Different association between renal dysfunction and clinical outcomes according to the presence of diabetes in patients undergoing endovascular treatment for peripheral artery disease

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ABSTRACT

Objective: Although chronic kidney disease (CKD) and diabetes are important prognostic factors in patients with peripheral artery disease, there are limited data regarding the outcomes of endovascular treatment (EVT) according to the severity of CKD, especially in the presence of diabetes. This study sought to compare clinical outcomes of lower limb EVT between patients with and patients without CKD according to the presence of diabetes.

Methods: Patients were enrolled from the Korean multicenter EVT registry and were divided according to the presence of diabetes, then further stratified by CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2). The primary outcome was major adverse limb events (MALEs; a composite of reintervention for target limb, reintervention for target vessel, and unplanned major amputation) at 2 years.

Results: A total of 3045 patients were eligible for analysis: 1277 nondiabetic patients (944 without CKD, 333 with CKD) and 1768 diabetic patients (951 without CKD, 817 with CKD). CKD was associated with a significantly increased risk of MALEs after EVT in diabetic patients (14.4% vs 9.9%; adjusted hazard ratio, 1.60; 95% confidence interval, 1.28-2.01; $P < .001$) but not in nondiabetic patients (7.6% vs 9.7%; adjusted hazard ratio, 0.78; 95% confidence interval, 0.53-1.14; $P = .203$; interaction $P = .018$). In analysis stratified by the severity of CKD among diabetic patients, end-stage renal disease was significantly associated with an increased risk of MALE.

Conclusions: CKD was associated with a significantly higher risk of MALEs after EVT in diabetic patients but not in nondiabetic patients. The increased risk of MALEs was mainly driven by patients with end-stage renal disease. (J Vasc Surg 2020;71:132-40.)

Keywords: Peripheral artery disease; Endovascular treatment; Renal dysfunction; Diabetes mellitus

Endovascular treatment (EVT) has become a major treatment option for peripheral artery disease (PAD) with long-term efficacy similar to that of bypass surgery.[1] Current guidelines recommend EVT as an effective treatment for claudication or critical limb ischemia in suitable anatomic situations.[2] However, the treatment decision should be made with careful clinical consideration because patients with PAD commonly have various risk factors and comorbidities associated with poor prognosis.[3,4]

Chronic kidney disease (CKD) is a strong prognostic factor in cardiovascular disease. Prevalence of CKD has been reported to be 36% in PAD patients,[5] and CKD is associated with high mortality as well as with adverse limb outcome after EVT.[6-8] However, there are limited data regarding the outcomes of EVT according to the severity of CKD. Although a single-center observational study reported that worsening CKD is associated with a higher amputation rate and mortality, that study included

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ClinicalTrials.gov identifier: NCT02748226.

Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2019.03.071

only femoropopliteal artery disease and a relatively small number of patients (145 patients with CKD).[9] Diabetes is another high-risk factor with unique characteristics in atherosclerotic disease.[10] Diabetic patients have more infrapopliteal arterial occlusive disease and undergo more amputations than nondiabetic patients.[11,12] In addition, diabetes has a negative impact on long-term patency and wound recurrence after EVT.[8,13] Despite high prevalence of diabetes and CKD, the relationship between those two high-risk comorbidities and its impact on clinical outcome after EVT have not been well studied. Therefore, we sought to compare long-term clinical outcomes of EVT between patients with and patients without CKD according to the presence of diabetes.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter retrospective cohort study
- **Key Findings:** Chronic kidney disease (CKD) was associated with an increased risk of major adverse limb events after endovascular treatment in 1768 diabetic patients but not in 1277 nondiabetic patients. The increased risk of major adverse limb events in diabetic patients was mainly driven by those with end-stage renal disease.
- **Take Home Message:** CKD is a well-known poor prognostic factor in peripheral artery disease. After endovascular treatment, CKD has a different association with long-term outcomes according to the presence of diabetes, another high-risk comorbidity.

METHODS

Study population. The Korean Vascular Intervention Society Endovascular therapy in Lower Limb Artery diseases (K-VIS ELLA) registry is a multicenter observational study with retrospective and prospective cohorts of patients with lower extremity artery disease treated with endovascular therapy. This study encompasses the retrospective patient cohort. This cohort comprises 3434 patients with 5097 limbs treated between January 2006 and July 2015 in 31 Korean hospitals. Inclusion criteria were patients 20 years old or older and lower extremity artery disease treated with endovascular therapy. After exclusion of 56 limbs with acute limb ischemia, 82 limbs with Buerger disease, 11 limbs without procedural and in-hospital data, 536 limbs without adequate follow-up data after hospital discharge, 448 limbs treated for planned repeated revascularization after the index procedure, and 34 limbs without available serum creatinine level, a total of 3045 patients with 3930 target limbs from the retrospective cohort were included in the final analysis (Fig 1). Patients' baseline clinical and lesion characteristics as well as medications at hospital discharge were obtained from electronic medical records. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of the participating hospitals. The Institutional Review Boards of the participating hospitals waived the requirement for informed consent for this retrospective study.

Definitions. The presence of hypercholesterolemia was defined as total cholesterol level >200 mg/dL or treatment with a lipid-lowering agent before hospital admission as documented in the medical record. Congestive heart failure was defined as the presence of a left ventricular ejection fraction <40%. Anemia was defined according to the criteria of the World Health Organization (<12.0 g/dL in women and <13.0 g/dL in men).[14] The presence of diabetes was identified by patients' history and medical records including outpatient clinic and prescriptions of oral hypoglycemic agent or insulin. If the presence of diabetes was not clearly recognizable, hemoglobin A_{1c} level was measured before EVT. Creatinine concentration was measured at the latest time point before EVT. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease study equation as follows: $186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female). CKD was defined as eGFR <60 mL/min/1.73 m^2, then further divided into eGFR of 45 to 60 mL/min/1.73 m^2, eGFR of 30 to 45 mL/min/1.73 m^2, eGFR of 15 to 30 mL/min/1.73 m^2, or end-stage renal disease (ESRD; advanced CKD with eGFR <15 mL/min/1.73 m^2 or treated with either dialysis or kidney transplantation) according to its severity.

PAD of the lower extremity was defined as the presence of ≥50% narrowing of a lower extremity artery. Even though no strict criteria for stent implantation were used, it was generally performed on the basis of the medical insurance indications of the Republic of Korea, which are flow-limiting dissection, residual stenosis >30% after EVT, and pressure gradient >15 mm Hg. Claudication was defined as Rutherford category 1, 2, or 3 disease (mild, moderate, or severe claudication, respectively), and critical limb ischemia was defined as Rutherford category 4, 5, or 6 disease (ischemic rest pain, minor tissue loss, or major tissue loss, respectively).[15] Target lesions of the aortoiliac and femoropopliteal arteries were classified according to the TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).[16] Multilevel disease was defined as the presence of significant obstructive lesions at more than one level in the same limb (aortoiliac, femoropopliteal, and infrapopliteal). Prescribed antiplatelet drugs included aspirin, clopidogrel, ticlopidine, ticagrelor, prasugrel, cilostazol, sarpogrelate, triflusal, beraprost, and limaprost. $P2Y_{12}$ adenosine diphosphate receptor inhibitors included clopidogrel, ticlopidine, ticagrelor, and prasugrel.

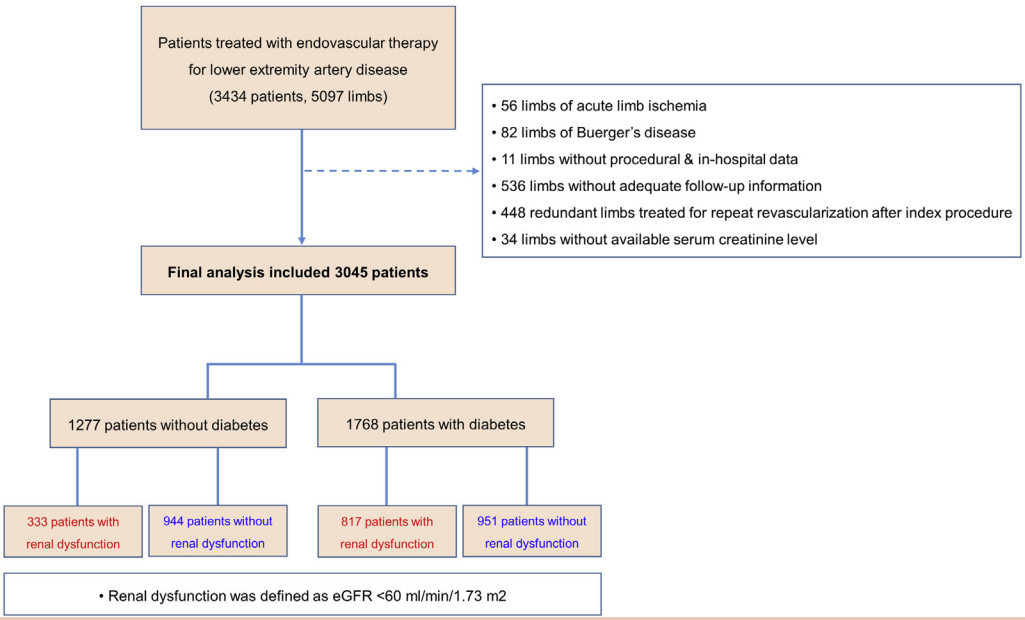

Fig 1. Study population. *CKD,* Chronic kidney disease; *eGFR,* estimated glomerular filtration rate.

Study outcomes. Study outcomes were compared between patients with and patients without CKD, stratified by the presence of diabetes. The primary outcome was major adverse limb events (MALEs; a composite of reintervention for target limb, reintervention for target vessel, or unplanned major amputation) at 2 years after EVT. Secondary outcomes were death by any cause, each individual component of the primary outcome, any reintervention, and unplanned minor amputation. Major amputation was defined as any procedure resulting in amputation at the level of the ankle or above. Minor amputation was defined as any procedure resulting in amputation below the ankle, including the foot or toes.

Statistical analysis. The unit of analysis was patients, not limbs, except for describing lesion characteristics including total number, level, and TASC class of target vessels. Continuous variables are presented as means ± standard deviations. To assess the significance of differences in variables between groups, Student *t*-test was used for continuous variables and the χ^2 test was used for categorical variables. Event rates were calculated on the basis of Kaplan-Meier censoring estimates and are presented as cumulative incidences, and the log-rank test was used to compare survival curves between groups. Multivariate Cox proportional hazards regression was used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariate Cox proportional hazards model was adjusted with age, sex, hypertension, congestive heart failure, coronary artery disease, previous amputation, anemia, Rutherford category, critical limb ischemia, medications (statin, beta blocker, calcium channel blocker, and diuretics), presence of multilevel disease, multivessel intervention, level of target vessel, total occlusion, TASC II class, and treatment modality, which were significantly different ($P < .05$) between patients with and patients without CKD. In addition, a multivariate marginal Cox model was used to adjust participating center effect. An interaction term between CKD and diabetes was tested in a multivariable Cox model. Stratified analysis was performed between eGFR ≥60 mL/min/1.73 m^2 (reference), eGFR 15 to 60 mL/min/1.73 m^2 (non-ESRD), and ESRD according to severity of CKD.

All probability values are two sided, and *P* values <.05 were considered statistically significant. R software version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

RESULTS

Baseline characteristics. Of the 3045 patients, 1768 had diabetes (58.1%) and 1277 did not have diabetes (41.9%). CKD existed in 46.2% of the diabetic group (817/1768 patients) and in 26.1% of the nondiabetic group (333/1277 patients; Fig 1).

Table I presents the comparison of baseline clinical characteristics between patients with and patients without CKD according to the presence of diabetes. In the nondiabetic group, patients with CKD were older than those without CKD, and more had hypertension and anemia. In the diabetic group, patients with CKD were more likely to be male, to have cardiovascular morbidities, and to have undergone a previous amputation. The prevalence of critical limb ischemia was higher in patients with CKD in both the nondiabetic and diabetic groups. Antiplatelet agents were prescribed for most of the study population (98.9%).

Table I. Baseline clinical characteristics according to the presence of chronic kidney disease (*CKD*) stratified by diabetes mellitus

	Nondiabetic patients (n = 1277)			Diabetic patients (n = 1768)		
	CKD (n = 333)	Non-CKD (n = 944)	*P* value	CKD (n = 817)	Non-CKD (n = 951)	*P* value
Age, years	71.9 ± 8.7	67.5 ± 10.4	<.001	68.4 ± 9.0	67.7 ± 8.8	.096
Male	266 (79.9)	814 (86.2)	.008	607 (74.3)	810 (85.2)	<.001
Body mass index, kg/m^2	23.1 ± 3.4	22.9 ± 3.5	.266	23.8 ± 3.7	24.0 ± 3.6	.421
Hypertension	270 (81.1)	566 (60.0)	<.001	710 (86.9)	691 (72.7)	<.001
Dyslipidemia	137 (41.1)	353 (37.4)	.253	319 (39.0)	376 (39.5)	.871
Coronary artery disease	175 (52.6)	473 (50.1)	.481	502 (61.4)	536 (56.4)	.034
Previous MI	47 (14.1)	102 (10.8)	.129	91 (11.1)	83 (8.7)	.106
Congestive heart failure	30 (9.0)	56 (5.9)	.072	69 (8.4)	28 (2.9)	<.001
Previous PTA	36 (10.8)	85 (9.0)	.390	86 (10.5)	91 (9.6)	.556
Previous bypass surgery	15 (4.5)	31 (3.3)	.392	19 (2.3)	24 (2.5)	.909
Previous amputation	10 (3.0)	16 (1.7)	.220	97 (11.9)	70 (7.4)	.002
Anemia	204 (61.3)	336 (35.6)	<.001	619 (75.8)	484 (50.9)	<.001
Serum creatinine, mg/dL	2.3 ± 3.1	0.9 ± 0.2	<.001	4.0 ± 7.1	0.9 ± 0.2	<.001
CKD severity[a]			<.001			<.001
eGFR ≥60	0 (0.0)	944 (100.0)		0 (0.0)	951 (100.0)	
45 ≤ eGFR <60	194 (58.3)	0 (0.0)		282 (34.5)	0 (0.0)	
30 ≤ eGFR <45	66 (19.8)	0 (0.0)		151 (18.5)	0 (0.0)	
15 ≤ eGFR <30	25 (7.5)	0 (0.0)		59 (7.2)	0 (0.0)	
ESRD	48 (14.4)	0 (0.0)		325 (39.8)	0 (0.0)	
Rutherford category			.015			<.001
1	35 (10.5)	145 (15.4)		56 (6.9)	107 (11.3)	
2	109 (32.7)	342 (36.2)		172 (21.1)	222 (23.3)	
3	114 (34.2)	304 (32.2)		166 (20.3)	242 (25.4)	
4	29 (8.7)	76 (8.1)		57 (7.0)	65 (6.8)	
5	34 (10.2)	61 (6.5)		225 (27.5)	185 (19.5)	
6	12 (3.6)	16 (1.7)		141 (17.3)	130 (13.7)	
Critical limb ischemia	75 (22.5)	153 (16.2)	.012	423 (51.8)	380 (40.0)	<.001
Discharge medications						
Aspirin	284 (87.1)	779 (84.4)	.274	684 (87.5)	821 (88.0)	.796
Clopidogrel	277 (85.0)	786 (85.2)	>.999	646 (82.6)	789 (84.6)	.305
Cilostazol	103 (31.6)	354 (38.4)	.035	252 (32.2)	370 (39.7)	.002
Any antiplatelet drugs	320 (98.2)	913 (98.9)	.448	773 (98.8)	926 (99.2)	.544
Warfarin	30 (9.2)	94 (10.2)	.688	40 (5.1)	55 (5.9)	.550
Statin	230 (70.6)	669 (72.5)	.552	526 (67.3)	685 (73.4)	.006
ACEI or ARB	139 (42.6)	344 (37.3)	.100	404 (51.7)	467 (50.1)	.538
Calcium channel blocker	124 (38.0)	266 (28.8)	.003	337 (43.1)	304 (32.6)	<.001
Beta blocker	132 (40.5)	290 (31.4)	.004	323 (41.3)	295 (31.6)	<.001
Diuretics	73 (22.4)	144 (15.6)	.007	195 (24.9)	164 (17.6)	<.001

ACEI, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *eGFR*, estimated glomerular filtration rate; *ESRD*, end-stage renal disease; *MI*, myocardial infarction; *PTA*, percutaneous transluminal angioplasty.
Values are presented as mean ± standard deviation or number (%).
[a]Estimated glomerular filtration rate was calculated by Modification of Diet in Renal Disease study equation.

Table II presents the angiographic and procedural profiles of the study patients. In both nondiabetic and diabetic groups, patients with CKD had higher prevalence of multilevel disease and a higher number of target lesions per limb. In both groups, patients with CKD underwent more EVT for below-knee lesions than patients without CKD.

Clinical outcomes at 2 years after EVT. The relationship between CKD and risk of MALEs was different according to the presence of diabetes (interaction term = .018, *P*

Table II. Baseline lesion characteristics according to the presence of chronic kidney disease (*CKD*) stratified by diabetes mellitus

	Nondiabetic patients (n = 1277)			Diabetic patients (n = 1768)		
	CKD (n = 333)	Non-CKD (n = 944)	*P* value	CKD (n = 817)	Non-CKD (n = 951)	*P* value
Multilevel disease	134 (40.2)	298 (31.6)	.005	351 (43.0)	353 (37.1)	.014
Baseline ABI <0.4	29 (8.7)	70 (7.4)	.522	74 (9.1)	71 (7.5)	.259
Baseline ABI >0.9	22 (6.6)	56 (5.9)	0.757	93 (11.4)	102 (10.7)	.716
Target vessel						
Total No.	444	1186		1299	1377	
No. per limb	1.3 ± 0.6	1.3 ± 0.6	.036	1.6 ± 0.8	1.4 ± 0.7	<.001
Level of target vessel						
Aortoiliac	197 (59.2)	591 (62.6)	.295	211 (25.8)	359 (37.7)	<.001
Femoropopliteal	170 (51.1)	438 (46.4)	.162	473 (57.9)	481 (50.6)	.002
Below knee	55 (16.5)	109 (11.5)	.025	388 (47.5)	357 (37.5)	<.001
TASC II class			.005			.463
A	52 (11.7)	189 (15.9)		148 (11.4)	170 (12.3)	
B	95 (21.4)	278 (23.4)		197 (15.2)	232 (16.8)	
C	129 (29.1)	253 (21.3)		238 (18.3)	234 (17.0)	
D	168 (37.8)	466 (39.3)		716 (55.1)	741 (53.8)	
Total occlusion	201 (45.3)	636 (53.6)	.003	608 (46.8)	695 (50.5)	.058
In-stent restenosis	8 (1.8)	25 (2.1)	.696	21 (1.6)	29 (2.1)	.350
Treatment modality			.266			<.001
Stent	741 (78.5)	247 (74.2)		604 (63.5)	422 (51.7)	
Balloon only	171 (18.1)	73 (21.9)		313 (32.9)	378 (46.3)	
Others[a]	32 (3.4)	13 (3.9)		34 (3.6)	17 (2.1)	

ABI, Ankle-brachial index; *TASC*, TransAtlantic Inter-Society Consensus.
Values are presented as mean ± standard deviation or number (%).
[a]Others included drug-coated balloon, thrombosuction, atherectomy, and stent graft.

value for the CKD × diabetes in a multivariate Cox model). In the nondiabetic group, risk of MALEs was not significantly different between patients with and patients without CKD (7.6% vs 9.7%; adjusted HR, 0.78; 95% CI, 0.53-1.14; $P = .203$; Table III; Fig 2). Mortality was significantly higher in patients with CKD than in those without CKD (13.7% vs 5.0%; adjusted HR, 1.89; 95% CI, 1.35-2.64; $P < .001$).

In the diabetic group, however, risk of MALEs was significantly higher in patients with CKD than in those without CKD (14.4% vs 9.9%; adjusted HR, 1.60; 95% CI, 1.28-2.01; $P < .001$). Patients with CKD had significantly higher risk of all individual components of MALEs (unplanned major amputation, reintervention for target limb, and reintervention for target vessel) than those without CKD. Mortality was also significantly higher in patients with CKD than in those without CKD (16.1% vs 4.9%; adjusted HR, 2.87; 95% CI, 2.36-3.49; $P < .001$).

Risk of MALEs and death stratified by severity of CKD.

When patients were divided into three groups of eGFR ≥60 mL/min/1.73 m^2 (reference group), eGFR of 15 to 60 mL/min/1.73 m^2 (non-ESRD CKD), and ESRD, an interaction term in predicting MALEs was .043 (*P* value for the severity of CKD × diabetes). In the diabetic group, the risk of MALEs was significantly different in patients with eGFR ≥60 mL/min/1.73 m^2, eGFR of 15 to 60 mL/min/1.73 m^2, and ESRD ($P < .001$ by log-rank test), mainly by those with ESRD (21.0% vs 9.9%; adjusted HR, 2.45; 95% CI, 1.88-3.18; $P < .001$, compared with eGFR ≥60 mL/min/1.73 m^2; Fig 3). In the nondiabetic group, however, the risk of MALEs was not significantly different for patients with eGFR ≥60 mL/min/1.73 m^2, eGFR of 15 to 60 mL/min/1.73 m^2, and ESRD ($P = .374$ by log-rank test). In addition, ESRD was not associated with a significantly increased risk of MALEs (10.7% vs 9.7%; adjusted HR, 1.06; 95% CI, 0.37-3.00; $P = .918$, compared with eGFR ≥60 mL/min/1.73 m^2) in the nondiabetic group.

In patients with eGFR ≥60 mL/min/1.73 m^2, eGFR of 15 to 60 mL/min/1.73 m^2, and ESRD, a risk of death was significantly different and highest in those with ESRD in both the diabetic and nondiabetic groups (Fig 3). Further stratified analyses by eGFR ≥60 mL/min/1.73 m^2, eGFR of 45 to 60 mL/min/1.73 m^2, eGFR of 30 to 45 mL/min/1.73 m^2, eGFR of 15 to 30 mL/min/1.73 m^2, or ESRD for risk of MALEs and death are described in the Supplementary Fig (online only).

Table III. Clinical outcomes at 2 years according to the presence of chronic kidney disease (*CKD*) stratified by diabetes mellitus

	CKD	Non-CKD	Unadjusted HR (95% CI)	*P* value	Adjusted HR[a] (95% CI)	*P* value
Nondiabetic	(n = 333)	(n = 944)				
MALEs	19 (7.6)	74 (9.7)	0.80 (0.48-1.33)	.386	0.78 (0.53-1.14)	.203
Unplanned major amputation	2 (0.6)	4 (0.5)	1.52 (0.28-8.32)	.627	1.05 (0.16-6.90)	.962
Reintervention for target limb	17 (6.9)	70 (9.2)	0.75 (0.44-1.28)	.299	0.78 (0.55-1.10)	.152
Reintervention for target vessel	15 (6.2)	64 (8.5)	0.73 (0.42-1.28)	.271	0.76 (0.52-1.10)	.148
Death	39 (13.7)	40 (5.0)	2.95 (1.90-4.59)	<.001	1.89 (1.35-2.64)	<.001
Unplanned minor amputation	6 (2.2)	6 (0.7)	3.01 (0.97-9.33)	.057	1.39 (0.37-5.18)	.623
Any reintervention	19 (7.7)	83 (10.8)	0.71 (0.43-1.17)	.183	0.73 (0.52-1.01)	.054
Diabetic	(n = 817)	(n = 951)				
MALEs	89 (14.4)	76 (9.9)	1.56 (1.14-2.11)	.005	1.60 (1.28-2.01)	<.001
Unplanned major amputation	23 (3.4)	11 (1.4)	2.65 (1.29-5.44)	.008	1.88 (1.13-3.12)	.016
Reintervention for target limb	69 (11.6)	65 (8.6)	1.41 (1.01-1.99)	.045	1.60 (1.18-2.17)	.002
Reintervention for target vessel	65 (11.0)	62 (8.3)	1.40 (0.99-1.98)	.059	1.58 (1.19-2.09)	.001
Death	105 (16.1)	39 (4.9)	3.47 (2.40-5.02)	<.001	2.87 (2.36-3.49)	<.001
Unplanned minor amputation	60 (8.7)	32 (3.7)	2.40 (1.56-3.69)	<.001	1.40 (0.84-2.33)	.191
Any reintervention	83 (13.8)	88 (11.5)	1.26 (0.93-1.70)	.135	1.36 (0.97-1.89)	.071

CI, Confidence interval; *HR,* Hazard ratio; *MALEs,* major adverse limb events.
Values are presented as number (%) or HR (95% CI). The cumulative incidences of clinical outcome were presented as Kaplan-Meier estimates at 2 years after the index procedure. HR and its 95% CI were calculated by Cox regression analysis.
[a]Adjusted HR was calculated by multivariate Cox regression analysis using variables including age, sex, hypertension, congestive heart failure, coronary artery disease, previous amputation, anemia, Rutherford category, critical limb ischemia, medications (statin, beta blocker, calcium channel blocker, and diuretics), presence of multilevel disease, multivessel intervention, level of target vessel, total occlusion, TransAtlantic Inter-Society Consensus (TASC) II class, treatment modality, and participating centers, which were significantly different ($P < .05$) between patients with and patients without CKD.

DISCUSSION

CKD is one of the strong prognostic factors in cardiovascular disease.[17] CKD promotes endothelial dysfunction that leads to accelerated atherosclerosis in both large and small arteries, which in turn contributes to cardiovascular morbidity and mortality.[18,19] In addition, enhanced dyslipidemia, hypertension, and oxidative stress play a role in activated inflammation with vascular calcification.[20] Patients with CKD have poor prognosis of PAD and also worse clinical outcome after EVT than those without CKD.[5,7-9] Diabetes and its effect on cardiovascular disease have been extensively studied. The incidence of PAD is higher in patients with diabetes, and diabetic patients have an increased risk of lower extremity amputation than nondiabetic patients.[12] Diabetes not only accelerates atherosclerosis but also promotes restenosis after angioplasty through various pathways, including endothelial dysfunction, abnormal coagulation system, and dysregulated growth factors. After balloon angioplasty, those mechanisms enhance thrombus formation, vasoconstriction, and neointimal growth at the site of vessel injury.[21-24] In addition, diabetes impairs collateral vessel development by disruption of normal arteriogenesis.[25] As a consequence of extensive molecular and cellular alterations, PAD patients with diabetes have a higher incidence of amputation and wound recurrence after EVT than those without diabetes.[8,11]

In PAD patients, both CKD and diabetes are common and increase the risk of amputation. However, there are limited data regarding the differential impact of CKD and diabetes on PAD patients after EVT. Therefore, we investigated a different association of CKD with clinical outcome of EVT according to the presence of diabetes. In our study, CKD was associated with an increased risk of death in both diabetic and nondiabetic patients. The result is consistent with that of a previous study.[26] CKD was associated with a significantly increased risk of a composite of unplanned major amputation and reintervention for target limb or target vessel after EVT in diabetic patients but not in nondiabetic patients.

There are possible explanations for the different association of CKD with adverse limb outcomes according to the presence of diabetes. First, the synergistic impact of CKD and diabetes on prognosis of PAD has been reported. One large observational study reported a strong association between CKD and lower limb amputation in diabetic patients, even those without PAD.[27] Because both CKD and diabetes encompass microvascular disease, there would be an increased risk of limb loss even after successful EVT in patients who concomitantly have those two high-risk comorbidities. Second, the characteristic features of diabetic PAD could affect the current results. Compared with nondiabetic patients, diabetic patients are known to have a higher incidence

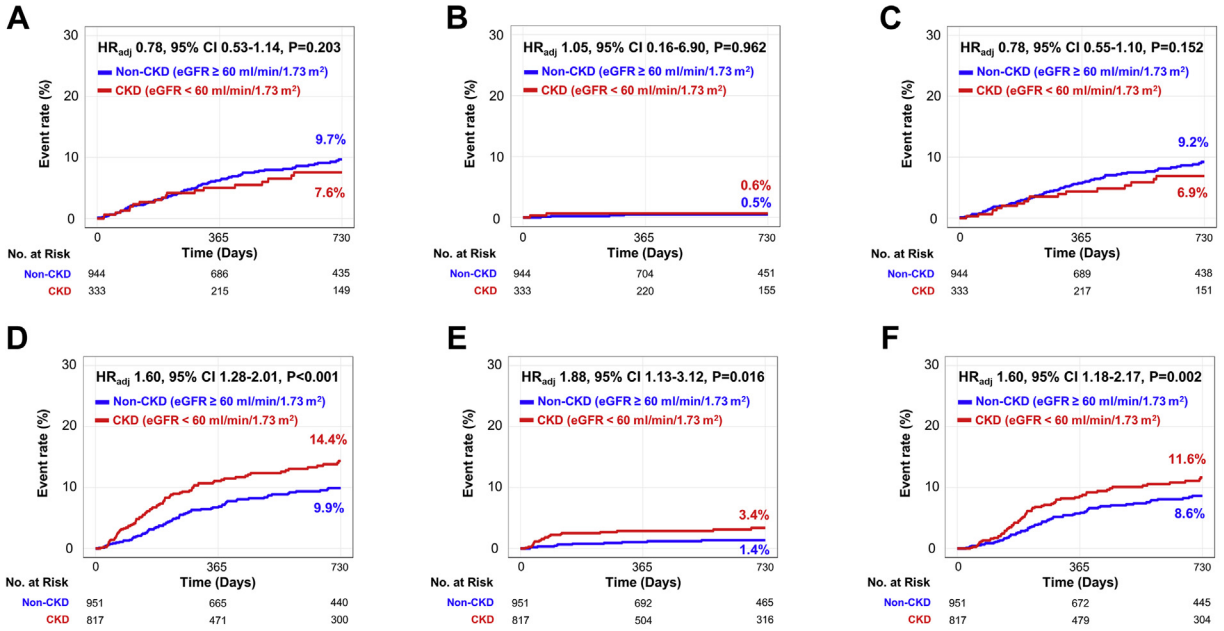

Fig 2. Clinical outcomes at 2 years between patients with and patients without chronic kidney disease (*CKD*) stratified by diabetes mellitus (DM). **A,** Major adverse limb event (MALE) in non-DM patients. **B,** Unplanned major amputation in non-DM patients. **C,** Reintervention for target limb in non-DM patients. **D,** MALE in DM patients. **E,** Unplanned major amputation in DM patients. **F,** Reintervention for target limb in DM. *CI,* Confidence interval; *eGFR,* estimated glomerular filtration rate; HR_{adj}, adjusted hazard ratio.

of high-risk features, such as below-knee lesions, vascular calcification, arterial occlusion, and reduced collateral circulation.[11,28,29] In our study, diabetic patients have more critical limb ischemia and below-knee lesions that resulted in higher use of only balloon angioplasty than in nondiabetic patients. The lesion and treatment differences might contribute to vulnerability to the negative impact of CKD in diabetic patients. Third, the severity of CKD was different between diabetic and nondiabetic patients. As diabetes remains a dominant primary cause of ESRD,[30] diabetic kidney disease has a markedly higher risk of progression to ESRD and a faster decline of glomerular filtration rate than nondiabetic kidney disease.[31] In our study, 14.4% of CKD was ESRD among nondiabetic patients, whereas 39.8% of CKD was ESRD among diabetic patients. Because ESRD is a powerful prognostic factor related to adverse outcomes in cardiovascular disease, a different proportion of ESRD among patients with CKD might contribute to the different association of CKD with clinical outcomes according to the presence of diabetes. However, compared with eGFR ≥60 mL/min/1.73 m^2, ESRD was associated with a significantly increased risk of MALEs only in the diabetic group, not in the nondiabetic group. This finding suggests that the results of this study would not be fully explained by the high proportion of ESRD in the diabetic group. On the contrary, mortality was significantly higher in patients with ESRD than in those with eGFR ≥60 mL/min/1.73 m^2 in both diabetic and nondiabetic groups, in line with the previous study.[32]

An interesting finding in our study is that patients with eGFR of 45 to 60, 30 to 45, and even <30 mL/min/1.73 m^2 did not have a higher risk of MALEs than those with eGFR >60 mL/min/1.73 m^2, and only ESRD patients had a significantly increased risk of MALEs among diabetic patients. Previous studies reported similar observations that the risk of amputation after surgical revascularization is elevated in patients who require hemodialysis but not in patients with CKD who do not require hemodialysis.[33,34] After surgical revascularization, patients with ESRD had a higher rate of limb loss due to uncontrolled infection, persistent ischemia, and prolonged healing even with a patent graft.[34,35] Although one observational study[9] reported that GFR was linearly associated with the risk of amputation after EVT, the result was mainly driven by patients with GFR <15 mL/min/1.73 m^2. Mortality tended to increase as eGFR was reduced irrespective of diabetes, which was consistent with the findings extensively studied.[6,26]

This study has several limitations. First, it was a nonrandomized observational study that had no comparative surgical or medical arm. Second, whether CKD had been stable could not be evaluated because a single creatinine value was used for analysis. To avoid inclusion of acute kidney injury by contrast-induced nephropathy in the analysis, the creatinine value obtained before the index procedure was used. Third, because data were collected from a multicenter registry, treatment strategies may have differed among participating centers, although center effect was adjusted by

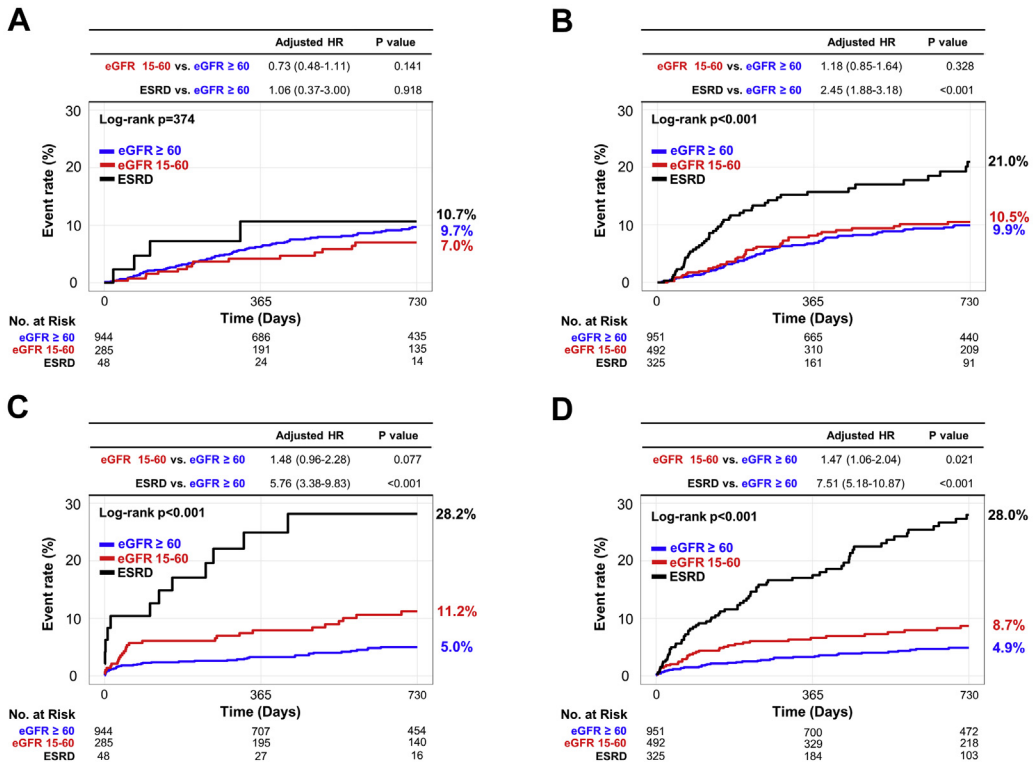

Fig 3. Clinical outcomes at 2 years according to the severity of chronic kidney disease (CKD) stratified by diabetes mellitus (DM). **A,** Major adverse limb event (MALE) in non-DM patients. **B,** MALE in DM patients. **C,** Death in non-DM patients. **D,** Death in DM patients. Clinical outcomes were compared between patients with estimated glomerular filtration rate (*eGFR*) ≥60 mL/min/1.73 m^2 (reference group), eGFR of 15 to 60 mL/min/1.73 m^2 (non-end-stage renal disease [*ESRD*] CKD), and ESRD. Adjusted hazard ratio (*HR* [95% confidence interval (CI)] was calculated by multivariable Cox regression model.

a marginal Cox model. Last, this study included Korean centers only. The results may therefore not be generalizable to other populations.

CONCLUSIONS

CKD was associated with a significantly higher risk of MALEs after EVT in patients with diabetes but not in those without diabetes. The different association of CKD with clinical outcomes was mainly driven by the high incidence of MALEs in ESRD patients with diabetes.

AUTHOR CONTRIBUTIONS

Conception and design: JK, TP, SC
Analysis and interpretation: JK, TP, KC, SC
Data collection: JK, TP, DC, YGK, JL, CHY, IC, CWY, PM, SWL, SRL, YSK, SC
Writing the article: JK, TP, SC
Critical revision of the article: JK, TP, KC, DC, YGK, JL, CHY, IC, CWY, PM, SWL, SRL, YSK, SC
Final approval of the article: JK, TP, KC, DC, YGK, JL, CHY, IC, CWY, PM, SWL, SRL, YSK, SC
Statistical analysis: JK, TP
Obtained funding: Not applicable
Overall responsibility: SC
JK and TP contributed equally to this article and share co-first authorship.

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Submitted Dec 18, 2018; accepted Mar 30, 2019.

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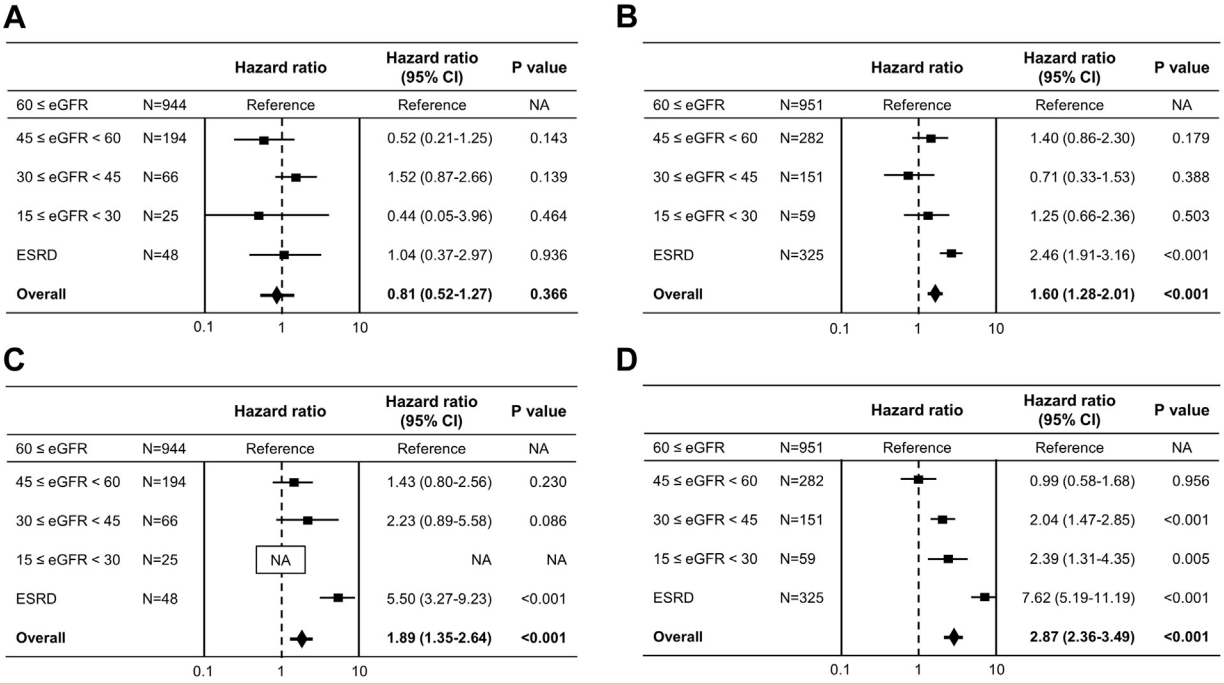

Supplementary Fig (online only). Adjusted risk of major adverse limb event (MALE) and death according to the severity of chronic kidney disease (CKD). **A,** MALE in nondiabetic patients. **B,** MALE in diabetic patients. **C,** Death in nondiabetic patients. **D,** Death in diabetic patients. *CI*, Confidence interval; *eGFR*, estimated glomerular filtration rate (mL/min/1.73 m^2); *ESRD,* end-stage renal disease; *NA,* not applicable.