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Clinical outcomes of multiple chronic total occlusions in coronary arteries according to three therapeutic strategies: Bypass surgery, percutaneous intervention and medication

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ABSTRACT

Background: Limited data exist regarding clinical outcomes of multiple chronic total occlusions (CTOs) according to therapeutic strategies, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and medical treatment (MT).
Methods: From March 2003 to February 2012, a total of 2024 patients with at least one CTO were enrolled in retrospective, single-center registry. 393 patients with at least two CTOs were categorized based on the intention-to-treat principle. Propensity-score matching was performed. The primary outcome was major adverse cardiac and cerebral events (MACCE).
Results: Of 393 patients with multiple CTOs, 169 patients (43%) were referred for CABG, 130 (33%) for PCI, and 94 (24%) for MT. Median overall follow-up duration was 46.5 (interquartile range 22.7 to 74.6) months. After propensity-score matching analysis, CABG had lower rates of MACCE when compared with PCI (HR = 0.43, 0.21–0.85, $P = 0.01$) and MT (HR = 0.10, 0.04–0.27, $P < 0.01$). Rates of repeat revascularization was significantly lower in CABG, compared with PCI (HR = 0.05, 0.01–0.40, $P < 0.01$) and MT (HR = 0.01, 0.00–0.54, $P = 0.02$). CABG had similar rates of cardiac death compared with PCI group (HR = 0.97, 0.37–2.53, $P = 0.95$), but had significantly lower rates of cardiac death compared with MT (HR = 0.24, 0.08–0.75, $P = 0.01$).
Conclusions: For management of multiple CTOs, MT alone was associated with higher incidence of cardiac death and MACCE compared with CABG. PCI was associated with higher incidence of MACCE, as driven by higher repeat revascularization rate. These findings suggest that CABG might be associated with better clinical outcome and considered as the preferred treatment strategy in patients with multiple CTOs.

1. Introduction

Chronic total occlusion (CTO) is found in up to 30% of diagnostic catheterizations in patients with coronary artery disease, and the incidence of multiple CTOs (≥2 CTOs) has been reported to be approximately 15% of patients with CTO [1,2]. Previously, patients with CTO were more likely to undergo surgery or receive medical treatment rather than percutaneous coronary intervention (PCI) due to its technical and procedural complexities and clinically uncertain benefit [3–7]. Recently, several observational studies indicated that PCI of CTO had benefits in symptom improvement, enhancement of left ventricular (LV) function and survival improvement [8–13]. However, in patients with multiple CTOs, practice trends with regard to management are poorly understood, and limited data exist regarding clinical outcomes according to the three potential therapeutic strategies: coronary artery bypass grafting (CABG), PCI, and medical treatment (MT) [2]. Therefore, we investigated the clinical outcomes and relative efficacies of these three possible therapeutic strategies for patients with multiple CTOs.

2. Methods

2.1. Study population

Between March 2003 and February 2012, a total of 2024 consecutive patients were enrolled in the retrospective Samsung Medical Center CTO registry. The inclusion criteria for the registry were: (1) at least

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one CTO detected on diagnostic coronary angiography and (2) symptomatic angina and/or a positive functional ischemia study. Exclusion criteria included: (1) previous CABG, (2) history of cardiogenic shock or cardiopulmonary resuscitation and (3) ST-segment elevation acute myocardial infarction (MI) during the preceding 48 hours. A CTO lesion was defined as the obstruction of a native coronary artery with a thrombolysis in myocardial infarction (TIMI) flow grade 0 for an estimated duration longer than three months. Duration was estimated based on the interval from the last episode of acute coronary syndrome (ACS), or in patients with no history of ACS, from the first episode of exertional angina consistent with the location of the occlusion or previous coronary angiogram [14–16]. For the purpose of analysis, multiple CTOs were defined as at least two native vessels with CTO lesions, excluding the left main coronary artery. The institutional review board of Samsung Medical Center approved this study and waived the requirement for informed consent.

2.2. Treatment strategy

All patients received antiplatelet therapy with either aspirin 81 to 325 mg daily or clopidogrel 75 mg daily if aspirin intolerance was reported. All patients were taking one or more anti-anginal medications, including a long-acting beta-blocker, calcium channel blocker or isosorbide mononitrate, alone or in combination, along with either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker as standard secondary prevention. The dosages of all medications were maximized as allowed by heart rate, blood pressure and side effects in the absence of justifiable relative contraindications. Revascularization of CTOs was accomplished by CABG or PCI with drug-eluting stent (DES), and each revascularization strategy was selected as a treatment option based on patient and physician preferences. In the case of CABG for CTOs, arterial grafting with off-pump coronary artery bypass was the preferred technique. PCI was performed using contemporary techniques such as bilateral injections, a specialized stiff, hydrophilic wire with a tapered tip, microcatheters, and a retrograde approach when available. The decision to pursue invasive treatment and selection of the access site, type of DES, use of intravascular ultrasound and use of glycoprotein IIb/IIIa receptor inhibitor were all left to the operator's discretion. All interventions and procedural anticoagulation were performed according to current standard guidelines. All patients received loading doses of aspirin (300 mg) and clopidogrel (300–600 mg) before PCI unless they had previously received these antiplatelet medications. Aspirin treatment was continued indefinitely, and the duration of clopidogrel treatment was also left to the discretion of the individual physician. Successful revascularization was defined as final residual stenosis less than 20% of the vessel diameter with TIMI flow grade ≥2 after revascularization as assessed by visual estimation of the angiograms [15]. Complete revascularization was considered that have been accomplished when all vessels with significant lesions, including CTO, were bypassed or successfully revascularized through the CABG or PCI [17].

2.3. Data collection

Clinical, angiographic, procedural and outcome data were collected using a web-based reporting system. Additional information was obtained by reviewing the medical records or by telephone contact, if necessary. All baseline and procedural cine coronary angiograms were reviewed and analyzed quantitatively at the angiographic core laboratory (Cardiac and Vascular Center, Samsung Medical Center, Seoul, Korea) with an automated edge-detection system (Centricity CA 1000, GE, Waukesha, WI, USA) using standard definitions [18].

2.4. Study outcomes and definition

The primary outcome was major adverse cardiac and cerebral event (MACCE) during follow-up. The secondary outcomes were all-cause death, cardiac death, cerebrovascular accident (CVA), MI, and repeat revascularization. Repeat revascularization was a composite of target vessel revascularization and non-target vessel revascularization treated with PCI or CABG. MACCE was defined as a composite of cardiac death, CVA, MI or repeat revascularization. All deaths were considered to be of cardiac origin unless a definite non-cardiac cause could be established. MI was defined as recurrent symptoms with new electrocardiographic changes compatible with MI or cardiac markers at least twice the upper limit of normal [19]. Perioperative or periprocedural enzyme elevation was not included in this definition of MI. The renal insufficiency is defined as an estimated glomerular filtration rate (eGFR) was lower than 60 ml/min/1.73 m^2 (using the Modified Diet in Renal Disease equation) at initial presentation. The extent of collateral flow was assessed according to the validated Rentrop classification scale and reviewed by experienced interventional cardiologists blinded to patient data in the same way of previous study [20,21]. We considered patients with high collateral flow to have Rentrop grade 2 or 3 collateral flow. The calculation of SYNTAX (SYNergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery) score was performed by study site and angiographic core laboratory blinded to patient data [22]. Surgical risk was assessed using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) [23].

2.5. Statistical analysis

All statistical analyses were performed using the intention-to-treat principle. Continuous variables were compared using Student's *t*-test or ANOVA and are presented as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical data were tested using Fisher's exact test or the Chi-square test. Survival curves were constructed using Kaplan–Meier estimates and compared with the log-rank test. The Cox proportional hazard model was used to compare the risks of adverse cardiac events between the CABG and PCI groups, between the CABG and MT groups and between the PCI and MT groups, respectively. Propensity scores were estimated using multiple logistic regression analysis. Full non-parsimonious models were developed and included all variables in Table 1. Cox regression analysis using pairs matched by a greedy algorithm and the nearest available pair-matching method among patients with an individual propensity score was also performed to evaluate the reduction in outcome risk [24,25]. The covariate balance achieved by matching was assessed by calculating the absolute standardized differences in covariates between each two groups. An absolute standardized difference <10.0% for the measured covariate suggests appropriate balance between the groups. In the propensity score-matched population, continuous variables were compared with a paired *t*-test or the Wilcoxon signed rank test, as appropriate, and categorical variables were compared with the McNemar's or Bowker's test of symmetry, as appropriate. The reduction in outcome risk was compared with the stratified Cox regression model. All tests were two or three-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed with the Statistical Analysis Software package (SAS version 9.2, SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline characteristics

During the study period, a total of 2024 patients were included in the registry. Patients with a single CTO (n = 1631) were excluded from analysis. The remaining 393 patients had multiple CTOs and were included in the final analysis. We classified the patients in one of three therapeutic strategies according to initial intention-to-treat principle as follows: 169 patients (43%) were referred for CABG, 130 patients (33%) for PCI, and 94 patients (24%) for MT. In the CABG group, the numbers of CTO lesions were 2.13 ± 1.04 per person and the numbers of bypassed coronary vessels were 3.91 ± 0.34 per person. Complete

Table 1
Baseline and angiographic characteristics in pre-matching populations of each group.

	CABG (n = 169)	PCI (n = 130)	MT (n = 94)	Overall *P*-value*
Age (years)	61.1 ± 9.6	62.0 ± 11.1	67.6 ± 12.6	<0.01
Male	147 (87.0)	113 (86.9)	75 (79.8)	0.23
Hypertension	105 (62.1)	84 (64.6)	61 (64.9)	0.87
Diabetes	101 (59.8)	57 (43.8)	55 (58.5)	0.02
Presentation of ACS	41 (24.3)	34 (26.2)	13 (13.8)	0.05
Renal insufficiency	6 (3.6)	20 (15.4)	9 (9.6)	<0.01
Dyslipidemia	56 (33.1)	41 (31.5)	21 (22.3)	0.17
Prior myocardial infarction	46 (27.2)	34 (26.2)	41 (43.6)	<0.01
Prior coronary intervention	28 (16.6)	29 (22.3)	26 (27.7)	0.10
Cerebrovascular disease	15 (8.9)	12 (9.2)	13 (13.8)	0.40
Current smoking	63 (37.3)	50 (38.5)	33 (35.1)	0.88
LVEF < 40%	52 (30.8)	22 (16.9)	30 (31.9)	0.01
Logistic EuroSCORE	4.3 (2.6–8.2)	4.4 (2.6–8.5)	5.2 (2.7–10.7)	0.11
CTO lesion				
LAD	99 (58.6)	72 (55.4)	52 (55.3)	0.81
LCX	126 (74.6)	97 (74.6)	66 (70.2)	0.70
RCA	136 (80.5)	95 (73.1)	78 (83.0)	0.15
Proximal or mid	153 (90.5)	107 (82.3)	81 (86.2)	0.11
Blunt stump	78 (46.2)	49 (37.7)	50 (53.2)	0.07
Calcification	44 (26.0)	25 (19.2)	25 (26.6)	0.30
High collateral flow	127 (75.1)	97 (74.6)	70 (74.5)	0.99
SYNTAX score	34.6 ± 10.4	26.9 ± 8.8	29.1 ± 10.2	<0.01

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MT, medication therapy; ACS, acute coronary syndrome; CTO, chronic total occlusion; LVEF, left ventricle ejection fraction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.
Continuous data are presented as mean value with standard deviation or median value with interquartile range; categorical data are presented as number (%).
* Statistically significant *P*-value < 0.05 for overall comparison of three treatment groups by ANOVA or chi-square analysis.

revascularization in the CABG group was archived in 156 patients (92.3%). Total arterial graft was performed in 127 patients (75.2%), and 137 patients (81.0%) operated with off-pump technique in CABG groups. In the PCI group, the numbers of CTO lesions were 2.03 ± 0.17 per person and the numbers of DES were 1.82 ± 1.26 per persons. First generation DES was used in 61 patients (47%) and second generation DES was in 48 patients (37%). In the remaining 21 patients (16%), stents could not be used due to failed or incomplete procedure. Overall complete revascularization in the PCI group was archived in 81 patients (62.3%). In the MT group, the numbers of CTO lesions were 2.08 ± 0.28 per person.

Baseline and angiographic characteristics of pre-matching patients according to the intention-to-treat principle are shown in Table 1. Compared with patients referred for PCI, patients referred for CABG were more likely to have diabetes, LVEF < 40%, and high SYNTAX score. Compared with patients referred for MT, patients referred for CABG were younger and less likely to have prior MI, but had higher SYNTAX score. Compared with patients referred for MT, patients referred for PCI were younger and less likely to have prior MI and LVEF <40%. Propensity-score matching was performed between each two groups, respectively. Between the CABG and PCI group, a total of 91 matched patient pairs were created, between the CABG and PCI group, 70 matched patient pairs were created, and between PCI and MT group, 70 matched patient pairs were created (Table 2). The c-statistics for the propensity score model were 0.78, 0.79 and 0.76, respectively.

3.2. Clinical outcomes

The median overall follow-up duration was 46.5 months (IQR 22.7 to 74.6 months), and median follow-up in the CABG group was 57.6 months (IQR 32.3 to 80.3 months), 42.3 months (IQR 22.1 to 68.3 months) in the PCI group, and 36.3 months (IQR 13.1 to 59.7 months) in the MT group. Table 3 and Fig. 1 show cumulative clinical outcomes of the study populations and unadjusted hazard ratios in each therapeutic group comparison. In univariate analysis of pre-mating populations, MACCE [19 (11.2%) in CABG, 26 (20.0%) in PCI, and 37 (39.4%) in MT] and repeat revascularization [1 (0.6%), 15 (11.5%), and 18 (19.1%)] were significantly lower incidences in the CABG group than the PCI ($P < 0.01$ and $P < 0.01$) or MT groups ($P < 0.01$ and $P < 0.01$). All-cause death [21 (12.4%) in CABG, 19 (14.6%) in PCI, 29 (30.9%) in MT] and cardiac death [10 (5.9%) in CABG, 9 (6.9%) in PCI, 18 (19.1%) in MT]

Table 2
Baseline and angiographic characteristics between each therapeutic groups in post-propensity matched population.

	Post-matching between CABG and PCI				Post-matching between CABG and MT				Post-matching between PCI and MT			
	CABG (n = 91)	PCI (n = 91)	*P*-value	SAD	CABG (n = 70)	MT (n = 70)	*P*-value	SAD	PCI (n = 70)	MT (n = 70)	*P*-value	SAD
Age (yr)	62.2 ± 9.9	60.8 ± 11.3	0.38	0.142	63.6 ± 9.5	65.1 ± 12.4	0.44	−0.148	65.1 ± 10.7	65.2 ± 12.9	0.94	−0.013
Male	80 (87.9)	79 (86.8)	0.82	0.033	60 (85.7)	57 (81.4)	0.49	0.127	58 (82.9)	59 (84.3)	0.82	−0.042
Hypertension	55 (60.4)	53 (58.2)	0.76	0.045	43 (61.4)	45 (64.3)	0.72	−0.059	43 (61.4)	44 (62.9)	0.86	−0.030
Diabetes	53 (58.2)	48 (52.7)	0.45	0.112	40 (57.1)	43 (61.4)	0.61	−0.087	34 (48.6)	39 (55.7)	0.39	−0.143
Presentation of ACS	24 (26.4)	23 (25.3)	0.86	0.026	13 (18.6)	11 (15.7)	0.65	0.066	13 (18.6)	12 (17.1)	0.82	0.032
Renal insufficiency	5 (5.5)	7 (7.7)	0.55	−0.118	4 (5.7)	5 (7.1)	0.73	−0.077	6 (8.6)	8 (11.4)	0.57	−0.079
Dyslipidemia	25 (27.5)	33 (36.3)	0.20	−0.186	21 (30.0)	16 (22.9)	0.33	0.151	17 (24.3)	16 (22.9)	0.84	0.031
Prior myocardial infarction	25 (27.5)	25 (27.5)	1.00	0.000	21 (30.0)	25 (35.7)	0.47	−0.128	25 (35.7)	28 (40.0)	0.60	−0.097
Prior coronary intervention	19 (20.9)	20 (22.0)	0.85	−0.029	13 (18.6)	16 (22.9)	0.53	−0.115	18 (25.7)	18 (25.7)	1.00	0.000
Cerebrovascular disease	8 (8.8)	7 (7.7)	0.78	0.039	10 (14.3)	9 (12.9)	0.80	0.050	7 (10.0)	10 (14.3)	0.43	−0.147
Current smoking	34 (37.4)	37 (40.7)	0.64	−0.068	25 (35.7)	23 (32.9)	0.72	0.059	26 (37.1)	25 (35.7)	0.86	0.029
LVEF < 40%	22 (24.2)	19 (20.9)	0.59	0.071	19 (27.1)	24 (34.3)	0.36	−0.154	15 (21.4)	20 (28.6)	0.33	−0.190
Logistic EuroSCORE (%)	5.2 (2.6–11.3)	3.8 (2.5–9.2)	0.18	0.131	5.5 (2.5–11.4)	4.6 (2.5–9.4)	0.49	−0.055	4.4 (2.2–10.0)	4.8 (2.5–9.7)	0.49	−0.035
CTO lesion												
LAD	50 (54.9)	51 (56.0)	0.88	−0.022	40 (57.1)	41 (58.6)	0.86	−0.029	37 (52.9)	38 (54.3)	0.86	−0.029
LCX	70 (76.9)	67 (73.6)	0.60	0.075	50 (71.4)	48 (68.6)	0.71	0.065	51 (72.9)	49 (70.0)	0.71	0.065
RCA	69 (75.8)	68 (74.7)	0.86	0.028	55 (78.6)	58 (82.9)	0.52	−0.108	55 (78.6)	58 (82.9)	0.52	−0.096
Proximal or mid	82 (90.1)	79 (86.8)	0.48	0.112	59 (84.3)	60 (85.7)	0.81	−0.049	58 (82.9)	60 (85.7)	0.64	−0.075
Blunt stump	37 (40.7)	36 (39.6)	0.88	0.022	31 (44.3)	33 (47.1)	0.73	−0.057	33 (47.1)	33 (47.1)	1.00	0.000
Calcification	21 (23.1)	20 (22.0)	0.85	0.025	19 (27.1)	17 (24.3)	0.69	0.065	16 (22.9)	15 (21.4)	0.83	0.036
High collateral flow	70 (76.9)	69 (75.8)	0.86	0.025	56 (80.0)	53 (75.7)	0.54	0.099	55 (78.6)	51 (72.9)	0.43	0.131
SYNTAX score	29.4 ± 8.0	28.9 ± 8.6	0.64	0.054	32.0 ± 10.7	30.9 ± 10.5	0.54	0.103	28.7 ± 9.3	29.1 ± 10.3	0.84	−0.037

SAD, standardized absolute difference; other abbreviations as in Table 1.

Table 3
Pre-matching hazard ratio for clinical outcomes in patients with multiple chronic total occlusions between each therapeutic groups.

Pre-matched population (CABG vs. PCI)	CABG	PCI	CABG vs. PCI	
(Total = 299)	(n = 169)	(n = 130)	Unadjusted HR (95% CI)	*P*-value
All-cause death	21 (12.4%)	19 (14.6%)	0.72 (0.39–1.34)	0.31
Cardiac death	10 (5.9%)	9 (6.9%)	0.72 (0.29–1.78)	0.49
CVA	8 (4.7%)	3 (2.3%)	1.70 (0.45–6.47)	0.43
Myocardial infarction	0 (0.0%)	5 (3.8%)	0.10 (0.00–16.49)	0.22
Repeat revascularization	1 (0.6%)	15 (11.5%)	0.04 (0.01–0.27)	<0.01
MACCE	19 (11.2%)	26 (20.0%)	0.43 (0.23–0.78)	<0.01
Pre-matched population (CABG vs. MT)	CABG	MT	CABG vs. MT	
(Total = 263)	(n = 169)	(n = 94)	Unadjusted HR (95% CI)	*P*-value
All-cause death	21 (12.4%)	29 (30.9%)	0.29 (0.17–0.52)	<0.01
Cardiac death	10 (5.9%)	18 (19.1%)	0.23 (0.10–0.51)	<0.01
CVA	8 (4.7%)	3 (3.2%)	1.04 (0.53–2.03)	0.89
Myocardial infarction	0 (0.0%)	5 (5.3%)	<0.01 (0.00–22.06)	0.21
Repeat revascularization	1 (0.6%)	18 (19.1%)	0.01 (0.002–0.11)	<0.01
MACCE	19 (11.2%)	37 (39.4%)	0.41 (0.31–0.55)	<0.01
Pre-matched population (PCI vs. MT)	PCI	MT	PCI vs. MT	
(Total = 224)	(n = 130)	(n = 94)	Unadjusted HR (95% CI)	*P*-value
All-cause death	19 (14.6%)	29 (30.9%)	0.41 (0.23–0.73)	<0.01
Cardiac death	9 (6.9%)	18 (19.1%)	0.31 (0.14–0.71)	<0.01
CVA	3 (2.3%)	3 (3.2%)	0.61 (0.12–3.06)	0.55
Myocardial infarction	5 (3.8%)	5 (5.3%)	0.65 (0.18–2.25)	0.49
Repeat revascularization	15 (11.5%)	18 (19.1%)	0.47 (0.23–0.94)	0.03
MACCE	26 (20.0%)	37 (39.4%)	0.42 (0.25–0.69)	<0.01

HR, hazard ratio; CI, confidence interval; CVA, cerebrovascular accident; MACCE, major adverse cardiac and cerebral events; other abbreviations as in Table 1.

had significantly lower incidence in the CABG group than in the MT group ($P < 0.01$ and $P < 0.01$), but were not significantly different when compared to the PCI group ($P = 0.31$ and $P = 0.49$). There was no statistical difference in the incidence of CVA and MI between each therapeutic group.

Table 4 and Fig. 2 represent post-propensity score matching analysis of clinical outcomes in the study population. The lower risk of CABG relative to PCI for repeat revascularization [hazard ratio (HR) 0.05, 95% confidence interval (CI) 0.01–0.40, $P < 0.01$] and MACCE (HR 0.43, 95% CI 0.21–0.85, $P = 0.01$) was significant. The lower risks of CABG relative to MT were represented in all-cause death (HR 0.37, 95% CI 0.16–0.82, $P = 0.01$), cardiac death (HR 0.24, 95% CI 0.08–0.75, $P = 0.01$), repeat revascularization (HR 0.01, 95% CI 0.00–0.54, $P = 0.02$) and MACCE (HR 0.10, 95% CI 0.04–0.27, $P < 0.01$). The lower risk of PCI relative to MT for repeat revascularization (HR 0.36, 95% CI 0.14–0.88, $P = 0.02$) and MACCE (HR 0.46, 95% CI 0.25–0.84, $p = 0.01$) was statistically significant.

4. Discussion

4.1. Main findings and clinical implication

The results of this study can be summarized as follows: (1) Of the three possible therapeutic strategies in management of multiple CTOs, CABG had the lowest incidence of repeat revascularization and MACCE compared with PCI or MT; (2) CABG had a significantly lower incidence of cardiac death compared with MT and had a similar incidence of cardiac death compared with PCI during the follow-up period.

In management of patients with multiple CTOs, we consider many issues, such as individualized risk/benefit analysis; clinical, angiographic or technical considerations; and associated comorbidities of patients [6, 26]. Nevertheless, we encounter a difficult problem in the selection of treatment modality [27]. Because there is limited data on clinical outcomes of therapeutic strategies in patients with multiple CTOs, there is no definitive evidence for an optimal treatment strategy [1]. Therefore, we investigated the clinical outcomes and the relative efficacies of three possible therapeutic strategies for patients with multiple CTOs at a single center. Although our study analyzed retrospective registry data, it is one of only a few trials reporting the clinical outcomes of patients with multiple CTOs.

4.2. Comparison with previous studies

In several previous studies, CTO revascularization was associated with improvement of angina symptoms and short-term mortality and long-term mortality [11,12,28]. On the other hand, no survival benefit was found in other studies [29,30]. The only randomized trial comparing medical therapy with revascularization in patients with sub-acute total coronary occlusion, the Occluded Artery Trial (OAT), showed no clinical benefit at 3-year follow-up after revascularization when compared with medical therapy in asymptomatic or poorly symptomatic patients with sub-acute MI [31]. However, most OAT patients had single occluded vessel disease of short duration, and 93% underwent single-vessel PCI. In our study, all patients had multiple CTO lesions and likely

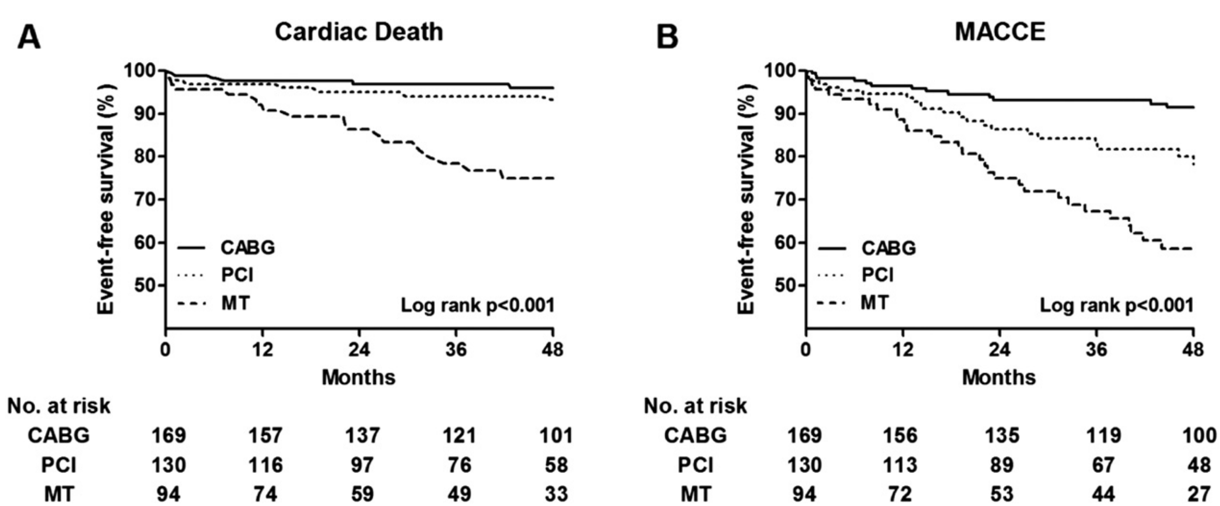

Fig. 1. Kaplan–Meier curve in respect of (A) cardiac death and (B) major adverse cardiac and cerebral events (MACCE) in pre-matching population according to three therapeutic strategies, as follows: coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and medication therapy (MT).

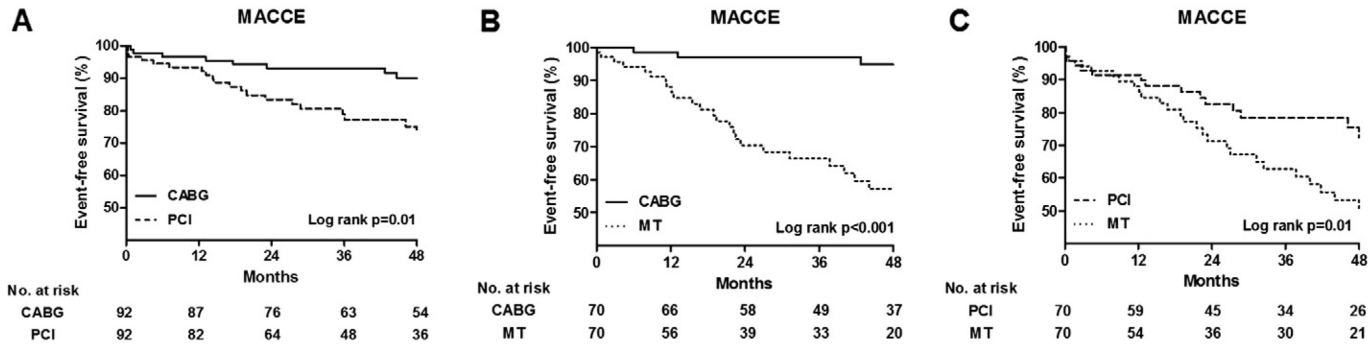

Fig. 2. Kaplan–Meier curve in major adverse cardiac and cerebral events (MACCE) in post-matching populations (A) between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) group, (B) between CABG and medication therapy (MT) group, (C) PCI and MT group.

had larger ischemic burdens of myocardium than seen in previous studies. Our results demonstrated that revascularization of multiple CTOs through CABG or PCI had a more favorable clinical outcome and relative effectiveness than MT alone. A similar tendency was shown in a nuclear sub-study of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [32]. Patients who underwent revascularization using PCI in addition to medical treatment had greater reduction in inducible ischemia compared with medical treatment alone and had a graded relationship between risk of events and extent and severity of residual ischemia. Benefit was greatest among patients with more severe baseline ischemia [32,33].

Subgroup analysis of the Coronary Angioplasty versus Bypass Revascularization investigation (CABRI) trial, one of a few studies evaluating CABG and PCI in patients with CTOs, demonstrated that CABG had better outcomes in these patients with multi-vessel disease in terms of subsequent morality and risk of acute MI [34]. In post hoc study of the All-Comer SYNTAX Trial, the presence of a total occlusion was less likely to result in complete revascularization in the PCI and CABG arms, with this effect being substantially more pronounced in the PCI arm and incomplete revascularization, compared with complete revascularization, has a detrimental impact on long-term clinical outcome, including mortality [35]. In recent meta-analysis of treatment strategy in patients with stable coronary artery disease, even though patients with CTO lesions were not separated in this analysis, CABG reduced the risk of death, MI, repeat revascularization compared with MT. All stent-based coronary revascularization technologies reduced the need for revascularization to a variable degree compared with MT [36].

Our data also demonstrate decreased risk of repeat revascularization and MACCE in the CABG group compared to the PCI or MT group in patients with multiple CTOs. This result is consistent with several previous trials that CABG, given the randomized evidence available in a relatively unselected population of coronary artery disease, is associated with better clinical outcomes in patients with complex coronary artery disease [37,38] and suggested that the magnitude of the superiority of CABG could be greater in selected population with multiple CTOs.

Table 4
Post-matching hazard ratio for clinical outcomes in patients with multiple chronic total occlusions between each therapeutic groups.

Post-matched population (CABG vs. PCI)	CABG	PCI	CABG vs. PCI	
(Total = 182)	(n = 91)	(n = 91)	HR (95% CI)	*P*-value
All-cause death	13 (14.3)	12 (13.2)	0.93 (0.42–2.05)	0.87
Cardiac death	9 (9.9)	8 (8.8)	0.97 (0.37–2.53)	0.95
CVA	3 (3.3)	1 (1.1)	2.69 (0.28–25.92)	0.39
Myocardial infarction	0 (–)	5 (5.5)	0.01 (0.00–18.84)	0.24
Repeat revascularization	1 (1.1)	14 (15.4)	0.05 (0.01–0.40)	<0.01
MACCE	13 (14.3)	23 (25.3)	0.43 (0.21–0.85)	0.01
Post-matched population (CABG vs. MT)	CABG	MT	CABG vs. MT	
(Total = 140)	(n = 70)	(n = 70)	HR (95% CI)	*P*-value
All-cause death	9 (12.9)	19 (27.1)	0.37 (0.16–0.82)	0.01
Cardiac death	4 (5.7)	13 (18.6)	0.24 (0.08–0.75)	0.01
CVA	1 (1.4)	1 (1.4)	0.82 (0.05–13.24)	0.89
Myocardial infarction	0 (–)	1 (1.4)	–	–
Repeat revascularization	0 (–)	16 (22.9)	0.01 (0.00–0.54)	0.02
MACCE	5 (7.1)	30 (42.9)	0.10 (0.04–0.27)	<0.01
Post-matched population (PCI vs. MT)	PCI	MT	PCI vs. MT	
(Total = 140)	(n = 70)	(n = 70)	HR (95% CI)	*P*-value
All-cause death	15 (21.4)	18 (25.7)	0.76 (0.38–1.51)	0.76
Cardiac death	8 (11.4)	14 (20.0)	0.52 (0.22–1.25)	0.14
CVA	2 (2.9)	2 (2.9)	0.86 (0.12–6.13)	0.88
Myocardial infarction	5 (7.1)	3 (4.3)	1.56 (0.37–6.53)	0.54
Repeat revascularization	7 (10.0)	16 (22.9)	0.36 (0.14–0.88)	0.02
MACCE	17 (24.3)	31 (44.3)	0.46 (0.25–0.84)	0.01

Abbreviations as in Tables 1 and 3.

4.3. Study limitation

Our study has some limitations. First, it was not a randomized trial; therefore, the selection of treatment group was likely influenced by patient characteristics and patient and doctor preferences. Patients with clinical co-morbidities, such as older age, prior MI, and LV dysfunction, more often received MT than CABG or PCI. As summarized in Table 1, the treatment groups differed from each other. Although the logistic EuroSCORE was similar between the three groups and propensity score matched analysis was performed, we cannot control potentially unknown variables of clinical co-morbidities. Second, it is not clear how generalized the results of the present study will be, because of the high rate of arterial graft use and off-pump technique in our registry. Third, we categorized patients based on the intention-to-treat principle, and it did not affect the completeness of revascularization. However, in real practice, we cannot accurately predict the completeness or incompleteness of revascularization in patients with multiple CTOs. Thus, the intention-to-treat principle may be favorable in real practice.

5. Conclusions

In conclusion, for management of patients with multiple CTOs, MT alone was associated with a higher risk of cardiac death and MACCE. PCI was also associated with a higher risk of MACCE, as driven by a higher repeat revascularization rate, but had a comparable risk of cardiac death compared to CABG. These findings suggest that CABG might be associated with better clinical outcome and considered as the preferred treatment strategy in patients with multiple CTOs. Further surgical randomized evidence would be needed in this specific population.

Conflict of interest

None declared.

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None.

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