certain' (angiographically confirmed), in cases where a previous angiogram confirmed the presence of TIMI 0 flow $>$3 months prior to the index procedure; (ii) 'likely' (clinically confirmed), objective evidence of an acute myocardial infarction (AMI) in the territory of the occluded artery without other possible culprit arteries of $>$3 months before the current angiogram; (iii) 'undetermined', TIMI 0 flow and angiographic anatomy suggestive of long-standing occlusion with stable anginal symptoms unchanged in the last 3 months or evidence of silent ischaemia.[1,9]

All baseline and procedural cine coronary angiograms were analysed and reviewed in each centres by consensus of two expert operators; in case of disagreement, an additional evaluation by a third expert operator was performed. Severe calcifications were defined as multiple persistent opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion. Severe tortuosity was defined as one or more bends of 90° or more, or three or more bends of 45–90° proximal to the diseased segment.

A 2D echocardiogram was performed in all patients. In presence of normal wall motion or hypokinesia in the territory subtended by the CTO artery, no further viability testing was performed; while in patients with akinesia or dyskinesia in CTO territory, assessment of viability was performed by myocardial scintigraphy or myocardial resonance imaging.[10]

Patients received medical anti-ischaemic therapy as established by practice standards: anti-ischaemic drug included β-blockers, calcium channels blockers, nitrates, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and other antianginal drugs alone or in combination. Optimal MT was defined according to the appropriate use criteria, as the use of at least two or more antianginal classes of

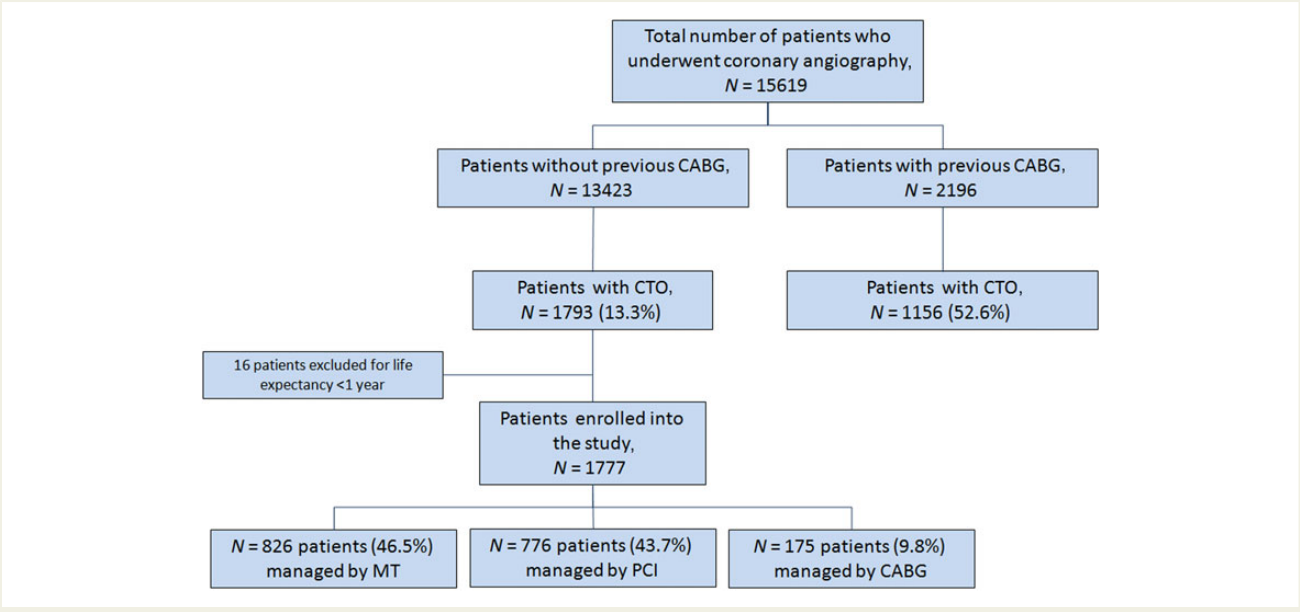

Figure 1 Flowchart of the study population. CABG, coronary artery bypass grafting; CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

therapies.[11] The MT was recorded at discharge after the index hospitalization.

The decision of the management strategy for each patient was left to the local heart team in the participating centre. Patients were categorized in PCI group, when the CTO lesion was attempted percutaneously regardless of the procedural success, while those in whom the CTO lesion was not attempted were categorized in MT group regardless of the management of other non-CTO lesions. In case of percutaneous treatment, the operators performed the procedures according to their understanding of each particular case needs. The choice of the appropriate CTO revascularization technique took into account the angiographic characteristics of the lesions and operator personal skills according to antegrade and retrograde techniques previously described.[12,13] The sequence of use of these wiring techniques and the guidewire selection was completely left to operator's discretion. In patients with more than one CTO, only one CTO vessel was attempted (the choice of the target CTO vessel was left to operator's discretion) and no further CTO attempt was performed during the study period.

A successful PCI was defined as a final residual stenosis $<30\%$, with a TIMI grade flow 3 after stent implantation. At the beginning of the procedure, patients received intravenous unfractionated heparin (80–100 IU/kg) to maintain an activated clotting time >300 s, and the activated clotting time was monitored every 30 min to determine if an additional bolus of unfractionated heparin was necessary. Glycoprotein IIb/IIIa inhibitors were administered after CTO recanalization at operator's discretion. The antiplatelet therapy after stent implantation was prescribed according to recognized standard of care.[14] In the majority of cases, a 300 or 600 mg loading dose of clopidogrel was administered prior to the procedure, and dual antiplatelet therapy with aspirin ($\geq$75 mg daily) and clopidogrel (75 mg daily) was prescribed for 12 months after discharge.

In case of surgical indication for myocardial revascularization, the patients were transferred to the referral cardio-surgical centre during the index hospitalization.

A 1-year follow-up period was obtained in all patients. Major adverse cardiac and cerebrovascular events were defined as a composite of cardiac death, stroke, and AMI. All deaths were considered of cardiac origin unless otherwise documented. Acute myocardial infarction was defined as creatine kinase (CK)-MB enzyme elevation >3 times the upper limit of the normal value, with or without the presence of new pathological Q waves, in 12-lead electrocardiogram (ECG).[15] In all patients, CK-MB were evaluated 6 h after the procedure and until normalization if the levels were abnormal. The incidence of re-hospitalization due to cardiac cause (new ischemic events, heart failure) during follow-up was also evaluated.

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviations and were compared using one-way analysis of variance. Categorical variables were presented as counts and percentages and compared with the χ^2 test when appropriate (expected frequency >5).Otherwise, the Fisher exact test was used.

The predictors of the management strategy were identified using a logistic regression for each therapeutic alternative (optimal MT, CABG, and PCI). All clinical and angiographic characteristics were tested. All univariate variables with a $P < 0.1$ were included in a statistical model in order to detect the independent predictors using multivariate regression analysis with the Wald method. The same methodology was used to identify the predictors of 1-year MACCE occurrence.

To reduce the impact of treatment selection bias and potential confounding factors, we performed a rigorous adjustment for significant differences in baseline clinical characteristics of patients by propensity score matching (PSM). The propensity score is defined as the conditional probability of receiving treatment given a set of selected covariates. We used a stratification matching model: after dividing the population into 9 equal 10 points layers, we matched the MT-treated units to the PCI-treated units based on the closest propensity score within each layer. We started from a population of 1602 units (in PSM 175 CABG cases were excluded) and after PSM we obtained a population of 1238 units, equally divided between PCI group and MT group. We consider the following variables: age, sex, hypertension, dyslipidaemia, diabetes, smoking status, clinical presentation, chronic kidney disease, prior

MI, prior PCI, and LVEF < 30%. Chi-square tests were re-run in the matched pairs to check whether differences between the two groups across the selected variables persisted after matching. Event-free survival during follow-up was evaluated according to the Kaplan–Meier method and survival among groups was compared using the log-rank test. All data were processed using the Statistical Package for Social Sciences, version 19 (SPSS, Chicago, IL, USA).

Results

Clinical and angiographic characteristics

At the end of the recruitment phase, a total of 1777 patients with 1968 CTOs were enrolled into the study, for an overall CTO prevalence of 13.3%. The occluded artery was more frequently the right coronary artery (49.7%) in comparison with left anterior descending (28.8%) and left circumflex (21.5%). The adopted therapeutic strategies were as follows: MT in 826 patients (46.5%), PCI in 776 patients (43.7%), and CABG in the remaining 175 patients (9.8%). *Table 1* summarized the clinical characteristics of the study population according to the chosen therapeutic strategy. Patients managed with MT were older and showed a higher prevalence of chronic renal failure in comparison with patients treated percutaneously (both $P < 0.001$). In patients managed by MT or referred to CABG, a pathological Q wave was more frequently observed in electrocardiogram when compared with those who underwent PCI (MT 57.4%, CABG 53.7%, PCI 40.5%; $P < 0.001$ for both MT vs. PCI and CABG vs. PCI, respectively). Whereas in patients managed with PCI LVEF was more frequently preserved and viability more frequently demonstrated in comparison with those treated by MT or CABG. Importantly, an optimal MT was prescribed in the majority (98.2%) of MT patients group, while only 55% of PCI group patients were on optimal MT ($P < 0.001$). According to angiographic characteristics, CTO lesions managed by PCI showed more frequently a blunt stump and bridge collaterals in comparison with the two other groups (all $P < 0.05$) (*Table 2*).

Predictors of management strategy

Low LVEF (OR 2.74, 95% CI 1.32–5.67; $P = 0.007$), chronic renal failure (OR 3.38, 95% CI 1.27–9.30, $P < 0.001$), the absence of myocardium viability in the CTO territory (OR 2.73, 95% CI 1.47–5.08; $P = 0.001$) were recognized as independent predictors of MT strategy.

Percutaneous coronary intervention treatment was predicted by the presence of viable myocardium (OR 1.48, 95% CI 1.20–1.83; $P < 0.001$), bridge collateralization (OR 1.55, 95% CI 1.25–1.91; $P < 0.001$), LAD as a culprit CTO artery (OR 1.53, 95% CI 1.22–1.91; $P < 0.001$), the absence of chronic renal failure (OR 0.54, 95% CI 0.41–0.85; $P = 0.004$), the absence of left ventricular function impairment (OR 0.59, 95% CI 0.40–0.72; $P < 0.001$), and a younger age (OR 0.98, 95% CI 0.97–0.99; $P < 0.001$).

Finally, patients were more frequently referred to CABG in case of multi-vessel coronary disease (OR 2.18, 95% CI 1.45–3.13; $P < 0.001$), in presence of more than one CTO lesion (OR 3.13, 95% CI 1.81–5.41; $P < 0.001$), and in absence of myocardium viability in CTO territory (OR 1.87, 95% CI 1.32–2.66; $P < 0.001$).

Clinical outcome

Table 3 showed procedural details and peri-procedural complications of CTO patients managed percutaneously. The rate of angiographic success of CTO PCI was 75.4%. At 1-year follow-up, patients managed by MT and CABG experienced higher rate of cardiac death (4.7% and 6.3% vs. 1.4%; $P < 0.001$) and overall MACCE (8.2% and 6.9% vs. 2.6%; $P < 0.001$) in comparison with those treated by PCI independently of angiographic success. Patients referred to CABG had higher incidence of stroke than those managed by MT and PCI (5.1% vs. 0.7% and vs. 0.1%, respectively; all $P < 0.001$), while patients managed with MT showed higher rates of AMI and re-hospitalization than those treated by PCI and CABG (3% vs. 1% vs. 0.6% and 3.9% vs. 1.9% vs. 2.9%, respectively; all $P < 0.05$) (*Table 4*).

Age (per 10-year increase) [odds ratio (OR) 1.60, 95% CI 1.29–1.98; $P < 0.001$), chronic renal failure (OR 3.22, 95% CI 2.0–5.2; $P < 0.001$), MT or CABG strategies (OR 2.69, 95% CI 1.62–4.47) were recognized as independent predictors of MACCE at 1-year follow-up (*Figure 2*).

Patients with successfully PCI for CTO showed a better 1-year outcome in comparison with other groups (*Figure 3*).

Outcome adjusted by propensity matched analysis

After propensity analysis execution, 539 could not be matched; thus, a total of 1238 patients was obtained (619 patients for each group). No differences were observed in clinical baseline characteristics (Supplementary material online, *Table S1*). The success rate in adjusted PCI group was 74%. *Table 5* summarizes the 1-year clinical outcome after propensity score analysis. As compared with patients treated by PCI, those managed by MT experienced higher incidence of MACCE (7.6 vs. 1.7%; $P < 0.001$), death (4.4 vs. 1.5%; $P = 0.002$), AMI (2.9 vs. 1.1%; $P = 0.03$), and re-hospitalization (4.4 vs. 2.3%; $P = 0.04$). *Figure 4* shows the Kaplan–Maier survival curves free from MACCE and from death according to the adopted strategy (PCI vs. MT).

Discussion

The IRCTO study was performed to determine the prevalence, the clinical and angiographic characteristics, and the management of CTO patients. Moreover, our study shows how clinical outcome of this patients' *subset* might change according to the different therapeutic strategies adopted in a real world all comers population.

Prevalence and characteristics of patients affected by chronic total occlusion lesions

The real prevalence of CTO lesions in patients affected by coronary artery disease (CAD) is unknown due to the fact that a great proportion of these patients are asymptomatic and thus, not referred to cardiological evaluation. In a large registry enrolling 6581 consecutive patients undergoing coronary angiography, a CTO lesion was observed in more than half patients (52%) affected by significant CAD.[16] More recently, in a veteran population, Jeroudi *et al.*[17] confirmed that coronary CTOs are highly prevalent in CAD patients without prior CABG (31% of cases).

Table 1 Baseline patients characteristics

	All patients (n = 1777)	MT (n = 826)	PCI (n = 776)	CABG (n = 175)
Age (years) (mean ± SD)	68.6 ± 11.5	70.1 ± 12.5*	67.0 ± 10.6	68.8 ± 8.9
Male (%)	1495 (84.1)	690 (83.5)	658 (84.8)	147 (84)
Diabetes mellitus (%)	535 (30.1)	245 (29.7)	232 (29.9)	58 (33.1)
Hypertension (%)	1390 (78.2)	645 (78.1)	604 (77.8)	141 (80.6)
Smoke (%)	791 (44.5)	384 (46.5)	324 (41.8)	83 (47.4)
Dyslipidaemia (%)	1114 (62.7)	533 (64.5)	476 (61.3)	105 (60)
Peripheral artery disease (%)	258 (14.5)	144 (17.6)†	78 (10.1)‖	36 (20.6)
COPD (%)	185 (10.4)	97 (11.7)	69 (8.9)	19 (10.9)
Chronic renal failure (%)	182 (10.2)	107 (13)†	56 (7.2)	19 (10.9)
Prior myocardial infarction (%)	772 (43.4)	372 (45)	318 (41)	82 (47)
Presence of Q wave (%)	882 (49.6)	474 (57.4)†	314 (40.5)‖	94 (53.7)
Prior PCI (%)	553 (31.1)	255 (30.9)	251 (32.3)	47 (26.8)
Clinical presentation (%)				
Asymptomatic	416 (23.4)	192 (23.2)	185 (23.8)	39 (22.3)
Stable angina	686 (38.6)	264 (32)*	356 (45.9)‖	66 (37.7)
Unstable angina	378 (21.3)	185 (22,4)	154 (19.8)	39 (22.3)
NSTEMI	164 (9.3)	95 (11.5)*	38 (4.9)‖	26 (14.8)
STEMI	133 (7.4)	90 (10.9)*‡	43 (5.6)	5 (2.9)
LVEF (%)				
≥50	830 (46.7)	337 (40.8)†	404 (52.1)	89 (50.9)
30–50	648 (36.5)	320 (38.7)‡	280 (36.1)‖	48 (27.4)
<30	299 (16.8)	169 (20,5)†	92 (11.9)‖	38 (21.7)
Demonstration of myocardium viability in CTO segment (%)	1356 (76.3)	532 (64.4)†,§	694 (89.4)‖	130 (74.3)
Multi-vessel coronary disease (%)	1082 (60.9)	545 (66)	481 (62)	56 (75)
Number of CTO (%)				
1	1596 (89.8)	760 (92)‡	696 (89.7)‖	140 (80)
2	171 (9.6)	61 (7.4)‡	78 (10.1)‖	32 (18.3)
3	10 (0.6)	5 (0,6)	2 (0.3)‖	3 (1.7)
Medication (%)				
β-Blockers	1458 (82.1)	702 (84.9)	613 (79)	143 (81.7)
Calcium channels blocker	758 (42.6)	446 (54)	238 (30.7)	74 (42.3)
Nitrates	645 (36.3)	388 (46.9)	196 (25.2)	61 (34.8)
ACE inhibitors	1139 (64.1)	512 (62)	527 (67.9)	100 (57.1)
Angiotensin receptor blockers	284 (16)	125 (15.1)	139 (17.9)	20 (11.4)
Statins	1486 (83.6)	705 (85.3)	644 (83)	137 (78.3)
Aspirin	1680 (94.5)	753 (91.2)	771 (99.3)	156 (89.1)
Anti-anginal agents (%)				
1	376 (21.2)	15 (1.8)†	349 (45)‖	12 (6.9)
2	1339 (75.3)	776 (94)†	406 (52.3)‖	157 (89.7)
≥3	62 (3.5)	35 (4,2)	21 (2.7)	6 (3.4)

CABG, coronary artery bypass grafting; CTO, chronic total occlusion; COPB, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MT, medical therapy; PCI, percutaneous coronary intervention.
*MT vs. PCI, $P < 0.05$.
†MT vs. PCI, $P < 0.001$.
‡MT vs. CABG, $P < 0.05$.
§MT vs. CABG, $P < 0.001$.
‖PCI vs. CABG, $P < 0.05$.

Table 2 Angiographic characteristics of chronic total occlusion lesions

	All lesions ($n = 1968$)	MT ($n = 897$)	PCI ($n = 858$)	CABG ($n = 213$)
Blunt stump (%)	600 (30.5)	244 (27.2)*	305 (35.5)†	51 (23.9)
Severe calcifications (%)	209 (10.6)	102 (11.4)	86 (10)	21 (9.8)
Severe tortuosity (%)	69 (3.5)	31 (3.4)	33 (3.8)	5 (2.3)
Bridge collaterals (%)	588 (29.9)	245 (27.3)*	295 (34.4)‡	48 (22.5)
CTO length (mm, mean ± SD)	28.8 ± 23.7	29.9 ± 28.4	27.7 ± 19	28.7 ± 16

CABG, coronary artery bypass grafting; CTO, chronic total occlusion; MT, medical therapy; PCI, percutaneous coronary intervention.
*MT vs. PCI, $P < 0.001$.
†MT vs. CABG, $P < 0.05$.
‡PCI vs. CABG, $P < 0.05$.

Table 3 Procedural details and peri-procedural complications of chronic total occlusion patients managed by percutaneous coronary intervention

	Successful PCI ($n = 585$)	Unsuccessful PCI ($n = 191$)	*P*-value
Procedural details			
Procedural time (min, mean ± SD)	92.5 ± 32.5	86.1 ± 29.3	0.065
Fluoroscopy time (min, mean ± SD)	33.3 ± 13.9	32.1 ± 14.1	0.691
Contrast load (min, mean ± SD)	342.7 ± 164.4	339.4 ± 153.9	0.449
DAP ($Gycm^2$, mean ± SD)	251 ± 19	249 ± 18	0.547
Peri-procedural complications			
Cardiac death, *n*(%)	1 (0.2)	1 (0.5)	0.432
Non-Q wave MI, *n*(%)	1 (0.2)	1 (0.5)	0.432
Q wave MI, *n*(%)	0	0	–
Coronary perforation, *n*(%)	12 (2.1)	5 (2.6)	0.411
Tamponade, *n*(%)	3 (0.5)	2 (1)	0.329
Need for emergency CABG, *n*(%)	1 (0.2)	1 (0.5)	0.432

CABG, coronary artery bypass grafting; DAP, dose area product; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 4 One year clinical outcome according to the treatment strategy

	MT ($n = 826$)	PCI ($n = 776$)	CABG ($n = 175$)
MACCE (%)	68 (8.2)†	20 (2.6)‖	12 (6.9)
Cardiac death (%)	39 (4.7)†	11 (1.4)¶	11 (6.3)
Stroke (%)	6 (0.7)§	1 (0.1)¶	9 (5.1)
AMI (%)	25 (3)*,‡	8 (1)	1 (0.6)
Re-hospitalization (%)	32 (3.9)*,‡	15 (1.9)	5 (2.9)
Ischaemic events (%)	21 (2.5)*	10 (1.3)	4 (2.3)
Heart failure (%)	11 (1.4)*,‡	5 (0.6)	1 (0.6)

AMI, acute myocardial infarction; MACCE, major adverse cardiac and cerebral events; MT, medical therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.
*MT vs. PCI, $P < 0.05$.
†MT vs. PCI, $P < 0.001$.
‡MT vs. CABG, $P < 0.05$.
§MT vs. CABG, $P < 0.001$.
‖PCI vs. CABG, $P < 0.05$.
¶PCI vs. CABG, $P < 0.001$.

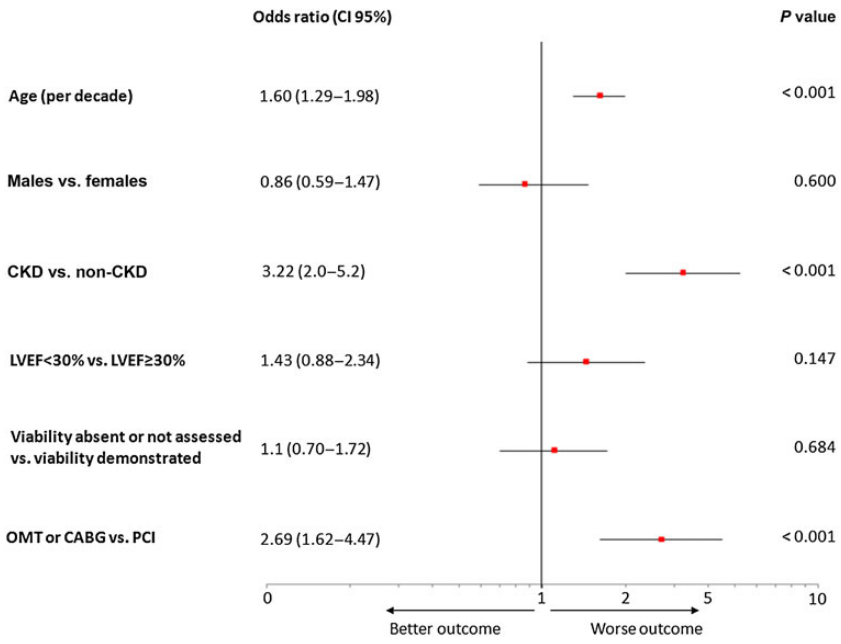

Figure 2 Predictors of 1-year major adverse cardiac and cerebro-vascular events. CABG, coronary artery bypass grafting; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; M, male; MT, medical therapy.

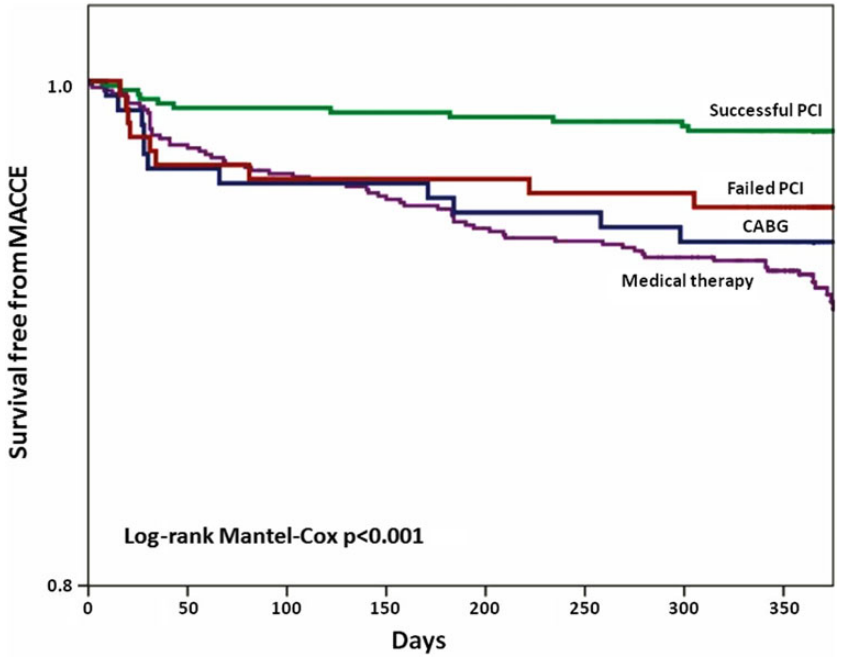

Figure 3 Kaplan–Meier analysis of freedom from major adverse cardiac and cerebrovascular events in patients with successful percutaneous coronary intervention, failed percutaneous coronary intervention, patients managed by medical therapy and those referred to coronary artery bypass grafting, before propensity score adjustment. CABG, coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular adverse events; PCI, percutaneous coronary intervention.

In the Canadian multicentre CTO registry, Fefer *et al.*[3] reported an overall CTO prevalence of 18.4% among 1697 patients undergoing non-emergent coronary artery angiography. The majority of CTO patients did not have signs of myocardial scar (Q waves at ECG) and showed a well-preserved myocardial function.[3]

In our study, the prevalence of CTOs was 13.3%, and the most common CTO artery was the RCA in accordance to previous reports.[3,16–18] Prior myocardial infarction was diagnosed in 43% of cases; an abnormal ECG related to CTO lesion was observed in almost 50% of cases while, viability in the territory subtending the CTO was shown in ~75% of patients.

Differently from Canadian multicentre CTO registry, where only 13% reported no or only mild symptoms (Canadian Cardiovascular Society class 0/1),[3] almost a quarter of our patients were completely asymptomatic and in 16.7% of cases CTO was revealed in the setting of AMI related to a non-CTO vessel.

Notably, more than two-thirds of our population had a multivessel coronary disease and multiple CTO lesions affected >10% of patients. These latter findings were similar to those reported in the European Registry of CTOs (ERCTO registry),[19] confirming that CTO lesions are associated with an extensive atherosclerosis burden. Furthermore, Jeroudi *et al.*[17] found that CTO patients were more likely to have both cardiac and non-cardiac comorbidities (particularly diabetes and peripheral artery disease) than those with non-occlusive coronary stenoses.

Table 5 Comparison of clinical outcome between medical therapy and percutaneous coronary intervention in treating chronic total occlusion patients, after propensity-matched analysis

	MT (n = 619)	PCI (n = 619)	P
MACCE (%)	47 (7.6)	17 (1.7)	<0.001
Cardiac death (%)	27 (4.4)	9 (1.5)	0.002
Stroke (%)	3 (0.5)	1 (0.3)	0.3
AMI (%)	18 (2.9)	7 (1.1)	0.03
Re-hospitalization (%)	27 (4.4)	14 (2.3)	0.04
Ischemic events (%)	19 (3.1)	9 (1.5)	0.03
Heart failure (%)	8 (1.3)	5 (0.8)	0.09

AMI, acute myocardial infarction; MACCE, major adverse cardiac and cerebrovascular events; MT, medical therapy; PCI, percutaneous coronary intervention.

Management strategy of chronic total occlusions patients

Christofferson *et al.*[16] reported that only a minority of CTO patients underwent percutaneous revascularization (11%). Indeed, the majority of them were referred to surgical revascularization (40%) or managed conservatively by MT (49%), differently from patients with non-CTO lesions.[16] Similarly, in the Canadian CTO registry, MT was the preferred strategy for treating CTOs (approximately two-thirds of patients), followed by CABG (~25%); whereas, PCI was attempted in less than 10% of cases.[3] Conversely, in our cohort 43.7% of CTO patients were treated by PCI, while the remaining patients were left on MT or referred to surgery (46.5 and 9.8%, respectively). Our data are in accordance to those of Jeroudi and colleagues,[17] who reported the use of PCI in 50% of CTOs patients.

On the other hand, patients enrolled in our study were relatively older than those of Canadian Registry, with lower prevalence of diabetes and higher rate of prior PCI. These reasons might explain in part the lower rate of CABG indication in IRCTO when compared with the Canadian registry.

Although the majority of interventionalists in the past used to avoid CTO PCI attempts, being these latter costly, associated with high radiation exposure and high probability of procedural failure,

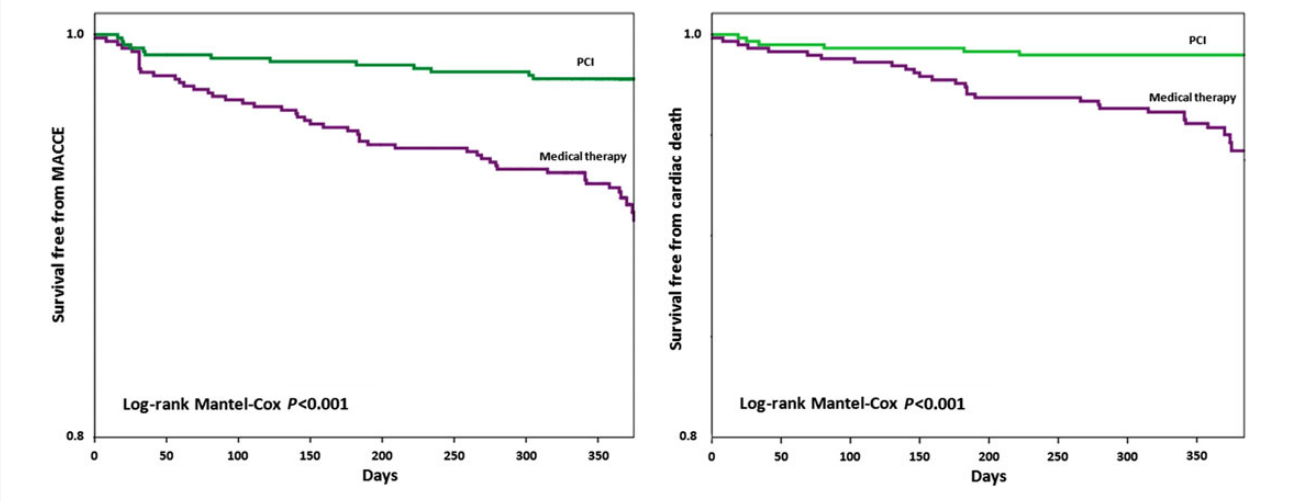

Figure 4 Kaplan–Meier analysis of freedom from major cardiac and cerebrovascular adverse events (left panel) and cardiac death (right panel) in patients treated with percutaneous coronary intervention vs. those managed by medical therapy after propensity score adjustment. MACCE, major adverse cardiac and cerebrovascular adverse events; PCI, percutaneous coronary intervention.

the recent progress in equipment and techniques[12,13,20] leading to the increase of success rate, and the reduction of peri-procedural complications have encouraged the widespread of percutaneous approach in treating CTO lesions.

Several factors might influence the decision-making process in the setting of a CTO. Our findings are similar to those reported in the Canadian multicentre CTO registry,[3] where low-risk patients were the most suitable candidates for CTO PCI. On the other hand, although patients with low LVEF could take benefit from a functional complete revascularization, their fragility may suggest managing them conservatively by MT, especially in absence of symptoms or viability.[21] Furthermore, operators could be more reluctant to perform cumbersome procedures in elderly patients with impaired renal function to avoid complications, particularly contrast-induced nephropathy.

Otherwise, there are two clinical scenarios involving CTO lesions: single- and multi-vessel CAD. In case of isolated CTO, symptoms are generally atypical, and angina could be less prominent than shortness of breath.[22] Furthermore, the potential benefit of a successful PCI could be diminished by the loss of the protective effect of collaterals. Hence, CTO PCI might be deferred until intensive MT is proven to be inadequate to satisfactorily improve symptoms. Differently, multi-vessel coronary disease was found to be a predictor for referring CTO patients to CABG, as recommended by the appropriate criteria of use for myocardial revascularization.[11]

Outcome according to the management strategy

According to the COURAGE trial, as an initial management strategy in patients with stable CAD, PCI did not reduce the long-term risk of death, MI, or other major cardiovascular events when compared with only optimal MT.[23] However, this latter study had likely considered CTOs to be technically unsuitable lesions for PCI, thus CTO patients have not been probably included. Conversely, our results supported that PCI might improve the cardiovascular outcome in comparison with MT in the setting of CTO lesions. Notably, at 1 year follow-up, the rate of cardiac death, MI, and overall MACCE observed in our MT group was relatively higher than those of COURAGE MT cohort. The current European guidelines assigned a class IA for PCI in the presence of stenotic lesions, while they classified the indication for CTO PCI as IIa only.[24] Thus, one question arises in light of these findings, is the presence of CTO rather not as harmless as it is assumed in current guidelines?

Data obtained from UK Central Cardiac Audit Database revealed that successful CTO PCI was associated with improved long-term survival independently from the treated CTO vessel [hazard ratio (HR) 0.72; 95% CI 0.62–0.83; $P < 0.001$] and that the greatest improvement was obtained in case of complete revascularization (0.70; 95% CI 0.56–0.82; $P = 0.002$).[25]

Several reasons may explain such a finding including the potential complications related to a failed CTO PCI, and the worse outcome associated with an incomplete revascularization.[26] Moreover, PCI failure can be the marker of disease burden and other comorbidities limiting the vigour of CTO PCI attempt. Thus, the role of revascularization for CTO lesion remains debatable. A meta-analysis by Joyal *et al.*[27] compared the outcomes of patients with successful vs. unsuccessful CTO PCI. This analysis demonstrated a survival benefit for those who underwent CTO recanalization (14.3 vs. 17.5%, OR: 0.56), and a reduction in need for subsequent CABG and in residual/recurrent angina.[27] Similarly in a more recent meta-analysis, Hoebers *et al.*[28] reported that successful recanalization of a CTO resulted in an improvement of survival (OR: 0.52). Conversely, in a cohort of 1110 patients with single CTO, Jaguszewski *et al.*[29] found that successful PCI does not improve long-term survival, nonetheless, is associated with reduced MACE and the need for further surgical revascularization.

Our results confirmed the data supporting the importance of CTO recanalization attempt in case of significant ischemic burden, multi-vessel disease and low LVEF despite an optimal MT, in order to obtain an improvement of outcome. When compared with other CTO PCI registries,[8,25] our PCI cohort showed a better cardiovascular outcome at 1-year clinical follow-up. On the other hand, by using ACEF (age, creatinine, and ejection fraction) score to predict the outcome of CTO patients managed by PCI, Di Serafino and colleagues[30] revealed that higher MACE rate was significantly associated with increasing ACEF tertile. Similarly in the current study, age and impaired renal function independently predicted worse 1-year cardiovascular outcome.

Very recently, Jang *et al.*[31] compared the outcome of 738 patients with well-developed collateral circulation (Rentrop 3) who were managed with MT alone ($n = 236$), CABG ($n = 170$), or PCI ($n = 332$). After a median follow-up duration of 42 months, lower incidence of cardiac death (HR: 0.29; 95% CI: 0.15–0.58; $P < 0.01$) and MACE (HR: 0.32; 95% CI: 0.21–0.49; $P < 0.01$) was observed in revascularization group (PCI and CABG) in comparison with MT group.[31] After PSM, the incidence of cardiac death (HR: 0.27; 95% CI: 0.09–0.80; $P = 0.02$) and MACE (HR: 0.44; 95% CI: 0.23–0.82; $P = 0.01$) were still significantly lower in revascularization group than in MT group.[31]

The lack of available randomized trials that would address the question of whether successful CTO PCI improved survival in comparison with MT remains one of the main arguments against the expansion of CTO PCI indication. In this respect, the Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients with Chronic Total Occlusion trial (NCT01078051) is currently randomizing patients with CTOs and stable angina to PCI vs. MT to assess the impact of the intervention on cardiac mortality and MI during a follow-up of 5 years.

Despite its non-randomized nature, the current IRCTO trial contributes to improve the evidence of the long-term benefit of CTO PCI in a real world population when compared with MT and CABG.

Study limitations

This study presents some limitations. First of all, although an appropriate propensity score-matched analysis was performed, the non-randomized nature of the study cannot completely exclude all selection bias. Third, the small number of patients referred to CABG could also introduce some selection bias in the data evaluation. Fourth, viability assessment was performed only in patients with akinesia or dyskinesia in myocardial region subtended CTO artery. Fifth, Syntax score was not assessed and the study does not take into account the status of functional complete revascularization after revascularization either percutaneously or surgically. Sixth, MACCE

definition did not include target vessel failure or revascularization. Sixth, we did not address an assessment of quality of life before and after each management strategy. Finally, data regarding PCI of non-CTO lesions in MT group and the rate of CTO grafted in patients undergoing CABG were not assessed as these topics were beyond the scope of the study. Nevertheless, our study represents the largest multicentre comparison of treatment strategies in patients affected by coronary CTOs.

Conclusions

The present study provides information regarding CTO prevalence in a contemporary catheterization laboratory practice with detailed characterization of clinical and angiographic parameters and management trends. More importantly, these data highlight at 1-year follow-up, a significant reduction in MACCE and cardiovascular death for CTO patients treated by PCI when compared with those managed by MT or referred to CABG.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The results of IRCTO were presented in the TCT congress in 2014 during oral presentation sessions.

Funding

This study was partially supported by the Italian Society of Invasive Cardiology (SICI-GISE).

Conflicts of interest: S.D.T., M.B.: performed statistical analysis. A.R.G.: handled funding and supervision. S.D.T., S.G., F.M., M.B.: acquired the data. A.R.G.: conceived and designed the research. S.D.T., M.B.: drafted the manuscript. R.G., G.C., A.M., G.N., A.G., F.V., A.D., P.R., A.C., G.B., A.R.G.: made critical revision of the manuscript for key intellectual content.

References

1. Sianos G, Werner GS, Galassi AR, Papafaklis MI, Escaned J, Hildick-Smith D, Christiansen EH, Gershlick A, Carlino M, Karlas A, Konstantinidis NV, Tomasello SD, Di Mario C, Reifart N; EuroCTO Club. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. *EuroIntervention* 2012;**8**:139–145.
2. Carlino M, Magri CJ, Uretsky BF, Brilakis ES, Walsh S, Spratt JC, Hanratty C, Grantham JA, Rinfret S, Thompson CA, Lombardi WL, Galassi AR, Sianos G, Latib A, Garbo R, Karmpaliotis D, Kandzari DE, Colombo A. Treatment of the chronic total occlusion: a call to action for the interventional community. *Catheter Cardiovasc Interv* 2015;**85**:771–778.
3. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA, Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 2012;**59**:991–997.
4. Råmunddal T, Hoebers LP, Henriques JP, Dworeck C, Angerås O, Odenstedt J, Ioanes D, Olivecrona G, Harnek J, Jensen U, Aasa M, Jussila R, James S, Lagerqvist B, Matejka G, Albertsson P, Omerovic E. Chronic total occlusions in Sweden – a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *PLoS ONE*. 2014;**9**:e103850.
5. Baks T, van Geuns RJ, Duncker DJ, Cademartiri F, Mollet NR, Krestin GP, Serruys PW, de Feyter PJ. Prediction of left ventricular function after drug-eluting stent implantation for chronic total coronary occlusions. *J Am Coll Cardiol* 2006;**47**:721–725.
6. Olivari Z, Rubartelli P, Piscione F, Ettori F, Fontanelli A, Salemme L, Giachero C, Di Mario C, Gabrielli G, Spedicato L, Bedogni F; TOAST-GISE Investigators. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). *J Am Coll Cardiol* 2003;**41**:1672–1678.
7. Galassi AR, Boukhris M, Tomasello SD, Marzà F, Azzarelli S, Giubilato S, Khamis H. Long-term clinical and angiographic outcomes of the mini-STAR technique as a bailout strategy for percutaneous coronary intervention of chronic total occlusion. *Can J Cardiol* 2014;**30**:1400–1406.
8. Galassi AR, Tomasello SD, Costanzo L, Campisano MB, Barrano G, Tamburino C. Long-term clinical and angiographic results of sirolimus-eluting stent in complex coronary chronic total occlusion revascularization: the SECTOR registry. *J Interv Cardiol* 2011;**24**:426–436.
9. Di Mario C, Werner GS, Sianos G, Galassi AR, Büttner J, Dudek D, Chevalier B, Lefevre T, Schofer J, Koolen J, Sievert H, Reimers B, Fajadet J, Colombo A, Gershlick A, Serruys PW, Reifart N. European perspective in the recanalisation of chronic total occlusions (CTO): consensus document from the EuroCTO Club. *EuroIntervention* 2007;**3**:30–43.
10. Galassi AR, Boukhris M, Azzarelli S, Marzà F, Tomasello SD. Percutaneous coronary interventions for chronic total occlusions: more benefit for the patient or for the interventionist's ego? *Can J Cardiol* 2015. doi: 10.1016/j.cjca.2015.03.001.
11. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2012;**59**:857–881.
12. Galassi AR, Tomasello SD, Costanzo L, Tamburino C. Anterograde techniques for percutaneous revascularization of chronic total coronary occlusions. *J Interv Cardiol* 2010;**2**:377–390.
13. Tomasello SD, Marzà F, Giubilato S, Galassi AR. Retrograde approach for revascularization of coronary chronic total occlusion. *Minerva Cardioangiol* 2012;**60**:461–472.
14. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–2555.
15. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–2351.
16. Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol* 2005;**95**:1088–1091.
17. Jeroudi OM, Alomar ME, Michael TT, El Sabbagh A, Patel VG, Mogabgab O, Fuh E, Sherbet D, Lo N, Roesle M, Rangan BV, Abdullah SM, Hastings JL, Grodin J, Banerjee S, Brilakis ES. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. *Catheter Cardiovasc Interv* 2014;**84**:637–643.
18. Galassi AR, Boukhris M, Tomasello SD, Marzà F, Azzarelli S, Giubilato S, Khamis H. Incidence, treatment, and in-hospital outcome of bifurcation lesions in patients undergoing percutaneous coronary interventions for chronic total occlusions. *Coron Artery Dis* 2015;**26**:142–149.
19. Galassi AR, Tomasello SD, Reifart N, Werner GS, Sianos G, Bonnier H, Sievert H, Ehladad S, Bufe A, Shofer J, Gershlick A, Hildick-Smith D, Escaned J, Erglis A, Sheiban I, Thuesen L, Serra A, Christiansen E, Buettner A, Costanzo L, Barrano G, Di Mario C. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. *EuroIntervention* 2011;**7**:472–479.
20. Tomasello SD, Giudice P, Attisano T, Boukhris M, Galassi AR. The innovation of composite core dual coil coronary guide-wire technology: A didactic coronary chronic total occlusion revascularization case report. *J Saudi Heart Assoc* 2014;**26**:222–225.
21. Boukhris M, Tomasello SD, Galassi AR. Should we give into temptation and attempt all chronic total occlusions? *Interv Cardiol* 2014;**6**:399–401.
22. Strauss BH, Shuvy M, Wijeysundera HC. Revascularization of chronic total occlusions: time to reconsider? *J Am Coll Cardiol* 2014;**64**:1281–1289.
23. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS, COURAGE Trial Research

Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**:1503–1516.
24. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.
25. George S, Cockburn J, Clayton TC, Ludman P, Cotton J, Spratt J, Redwood S, de Belder M, de Belder A, Hill J, Hoye A, Palmer N, Rathore S, Gershlick A, Di Mario C, Hildick-Smith D; British Cardiovascular Intervention Society; National Institute for Cardiovascular Outcomes Research. Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central Cardiac Audit Database. *J Am Coll Cardiol* 2014;**64**:235–243.
26. Tamburino C, Angiolillo DJ, Capranzano P, Dimopoulos K, La Manna A, Barbagallo R, Tagliareni F, Mangiafico S, Guzman LA, Galassi AR, Bass TA. Complete versus incomplete revascularization in patients with multivessel disease undergoing percutaneous coronary intervention with drug-eluting stents. *Catheter Cardiovasc Interv* 2008;**72**:448–456.
27. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J* 2010;**160**:179–187.
28. Hoebers LP, Claessen BE, Elias J, Dangas GD, Mehran R, Henriques JP. Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. *Int J Cardiol* 2015; **187**:90–96.
29. Jaguszewski M, Ciecwierz D, Gilis-Malinowska N, Fijalkowski M, Targonski R, Masiewicz E, Strozyk A, Duda M, Chmielecki M, Lewicki L, Dubaniewicz W, Burakowski S, Drewla P, Skarzynski P, Rynkiewicz A, Alibegovic J, Landmesser U, Gruchala M. Successful versus unsuccessful antegrade recanalization of single chronic coronary occlusion: Eight-year experience and outcomes by a propensity score ascertainment. *Catheter Cardiovasc Interv.* 2015;**86**:E49–E57.
30. Di Serafino L, Borgia F, Maeremans J, Pyxaras SA, De Bruyne B, Wijns W, Heyndrickx G, Dens J, Di Mario C, Barbato E. The age, creatinine, and ejection fraction score to risk stratify patients who underwent percutaneous coronary intervention of coronary chronic total occlusion. *Am J Cardiol* 2014;**114**: 1158–1164.
31. Jang WJ, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Kim WS, Lee YT, Gwon HC. Long-term survival benefit of revascularization compared with medical therapy in patients with coronary chronic total occlusion and well-developed collateral circulation. *JACC Cardiovasc Interv* 2015;**8**:271–279.