

Current Perspectives on Coronary Chronic Total Occlusions

The Canadian Multicenter Chronic Total Occlusions Registry

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- Objectives** The purpose of this study was to determine the prevalence, clinical characteristics, and management of coronary chronic total occlusions (CTOs) in current practice.
- Background** There is little evidence in contemporary literature concerning the prevalence, clinical characteristics, and treatment decisions regarding patients who have coronary CTOs identified during coronary angiography.
- Methods** Consecutive patients undergoing nonurgent coronary angiography with CTO were prospectively identified at 3 Canadian sites from April 2008 to July 2009. Patients with previous coronary artery bypass graft surgery or presenting with acute ST-segment elevation myocardial infarction were excluded. Detailed baseline clinical, angiographic, electrocardiographic, and revascularization data were collected.
- Results** Chronic total occlusions were identified in 1,697 (18.4%) patients with significant coronary artery disease (>50% stenosis in ≥ 1 coronary artery) who were undergoing nonemergent angiography. Previous history of myocardial infarction was documented in 40% of study patients, with electrocardiographic evidence of Q waves corresponding to the CTO artery territory in only 26% of cases. Left ventricular function was normal in >50% of patients with CTO. Half the CTOs were located in the right coronary artery. Almost half the patients with CTO were treated medically, and 25% underwent coronary artery bypass graft surgery (CTO bypassed in 88%). Percutaneous coronary intervention was done in 30% of patients, although CTO lesions were attempted in only 10% (with 70% success rate).
- Conclusions** Chronic total occlusions are common in contemporary catheterization laboratory practice. Prospective studies are needed to ascertain the benefits of treatment strategies of these complex patients. (J Am Coll Cardiol 2012;59:991-7) © 2012 by the American College of Cardiology Foundation

There is growing interest in percutaneous treatment of chronic total occlusions (CTO) in coronary arteries due to improvements in technique and observational evidence that successful treatment of coronary CTO is associated with significant changes in cardiac function and outcome (1-6). However, there are scant data in the literature about the prevalence, clinical characteristics, and treatment decisions regarding patients identified with CTO during diagnostic

coronary angiography, particularly in the contemporary catheterization laboratory setting. Two retrospective studies from the 1990s suggested that the prevalence of CTO in patients with coronary artery disease (CAD) on coronary angiograms ranged from 33% to 52%, depending on the definition of CAD (stenoses either $\geq 50\%$ or $\geq 70\%$) (7,8). These studies were limited by small numbers (7), and because the retrospective design, information regarding patient and lesion characteristics (including duration of chronicity) was lacking. The purpose of our study was to provide current data on the prevalence of CTO in current catheterization laboratory practice, and to provide detailed clinical and angiographic characteristics, and treatment strategy of patients identified with de novo CTO in a large prospective registry of consecutive patients undergoing coronary angiography at 3 academic Canadian institutions.

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Abbreviations and Acronyms

ACS	= acute coronary syndrome(s)
CAD	= coronary artery disease
CCS	= Canadian Cardiovascular Society
CTO	= chronic total occlusion
LV	= left ventricular
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
PCI	= percutaneous coronary intervention

Methods

The Canadian Multicenter CTO Registry is a prospective registry of consecutive CTO patients identified at coronary angiography at 3 participating sites. Permission to collect data was provided by each participating hospital research ethics board. Clinical data regarding sociodemographic characteristics, clinical and comorbid conditions, and left ventricular (LV) function, as well as details of the index occlusion of interest and general coronary anatomy were collected from the APPROACH (Alberta Provincial Project for Outcome

Assessment in Coronary Heart Disease) database, which captures detailed clinical information on patients undergoing coronary angiography (9). The CTO study population was compared to a consecutive cohort of 7,680 patients who were not post-CABG and underwent nonemergent coronary angiography at 2 of the centers during the same period. Specific angiographic characteristics were collected and recorded on the Coronary Artery Reporting and Archiving Tool (CARAT). At 1 of the sites, CTO identification and characteristics were verified with a second review of all angiograms that had been identified as containing CTO by angiography operators.

The study population consisted of all patients undergoing coronary angiography excluding patients with prior CABG and those undergoing primary PCI due to ST-segment elevation myocardial infarction (MI). The prevalence of CTO in study patients was determined using 2 denominators: 1) all patients undergoing angiography; and 2) patients with CAD (defined as a stenosis $\geq 50\%$ in at least 1 coronary artery). Chronic total occlusion was defined as 100% luminal diameter stenosis without a discernable lumen and the absence of antegrade flow, known or assumed to be ≥ 6 week's duration, on the basis of prior angiography or presence of a concordant acute coronary syndrome (ACS). An ACS was defined as hospitalization for anginal type chest pain or equivalent at rest or with minimal exertion or of worsening quality and/or cardiac biomarker rise and/or electrocardiographic changes consistent with ischemia. Lesions with bridging collaterals were identified as CTO, and lesions defined as CTO but duration was unknown were classified as "CTO duration unknown."

Additional angiographic data included the number of diseased coronary arteries (defined as stenosis $\geq 50\%$), the extent of CAD expressed as the Duke coronary score (a score of 7 to 13 was considered high risk) (10), the location and angiographic severity of additional coronary lesions (defined as $\geq 50\%$ diameter stenosis), lesion length of the

occlusion, vessel tortuosity, calcification, and CTO location at the site of a significant bifurcation.

Data on LV function were collected from echocardiography, and when absent, from LV angiography or nuclear studies. The LV function was classified by ejection fraction (EF) as follows: grade 1, normal LV function (LVEF $\geq 55\%$); grade 2, mildly reduced LV function (LVEF 40% to 55%); grade 3, moderately reduced LV function (LVEF 30% to 39%); and grade 4, severely reduced LV function (LVEF $< 30\%$).

All electrocardiograms were interpreted by a cardiologist investigator (P.F., A.B.O., S.Y.) using the revised European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation definitions for electrocardiographic definition of MI (11), which include the following criteria: any Q wave in leads V_2 to V_3 ≥ 0.02 s or QS complex in leads V_2 and V_3 ; Q wave ≥ 0.03 s and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V_4 to V_6 in any 2 leads of a contiguous lead grouping (I, aVL, V_6 ; V_4 to V_6 ; II, III, and aVF); and R wave ≥ 0.04 s in V_1 to V_2 and R/S ≥ 1 with a concordant positive T wave in the absence of a conduction defect.

Information regarding subsequent revascularization procedures was abstracted from the APPROACH study where possible or by review of the PCI and CABG reports.

Statistical analysis. Statistical analyses were performed in SAS version 9 (SAS Institute, Cary, North Carolina). Baseline frequency data were assessed using Fisher's exact test; continuous data were assessed using the general linear model with the least-squares mean option. A similar analysis was performed for the comparisons of the 3 follow-up treatment groups, where probability of ≤ 0.05 or ≤ 0.01 was maintained for each variable by using p values ≤ 0.0169 or ≤ 0.0033 , respectively, for each of the 3 pairs of comparisons. A p value ≤ 0.05 was considered statistically significant.

Results

During the study period (April 1, 2008, to July 31, 2009), a total of 14,439 patients underwent coronary angiography at the 3 participating centers. At least 1 coronary CTO was present in 2,630 patients, for an overall prevalence of CTO of 18.2%. In the excluded patient groups, the prevalence of CTO in 1,469 post-CABG patients was 54% (including multiple CTOs in 58% of these patients) and 10% nonculprit CTOs in 1,453 patients who underwent primary PCI for acute ST-segment elevation MI.

The overall prevalence of CTO in the study population using definition 1 (all patients) was 14.7%, and using definition 2 (patients with CAD), it was 18.4%. In approximately half of the patients, the CTO was of unknown duration. The mean age of CTO patients was 66 ± 11 years, and 81% were male (Table 1). Only 40% of the patients had a history of prior MI, and 12% had a history of heart failure. Nearly half of the CTO patients presented

Table 1 Baseline Characteristics of Patients With Coronary CTOs

	CTO Group (n = 1,697)	Control Group (n = 7,680)	p Value
Age, yrs	66 ± 11	64 ± 12	<0.001
Male	1,365 (80)	5,391 (70)	<0.001
Diabetes mellitus	573 (34)	1,975 (26)	<0.001
Hypertension	1,254 (75)	5,115 (68)	<0.001
Hyperlipidemia	1,374 (82)	5,826 (78)	<0.001
Prior MI	654 (40)	1,704 (23)	<0.001
Prior PCI	376 (22)	1,631 (22)	0.51
Smoker			
Current	419 (33)	1,611 (24)	<0.001
Previous	496 (39)	2,740 (41)	0.21
Heart failure	204 (12)	677 (9)	<0.001
Peripheral vascular disease	129 (8)	310 (4)	<0.001
Cerebrovascular disease	144 (9)	499 (7)	0.003
Dialysis	31 (2)	107 (1)	0.18
Malignancy	72 (4)	372 (5)	0.52
Indication type			
Acute coronary syndrome	752 (46)	4,352 (67)	<0.001
Stable coronary disease	881 (54)	2,163 (33)	<0.001
CCS class			
0	79 (5)	250 (3)	0.005
1	110 (7)	464 (6)	0.43
2	376 (22)	1,516 (20)	0.017
3	301 (18)	1,010 (13)	<0.001
4	795 (47)	4,179 (54)	<0.001
Medications			
Aspirin	1,504 (90)	6,564 (87)	<0.001
Beta-blockers	1,244 (74)	5,385 (71)	0.014
Insulin	125 (10)	560 (8)	0.048
ACEI/ARB	1,074 (65)	893 (12)	<0.001
Long-acting nitrates	419 (25)	1,910 (25)	0.58
Lipid lowering/statins	1,329 (79)	5,445 (73)	<0.001

Values are mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CCS = Canadian Cardiovascular Society; CTO = chronic total occlusion; MI = myocardial infarction; PCI = percutaneous coronary intervention.

with an ACS, and only 13% reported no or only mild symptoms (Canadian Cardiovascular Society [CCS] class 0/1). Left ventricular function was normal (grade 1) in >50% of patients, and only 17% had significantly reduced LV function (grade 3 to 4). Differences between patients with CTO and the general catheterization laboratory patients undergoing nonurgent coronary angiography are shown in Table 1. Notably, they tended to be older and sicker, as shown by greater prevalence of all risk factors. Although the absolute differences are small, they also were more likely to have heart failure and concomitant peripheral vascular and cerebrovascular disease, but were less likely to present with an ACS.

The distribution of solitary CTOs showed that 47% were in the right coronary artery (RCA), whereas only 20% had a solitary CTO in the left anterior descending artery, and 16% in the left circumflex branch. Chronic occlusions in >1 coronary artery were observed in 17%. The CTO location was in the proximal or middle portion of the coronary

arteries in 78% of cases (distribution of proximal or mid-vessel occlusion per vessel: left anterior descending artery 84%; left circumflex branch 63%; RCA 80%). Multivessel CAD (>50% diameter stenosis) was present in 76% of patients with CTOs, and 7% exhibited significant (>50%) stenosis of the left main trunk.

Angiographic characteristics of the subgroup of patients whose angiograms were verified by a second review were available for 512 vessels with CTO. Baseline characteristics of this group were similar to those of the entire study group. Occlusion duration was uncertain in 278 (54%) patients. A reference angiogram performed >6 weeks before the index angiogram was available for 12 patients (2%). No ACS <6 weeks was listed for 275 patients (54%), whereas a concordant ACS ≥6 weeks was recorded for 125 patients (24%). Bridging collaterals were present in 122 (24%) patients.

Electrocardiograms were analyzed from 2 of the participating centers and were available for 1,287 (93%) patients. Left and right bundle branch block were found in 6% and 7% of patients, respectively. Atrial fibrillation was present in 5%. Significant Q waves corresponding to the CTO territory were found for 32% of the RCA, 13% for the left anterior descending artery, and 26% for the left circumflex branch.

Most CTOs (64%) were managed medically, defined as absence of revascularization (Fig. 1). In 26% of patients, CABG was performed, with the CTO artery grafted in 88% of these patients. Whereas PCI to either CTO or non-CTO arteries was undertaken in 515 (30%) patients, an attempt to treat the CTO artery was made in only 162 patients (10% of CTO patients), with an overall success rate of 70%.

Characteristics of patients according to CTO management strategy chosen are shown in Table 2. Compared with patients referred for medical therapy, patients referred for

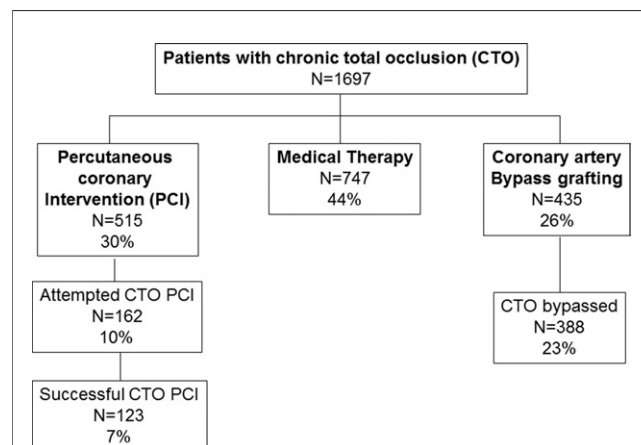


Figure 1 Management of CTO Registry Patients

Flow chart of chronic total occlusion (CTO) registry patients showing management up to 12 months after index angiography. PCI = percutaneous coronary intervention.

Table 2 Patient Characteristics by CTO Treatment Allocation

	No Intervention (A) (n = 1,100)	CABG (B) (n = 435)	PCI (C) (n = 162)	p Values			
				Overall	B vs. A	C vs. A	C vs. B
Clinical variables							
Age, yrs	67 ± 0.3	66 ± 0.6	63 ± 0.8	*	—	*	—
Male	867 (80)	364 (84)	122 (75)	—	—	—	—
Diabetes mellitus	375 (34)	162 (37)	33 (20)	†	—	†	†
Hypertension	825 (76)	310 (71)	106 (65)	—	—	—	—
Renal insufficiency	136 (12)	34 (8)	6 (4)	*	*	†	—
Hyperlipidemia	893 (82)	345 (79)	123 (76)	—	—	—	—
Prior myocardial infarction	482 (44)	126 (29)	41 (25)	†	†	†	—
Prior coronary intervention	287 (26)	55 (13)	30 (19)	†	†	—	—
Heart failure	151 (14)	43 (10)	10 (6)	†	—	—	—
Peripheral vascular disease	95 (9)	27 (6)	7 (5)	—	—	—	—
Cerebrovascular disease	107 (10)	32 (7)	17 (10)	—	—	—	—
Malignancy	55 (5)	16 (4)	1 (1)	—	—	—	—
Current/former smoker	609 (56)	261 (60)	79 (49)	—	—	—	—
Left ventricular grade							
1-2, LVEF >30%	633 (81)	273 (85)	92 (90)	—	—	—	—
3-4, LVEF ≤30%	140 (19)	47 (15)	10 (10)	—	—	—	—
CCS angina class							
0	59 (5)	31 (7)	8 (5)	—	—	—	—
1	69 (6)	30 (7)	10 (7)	—	—	—	—
2	232 (21)	101 (24)	38 (25)	—	—	—	—
3	184 (18)	82 (20)	33 (22)	—	—	—	—
4	553 (50)	176 (42)	61 (41)	—	—	—	—
Coronary anatomy							
Left main disease	54 (5)	95 (22)	6 (4)	†	†	—	†
3-vessel CAD	579 (53)	230 (53)	51 (31)	†	—	†	†
CTO artery							
Left anterior descending	207 (19)	83 (19)	47 (29)	—	—	—	—
Left circumflex	174 (16)	52 (12)	36 (22)	—	—	—	—
Right coronary	545 (50)	196 (45)	55 (34)	—	—	—	—
>1 CTO	164 (15)	104 (24)	24 (15)	—	—	—	—
High-risk coronary index	632 (59)	255 (61)	52 (35)	†	—	†	†

Values are mean ± SD or n (%). *Statistically significant (p < 0.05 overall or p < 0.0170 for individual pairs of treatments). †Highly significant (p < 0.01 overall or p < 0.0033 for individual pairs of treatments).

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

CABG were less likely to have renal insufficiency, prior MI, or coronary intervention, and were more likely to have left main trunk involvement. Compared with patients referred for CTO PCI, patients referred for CABG were more likely to have diabetes mellitus, triple-vessel disease, and left main trunk involvement. Compared with patients referred for medical therapy, patients referred for CTO PCI were younger and less likely to have diabetes, renal insufficiency, prior MI, and complex coronary anatomy (triple-vessel disease and/or high-risk coronary index). They were less likely to have left main trunk involvement compared with patients treated by CABG. Patients treated medically tended to be slightly older than patients in the other 2 groups and had higher prevalence of high-risk findings such as renal insufficiency, prior MI, and prior PCI. No significant differences were noted in laboratory data such as hemoglobin level and estimated glomerular filtration rate.

Significant differences in management were noted among the 3 participating centers (Fig. 2), especially with regard to

PCI to the CTO (16% of CTO patients in center 2, 9% of CTO patients in center 1, and 1% of CTO patients in center 3; p < 0.001), whereas no differences among centers were noted in the referral rate for CABG (25% of CTO patients in center 1, 28% in center 2, and 22% in center 3; p = NS).

Discussion

The Canadian Multicenter CTO Registry was established to determine the prevalence, clinical characteristics, and clinical management of CTO in patients undergoing coronary angiography in a contemporary catheterization laboratory setting. The main findings of the study are that the overall prevalence of CTO in patients with CAD referred for nonemergent coronary angiography is 18.4%, that the majority of CTO patients had absence of Q waves with well-preserved myocardial function, and that despite >87% of CTO patients with CCS class ≥2 symptoms, CTO revascularization was only attempted in 36% of the CTO patients.

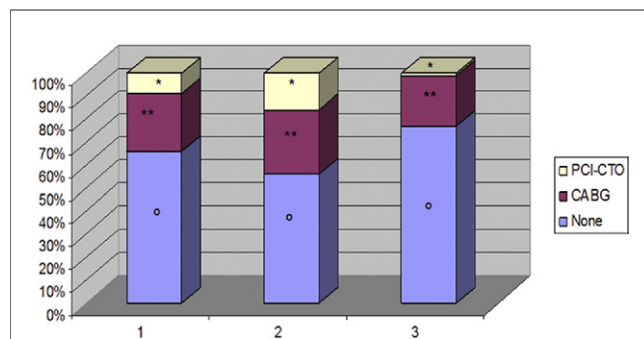


Figure 2 Management of CTO Registry Patients by Treating Center

Management decisions regarding registry patients with chronic total occlusion (CTO) according to treating center. **Yellow bars** indicate percutaneous coronary intervention (PCI) CTO; **dark purple bars** indicate coronary artery bypass graft surgery (CABG); and **light purple bars** indicate none. * $p < 0.001$; ** $p = NS$; ° $p < 0.001$.

The true prevalence of CTO in the general population is unknown as a certain proportion of patients with CTO are asymptomatic or minimally symptomatic. Previous studies assessing prevalence have differed with regard to the reference population. Kahn et al. (7) found a CTO prevalence of 35% among 333 consecutive patients undergoing diagnostic catheterization at a community hospital over 1 year and were found to have at least 1 coronary stenosis $\geq 50\%$. Christofferson et al. (8), in a registry of 8,004 consecutive patients at a single center undergoing diagnostic catheterization between 1990 and 2000, reported a 52% prevalence of CTO among patients with at least 1 coronary stenosis $\geq 70\%$. Only limited information about the clinical presentation was available in these studies because of the retrospective design, and thus some of these cases could have been acute or subacute occlusions. In contrast, the present study prospectively collected data in a large cohort of patients, and CTO was classified only after systematic review of both clinical and angiographic information.

Clinical characteristics. This is the first study to report on the symptom status and clinical presentation of unselected consecutive patients diagnosed with a CTO on coronary angiography. Almost half of our patients underwent coronary angiography because of ACS. Among patients with stable coronary disease, approximately 74% were symptomatic (CCS ≥ 2). However, the symptoms cannot be definitely attributed to the CTO in multivessel disease cases. Only 5% of patients with a CTO were asymptomatic in this study. Previous studies have suggested that the potential benefits of CTO revascularization are related to the presence of myocardial viability (12).

Several clinical and angiographic characteristics in a significant number of study patients highlight the major potential for reducing ischemia by a CTO intervention. Notably, only 40% of patients undergoing angiography had known previous MI, and less than one-third had electro-

cardiographic evidence of previous MI. Data on LV function showed that $>50\%$ of the patients with CTO had normal LV function, and only a small minority of patients had heart failure. Of interest, previous studies of CTO patients specifically referred for PCI have reported previous MI in 42% to 68% (4,12-16). The discrepancy between the revascularization rates of CTO either by surgery or by PCI (approximately 32% in our study) and normal or near normal LV function suggests that a substantial proportion of CTO patients with indirect evidence of myocardial viability are not undergoing some form of revascularization. To clarify this issue, future studies should include objective assessment of viability in the CTO territory.

Angiographic characteristics. Few studies have prospectively assessed angiographic characteristics of CTO. The CTO was located in the RCA in $>50\%$ of de novo cases; that finding is consistent with angiographic findings from the National Heart, Lung, and Blood Dynamic Registry (17). In addition, we performed a detailed angiographic assessment of angiographic CTO characteristics at 1 of the participating centers (Sunnybrook Medical Centre) in a subgroup of 512 CTO. Despite using contemporary criteria for definition of CTO, a CTO duration could not be established in 54% of cases. Similar findings were reported recently in a registry of 202 consecutive patients with CTO, in which duration of CTO was indeterminate in 39% of patients. Interestingly, indeterminate duration of CTO in this study was a predictor of PCI procedural failure and major adverse cardiac events (18). Other characteristics helped in estimating the CTO chronicity, including lack of an ACS within the previous 6 weeks in 54% and bridge collaterals in 24%. A previous study (7) noted unfavorable characteristics for PCI in 18% of all patients and in 29% of patients with multivessel CAD. These characteristics may explain, in part, why PCI to CTO is undertaken relatively infrequently.

Patient management. Several studies have reported on successful PCI of CTO in selected patients, but practice trends with regard to management and referral pattern for an all-comers population are poorly understood. In this study, 64% of the CTOs were managed medically, whereas CABG surgery was performed in 26% of patients. In patients undergoing CABG, the CTO vessel was grafted in 88% of patients. Although 30% of patients overall had a PCI procedure, only 162 patients (10% of CTO patients) had a PCI attempt to the CTO. In all, 511 (30%) patients had successful revascularization of their CTO by either surgery or PCI. Previous large PCI registries have found that CTO represent 12% to 15.6% of the overall PCI patient population (17,19).

An analysis from the National Cardiovascular Data Registry attempted to assess the PCI attempt rate among patients diagnosed with a CTO on diagnostic angiography. The annual rate ranged from 11.7% of CTO in 2005 to 13.6% of CTO in 2004 (19). In our study, there was wide

variability between high-volume PCI centers in the proportion of overall CTO cases that were treated by PCI, ranging from 1% to 16%. There are several possible reasons for this disparity, including performance of angiography by cardiologists with differing views of the perceived benefits of CTO interventions or the expectations of successful PCI revascularization within individual institutions. Disparity in the rates of CTO PCI attempts have been reported before and have been linked to operator PCI volume (20). Previous studies also report that only 11% to 15% undergoing PCI for CTO were asymptomatic (4,12). Indeed, in our study, 88% of CTO patients treated with angioplasty were symptomatic (i.e., CCS class 2 to 4).

The success rate (70%) observed in our study is consistent with that of many previous registries (5), although more recent studies from CTO specialized centers have reported success rates >80% (21,22).

Not unexpectedly, patients referred for CABG were more likely to be older, with more comorbidities and more extensive CAD, including left main involvement, than patients referred for PCI. However, there were no differences in the location of the CTO artery, the presence of >1 CTO, symptom status, and LV function between CABG and PCI patients. In general, patients referred for medical therapy had more high-risk characteristics such as higher prevalence of renal insufficiency and prior MI and PCI, which may explain, in part, why revascularization procedures were not undertaken in these patients.

Study limitations. The major limitation of this observational study is the lack of randomization to different treatment strategies. The inclusion of only 3 institutions may be related to the large variability noted in treatment allocation between centers. A larger sample may have reduced this variability. Another weakness is the lack of accurate documentation of viability or ischemia in the territory supplied by the CTO, or whether this information was related to the decision to intervene in the CTO or not. Nevertheless, our study does identify current prevalence, clinical characteristics, and treatment allocation in the real world in 3 large-volume centers in Canada.

Conclusions

The present study provides information for CTO prevalence in a contemporary catheterization laboratory practice with detailed characterization of clinical and angiographic parameters and management trends. The results show that approximately 1 in 5 non-CABG patients with significant CAD were found to have a CTO. In addition, most patients are symptomatic and have preserved LV systolic function without a clinical history of a prior MI or the presence of Q waves on electrocardiography. Despite major advances in surgical and percutaneous revascularization over the last decade, many patients with a CTO were managed medically, with rates similar to

those reported by older registries (20). Randomized controlled trials are needed to compare medical management with revascularization of CTO.

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- Key Words:** chronic total occlusion ■ coronary artery disease ■ prevalence ■ revascularization ■ treatment.