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Original Article

Influence of chronic kidney disease on the outcome of patients with chronic total occlusion

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Abstract: *Objective:* Chronic kidney disease (CKD) predicted a poor prognosis in patients with coronary artery disease. There is a paucity of data on outcomes after revascularization in patients with chronic total occlusion (CTO) and CKD. This study aims to investigate the impact of CKD on the revascularization of CTO. *Methods:* This study enrolled 1,092 CTO patients received treatments in our hospital between February 2009 and January 2014. Major adverse cardiac and cerebrovascular events (MACCE) and all-cause mortality were compared to evaluate medium- and long-term outcomes. Median follow-up was 39 months (interquartile range, 27-52 months). *Result:* CKD decreased cumulative MACCE-free survival rate (54.4 ± 6.2% vs. 70.9 ± 2.5%, $P < 0.001$) and cumulative survival rate (68.6 ± 6.3% vs. 90.5 ± 1.6%, $P < 0.001$). Revascularization was associated with better outcomes among patients with (MACCE-free survival rate: 64.8 ± 5.7% vs. 20.1 ± 15.3%, $P = 0.009$; survival rate 78.4 ± 5.6% vs. 38.7 ± 17.4%, $P = 0.006$) or without CKD (MACCE-free survival rate 73.9 ± 2.7% vs. 61.0 ± 5.4%, $P = 0.001$; survival rate 92.9 ± 1.5% vs. 83.8 ± 4.0%, $P = 0.009$). The benefit from revascularization was attenuated by CKD. Compared with percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) had similar cumulative survival rates among patients, whether with or without CKD, but was associated with a higher cumulative MACCE-free survival rate (80.5 ± 3.4% vs. 68.5 ± 4.0%, $P = 0.017$) among patients without CKD. *Conclusion:* CKD attenuated the benefit from revascularization for CTO. Moreover, CABG was not superior to PCI among CTO patients, but with a reduction in MACCE in patients without CKD.

Keywords: Chronic total occlusion, chronic kidney disease, revascularization; percutaneous coronary intervention, coronary artery bypass grafting

Introduction

Chronic kidney disease (CKD) was associated with a poor prognosis in patients with coronary artery disease (CAD) [1-4]. As the last stage of coronary atherosclerosis, chronic total occlusion (CTO) lesions account for one third of CAD confirmed by the non-emergency coronary angiography (CAG) [5]. However, relatively few evidence of the influence of CKD on patients with CTOs has been reported. Moreover, despite technical advancement and progress of interventional equipment, which improve the successful rate and the prevalence of percutaneous coronary intervention (PCI) for CTOs, there is a paucity of data on outcomes after revascularization in patients with CTO and CKD. This study aims to observe the impact of CKD on the prognosis of patients with CTO and to evaluate the benefit from different revascularization strategy among patients with CTOs and CKD.

Methods

This retrospective study enrolled 1092 CTO patients received successful revascularization and medicine treatment in cardiology center of Shandong Provincial Hospital between January 2009 and January 2014. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong University. All participants specifically consent to participate in this study. And written informed consent was obtained from all participants. All data obtained from medical records in a fully anony-

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	Total (n = 1092)	With CKD (n = 210)	Without CKD (n = 882)	*P* Value
Age (± SD), y	62.5 ± 6.4	63.3 ± 5.9	62.3 ± 6.5	0.033
Agedness (≥ 65), n (%)	455 (41.7)	100 (47.6)	355 (40.2)	0.052
Male, n (%)	692 (63.4)	129 (61.4)	563 (63.8)	0.516
Clinical data, n (%)				
Hypertension, n (%)	697 (63.8)	138 (65.7)	559 (63.4)	0.527
DM, n (%)	470 (43.0)	116 (55.2)	354 (40.1)	< 0.001
Hypercholesterolemia, n (%)	174 (15.9)	50 (23.8)	124 (14.1)	0.001
Smoking, n (%)	309 (28.3)	75 (35.7)	234 (26.5)	0.008
Pre-MI, n (%)	506 (46.3)	99 (47.1)	407 (46.1)	0.794
Pre-TIA/Stroke, n (%)	121 (11.1)	31 (14.8)	90 (10.2)	0.059
LVEF (± SD)	51.4 ± 4.5	49.4 ± 4.7	51.8 ± 4.3	< 0.001
LVEF < 50%, n (%)	345 (31.6)	97 (46.2)	248 (28.1)	< 0.001
Clinial symptom				
SAP	346 (31.7)	63 (30.0)	283 (32.1)	
UAP	448 (41.0)	76 (36.2)	372 (42.2)	
STEMI	154 (14.1)	35 (16.7)	119 (13.5)	
NSTEMI	144 (13.2)	36 (17.1)	108 (12.2)	
Angiographic characteristics				
MVCAD, n (%)	1013 (92.8)	196 (93.3)	817 (92.6)	0.724
Diseased vessels per patient (± SD)	2.28 ± 0.59	2.35 ± 0.60	2.26 ± 0.58	0.047
CTO vessel per patient (± SD)	1.08 ± 0.28	1.06 ± 0.24	1.09 ± 0.28	0.187
CTO located in				0.273
LAD, n (%)	534 (48.9)	111 (52.9)	423 (48.0)	
Circumflex, n (%)	252 (23.1)	41 (19.5)	211 (23.9)	
RCA, n (%)	395 (36.2)	71 (33.8)	324 (36.7)	
SYNTAX Score (± SD)	28.4 ± 6.0	31.4 ± 6.4	27.6 ± 5.6	< 0.001
Treatment, n (%)				0.015
Revascularization	858 (78.6)	152 (72.4)	706 (80.0)	
PCI	475 (43.5)	86 (41.0)	389 (44.1)	
CABG	383 (35.1)	66 (31.4)	317 (35.9)	
Drug treatment	234 (21.4)	58 (27.6)	176 (20.0)	

CABG, Coronary artery bypass grafting; CTO, chronic total occlusion; DM, diabetic mellitus; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVCAD, multivessel coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAP, stable angina; STEMI, ST-segment elevation myocardial infarction; SYNTAX, the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIA, transient ischemic attacks; UAP, Unstable angina.

mized and de-identified manner, none of the authors have access to identifying information.

All patients had at least one occluded main epicardial vessel which was ascertained by at least 2 experienced interventional cardiologists after careful assessment for coronary angiograph (CAG), medical history and cardiac symptoms in the previous 3 months. Patients with severe concomitant cardiac valve disease, left main coronary disease or previous revascularization procedure were excluded. All patients with diabetes, hypertension, and hypercholesterolemia were receiving respective medical therapy. The demographic data, cardiac symptoms, medical history, comorbidity, smoking habit, angiographic data, left ventricular ejection fraction (LVEF), lipid profile, serum creatinine of all patients were obtained from in-hospital database. The Synergy between Percutaneous Coronary Intervention with TAXUS and

Table 2. MACCE data of CTO patients

Event	Treatment		With CKD			Without CKD			All patients
	Medicine	Revascu-larization	Medicine	Revascu-larization	Overall	Medicine	Revascu-larization	Overall	
MACCE, n (%)	72 (30.8)	138 (16.1)	24 (41.4)	36 (23.7)	60 (28.6)	48 (27.3)	102 (14.4)	150 (17.0)	210 (19.2)
All-cause death, n (%)	32 (13.7)	43 (5.0)	15 (25.9)	17 (11.2)	32 (15.2)	17 (9.7)	26 (3.7)	43 (4.9)	75 (6.9)
MI, n (%)	32 (13.7)	61 (7.1)	12 (20.7)	15 (9.9)	27 (12.9)	20 (11.4)	46 (6.5)	66 (7.5)	93 (8.5)
Revascularization, n (%)	25 (10.7)	50 (5.8)	6 (10.3)	6 (3.9)	12 (5.7)	19 (10.8)	44 (6.2)	63 (7.1)	75 (6.9)
TIA/Stroke, n (%)	21 (9.0)	45 (5.2)	6 (10.3)	12 (7.9)	18 (8.6)	15 (8.5)	33 (4.7)	48 (5.4)	66 (6.0)

CKD, chronic kidney disease; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; TIA, transient ischemic attacks.

Cardiac Surgery score (SYNTAX score) were calculated for all patients. According to SYNTAX score, all patients were stratified as follow: SYNTAX score ≤ 22, 22 < SYNTAX score ≤ 32 and SYNTAX score > 32. Between September 6th, 2014 and September 22nd, 2014, follow-up was carried out by telephone call to determine the rate of MACCE after hospital discharge.

The definition of a CTO is the presence of thrombolysis in myocardial infarction (TIMI) 0 flow within the occluded segment with an estimated occlusion duration of ≥ 3 months [6]. The following end points were evaluated to compare outcomes of patients: major adverse cardiac and cerebrovascular events (all-cause mortality, myocardial infarction, revascularization and TIA/stroke) and all-cause mortality. Staged PCI was not regarded as revascularization event in the follow up. According to the KDOQI guideline, CKD is defined as abnormalities of kidney structure or function, present for ≥ 3 months. In this study, patients with CKD G3, G4 or G5 (GFR < 60 mL/min/1.73 m^2) were defined as patients with CKD. The GFR of all patients was estimated by using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula [7]. Data are presented as mean ± SD or as percentages. The χ^2 or Fisher exact test is used for categorical data comparison. Survival curves were constructed for time-to-event variables using Kaplan-Meier methods and compared using log-rank tests. Cox proportional-hazards methods were used to identify predictors of all-cause mortality and MACCE. The multivariate models were built by stepwise variable selection, with entry criteria set at the P = 0.05 level and exit criteria set at the P = 0.10 level. Statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, Illinois).

Results

Baseline clinical data

Baseline clinical characteristics of all patients are summarized in **Table 1**. Patients had prevalence of cardiovascular risk factors such as hypertension in 66.2%, diabetes mellitus in 43.4%, hypercholesterolemia in 15.9%, and smoking habit in 29.9% of patients.

A total of 210 patients (19.2%) were complicated with CKD. Both patients with and without CKD had similar proportions of agedness, male, hypertension, multivessel coronary artery disease (MVCAD) and similar rates of histories of pre-MI and pre-TIA/Stroke. However, compared with patients without CKD, patients with CKD were older (63.4 ± 5.9 vs. 62.3 ± 6.5, P = 0.033) and had lower left ventricular ejection fraction (LVEF, 49.3 ± 4.6% vs. 51.8 ± 4.3%, P < 0.001), more diseased vessels per patient (2.35 ± 0.60 vs. 2.26 ± 0.58, P = 0.042), higher SYNTAX score (30.1 ± 5.9 vs. 27.3 ± 5.5, P = 0.04) and higher rate of DM (55.2% vs. 40.1%, P < 0.001), hypercholesterolemia (23.8% vs. 14.1%, P = 0.001), smoking (35.7% vs. 26.5%, P = 0.008), LVEF < 50% (46.2% vs. 28.1%, P < 0.001). Moreover, less patients with CKD (80.0% vs. 72.4%, P = 0.015) received revascularization.

Medium- and long-term outcomes

In present study, 72 (6.6%) patients were lost to follow-up. Within the follow-up (median follow-up time, 39 months; interquartile range, 27-52 months), 210 (19.2%) patients experienced MACCE. Data is summarized in **Table 2**. Cumulative MACCE-free survival rate (72.2 ± 2.5% vs. 53.8 ± 5.4%, P < 0.001) and cumulative survival rate (90.1 ± 1.7% vs. 74.6 ± 4.9%,

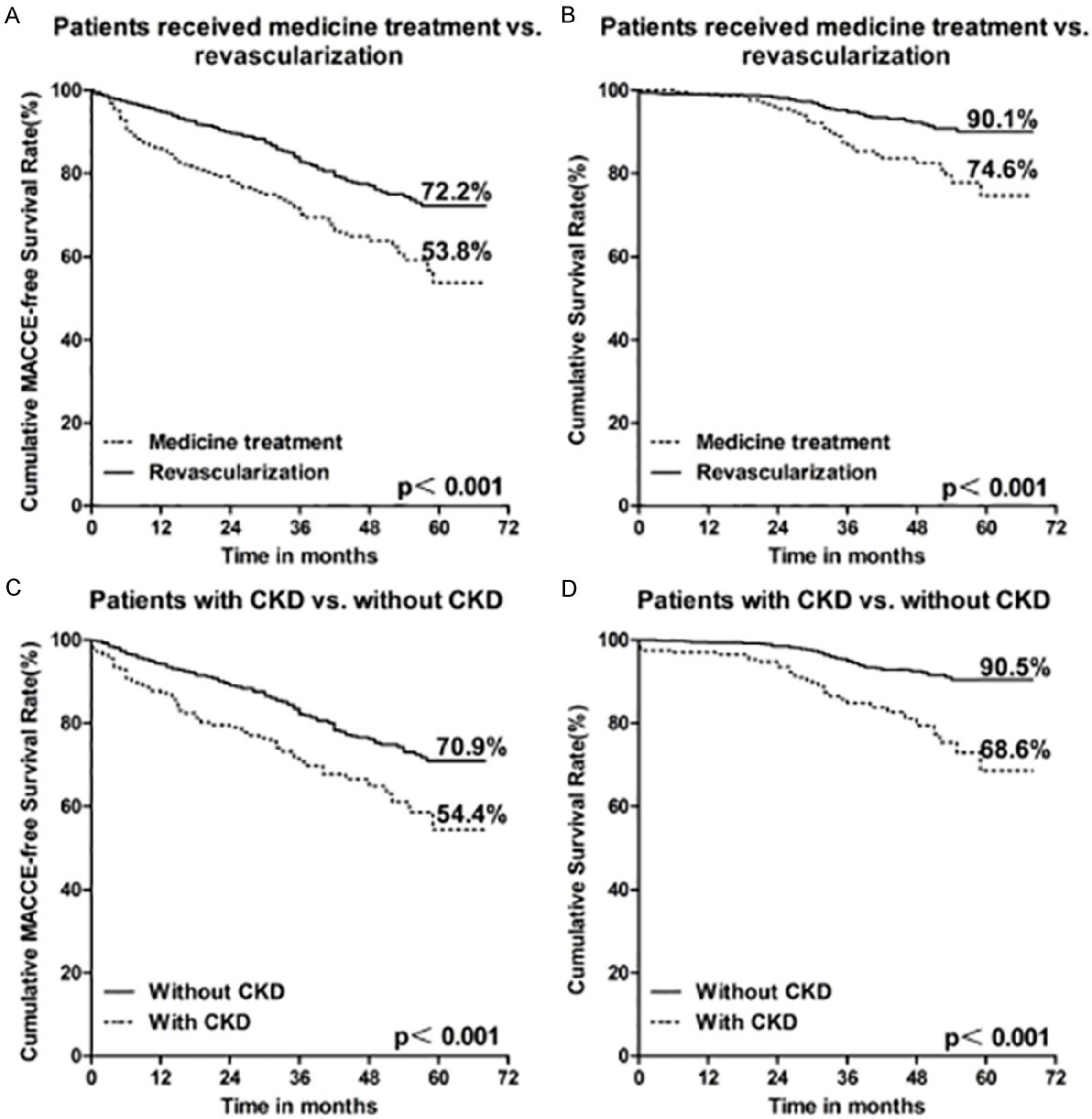

Figure 1. Kaplan-Meier curves for cumulative MACCE-free survival rate and cumulative survival rate for patients received conservative medicine treatment vs. revascularization and for patients with vs. without CKD. A, B: Compared with patients received conservative medicine treatment, patients received revascularization for CTO had relative higher cumulative MACCE-free survival rate (72.2 ± 2.5% vs. 53.8 ± 5.4%, $P < 0.001$) and cumulative survival rate (90.1 ± 1.7% vs. 74.6 ± 4.9%, $P < 0.001$). C, D: CKD is associated with decrease cumulative MACCE-free survival rate (54.4 ± 6.2% vs. 70.9 ± 2.5%, $P < 0.001$) and cumulative survival rate (68.6 ± 6.3% vs. 90.5 ± 1.6%, $P < 0.001$) among total patients with CTO.

$P < 0.001$) were higher in patients received revascularization compared with those received medicine treatment, respectively (**Figure 1A** and **1B**). On the other hand, cumulative MACCE-free survival rate (54.4 ± 6.2% vs. 70.9 ± 2.5%, $P < 0.001$) and cumulative survival rate (68.6 ± 6.3% vs. 90.5 ± 1.6%, $P < 0.001$) were significantly lower among patients with CKD (**Figure 1C** and **1D**).

After variable screen by Pearson correlation analysis between stratification of SYNTAX score and other variables about coronary artery lesions, stratification of SYNTAX score was viewed as main variable. The following variables were tested by log-rank test and entered into a stepwise multivariable Cox proportional hazard model for medium- and long-term survival and MACCE-free survival: agedness, gen-

Table 3. Independent predictors of MACCE in patients with CTO

Variables	Hazard ratio	95.0% CI for HR	*P* value
MACCE			
Conservative treatment	1.701	1.270-2.279	< 0.001
Agedness	1.516	1.150-1.999	0.003
DM	1.588	1.201-2.101	0.001
Previous TIA/stroke	1.897	1.329-2.708	< 0.001
LVEF < 50%	1.591	1.173-2.158	0.003
Stratification of SYNTAX score	1.761	1.367-2.269	< 0.001
All-cause mortality			
Conservative treatment	1.895	1.189-3.021	0.007
Agedness	2.632	1.612-4.296	< 0.001
LVEF < 50%	2.367	1.379-4.065	0.002
CKD	2.121	1.311-3.432	0.002
Stratification of SYNTAX score	1.76	1.125-2.755	0.013

CI, confidence interval; CKD, chronic kidney disease; DM, diabetic mellitus; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; SYNTAX, the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIA, transient ischemic attacks.

der, LVEF < 50%, pre-MI, pre-TIA/Stroke, hypertension, hypercholesterolemia, diabetic mellitus, smoking, stratification of SYNTAX score, treatment strategy and CKD.

Independent predictors of MACCE and all-cause mortality among all patients are listed in **Table 3**. Conservative treatment (hazard ratio [HR] 1.701; 95% confidence interval [CI], 1.270-2.279, *P* < 0.001), agedness, DM, pre-TIA/stroke, LVEF < 50%, stratification of SYNTAX score were associated with a significantly higher MACCE in patients with CTO. Conservative treatment (HR 1.895, 95% CI, 1.189-3.021, *P* = 0.007), agedness, LVEF < 50%, and stratification of SYNTAX score were independent predictors of all-cause mortality in patients with CTO. CKD was not an independent predictor of MACCE but was associated with a lower survival rate (HR 2.121, 95% CI, 1.311-3.432, *P* = 0.002) independently in patients with CTO.

Outcomes in patients with CKD received drug treatment versus revascularization

Table 2 also shows that 24 patients (41.4%) with CKD treated with medicine and 36 patients (23.7) with CKD received revascularization experienced MACCE. As shown by **Figure 2C** and **2D**, revascularization was associated with significantly higher cumulative MACCE-free survival rate (64.8 ± 5.7% vs. 20.1 ± 15.3%, *P* = 0.009) and cumulative survival rate (78.4 ± 5.6% vs. 38.7 ± 17.4%, *P* = 0.006) compared with medicine treatment in patients with CKD. **Table 4** shows agedness and hypercholesterolemia were independently associated with MACCE and all-cause mortality in patients with CKD. Moreover, conservative treatment (HR 2.041, 95% CI, 1.004-4.146, *P* = 0.049) was an independent predictor of medium- and long-term all-cause mortality.

Outcomes in patients without CKD received medicine treatment versus revascularization

Table 2 also lists MACCE data in patients without CKD. In this cohort, 48 patients (27.3%) treated with medicine and 102 patients (14.4%) received revascularization experienced MACCE. **Figure 2A** and **2B** display revascularization was associated with significantly higher cumulative MACCE-free survival rate (73.9 ± 2.7% vs. 61.0 ± 5.4%, *P* = 0.001) and cumulative survival rate (92.9 ± 1.5% vs. 83.4 ± 4.0%, *P* = 0.009) among patients without CKD. Independent predictors of MACCE and all-cause mortality in CTO patients without CKD are also listed in **Table 4**. Conservative treatment (HR 1.647, 95% CI 1.155-2.349, *P* = 0.006) was an independent predictor of MACCE but not all-cause death in patients without CKD. In addition, agedness and LVEF < 50% were independent predictors of both MACCE and all-cause mortality. Moreover, stratification of SYNTAX score, DM and pre-TIA/stroke were strong predictors of MACCE, while pre-MI was independently associated with all-cause mortality among patients without CKD.

Outcomes of patients with versus without CKD among patients received revascularization

In patients received revascularization, 36 patients (23.7%) with CKD and 102 patients (14.4%) without CKD experienced MACCE (**Table 2**). **Figure 2E** and **2F** also reveal that CKD was associated with lower cumulative MACCE-free survival rate (64.8 ± 5.7% vs. 73.9 ± 2.7%, *P* = 0.007) and cumulative survival

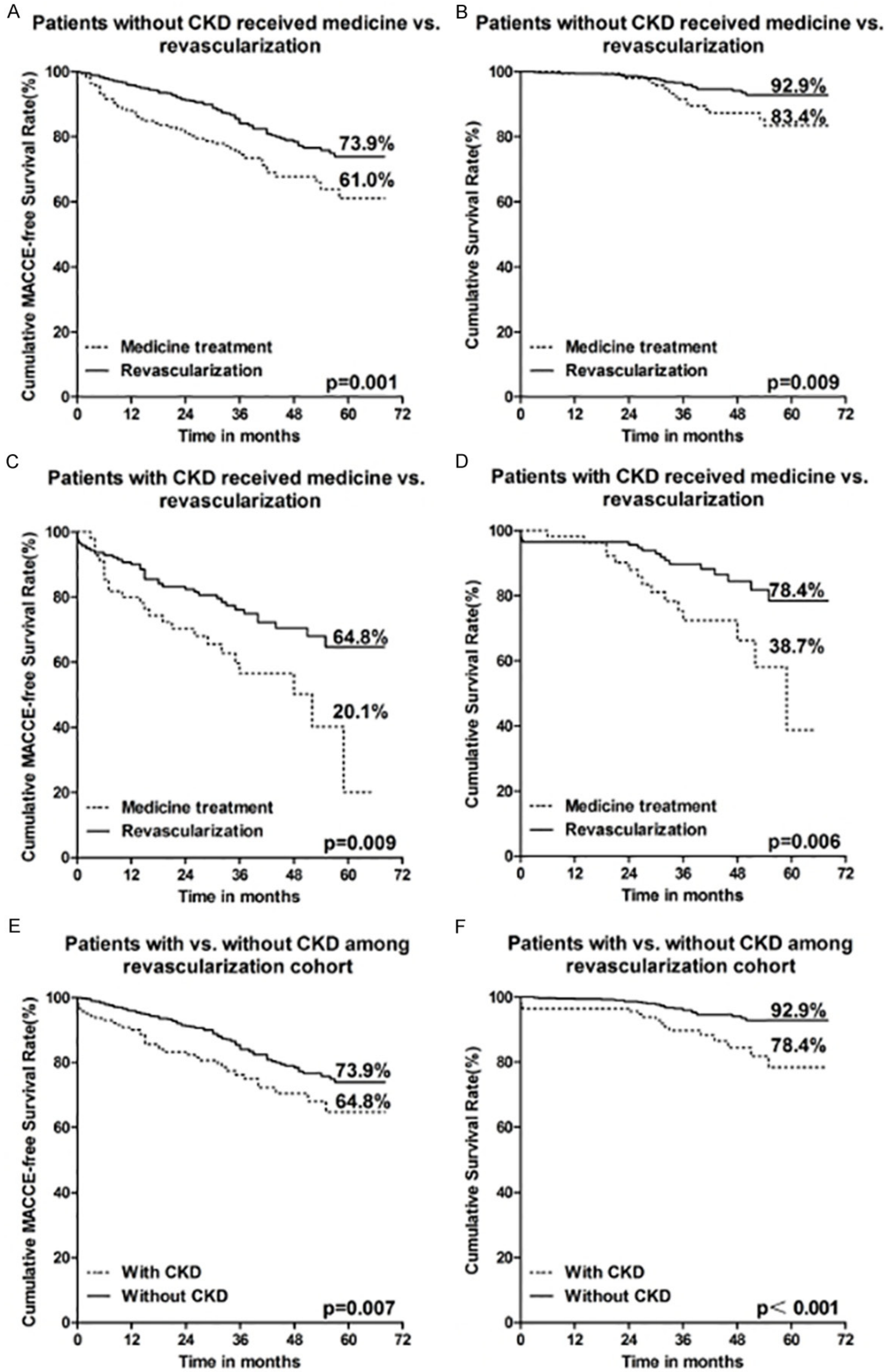
A
Patients without CKD received medicine vs. revascularization
Cumulative MACCE-free Survival Rate(%)
73.9%
61.0%
Medicine treatment
Revascularization
p=0.001
Time in months
B
Patients without CKD received medicine vs. revascularization
Cumulative Survival Rate(%)
92.9%
83.4%
Medicine treatment
Revascularization
p=0.009
Time in months
C
Patients with CKD received medicine vs. revascularization
Cumulative MACCE-free Survival Rate(%)
64.8%
20.1%
Medicine treatment
Revascularization
p=0.009
Time in months
D
Patients with CKD received medicine vs. revascularization
Cumulative Survival Rate(%)
78.4%
38.7%
Medicine treatment
Revascularization
p=0.006
Time in months
E
Patients with vs. without CKD among revascularization cohort
Cumulative MACCE-free Survival Rate(%)
73.9%
64.8%
With CKD
Without CKD
p=0.007
Time in months
F
Patients with vs. without CKD among revascularization cohort
Cumulative Survival Rate(%)
92.9%
78.4%
With CKD
Without CKD
p< 0.001
Time in months

Figure 2. Kaplan-Meier curves for cumulative MACCE-free survival rate and cumulative survival rate for patients received conservative treatment vs. revascularization among patients without or with CKD and for patients with vs. without CKD among patients received revascularization, respectively. A, C: Compared with patients received conservative medicine treatment, patients received revascularization for CTO had relative higher cumulative MACCE-free survival rate (patients without CKD 73.9 ± 2.7% vs. 61.0 ± 5.4%, *P* = 0.001; patients with CKD 64.8 ± 5.7% vs.20.1 ± 15.3%, *P* = 0.009). B, D: Cumulative survival rate (patients without CKD 92.9 ± 1.5% vs. 83.4 ± 4.0%, *P* = 0.009; patients with CKD 78.4 ± 5.6% vs. 38.7 ± 17.4%, *P* = 0.006). E, F: Among patients received revascularization, CKD is associated with significantly decreased cumulative MACCE-free survival rate (64.8 ± 5.7% vs. 73.9 ± 2.7%, *P* = 0.007) and cumulative survival rate (78.4 ± 5.6% vs. 92.9 ± 1.5%, *P* < 0.001).

Table 4. Independent predictors of MACCE and all-cause mortality in CTO patients with and without CKD

Events	With CKD				Without CKD			
	Variables	HR	95.0% CI for HR	*P* value	Variables	HR	95.0% CI for HR	*P* value
MACCE								
	Agedness	3.379	1.500-7.608	0.003	Medicine treatment	1.647	1.155-2.349	0.006
	Hypercholesterolemia	2.247	1.063-4.753	0.034	Agedness	1.425	1.026-1.979	0.034
					LVEF < 50%	1.688	1.178-2.418	0.004
					Stratification of SYNTAX score	1.527	1.144-2.040	0.004
					DM	1.617	1.169-2.235	0.004
					Previous TIA/stroke	2.278	1.492-3.477	< 0.001
All-cause mortality								
	Medicine treatment	2.041	1.004-4.146	0.049	Agedness	2.393	1.273-4.501	0.007
	Agedness	3.563	1.658-7.658	0.001	LVEF < 50%	2.412	1.212-4.798	0.012
	Hypercholesterolemia	2.3	1.098-4.817	0.027	Previous MI	2.138	1.087-4.205	0.028

CI, confidence interval; CKD, chronic kidney disease; CTO, chronic total occlusion; DM, diabetic mellitus; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; SYNTAX, the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIA, transient ischemic attacks.

Table 5. Independent predictors of MACCE and all-cause mortality among patients received vascularization

Variables	HR	95.0% CI for HR	*P* value
MACCE			
Agedness	1.558	1.109-2.190	0.011
DM	1.558	1.103-2.201	0.012
Hypercholesterolemia	1.54	1.041-2.277	0.031
Previous TIA/stroke	2.003	1.326-3.026	0.001
LVEF < 50%	1.912	1.323-2.764	0.001
Stratification of SYNTAX score	1.64	1.205-2.234	0.002
All-cause mortality			
Agedness	2.333	1.243-4.376	0.008
LVEF < 50%	3.968	1.940-8.113	< 0.001

CI, confidence interval; DM, diabetic mellitus; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; SYNTAX, the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIA, transient ischemic attacks.

rate (78.4 ± 5.6% vs. 92.9 ± 1.5%, *P* = 0.001) among patients received revascularization. Independent predictors identified by multivariable Cox proportional hazard model are listed in **Table 5**. Agedness and LVEF < 50% were independent predictors of MACCE and all-cause mortality among patients received revascularization. In addition, DM, hypercholesterolemia, pre-TIA/stroke and stratification of SYNTAX score were associated with MACCE independently in this cohort. However, CKD was not an independent predictor of prognosis of patients received revascularization.

Outcomes in patients received PCI versus CABG

Figure 3 shows Kaplan-Meier curves for cumulative MACCE-free survival rate and cumulative survival rate for patients underwent PCI versus CABG. Among all patients received revascularization, CABG was associated with a significantly higher cumulative MACCE-free survival rate (76.3 ± 3.4% vs. 68.6 ± 3.5%, *P* = 0.040) and a similar cumulative survival rate (89.6 ± 2.8% vs. 90.3 ± 2.0%, *P* = 0.486) compared with PCI (**Figure**

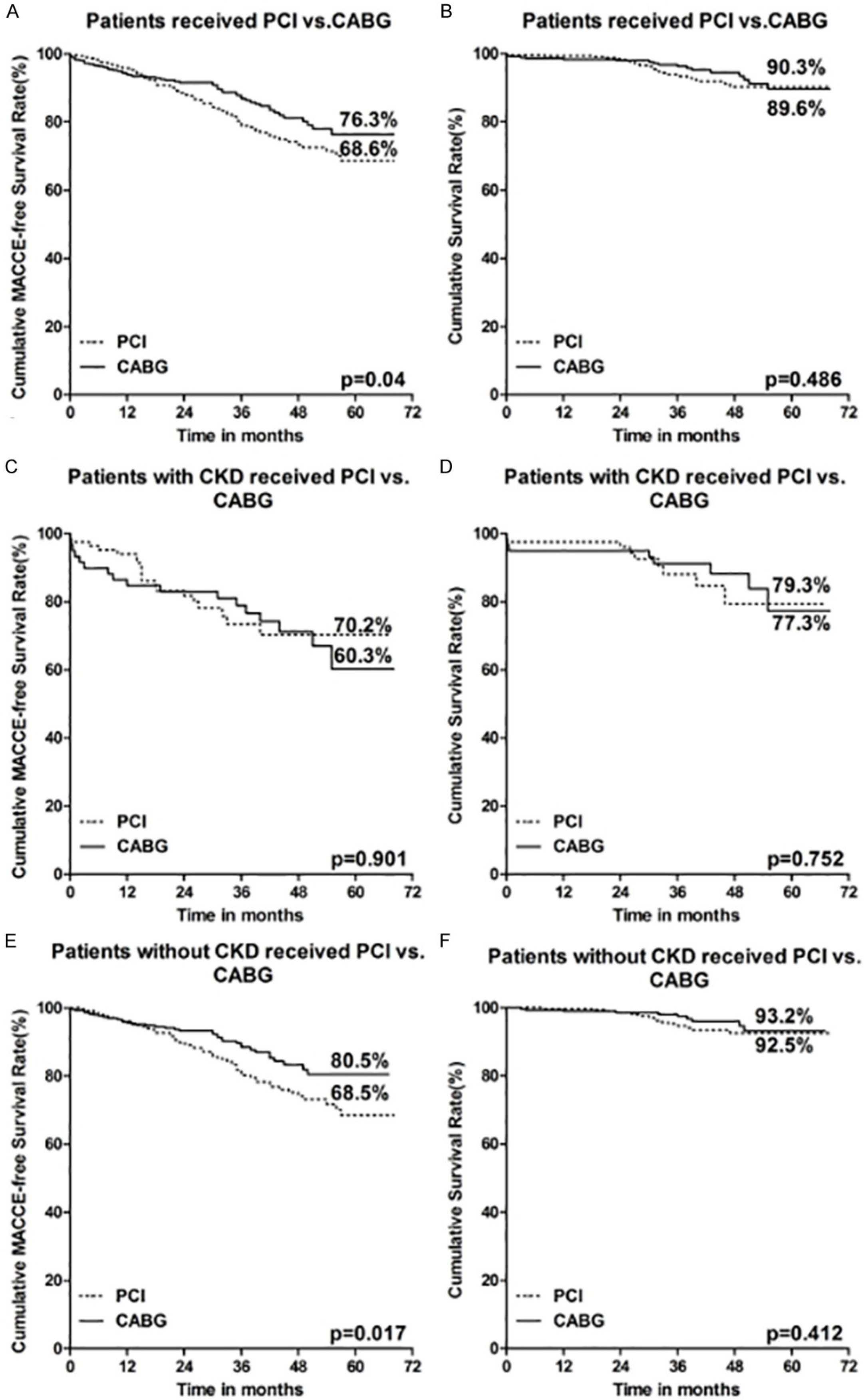
A
Patients received PCI vs.CABG
Cumulative MACCE-free Survival Rate(%)
76.3%
68.6%
PCI
CABG
p=0.04
Time in months
B
Patients received PCI vs.CABG
Cumulative Survival Rate(%)
90.3%
89.6%
PCI
CABG
p=0.486
Time in months
C
Patients with CKD received PCI vs. CABG
Cumulative MACCE-free Survival Rate(%)
70.2%
60.3%
PCI
CABG
p=0.901
Time in months
D
Patients with CKD received PCI vs. CABG
Cumulative Survival Rate(%)
79.3%
77.3%
PCI
CABG
p=0.752
Time in months
E
Patients without CKD received PCI vs. CABG
Cumulative MACCE-free Survival Rate(%)
80.5%
68.5%
PCI
CABG
p=0.017
Time in months
F
Patients without CKD received PCI vs. CABG
Cumulative Survival Rate(%)
93.2%
92.5%
PCI
CABG
p=0.412
Time in months

Figure 3. Kaplan-Meier curves for cumulative MACCE-free survival rate and cumulative survival rate for patients received PCI vs. CABG among the cohort of revascularization and among patients with or without CKD, respectively. A: Generally, compared with patients underwent CABG, patients underwent PCI had a lower cumulative MACCE-free survival rate (68.6 ± 3.5% vs. 76.3 ± 3.4%, *P* = 0.040). B: There was no significant difference on cumulative survival rate between patients underwent PCI and those received CABG (90.3 ± 2.0% vs. 89.6 ± 2.8%, *P* = 0.486). C, D: Among patients with CKD, patients underwent PCI and those underwent CABG had similar cumulative MACCE-free survival rate (70.2 ± 6.2% vs. 60.3 ± 9.2%, *P* = 0.901) and cumulative survival rate (79.3 ± 7.2% vs. 77.3 ± 8.4%, *P* = 0.752). E, F: Among patients without CKD, patients underwent CABG had a increased cumulative MACCE-free survival rate (80.5 ± 3.4% vs. 68.5 ± 4.0%, *P* = 0.017) and a similar cumulative survival rate (93.2 ± 2.4% vs. 92.5 ± 1.9%, *P* = 0.412).

3A and **3B**). Among patients without CKD, patients underwent CABG had higher cumulative MACCE-free survival rate (80.5 ± 3.4% vs. 68.5 ± 4.0%, *P* = 0.017) and similar survival rate (93.2 ± 2.4% vs. 92.5 ± 1.9%, *P* = 0.412) compared with those underwent PCI (**Figure 3E** and **3F**). However, there was no significant difference in cumulative MACCE-free survival rate (70.2 ± 6.2% vs. 60.3 ± 9.2%, *P* = 0.901) or cumulative survival rate (79.3 ± 7.2% vs. 77.3 ± 8.4%, *P* = 0.752) between patients underwent PCI and those underwent CABG in CKD cohort (**Figure 3C** and **3D**).

Discussion

CKD is increasingly recognized as a global public health problem, and epidemiological investigations confirmed the trend of increasing morbidity of CKD. The overall prevalence of CKD was 10.8% in China [8]. The data from NHANES showed that the morbidity of CKD during White and African Americans were 19.03% and 19.00%, respectively [9]. CKD had many common risk factors with CAD, such as hypertension, DM, smoking, chronic inflammation and lipid metabolism disorder. Renal dysfunction, even mild degree of impairment [1], is associated with increased cardiovascular morbidity and mortality [10, 11]. Preoperative renal insufficiency is a strong predictor of postoperative renal failure and mortality in patients underwent CABG (2, 3) or PCI (4). As a common complication after CABG, acute kidney injury (AKI) is closely associated with high mortality [12]. Multivariate Cox model identified GFR as a risk factor of overall death and cardiovascular death in the follow up of CAD patients after revascularization [13]. On the other hand, cardiovascular disease is the leading cause of death among CKD patients [14].

CTO is the last stage of coronary artery atherosclerosis. Before PCI was regularly used to treat acute myocardial infarction, CTO lesions accounted for one third of coronary artery atherosclerosis disease confirmed by the non-emergency CAG [5, 15], while the rate of CTO decreased significantly in some large registries because of the progress of PCI over the years [16, 17]. The mortality in patients with CTOs was significantly higher compared with those without CTOs [5, 18-20]. Moreover, CTO lesions were associated with worse outcomes after PCI [20-22]. To date, few studies reported the true rate of revascularization among all patients with CTOs. A large registry in Sweden reported the majority of patients with CTO lesions still are treated conservatively [16]. In addition, the benefit from revascularization for CTO remains controversial [23-27]. However, successful revascularization for CTOs is associated with the improvement of living quality [28], the reduction of the need for subsequent CABG surgery [25] and the improvement of long-term survival [22, 25, 27, 29, 30] in most studies. Previously, PCI for CTOs has a significantly lower success rate than that for non-CTO lesions, so CABG was regarded as the main method of revascularization for CTOs. However, because of severe trauma, longer hospital stays and recovery process, and limited physical activity after surgery, CABG is not always accepted by CAD population universally. With the progress of technology and devices, outcomes and success rate of PCI significantly improved [24, 30, 31].

To date, there is little data on the prevalence of CKD among patients with CTOs. Given the correlation between CKD and CAD, the rate of CTO lesions among patients with CKD may be higher than that among patients without CKD. A Canada study reported that the prevalence of CTO in a non-infarct-related artery was 13% in patients with CKD compared with 7% in those without CKD (*P* = 0.0003) [21]. Therefore, the huge number of patient with CTO and CKD could not be ignored. Decision-making in treatment strategies in patients with CKD and CTO remains the priority for cardiologists.

In this study, patients with CTO and CKD were older, and with lower LVEF, higher SYNTAX score and higher percentages of comorbidities, such as diabetic mellitus, hypercholesterolemia and LVEF < 50%. Despite high prevalence and risk of coronary disease in this population, CKD is associated with a lower rate of revascularization for CTOs. Other researchers also reported the lower rate of revascularization for CAD among patients with CKD compared with those without CKD [32]. Higher SYNTAX score among patients with CTO and CKD is consistent with a previous Korean study which demonstrated that decreased renal function is associated with the severity of CAD (32). CKD is associated with significantly higher MACCE risk and all-cause mortality risk in patients with CTO. Moreover, in consistent with previous reports on general patients with CAD [1, 10, 13], our study confirms that CKD is an independent predictors of all-cause mortality risk in CTO patients (HR 2.121, 95% CI, 1.311-3.432, P = 0.002).

Prior studies have described discordant results when evaluating long-term survival following CTO PCI. Most studies [33, 34] including a meta-analysis [30] have demonstrated a survival benefit from successful revascularization for CTO. However, investigators at the Mayo Clinic reported failure PCI for CTO was not associated with decreased long-term survival [35]. Safley et al. reported that there was not a measurable improvement in survival between successful PCI for CTO and failed PCI for CTO in patient with DM and CTO [36]. Our study provides evidence that revascularization for CTO was associated with better outcomes among patients either with or without CKD at medium- and long-term follow-up. However, the benefit from revascularization for CTOs was attenuated by CKD. We also found that agedness and LVEF < 50% were strong associated with poor prognosis after revascularization among patient with CTO.

The priority of revascularization strategies still remains controversial. Hemmelgarn et al. demonstrated that compared with PCI, CABG was associated with a significantly lower mortality in CAD patients with CKD but not in the dialysis patients [37]. Inversely, Marui et al. reported the risk of all-cause death was similar between PCI and CABG in patients with multivessel and/or left main disease undergoing dialysis [38, 39]. Ashrith et al. [40] and Kannan et al. [41] reported patients with CAD benefited to long-term survival from CABG similarly. Wang et al. revealed that treatment with CABG or PCI with multi-vessel stenting led to similar outcomes of death in CKD patients with multi-vessel CAD [42]. In our study, there was no difference in cumulative survival rate at medium- and long-term follow-up between patients with underwent CABG and those received PCI among patients with CTO and CKD. Compared with CABG, PCI was associated with a higher risk of MACCE in patients without CKD. Therefore, with progress of experience and devices, PCI is not inferior to CABG among CTO patients with CKD.

In conclusion, CKD increased MACCE and all-cause mortality in patients with CTO. CTO patients benefited from revascularization, either with or without CKD; however, the benefit from revascularization was attenuated by CKD. On the other hand, CABG was not superior to PCI at medium- and long-term cumulative survival rate, but CABG was associated with a reduction in MACCE in patients without CKD.

This retrospective study is not a random control observation, and enrolled relatively few CTO patients with CKD. In present study, the rate of revascularization among patients with CTO is relatively higher than that reported in previous studies including SCAAR which is the large registry in Sweden [16]. The relatively higher rate of revascularization may be due to the fact that many patients who failed or refused to receive revascularization in other hospitals underwent PCI or CABG in our cardiology center. Probable selection bias among patients received revascularization may decrease MACCE risk of PCI. In addition, in interpreting the results, we must consider that follow-up times of newly diagnosed patients were relatively short. In this study, these patients were enrolled to enlarge the sample size. However, short follow-up time may result in decreasing the MACCE risk of the newly diagnosed patients and producing some bias in the data of outcomes. To date, there are few random, control studies on CTO. So, random, multicenter, control and long term follow-up observation is necessary to increase the cogency of revascularization for CTOs and to evaluate the benefit from different revascularization strategies among CKD patients.

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Disclosure of conflict of interest

None.

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