Impact of diabetes mellitus on 5-year clinical outcomes in patients with chronic total occlusion lesions

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Background **Diabetes mellitus (DM) is a major predictor of cardiovascular morbidity and mortality. However, there are limited data on the impact of DM in patients who have chronic total occlusion (CTO) lesion on long-term outcomes.**

Patients and methods **A total of 822 CTO patients who underwent coronary angiography, treated by either percutaneous coronary intervention or optimal medical therapy, were enrolled and divided into two groups: (i) diabetic group ($n = 363$) and (ii) nondiabetic group ($n = 459$). Individual and composite major clinical outcomes were compared up to 5 years.**

Results **Propensity score matching analysis was carried out generating two groups (298 pairs, $n = 596$, *C*-statistic = 0.655) with balanced baseline characteristics. Up to 5 years, the DM group showed a higher trend toward revascularization (19.5 vs. 13.5%, $P = 0.051$) and major adverse cardiovascular events (MACE) (24.7 vs. 19.1%, $P = 0.097$) compared with the nondiabetic group. However, there was no difference in the incidence of death and myocardial infarction between the two groups. Subgroup analysis showed that the chronic kidney disease (CKD) subgroup was associated with a higher incidence of all-cause death, cardiac death, myocardial infarction, revascularization, and MACE in comparison with diabetic patients without CKD and nondiabetic patients, respectively (total MACE: 39 vs. 20.5 vs. 19.2% , $P = 0.001$). Insulin-dependent diabetic patients had a significantly higher incidence of MACE (hazard ratio = 1.58; 95% confidence interval: 1.04–2.40; $P = 0.03$) compared with the nondiabetic patients.**

Conclusion **Diabetic patients with CTO were associated with a trend toward a higher incidence of revascularization and total MACE up to 5 years. Insulin-dependent and diabetic patients with CKD subgroups had a significantly higher incidence of total MACE.** ***Coron Artery Dis*** **00:000–000**

Coronary Artery Disease 2017, **00**:000–000

Keywords: chronic total occlusion, diabetes mellitus, percutaneous coronary intervention

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Received 5 June 2017 **Revised** 7 August 2017 **Accepted** 20 August 2017

Introduction

Diabetes mellitus (DM) is a well-known major risk factor for the development of cardiovascular diseases (CVDs) and associated clinical complications [1]. The development of cardiovascular risk is not only related to the development of type 2 DM but also insulin resistance, often referred to as metabolic syndrome, which is associated with early appearance of cardiovascular risk, before the development of type 2 DM [2].

Coronary chronic total occlusions (CTO) are one of the most challenging lesions to treat because of the relatively higher failure rates and technical complexity for recanalization [3]. CTO is associated with a higher mortality rate, especially in patients with acute myocardial infarction (MI), multivessel disease or left main [4–9]. It is also associated with a reduced left ventricular ejection fraction (<40%) and further deterioration of left ventricular ejection fraction in ST-segment elevation myocardial infarction (STEMI) patients.

Successful percutaneous coronary intervention (PCI) for coronary CTO has been associated with reduced long-term cardiac mortality and need for coronary artery bypass graft surgery [10]. CTO–PCI is also associated with better outcomes and improvements in left ventricular function, reducing angina symptoms compared with failed CTO–PCI [11–13]. Therefore, CTO–PCI is a class IIa recommendation in the current guidelines in patients with appropriate indications and suitable anatomy. If performed by operators with appropriate expertise, it is known to yield over an 80% success rate [14,15].

 DOI: 10.1097/MCA.0000000000000562

However, the benefits of CTO recanalization over planned optimal medical therapy (OMT) were studied in the (DECISION-CTO) randomized clinical trial, which showed that there were no differences in individual outcomes between the two treatment modalities over a 5-year follow-up [16].

There are limited data on the impact of DM in patients who have coronary CTO lesions on long-term clinical outcomes. The aim of this study is to estimate the impact of DM on the 5-year clinical outcomes in patients with coronary CTO lesions irrespective of the treatment strategy used with these patients.

Patients and methods

We obtained the data from the CTO registry of Korea University Guro Hospital (KUGH), Seoul, South Korea. In brief, it is a single-center, prospective, all-comer registry between January 2004 and May 2014 that is designed to reflect the 'real-world' practice. Data were collected by well-trained study-coordinators using a standardized case report form. The participants or their legal guardians were provided a thorough literal and verbal explanation of the study procedures before they provided a written consent to participate in the study. The study protocol was approved by the Medical Device Institutional Review Board of KUGH. The authors of this manuscript have certified that the information presented here is true and correct as reflected in the records of the Medical Device Institutional Review Board (#MD07014).

Patient population

Of 4909 consecutive patients who were diagnosed with significant coronary artery disease (≥70% coronary stenosis) by coronary angiography during the above-mentioned period, a total of 822 consecutive patients who was diagnosed with coronary CTO lesion and treated with either PCI or OMT were enrolled in the CTO registry of KUGH. These patients were divided into two groups according to the presence of DM: (i) the diabetic group ($n = 363$) and (ii) the nondiabetic group ($n = 459$). After propensity score matching (PSM) analysis was carried out to adjust for potential confounders, two propensity-matched groups (298 pairs, $n = 596$, C-statistic = 0.655) were generated whose baseline characteristics were well balanced.

Study definitions

DM was defined according to the definition of the American Diabetes Association as follows [17]: (a) fasting plasma glucose of at least 126 mg/dl (7.0 mmol/l), or (b) 2-h plasma glucose of at least 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test, or (c) glycated hemoglobin of at least 6.5% (48 mmol/mol), or (d) presence of classic symptoms of hyperglycemia or hyperglycemic crisis with random plasma glucose of at least 200 mg/dl (11.1 mmol/l) [17]. CTO lesion was defined as a complete blockage of a coronary artery (typically described > 99% stenosis) for longer than 3 months, with a clinically significant decrease in blood flow [thrombolysis in myocardial infarction (TIMI) 0–1]. Chronic kidney disease (CKD) was defined as the presence of kidney damage or glomerular filtration rate less than 60 ml/min/1.73 m^2 for 3 or more months and could be diagnosed without knowledge of its cause [18]. Major adverse cardiovascular events (MACE) were defined as the composite of all-cause death, MI, and revascularization including PCI [target lesion revascularization (TLR), and/or target vessel revascularization (TVR)] and coronary artery bypass graft.

Medical treatment

All patients received a dual antiplatelet regimen including aspirin and clopidogrel. Aspirin 200–300 mg was preloaded orally, followed by a daily administration of 100 mg indefinitely. Clopidogrel 300-600 mg was preloaded before PCI, followed by a daily administration of 75 mg for at least 1 year. Adjunctive cilostazol to the dual antiplatelet regimen was considered a triple antiplatelet therapy and was administered to high-risk patients depending on the physician's discretion. Cilostazol was administered by 200 mg postloading and then 100 mg twice daily for at least 1 month.

Antithrombotic therapy used for PCI included enoxaparin 1 mg/kg twice daily administered before PCI and after PCI during the hospital stay (within 7 days) and a reduced dose of unfractionated heparin (a bolus of 50–70 U/kg) was administered before PCI for the first hour of the procedure. Glycoprotein IIb/IIIa blocker was administered depending on the physician's discretion.

OMT included dual antiplatelet therapy; anti-ischemic therapy (β-blockers, calcium channel blockers alone or in combination, and isosorbide mononitrate); angiotensin-converting-enzyme inhibitor, angiotensin II receptor antagonists for hypertensive patients and patients with reduced ejection fraction; and statin therapy to reach the low-density lipoprotein target of less than 70 mg/dl. Lifestyle modification for diet, weight loss, glycemic control, and smoking cessation was advised to patients along with the OMT.

Percutaneous coronary intervention procedure

Indications for performing PCI to CTO lesions included patients with intolerable angina despite OMT, or large ischemic area (>10%), or ischemic impairment of myocardial systolic function with evidence of myocardial viability by a noninvasive stress test [19]. Generally, simple predilation was performed to achieve an adequate luminal diameter, which was necessary to accommodate for the unexpanded drug-eluting stents and their delivery system. Thrombus aspiration or mechanical thrombectomy was performed if clinically indicated.

Statistical analysis

All statistical analyses were carried out using SPSS software (version 20.0; SPSS-PC, Inc., Chicago, Illinois, USA). As testing of our continuous variables has shown that they are approximately normally distributed, Student's *t*-test and the analysis of variance test were used for the analysis of continuous variables in different subgroups and they were expressed as mean ± SD. Categorical data were expressed as percentages and were compared using χ^2 statistics or Fisher's exact test. A P value of 0.05 was considered statistically significant.

PSM was performed to adjust any potential confounders using the logistic regression model. We tested all available variables that could be of potential relevance to estimate the propensity scores as follows: age, sex, cardiovascular risk factors (hypertension, dyslipidemia, cerebrovascular disease peripheral artery disease, CKD, heart failure, and smoking), and angiographic and procedural characteristics (significant coronary lesion artery, CTO lesion artery, lesion locations). PSM was performed using a 1 : 1 matching protocol using the nearest-neighbor matching algorithm, with a caliper width equal to 0.05 of the SD of the propensity score, yielding 298 well-matched pairs.

Various clinical outcomes up to 5 years were estimated by the Kaplan–Meier analysis, and differences between the groups were compared using the log-rank test before and after PSM. Proportional hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models to assess the HRs between the study groups.

Study endpoints

Primary endpoint, individual major clinical outcomes, and MACE, the composite of all-cause death, MI, stroke, and revascularization, were compared between the two groups for up to 5 years of clinical follow-up. The secondary endpoint was to determine the coeffect of other risk factors in addition to diabetes using a subgroup analysis over a 5-year follow-up.

Results

A total of 822 consecutive CTO patients who underwent coronary angiography, treated either by PCI or by OMT, were enrolled in this study. They were divided into two groups according to the presence of DM: (i) the diabetic group ($n = 363$) and (ii) the nondiabetic group ($n = 459$). After a PSM analysis was carried out, two well-matched groups were generated (298 pairs, $n = 596$, C-statistic = 0.655).

The baseline characteristics and coronary angiographic findings are presented in Tables 1 and 2. In the entire population, the diabetic group had more women, and a higher incidence of hypertension and CKD than the nondiabetic group. Furthermore, angiographically, the diabetic group showed a higher number of diseased vessels and a higher frequency of right coronary artery CTO lesions.

After PSM matching, except for heart rate, which still showed a significant difference between the two groups, there were no considerable differences in the baseline clinical, procedural and angiographic characteristics, such as age, sex, smoking, hypertension, dyslipidemia, MI, stroke, peripheral arterial disease, CKD history, frequency of PCI-treated CTO, number of vessels treated, and frequency of multivessel disease between both matched groups.

Various clinical outcomes over the 5-year clinical follow-up (48.8 ± 19.5 months) were analyzed by Kaplan–Meier curved analysis and are presented in Table 3. In the entire cohort, the diabetic group showed a higher trend of revascularization rates, especially the non-TVR rate, than the nondiabetic group, whereas there were no significant differences in the clinical outcomes between the two groups including all-cause death, cardiac death, MI, TLR, and TVR (Fig. 1).

In the PSM population, the higher trend of revascularization was more defined; the diabetic group also showed a higher trend of total MACE compared with the nondiabetic group. However, there were still no significant differences in other individual clinical outcomes such as all-cause death, cardiac death, MI, TLR, and TVR after PSM (Fig. 1).

Subgroup analysis was carried out to determine the coeffect of other risk factors in addition to diabetes over a 5-year follow-up. Diabetic patients with CKD showed a significantly higher incidence of all-cause death, cardiac death, MI, and total revascularization, especially non-TVR, and MACE (HR = 1.34; 95% CI: 1.05–1.71; $P = 0.01$) in comparison with diabetic patients without CKD and nondiabetic patients (Table 4).

Insulin-dependent diabetic patients had a higher risk and had a significantly higher incidence of total MACE (HR = 1.58; 95% CI: 1.04–2.40; $P = 0.03$) compared with nondiabetic patients, and had a higher trend toward non-TVR and MACE compared with the non-insulin-dependent diabetic and nondiabetic subgroups (Table 5).

Diabetic patients with dyslipidemia showed a higher trend toward cardiac death compared with diabetic patients without dyslipidemia and nondiabetic patients (Table 4), whereas diabetic patients with hypertension did not show any significant difference in outcome compared with diabetic patients without hypertension and nondiabetic patients over the 5-year follow-up (Table 5).

Discussion

The main findings of this study are as follows: (i) diabetic patients with CTO treated either by PCI or by OMT

Table 1 Baseline characteristics in the entire cohort and propensity-matched groups

	Entire patients [*n* (%)]				Matched patients [*n* (%)]			
Variables	Diabetes (*n* = 363)	Nondiabetes (*n* = 459)	*P* value	SD	Diabetes (*n* = 298)	Nondiabetes (*n* = 298)	*P* value	SD
Sex: male	251 (69.1)	350 (76.3)	0.022	0.84	213 (71.5)	216 (72.5)	0.784	0.12
Age (mean ± SD) (years)	64 ± 9	64 ± 11	0.847	0.01	64 ± 9	64 ± 12	0.944	−0.01
Left ventricular ejection fraction (mean ± SD) (%)	49 ± 13	50 ± 11	0.085	−0.13	49 ± 12	51 ± 11	0.173	−0.11
Blood pressure (mean ± SD)								
Systolic	140 ± 24	137 ± 25	0.138	0.10	140 ± 24	138 ± 24	0.197	0.11
Diastolic	79 ± 35	78 ± 14	0.773	0.02	77 ± 13	78 ± 15	0.573	−0.05
Heart rate (mean ± SD)	75 ± 15	71 ± 13	0.000	0.29	74 ± 15	70 ± 13	0.001	0.28
Myocardial infarction	77 (21.2)	99 (21.6)	0.902	0.08	58 (19.5)	66 (22.1)	0.419	0.59
STEMI	27 (7.4)	47 (10.2)	0.163	0.94	22 (7.4)	26 (8.7)	0.547	0.47
NSTEMI	50 (13.8)	51 (11.1)	0.248	−0.76	36 (12.1)	39 (13.1)	0.711	0.28
Hypertension	263 (72.5)	273 (59.5)	< 0.001	−1.60	205 (68.8)	202 (67.8)	0.792	−0.12
Dyslipidemia	117 (32.2)	133 (29)	0.314	−0.59	92 (30.9)	91 (30.5)	0.929	−0.06
Stroke	45 (12.4)	44 (9.6)	0.198	−0.85	33 (11.1)	32 (10.7)	0.895	−0.10
Hemorrhagic	14 (4.1)	8 (2.0)	0.099	−1.19	10 (3.6)	7 (2.8)	0.587	−0.47
Ischemic	31 (9.1)	36 (9.1)	0.990	0.01	23 (8.2)	25 (9.8)	0.520	0.53
Chronic kidney disease	41 (11.3)	22 (4.8)	0.001	−2.29	17 (5.7)	19 (6.4)	0.731	0.27
Smoking history	185 (51.0)	260 (56.6)	0.105	0.78	157 (52.7)	156 (52.3)	0.935	−0.05
Current	125 (34.4)	179 (39.0)	0.178	0.75	109 (36.6)	106 (35.6)	0.798	−0.17
CCS Classification			0.753				0.898	
I	165 (45.5)	192 (41.8)		−0.55	129 (43.3)	126 (42.3)		−0.15
II	72 (19.8)	93 (20.3)		0.10	66 (22.1)	61 (20.5)		−0.36
III	60 (16.5)	83 (18.1)		0.37	50 (16.8)	52 (17.4)		0.16
IV	66 (18.2)	91 (19.8)		0.38	53 (17.8)	59 (19.8)		0.46

CCS, Canadian Cardiovascular Society; NSTEMI, non-ST-segment elevation myocardial infarction; SD, standardized difference; STEMI, ST-segment elevation myocardial infarction.

Table 2 Angiographic and procedural characteristics

	Entire patients [*n* (%)]				Matched patients [*n* (%)]			
Variables	Diabetes (*n* = 363)	Nondiabetes (*n* = 459)	*P* value	SD	Diabetes (*n* = 298)	Nondiabetes (*n* = 298)	*P* value	SD
PCI procedure	279 (76.9)	361 (78.6)	0.539	0.20	234 (78.5)	236 (79.2)	0.841	0.08
Multivessel disease	256 (70.5)	310 (67.5)	0.359	−0.36	197 (66.1)	212 (71.1)	0.185	0.61
Number of vessels (mean ± SD)	2 ± 0.8	1.9 ± 0.7	0.011	0.18	1.9 ± 0.8	2 ± 0.7	0.918	−0.01
Significant coronary lesion								
LAD	265 (73.0)	316 (68.8)	0.194	−0.50	212 (71.1)	210 (70.5)	0.857	−0.08
LCX	220 (60.6)	266 (58.0)	0.442	−0.35	171 (57.4)	175 (58.7)	0.740	0.18
RCA	258 (71.1)	289 (63.0)	0.014	−0.99	200 (67.1)	202 (67.8)	0.861	0.08
LM	36 (9.9)	34 (7.4)	0.200	−0.85	25 (8.4)	25 (8.4)	> 0.99	0.00
Ramus	10 (2.8)	24 (5.2)	0.077	1.24	9 (3.0)	6 (2.0)	0.433	−0.63
Multivessel CTO	40 (11.0)	60 (13.1)	0.371	0.59	33 (11.1)	29 (9.7)	0.591	−0.42
Number of CTO vessels (mean ± SD)	1.1 ± 0.3	1.1 ± 0.3	0.252	−0.08	1.1 ± 0.3	1.1 ± 0.3	0.695	0.03
LAD	113 (31.1)	168 (36.6)	0.101	0.94	93 (31.2)	100 (33.6)	0.540	0.41
LCX	102 (28.1)	149 (32.5)	0.177	0.79	94 (31.5)	87 (29.2)	0.533	−0.43
RCA	186 (51.2)	200 (43.6)	0.029	−1.12	142 (47.7)	141 (47.3)	0.935	−0.05
Ramus	2 (0.6)	5 (1.1)	0.473	0.59	2 (0.7)	1 (0.3)	> 0.99	−0.47
CTO location			0.117				0.584	
Proximal	163 (44.9)	239 (52.1)		1.03	136 (45.6)	147 (49.3)		0.54
Mid	146 (40.2)	164 (35.7)		−0.73	116 (38.9)	112 (37.6)		−0.22
Distal	54 (14.9)	56 (12.2)		−0.73	46 (15.4)	39 (13.1)		−0.62
Collateral grade			0.606				0.427	
I	33 (9.1)	47 (10.2)		0.37	28 (9.4)	31 (10.4)		0.32
II	56 (15.4)	72 (15.7)		0.07	47 (15.8)	46 (15.4)		−0.09
III	161 (44.4)	183 (39.9)		−0.69	133 (44.6)	115 (38.6)		−0.94
IV	113 (31.1)	157 (34.2)		0.54	90 (30.2)	106 (35.6)		0.94
Failed CTO procedure	23 (6.3)	44 (9.6)	0.091	1.15	21 (7.0)	28 (9.4)	0.297	0.82
Residual CTO	179 (49.3)	231 (50.3)	0.772	0.14	145 (48.7)	140 (47.0)	0.682	−0.24

CTO, chronic total occlusion; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standardized difference.

were associated with a higher trend toward any revascularization, particularly non-TVR and total MACE, compared with the nondiabetic patients. (ii) There was no significant difference in the incidence of all-cause death, cardiac death, and MI between the two groups. (iii) Diabetic patients with concomitant CKD had a

Table 3 Various clinical outcomes up to 5 years by Kaplan–Meier curved analysis

Outcomes	Incidence of event at 5 years [*n* (%)]				
	Diabetes (*n* = 363)	Nondiabetes (*n* = 459)	Log-rank test	Hazard ratio (95% confidence interval)	*P* value
Entire patients					
All-cause death	25 (7.6)	24 (5.7)	0.284	–	–
Cardiac death	14 (4.2)	13 (3.2)	0.381	–	–
Myocardial infarction	15 (4.7)	12 (2.9)	0.200	–	–
STEMI	6 (1.8)	7 (1.6)	0.848	–	–
Revascularization	61 (19.4)	65 (15.9)	0.188	–	–
Target lesion (CTO vessel)	28 (8.9)	31 (7.5)	0.496	–	–
Target vessel (CTO vessel)	31 (9.9)	39 (9.3)	0.854	–	–
Nontarget vessel (non-CTO vessel)	44 (14.1)	40 (9.9)	0.074	1.47 (0.96–2.26)	0.076
Stroke	6 (1.9)	3 (0.7)	0.160	–	–
Total MACE	82 (25.1)	88 (20.8)	0.140	–	–
TLR MACE	42 (12.9)	45 (10.8)	0.332	–	–
Matched patients					
All-cause death	20 (7.4)	18 (6.5)	0.698	–	–
Cardiac death	11 (4.1)	11 (4.2)	0.968	–	–
Myocardial infarction	11 (4.3)	7 (2.7)	0.331	–	–
STEMI	6 (2.2)	3 (1.0)	0.307	–	–
Revascularization	50 (19.5)	35 (13.5)	0.051	1.53 (0.99–2.36)	0.053
Target lesion (CTO vessel)	21 (8.2)	16 (6.1)	0.342	–	–
Target vessel (CTO vessel)	24 (9.4)	18 (6.9)	0.281	–	–
Nontarget vessel (non-CTO vessel)	36 (14.1)	24 (9.2)	0.080	1.57 (0.94–2.64)	0.083
Stroke	6 (2.3)	2 (0.8)	0.153	–	–
Total MACE	66 (24.7)	52 (19.1)	0.097	1.35 (0.94–1.95)	0.098
TLR MACE	32 (12.1)	26 (9.9)	0.347	–	–

CTO, chronic total occlusion; MACE, major adverse cardiac events (defined as the composite of all-cause death, myocardial infarction, stroke, and revascularization; STEMI, ST-segment elevation myocardial infarction); TLR, total lesion revascularization.

significantly higher incidence of all-cause death, cardiac death, MI, any revascularization (mainly non-TVR), total MACE, and TLR MACE over 5 years of clinical follow-up. (iv) Insulin-dependent diabetic patients had a significantly higher incidence of total MACE compared with the nondiabetic patients.

DM is known to be an independent risk factor for CVD and is usually associated with more adverse cardiovascular events [20]. Recently, the first and only randomized trial to date comparing CTO revascularization versus OMT in stable patients (DECISION-CTO) on 834 patients from 19 Asian institutions has shown no differences in any of the individual outcomes between the study arms over a 5-year follow-up. Subgroup analysis of this study population also confirmed that OMT was noninferior to CTO–PCI in the diabetic subgroup of patients [16]. However, there are limited data discussing the impact of DM as a predictor of adverse outcomes on patients with coronary CTO lesions on long-term clinical follow-up.

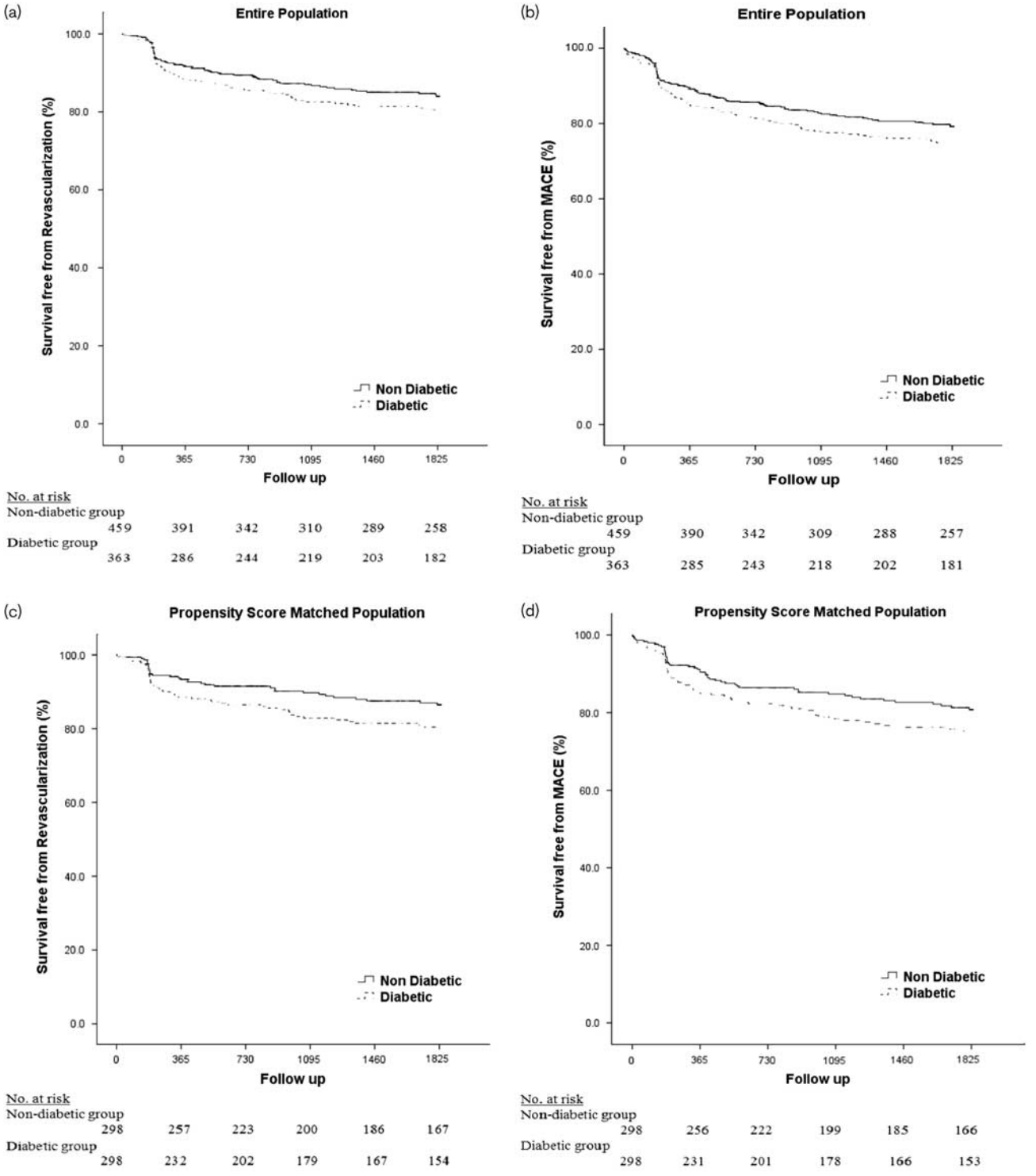
There was a significant increase in the risk of mortality following contemporary PCI in diabetic patients compared with nondiabetic patients when identifiable confounders were controlled by multivariate modeling, despite advances in interventional techniques [21,22]. Previous studies that compared the outcome of diabetic and nondiabetic patients undergoing successful PCI of CTO reported that diabetic patients were associated with higher in-hospital adverse events [23] and DM was a predictive factor for MACE in elderly patients with CTO treated with PCI. Other factors including the type of stent, final minimal luminal diameter, DM with renal impairment, and glycated hemoglobin level on admission were predictive factors of worse prognosis [24].

Although diabetes was not associated with significant outcomes in this study, diabetic patients had a higher trend toward any revascularization and total MACE compared with the nondiabetic group, which reinforces the effect of diabetes as a strong predictor of adverse outcomes in CVD patients.

Post-PCI short-term and long-term adverse cardiovascular outcomes such as mortality, MI, TLR, MACEs, and stent thrombosis are significantly higher in insulin-treated DM patients compared with non-insulin-treated DM patients [25–27]. In a previous study, a 12-month follow-up of patients undergoing PCI for CTO lesions showed that TLR and total MACEs were more common in the DM group than in the non-DM group, whereas DM patients on insulin had a higher incidence of all-cause death, TLR, TVR, TLR-MACEs, TVR-MACEs, and total MACEs [27]; all these studies confirm the increased risk of the insulin-dependent subgroup of patients with coronary CTO for adverse clinical outcomes.

In this study, diabetic patients with CKD were associated with a significantly higher incidence of adverse clinical outcomes including all-cause death, cardiac death, any MI, and any revascularization, especially the non-TVR and total MACE. A similar study involving patients who

Fig. 1



Five-year clinical outcomes as analyzed by Kaplan–Meier curved analysis. (a) Total revascularization in the entire population, (b) Major adverse cardiac events (MACE) in the entire population, (c) Total revascularization in the propensity score-matched population, (d) MACE in the propensity score-matched population. There was a trend toward higher revascularization and MACE in diabetic than nondiabetic patients, which was more defined in the propensity score-matched population.

Table 4 Clinical outcomes of the CKD and dyslipidemia subgroups up to 5 years of follow-up

	Incidence of event at 5 years [*n* (%)]				Incidence of event at 5 years [*n* (%)]			
Outcomes	DM with CKD (*n* = 41)	DM without CKD (*n* = 322)	Nondiabetic (*n* = 459)	Log-rank test	DM with dyslipidemia (*n* = 117)	DM without dyslipidemia (*n* = 246)	Nondiabetic (*n* = 459)	Log-rank test
All-cause death	6 (14.6)	19 (5.9)	24 (5.2)	0.035	9 (7.7)	16 (6.5)	24 (5.2)	0.504
Cardiac death	4 (9.8)	10 (3.1)	13 (2.8)	0.039	8 (6.8)	6 (2.4)	13 (2.8)	0.06
Myocardial infarction	4 (9.8)	11 (3.4)	12 (2.6)	0.016	7 (6)	8 (3.3)	12 (2.6)	0.18
STEMI	0 (0)	6 (1.9)	7 (1.5)	0.684	2 (1.7)	4 (1.6)	7 (1.5)	0.976
Revascularization	12 (29.3)	49 (15.2)	65 (14.2)	0.003	21 (17.9)	40 (16.3)	65 (14.2)	0.408
Target lesion (CTO vessel)	4 (9.8)	24 (7.5)	31 (6.8)	0.483	9 (7.7)	19 (7.7)	31 (6.8)	0.766
Target vessel (CTO vessel)	5 (12.2)	26 (8.1)	39 (8.5)	0.393	10 (8.5)	21 (8.5)	39 (8.5)	0.967
Nontarget vessel (non-CTO vessel)	41 (22.0)	35 (10.9)	40 (8.7)	0.003	16 (13.7)	28 (11.4)	40 (8.7)	0.167
Total MACE	41 (39)	66 (20.5)	88 (19.2)	0.001	28 (23.9)	54 (22)	88 (19.2)	0.351
TLR MACE	8 (19.5)	34 (10.6)	45 (9.8)	0.054	17 (14.5)	25 (10.2)	45 (9.8)	0.32

CKD, chronic kidney disease; CTO, chronic total occlusion; DM, diabetes mellitus; MACE, major adverse cardiac events (defined as the composite of all-cause death, myocardial infarction, stroke, and revascularization; STEMI, ST-segment elevation myocardial infarction); TLR, total lesion revascularization.

Table 5 Clinical outcomes of hypertensive, and insulin-dependent subgroups up to 5 years of follow-up

	Incidence of event at 5 years [*n* (%)]				Incidence of event at 5 years [*n* (%)]			
Outcomes	DM with HTN (*n* = 163)	DM without HTN (*n* = 100)	Nondiabetic (*n* = 459)	Log-rank test	Insulin-dependent DM (*n* = 85)	Non-insulin-dependent DM (*n* = 278)	Nondiabetic (*n* =459)	Log-rank test
All-cause death	17 (6.5)	8 (8)	24 (5.2)	0.466	8 (9.4)	17 (6.1)	24 (5.2)	0.327
Cardiac death	7 (2.7)	7 (7)	13 (2.8)	0.074	5 (5.9)	9 (3.2)	13 (2.8)	0.352
Myocardial infarction	12 (4.6)	3 (3)	12 (2.6)	0.3.17	5 (5.9)	10 (3.6)	12 (2.6)	0.279
STEMI	3 (1.1)	3 (3)	7 (1.5)	0.427	7 (1.5)	5 (1.8)	7 (1.5)	0.886
Revascularization	46 (17.5)	15 (15)	65 (14.2)	0.351	20 (23.5)	41 (14.7)	65 (14.2)	0.121
Target lesion (CTO vessel)	18 (6.8)	10 (10)	31 (6.8)	0.45	9 (10.6)	19 (6.8)	31 (6.8)	0.499
Target vessel (CTO vessel)	19 (7.2)	12 (12)	39 (8.5)	0.34	10 (11.8)	21 (7.6)	39 (8.5)	0.605
Nontarget vessel (non-CTO vessel)	34 (12.9)	10 (10)	40 (8.7)	0.135	15 (7.6)	29 (10.4)	40 (8.7)	0.053
Total MACE	61 (23.2)	21 (21)	88 (19.2)	0.334	26 (30.6)	56 (20.1)	88 (19.2)	0.097
TLR MACE	25 (9.5)	17 (17)	45 (9.8)	0.076	14 (16.5)	28 (10.1)	45 (9.8)	0.227

CTO, chronic total occlusion; DM, diabetes mellitus; HTN, hypertension; MACE, major adverse cardiac events (defined as the composite of all-cause death, myocardial infarction, stroke, and revascularization; STEMI, ST-segment elevation myocardial infarction); TLR, total lesion revascularization.

presented with STEMI and underwent primary PCI showed that the prevalence of CTO in a non-infarct-related artery in patients with CKD was twice that of patients without CKD and CKD was a strong independent predictor of early and late mortality [28]. However, the impact of the CKD on CTO patients should be assessed further to determine whether this result of adverse outcomes is because of the added risk of CKD to DM, or CKD itself being an independent risk factor for adverse cardiovascular outcomes in patients with CTO lesion.

Limitations

There are some limitations to this study. First, the present study was analyzed retrospectively, and PSM analysis was carried out to minimize the confounding factors that might have influenced the results otherwise. Also, the registry was designed with an all-comer prospective registry from 2004. However, we could not adjust for all of the limiting factors not found through medical records or collected through telephone contacts. Second, the present study is an observational study with a relatively small study population, and therefore further well-designed randomized trials with larger study populations are needed to confirm these findings.

Conclusion

Diabetes is associated with a higher trend toward any revascularization, particularly non-TVR and total MACE in the 5-year follow-up of CTO patients treated either by PCI or by OMT. This study implies that diabetic patients with CTO should be managed more carefully during clinical follow-up. Insulin-dependent and CKD subgroups significantly increased the incidence of adverse events in diabetic patients with CTO. Further

randomized studies are needed to confirm the outcome of diabetes on CTO patients, with special attention to insulin-dependent and CKD subgroups.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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