Survival of Patients with Chronic Total Occlusion of the Right Coronary Artery

Hussein Sliman MD[1], Moshe Y. Flugelman MD[1], Idit Lavi MsC[2], Barak Zafrir MD[1], Avinoam Shiran MD[1], Amnon Eitan MD[1] and Ronen Jaffe MD[1]

Departments of [1]Cardiology and [2]Community Medicine and Epidemiology, Carmel Medical Center, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** The impact of revascularization of coronary chronic total occlusion (CTO) on survival is unknown. Several studies, which included subjects with varied coronary anatomy, suggested that CTO revascularization improved survival. However, the contribution of CTO revascularization to improved outcome is unclear since it was more commonly achieved in subjects with fewer co-morbidities and less extensive coronary disease.

Objectives: To study the association between CTO revascularization and survival in patients with uniform coronary anatomy consisting of isolated CTO of the right coronary artery (RCA).

Methods: A registry of 16,832 coronary angiograms was analyzed. We identified 278 patients (1.7%) with isolated CTO of the RCA who did not have lesions within the left coronary artery for which revascularization was indicated. Survival of 52 patients (19%) who underwent successful percutaneous coronary intervention was compared to those who did not receive revascularization.

Results: Revascularized patients were younger (60.2 vs. 66.3 years, $P = 0.001$), had higher creatinine clearance (106 vs. 83 ml/min, $P < 0.0001$), and had fewer co-morbidities than those who did not receive revascularization. Lack of CTO revascularization was a univariable predictor of mortality (hazard ratio [HR] = 2.65, 95% confidence interval [95%CI] 1.06–6.4) over 4.3 ± 2.5 years of follow-up. On multivariable analysis, the only predictors of mortality were increased age (HR 1.04, 95%CI 1.01–1.07), reduced creatinine clearance (HR 1.02, 95%CI 1.01–1.03), and ejection fraction below 55% (HR 2.24, 95%CI 1.22–4.11).

Conclusions: Among patients with isolated RCA CTO who underwent extended follow-up, revascularization was not an independent predictor of increased survival.

IMAJ 2020; 22: 169–172

KEY WORDS: chronic total occlusion, percutaneous coronary intervention, revascularization, right coronary artery

Among patients with coronary disease, chronic total occlusions (CTO) are found in approximately 20% of coronary angiograms [1]. Recent technical and technological advances have increased success rates of percutaneous coronary interventions (PCI) in this lesion subset [2-4]. Indications for treating CTO are controversial [5,6]. The natural history of coronary artery disease is characterized by recurrent ischemic events, which may be especially hazardous in the presence of a pre-existing CTO. Revascularization of a CTO may potentially limit myocardial ischemia if the donor vessel, which perfuses the distal vascular bed via collaterals, subsequently occludes. Alternatively, the revascularized CTO may serve as a conduit for collateral blood supply in the event of future occlusion of a coronary artery subtending a different myocardial territory. Observational studies have suggested reduced mortality in CTO patients who underwent PCI, however this may be due to selection bias, with healthier subjects being selected to undergo revascularization procedures [7-9]. Since CTO may be located in different segments of the coronary vasculature and occur as a single lesion or as part of complex multivessel disease, it is difficult to draw conclusions regarding benefits of revascularization from published registries that included subjects with varied coronary anatomy, ranging from single-vessel disease to diffuse multi-vessel disease. Since rate of progression of coronary disease is variable, extended follow-up may be required to appreciate the clinical benefit CTO revascularization. To better understand the prognostic implications of revascularizing chronic coronary occlusions, we studied a cohort of patients with uniform coronary anatomy who had CTO of the right coronary artery (RCA) without significant disease of the left coronary artery and performed extended clinical follow-up.

PATIENTS AND METHODS

DATA COLLECTION

All diagnostic coronary angiograms and PCI procedures performed at our institute are prospectively documented in a digital database. The database includes a detailed description of the coronary anatomy and coronary interventions as well as echocardiography and myocardial perfusion scan (MPS) reports. The institutional catheterization database was retrospectively analyzed to detect all patients in whom angiography revealed a CTO of the RCA without significant coronary disease within

the left coronary artery for which revascularization was indicated [5,10]. Coronary CTO were defined as a 100% stenosis with thrombolysis in myocardial infarction (TIMI) grade 0 flow for more than 3 months [6]. Exclusion criteria included left dominant coronary circulation, coronary stenosis ≥ 50% within the left main coronary artery or ≥ 70% within the proximal and middle segments of the left anterior descending or circumflex arteries, history of coronary bypass surgery, acute RCA occlusion, PCI to the RCA during the index procedure, referral for coronary bypass surgery during the index hospitalization, and death during the index hospitalization. We reviewed reports of all angiograms performed between January 2008 and August 2018. When patients with angiographically proven CTO of the RCA during the study period had documentation of the CTO on a previous angiogram, the index date was considered 1 January 2008. Follow-up was performed until death, a maximum follow-up period of 7 years, or termination of data collection on 1 December 2018, whichever occurred first. Patients were stratified according to whether the occluded vessel was revascularized by PCI. Demographic and clinical characteristics were documented.

Indications for CTO revascularization at our institute include presence of angina pectoris as well as asymptomatic myocardial ischemia. Ischemia was assessed by MPS and was presumed when the occluded vessel subtended viable myocardium [11,12]. Myocardial viability was confirmed when myocardial contractility was demonstrated on echocardiography or left ventriculography. In all other cases, viability was assessed by MPS.

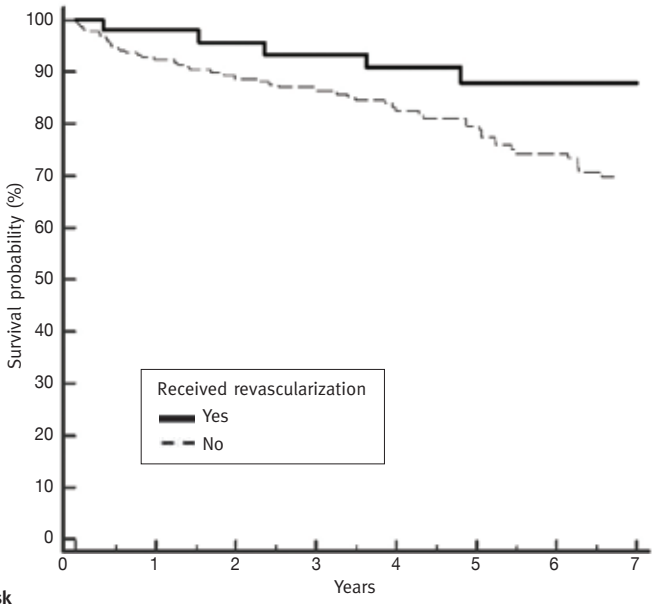
The study endpoint was all-cause mortality. This outcome was selected due to the retrospective study design, with intention to avoid reporting bias, which may influence detection of other clinical outcomes. Deaths were ascertained by reviewing patient records in the institutional database, which is linked to the Ministry of Interior database, which records all cases of mortality.

Table 1. Demographic and clinical patient characteristics

	No revascularization (n=226)	Revascularization (n=52)	*P* value
Age at index procedure (years)	66.5 ± 11.7	60.2 ± 9.6	0.001
Female gender	44 (19.6)	11 (21.2)	0.795
Diabetes mellitus	146 (64.6)	26 (50.0)	0.051
Hypertension	216 (95.6)	50 (96.2)	1.000
Peripheral vascular disease	75 (33.2)	8 (15.4)	0.011
Cerebrovascular disease	33 (14.6)	2 (3.8)	0.035
Creatinine clearance (ml/min)	83.6 ± 35.9	106.3 ± 33.1	0.00004
Ejection fraction (%)	50.9 ± 11.4	56.0 ± 9.8	0.001
Lack of myocardial viability in RCA territory	79 (35.0)	3 (5.8)	0.00007

Values are mean ± standard deviation or n (%)
RCA = right coronary artery

Figure 1. Kaplan-Meier survival chart



Number at risk

Revascularized	52	45	40	38	35	27	23	0
Not revascularized	226	193	162	141	122	107	86	0

STATISTICAL ANALYSIS

Continuous variables were summarized as mean ± standard deviation, and categorical variables were presented as numbers and proportions. Chi-square test was used to compare categorical variables and Student's *t* test was used to compare continuous variables. The Kaplan-Meier estimate was used to generate a survival curve and log-rank testing was used to compare survival between the groups of patients that received revascularization and those who did not. We assessed the association between demographic and clinical characteristics and mortality using Cox proportional univariable and multivariable models. For each participant, we calculated the time interval from the index coronary angiogram to the end of the follow-up period or death, out to a maximum of 7 years. Hazard ratio (HR) and 95% confidence interval (95%CI) for the study outcome were calculated from the models. The results were considered statistically significant for 2-sided *P* value < 0.05. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). The study was approved by the institutional review board and no informed consent was required.

RESULTS

During the study period 16,832 diagnostic coronary angiograms were performed at our institute. Of these angiograms,

278 (1.7%) documented CTO of the RCA without lesions within the left coronary artery that required revascularization. Percutaneous revascularization of the CTO was performed in 52 of these patients. Baseline demographic and clinical variables are detailed in Table 1. Patients in whom the CTO was not revascularized were older and had lower left ventricular ejection fraction and worse renal function compared to those who underwent PCI. During the follow-up period 57 patients died, 52 (23.0%) in the group of patients who did not receive revascularization and 5 (9.6%) in the group who underwent successful PCI.

Kaplan-Meier curves revealed superior cumulative survival in patients who received revascularization compared to those who did not after 7 years of follow-up (88.0% vs. 68.0% $P = 0.03$) [Figure 1]. Predictors of mortality on univariable analysis included lack of CTO revascularization (hazard ratio [HR] 2.65, 95% confidence interval [95%CI] 1.01–6.64, $P = 0.037$), increased age HR 1.06, 95%CI 1.03–1.09, $P < 0.0001$), diabetes mellitus (HR 2.84, 95%CI 1.47–5.48, $P = 0.002$), reduced creatinine clearance (HR 1.02, 95%CI 1.01–1.03, $P < 0.0001$), peripheral vascular disease (HR 2.30, 95%CI 1.37–3.90, $P = 0.002$), cerebrovascular disease (HR 2.01, 95%CI 1.08–3.72, $P = 0.028$), left ventricular ejection fraction < 55% (HR 3.15, 95%CI 1.78–5.53, $P < 0.0001$), and lack of myocardial viability in the RCA territory (HR 1.83, 95%CI 1.06–3.15, $P = 0.03$) [Table 2]. On multivariable analysis the only independent predictors of mortality were increased age (HR 1.04, 95%CI 1.01–1.07, $P = 0.013$), reduced creatinine clearance (HR 1.02, 95%CI 1.01–1.03, $P = 0.002$), and ejection fraction < 55% (HR 2.24, 95%CI 1.22–4.11, $P = 0.01$) [Table 3].

Table 2. Univariable predictors of 7-year mortality, Cox proportional hazard model

	7-year mortality N=57	Hazard ratio	95% confidence interval	*P* value
CTO revascularization				
Yes	5/52 (9.6)	Ref.		
No	52/226 (23.0)	2.65	1.01–6.64	0.037
Age	71.0 11.4	1.06	1.03–1.09	< 0.0001
Diabetes mellitus				
No	11/106 (10.4)	Ref.		
Yes	46/172 (26.7)	2.84	1.47–5.48	0.002
Creatinine clearance	62.6 ± 36.3	1.02	1.01–1.03	< 0.0001
Peripheral vascular disease				
No	29/195 (15.0)	Ref.		
Yes	28/83 (33.7)	2.30	1.37–3.90	0.002
Cerebrovascular disease				
No	44/243 (18.0)	Ref.		
Yes	13/35 (37.0)	2.01	1.08–3.72	0.028
Ejection fraction				
≥ 55%	19/146 (13.0)	Ref.		
< 55%	34/103 (33.0)	3.15	1.78–5.53	< 0.0001
Missing	4/29 (13.8)			
Lack of viability within RCA territory				
No	27/148 (18.2)	Ref.		
Yes	25/82 (30.5)	1.83	1.06–3.15	0.03
Missing	5/48 (10.4)			

Values are ratio (%)

CTO = chronic total occlusion, RCA = right coronary artery

Table 3. Multivariable predictors of 7-year mortality, Cox proportional hazard model

	Hazard ratio	95% confidence interval	*P* value
CTO revascularization	1.20	0.45–3.20	0.72
Age	1.04	1.01–1.07	0.013
Diabetes mellitus	1.74	0.87–3.48	0.12
Creatinine clearance	1.02	1.01–1.03	0.002
Peripheral vascular disease	1.16	0.65–2.08	0.61
Cerebrovascular disease	0.97	0.50–1.88	0.93
Ejection fraction < 55%	2.24	1.22–4.11	0.01
Lack of viability in RCA territory	1.72	0.23–13.20	0.60

CTO = chronic total occlusion, RCA = right coronary artery

DISCUSSION

We identified a cohort of patients with isolated CTO of the RCA and performed extended follow-up. Patients who underwent revascularization were healthier and younger. Revascularization of the CTO was not found to be an independent predictor of survival on multivariable analysis.

Chronic total coronary occlusions occur commonly and are associated with adverse outcomes [6]. Suggested indications for revascularizing CTO include reduction of myocardial ischemia [13], alleviation of anginal symptoms and quality of life [14-16], improvement of cardiac function [17], and prevention of malignant arrhythmia [18]. Since myocardial perfusion in the territory subtended by the occluded vessel depends on flow via collaterals which originate elsewhere in the coronary vasculature, progression of disease in a different coronary artery may lead to life-threatening ischemia. In addition, CTO revascularization may facilitate perfusion of a different myocardial territory in the event of subsequent coronary occlusion elsewhere. Large registries have documented an association between complete coronary revascularization and improved survival [19]. Coronary CTO is a major factor limiting achievement of percutaneous revascularization in patients with coronary disease [20]. Several registries of patients with CTO have suggested that revascularization confers a survival benefit [7-9]; however, these non-randomized studies were prone to selection bias in which patients with fewer co-morbidities and less extensive coronary disease may have been selected to undergo PCI. The present study is unique in that is the only reported analysis that focused on a group of patients with uniform coronary anatomy. We intentionally excluded patients with significant

disease within the left coronary disease for which revascularization confers a proven survival advantage [5,10]. To increase ability to detect a possible impact of CTO revascularization on survival, we performed extended follow-up. Although CTO revascularization was associated with significantly improved survival on univariable analysis, this was not confirmed on multivariable analysis.

LIMITATIONS

This is a single-center non-randomized study; however, prospective randomized studies of a population with uniform coronary anatomy such as the cohort included in the present study are unlikely to be performed and are liable to be affected by significant crossover between patient groups. The study was retrospective, and prospective studies of unselected patients with extended follow-up are difficult to perform. The sample size was relatively small; however, a large number of coronary angiograms was reviewed to identify the study cohort. Data regarding administration of optimal medical therapy and revision of the coronary angiograms by a core laboratory are missing due to the retrospective design of the study. Due to retrospective study design we were not able to reliably identify patients who were subjected to unsuccessful revascularization attempts and to document procedural details.

CONCLUSIONS

In this real-world cohort of subjects with isolated RCA CTO with extended follow-up, those who received revascularization were younger and had fewer co-morbidities than those who did not undergo PCI. Revascularization of the occluded RCA was not an independent predictor of increased survival. Prospective randomized trials with long-term follow-up are required to identify specific patient populations who may benefit from CTO revascularization.

Correspondence
Dr. R. Jaffe
Dept. of Cardiology, Carmel Medical Center, Haifa 34362, Israel
email: jafferonen@gmail.com; jaffe@clalit.org.il

References

1. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 2012; 59: 991-97.
2. Brilakis ES, Banerjee S, Karmpaliotis D, et al. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (national cardiovascular data registry). *JACC Cardiovasc Interv* 2015; 8: 245-53.
3. Maeremans J, Walsh S, Knaapen P, et al. The hybrid algorithm for treating chronic total occlusions in europe: the recharge registry. *J Am Coll Cardiol* 2016; 68: 1958-70.
4. Konstantinidis NV, Werner GS, Deftereos S, et al. Euro CTO Club. Temporal trends in chronic total occlusion interventions in europe. *Circ Cardiovasc Interv* 2018; 11: e006229.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eurointervention* 2019; 14: 1435-1534.
6. Galassi AR, Werner GS, Boukhris M, et al. Percutaneous recanalization of chronic total occlusions: 2019 consensus document from the Euro CTO Club. *Eurointervention* 2019; 15: 198-208.
7. Jang WJ, Yang JH, Choi SH, et al. 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: 271-79.
8. Christakopoulos GE, Christopoulos G, Carlino M, et al. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *Am J Cardiol* 2015; 115: 1367-75.
9. George S, Cockburn J, Clayton TC, et al. 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: 235-43.
10. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology appropriate use criteria task force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2017; 69: 2212-41.
11. Werner GS, Surber R, Ferrari M, Fritzenwanger M, Figulla HR. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. *Eur Heart J* 2006; 27: 2406-12.
12. Sachdeva R, Agrawal M, Flynn SE, Werner GS, Uretsky BF. Reversal of ischemia of donor artery myocardium after recanalization of a chronic total occlusion. *Catheter Cardiovasc Interv* 2013; 82: E453-58.
13. Safley DM, Koshy S, Grantham JA, et al. Changes in myocardial ischemic burden following percutaneous coronary intervention of chronic total occlusions. *Catheter Cardiovasc Interv* 2011; 78: 337-43.
14. Rossello X, Pujadas S, Serra A, et al. Assessment of inducible myocardial ischemia, quality of life, and functional status after successful percutaneous revascularization in patients with chronic total coronary occlusion. *Am J Cardiol* 2016; 117: 720-26.
15. Werner GS, Martin-Yuste V, Hildick-Smith D, et al. EUROCTO trial investigators. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J* 2018; 39: 2484-93.
16. Safley DM, Grantham JA, Hatch J, Jones PG, Spertus JA. Quality of life benefits of percutaneous coronary intervention for chronic occlusions. *Catheter Cardiovasc Interv* 2014; 84: 629-34.
17. Galassi AR, Boukhris M, Toma A, et al. Percutaneous coronary intervention of chronic total occlusions in patients with low left ventricular ejection fraction. *JACC Cardiovasc Interv* 2017; 10: 2158-70.
18. Nombela-Franco L, Iannaccone M, Anguera I, et al. Impact of chronic total coronary occlusion on recurrence of ventricular arrhythmias in ischemic secondary prevention implantable cardioverter-defibrillator recipients (vacto secondary study): Insights from coronary angiogram and electrogram analysis. *JACC Cardiovasc Interv* 2017; 10: 879-88.
19. Hannan EL, Racz M, Holmes DR, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 2006; 113: 2406-12.
20. Farooq V, Serruys PW, Garcia-Garcia HM, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: The SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol* 2013; 61: 282-94.

"The road to wisdom? Well, it's plain and simple to express: Err and err again but less and less and less"

Piet Hein (1905–1996), Danish polymath(mathematician, inventor, designer, author and poet), often writing under the Old Norse pseudonym Kumbel, meaning "tombstone"